UNIVERSITÉ DE GENÈVE

FACULTÉ DES SCIENCES

Section des sciences pharmaceutiques

Professeure Marie P. Schneider

AN INTERPROFESSIONAL INTERVENTION TO SUPPORT ADHERENCE TO COMPLEX AND POLYPHARMACY TREATMENTS IN PATIENTS WITH SOLID CANCER AND PATIENTS WITH DIABETIC KIDNEY DISEASE

THÈSE

présentée aux Facultés de médecine et des sciences de l'Université de Genève

pour obtenir le grade de Docteur ès sciences en sciences de la vie,

mention Sciences pharmaceutiques

par

Carole BANDIERA

De France

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Genève, le 28 mars 2023

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N.B. - La thèse doit porter la déclaration précédente et remplir les conditions énumérées dans les "Informations relatives aux thèses de doctorat à l'Université de Genève".

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–Michelle Obama

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PREFACE

This thesis manuscript is submitted for the degree of Doctor of Philosophy (PhD) ès Sciences, Life Sciences, majoring in pharmaceutical sciences.

This thesis work, aiming at evaluating the impact of an interprofessional medication adherence program on medication adherence in different populations of chronically ill patients, was affiliated to the University of Geneva (Geneva, Switzerland), and was carried out at the community pharmacy and the policlinic of the Center for Primary Care and Public Health *Unisanté* and the Medical Departments of Oncology, Nephrology and Hypertension, Endocrinology, Diabetes and Metabolism of the Lausanne University Hospital (*Centre Hospitalier Universitaire Vaudois*, CHUV, Lausanne, Switzerland).

Valuable collaborations were undertaken with the Center for Research and Innovation in Clinical Pharmaceutical Sciences (CRISP) of the CHUV, the *Département Epidémiologie et Systèmes de Santé* (DESS) at *Unisanté*, the Departments of Infectious Diseases of the CHUV and the Bern University Hospital (Bern, Switzerland), the Nursing Science Department of Public Health of the University of Basel (Basel, Switzerland) and the Cancer Research Institute of the University of South Australia (Adelaide, Australia).

I hereby declare that the research has been conducted following the Helsinki principles. The research represents original work, and does not contain any materials previously published, except where due reference is made in the text.

I have no conflicts of interest to declare.

RESEARCH OUTPUT

1. Publications in peer-reviewed scientific journals

2023 **Bandiera C**, Locatelli I, Courlet P, Cardoso E, Zaman K, Stravodimou A, Dolcan A, Sarivalasis A, Zurcher J-P, Aedo-Lopez V, Dotta-Celio J, Peters S, Guidi M, Wagner D, Csajka C, Schneider MP. *Adherence to the CDK 4/6 inhibitor palbociclib and omission of dose management supported by pharmacometric modelling as part of the OpTAT study*. Cancers 2023, 15, 316. https://www.mdpi.com/2072-6694/15/1/316

2022 **Bandiera, C**, Lam, L, Locatelli, I, Dotta-Celio J, Duarte D, Wuerzner G, Pruijm M, Zanchi A, Schneider MP. *Understanding reasons and factors for participation and non-participation to a medication adherence program for patients with diabetic kidney disease in Switzerland: a mixed methods study.* Diabetol Metab Syndr 14, 140 (2022). https://doi.org/10.1186/s13098-022-00898-7

2022 **Bandiera C**, Pasquier J, Locatelli I, Niquille A, Wuerzner G, Dotta-Celio J, Hachfeld A, Wandeler G, Wagner AD, Csajka C, Zanchi A, Cavassini M, Schneider MP. *Medication Adherence Evaluated Through Electronic Monitors During the 2020 COVID-19 Pandemic Lockdown in Switzerland: A Longitudinal Analysis*. Patient Prefer Adherence. 2022; 16:2313-2320, https://doi.org/10.2147/PPA.S377780

2022 **Bandiera C** & Ribaut J, Dima AL, Allemann SS, Molesworth K, Kalumiya K, Käser F, Olson MS, Burnier M, van Boven JFM, Szucs T, Albrecht D, Wilson I, De Geest S and Schneider MP (2022) *Swiss Priority Setting on Implementing Medication Adherence Interventions as Part of the European ENABLE COST Action*. Int J Public Health 67:1605204, doi: 10.3389/ijph.2022.1605204

2022 Courlet P & Cardoso E, **Bandiera C**, Stravodimou A, Zurcher J.-P, Chtioui H, Locatelli I, Decosterd LA, Darnaud L, Blanchet B, Alexandre J, Wagner D, Zaman K, Schneider MP, Guidi M & Csajka C, *Population Pharmacokinetics of Palbociclib and Its Correlation with Clinical Efficacy and Safety in Patients with Advanced Breast Cancer*. Pharmaceutics, Jun 2022, 14, 1317; doi: 10.3390/pharmaceutics14071317

2022 **Bandiera C** & Skrabal Ross X, Cardoso E, Wagner D, Csajka C, Olver I, Patterson P, Suppiah V, Gunn KM & Schneider MP, *Interventions to support adherence to oral anticancer therapies: research challenges, lessons learned, and strategies to overcome them from Australia and Switzerland*. Support Care Cancer, Jan 2022; doi: 10.1007/s00520-021-06710-y

2021 **Bandiera C** & Cardoso E, Locatelli I, Digklia A, Zaman K, Diciolla A, Cristina V, Stravodimou A, Veronica AL, Dolcan A, Sarivalasis, A, Liapi A, Bouchaab H, Orcurto A, Dotta-Celio J, Peters S, Decosterd L, Widmer N, Wagner D, Csajka C & Schneider MP, *Optimizing Oral Targeted*

Anticancer Therapies Study for Patients With Solid Cancer: Protocol for a Randomized Controlled Medication Adherence Program Along With Systematic Collection and Modeling of Pharmacokinetic and Pharmacodynamic Data, JMIR Res Protoc, Jun 2021;10(6):e30090; doi: 10.2196/30090

2021 **Bandiera C**, Dotta-Celio J, Locatelli I, Nobre D, Wuerzner G, Pruijm M, Lamine F, Burnier M, Zanchi A & Schneider MP, *Interprofessional Medication Adherence Program for Patients With Diabetic Kidney Disease: Protocol for a Randomized Controlled and Qualitative Study (PANDIA-IRIS);* JMIR Res Protoc, Mar 2021;10(3):e25966; doi: 10.2196/25966

2020 Schneider MP, **Bandiera C**, Dotta-Celio J, Zanchi A, *Adhésion thérapeutique et collaboration médecin-pharmacien. L'exemple du patient avec néphropathie diabétique*; Rev Med Suisse, Jun 2020; 16:1210-3; doi: 10.53738/REVMED.2020.16.697.1210

2. Peer-reviewed conference proceedings

2023 **Bandiera C**, Locatelli I, Courlet P, Cardoso E, Zaman K, Stravodimou A, Sarivalasis A, Aedo-Lopez V, Zurcher J-P, Guidi M, Wagner D, Csajka C, Schneider MP, *Adherence to palbociclib and omitted doses management supported by pharmacometric modeling.* Abstracts of the 26th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Berlin, Germany, 17–19 November 2022. Int J Clin Pharm (2023). doi: 10.1007/s11096-023-01537-5

2023 **Bandiera C**, Cardoso E, Locatelli I, Digklia A, Zaman K, Diciolla A, Cristina V, Stravodimou A, Aedo-Lopez V, Dolcan A, Sarivalasis A, Bouchaab H, Liapi A, Orcurto A, Dotta-Celio J, Peters S, Decosterd L, Widmer N, Wagner D, Csajka C, Schneider MP, *An interprofessional medication adherence program to optimize adherence to oral anticancer therapies: a randomized-controlled trial. A*bstracts of the 26th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Berlin, Germany, 17–19 November 2022. Int J Clin Pharm (2023). doi: 10.1007/s11096-023-01537-5

2022 **Bandiera C**, Pasquier J, Locatelli I, Niquille A, Wuerzner G, Dotta-Celio J, Hachfeld A, Wandeler G, Wagner D, Csajka C, Zanchi A, Cavassini C, Schneider MP, Medication adherence evaluated through electronic monitors during the COVID-19 pandemic lockdown in Switzerland; Pharmacy practice research summer meeting for PhD students, postdoctoral fellows and supervisors conference abstracts 2022. (2022). Pharmacy Education, 22(5), p. 1–48; doi.org/10.46542/pe.2022.225.148

2022 **Bandiera C**, Lam L, Dotta-Celio J, Duarte D, Wuerzner G, Pruijm M, Zanchi A, Schneider MP, Understanding risk factors and reasons of non-participation to an interventional study to monitor medication adherence in patients with diabetic kidney disease; Abstracts 8th PCNE working symposium 'Navigating research on pharmaceutical care'. Feb 2022, Lisbon, Portugal. Int J Clin Pharm (2022) ; doi: 10.1007/s11096-022-01407-6

2021 **Bandiera C**, Pasquier J, Locatelli I, Schneider MP, How to clean adherence electronic monitoring data using a semi-automated procedure?; Abstracts of the 25th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, Nov 2021. Int J Clin Pharm 44, 276–299 (2022); doi: 10.1007/s11096-021-01373-5

2020 **Bandiera C**, Dotta-Celio J, Duarte D, Wuerzner G, Pruijm M, Lamine F, Zanchi A, Schneider MP, Non-participation of diabetic nephropathy patients in an interventional medication adherence study; Abstracts of the 24th annual meeting of ESPACOMP, the International Society for Medication Adherence, Nov 2020. Int J Clin Pharm 43, 286–308 (2021); doi: 10.1007/s11096-020-01213-y

3. Contributions to conferences (oral presentation or poster)

Oral presentations

2022 **Bandiera C**, Locatelli I, Courlet P, Cardoso E, Zaman K, Stravodimou A, Sarivalasis A, Aedo-Lopez V, Zurcher J-P, Guidi M, Wagner D, Csajka C, Schneider MP, *Adherence to palbociclib and omitted doses management supported by pharmacometric modeling, ESPACOMP Nov 2022,* Berlin, Germany.

2022 **Bandiera C**, Pasquier J, Locatelli I, Schneider MP, *A semi-automated procedure to clean and enrich electronic monitoring adherence data, The CleanADHdata.R script*, Adherence Data Analysis, workshop ESPACOMP Nov 2022, Berlin, Germany.

2021 **Bandiera C**, Pasquier J, Locatelli I, Schneider MP, *How to enrich adherence electronic monitoring data using a semi-automated procedure?*; Online workshop Adherence Data Analysis, Oct 5th 2021, Nov, Online ESPACOMP Congress

2020 **Bandiera C**, Schneider MP, *Oral anticancer drug adherence program: cyclic regimen*; Online Workshop Adherence Data Analysis, Nov 17th 2020, Online ESPACOMP Congress

Award for the best poster presentation “Jean-Michel Métry Poster Prize”

2022 **Bandiera C**, Cardoso E, Locatelli I, Digklia A, Zaman K, Diciolla A, Cristina V, Stravodimou A, Aedo-Lopez V, Dolcan A, Sarivalasis A, Bouchaab H, Liapi A, Orcurto A, Dotta-Celio J, Peters S, Decosterd L, Widmer N, Wagner D, Csajka C, Schneider MP, *An interprofessional medication adherence program to optimize adherence to oral anticancer therapies: a randomized-controlled trial, ESPACOMP 2022, Berlin, Germany*

Poster prize nomination

2022 **Bandiera C**, Lam L, Dotta-Celio J, Duarte D, Wuerzner G, Pruijm M, Zanchi A , Schneider MP, *What are the factors and reasons for non-participation to an adherence program among patients with diabetic kidney disease?;* Feb 11th 2022, Pharmaceutical Care Network in Europe (PCNE) Congress, Lisbon, Portugal

Poster presentations

2022 **Bandiera C**, Pasquier J, Locatelli I, Niquille A, Wuerzner G, Dotta-Celio J, Hachfeld A, Wandeler G, Wagner D, Csajka C, Zanchi A, Cavassini C, Schneider MP, *Medication adherence evaluated through electronic monitors during the COVID-19 pandemic lockdown in Switzerland*; Jul 4-5th 2022, International Pharmaceutical Federation (FIP) Congress, Utrecht, The Netherlands

2022 **Bandiera C**, Lam L, Dotta-Celio J, Duarte D, Wuerzner G, Pruijm M, Zanchi A, Schneider MP, *What are the factors and reasons for non-participation to an adherence program among patients with diabetic kidney disease?*; Jun 3rd 2022, Swiss Society of General Internal Medicine (Société Suisse de Médecine Interne Générale, SSMIG), Lausanne, Switzerland

2021 **Bandiera C**, Pasquier J, Locatelli I, Schneider MP, *How to clean adherence electronic monitoring data using a semi-automated procedure?* ; Online video presentation, Nov 8-19th 2021, Online ESPACOMP Congress

2020 **Bandiera C**, Dotta-Celio J, Duarte D, Wuerzner G, Pruijm M, Lamine F, Zanchi A, Schneider MP, *Non-participation of patients with diabetic kidney disease in an interventional medication adherence (PANDIA-IRIS) study*; Online video presentation, Nov 10-20th 2020, Online, ESPACOMP Congress

2019 **Bandiera C,** Wehrli S, Cardoso E, Wagner D, Csajka C, Schneider MP, *How to recruit more patients? In the study: Optimizing Targeted Anticancer Therapies (OpTAT);* Nov 21-23rd 2019, Nov, ESPACOMP Congress, Porto, Portugal

4. Outreach activities

Oral presentation to the 8th annual research symposium, *Unisanté*

2022 **Bandiera C**, *Préparation d'un départ à l'étranger en tant que post-doc*, 8th annual research symposium, *Unisanté*, Lausanne, Switzerland

Oral presentation to the *PharmaMontana* Congress for pharmacists

2022 **Bandiera C** & Nathanaël Berciu, *Oncologie : les besoins des patients*. PharmaMontana Congress, Sep 22th 2022, Crans-Montana, Switzerland

Oral presentation at the monthly online session of the "*Réseau Romand Universitaire de Pharmacie Pratique (R2P2)*"

2022 **Bandiera C**, *Adhésion médicamenteuse de patients avec une maladie chronique : analyse des données électroniques et recrutement des patients*, R2P2 monthly research meeting, Jun 27th 2022, Online

Participation to the competition “My Thesis in 180 seconds”

2022 **Bandiera C**, *Adhésion médicamenteuse chez des patients chroniques sévèrement atteints dans leur santé : patients souffrant d’un cancer solide et patients diabétiques avec atteinte rénale ; Comment aider les patient-es à mieux gérer leurs médicaments ?* (Video available on Pr M. P. Schneider’s research group website); Pre-final, Feb 24th 2022, University of Geneva, Geneva

Participation to two educational videos presenting the Faculty of Pharmacy to high school students

2021 **Bandiera C** & Schneider MP, Master of pharmacy presentation to undergraduate students; Jan 21st 2021**,** Geneva

2021 Rivara Menten E, **Bandiera C**, Allemann E, Bachelor of pharmaceutical sciences presentation to undergraduate students; Jan 18th 2021**,** Geneva

Workshop moderator

2023 **Bandiera C**, *Immersion Interprofessionnelle à Pharma24*, Interprofessional week for students in healthcare, Jan 9th 2023, Geneva

2021 **Bandiera C** & Flornoy A, Schneider MP, Online *Quizz interpro: role du pharmacien*, moderator, Interprofessional week for students in healthcare, Jan 11th 2021, Geneva

2020 **Bandiera C** & Flornoy A, Schneider MP, *Rôle des pharmaciens et Interprofessionnalité, m*oderator, Interprofessional week for students in healthcare, University of Geneva, Jan 6th 2020**,** Geneva

Oral presentation at the monthly research symposium of *Unisanté*

2019 **Bandiera C** & Clair C, *Recrutement des patients dans les études cliniques PANDIA et OpTAT et DiSCGO*, *Unisanté* monthly research meeting, Nov 5th 2019, *Unisanté*, Lausanne

Oral presentations to the Department of Oncology

2019-2020 **Bandiera C**, Wehrli S, Schneider MP, *Optimization of Targeted Anticancer Therapies (OpTAT): a systematic collection and modeling of pharmacokinetic data and elaboration of an adherence program,* Jan 14th and Jun 17th 2019, Feb 10th and Aug 17th 2020**,** Lausanne University Hospital (CHUV), Lausanne

Oral presentations to the Department of Nephrology and Hypertension, the Department of Endocrinology, Diabetes and Metabolism (CHUV), and the policlinic of *Unisanté*

2019-2020 **Bandiera C** & Clair C, Birrer P, Egger M, Schneider MP, *Étude PANDIA et DISCGO-RCT-Update,* Jan 24th, Feb 7th, Mar 19th, Jun 24th, 25th, Jul 18th, Sep 26th**,** Dec 5th, 9th and 10th 2019, Feb 7th and Jul 23rd 2020**,** CHUV and *Unisanté*, Lausanne

5. Other artefacts with documented use

Article in "*LeJournal de l'UNIGE*" (University of Geneva)

2023 Interview for a didactic article «*La non-adhésion aux traitements coûte 125 milliards d'euros par année à l'Europe*», Anton Vos, LeJournal, University of Geneva, Apr 2023

Policy Brief

2023 Ribaut J & **Bandiera C**, Molesworth K, Dima A L, Samuel S A, Kalumiya K, Käser F, Olson M S, Burnier M, van Boven J F M, Szucs T, Wilson I, Schneider MP & De Geest S, Policy Brief - *Swiss Priority Setting on Implementing Medication Adherence Interventions – the European ENABLE COST Action,* 2023, planned dissemination in April 2023

Research reports to the funders

2022 Schneider MP, **Bandiera C**, *Patients diabétiques et insuffisants rénaux : un programme interdisciplinaire de soutien à l'adhésion thérapeutique (PANDIA-IRIS), Rapport final pour le Fonds de qualité et de recherche RBP IV/1,* final report to the funders, Dec 2022

2022 Schneider MP, **Bandiera C**, *Soutenir l'adhésion médicamenteuse des patient·es traité·es par thérapies orales anticancéreuses (Etude OpTAT), Rapport final pour le Fonds de Recherche Suisse Contre le Cancer*, final report to the funders, Aug 2022

2021 **Bandiera C**, Schneider MP, *Patients diabétiques et insuffisants rénaux : un programme interdisciplinaire de soutien à l'adhésion thérapeutique (PANDIA-IRIS), Rapport intermédiaire n°3 pour le Fonds de qualité et de recherche RBP IV/1,* Aug 2021

2019 **Bandiera C**, Schneider MP, *Patients diabétiques et insuffisants rénaux : un programme interdisciplinaire de soutien à l'adhésion thérapeutique (PANDIA-IRIS), Rapport intermédiaire n°2 pour le Fonds de qualité et de recherche RBP IV/1,* Oct 2019

2019 **Bandiera C,** Cardoso E, Wagner D, Csajka C, Schneider MP, *Optimizing targeted anti-cancer therapies (OpTAT), from better medication adherence to individualized treatment. Midterm study report.* Swiss Cancer research Foundation, Jul 2019

Development of the CleanADH.data R-script and related files

2022 **Bandiera C** & Pasquier J, Locatelli I, Schneider MP, *A semi-automated procedure to clean electronic adherence monitoring data: the R script CleanADHdata.R*. Feb 2021-Nov 2022**.** Available on GitHub - jpasquier/CleanADHdata

6. Unpublished work: manuscripts in preparation

2023 **Bandiera C** & Pasquier J, Locatelli I, Schneider MP, *A semi-automated procedure to clean electronic adherence monitoring data: a tutorial to use the R script CleanADHdata.R.*

2023 **Bandiera C**, Cardoso E, Locatelli I, Zaman K, Digklia A, Diciolla A, Stravodimou A, Cristina V, Aedo-Lopez V, Dolcan A, Sarivalasis A, Bouchaab H, Pasquier J, Dotta-Celio J, Peters S, Wagner D, Csajka C, Schneider MP. *A pharmacist-led interprofessional medication adherence program improved adherence to oral anticancer therapies: the OpTAT randomized controlled trial.*

2023 **Bandiera C**, Dotta-Celio J, Locatelli I, Nobre D, Wuerzner G, Pruijm M, Lamine F, Burnier M, Zanchi A & Schneider MP. *The differential impact of a 6- versus 12-month pharmacist-led interprofessional medication adherence program on medication adherence in patients with diabetic kidney disease: the randomized PANDIA-IRIS study.*

7. Teaching activities

Jan 2023 Course (1.5 hours) for pharmacists in community pharmacies, conference for continuing education hold by *PharmaGenève*; Carole Bandiera, Dre Audrey Simon, "*Le patient oncologique et l'équipe interprofessionnelle: l'exemple du myélome multiple*". Involvement of community pharmacists to maximize adherence to oral chemotherapy to treat multiple myeloma, validation of prescriptions.

Nov 2021-22 Course and workshop (4 hours) for master students in pharmacy at the University of Geneva. Carole Bandiera, Pre MP Schneider, « *Capsule médicament et patient: cancer, étude de cas de communication* ». Challenges for communicating with patients with cancer, management of patients' and healthcare professionals' emotions, answering patients' needs, use of alternative medicines and potential risks, case studies.

May 2022 Workshop (4 hours) for hospital pharmacists attending the Master of Advanced Studies (MAS) in hospital pharmacy. Pre MP Schneider, Beatriz Santos, Carole Bandiera *"Entretien motivationnel en pratique*", decrypting the four key steps in motivational interviewing and practical exercises.

May 2022 Course (1 hour) for nurse specialists (*Master d'infirmière praticienne spécialisée);* Pre MP Schneider, Carole Bandiera, *« L'adhésion thérapeutique* ». Basis of medication adherence research, consequences of medication nonadherence, adherence tools, behavioral models, case studies.

Apr 2022 Course (1.5 hours) for pharmacists attending the Certificate of Advanced Studies (CAS) in pharmacotherapy. Carole Bandiera, Dre Athina Stravodimou, "*Le traitement oral ciblé du cancer du sein : update et interprofessionnalité*". Validation of a prescription with palbociclib, medication interactions and literature sources, communication in health with oncologists and patients.

Feb 2022 Course (1.5 hours) for pharmacists in community pharmacies, conference for continuing education hold by *PharmaGenève*; Carole Bandiera, Dre Athina Stravodimou, "*Le traitement oral ciblé du cancer du sein: update et interprofessionnalité*". Adherence to oral chemotherapy, complementary medicines used by patients and potential risks.

LIST OF ABBREVIATIONS

CAS	Certificate of Advanced Studies
CHF	Swiss Franc
CHUV	Centre Hospitalier Universitaire Vaudois
CI	Confidence Interval
CM	Complementary Medicines
CML	Chronic Myeloid Leukemia
COM-B	Capability Opportunity Motivation-Behavior
CovADH study	Covid-19 and ADHerence study
COVID-19	Coronavirus disease 2019
CRFs	Case Report Forms
CRISP	Centre for Research and Innovation in Clinical Pharmaceutical Sciences
CTE	*Centre de Therapies Expérientales*
DESS	*Département Epidémiologie et Systèmes de Santé*
DISCGO	Diabetes and Smoking Cessation: a Gender-Oriented
DKD	Diabetic Kidney Disease
DOT	Direct Observation Therapy
DRP	Drug-Related Problems
eGFR	estimated Glomerular Filtration Rate
eHealth	electronic Health
EM	Electronic Monitor
EMERGE	ESPACOMP Medication Adherence Reporting Guideline
ENABLE-COST action	European Network to Advance Best practices & technoLogy on medication adherencE, a Cooperation in Science and Technology action

e-prescriptions	Electronic-prescriptions
ESPACOMP	International Society for Medication Adherence
ESRD	End Stage Renal Disease
EUR	Euros
FIP	International Pharmaceutical Federation
GEE	Generalized Estimated Equations
GI clinic	Gastrointestinal clinic
GPs	General practitioners
GYN clinic	Gynecology clinic
HbA1c	Hemoglobin A1c
HCPs	Health Care Providers
HIV	Human Immunodeficiency Viruses
IMAP	Interprofessional Medication Adherence Program
IMPACT	Swiss Implementation Science Network
IV	Intravenous
LADA	Latent Autoimmune Diabetes in Adult
LCD	Liquid Cristal Display
MEL clinic	Melanoma clinic
MEMS	Medication Event Monitoring System
NEURO clinic	Neurology clinic
OAT	Oral Anticancer Therapies
OpTAT study	Optimizing Targeted Anticancer Therapies study
ORL clinic	Otorhinolaryngology clinic
PANDIA-IRIS	*Patient·es diabétiques et insuffisants rénaux : un programme interdisciplinaire de soutien à l'adhésion thérapeutique*
PART-PANDIA study	Participation to PANDIA-IRIS study

PCNE	Pharmaceutical Care Network in Europe
PD	Pharmacodynamics
PK	Pharmacokinetics
PKI	Protein Kinase Inhibitors
Pop-PK	Population Pharmacokinetic
RCTs	Randomized Controlled Trials
SARC clinic	Sarcoma clinic
Sars-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SEN clinic	Senology clinic
SMD	Standardized Mean Difference
SMS	Short Messages Service
SSMIG	*Société Suisse de Médecine Interne Générale*
TDM	Therapeutic Drug Monitoring
TEOS	Timelines-Events-Objectives-Sources
THOR clinic	Thoracic clinic
TI	Ticino canton of Switzerland
URO clinic	Urology clinic
USA	United States of America
USD	United States Dollars
WHO	World Health Organization

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Figure 1: The relationship between the medication adherence process and the prescription process, adapted from Vrijens and al., A new taxonomy for describing and defining adherence to medications. BJCP, 2012[37] and De Geest and al., ESPACOMP Medication Adherence Reporting Guideline (EMERGE), Ann Intern Med, 2018[42] 6
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ABSTRACT

Background Medication nonadherence (i.e., the extent to which a patient behavior deviates from the medical prescription) is prevalent in the population of chronically ill patients. The Interprofessional Medication Adherence Program (IMAP) aims at supporting patient medication adherence (i.e., implementation and persistence) with an interactive digital technology (electronic monitoring (EM)) providing adherence feedback, regular 15-minute motivational interviews between the patient and the pharmacist, and a shared medication adherence report to the physician and the nurse. Through two randomized and controlled trials embedded in routine practice, this thesis evaluated the impact of the IMAP on medication adherence i) in patients with solid cancer treated with protein kinase inhibitors (PKI) (the OpTAT study) and ii) in patients with diabetic kidney disease (DKD) (the PANDIA-IRIS study). While the COVID-19 pandemic hit research in 2020, medication adherence was explored during the lockdown (CovADH study).

Methods In the **OpTAT study**, patients were randomized in two parallel groups: while the intervention group benefited from the IMAP during 12 months, the control group received standard care plus EM without intervention. We used model-based pharmacokinetic (PK) and pharmacodynamic (PD) simulations to investigate the relationship between implementation to palbociclib (a PKI with a cyclic regimen), plasma concentrations and neutropenia. In the **PANDIA-IRIS study**, patients were randomized in two groups: in group A, the IMAP was delivered during 12 months, versus 6 months in group B. Patients entered then a follow-up phase without intervention (12 months in group A vs. 18 months in group B), during which EM data were blinded. Adherence was monitored continuously for 24 months post-inclusion in both groups. We measured implementation and persistence to antidiabetics, antihypertensive drugs and statins. In the **PART-PANDIA study**, a mix quantitative-qualitative methodology was performed to analyze patient (non-)participation in the PANDIA-IRIS study. Thematic analysis and inductive coding were performed on the verbatim transcriptions of semi-structured qualitative interviews. In the retrospective **CovADH study**, we compared medication implementation before, during and after the lockdown.

Prior to statistical analysis, the raw longitudinal EM databases were cleaned and enriched using a semi-automated procedure developed in the statistical software R (CleanADHdata.R) to increase data cleaning reproducibility. Then, medication implementation was compared between groups using generalized estimating equation (GEE) models, in which relevant covariates were included in the OpTAT study. When sufficient data allowed it, medication persistence was analyzed using Kaplan-Meier survival curves.

Results In the **OpTAT study**, we showed that PKI implementation was constantly higher in the intervention (n=58) than in the control group (n=60), 98.1% and 94.9% (Δ3.2%, 95% confidence interval (CI) 2.6%; 3.7%) at 6 months. The intervention benefited most to men, those who had initiated PKI for more than 60 days, patients without a diagnosis of metastasis, those aged less than 60 years old and those who had never used any adherence tool in the past. The IMAP had no impact on persistence to PKI. When analyzing adherence to palbociclib, the impact of the intervention was larger in patients older than 65 and those with longer disease and treatment experience. We found that patients who missed doses during the ON phase of the cycle sometimes caught them up during the OFF phase; we showed that this behavior increased the risk of severe neutropenia in the next cycle. Last, our data showed that oncologists prescribed frequent PKI interruptions to help patients recover from side effects. In the **PANDIA-IRIS study**, we showed that implementation to antidiabetics (n=57) and antihypertensive drugs (n=57) constantly increased while patients were benefiting from the IMAP and decreased progressively during the follow-up phase post-intervention. At 12 months, in group A and B, implementation to antihypertensive drugs was respectively of 97.9% and 92.1% (Δ5.8%, 95%CI 4.8%; 6.7%); at 24 months, respectively 94.4% and 85.9% (Δ8.5%, 95%CI 6.6%; 10.7%). The IMAP did not affect implementation to statins (n=44). The **PART-PANDIA study** showed that factors associated with an increased risk of non-participation to the IMAP were female sex (OR 3.8, 95%CI 1.4; 10.0, p=0.007) and time since diabetes diagnosis (OR 1.05, 95%CI 1.01; 1.09, p=0.019). While patients who participated in the study found the intervention useful to improve their adherence, patients who declined to participate explained that they did not perceive a need for the intervention, they perceived the study as a burden and shared that the intervention would have been beneficial if introduced earlier in their therapeutic journey. In the **CovADH study**, we showed that medication implementation remained steady before, during and after the lockdown in 2020 in patients included in IMAP.

Conclusions and Perspectives This thesis showed that the IMAP supports, improves and maintains medication implementation in patients with solid cancers and in patients with DKD. To further strengthen the results obtained, interprofessional collaborative practice should be reinforced to optimize the recruitment, engagement and retention of outpatients in cognitive-behavioral programs to support medication adherence such as the IMAP. Defining roles and responsibilities and developing complementary competencies of healthcare providers will help to bridging the gap between clinical and behavioral sciences. In this perspective and for the first time, the Swiss ENABLE (European network to advance best practices & technology on medication adherence) policy brief that we have just published contains all the needed information to influence policies and practices in Switzerland in order to scale up medication adherence interventions nationally as a standard of care.

RÉSUMÉ

Contexte La non-adhésion médicamenteuse (=le processus selon lequel le comportement des patient·es s'écarte de la prescription médicale) est prévalente chez les patient·es atteint·es de maladies chroniques. Le programme interprofessionnel d'adhésion aux médicaments (IMAP) vise à soutenir l'adhésion médicamenteuse (=l'implémentation et la persistance) grâce à une technologie numérique interactive (le pilulier électronique) fournissant un feedback sur le comportement du/de la patient·e, des entretiens motivationnels réguliers de 15 minutes entre le/la patient·e et le/la pharmacien·ne, et un rapport sur l'adhésion médicamenteuse partagé au/à la médecin et au/à l'infirmièr·e. Par le biais de deux essais randomisés et contrôlés intégrés dans la pratique de routine, cette thèse a évalué l'impact de l'IMAP sur l'adhésion médicamenteuse i) chez des patient·es atteint·es de cancers solides traité·es par inhibiteurs des protéines kinases (IPK) (étude OpTAT) et ii) chez des patient·es atteint·es de néphropathie diabétique (étude PANDIA-IRIS). Alors que la pandémie COVID-19 a frappé la recherche en 2020, l'adhésion médicamenteuse a été investiguée pendant le confinement (étude CovADH).

Méthodes Dans **l'étude OpTAT**, les patient·es ont été randomisé·es dans deux groupes parallèles : tandis que le groupe intervention a bénéficié de l'IMAP pendant 12 mois, le groupe contrôle a reçu des soins standards et a utilisé le pilulier électronique, mais sans intervention. Nous avons utilisé des simulations pharmacocinétiques (PK) et pharmacodynamiques (PD) basées sur des modèles pour étudier la relation entre l'implémentation au palbociclib (un IPK avec une posologie cyclique), les concentrations plasmatiques et la neutropénie. Dans **l'étude PANDIA-IRIS**, les patient·es ont été randomisé·es en deux groupes : dans le groupe A, l'IMAP a été délivré pendant 12 mois, contre 6 mois dans le groupe B. Les patient·es sont ensuite entré·es dans une phase de suivi sans intervention (12 mois dans le groupe A contre 18 mois dans le groupe B) durant laquelle les données des piluliers ont été enregistrées en aveugle. Dans les deux groupes, l'adhésion a été monitorée en continu pendant 24 mois. Nous avons exploré l'implémentation et la persistance aux antidiabétiques, aux antihypertenseurs et aux statines. Dans **l'étude PART-PANDIA**, une méthodologie mixte quantitative-qualitative a été utilisée pour analyser la (non-)participation des patient·es à l'étude PANDIA-IRIS. Une analyse thématique et un codage inductif ont été effectués sur la base des transcriptions verbatim d'entretiens qualitatifs semi-structurés. Dans l'étude rétrospective **CovADH**, nous avons comparé l'implémentation avant, pendant et après le confinement.

Avant de procéder aux analyses statistiques, les bases de données longitudinales brutes des piluliers ont été nettoyées et enrichies à l'aide d'une procédure semi-automatique développée

dans le logiciel statistique R (CleanADHdata.R) afin de garantir la reproductibilité du nettoyage des données brutes. Ensuite, l'implémentation a été comparée entre les groupes en utilisant des modèles d'équations d'estimation généralisées (GEE), dans lesquels des covariables pertinentes ont été incluses dans l'étude OpTAT. Lorsque les données le permettaient, la persistance a été analysée à l'aide des courbes de survie de Kaplan-Meier.

Résultats Dans **l'étude OpTAT**, nous avons montré que l'implémentation aux IPK était constamment plus élevée dans le groupe intervention (n=58) par rapport au groupe contrôle (n=60), 98,1% et 94,9% (Δ 3,2%, IC (intervalle de confiance) 95% 2,6% ; 3,7%) à 6 mois. L'intervention a été particulièrement bénéfique pour les hommes, ceux/celles qui avaient initié l'IPK depuis plus de 60 jours, aux patient·es sans diagnostic de métastases, à ceux/celles âgé·es de moins de 60 ans et à ceux/celles qui n'avaient jamais utilisé d'outils d'adhésion dans le passé. L'IMAP n'a pas eu d'impact sur la persistance aux IPK. En analysant l'adhésion au palbociclib, l'impact de l'intervention était plus important chez les patientes âgées de plus de 65 ans et chez celles qui avaient une plus longue expérience de la maladie et du traitement. Nous avons constaté que les patientes qui manquaient des doses pendant la phase ON du cycle les rattrapaient parfois pendant la phase OFF ; nous avons montré que ce comportement augmentait le risque de neutropénie sévère lors du cycle suivant. Enfin, nos données ont montré que les oncologues prescrivaient fréquemment des interruptions des IPK pour aider les patient·es à se rétablir des effets secondaires. Dans **l'étude PANDIA-IRIS**, nous avons montré que l'implémentation aux antidiabétiques (n=57) et aux antihypertenseurs (n=57) augmentait constamment pendant que les patient·es bénéficiaient de l'IMAP et diminuait progressivement pendant la phase de suivi post-intervention. A 12 mois, dans les groupes A et B, l'implémentation aux antihypertenseurs était respectivement de 97,9% et 92,1% (Δ5,8%, IC95% 4,8% ; 6,7%) ; à 24 mois, respectivement de 94,4% et 85,9% (Δ8,5%, IC95% 6,6% ; 10,7%). L'IMAP n'a pas eu d'impact sur l'implémentation aux statines (n=44). **L'étude PART-PANDIA** a montré que les facteurs associés à un risque accru de non-participation à l'IMAP étaient le sexe féminin (OR 3,8, IC95% 1,4 ; 10,0, p=0,007) et la durée depuis le diagnostic du diabète (OR 1,05, IC95 % 1,01 ; 1,09, p=0,019). Alors que les patient·es qui ont participé à PANDIA-IRIS ont trouvé que l'intervention était utile pour améliorer leur adhésion médicamenteuse, les patient·es qui ont refusé de participer ont expliqué qu'ils ne percevaient pas la nécessité de l'intervention, qu'ils percevaient l'étude comme un fardeau et ont déclaré que l'intervention aurait été bénéfique si elle avait été introduite plus tôt dans leur parcours thérapeutique. Dans **l'étude CovADH**, nous avons montré que l'implémentation médicamenteuse est restée stable avant, pendant et après le confinement en 2020 chez les patient·es inclus·es dans l'IMAP.

Conclusions et perspectives Cette thèse a montré que l'IMAP soutient, améliore et maintient l'implémentation médicamenteuse chez les patient·es atteint·es de cancers solides et chez les patient·es atteint·es de néphropathie diabétique. La collaboration interprofessionnelle devrait être davantage renforcée pour optimiser le recrutement, l'engagement et la rétention des patient·es dans les programmes cognitivo-comportementaux tels que l'IMAP. La définition des rôles et des responsabilités des professionnel·les de la santé, et le développement de compétences complémentaires participeront à combler le fossé entre les sciences cliniques et comportementales. Dans cette perspective, et pour la première fois, le policy brief suisse ENABLE (European Network to Advance Best practices & technoLogy on medication adherence) que nous venons de publier contient toutes les informations nécessaires pour influencer les politiques et les pratiques en Suisse afin d'implémenter les interventions de soutien de l'adhésion médicamenteuse au niveau national en tant que standard des soins.

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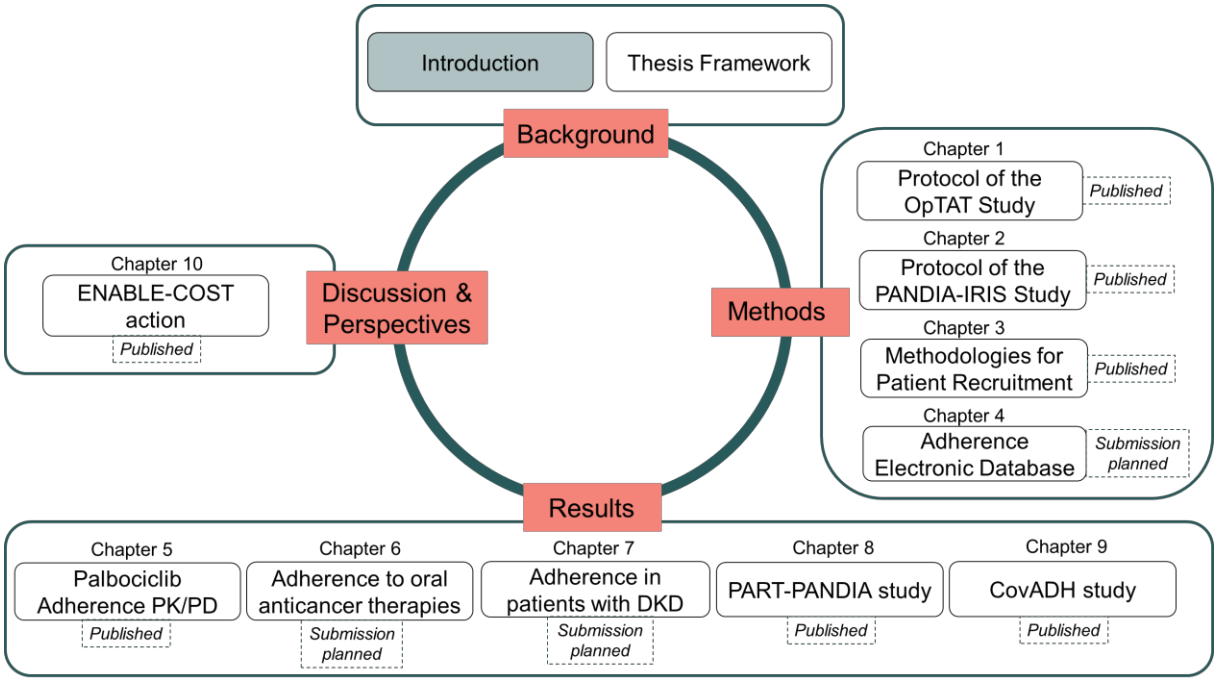
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INTRODUCTION



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

1. Chronically ill Patients in the Swiss Healthcare System

In the last decades, the quality of life and life expectancy of chronically ill patients have increased thanks to research and advancements in medical treatments, medical technologies and quality of care. While the therapeutic arsenal is more and more personalized, accurate, targeted and efficient, it is also costly. The complexity of the treatment increases with polymorbidity, defined in a patient diagnosed with at least two chronic diseases[1, 2]. The major chronic diseases commonly reported are cardiovascular diseases, cancers, chronic-respiratory diseases, chronic kidney diseases, arthritis and diabetes, even though attention should also be given to other conditions (e.g., obesity, infectious diseases, mental illness), syndromes (e.g., chronic fatigue, back pain) and functional disabilities (e.g., visual impairment)[3-5]. Polymorbidity is associated with a decreased quality of life[6] and increased healthcare costs[7-9] and mortality[10]. The prevalence of polymorbidity is high, for example in Switzerland, it is estimated that almost 80% of patients are polymorbid at hospital discharge[11]. Polymorbidity aligns with polypharmacy in most chronically ill patients[12] (i.e., when a patient is prescribed at least 5 daily medications[13]). The consumption of medicines (i.e., prescribed medications or over-the-counter drugs) has constantly increased during the last decades: from 38% of the Swiss population taking at least one medicine in 1992 to 50% nowadays[14]. Notably, among over-the-counter drugs, the use of complementary medicines (CM) (e.g., homeopathy, herbal medicine, acupuncture) is quite prevalent as 25% of the Swiss population reported having used at least one CM in the past 12 months preceding the survey[15]. Although often necessary, polypharmacy can impact medication safety (e.g., due to drug-drug interactions or cumulative side effects). The process of deprescribing, consisting in the withdrawal of inappropriate medications under the supervision of health care providers (HCPs), is an emerging process still underinvestigated in the scientific literature[16]. In a nutshell, polymorbidity and polypharmacy both lead to a higher complexity of care management, which requires an interprofessional team working in partnership with the patient and carers[17].

The strategy of patient-centered healthcare defines patients as experts of their conditions[18]. As part of this paradigm, patients' capacity to be involved in their care increases, improving their health literacy and their participation in shared decision-making processes: this patient's new position is supported by the concept of patient empowerment[19]. Patient partnership and engagement play a key role in the education of HCPs and represent promising changes in the organization of models of care to improve the management of chronic diseases[20]. Facing the challenges of aging, polymorbid and polymedicated chronically ill patients, the Swiss healthcare system needs to evolve towards a mutation process for a better coordination and continuity of care to improve patients' clinical outcomes, patients' satisfaction and quality of life[21] and contain healthcare costs[22].

2. Pharmacists in the Swiss Healthcare System

2.1. Pharmaceutical Care

In Switzerland in 2012, Mrs. Ruth Humbel, a Swiss politician in the national council, stated a postulate called « *Place des pharmacies dans les soins de base* » to clarify the role of pharmacists as HCPs in the Swiss primary care system. This postulate suggests positioning and valorising pharmacists more firmly as providers in ambulatory care and expand their activities, particularly facing the challenge of the increasing shortage of HCPs[23]. The Swiss Federal Council approved this postulate and edited a report in 2016, concluding that pharmacists' main role is not only defined by drug delivery or compounding, but it encompasses patient-centered pharmaceutical care to ensure treatment safety, efficacy and economicity. Pharmaceutical care is defined as pharmacists-led services aiming to optimize medicines use and improving health outcomes[24]. The pharmacists identify drug-related problems (DRP), resolve them with other HCPs and prevent the emergence of DRP by carefully monitoring the treatment plan[25]. Importantly, in an Asian study identifying pharmaceutical care issues, patients who do not take their medications as prescribed by the provider was the most common inappropriate drug use encountered by pharmacists[26]. Besides medication reviews, the pharmacists provide counselling and therapeutic education along with supporting patients' medication management and adherence to the prescription.

With their pharmacological and pharmaceutical knowledge, pharmacists contribute to the efficiency of the healthcare system, have a major role in healthcare promotion, facilitate the access to primary care and guarantee an equitable access to medications, while ensuring a minimal ecological footprint as possible[27]. The recent developments of these pharmaceutical services along with the new roles assigned to pharmacists strengthen the importance of interprofessional collaborations between HCPs to ensure coordination of care (i.e., planning care with the patient and carers, taking into account patients' needs and preferences[28]).

2.2. Pharmacists' Role and Responsibilities Within An Interprofessional Team

To ensure coordination of care, HCPs must reduce working "in silos", which means working individually without collaborative practice. If a lack of coordination and communication occur between these stakeholders, prescriptions errors, duplication, repeated exams and ineffective workflow can impact patient health outcomes. The World Health Organization (WHO) defines interprofessional collaborative practices when several HCPs from different backgrounds collaborate by sharing knowledge and practices as a team in which patients, family and carers are included, to improve patients' clinical outcomes[29]. In Switzerland, one of the most successful interprofessional programs between pharmacists and physicians is called « *Cercles de qualité* ». This program consists in regular meetings between pharmacists and physicians

to explore specific DRP in order to decrease their prevalence[23]. As a matter of fact, a recent meta-analysis showed that involving pharmacists by delivering audit and feedback on the prescribing process in general practice settings was effective in improving evidence-based prescribing behaviors[30], which ultimately optimizes patient care.

The reorganisation of the healthcare system to foster interprofessional practices is part of the Swiss health policy priority entitled "*Santé 2030*". Computerization is part of this strategy to strengthen and facilitate communication between HCPs. As an example, the electronic patient record allows rapid, regular and traceable documentation of each action provided by the HCPs[31]. It allows sharing observations, recommendations or adaptations to the treatment plan (i.e., drug side effects, medication management, medication adherence support strategy) and harmonize patient treatment trajectory[32]. This technology has the potential to improve coordination of care at the interfaces between pharmacies, hospitals, ambulatory sectors, nursing homes, home-care services and medical offices.

Although medication management was the sole responsibility of the patient for long, we now know that this process needs to be mastered, which requires education and follow-up. The patient's medication management must be described, shared and optimized interprofessionally. As experts of medications and dispensers of the medications of all prescribers, one of the key missions of pharmacists is to help patients cope with the burden of their treatments by monitoring and ensuring patient optimal medication adherence during their therapeutic itinerary alongside with physicians and nurses.

3. Medication Adherence, a Major Public Health Concern

3.1. Historical Background of Medication Adherence

Hippocrates (460 Before Christ) was the first physician to understand that some patients may not take their medicines as prescribed. However, it was only in the 20th century that nonadherence became a real public health concern, when providers understood that patients diagnosed with tuberculosis who failed to follow medical prescriptions could contaminate other people in their social or professional clusters. These patients, considered back then as "irresponsible" and "ignorant"[33], were mostly stigmatized as vulnerable patients suffering from social disparities (e.g., immigrants, homeless, alcohol-dependent people). Detention programs were even initiated to control their "disobedience". It is only when physicians observed that veterans from World War II were also not taking their anti-tuberculosis treatments that researchers started to explore patients' beliefs and behaviors towards their medication management. Research was then drawing on the theories of the neurologist and psychiatrist Sigmund Freud, founder of psychoanalysis. Indeed, one of the theories developed

by Freud was the “talking cure”, explained by the fact that a patient can be alleviated from his/her symptoms by talking about them[34]. A parallel can be drawn with patient medication self-management, as one can suppose that talking about the prescribed medications could unburden patients and allow them to express their concerns and beliefs. In the 1970s, Sackett and Haynes defined “patient compliance” as a person’s behavior towards medical advice[35, 36]. In 1985, a former surgeon General C. Everett Koop raised the concern of non-compliance by saying, « Drugs don’t work in patients who don’t take them ». A decade later, in 1997, Lerner explained how to nuance the word “compliance”, which was considered judgemental and paternalist, towards a formulation encompassing an autonomous behavior corresponding to the patient’s choice[33]. As a result, the term “compliance” has been progressively replaced by “adherence” over the last 20 years[37], acknowledging the collaborative effort between patients and their interprofessional providers, paramount to engage patients in their care[38]. In 1996, under the guidance of Pr. John Urquhart, a group of researchers in the Netherlands and Belgium initiated the first symposium on medication adherence, which became the actual International Society for Medication Adherence (ESPACOMP)[39].

Medication adherence is now commonly defined as the extent to which patients take their treatments as prescribed by the HCPs, following the prescribing process, whether this latter happens within a shared decision-making process or not[37]. In 2003, the WHO established a report, alerting about the silent epidemic of medication nonadherence, estimating that 50% of chronically ill patients do not take their medications as prescribed[40]. Recently, a report from the Organisation for Economic Co-operation and Development reported that only 50-70% of patients with diabetes, hypertension and hyperlipidemia take their medications as prescribed[41], confirming the worldwide concern of medication nonadherence.

3.2. Definition of Medication Adherence

In 2012, the ABC taxonomy standardized the definition of medication adherence by defining three key quantifiable phases: i) initiation, ii) implementation and iii) discontinuation of the treatment[37] (Fig. 1).

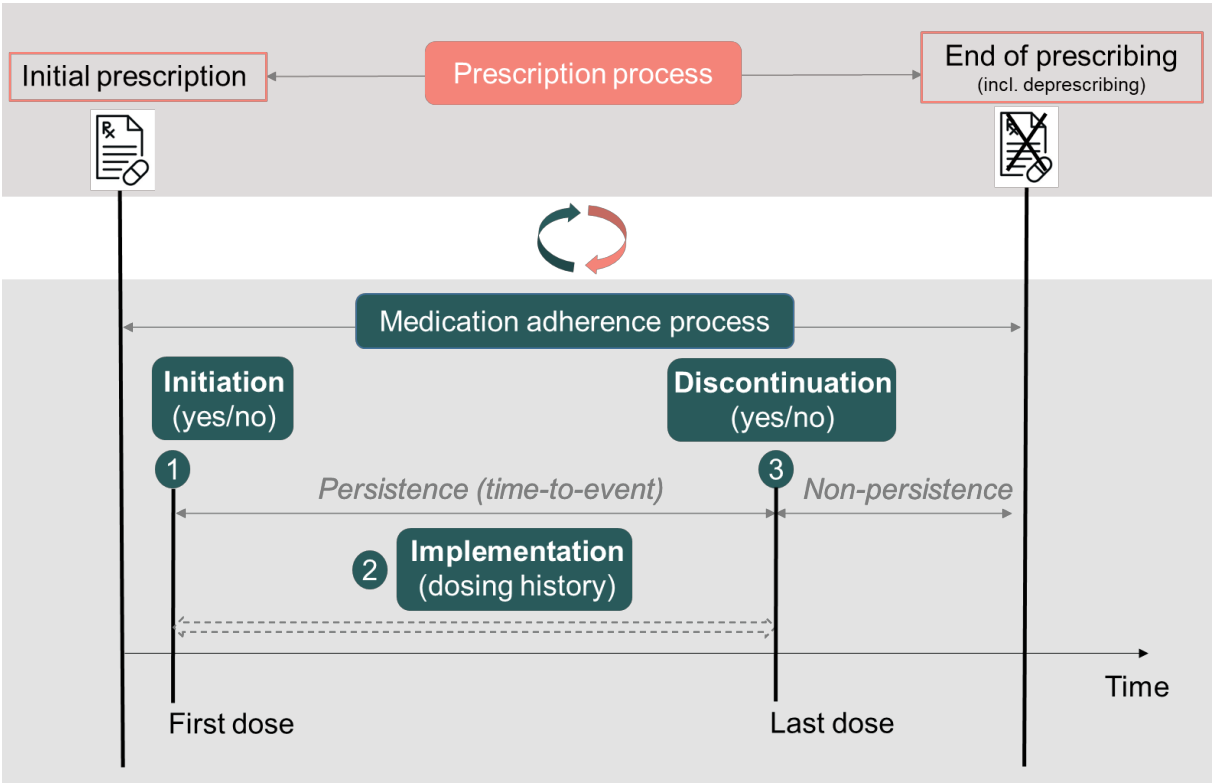


Figure 1: The relationship between the medication adherence process and the prescription process, adapted from Vrijens and al., A new taxonomy for describing and defining adherence to medications. *BJCP, 2012[37] and De Geest and al.,* ESPACOMP Medication Adherence Reporting Guideline (EMERGE), *Ann Intern Med, 2018[42]*

i. The **initiation** of the medication corresponds to the first dose taken by the patient[42], characterized by a binary variable (i.e., initiation or non-initiation). Few studies have explored patient initiation to their prescribed medications, as quantifying the dates of providers' prescriptions and dispensations are challenging. However, it is estimated that 4-31% of patients never honored their first prescription[41]. A study analyzed all 195'930 consecutive electronic-prescriptions (e-prescriptions) written in a period of 12 months to 75'589 patients and concluded that 22% of e-prescriptions were not filled; this proportion reached 28% when considering only newly prescribed medications[43]. Notably, new prescriptions for antihypertensive, antidiabetic and antihyperlipidemia drugs were approximately 9% less likely to be filled compared to all e-prescriptions[43], which highlights the need to better support medication initiation in these chronically ill patients.

ii. The **implementation** of the treatment is the extent to which a patient dosing history corresponds to the prescribed dosing regimen, including the correct timing and required

conditions (e.g., fasted conditions), from initiation to the last dose taken. It is estimated that 30-50% of patients with diabetes, hypertension and hyperlipidemia do not implement their treatment optimally (i.e., less than 80% of doses prescribed taken)[41]. Most adherence studies evaluate implementation through dosing history[42], in which implementation is a binary variable (1=correct medication intake ; 0=incorrect medication intake). Implementation is frequently calculated as the aggregate proportions of days with correct doses taken over the number of days in the monitored period. Importantly, medication implementation can also be characterized longitudinally by calculating the proportion of patients with a correct medication intake at each day of the monitored period. Generalized Estimated Equation (GEE)[44] is used to model implementation longitudinally, taking into account the interdependence of repeated measures of medication intake (outcome 1/0) for each patient over time.

iii. A treatment **discontinuation** occurs when the patient takes the last dose of a prescribed treatment, earlier than planned by the prescriber, and is characterized by a binary variable (i.e., discontinuation or not). This event is correlated with the measure of treatment **persistence**, characterized by the time-to-event between treatment initiation and discontinuation, which can be analyzed by Kaplan-Meier estimator in survival analysis[45]. Another approach is to estimate the proportion of patients covered (i.e., still under treatment) at a defined time point[46]. Nonpersistence is prevalent in chronically ill patients. Two years post-treatment initiation, less than 50% of patients with hypertension, diabetes or hyperlipidemia are still persistent to their medications[41]. The proportion of patients who discontinued their new prescription for an antihypertensive drug can even reach more than 60% during the first year, as it was estimated in as a recent retrospective study including 25’582 patients aged older than 40 years[47].

Late or non-initiation, suboptimal implementation and early discontinuation are different behaviors, yet complementary indicators of medication nonadherence.

3.3. Medication Nonadherence

Determinants of Medication Nonadherence

Medication adherence is a dynamic process, evolving across trajectories over time. Major clinical events (e.g., hospitalizations) or personal events (e.g., giving birth[48]) are key events with high potential for impacting medication adherence. For instance, a patient can postpone the initiation of the prescribed medication because of doubts concerning the indication of the prescription, but then have a high and stable medication implementation; or a patient who

implements optimally his/her medication can decide to discontinue it earlier than prescribed because of pill-fatigue, costs or beliefs[49]. As a matter of fact, medication adherence is a complex behavior that can be impacted by more than 700 determinants[50] (i.e., barriers and facilitators for medication adherence), which can evolve over time –the interactions between determinants can also evolve. Whereas one can think that forgetting to take the medication is one of the main reasons for medication nonadherence, there are numerous factors that may influence medication forgetfulness. The determinants of medication adherence can be categorized into five main categories[40] (Fig. 2): factors related to the patient (e.g., personal understanding, beliefs, priorities, perspectives), the disease (e.g., symptoms, prognostic), the treatment (e.g., adverse effects, regimen complexity), the social and economic environments (e.g., food insecurity and housing instability[51], social support, low income) and the healthcare system (e.g., patient's out-of-pocket costs for medical follow-up and treatments[52, 53], medication adherence support programs). To note, the possible drastic change of adherence over the therapeutic itinerary and patients not being informed and educated to talk about their nonadherence are the main reasons why clinicians do not estimate patient medication adherence accurately: they often overestimate or underestimate it[54, 55].

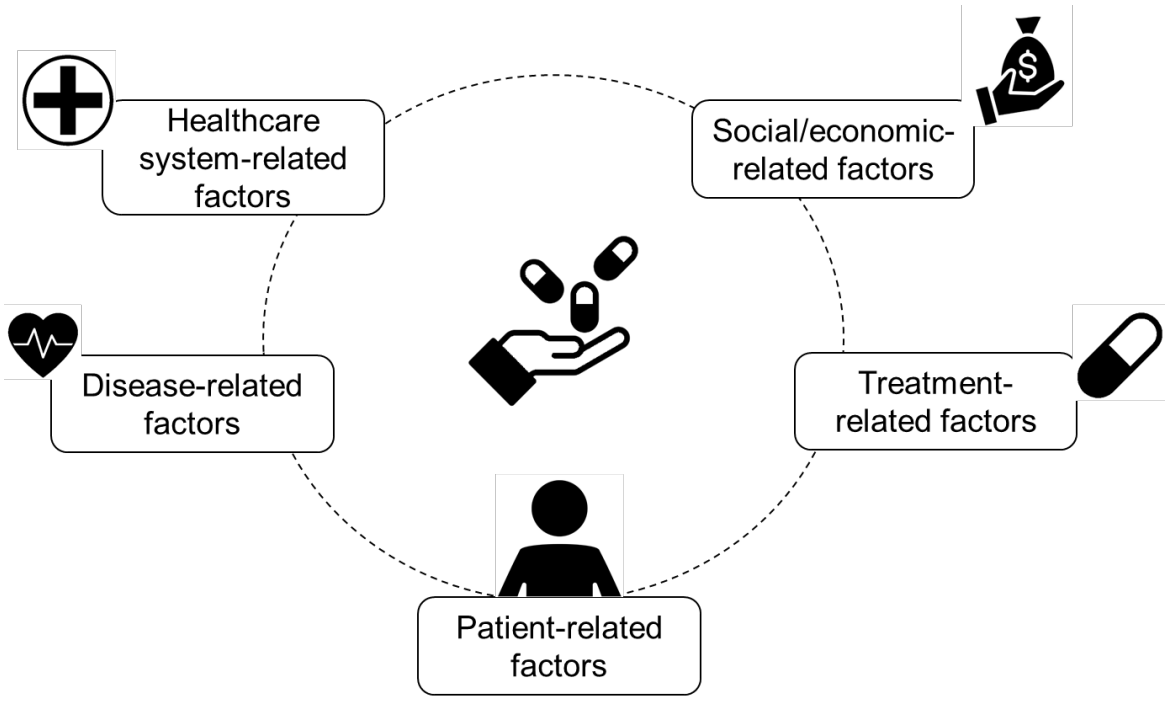


Figure 2: Determinants of medication adherence, adapted from Sabate, E., Adherence to long-term therapies: evidence for action, Geneva: World Health Organization (WHO), 2003*[40], license CC BY-NC-SA*

As part of these determinants, medication nonadherence is intentional (e.g., omitting doses, decreasing doses, discontinuation) or unintentional (e.g., forgetting, running out of

medications, falling asleep before taking the medications). The distinction between intentional and unintentional nonadherence is not clear as unintentional nonadherence can be partly influenced by intentions. Besides, unintentional suboptimal implementation may be a risk factor for later intentional suboptimal implementation[56], just as suboptimal implementation is a risk factor for premature discontinuation[45, 57].

Consequences of Medication Nonadherence

Patient nonadherence leads to treatment failure or poor clinical outcomes[41, 58, 59] (e.g., high adherence prevents from adverse coronary events post-myocardial infarction[60], while poor adherence results in the loss of a complete cytogenetic response in patients with chronic myeloid leukemia treated with imatinib[61]), an increased risk of hospitalizations (e.g., adherence to medications is the strongest predictor of hospitalization in patients with heart failure[62]) or disease symptoms[63]. Furthermore, nonadherence increases the rate of multi-mortality[64] (e.g., poor adherence to antiretroviral agents predicts viral failure as well as all-cause mortality in patients with Human Immunodeficiency viruses (HIV)[65]). In Europe, it is estimated that medication nonadherence is responsible for 200'000 premature deaths per year[41].

Besides its clinical impact, medication nonadherence has an economic impact. It is estimated to be of EUR 125 billion excess healthcare costs per year for European governments, related to the excess use of health services such as increased hospitalizations, emergency and outpatient visits[41]. In Switzerland, health insurances estimate that enhancing medication adherence could decrease healthcare costs by a factor 4[66, 67]. Last but not least, medication nonadherence has also an environmental impact in terms of medications waste or overprescribing due to poor clinical outcomes[68].

3.4. Measuring Medication Adherence and Reporting Outcomes

In-depth Description of Selected Methods to Measure Medication Adherence

In a clinical trial context or in routine clinical practice, medication adherence can be measured through a range of various methods. Some allow direct and objective measures, such as the Therapeutic Drug Monitoring (TDM), which measures drug plasma concentration, or the Direct Observation Therapy (DOT), a method used when providers directly observe the patient swallowing each dose of the drug. In addition, several indirect and objective methods exist, such as i) medication refill, which corresponds to the number of medication boxes that the patient obtained from a pharmacy during a defined period; ii) the pill count, which is the count of the difference between pills delivered to the patient and returned to the pharmacy after the monitored period; iii) the electronic monitor (EM), an interactive digital technology which registers date and hour of opening a pill bottle. Finally, indirect and subjective measures are

collected through self-report questionnaires, in which patients are asked to recall and report their medication self-management or medication adherence in the last days or weeks depending on the instrument used. To note, patient self-report is important to validate the method to measure medication adherence (e.g., the timing of the last drug intake in TDM, medication swallowed at each EM opening), otherwise assumptions have to be made[69].

It is usually recommended to combine objective and subjective methods to obtain the most reliable measure of medication adherence, while capturing patients' own perceptions and beliefs about medications and individual determinants for medication adherence[70-72].

Across the adherence studies presented in this thesis, the EM was the core method used to measure medication adherence together with pill count and TDM. These three methods are further detailed in the following paragraphs.

i) The Electronic Monitor

The electronic monitor "Medication Event Monitoring System" (MEMS and MEMS AS; AARDEX Group, Sion, Switzerland) (Fig. 3) is composed of a box, which contains the patient's oral prescribed chronic medication, and a cap. The chip located in the EM's cap registers the date and hour of each EM opening; these time-points are considered as a proxy for drug intake. On the top of the EM cap, a Liquid Cristal Display (LCD) screen shows to the patient the number of daily EM openings registered from 3:00 a.m. to 2:59 a.m. on the next day and the number of hours since the last opening (from 1 to more than 24 hours). At each patient visit to the pharmacy, the adherence data are uploaded through a software (e.g., MedAmigo™, MEMS and MEMS AS, AARDEX Group).



Figure 3: The electronic monitor MEMS (MEMS and MEMS AS, AARDEX® Group)

Measuring medication adherence by EM has some advantages. Indeed, the EM is often considered as one of the gold standard to measure medication implementation as it allows obtaining a longitudinal pattern of medication implementation over time instead of aggregated measures[73]. Using the EM captures real-time patient medication adherence along with

providing a day-by-day electronic monitoring feedback to the patient through the LCD display.

A recent meta-analysis included 47 randomized and controlled trials (RCTs) in which the intervention consisted in improving adherence by using the EM (i.e., EM alone, EM coupled with a reminder or EM coupled with motivational interviews delivered by HCPs). The difference between medication implementation in the intervention and control groups was expressed as a mean difference in each RCT study, and then standardized to take into account the different methods to measure medication adherence across studies (i.e., a standardized mean difference (SMD) of 0 being a null effect between groups, a negative value being in favour of the control groups). Overall, medication adherence of patients included in intervention groups using EM was significantly improved compared to control groups: SMD=0.93, confidence interval (CI): 0.69; 1.17, $p<0.0001$[74]. The intervention that used EM only to monitor adherence had not effect on adherence (SDM=0.24, CI: -0.35; 0.84), whereas adherence was improved when the EM was coupled with a feedback from a HCP (SDM=0.75, CI: 0.54; 0.93) or coupled with a reminder (SDM=1.51, CI: 0.81; 2.22) or both (SDM=1.05, CI: 0.77; 1.33)[74]. However, the interventions using EM often showed no significant improvement of clinical outcomes[74].

Another systematic review including 10 RCTs showed that EM-individualized feedback was efficient to improve medication adherence compared to usual care[75]. In most of the studies identified in this systematic review, the EM feedback was presented with a chronology plot that was discussed and commented as part of face-to-face motivational interviews between the patient and a HCP to support medication adherence[75]. As a matter of fact, interventions combining EM feedback and motivational interviewing delivered by trained HCPs are key components of adherence interventions that synergistically improve medication adherence. In summary, the EM is used to measure and collect patient adherence data over time along with EM feedback as the basis for the intervention to improve medication adherence.

Some limitations need to be considered when using EM to measure medication adherence. Indeed, a patient may not use the EM as expected, as the patient may use “pocket-doses”, characterized when the patient takes some doses outside of the EM to swallow them later on –pocket-doses are methodologically detrimental especially if not swallowed on the same day, or when the patient uses the EM inconsistently (e.g., the EM is not used on certain days or during the holidays). Such discrepancies tend to underestimate the real level of patient medication adherence[76]. Another example of EM misuse is the “curiosity check”[69], characterized when the patient opens the EM without taking the dose. To alleviate this misuse, the medication intake is considered as correct if at least the number of prescribed openings is achieved on a given day. Thus, the patient’s behavior and acceptability toward the EM use is

to be rigorously investigated in all adherence studies[74]. Moreover, investigators should be aware that medication adherence can be overestimated during the first 40 days of the monitoring period, as patients may pay more attention to their medication management while they are accommodating to the EM, before going back to their normal behavior[77]. This phenomenon is known as the Hawthorne effect (i.e., patients change their usual behavior when they are feeling observed[78]). Nevertheless, the more the observation period is long (e.g., more than 12 months), the less these measurements bias impact the quality of the results[79].

ii) The Pill Count

Medication adherence can also be estimated by pill count. This method allows estimating the number of pills taken by the patient by calculating the difference between the number of pills delivered and given back at the end of the monitored period, over the number of pills that should have been taken according to the prescription[80]. Pill count is used to ensure conciliation with EM data (e.g., in case of multi-dose intake per EM opening). However, pill count is an aggregate measure, which does not provide longitudinal patterns of adherence over time and does not allow differentiating suboptimal implementation from treatment discontinuation[71]. Despite the low quality of data provided, this measurement has often been used in adherence clinical trials, where spare medication has to be returned to the investigation center[81].

iii) Therapeutic Drug Monitoring (TDM) and Population Pharmacokinetic Modelling

Drugs and metabolites plasma concentrations can be measured through TDM in case of narrow therapeutic index drugs, poor medication efficacy, risk of medication interactions or drug toxicity. The measurement is based on a sample of patients' blood, urine, hair or saliva, using various analytical methods, such as high-performance liquid chromatography coupled to mass spectrometry[82]. The measured drug concentration is interpreted based on the reference therapeutic concentration ranges predicting drug efficacy with limited toxicity[82, 83]. For instance, the reference concentration range for patients with a normal kidney function taking 500-750mg/day of lithium for bipolar disorders is between 0.4 and 0.8 mmol/L[84]. The minimal concentration to achieve clinical outcomes with the tyrosine kinase inhibitor imatinib – prescribed in chronic myeloid leukemia– is of 1000ng/mL[85], whereas its toxicity threshold is poorly described in the literature. Based on TDM, the clinician adapts the regimen to each individual so that the patient's measured drug concentration fits into the targeted reference concentration range. Although the method is costly and potentially invasive, measuring the patient's drug plasma concentration can be used to evaluate medication adherence, as it allows confirming or not drug ingestion, as well as semi-quantifying medication implementation if the time of the last drug intake is rigorously reported[71, 83, 86]. However, the drug

concentration has a low sensibility to predict medication adherence, as i) it only allows an isolated measure of adherence; ii) a low drug concentration can be attributed to other factors than nonadherence, such as inter-individual variability factors, and iii) patients may improve their medication adherence before medical consultations[87], leading to an overestimation of medication adherence (the so-called “White coat effect”[88]).

To inform TDM, we need to have knowledge on factors that can induce pharmacokinetic (PK) variability (e.g., absorption, distribution, metabolism and clearance of the drug), taking into account intra- and inter-individual variabilities (i.e., due to covariates such as age, gender, smoking and co-treatments), as well as the relationship between PK and pharmacodynamics (PD) properties of the drug. To describe the PK of a drug in a certain population, plasma drug concentrations are measured in multiple patients. A population pharmacokinetic model (pop-PK) can be developed to estimate the PK parameters of the drug (e.g., clearance, volume of distribution) and identify the cause of the PK inter-variability (e.g., drug-drug interactions, drug-food interactions, impact of smoking, genetic variability). Furthermore, the drug’s PD properties can be included into the pop-PK model to analyze the PK-PD relationship (e.g., the influence of the drug concentrations on neutrophil blood count)[89, 90]. Finally, a pop-PK model allows simulating drug plasma concentrations to inform on the relationship between medication adherence, PK and PD.

The pop-PK model of palbociclib, a protein kinase inhibitor prescribed in advanced breast cancer, has been developed by the Centre for Research and Innovation in Clinical Pharmaceutical Sciences (CRISP) at the Lausanne University Hospital, based on the adherence data and the blood draw samples collected as part of the Optimizing Targeted Anticancer Therapies (OpTAT) study[90].

Guidelines to Report Medication Adherence Research

Based on the ABC taxonomy[37], the ESPACOMP Medication Adherence Reporting Guideline (EMERGE), created in 2018, provided recommendations to improve standardization in reporting the methodology, analysis and findings across medication adherence studies[42]. The minimum reporting criteria that should be clearly described are: i) the phases of medication adherence studied (i.e., initiation, implementation and discontinuation); ii) the operational definition of medication adherence used for each phase; iii) the method for medication adherence measurement in each phase (e.g., electronic healthcare data, electronic monitoring) along with its quality and limitations and iv) the reporting of medication adherence results within each phase[42]. Among other key characteristics to report, the investigator should explain the context and the setting of the research, the characteristics of the healthcare system, the healthcare team involved in the research as well as the relationship between

patient non-participation, drop-outs and adherence results[42]. Importantly, if adherence is a quantifiable outcome, the statistical analysis performed should be clearly described for accurate sample-size calculation and medication adherence outcome reporting, along with their potential bias and limitations. Finally, the strategies that could help to translate the adherence intervention into routine clinical practice are recommended to be investigated early on in the first stages of the development of adherence studies (i.e., during the protocol elaboration) and should be described as a separate outcome[42].

Following the ABC taxonomy and EMERGE guideline, the Timelines-Events-Objectives-Sources (TEOS) framework defines operational definitions of medication adherence to assist researchers in choosing the most suitable measurement of medication adherence according to the study design[91]. First, researchers should carefully investigate treatment *timelines*, based on the disease and the recommended treatment regimen and doses, taking into account the conditions of the treatment dispensing and the actual use of the treatment by the patient over time[91]. Second, researchers should describe *event*s within these timelines, meaning the first and last dose recommended in the prescription sheet compared to the actual first and last dose taken by the patient[91]. Third, the choice of the medication adherence measurement relies on the study *objectives and design*. Thus, investigators should clearly investigate the most appropriate measurements needed in terms of accuracy and reliability to answer the research questions, by defining in advance the statistical analysis that will be performed after data collection. Fourth, the *sources* of medication adherence data must be checked for their availability, quality and suitability according to the study objectives (e.g., large public healthcare refill databases are only available in some countries and are not suitable for measuring adherence in short monitoring periods)[91] .

In summary, while the measurement of medication adherence should be defined based on the four parameters of the TEOS framework within each phase described in the ABC taxonomy, the report of adherence studies should rigorously follow the EMERGE guidelines to improve transparency and quality of adherence research.

4. Interventions to Support Medication Adherence

4.1. The Successful Components of Medication Adherence Interventions

In 2014, a Cochrane updated systematic review assessed the impact of medication adherence interventions on the improvement of medication adherence and clinical outcomes[92]. Only 17/182 (9%) RCTs had a low risk of bias and among them, only 5/17 (29%) showed an improvement of medication adherence and clinical outcomes[92]. However, no common components of these successful interventions could be drawn. Indeed, these interventions

were complex and used multifactorial approaches: while carers, family and HCPs were involved in supporting patients with their medication management, the core of the interventions included counselling and education through motivational interviewing or behavioral therapy, or daily reinforcement of medication adherence[92]. Among the other RCTs identified, interventions aimed to explore patients' beliefs about medications, providing social support and improving transition and coordination in care[92]. The high heterogeneity in terms of populations, diseases, medications monitored, adherence interventions, the measurements of adherence and clinical outcomes limits the comparability of the results[92].
Nieuwlaat and al. concluded that we currently lack evidence of a clear impact of interventions to improve adherence and clinical outcomes[92]. Indeed, still too few studies provide a quantifiable relationship between the improvement of medication adherence and clinical outcomes[75, 92] –a moderate to low impact is often reported. For instance, an improvement of 3% of patient-reported persistence to antiplatelet agents had no impact on major adverse cardiovascular events in a RCT[93]. While the effect of a phone-motivational interview resulted in an improved adherence of 4.7% to antihyperlipidemia, antihypertensive and antidiabetic medications in another RCT, no impact was found on low-density lipoprotein cholesterol, blood pressure or hemoglobin A1c (HbA1c)[94].

In 2017, Conn and Ruppar assessed medication adherence outcomes in 771 interventions and concluded that the core of interventions should focus on supporting the patient's medication management habits through behavioral strategies rather than focusing on changing the patient's beliefs and knowledge[95]. To note, most of the effective interventions were delivered face-to-face by pharmacists[95]. Another systematic review explained that psychosocial interventions exploring the affective sphere of chronically ill patients (e.g., social support and environment, emotions) to improve adherence are scarce in the literature, whereas such determinants impact patients' behaviors towards medication adherence[96]. Yet, simplification of regimens, reminders and financial incentives could also be successful components of adherence interventions[97]. As a matter of fact, when delivered on the long-term (>10 months), multifactorial interventions composed of educational, behavioral and technical strategies improve medication adherence[98]. Notably, the EM- or technology-based feedback seems to be a key component of effective interventions[74, 75, 99]. However, such interventions are still rarely reported in the literature[100].

Developing a successful socio-cognitive behavioral intervention requires an appropriate theoretical framework to deliver the intervention, yet tailored to patients' needs and preferences. Most models derive from the Health Belief Model, which explores the perceived susceptibility to the disease (i.e., the individual perception of the risk of being ill), the perceived disease severity, the perceived benefits and barriers of a recommended health action, the cue

to action to accept a health recommendation and the patient's self-efficacy (i.e., the self-confidence and capability to perform a recommended behavior)[101, 102]. In addition, the Social Cognitive Theory investigates the influence of patients' environment, past experiences, beliefs and preferences on their medication management[102, 103]. For instance, several theoretical models have been used to support adherence to antiretroviral therapies in patients with HIV. Among them, the Information-Motivation-Behavior skills model articulates the interplay between patients' needs for information about the treatment, the disease and adherence, patients' level of motivation to adhere to the prescription and patients' personal skills to take the treatment[104].

In 2011, Michie et al. proposed the Capability Opportunity Motivation-Behavior (COM-B) model, showing that a health behavior is closely interrelated to capability, motivation and opportunity. The behavior change wheel is a non-linear model integrating these components, on which policies (i.e., guidelines, legislation, service provision) have an influence[105]. In 2022, Unni and Bae proposed a hierarchical model to explore patients' behavior in medication adherence, based on exploring and improving step-by-step i) the patient's health literacy; ii) the perceived severity and susceptibility to the disease and the treatment, and iii) the patient's self-efficacy and social support to ultimately maximize adherence[106].

Motivational interviewing provides a framework to encourage behavior intentions to optimize medication adherence through semi-structured interactions between a patient and an interventionist with a health background. This communication method aims to induce the patient's motivation for a behavior change, and to strengthen and maintain the behavior change over time. Motivational interviewing is patient-centered, guided upon the patient's needs and own resources to change his/her behavior. Four consecutive main processes characterize motivational interviewing: 1) engaging the relationship between a HCP and a patient, 2) focusing on the shared goals to be achieved, 3) evoking a behavior change, based on the patient's own ideas and motivations, and 4) planning the change when the patient is ready[107]. Communication tools and spirits are used throughout the interview (e.g., open-ended questions, active and reflective listening, silence, pacing the interview with summaries, empathy)[107]. Importantly, when mastered, interventions delivered with motivational interviewing are among the most effective to enhance medication adherence[107-109]. In the meta-analysis from Palacio et al., including 17 RCTs in which the effect of motivational interviewing interventions on medication adherence was compared to a control group, medication adherence was higher in interventions compared to control groups (pooled relative risk of 1.17; 95%CI 1.05; 1.31, $p<0.01$)[109]. Notably, the effect seems more important when the interview is face-to-face[107] and when the providers are adequately trained in communication skills and in delivering motivational interviews[107, 110, 111].

In a nutshell, enhancing medication adherence requires multifactorial approaches, in which behavioral sciences and health communication are actively used in partnership with the patient, aiming to identify and address the wide variety of determinants of adherence in the patient's care itinerary[38].

4.2. A Successful *Implementation*[1] of a Complex Adherence Intervention: The IMAP

Due to the complexity of implementing socio-cognitive behavioral interventions in routine clinical practice, most evidenced-based interventions are still not translated into patients' usual care. Nevertheless, some examples of interventions were successfully implemented and showed an improvement of medication adherence in the real-world setting, such as the New Medicine Service in the United Kingdom[112, 113] –in which community pharmacists explore treatment experiences, concerns and adherence after a new treatment initiation–, or the Interprofessional Medication Adherence Program (IMAP) in Switzerland[114].

The IMAP, led by community pharmacists, has been developed in the community pharmacy of the Center for Primary Care and Public Health *Unisanté* (Lausanne, Switzerland) in 1995, and is routinely implemented in clinical practice since then (Fig. 4)[114]. All patients included in the IMAP use the EM (MEMS and MEMS AS; AARDEX Group, Sion, Switzerland), which is refilled by pharmacy technicians at each patient pharmacy visit[115]. The intervention consists in a 15-minute motivational interview between the patient and the pharmacist, based on the EM adherence feedback. The intervention is repeated monthly until adherence improves, followed by regular interviews to reinforce and maintain adherence over time.

At the beginning of the interview, the pharmacist evaluates patient self-estimation of adherence and checks the EM use through a set of questions (e.g., estimation of omitted doses during the monitored period, identification of periods during which the EM was not used, number of pocket-doses used, usual time between the EM opening and the medication intake). After this validation, the EM adherence feedback, presented as a chronology graph, is discussed with the patient (Fig. 4). The intervention is built upon the Fisher theoretical model (Information-Motivation-Behavior skills)[104]: the pharmacist explores the patient's daily medication management, motivation to take the treatment, beliefs and concerns about medications, side effects management and provides relevant information based on the patient's needs. Factors influencing adherence as socioeconomic determinants (e.g., social support), access to healthcare or mental health, substance abuse and addiction are evaluated. Pharmacists are

[1] The term "implementation" is used here to describe implementation science and not the implementation-component of adherence, it is thus indicated in italics.

regularly trained in motivational interviewing in order to actively listen to the patient and intervene in a non-judgmental and empathic way[114].

Interprofessionality is the cornerstone of the IMAP. Indeed, the physician identifies eligible patients, offers them to attend to the IMAP and sets adherence goals in collaboration with patients, pharmacists and nurses. After each interview, the pharmacist sends a short and structured report to the interprofessional team (e.g., physicians, nurses, psychologists, dieticians, social workers) summarizing the content of the interview (Fig. 4). In case of suboptimal or uncontrolled medication adherence, challenges and strategies to improve adherence, based on patients' needs, are regularly discussed in interprofessional meetings.

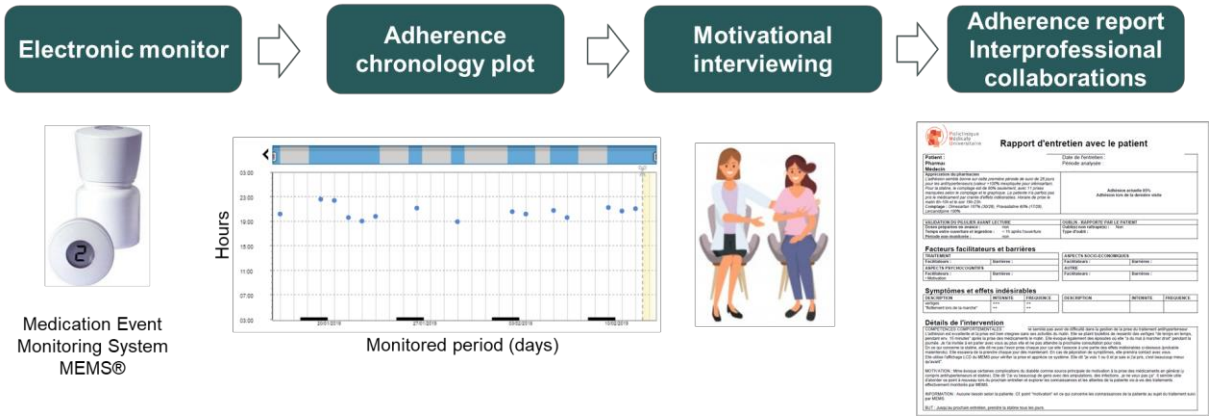


Figure 4: The Interprofessional Medication Adherence Program at the community pharmacy of Unisanté (Lausanne, Switzerland)

NB: the adherence chronology plot is used as a feedback instrument to discuss medication adherence with the patient. The x-axis represents the days during the monitoring period since the last visit and the y-axis represents the hour of the day. The black rectangles in the x-axis represent the weekends. The blue dots show the date and hour of each medication intake and the grey rectangles indicate the days with suboptimal medication implementation.

The evaluation of the effect of the IMAP on medication adherence across different chronic conditions showed a significant, better retention in care for HIV patients compared to standard of care[116], an increased medication adherence in patients with hypertension[117] and a valuable support to ensure responsible use of fingolimod in patients with multiple sclerosis[118]. Besides, an observational study conducted with patients treated with oral anticancer therapies (OAT) for solid cancers allowed to better characterize medication adherence in this population[44].

5. Patients with Cancer and Medication Adherence to Oral Anticancer Therapies

5.1. Epidemiology and Biology of Cancer

Worldwide in 2020, 19.3 million people were diagnosed with cancer, and 10.0 million died from this disease[119]. Female breast cancer is the most commonly diagnosed cancer (2.3 million people newly diagnosed in 2020), followed by lung, colorectal, prostate and stomach cancers[119]. Lung cancer is the first cause of cancer death (1.8 million deaths in 2020)[119]. In Switzerland, cancer is the first cause of death in men aged 45-84 years old and in women aged 25-84 years old. More than 40'000 new cancer cases were diagnosed in the Swiss population in 2018[120]. This disease represents an important burden for the healthcare systems worldwide as it is estimated that 28.9 million patients will be diagnosed with cancer in 2040[119].

A cancer is characterized by the excessive proliferation of abnormal cells that have been modified genetically to grow and replicate rapidly. The aggregation of these cells can form a solid tumor in an organ (e.g., breast cancer), or can be spread in the blood, bone marrow or lymph nodes (e.g., chronic myeloid leukemia)[121]. When the cancer cells are moving from the original tumor site through blood and lymphatic vessels, they settle in a distal site, forming another tumor apart, called a metastasis[122]. Various biochemical factors play a role during this process (i.e., separation from the initial tumor, travel, cling to a distal site and growth), which can be targeted by dedicated agents[122]. While research on the mechanisms behind metastasis cancers has shown progress in the last decade, the mechanisms are still not well depicted and understood[122]. As a matter of fact, cancer metastasis are responsible for 90% of cancer deaths[123].

While the incidence of cancer is rising since 1960, partly due to the increase of diagnostic tests, the mortality rate is decreasing in both men and women in developed countries, mainly thanks to early diagnosis and new developments of cancer treatments (e.g., immunotherapy, oral targeted anticancer therapies)[124].

5.2. Oral Anticancer Therapies

In the last 20 years, cancer care has been revolutionized by oral anticancer therapies (OAT), which complement or substitute traditional intravenous (IV) chemotherapy. Different types of OAT exist: cytotoxic, targeted, immunomodulatory and hormone antagonist agents[125]. An OAT is prescribed according to several care objectives: neoadjuvant (i.e., treatment prescribed prior to the main treatment, aiming to increase the therapeutic success of the main treatment, as decreasing tumor size before surgery), adjuvant (i.e., treatment prescribed after the main treatment, aiming to maintain a cancer remission)[126] and palliative (i.e., aiming at stabilizing the tumor growth in metastatic cancers and addressing symptoms to improve quality of life).

The number of OAT approved in the pharmaceutical market has been growing rapidly. In 2020, 11 new OAT were launched in the Swiss pharmaceutical market, representing almost one quarter of new compounds delivered in community pharmacies[127, 128].

Among targeted OAT, the Protein Kinase Inhibitors (PKI) –among whom tyrosine, serine/threonine kinase inhibitors– prescribed in hematological malignancies or solid tumors, have shown impressive benefits on patients' clinical outcomes, survival and quality of life. A protein kinase phosphorylates targeted proteins, resulting in a functional change of the proteins, thereby impacting their activity. In the cancer cells, protein kinases mutate, leading to the unregulated activation of cell signalization pathways favouring uncontrolled cancer cell growth, division and spread[129]. PKI are antagonists of these mutated protein kinases. The specificity of PKI limits a generalized toxicity: this mechanism of action is different from chemotherapy, which is intended to directly kill cells that are dividing and growing rapidly. However, cancer cells can develop resistance to PKI by i) modifying their targeted protein kinases so that the PKI cannot interact with them anymore, or ii) developing new ways of growing and spreading by bypassing the protein targeted by the PKI[130]. Imatinib, launched in the pharmaceutical marked in 2001, was the first PKI to improve significantly survival in patients with chronic myeloid leukemia (CML)[131]. Since then, progress has been made to increase the specificity of PKI along with reducing drug resistance[132].

Patients often report preferences for OAT as the administration is more convenient than IV chemotherapy, allowing patient self-management in their own personal and social environment at distance from hospitals, which improves their quality of life[133]. However, OAT present specific challenges. As examples, OAT are prescribed on the long term, e.g., for longer durations than traditional chemotherapy, and patients may have to cope with OAT off-label dosing reductions, transient interruptions and complex regimens that are common in routine clinical practice[134]. Moreover, contact with HCPs is less frequent compared to periodic administration of IV chemotherapy at the hospital, and patients have to manage OAT toxicity and side effects at home without a direct medical supervision. These factors can lead to a suboptimal adherence to OAT.

5.3. Adherence to OAT

A Suboptimal Adherence to OAT and its Consequences

Determinants for OAT nonadherence reported in the literature are multifactorial; an overview is presented in Fig. 5[135-146].

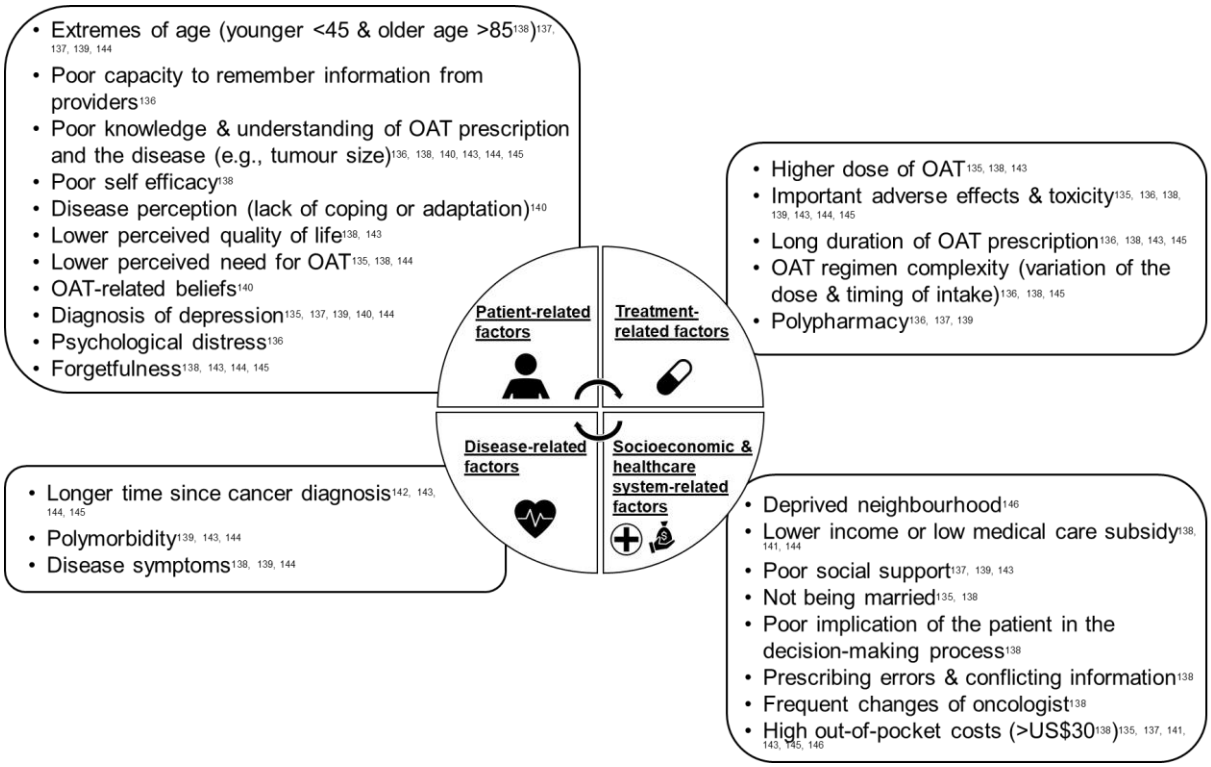


Figure 5: An overview of the main determinants for OAT nonadherence

Few studies distinguish between determinants impacting implementation, on the one hand, and discontinuation on the other hand[144]. However, literature shows that the main determinants of non-persistence are the high incidence of side effects and toxicity[139, 147]. Factors for suboptimal implementation are side effects, beliefs about OAT and out-of-pocket costs. While side effects management and beliefs can be addressed in multifactorial interventions, it is urgent that healthcare policies improve the access to OAT by addressing their high costs (e.g., favouring the prescriptions of generics when available)[128, 141].

Regarding OAT initiation, patients often weigh the pros and cons of taking OAT by counter-balancing extension of life vs. quality of life[148, 149]. Thus, HCPs should better consider the patients' and carers' determinants of medication initiation to prevent nonadherence to OAT through shared decision-making processes[149].

Indeed, while one can think that adherence to OAT is necessarily optimal due to the severity of the disease, systematic reviews estimate that at least one fourth to one third of patients do not implement or are not persistent to their OAT as prescribed[135, 150, 151].
In 2022, a systematic review concluded that an average of 68% of patients taking OAT for multiple myeloma were adherent[139]. In a recent retrospective cohort study including more than 37'000 patients with cancer in the USA, adherence to OAT was ranging from 33% to 70%[141]. In 2016, Greer et al. estimated in their systematic review that adherence to OAT – mainly endocrine therapies to treat breast cancer and PKI for CML– varies from 46% to

100%[135]. In their systematic review, Huang et al. reported that adherence to OAT –mainly PKI for CML– could be as poor as 23%[151]. Regarding OAT discontinuation (regardless of definition used), 36% of patients discontinued OAT prescribed in multiple myeloma[139]. The median time from OAT initiation to discontinuation is usually less than 6 months –84 days in patients with CML and 120 days in patients with metastatic prostate cancer[152]. In breast cancer survivors, discontinuation ranges between 31 and 73% at the end of the 5 years of adjuvant hormonal therapy[153]. Globally, adherence to OAT decreases over time since cancer diagnosis[135, 154, 155].

Nonadherence and nonpersistence to OAT are intrinsically linked and lead to multiple adherence trajectories as shown in endocrine therapies: some patients have a persistent high implementation, others have a rapid or moderate discontinuation after initiation, a rapid decline in implementation after initiation followed by an improvement of implementation over time or a constant slow implementation decline[156].

These evolving patterns of OAT adherence over time lead to disregarding patient adherence. HCPs are often not aware of such nonadherence behaviors and often overestimate adherence to OAT: in a study including 86 patients with CML, only 23% of patients self-reported being optimally adherent whereas oncologists estimated that 94% of them were adherent[54]. Ignorance of OAT nonadherence is shown in oncology clinical trials evaluating OAT effectiveness, in which only 20% of trials report adherence to OAT in their documentation for market authorization[157, 158]. In these trials, adherence is often estimated with pill count, whereas using an EM could improve the accuracy of the measure[158]. Importantly, nonadherence in clinical trials may lead to unexpected poor clinical outcomes, which could justify an increase of the dose considered efficient to reach targeted clinical outcomes. As a result, marketing higher doses than necessary can seriously increase adverse effects in clinical practice[158], which finally leads to: i) prescription of alternative dosing regimen, transient interruptions of OAT to cope with side effects or change of the treatment and ii) a decrease in medication adherence. This vicious circle is to be taken seriously, as research shows that nonadherence to OAT is a predictor for poor clinical outcomes and mortality. For instance, suboptimal implementation and non-persistence to adjuvant hormonal therapy decrease survival[154, 156, 159, 160] and quality-adjusted life years[160]. Nonadherence to OAT in metastatic renal cell carcinoma increases mortality[146], and nonadherence to PKI in CML is associated with poorer cytogenetic response and OAT failure [61, 161-163] and increases inpatient visits[164]. However, further studies are needed to confirm the association between nonadherence to OAT and clinical outcomes in other solid cancers such as melanoma, sarcoma and lung, gynecologic or otorhinolaryngologic (ORL) cancers[165].

Limitations and Gaps in Studies Quantifying Adherence to OAT

When quantifying adherence to OAT, several limitations are to be acknowledged. First, studies often evaluated adherence to endocrine therapies in breast cancer survivors or adherence to PKI in CML, and data on adherence to OAT, especially for palliative treatment lines, is lacking in other solid cancers. Besides, most studies are highly heterogeneous in terms of the population studied (e.g., age, comorbidities, social disparities). The time of follow-up is often short and sample size small or convenient (i.e., less than 100 patients often followed during less than 12 months). Second, the methodology for measuring medication adherence varies (e.g., pill-count, pharmacy refill, EM, self-report questionnaires), yet patient self-report is being used most. However, adherence measured with self-report questionnaires is often higher than estimated with objective methods in this population[139, 166]. Third, methodological concerns and moderate to high risk of bias are often reported, such as unclear handling of missing data (e.g., drop-outs, non-responders to questionnaires)[135]. Forth, the choice of the threshold to consider an optimal medication adherence to OAT is often various and not justified (i.e., adherence is often considered optimal if >80 %, >85% or >90% of the doses prescribed are taken)[139, 153, 167, 168]. Moreover, the operational definitions to calculate medication adherence outcomes across the three phases (i.e., initiation, implementation and persistence) are often lacking[135, 151, 153], especially regarding the distinction between OAT implementation and persistence. Last, reasons for OAT nonimplementation or discontinuation are to be better monitored and reported, as often unavailable in large retrospective studies using administrative database (e.g., insurance claims data)[139, 152]. All these limitations makes it difficult to compare the quantified adherence to OAT across studies.

5.4. Interventions to Improve Adherence to OAT

Characteristics of the Interventions, their Effectiveness and Limitations

In the literature, pharmacists and nurses are mostly involved in interventions to support adherence to OAT[144, 169, 170]. The core of these interventions is overall heterogeneous, and often composed of one or several of the following components: i) educating and counselling the patient regarding the OAT and the disease (e.g., through face-to-face interviews, phone calls, mail letters, home visits)[135, 150, 167, 169-173]; ii) behavioral interventions tailored to patients' needs (e.g., supporting a behavior change using motivational interviewing)[150, 169, 170, 174] –other behavioral interventions consist in providing reminders or delivering pre-filled pillboxes[135, 167, 170]; iii) monitoring OAT adverse effects[171-173] and iv) supporting dose adjustments of the OAT based on interprofessional collaborations (e.g., doses simplification or alternative regimen)[150, 171, 172]. Interestingly, digital technologies are increasingly used in the interventions[170, 175], mostly by delivering

Short Messages Service (SMS) or mobile apps to patients[176]. While most of the mobile-based interventions seem acceptable for patients[176], patients' characteristics (e.g., age, polypharmacy) and preferences should be scrutinized to better design adherence interventions using electronic health (eHealth) technologies[177].

Even if interventions to support adherence to OAT are increasingly reported in the literature, their evaluation and effectiveness remain limited. Overall, it is difficult to draw consensus conclusions due to the inconsistencies of the results across studies[135, 150, 167, 169, 170, 178, 179]. For instance, in the systematic review of Elston et al., only half of the studies (12/24) showed a significant relationship between the intervention and adherence to OAT[169]. Greer et al. stated that none of the five evaluated RCTs showed a significant difference of medication adherence between the intervention and control groups[135]. Rosenberg et al. recently concluded that less than half of the studies with a comparison sample showed a significant improvement of medication adherence or persistence with the intervention[173]. However, pharmacist-led programs, tailored to patients' needs and preferences and providing routine monitoring of adherence, are promising because of their multi-component and multi-levelled interventions addressing various determinants[170-173].

In addition to limitations previously cited in studies quantifying adherence to OAT (e.g., small follow-up time and sample size[135, 136, 150, 167, 172, 173]), further limitations are to be acknowledged regarding interventions on adherence to OAT. First, the design of the intervention is often observational without control groups[135, 150, 171, 173]. Randomized and controlled interventions implemented in routine practice are scarce in the literature, which prevents to demonstrate a real impact of the intervention on the improvement of medication adherence compared to usual care. Second, behavioral interventions are rarely embedded into a theoretical framework or an educational model, which lowers the impact but also the quality and standardization of the interventions[140, 170]. For example, in a recent systematic review, only 2/24 studies followed a behavioral theory to provide the intervention[169]. Third, methodological issues and risk of bias are frequently reported, such as unclear adherence data collection and analysis[171] or a high attrition rate[172]. Fourth, the measure of adherence is often isolated on the time points (e.g., often evaluated before and after the intervention and at each medical visit[136, 172]) rather than longitudinally. Fifth, few interventions concomitantly explored the impact of improvement of medication adherence on clinical outcomes (e.g., progression-free survival) and patient-reported experience and outcomes such as quality of life[135, 150, 167, 180, 181].

Future Research Directions to Improve Adherence to OAT

First, HCPs and behavioral scientists should be involved as soon as possible in the design of behavioral interventions[140, 170] to better design the intervention as part of a theoretical model. Second, while most of the interventions involved pharmacists and nurses, other stakeholders should be involved, such as oncologists, psychologists, dieticians and social workers to address all determinants of adherence to OAT. Indeed, communication between patients and carers within interprofessional teams should be strengthened as one of the major components of the interventions. Last, besides monitoring adherence to OAT, adherence to co-treatments should also warrant attention, as it has been shown that adherence to cardiovascular disease-related medications can be suboptimal or even worse in patients with cancer compared to the general population[142].

A recent call to action has targeted several priorities to improve adherence to OAT from drug formulations to patient care[128]. Among them, i) pharmaceutical industries should explore several dose strengths during OAT development so that oncologists could better adapt the dose to each individual according to efficacy and tolerance; ii) in the clinical trials, investigators should better monitor patient-reported experience outcomes; iii) in collaboration with other HCPs, community pharmacists have a major role in educating, monitoring and supporting adherence to OAT and iv) research in adherence to OAT, particularly interventions including medication adherence-enhancing technologies, should be further developed and supported[128].

In this context, the Optimizing Targeting Anticancer Therapies (OpTAT) study has been implemented at the community pharmacy of *Unisanté* and at the Department of Oncology of the Lausanne University Hospital. The OpTAT study is a RCT, which aims to evaluate the impact of the interprofessional medication adherence program implemented at the community pharmacy of *Unisanté* on patient adherence to OAT during 12 months.

6. Medication Adherence in Patients with Diabetic Kidney Disease

6.1. Diabetes and its Complications

Epidemiology and Types of Diabetes

Nowadays, more than 537 million adults live with diabetes worldwide, and 6.7 million people died from this disease and its complications in 2021[182]. To note, three-quarter of patients with diabetes live in developing countries[182], where the prevention and disease screening are less implemented than in high-income countries. In Switzerland, 6% of the adult population has diabetes[182]. This pandemic is a major public health issue as the prevalence is constantly increasing, partly due to an aging population and a sedentary lifestyle; it is expected that 643 million people will have diabetes by 2030 worldwide[182]. Besides, the global health economic burden of adult patients with diabetes increased from USD 232 billion in 2007 to USD 966 billion in 2021[182]. In Switzerland, healthcare costs attributable to diabetes were estimated to be of CHF 170 million in 2009, of which CHF 125 million were attributable to the treatment of complications[183]. Importantly, the International Diabetes Federation Atlas edition of 2021 reports that the highest diabetes-related expenditure per patient with diabetes (USD 12'828/person) is attributed to Switzerland[182].

Diabetes is a chronic disease diagnosed when the level of glucose in the blood is higher than normal and uncontrolled. Different types of diabetes exist. The most frequent is the type 2, caused by the decrease of insulin sensitivity in targeted tissues, mostly diagnosed in sedentary patients with excess weight. Type 1 diabetes is due to the autoimmune destruction of beta cells in the pancreas, leading to a lack of insulin production. Mostly diagnosed in children and adolescents, its prevalence is estimated to be of 10% of the diabetic population. The Latent Autoimmune Diabetes in Adult (LADA) is another form of diabetes –to which the prevalence is close to type 1 diabetes–, and is caused by the autoimmune destruction of beta cells in the pancreas in people aged between 30 and 40 years old[184]. Patients with LADA develop dependence to insulin over time. However, because of the similar clinical characteristics with type 2 diabetes, these patients are often misdiagnosed[184].

Diabetic Kidney Disease: A Frequent Diabetes Complication

Diabetes complications are frequent in uncontrolled and sub-treated diabetes. Complications severely impact patients' quality of life, increase the number of outpatient visits[185] and is associated to multi-cause mortality[186]. Indeed, uncontrolled hyperglycemia leads to microvascular (i.e., retinopathy, nephropathy, neuropathy) and macrovascular (i.e., atherosclerosis) complications over time[187]. While diabetic retinopathy is the leading cause of preventable blindness in adults, diabetic kidney disease (DKD) is the leading cause of End Stage Renal Disease (ESRD)[188, 189].

It is estimated that up to 40% of patients with diabetes will develop a kidney disease over time[190, 191]. DKD is characterized by a reduced estimated Glomerular Filtration Rate (eGFR) and/or an increased albumin urinary elimination –staged in microalbuminuria in incipient nephropathy to macroalbuminuria in DKD[191]. In patients with DKD, the eGFR declines over time[192]; in Switzerland, it declines by -1.15 mL/min/1.73m^2/year in men and by -1.03 mL/min/1.73m^2/year in women[193]. In Switzerland, a consensus statement was recently published to improve disease management and quality of care in DKD patients[194]. The therapeutic arsenal aims to slow down the renal decline progression, preventing cardiovascular events and multi-cause complications by controlling intensively the eGFR, urine albumin-creatinine ratio, blood pressure, level of blood glucose and lipid, thereby improving both quality of life and survival[190, 192]. As a consequence, patients with DKD are polymedicated, with a mean of 10 prescribed chronic oral medications[195]. Thus, self-management and self-efficacy are paramount in patients with DKD to cope with the medication and disease burden. Such complex care requires an interprofessional team (e.g., endocrinologists, nephrologists, general practitioners (GPs), pharmacists, specialist nurses, dieticians, psychologists) to achieve clinical outcomes thanks to the patient's multiple healthy behaviors built upon patient education and long-term support, e.g., medication adherence, healthy diet, reduced weight, physical activity, smoking cessation, prevention of addiction to alcohol. Thus, interventions to support patient self-management should use multilevel strategies.

6.2. Multilevel Interprofessional Self-Management Education Interventions in Patients With Diabetes and DKD

Self-Management Education Interventions in Patients With Diabetes

Interprofessional programs to enhance education in patients with diabetes have been increasingly reported in the literature (i.e., 102 diabetes self-management programs were identified in Europe in 2017[196]). Physicians, nurses and dieticians often deliver the interventions (pharmacists are involved in only 2-4% of the interventions[196]), which mostly focus on: i) providing education and counselling to increase knowledge and addressing the patient's disease beliefs, perceived benefits for the antidiabetic treatments and perceived disease severity and susceptibility[197, 198]; ii) enhancing patient self-efficacy, for instance, with promoting regular self-blood glucose monitoring; iii) improving adherence to medication; iv) encouraging a healthy lifestyle and v) favouring multiple behavior changes through cognitive behavioral therapies and motivational interviewing. When combining these strategies, the interventions showed significant improvement of patients' knowledge, quality of life and clinical outcomes (e.g., decrease in glycated hemoglobin HbA1c)[196, 199-201]. However, involving patients to such programs can be challenging[202, 203]. To improve patient participation, it is

recommended to tailor the interventions to specific patient groups[196], such as patients with DKD.

Self-Management Education Interventions in Patients With DKD

Interventions to improve self-management and clinical outcomes dedicated to patients with DKD are scarce in the literature. In the few interventions evaluated, an interprofessional team is generally involved within the hospitals, general practices or the outpatient clinics and the goal attainment is used to evaluate clinical outcomes[204]. According to a recent scoping review, interventions to improve patients' care can also be implemented outside of the clinic – entitled "nonconventional strategies"[205]–, in which the providers visit the patient at home, or the patient participates to group counselling to reinforce education, self-management and glycemic control. The programs can be led by nurses in family practice clinics and the intervention can be provided by telemedicine[206] or phone calls[205] and can use various technologies (e.g., continuous glucose monitoring devices which allow sending blood sugar levels to the provider).

While there is evidence of the impact of the interventions on self-management, the evidence of the impact on patients' clinical outcomes remains limited[205, 207]. For instance, in their meta-analysis including 3 RCTs, Helou et al. showed that education sessions and goal attainment strategies led by an interprofessional team improved HbA1c in DKD patients, but no consensual conclusions could be drawn about the impact on eGFR, blood pressure and blood total cholesterol[208]. While the systematic review by Zimbudzi et al., including 8 studies, showed a moderate-quality positive effect of such interventions on patient self-management activities, the authors reported a low-quality impact on patients' systolic blood pressure control and HbA1c compared to usual care, and no effect was reported on eGFR[204].

The scarce self-management interventions documented in the literature in patients with DKD are mainly delivered by endocrinologists, nephrologists, nurses, dieticians, social workers and GPs[204, 208]. Such interventions are mostly oriented to provide information regarding the disease or the diet, self-efficacy in monitoring blood pressure and blood glucose level[204]. Drug-related problems (i.e., drug-drug interactions, medication adherence) are rarely evaluated, which may be the reason why pharmacists are rarely involved in the interventions, whereas patients acknowledge their role in supporting their self-management, for instance by providing weekly pillboxes or bridging medication gap while waiting for the new prescription[209]. In Asia, isolated pharmacist-led interventions aiming to decrease the disease progression in patients with DKD seem to be promising to achieve clinical outcomes: a pharmacist-led Malaysian randomized intervention –which consisted in counselling and education about the disease and its complication for one year– decreased HbA1C and

neuropathy-related symptoms in the intervention group[210]. Another pharmacist-led intervention in China –consisting in regular laboratory assessments, goal attainment follow-up and supporting patient adherence through self-report– decreased the occurrence of ESRD and death in the non-randomized intervention group[211]. Thus, the involvement of pharmacists within interprofessional teams may contribute to improving the impact of the interventions on patients' clinical outcomes.

6.3. Optimizing Care in Patients With DKD: What About Improving Medication Adherence?

Medication Adherence and its Determinants in Patient with DKD

While medication nonadherence in patients with DKD is associated with poorer clinical outcomes –such as lower blood glucose and lipid control[212], an increased renal progression towards ESRD[213] and a higher risk of mortality[214]–, medication adherence is rarely monitored in this population. Approximately 40% of patients with DKD are estimated to be nonadherent to their medications[215, 216]. For instance, only 23.7% of patients with DKD interviewed in an outpatient clinic of a tertiary hospital in Malaysia reported being highly adherent to their medications, and 39.6% of patients reported having a low adherence[216]. Similarly, the proportion of nonadherent patients with DKD was 38.7% in a study led in a renal ambulatory clinic of a public hospital in Ethiopia[215].

The determinants of medication nonadherence in this population are numerous (Fig. 6)[209, 215-218]. Indeed, DKD is associated with a high emotional burden related to polymorbidity and polypharmacy. While one's individual past therapeutic journey has a key role in the perception of the treatment benefit –some patients regret a past medication nonadherence having led to DKD–, the evolution of the disease in the future is also a source of high concern –some patients experience distress about the fear of developing ESRD leading to dialysis[209, 217]. Medication adherence will result from a balance between the perceived benefits and risks of the treatment. This balance can be modified by socioeconomic factors that have a major importance in patients living with vulnerability[215]. Determinants should be better understood to be specifically addressed in interventions to support patient adherence to their medications.

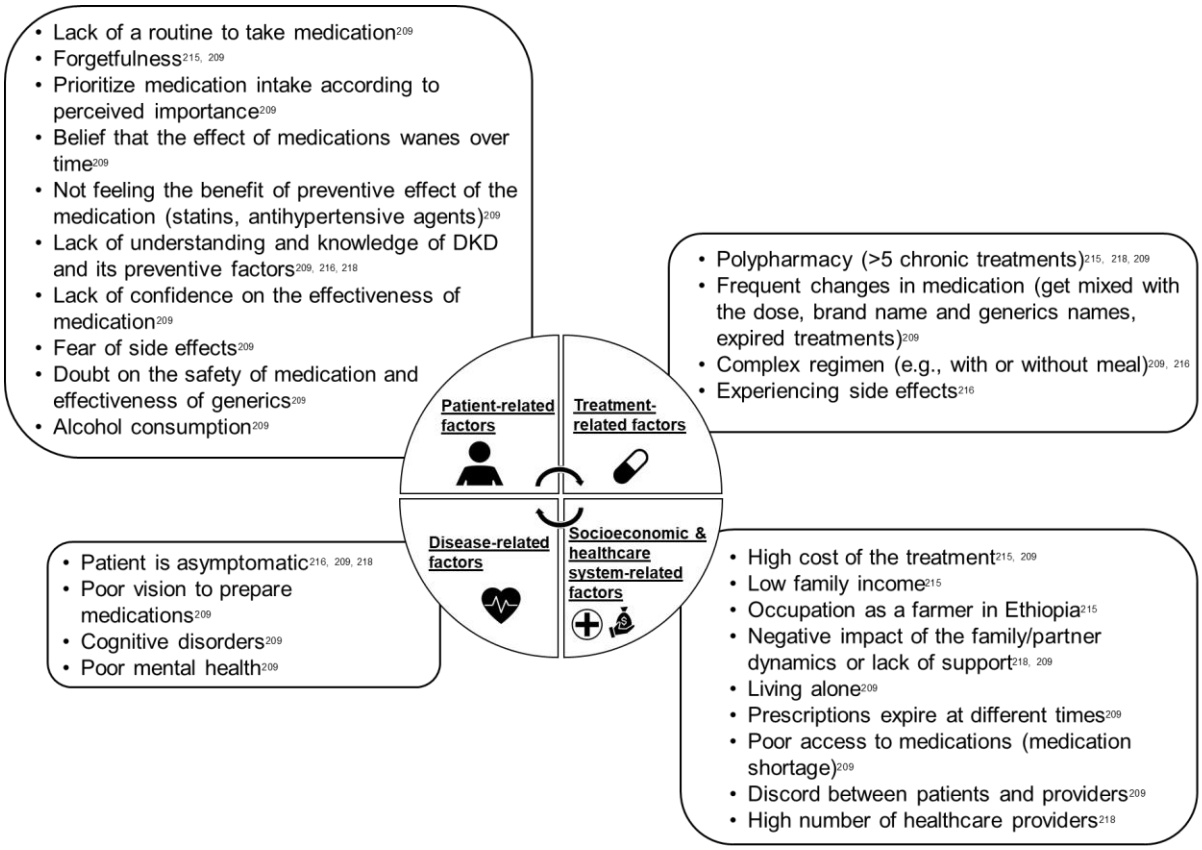


Figure 6: Determinants of treatment nonadherence in patients with DKD

Interventions to Improve Adherence in Patients with DKD

Despite the high prevalence of medication nonadherence in this population, interventions to specifically improve adherence are scarce, and when reported, they show limited to no impact on adherence. For instance, in the systematic review by Zimbudzi et al., only one study aimed to increase blood pressure self-monitoring along with medication adherence (evaluated with pill count) and did not show a positive impact on adherence –in the intervention and control groups respectively, nonadherence to medication was estimated at study end in 42% and 34% of patients[204, 219].

There are several limitations of the scarce studies evaluating medication adherence in patients with DKD. First, medication adherence is often assessed as a minor component of the multifaceted interventions and is considered as a secondary outcome. When medication adherence is assessed, the methodology is not clearly documented or is often evaluated with non-objective methods such as self-reported questionnaires, for which the validity is not always stated. Overall, the design of the interventional studies are often observational rather than controlled by randomization and the measure of clinical outcomes is not longitudinal (i.e., provided at baseline and at study end). The sample size is often small –patients with severe renal failure or treated with dialysis are often excluded–, and the attrition rate is high in most studies[204, 208, 220]. The evaluation of patient satisfaction and experiences about the

interventions is often lacking. Last but not least, medication adherence interventions should be elaborated upon behavior change interventions based on theoretical approaches[105], including a careful evaluation of mental health[196, 221]. To conclude, providers with psychosocial and behavior health backgrounds should be fully part of the interprofessional team to support patient self-management and medication adherence.

In this context, the *Patients diabétiques et insuffisants rénaux : un programme interdisciplinaire de soutien à l'adhésion thérapeutique* (PANDIA-IRIS study) has been implemented at the community pharmacy and the policlinic of *Unisanté*, the Department of Nephrology and Hypertension, the Department of Endocrinology, Diabetes and Metabolism of the Lausanne University Hospital. The PANDIA-IRIS study is a RCT, which aims to evaluate the differential impact of the duration (6 months versus 12 months) of the Interprofessional Medication Adherence Program on patient adherence. As part of this study, the collaboration between pharmacists, endocrinologists, nephrologists and nurses was described in an article published in the *Revue Médicale Suisse* in June 2020[222] (Appendix 1).

7. The COVID-19 Pandemic Hit Clinical Care and Research in 2020

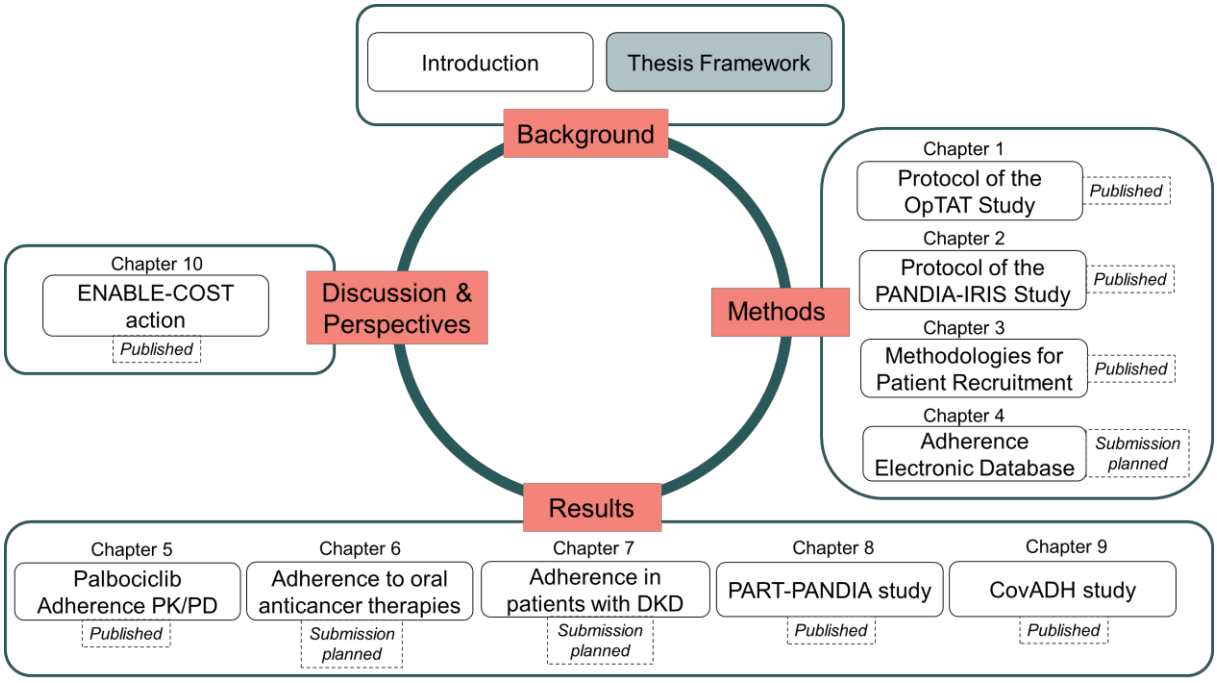
The highly infectious Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov-2) is at the origin of the Coronavirus (COVID)-19 pulmonary disease pandemic that hit the world in early 2020. Since then, healthcare systems have been under pressure to answer the population healthcare needs. To date (February 15th, 2023), 673 million cases have been reported worldwide (4.41 million cases in Switzerland) and 6.86 million people (14'202 people in Switzerland) died from this disease[223]. To protect the population from transmission and to slow down the pandemic, many governments enforced lockdowns; the Swiss Federal Council encouraged the population to respect a lockdown from March to June 2020. Indeed, vulnerable patients (e.g., immunosuppressed patients, patients with polymorbidity) were particularly at risk of infections. For instance, patients with renal failure, especially patients receiving renal replacement therapy and patients following dialysis, were at higher risk of COVID-19 contamination, and therefore had a higher risk of hospitalization, acute renal failure and death following an infection of Sars-Cov-2[224-226]. Patients with recent cancer treatment were also vulnerable as mortality was higher in this population compared to patients without cancer[227]. Notably, among patients with cancer, the mortality following an infection of Sars-Cov-2 was higher in patients with hematological and lung cancers[228]. Besides, cancer care was impacted; for instance in France, less tumor surgery excisions and radiotherapy sessions were provided during compared to before the pandemic[229]. Facing high concerns regarding their cancer care and isolation due to quarantine, patients were in need for psychosocial

support[230]. To help patients cope with the anxiety generated by the sanitary context, the Department of Oncology of the Lausanne University Hospital implemented a telehealth monitoring by regular phone calls delivered by an interprofessional team, which improved patient self-management throughout the pandemic[231].

While clinical care was impacted by the pandemic, clinical research –not related to the pandemic– was also seriously affected. Indeed, clinicians had to stop their research activities to be available for patient care. When the research resumed, the *implementation* of the studies needed to be adapted to prevent patients from coming to the study sites (i.e., mostly hospitals), data were collected remotely and design and research questions were adapted to the sanitary context[232]. Outpatient centres needed to adapt their routine activities to support the population throughout the pandemic; for instance, community pharmacies have increased their strategic role by supplying protection materials (e.g., masks, hand sanitizers) and renewing medications without prescriptions, providing information to patients[233], reassuring them, screening affected patients through Sars-Cov-2 tests and by vaccinating the population. At the community pharmacy of *Unisanté*, the IMAP procedures were adapted as follows: i) the inclusion of new patients into the IMAP was stopped; ii) pharmacists led the interviews by phone calls whenever possible and iii) pharmacy technicians sent medications to patients by mail so that patients could refill the EM by themselves at home[233]. As a consequence, the intervention delivered as part of the OpTAT and PANDIA-IRIS studies needed to be adapted accordingly. The study procedures were adapted; the recruitment of patients was stopped in both studies during the lockdown and the baseline period prior to the intervention was extended in the OpTAT study. These adaptations allowed to pursue research, while all included patients kept using their EM during the lockdown.

In this context, we analyzed EM data of patients attending the IMAP during the lockdown to conduct the CovADH (Covid-19 and Adherence study), which aimed to investigate medication adherence during the lockdown.

THESIS FRAMEWORK



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

1. Main Works

This thesis is built upon two RCTs implemented in clinical practice, in which patients with solid cancer were included in the **OpTAT study** and patients with diabetic kidney disease (DKD) in the **PANDIA-IRIS study**. While the RCT-designs of these studies are different, the core of the intervention is the same, i.e., the IMAP. The **global aim of this thesis** was to evaluate the impact of the IMAP on medication adherence in these two populations of chronically ill patients. The recruitment process, reasons and factors for patient participation and non-participation were investigated in both studies.

While the COVID-19 pandemic hit research in 2020, we conducted the **CovADH study** to investigate medication adherence during the lockdown.

These three adherence studies generated large EM adherence database. To improve the quality of EM adherence database, a semi-automated procedure was developed in the statistical software R, called the **CleanADHdata.R script**, to clean and enrich EM adherence database before analysis.

While medication adherence is a public health concern, this suboptimal behavior at the level of chronically ill patients is still not addressed by health authorities in Switzerland. In a commentary paper, we described policy strategies to foster and scale up the translation of medication adherence-enhancing technology programs into the Swiss daily clinical practice, as part of the European Network to Advance Best practices & technoLogy on medication adherencE (**ENABLE**), a Cooperation in Science and Technology (**COST**) action.

2. Research Questions

The research questions of this thesis are summarized in Table 1.

Table 1: Research questions of the thesis

Fields of the research	Research questions
Cleaning and enrichment of electronic monitoring adherence database	
CleanADHdata.R script	➢ How to clean and enrich EM adherence database before analysis by developing and using the CleanADHdata.R script?
The OpTAT study	
Study *implementation*	➢ What are the challenges and strategies for implementing an interventional study to support adherence to OAT in clinical practice?

Adherence to OAT	➢ What is the longitudinal impact of the IMAP on patient medication implementation, persistence and adherence to PKI compared to the control group? ➢ What is the impact of the IMAP on patient beliefs about medicines and quality of life at 6- and 12-month post-inclusion in both the intervention and control groups? ➢ Is there a difference in terms of beliefs about medicines and quality of life between patients who accepted and those who refused to participate to the OpTAT study? ➢ What is the impact of clinical and demographic covariables on implementation to PKI in both groups? ➢ What is the comparative analysis of patient implementation to PKI when considering on-labelled regimen (i.e., marketed by pharmaceutical industries) versus off-label regimen (i.e., taking into account PKI interruptions prescribed by the oncologists)?
Adherence, pharmacokinetics and pharmacodynamics of palbociclib	➢ What is the longitudinal impact of the IMAP on patient medication implementation and persistence to palbociclib in women with advanced breast cancer compared to the control group? ➢ What is the impact of clinical and demographic covariables on implementation to palbociclib in both groups? ➢ What is the impact of a missed dose that is caught up at cycle end on palbociclib drug concentrations (i.e., pharmacokinetics) and on neutropenia (i.e., pharmacodynamics)?
The PANDIA-IRIS study	
Adherence to antidiabetics, antihypertensive drugs and statins	➢ What is the longitudinal differential impact of a 6-month versus 12-month IMAP on implementation and persistence to antidiabetics, antihypertensive drugs and statins in patients with DKD at 6, 12, 18 and 24-month post-inclusion?

Participation to the PANDIA-IRIS study	➢ What are the differences of sociodemographic and clinical variables between participants and non-participants to the PANDIA-IRIS study? ➢ What are the reasons and factors for participation and non-participation to the PANDIA-IRIS study?
The CovADH study	
Medication implementation during the 2020 COVID-19 lockdown	➢ What is the longitudinal difference in medication implementation before, during and after the 2020 COVID-19 lockdown in chronically ill patients attending the IMAP? ➢ Is the pattern of longitudinal medication implementation in 2020 different from 2019?
The COST-ENABLE action	
Translation of adherence programs into clinical practice	➢ What are the priority policy strategies for implementing medication adherence-enhancing technology programs into the standard of care in Switzerland?

3. Thesis Manuscript Outline

To answer the research questions, the thesis manuscript is organized as follows:

The **methods** of this thesis are presented in four chapters:

- **Chapter 1**: The Optimizing Targeted Anticancer Therapies (OpTAT) Study Protocol
- **Chapter 2**: The "*Patient·es diabétiques et insuffisants rénaux : un programme interdisciplinaire de soutien à l'adhésion thérapeutique*" (PANDIA-IRIS) Study Protocol
- **Chapter 3**: Methodologies for Patient Recruitment in Clinical Trials
- **Chapter 4**: Preparation and Analysis of Adherence Electronic Monitoring Database

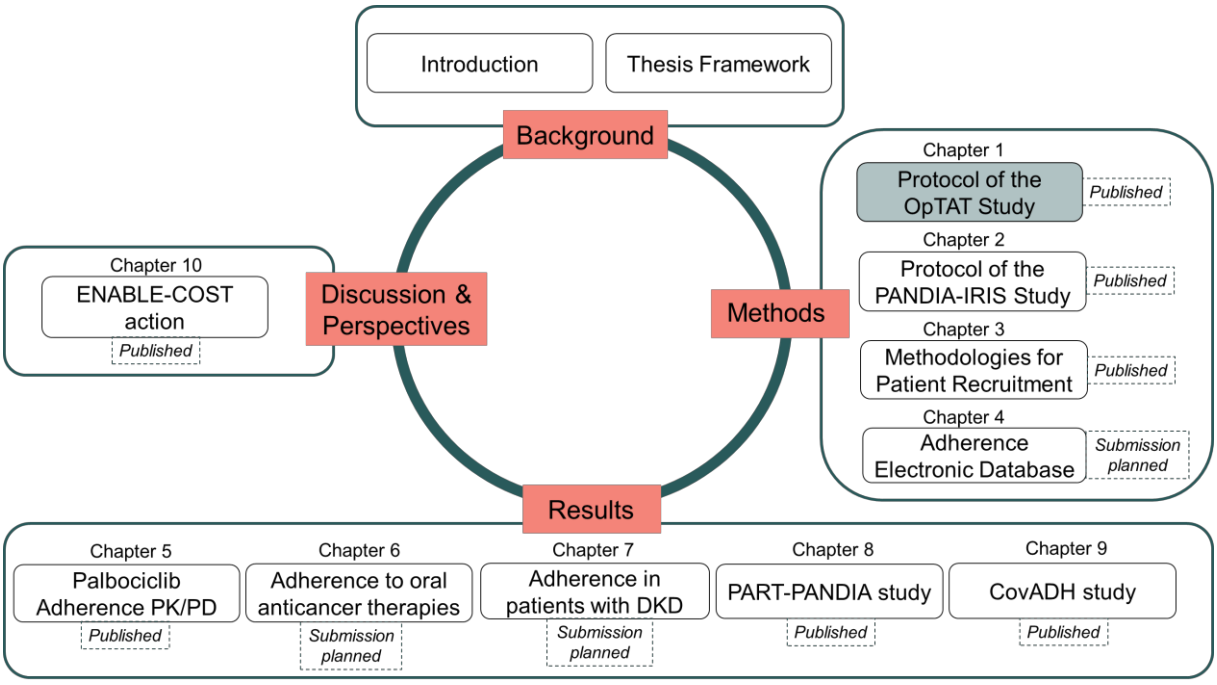
The **results** of this thesis are presented in five chapters (Chapters 5 and 6 from the OpTAT study, Chapters 7 and 8 from the PANDIA-IRIS study and Chapter 9 from the CovADH study):

- **Chapter 5**: Adherence to Palbociclib and Omission of Dose Management as part of the OpTAT Study
- **Chapter 6**: Adherence to Oral Anticancer Therapies (OpTAT Study)
- **Chapter 7**: Adherence to Antidiabetics, Antihypertensive Drugs and Statins in Patient with Diabetic Kidney Disease (PANDIA-IRIS study)
- **Chapter 8**: The "Participation to PANDIA-IRIS" (PART-PANDIA) study
- **Chapter 9**: The COVID-19 and Adherence (CovADH) study

The **discussion and perspectives** of this thesis are presented in the last chapter:

- **Chapter 10**: The thesis is discussed around the publication of the commentary *Swiss Priority Setting on Implementing Medication Adherence Interventions as Part of the European ENABLE COST Action*

CHAPTER 1: THE OPTIMIZING TARGETED ANTICANCER THERAPIES (OPTAT) STUDY PROTOCOL



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

Chapter 1 presents the protocol of the OpTAT study as published in *JMIR Research Protocols* in June 2021. The OpTAT study was designed by a multidisciplinary team from the School of Pharmaceutical Sciences (University of Geneva), the Community pharmacy of *Unisanté*, the Service of Clinical Pharmacology and Center for Research and Innovation in Clinical Pharmaceutical Sciences (Lausanne University Hospital (CHUV) and University of Lausanne), the *Centre de Therapies Expérientales* (CTE) and the Department of Oncology (CHUV).

Protocol

Optimizing Oral Targeted Anticancer Therapies Study for Patients With Solid Cancer: Protocol for a Randomized Controlled Medication Adherence Program Along With Systematic Collection and Modeling of Pharmacokinetic and Pharmacodynamic Data

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Abstract

Background: The strengthening or substitution of intravenous cytotoxic chemotherapy cycles by oral targeted anticancer therapies, such as protein kinase inhibitors (PKIs), has provided impressive clinical benefits and autonomy as well as a better quality of life for patients with cancer. Despite these advances, adverse event management at home and medication adherence remain challenging. In addition, PKI plasma concentrations vary significantly among patients with cancer receiving the same dosage, which could explain part of the observed variability in the therapeutic response.

Objective: The aim of this optimizing oral targeted anticancer therapies (OpTAT) study is to optimize and individualize targeted anticancer treatments to improve patient care and self-monitoring through an interprofessional medication adherence program (IMAP) combined with measurement PKI plasma concentrations.

Methods: The OpTAT study has two parts: (1) a 1:1 randomized medication adherence program, in which the intervention consists of regular motivational interviewing sessions between the patient and the pharmacist, along with the delivery of PKIs in electronic monitors, and (2) a systematic collection of blood samples and clinical and biological data for combined pharmacokinetic and pharmacodynamic analysis. On the basis of the electronic monitor data, medication adherence will be compared between groups following the three operational definitions: implementation of treatment during the persistent period, persistence with treatment and longitudinal adherence. The implementation will be described using generalized estimating equation models. The

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persistence of PKI use will be represented using a Kaplan-Meier survival curve. Longitudinal adherence is defined as the product of persistence and implementation. PKI pharmacokinetics will be studied using a population approach. The relationship between drug exposure and efficacy outcomes will be explored using Cox regression analysis of progression-free survival. The relationship between drug exposure and toxicity will be analyzed using a pharmacokinetic-pharmacodynamic model and by logistic regression analysis. Receiver operating characteristic analyses will be applied to evaluate the best exposure threshold associated with clinical benefits.

Results: The first patient was included in May 2015. As of June 2021, 262 patients had participated in at least one part of the study: 250 patients gave at least one blood sample, and 130 participated in the adherence study. Data collection is in process, and the final data analysis is planned to be performed in 2022.

Conclusions: The OpTAT study will inform us about the effectiveness of the IMAP program in patients with solid cancers treated with PKIs. It will also shed light on PKI pharmacokinetic and pharmacodynamic properties, with the aim of learning how to adapt the PKI dosage at the individual patient level to increase PKI clinical suitability. The IMAP program will enable interprofessional teams to learn about patients' needs and to consider their concerns about their PKI self-management, considering the patient as an active partner.

Trial Registration: ClinicalTrials.gov NCT04484064; https://clinicaltrials.gov/ct2/show/NCT04484064.

International Registered Report Identifier (IRRID): DERR1-10.2196/30090

(JMIR Res Protoc 2021;10(6):e30090) doi: 10.2196/30090

KEYWORDS

neoplasms; medication adherence; oral anticancer therapies; interprofessional program; adherence electronic measure; pharmacokinetics; pharmacodynamics; NONMEM; motivational interviewing

Introduction

Background

On the basis of the Global Cancer Observatory estimates, cancer was responsible for almost 10 million deaths globally in 2020 [1], making it a leading cause of death [2]. In Switzerland, more than 40,000 new patients are diagnosed with cancer each year [3]; however, the mortality rate of many cancers is decreasing, mainly because of the implementation of both screening programs and novel targeted and immune-related therapies [4].

For 15 years, the strengthening or alternatively the substitution of intravenous cytotoxic chemotherapy cycles by oral, sometimes long-term, targeted anticancer therapies has offered impressive clinical benefit and autonomy as well as a better quality of life for patients with cancer. Targeted cancer therapies involve protein kinase inhibitors (PKIs) and inhibitors of growth factor receptors, which are used to treat a variety of cancers, including gastrointestinal stromal tumors; kidney, thyroid, colorectal, lung, and breast cancers; melanoma; and sarcomas. Although treatment failure and poor tolerance are common in clinical practice, they cannot all be attributed to solid tumor multidrug resistance, as they can also be triggered by suboptimal medication adherence or inadequate drug plasma concentrations.

Suboptimal medication adherence is one of the causes of cancer progression and higher costs for health systems [5-7]. Thus, supporting patient drug self-management is key to achieving the best clinical outcome. In the past decade, interventional studies have focused mainly on patients with breast cancer treated with hormonal treatments and patients with chronic myeloid leukemia using imatinib. Evaluations of interventions to support PKI adherence in other solid cancers are scarce. In a systematic review, adherence to oral anticancer therapies was estimated to vary between 46% and 100% [8]. This review addressed adherence to various classes of oral anticancer therapies using various measures of adherence among patients with solid cancers, multiple myeloma, and chronic leukemia. Adherence estimation is not often reliable, as it is frequently evaluated through a moderate-quality methodology using subjective self-report questionnaires [9-11]. The link between longitudinal medication adherence, clinical factors, quality of life, survival, and cancer progression has been underinvestigated in the literature [12].

Since 1995, a routine interprofessional medication adherence program (IMAP) has been implemented at the University Community Pharmacy of the Center for Primary Care and Public Health Unisanté (Lausanne, Switzerland) to support drug self-management in patients with chronic illness [13]. Before initiating the optimizing oral targeted anticancer therapies (OpTAT) study, we conducted a feasibility study in which the included patients were mostly diagnosed with gastrointestinal stromal tumors or breast cancer. Adherence was estimated for several classes of oral anticancer therapies (capecitabine, letrozole, exemestane, imatinib, sunitinib, and temozolomide). We showed that patients with cancer agreed to participate and adopted the program; 12-month persistence was estimated at 85%, and the 12-month implementation rate was 97% in persistent patients [14].

Oral PKIs are licensed at a fixed dose despite the variable plasma concentrations observed in real-life situations [15,16]. This substantial interpatient pharmacokinetic variability may be explained by demographic (eg, age, body weight, and sex) and environmental factors (eg, concomitant medication and smoking), relevant physiopathological conditions (eg, organ failure and albumin levels) [17,18], genetic polymorphisms of metabolic enzymes or drug transporters, and patient behavior (eg, medication adherence) [12]. The characterization of pharmacokinetic variability is essential in oncology, given the risk of under- or overexposure, which may contribute to

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insufficient efficacy or undesirable toxicity in patients with cancer, respectively. Moreover, considerable efforts remain to be undertaken to characterize the correlation between drug plasma concentrations and the therapeutic response of most PKIs and to define the therapeutic targets associated with clinical benefits in the context of therapeutic drug monitoring [19].

Objectives

The global aims of the OpTAT study are to establish the necessary knowledge to build rational monitoring strategies through medication adherence monitoring and patient-adjusted dosage in real-life conditions, which should contribute to optimizing the therapeutic benefit of PKIs, in order to improve outpatient cancer care.

The primary objectives are to better characterize the prospective and longitudinal patterns of PKI adherence in patients participating in a medication adherence program versus a control group and to identify key driver-modifiable adherence factors.

The secondary objectives are to quantify interpatient variability, identify sources of variability in serum PKI levels, and characterize the relationships between the serum concentration, the therapeutic response and the toxicity of these treatments in a population of patients with solid cancer.

The hypothesis states that the medication adherence program will increase PKI implementation and persistence before the treatment is stopped for any reasons beyond the patient's control or therapeutic change compared with the control group. Moreover, it is hypothesized that interpatient variability in PKI plasma concentrations plays a fundamental role in the heterogeneity of the therapeutic response and may play a role in PKI adherence.

Methods

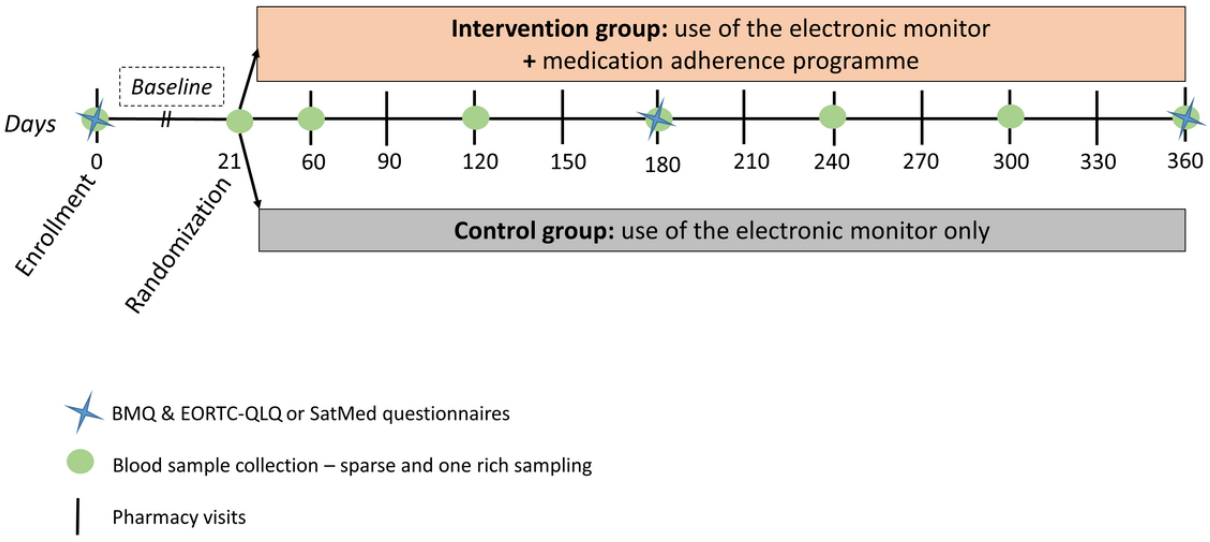
Ethical Considerations

The local ethics committee (Vaud, Switzerland) approved the OpTAT study in April 2015. Since then, two amendments have been accepted in July 2017 and October 2020. The study will be conducted in accordance with the current version of the Declaration of Helsinki and international good clinical practice principles. The protocol was peer-reviewed by five experts in April 2017 (Multimedia Appendix 1), leading to the founding of the study by the Swiss Cancer Research Foundation. This protocol was written according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 2) [20].

Trial Design

This monocentric prospective study comprises two parts: (1) an open randomized controlled medication adherence study and (2) an observational pharmacokinetic and pharmacodynamic study. This design (Figure 1) explores whether medication adherence evolves differently in each group and explores the interplay between adherence and PKI pharmacokinetic parameters.

Figure 1. Design of the optimizing oral targeted anticancer therapies study. BMQ: Belief about Medicines Questionnaire; EORTC-QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SatMed: Treatment Satisfaction with Medicines Questionnaire.



Enrollment of Participants

This translational study will be conducted at the Medical Oncology Service of the Department of Oncology of the Lausanne University Hospital (CHUV) outpatient clinic (Lausanne, Switzerland) in collaboration with the Community Pharmacy of the Center for Primary Care and Public Health Unisanté (Lausanne, Switzerland) and the Center for Research and Innovation in Clinical Pharmacy Sciences (CHUV).

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Adult patients aged >18 years who were treated with a PKI for solid tumors and followed at the CHUV were eligible to participate in this study. Participants with an inability to make decisions, with cognitive disorders, under tutelage, or not fluent in French or English or without the aid of an interpreter will be excluded from the study. Patients will be excluded solely from the medication adherence part of the study if they do not self-manage oral anticancer treatment (ie, nursing homes and home care services) or if they are already enrolled in an interventional study. If one PKI is switched to another PKI during the study, the patient will continue to participate in the study. However, if the PKI treatment is stopped or changed to a non-PKI anticancer treatment, the participant exits the OpTAT study; but, the data collected are kept for analysis.

The OpTAT study is voluntary, and patients will need to sign an informed consent form to participate in the medication adherence study, the pharmacokinetic and pharmacodynamic study, or both. The recruitment of participants began in May 2015. It ended in March 2021 for the medication adherence part but is ongoing until December 2021 for the pharmacokinetics part.

Oncologists were asked to refer eligible patients to a pharmacist PhD student or to the research staff from the Center of Experimental Therapeutics (CHUV), who will present the informed consent form to the patient after the medical visit. The participants will follow their treatment as usual, and no changes in the usual medical procedure will be made. No payment or compensation will be provided to the patients or to the oncologists as the patients are being seen as part of their routine follow-up clinical care.

Randomized Controlled Medication Adherence Study

Instruments: Use of the Electronic Monitors MEMS and Questionnaires in Both Groups

All patients participating in the medication adherence study will use an electronic monitor (MEMS and MEMS AS, AARDEX Group) for 12 months or until PKI is stopped. The electronic monitor registers the date and time of each opening, and a liquid-crystal display monitor on top of the cap indicates the number of daily openings to the patient. All patients included in the study will be asked to complete two validated questionnaires at three timepoints: inclusion, 6 months postinclusion, and at the end of the study. The first questionnaire is the *Belief about Medicines Questionnaire*, which assesses the patient's cognitive representation of medication [21]. The second is the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* (version 3.0), which assesses the quality of life of patients with cancer [22]. During the initial months of the study implementation, the patients with cancer filled out the *Treatment Satisfaction with Medicines Questionnaire* [23]; however, it was switched to the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire*, as the latter was more adapted to patients treated with a PKI. The questionnaires were translated and validated in French, with satisfactory psychometric properties [24-26].

Repeated Medication Adherence Interviews and Feedback (Intervention Group)

Patients included in the intervention group will visit the routine IMAP of the pharmacy of Unisanté. They will attend 15- to 30-minute medication adherence interviews, which will take place after each clinical appointment over 12 months. On the basis of the information-motivation-behavior model embedded in sociocognitive theory [27], the pharmacist will explore in depth the home drug self-management skills, side effect management, motivation, self-efficacy, and consider cofactors such as depression, anxiety, and drug or alcohol addiction. Patients' beliefs about PKIs will be explored, and information about the PKI will be delivered and discussed at each visit. Determinants of and gaps in medication adherence will be discussed with the pharmacist in an empathetic and nonjudgmental way using motivational interviewing skills.

The electronic monitor data will be uploaded to MEDAMIGO software (MEMS and MEMS AS), which generates graphs of electronic monitor daily openings. Feedback on adherence to PKI therapy, based on the information generated by the electronic monitor, will be provided to and discussed with the patient. Interprofessionality is a cornerstone of the program, and pharmacists will summarize the intervention in a semistructured report sent to the oncologist after each intervention. During the COVID-19 pandemic, motivational interviews will be conducted by phone calls with patients considered by clinicians to be at a high risk of SARS-CoV-2 infection. All pharmacists who perform the medication adherence intervention must have attended specific training to lead motivational interviews (two full-day medication adherence initial training and continuous education based on the debriefing of a motivational interview with a patient every 12-18 months) [13].

Control Group

Patients included in the control group will use an electronic monitor but will be considered standard-of-care patients as they will not receive any medication adherence intervention. The electronic monitor opening data of the control group will be concealed from the patients, pharmacy team, clinicians, and investigators until the end of the study. If an oncologist expressively asks for adherence data because of stringent and urgent clinical matters, the patient will be excluded from the OpTAT study and referred to the routine medication adherence program of the Community Pharmacy of the Center for Primary Care and Public Health Unisanté.

Assignment of the Intervention

The collection of adherence data patterns in both groups at baseline is crucial to check whether adherence patterns are homogeneous between the groups before the intervention starts. In both groups, patients will use an electronic monitor for at least 21 days before randomization. At the end of the baseline period, the patients will be randomized 1:1 to either attend the medication adherence program (intervention group) or be part of the standard of care (control group; Figure 1). The randomization lists will stratify participants according to their cancer type and the time elapsed between PKI initiation and the

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time of inclusion (less or more than 30 days). The randomization sheet lists 1 (intervention group) or 0 (control group) and will be provided by an independent researcher from the Unisanté Research Support Unit. The randomization list established by Excel (version 2016, Microsoft) will be based on variable size block randomization to prevent predictability and ensure a balanced allocation to each group. After randomization, the patient, research team, pharmacy, and clinical team will all be aware of the assigned group.

Observational Pharmacokinetic and Pharmacodynamic Study

A total of 10 mL of peripheral blood samples will be collected for up to a maximum of 8 samples per patient or until PKI is stopped at an unselected time after the last PKI intake. The blood samples will be centrifuged, the plasma will be frozen and stored until PKI levels are measured, and the dry pellet will be analyzed for the exploration of genetic variants involved in PKI pharmacokinetics. Moreover, for patients who accept, 6 × 5 mL blood samples will be collected over a maximum of 12 hours during one visit to the hospital. Specific information on pharmacokinetic data will be collected at each blood draw, and all relevant clinical and biological information will be obtained from the medical files of the patients (detailed in the *Collection and Management of Data* section).

Outcomes

Primary Outcomes: Randomized Controlled Medication Adherence Study

The primary outcome was global adherence, defined as the percentage of days with correct medication use of each subject. The sample size was calculated to ensure sufficient power to test the difference in the mean logit global adherence between groups (see the *Sample Size* section). Medication adherence will also be compared between groups following the three operational definitions defined by the EMERGE (European Society for Patient Adherence, Compliance, and Persistence Medication Adherence Reporting Guideline) guidelines: implementation of treatment during the persistent period (daily management of oral targeted anticancer drugs), persistence with treatment (the distribution of times between enrollment and discontinuation), and longitudinal adherence (the product of persistence and implementation) [14,28,29].

Secondary Outcomes: Pharmacokinetic and Pharmacodynamic Data

The plasma concentrations of the PKI and active metabolites, if appropriate, will be measured using validated methods of liquid chromatography-tandem mass spectrometry for each blood sample collected [30,31]. Internal standards will be used to optimize the analytical accuracy and precision of the method, essentially by abrogating the influence of matrix effects and inherent variability in the extraction procedure. The pharmacokinetic variables quantifying PKI exposure will then be calculated from population-based individual Bayesian pharmacokinetic parameters and expressed as the area under the curve and trough drug concentrations (minimum drug concentration) [32]. The efficacy of anticancer drugs will be expressed as progression-free survival, which is the time interval between PKI initiation and the date of tumor progression, defined according to the standardized criteria *Response Evaluation Criteria In Solid Tumors* [33], or death from any cause. If a patient is event-free (progression or death), the time will be censored at the last follow-up visit, the end of the study follow-up, or treatment discontinuation. The response to treatment will be assessed according to local standards, usually every 3 months, using a computed tomography scan or positron emission tomography scan. In addition, an overall survival analysis will be undertaken in an exploratory manner. The toxicity of PKI will be assessed according to the National Cancer Institute–Common Terminology Criteria for Adverse Events [34].

Sample Size

Randomized Controlled Medication Adherence Study

We assumed that the mean longitudinal adherence will remain stable at 95% in the intervention group during the follow-up period, whereas it would decrease from 95% to 80% in the control group during the 340 days from randomization to the end of follow-up. We also assumed an SD for the logit of longitudinal adherence of 1.8, for both groups and at all timepoints. This corresponds to 95% individual adherence in the intervals 10%-99.3% and 35%-99.9% in the control and intervention groups, respectively, at the end of follow-up. A sample size calculation was performed to simulate individual series of daily medication (1=at least the correct number of daily openings of the electronic monitor; 0=fewer daily openings than prescribed) according to the above parameters to consider both the interindividual variability (SD 1.8) and the intraindividual variability (the measurement error). Considering that the number of measures of a subject will be 340 and assuming a 10% dropout in the middle of the year, 120 patients must be included in the study (60 in each group) to reach a power of 80% with a .05 significance level when comparing the mean of the logit of global adherence between groups using a two-tailed Student *t* test. Differences are considered statistically significant if $P<.05$.

Pharmacokinetic and Pharmacodynamic Study

It has been empirically determined that at least 50 patients with several samples per PKI are necessary to characterize drug pharmacokinetics and variability.

Collection and Management of Data

In collaboration with the investigators, the community pharmacy of Unisanté will manage the PKI adherence data, and the Center of Experimental Therapeutics will manage the blood samples as well as the clinical, biological, and sociodemographic data. The schedule of enrollment, intervention, and assessments is shown in Multimedia Appendix 3. Sociodemographic and relevant clinical and biological information regarding the evaluation of the disease will be obtained from the administrative and electronic patient medical records (Soarian, Cerner). The data will be registered prospectively in the REDCap (Research Electronic Data Capture; Vanderbilt University) platform, a secure web application for research data collection, providing a unique study identification number for each patient. To ensure confidentiality and data quality, only principal investigators will have access to this file. After the

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analysis, the database will be registered in the secured data repository of the University of Geneva (Yareta). Patient blood samples will be stored in the Center of Experimental Therapeutics, and the health data will be stored in the data warehouse of the CHUV for a maximum of 15 years after the end of the study before destruction.

Data Analyses

Medication Adherence Analysis

Adherence to PKI will be assessed using electronic monitor, calculated pill counts, and patient reports. Medication behavior will be described with a binary variable (1=at least the correct number of daily openings of the electronic monitor; 0=fewer daily openings than prescribed) in each group. This coding method is commonly used; however, this code cannot discriminate overadherence, which is considered in the same way as optimal adherence. The implementation will be described in each group using generalized estimating equation models; persistence with PKI (ie, adherence until PKI discontinuation) will be represented using a Kaplan-Meier survival curve [14]. Global adherence will be estimated in each group with the proportion of patients with correct medication taking, defined as ≥95% days with correct dosing during days 1 to 360, compared between groups using a chi-square test. As ≥95% days with the correct dosing threshold is an assumption, we will perform sensitivity analysis with other thresholds such as 90%, 85%, and 80%. Multivariate logistic regression models will be used to evaluate whether any detected effect of the intervention remained after adjusting for potential sociodemographic or clinical confounders. As a secondary analysis, the difference in medication taking will be explored across genders.

A systematic computerized term search in the adherence reports of the intervention group will be performed to identify the most frequent variables affecting PKI adherence, and a regression model will be used to discover their association with adherence [35].

Sociodemographic data and quality of life and beliefs about medication of patients who refused to participate and completed both questionnaires versus those who accepted to participate in the adherence study will be compared at baseline. For patients included in the adherence study, the results of the questionnaires will be compared at randomization, 6 months, and at the end of the study. Changes in *Belief about Medicines Questionnaire* and *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* or the *Treatment Satisfaction with Medicines Questionnaire* will be described longitudinally for the included patients and transversely per group at 6 and 12 months. Medians and IQRs or proportions will be used as appropriate. Nonparametric tests (eg, Mann-Whitney-Wilcoxon) or Fisher exact test of two proportions will be used to test the differences between groups.

Ultimately, the adherence patterns and their relationship with drug exposure and clinical response will be evaluated in an exploratory analysis.

To minimize interpretation bias, the statistician will not be aware of the group assignments during the analysis. The data will be analyzed in an intention-to-treat manner. All statistical analyses will be performed using the R statistical package (version 3.6, The R Foundation for Statistical Computing) [36].

Population Pharmacokinetic Analysis

Population pharmacokinetic analyses will be performed using nonlinear mixed regression models with the software program NONMEM (Icon Development Solutions). This approach allows for the characterization of the average pharmacokinetic profile of PKI from data pooled over all sampled individuals and the quantification of inter- and intraindividual variability. This approach allows us to analyze sparse (few drug concentrations per patient) and unbalanced data. The built models integrate active metabolites when appropriate. The impact of potential sources of variability will be evaluated using linear and nonlinear functions.

Relationships Between PKI Exposure, Efficacy, and Toxicity

The correlation between PKI exposure and efficacy will be explored using Cox regression analysis of progression-free survival. The correlation between PKI exposure and toxicity will be explored by pharmacokinetic and pharmacodynamic models using the software program NONMEM or by logistic regression analysis. Receiver operating characteristic analyses will be used to evaluate the best exposure threshold to predict clinical outcomes and performance (in terms of area under the receiver operating characteristics curve and sensitivity and specificity).

Missing Data

Missing data will not be imputed but will be clearly identified and considered during the analysis process (nature and frequency) and described in the publication.

Patient and Public Involvement

Patients or the public will not be involved in the design, conduct, reporting, or dissemination plans of this research. The participants will be informed about the study results after the final publication using lay language.

Results

The first patient was included in May 2015. Until June 2021, 262 patients have participated in at least one part of the study (250 patients have given at least one blood sample, and 130 have been included in the adherence study). In June 2021, 51 patients treated with palbociclib have provided at least one blood sample, and the adherence study currently includes 43 participants with breast cancer, which corresponds to most of the included participants. Moreover, so far, at least one blood sample has been collected from patients treated with 31 different PKIs and their combination (Multimedia Appendix 4).

Data collection is in process, and the final analysis will be performed in 2022. The results of the study will be submitted to local, national, and international conferences and to peer-reviewed open access journals for publication.

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Discussion

Strength of the Study

The OpTAT study is based on a mixed methodology involving a randomized controlled medication adherence study, along with pharmacokinetic and pharmacodynamic data collection. The methodology is robust, as adherence data will be assessed through electronic monitoring, often considered the gold standard, in both the intervention and control groups. Participants randomized to the intervention group will be included in a routine medication adherence program (IMAP) that has previously been shown to lead to significant improvements in terms of medication adherence; clinical outcomes; and retention in care of other chronically ill patients, such as those with HIV [13,14,37-39]. Moreover, the association between longitudinal adherence and clinical data as well as quality of life and beliefs about medicines through questionnaires will be explored, and the literature in this area is scarce.

The second strength of this study is the pharmacokinetic analysis of a wide range of PKIs. PKIs are marketed under a single regimen according to *the one dosage fits all patients* paradigm, which may be an important source of side effects that are potentially detrimental to the continuation of the course of the treatment and patient adherence. Hence, our ultimate and cutting-edge development is to combine an analysis of PKI adherence, pharmacokinetics, and pharmacodynamics.

Limitations of the Study

This study has some limitations. First, the adherence data will be collected over 12 months, a time frame during which several stops and breaks in the treatment regimen can occur. This will be a challenge for data analysis; however, the adherence team and the statistician, who will perform the analysis, have already dealt with this kind of data and are experts in this field [14]. Second, we expect some variability in the frequency of adherence visits among participants. Indeed, the adherence interviews are scheduled after each patient's clinical appointment, and the frequency can vary from a quarterly to a monthly visit depending on the organization of the clinic and the severity of the patient's disease. Third, the use of an electronic monitor can introduce a Hawthorne effect during the first 6 weeks of the study, which disappears afterward [40]. This effect is explained by the fact that patients who know they are being observed may improve their usual medication behavior. The impact of this effect will be explored in the analysis. Fourth, the number of blood samples may not be sufficient to initiate a population pharmacokinetic analysis for each monitored PKI. All limitations will be considered while analyzing the results and will be detailed in the final publication.

Conclusions

The OpTAT study will strengthen knowledge on the effectiveness of the routine IMAP medication adherence program in patients with solid cancers treated with PKIs. The IMAP will enable interprofessional teams to learn about patients' needs and concerns about their PKI self-management. The study will also shed light on PKI pharmacokinetics and its relationship with pharmacodynamic properties, with the aim of adapting dosage regimens at the individual patient level, increasing the clinical suitability of PKIs.

Adherence combined with pharmacokinetic data will inform pharmacists and clinicians on how to support patients during the entire course of their PKI treatment and how to manage adaptations of treatment efficiently, with the patient as an informed partner.

Acknowledgments

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Authors' Contributions

CB and EC wrote the manuscript. All coauthors reviewed and approved the manuscript. IL reviewed the statistical aspects of the protocol. CC, MPS, EC, CB, DW, LD, and NW contributed to the development of the study protocol. A Digklia, KZ, A Diciolla, VC, AS, ALV, A Dolcan, A Sarivalasis, AL, HB, AO, SP, and DW identified and followed the patients clinically. MPS, EC, CB, and JDC organized the implementation of the study within the medication adherence program (IMAP) at the pharmacy of Unisanté.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review reports from the Scientific Office of the Swiss Cancer League/Swiss Cancer Research.
[PDF File (Adobe PDF File), 2624 KB-Multimedia Appendix 1]

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Multimedia Appendix 2

SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist completed for the optimizing oral targeted anticancer therapies protocol.
[PDF File (Adobe PDF File), 170 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Schedule of enrollment, intervention, and assessments of the optimizing oral targeted anticancer therapies study.
[DOCX File , 15 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Protein kinase inhibitors and their combination included in the optimizing oral targeted anticancer therapies study.
[DOCX File , 13 KB-Multimedia Appendix 4]

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Abbreviations

CHUV: Lausanne University Hospital
EMERGE: European Society for Patient Adherence, Compliance, and Persistence Medication Adherence Reporting Guideline
IMAP: Interprofessional medication adherence program
OpTAT: Optimizing oral targeted anticancer therapies
PKI: Protein kinase inhibitor
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

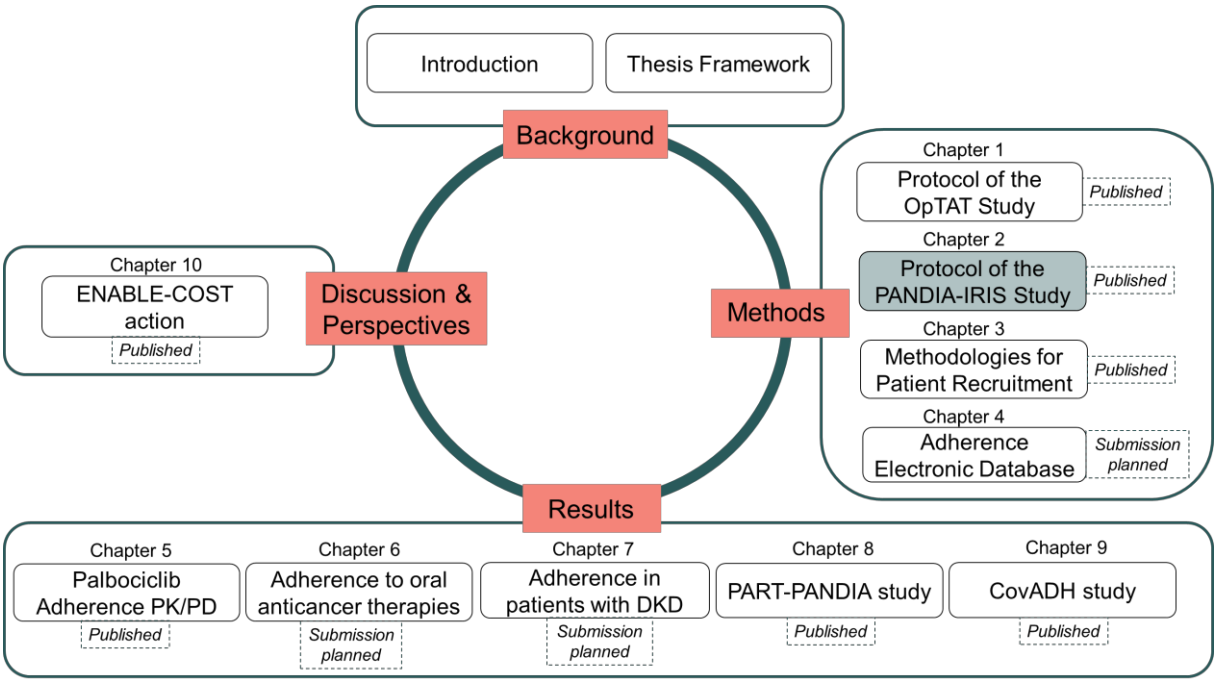
Edited by T Derrick; This paper was externally peer-reviewed by the Scientific Office of the Swiss Cancer League/Swiss Cancer Research. See the Multimedia Appendix for the peer-review report; Submitted 19.05.21; accepted 26.05.21; published 29.06.21.

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CHAPTER 2: THE "*PATIENT·ES DIABÉTIQUES ET INSUFFISANTS RÉNAUX : UN PROGRAMME INTERDISCIPLINAIRE DE SOUTIEN À L'ADHÉSION THÉRAPEUTIQUE*" (PANDIA-IRIS) STUDY PROTOCOL



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

Chapter 2 presents the protocol of the PANDIA-IRIS study as published in *JMIR Research Protocols* in March 2021. The PANDIA-IRIS study was designed by a multidisciplinary team from the School of Pharmaceutical Sciences (University of Geneva), the community pharmacy of *Unisanté*, the Service of Nephrology and Hypertension and the Service of Endocrinology, Diabetes and Metabolism (CHUV).

Protocol

Interprofessional Medication Adherence Program for Patients With Diabetic Kidney Disease: Protocol for a Randomized Controlled and Qualitative Study (PANDIA-IRIS)

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Abstract

Background: Despite effective treatments, more than 30% of patients with diabetes will present with diabetic kidney disease (DKD) at some point. Patients with DKD are among the most complex as their care is multifactorial and involves different groups of health care providers. Suboptimal adherence to polypharmacy is frequent and contributes to poor outcomes. As self-management is one of the keys to clinical success, structured medication adherence programs are crucial. The PANDIA-IRIS (patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique) study is based on a routine medication adherence program led by pharmacists.

Objective: The aim of this study is to define the impact of the duration of this medication adherence program on long-term adherence and clinical outcomes in patients with DKD.

Methods: This monocentric adherence program consists of short, repeated motivational interviews focused on patients' medication behaviors combined with the use of electronic monitors containing patients' medications. When patients open the electronic monitor cap to take their medication, the date and hour at each opening are registered. In total, 73 patients are randomized as 1:1 in 2 parallel groups; the adherence program will last 6 months in the first group versus 12 months in the second group. After the intervention phases, patients continue using their electronic monitors for a total of 24 months but without receiving feedback. Electronic monitors and pill counts are used to assess medication adherence. Persistence and implementation will be described using Kaplan-Meier curves and generalized estimating equation multimodeling, respectively. Longitudinal adherence will be presented as the product of persistence and implementation and modelized by generalized estimating equation multimodeling. The evolution of the ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron Modified-Release Controlled Evaluation) and UKPDS (United Kingdom Prospective Diabetes Study) clinical scores based on medication adherence will be analyzed with generalized estimating equation multimodeling. Patients' satisfaction with this study will be assessed through qualitative interviews, which will be transcribed verbatim, coded, and analyzed for the main themes.

Results: This study was approved by the local ethics committee (Vaud, Switzerland) in November 2015. Since then, 2 amendments to the protocol have been approved in June 2017 and October 2019. Patients' recruitment began in April 2016 and ended in

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October 2020. This study was introduced to all consecutive eligible patients (n=275). Among them, 73 accepted to participate (26.5%) and 202 (73.5%) refused. Data collection is ongoing and data analysis is planned for 2022.

Conclusions: The PANDIA-IRIS study will provide crucial information about the impact of the medication adherence program on the adherence and clinical outcomes of patients with DKD. Monitoring medication adherence during the postintervention phase is innovative and will shed light on the duration of the intervention on medication adherence.

Trial Registration: Clinicaltrials.gov NCT04190251_PANDIA IRIS; https://clinicaltrials.gov/ct2/show/NCT04190251

International Registered Report Identifier (IRRID): DERR1-10.2196/25966

(JMIR Res Protoc 2021;10(3):e25966) doi: 10.2196/25966

KEYWORDS

medication adherence; patient compliance; diabetes mellitus; diabetes complications; diabetic nephropathies; chronic kidney disease; kidney failure; renal insufficiency; electronic monitoring; interprofessional program

Introduction

Currently, approximately 463 million people have been diagnosed with diabetes worldwide [1]. In Switzerland, it is estimated that approximately 500,000 people have diabetes, representing 5.7% of the population [2,3]. Diabetes is associated with a burden of microvascular and macrovascular complications. Diabetic kidney disease (DKD), a microvascular complication of diabetes, affects 30%-40% of the patients with diabetes. Although DKD is the main cause of end-stage renal disease (ESRD), most patients will die of cardiovascular complications before reaching ESRD. Patients with DKD are among the most complex patients receiving diabetes care. Their care is multifactorial and multidisciplinary, involving different groups of health care providers. The multifactorial approach involves pharmacological treatment of various cardiovascular risk factors, including glucose levels, cholesterol levels, and blood pressure levels, and the pharmacological treatment of complications secondary to the reduced renal function. Patients with DKD often take more than 5 daily treatments. Polypharmacy is associated with suboptimal adherence, with risk of an accelerated decline in renal function and ESRD [4]. Although 40% of the patients with DKD do not adhere to their treatments [5,6], literature on medication adherence intervention programs addressing specifically DKD patients is scarce. Recent evaluations showed better metabolic and blood pressure control in patients participating in such programs [7,8]. Furthermore, a high level of self-management, including taking medications, increases the quality of life [6,9]. However, the results of most studies were not conclusive, as medication adherence was evaluated by subjective questionnaires with poor reliability. A feasibility study in patients with DKD who participated in an intervention combining a medication plan and regular phone calls by a specialist nurse did not demonstrate an increase in the medication adherence [10]. Another study concluded that intensive behaviors and interprofessional interventions delayed renal function decline [11]. However, to our knowledge, no study has evaluated the long-term impact of an adherence program or the optimal duration of such a program. It is necessary to better understand the needs of patients with DKD in terms of medication management to achieve better medication adherence and clinical outcomes and slow cardiovascular and renal disease progression.

In 1993, the pharmacy of Unisanté developed an interprofessional medication adherence program (IMAP) to support patients with chronic diseases with their drug management, combining the use of a medication event monitoring system (MEMS and MEMS AS, Aardex Group) and motivational interviews [12]. The first few studies showed encouraging results in improving medication adherence, clinical targets, and retention in care for chronically ill patients [13-18]. The PANDIA-IRIS (patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique) study is based on this routine medication adherence program led by pharmacists. The global aim of this study is to evaluate the impact of the medication adherence program on long-term adherence and clinical outcomes in patients with DKD.

Methods

Ethical Considerations

The PANDIA-IRIS study was approved by the local ethical committee (Vaud, Switzerland) in November 2015. Since then, 2 amendments to the protocol version 4 have been accepted—in June 2017 and October 2019. This study is being carried out in accordance with the protocol and with the principles of the current version of the Declaration of Helsinki. The results of this study will be submitted to local, national, and international conferences and to a peer-reviewed journal for publication. This protocol has been written according to the SPIRIT reporting guidelines [19].

Objectives

The primary objective of the PANDIA-IRIS study is to assess whether the length of the IMAP (12 vs 6 months) has an impact on medication adherence at 6, 12, 18, and 24 months after enrolment. As a secondary objective, this study will explore whether IMAP intervention changes the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) [20] and UKPDS (United Kingdom Prospective Diabetes Study) [21] clinical scores of patients with type 2 diabetes at 6, 12, 18, and 24 months after enrolment. Another secondary objective is to explore patient satisfaction with the medication adherence program through 30-minute semistructured qualitative interviews between an investigator and a subgroup of 14 patients included

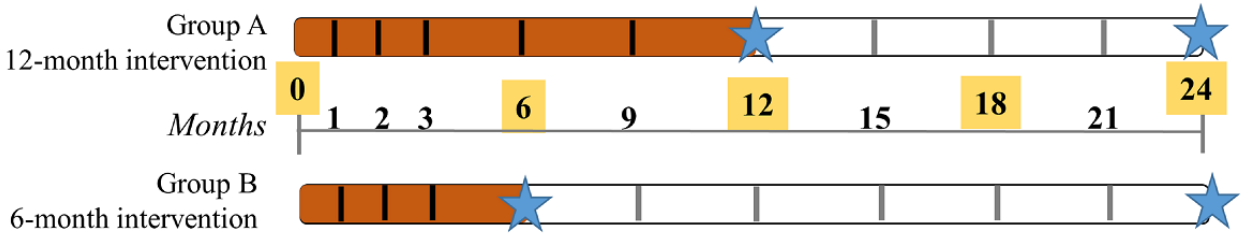
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in the PANDIA-IRIS study. The main hypothesis is that patients participating in the 12-month adherence program will have better implementation and persistence, a higher long-term medication adherence rate, and better ADVANCE and UKPDS clinical scores at 12, 18, and 24 months after enrolment than patients in the 6-month intervention group.

Trial Design

The PANDIA-IRIS design uses a mixed approach as it combines (1) a monocentric, prospective, and open randomized controlled trial and (2) a qualitative study. Patients will be randomized 1:1 in 2 parallel groups; patients of group A will attend the medication adherence program for 12 months and patients randomized to group B will attend the program for 6 months. Satisfaction with this study will be evaluated with selected patients through a qualitative interview at the end of the intervention phase or at the end of this study, or at drop-out (Figure 1). The legend for Figure 1 is available in Multimedia Appendix 1.

Figure 1. Design of the PANDIA-IRIS (Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique) study.



Enrolment of the Participants

This monocentric study is being conducted in the diabetes and kidney outpatient clinics in the University Hospital (CHUV, Lausanne, Switzerland), as well as in the outpatient clinic and the University community pharmacy of the Center for Primary Care and Public Health (Unisanté, Lausanne). The PANDIA-IRIS study is voluntary and each patient had to sign an informed consent form to be enrolled. Recruitment began in April 2016 and ended in October 2020. Eligible patients were identified each week through electronic database screening of all patients with diabetes followed in the University Hospital outpatient clinics. Investigators introduced this study to the eligible patients during a clinical appointment. Recruitment for the qualitative study began in July 2017 and ended in August 2020.

Randomized Controlled Medication Adherence Study

The inclusion and exclusion criteria are presented in Textbox 1 and Textbox 2, respectively.

Textbox 1. Inclusion criteria for the participants.

- Adults older than 18 years who are being followed in the University Hospital and have type 2, type 1, latent autoimmune diabetes in adults, or corticoid-induced diabetes
- One of the following biochemical criteria: estimated glomerular filtration rate (eGFR)≤60 mL/min/1.73 sq m, eGFR>60 mL/min/1.73 sq m that has deceased >5 mL/min/year, urine albumin/creatinine ratio >30 mg/mmol, patients hospitalized at least twice for acute renal impairment in the past 5 years.
- Treatment with at least one of the following drug classes: oral antidiabetic drugs (metformin, dipeptidyl peptidase-IV inhibitors, sodium-glucose cotransporter-2 inhibitors, sulfonylureas, glinides), statins, diuretics, beta-blockers, calcium antagonists, alpha-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or aspirin.
- Fluency in French or English. If not, the presence of an interpreter at each medication adherence visit.
- Full blood test (eGFR, glycated hemoglobin, albumin/creatinine ratio or total, high density lipoprotein and low-density lipoprotein cholesterol) in the 6 months prior to inclusion.

Textbox 2. Exclusion criteria for the participants.

- Incapacity to make decisions, having cognitive disorders, or being under tutelage
- Pregnancy
- Active cancer (not in the remission phase)
- Treatment of the patient is managed by nursing homes or home care services
- Patients already included in an intervention study

All the pharmacists providing the IMAP intervention were trained in motivational interviewing at the University community pharmacy of Unisanté [12]. The technicians were trained in how to complete the electronic monitor data, count pills, and use the

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MedAmigo software (MEMS and MEMS AS, Aardex Group) to upload electronic monitor adherence data and generate a medication adherence report.

Qualitative Study

Semistructured interviews are conducted with a subgroup of 14 patients included in the PANDIA-IRIS study either at the end of the intervention phase so that the patient remembers the motivational interviews well or at the end of the study so that the patient can discuss the postintervention monitoring phase, or at drop-out. To ensure heterogeneity among the selected patients, patients meeting at least one of the following criteria will be enrolled prospectively: male, female, patients from group A, patients from group B, patients who completed the 24 months of the study, patients who just ended the intervention phase, patients who dropped out, and patients having an adherence rate >95% or <80%.

Intervention

Use of the Electronic Monitor

In both groups, patients use electronic monitors for 24 months. Electronic monitors register the date and hour of each opening, which corresponds to the moment of the drug intake as long as both behaviors are consecutive. Nevertheless, one limitation of this tool is that patients could open the electronic monitor without taking the drug or swallowing it long after the electronic monitor opening. In order to limit this bias and before showing the electronic monitor data to the patient at each pharmacy visit, pharmacists check with the patients that each opening corresponds to the drug intake. They ask the patient about the usual lapse of time between each opening and the real time of the drug intake. The liquid-crystal display (LCD) screen on top of the electronic monitor cap resets at 3 AM each morning. Hence, each time the patient opens the electronic monitor cap, the LCD shows the number of cumulative openings until 3 AM on the next day. The LCD screen reminds the patient about whether the medication has been taken or not.

Drugs to monitor are prioritized based on the following algorithm, which we constructed based on side-effect profiles: (1) all oral antidiabetic drugs, (2) statins, (3) diuretics, (4) beta-blockers, (5) calcium antagonists, (6) alpha-blockers, (7) angiotensin-converting-enzyme inhibitors, (8) angiotensin II receptor blockers, and (9) aspirin. Moreover, in each class, eligible drugs taken more than once a day prioritize monitoring. The maximum number of monitored drugs is 6. Physicians can modify the treatments at any time. If a patient has to stop all the monitored drugs, he or she will stop the study but the data collected until then will be kept for analysis. If a drug is switched to another eligible drug, the new prescribed drug will be monitored.

Medication Adherence Intervention

All included patients will benefit from the IMAP in addition to routine clinical care. The frequency of IMAP visits is the same in both groups throughout the 24 months: once per month for the first 3 months, followed by 1 visit every 3 months (Figure 1). Pharmacists lead short, repeated semistructured motivational interviews based on the theoretical Fisher model [22]. First, patients' knowledge of treatments is evaluated. Then, motivation to take the treatment, self-efficacy, daily medication behaviors, and side-effect management are explored in an empathetic nonjudgmental way. The graph representing electronic monitor daily openings (dates and hours) since the last visit is shown to the patient as feedback. Adherence results are discussed to reinforce acquired adherent behaviors and to understand nonadherent episodes, and then, solutions with tailored elements are constructed to address nonadherence. To ensure interprofessional collaboration, the pharmacist sends a semistructured report after each medication adherence interview to the clinical team, including the endocrinologist, nephrologist, general practitioner, nurse, dietician, and psychologist. During the COVID-19 pandemic, adherence interviews are conducted through phone calls for some patients, if the clinicians considered them at high risk of complications following infection by SARS-CoV-2. If the interview is conducted by phone, it is notified on the case report form.

Qualitative Study

At the end of the intervention phase or at the end of this study or at drop-out, patients are invited to express their opinions on the medication adherence program and the overall study. Patients who signed the informed consent form specific to the qualitative part of the PANDIA-IRIS study participate in 30-minute in-depth semistructured interviews. The main themes covered are the evaluation of the quality of the medication adherence interview, the positive and negative aspects of the program, the opinions of the patient regarding the electronic monitor, and if the patients completed this study, the perceived impact of the program during the 12-month to 18-month follow-up period.

Postintervention Monitoring Phase

After the intervention phase, patients will still use electronic monitors with their LCD screens, but their adherence data will be double-blinded. Patients will not receive any feedback or motivational interviews about their daily drug management. The clinical team will not obtain any adherence reports. Due to ethical reasons, if the medication adherence rate detected by the MedAmigo software is less than 30% for at least one drug for 2 consecutive pharmacy visits, the software will automatically notify the pharmacist, and the patient will stop the study and will be oriented to the routine IMAP. If a physician in charge of a patient explicitly asks to access the adherence data during the postintervention monitoring phase for clinically urgent and important reasons, the principal investigator will sign a permission form that will be included in the case report form, and the patient will stop the study. All the data collected until then will be kept for analysis. At 18 months after the inclusion, during the postintervention monitoring phase, blood and urine samples will be collected to determine the clinical values at this time point. Indeed, the frequency of blood and urine samples collection differs between patients, and collecting laboratory values for each patient at this precise time point will ensure consistency in the analysis.

Assignment of Interventions

Patients are randomized 1:1 at inclusion to either the 12-month or 6-month intervention group. According to the risk of

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nonadherence due to the adverse effects of statins or the complexity of the drug regimen, 4 randomization groups were created: patients treated with statins, patients who have to take at least one drug more than once daily, patients with both of the former conditions, and patients with none of the former conditions. Then, the randomization is performed in each strata and is coded with 0, corresponding to group A, where patients receive the intervention for 12 months, or 1, corresponding to group B, where patients receive the intervention for 6 months. The randomization code is generated by a random repetition of 4 and 6 blocks composed of 1 or 0 (Excel, Microsoft) to prevent predictability of the sequence. The randomization sheets were created by an independent researcher from the Unisanté Research Support Unit. The allocation is established for each consecutive patient by unsealing the randomization sheet. This study is open, and the clinical team as well as the patients are aware of the allocation group.

Outcomes

Primary Outcomes

The global adherence outcome is defined as the percentage of days a patient correctly takes the medication across the individual study duration. The mean global adherence will be compared between groups. According to the EMERGE (ESPACOMP Medication Adherence Reporting Guidelines), medication behaviors will also be described longitudinally in both groups through 3 operational definitions: implementation, persistence, and longitudinal adherence at 6, 12, 18, and 24 months after enrolment [23].

Secondary Outcomes

The ADVANCE and UKPDS clinical scores will be assessed and compared at baseline, 6, 12, 18, and 24 months after enrolment for patients with type 2 diabetes in both groups. The ADVANCE score indicates the risk of developing cardiac complications associated with type 2 diabetes within 4 years and estimates the risk of developing renal complications within 5 years or more than 5 years. The UKPDS score calculates the risk of fatal coronary heart disease or stroke in patients with type 2 diabetes with no antecedent cardiovascular disease. These scores are calculated on the following parameters: sex, ethnicity, smoking status, time since diabetes diagnosis, blood pressure, glycated hemoglobin, total and high-density lipoprotein cholesterol, atrial fibrillation, albumin in urine, abdominal circumference, and BMI [24].

During the postintervention monitoring phase, the number of patients with less than 30% adherence for at least one drug during 2 consecutive visits as well as the time-to-event will be compared between the groups. We will also describe implementation and persistence at 6 months and 12 months after the end of the intervention in both groups to explore the impact of the length of the intervention on adherence. Patient satisfaction regarding the program will be analyzed through qualitative interviews.

Sample Size

An expert committee composed of nephrologists, endocrinologists, nurses, pharmacists, and statisticians agreed that the difference in the mean global adherence between groups should be 5%. The hypothesis states that the adherence rate will average 97.5% in the 12-month intervention group and 92.5% in the 6-month intervention group. A standard deviation of 1.7 was assumed in the logit scale in both groups. This corresponds to 95% global adherence in the intervals (57.5%-99.9%) and (30.0%-99.7%) for the 12-month intervention group and the 6-month intervention group, respectively. According to these parameters, a sample size calculation was made simulating individual series of daily medication (1=at least the correct number of daily openings of the electronic monitor for all drugs monitored; 0=fewer daily openings than prescribed for at least one drug monitored), in order to consider both the interindividual variability (SD 1.7) and the intraindividual variability (the measurement error). Considering that the mean number of measures of a subject will be 365, 72 patients must be included in this study (36 participants in each group) to have a power of 80% and a two-tailed alpha error of .05. Regarding the qualitative study, the expert committee agreed that a subgroup of 14 included patients will attend the qualitative interview but more patients may be included if data saturation is not reached after the completion of 14 interviews.

Participant Timeline and Data Collection

Data collection is performed by the investigators and is prospectively registered in the platform Research Electronic Data Capture (RedCap), a secure web app for building databases. Each patient has a unique study number generated by RedCap. First, during recruitment, if eligible patients refuse to participate, their reasons for doing so are recorded. For patients included in this study, their sociodemographic data are provided by the administrative software of the hospital at inclusion. Clinical data for each visit are provided by the patient electronic clinical file (Soarian, Cerner) and reported in the case report form. The participant timeline and data collection process are shown in Multimedia Appendix 2 [25] for both groups. Electronic monitor data are uploaded on the secured MedAmigo web portal at each medication adherence visit during the intervention and at each medication refill during the follow-up for both groups. Concomitantly, the patient's electronic monitor use is systematically checked by the pharmacist through a set of validation questions (ie, identification of nonmonitored periods, eg, during hospitalizations, whether medication was sometimes prepared in advance for a later use since the last visit). A pill count is performed by the technician during the intervention phase and by a blinded independent researcher during the postintervention monitoring phase. The participants who leave this study before completion are not replaced and are considered as dropouts but the data collected until then will be kept for analysis. The data monitoring committee is composed of the main investigators of the PANDIA-IRIS study. After the end of this study analysis, data will be archived and kept for 10 years in the secure data warehouse of the University Hospital before destruction. The database of the PANDIA-IRIS study will be shared in a secured data repository of the University of Geneva (Yareta) at the end of the analysis.

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Data Analysis

Sociodemographic and Clinical Data

Sociodemographic and clinical data will be presented as percentages, means, and standard deviations or medians and interquartile ranges depending on the distribution of the data.

Medication Adherence

All dates and the timing of electronic monitor activation will be used to analyze medication adherence. Electronic monitor data will be reconciled with pill counts and patient reports [26]. The global adherence will be calculated as the percentage of days during which the drug is taken properly across the individual study duration. Two-sided Student *t* test will be used to compare the mean probabilities between groups in the logit scale. A difference between groups will be considered statistically significant if $P<.05$. Medication behaviors are characterized by implementation, persistence, and longitudinal adherence [27].

Implementation evaluates at each day the proportion of patients taking at least the correct dose prescribed on that day among the patients who are still participating in the program. For each participant, the daily medication behaviors will be described with a binary variable (1=at least the correct number of daily openings of the electronic monitor for all drugs monitored; 0=fewer daily openings than prescribed for at least one drug monitored). This code is commonly used and cannot discriminate overadherence, which will be considered as adherence. Implementation will be modeled with the generalized estimating equation multimodeling [28].

Persistence corresponds to the distribution of times between inclusion in the study and discontinuation (ie, unilateral stopping of treatment by the patient). Persistence will be described with a Kaplan-Meier survival curve. The log rank test will be used to compare the persistence between groups [28].

Longitudinal adherence is defined at each day as the proportion of patients taking at least the correct dose prescribed on that day among all the patients included in the study. Longitudinal adherence will be presented as the product of persistence and implementation and modelized by generalized estimating equation multimodeling [28]. In an exploratory analysis, univariable and multivariable regressions will analyze the associations among medication behaviors (combining persistence and implementation), sociodemographic and clinical data at inclusion, and changes in the clinical and biochemical variables at the completion of the study.

The number of patients with adherence rates less than 30% in the postintervention monitoring phase for at least one drug during 2 consecutive pharmacy visits will be compared between groups with a chi-squared test or with Fisher exact test if the sample size is less than 5 patients. The statistician who will perform the analysis will not be aware of the group allocation until the data are completely frozen. Statistical analysis will be performed with the R statistical package (version 3.6, The R Foundation for Statistical Computing) [29].

ADVANCE and UKPDS Clinical Scores

The changes in the ADVANCE and UKPDS scores during the 24-month study will be analyzed with generalized estimating equation multimodeling, considering collected covariables such as sociodemographic data, monitored treatments, and medication adherence.

Qualitative Study

Audio recordings will be transcribed verbatim, and a content analysis will be performed using MAXQDA (VERBI GmbH) software. The codes will be labeled and categorized into themes. To ensure the codification validity, 2 investigators will codify the verbatim transcription independently and discrepancies will be discussed.

Missing Data

Missing data will be clearly identified in the results tables and will not be computerized.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research. Once the results of the PANDIA-IRIS study will be published, the included patients will be informed about the results through a summary flyer using lay language.

Results

Patients' recruitment began in April 2016, ended in October 2020, and it was a challenging task. Indeed, this study was introduced to all consecutive eligible patients (n=275). In total, 73 out of 275 patients accepted to participate (26.5%) and 202 (73.5%) patients refused. Most patients who refused to participate argued that they had developed satisfactory skills and habits in drug self-management over time and that this study would disturb their routine. For instance, most patients already used a weekly pill organizer and were not ready to replace it with electronic monitors. Nevertheless, investigators could not confirm that these patients had no adherence issue. A new quantitative and qualitative substudy has been planned to understand the sociodemographic and clinical variables that differ between the patients who accepted versus those who refused to participate. Qualitative interviews will be conducted with a representative number of patients who refused to participate to understand their personal reasons for nonparticipation in order to further improve the routine IMAP. Patient recruitment is completed, and sociodemographic and clinical data are prospectively collected for the included patients until October 2022. Data analysis will be performed and results will be submitted for publication in a peer-reviewed open access journal.

Discussion

Strengths of This Study

The PANDIA-IRIS study is the first study to analyze the impact of a pharmacist-led adherence program on long-term medication adherence and cardiovascular scores in patients with diabetes and renal impairment. This study is based on a robust

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methodology; patients use electronic monitors, often considered as close to the gold standard to assess medication adherence. Moreover, patients are included in the routine IMAP that already led to significant improvements in the medication adherence and clinical outcomes of other chronically ill patients [12,17,18]. The mixed methodology is another strength of this study; the qualitative satisfaction interviews led with a representative number of included patients will enable the research and pharmacy teams together to further adapt the program to the specific needs of patients having DKD.

Limitations

This study has some limitations. First, patients are included for 24 months in this study, which is a relatively long period of time, thereby increasing the probability of change in regimen over time and dropouts. In addition, the adherence data analysis is complex as patients use more than 1 electronic monitor. However, complex medication adherence data analysis was previously developed by the investigators, and the statistician who will perform the analysis is an expert in this field. Secondly, we cannot exclude the Hawthorne effect during the first 6 weeks of this study, explained by the fact that participants might improve their usual medication adherence behaviors as they feel observed [30]. We will analyze adherence as a trajectory (longitudinal, repeated measures) and we will pay attention to this risk during our analysis. All limitations and their possible impacts on the results will be clearly depicted in the final publication.

Conclusion

The PANDIA-IRIS study will provide crucial information about the impact of the medication adherence program on adherence and the clinical outcomes of the patients with DKD who are known for polypharmacy challenges and who are engaged in complex and multifactorial care. Monitoring medication adherence during the postintervention phase is innovative in this field. This analysis will help health care providers to better support medication adherence in patients with DKD.

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Authors' Contributions

CB wrote the manuscript. MS and AZ reviewed it. IL reviewed the statistical part of the protocol. All authors contributed to the elaboration of this study protocol and to the final manuscript. CB, JDC, DN, FL, MP, GW, and MB identified and followed the patients clinically. This work is supported by a grant from Santésuisse/Curafutura/PharmaSuisse. The sponsors of the PANDIA-IRIS study are the Lausanne University Hospital and the polyclinic of the Center for Primary Care and Public Health (Unisanté, Lausanne, Switzerland).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Caption of the design of the PANDIA-IRIS study.
[PNG File , 60 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Schedule of enrollment, interventions, and data collection for the PANDIA-IRIS study.
[DOCX File , 19 KB-Multimedia Appendix 2]

Multimedia Appendix 3

CONSORT-eHEALTH checklist (V1.6.1).
[PDF File (Adobe PDF File), 525 KB-Multimedia Appendix 3]

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Abbreviations

ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation
DKD: diabetic kidney disease
ESRD: end-stage renal disease
IMAP: interprofessional medication adherence program
LCD: liquid-crystal display
MEMS: medication event monitoring system
PANDIA-IRIS: Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique
RedCap: research electronic data capture
UKPDS: United Kingdom Prospective Diabetes Study

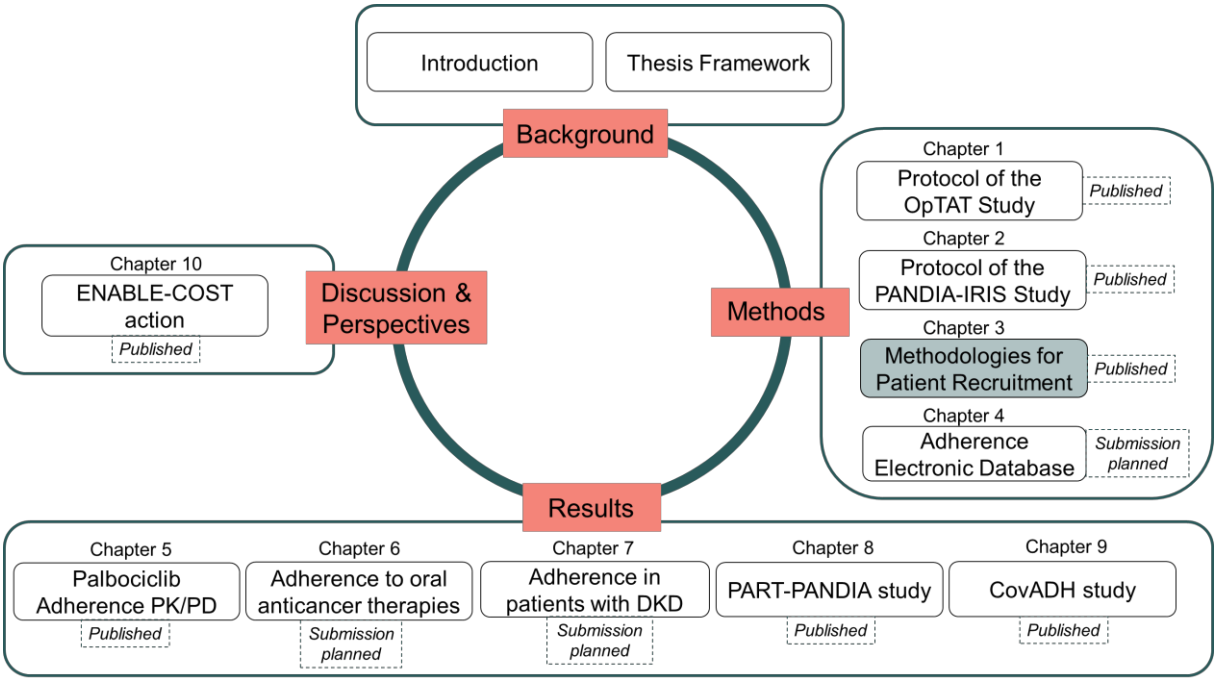
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CHAPTER 3: METHODOLOGIES FOR PATIENT RECRUITMENT IN CLINICAL TRIALS



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

One of the most difficult tasks when conducting a clinical trial is to achieve the targeted sample size by recruiting enough participants without any recruitment bias. Indeed, the statistical power of a test –i.e., the capacity of a statistical test to detect a significant effect between groups when there is one– is crucial to draw solid conclusions. However, it is not uncommon that clinical trials must be prematurely stopped because of the lack of participants[234, 235]. Recruiting patients requires time, resources, interprofessional collaborations and a standardized research procedure. Investigators are advised to describe *implementation* strategies to minimize barriers to enrollment and optimize the recruitment process in the early stages of the development of a clinical trial to avoid losing the invested resources.

Chapter 3 presents the challenges we faced while including patients to the OpTAT and the PANDIA-IRIS studies as well as the strategies implemented to optimize patient recruitment.

1. Patient Recruitment in the OpTAT Study

Eligible patients included in the OpTAT study were adults treated with oral anticancer therapies (OAT) for solid cancers. Patients were recruited at the Department of Oncology of the Lausanne University Hospital (CHUV) in nine oncology clinics: the melanoma (MEL), sarcoma (SARC), gastrointestinal (GI), senology (SEN), thoracic (THOR), otorhinolaryngology (ORL), urology (URO), gynecology (GYN) and neurology (NEURO) clinics. The targeted sample size to complete in the adherence part of the OpTAT study was 120 patients (60 in each group)[236]. Patients' recruitment lasted 5 years and 9 months (i.e., from July 2015 to April 2021). To note, due to the coronavirus disease (COVID-19) pandemic, recruitment was interrupted between March and June 2020. In total, the adherence part of the OpTAT study was offered to 241 patients, of whom 111 refused to participate and 130 accepted (43 patients were included from the SEN clinic, 39 from GI, 12 from MEL, 10 from SARC, 9 from URO, 8 from GYN, 5 from THOR and 4 from the ORL clinic). The proportion of patients who refused to participate was of 46.1% (111/241). However, the targeted sample size was reached. The cumulative number of patients included in each oncology clinic is presented in Fig. 7.

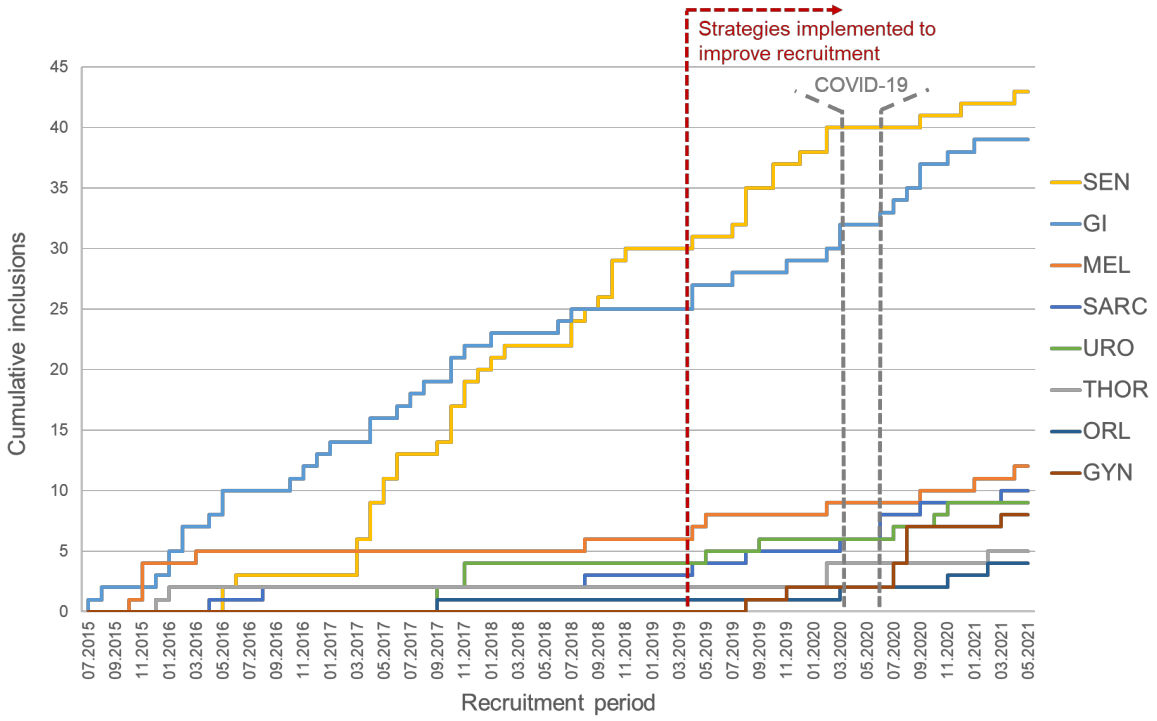


Figure 7: Recruitment of patients in the adherence part of the OpTAT study

NB: the dotted red line represents the date from which the strategies to improve the recruitment process were implemented. The period between the dotted grey lines represents the COVID-19 lockdown in Switzerland, during which the recruitment was interrupted.

Recruitment process prior to *implementation* of recruitment strategies

To include patients in the OpTAT study, oncologists were asked to: i) screen eligible patients among those who attended their medical consultations, ii) announce them to the investigators, by writing emails or by phone calls and iii) introduce the study to patients and inform them that an investigator will provide in-depth information to them in the waiting room before or after the next medical appointment.

Challenges: the recruitment was slower than expected

In January 2019, 75 patients were included, whereas the investigators planned to recruit 120 participants. To improve the inclusion rate, the barriers to patient enrollment were scrutinized.

First, oncologists did not refer all eligible patients to the research team. Thus, the study was not systematically offered to each single eligible patient. The additional workload associated with the screening of eligible patients, the lack of time for both clinical and research activities and the lack of awareness of the study in the Department of Oncology because of continuous rotations of new interns may have hampered the screening process of eligible patients. Indeed, the communication on the study to each of the numerous stakeholders involved in patients' care in the nine different clinics (e.g., nurses, chief oncologists, intern oncologists, clinical pharmacists, dieticians, psychologists) was challenging.

Second, the involvement of oncologists in detecting eligible patients was heterogeneous across oncology clinics: the majority of eligible patients were screened in the senology and the gastrointestinal clinics, as shown in Fig. 7, whereas numerous patients were also eligible in the other clinics. Besides, while some oncologists took time to describe the main objectives of the study and informed the patient that an investigator will introduce the study to them, some oncologists did not. Thus, some patients approached by the investigators were not aware and ready to receive information about the OpTAT study, which may have impacted their decision to participate.

Third, the additional time dedicated to the study presentation was not planned as part of the patients' medical visit. Thus, patients needed to dedicate personal time to the study presentation, which could have been perceived as an additional burden of their care. Moreover, no specific office was available or dedicated to research purposes and the investigator presented the study to the patient in the waiting room, which limited the confidentiality of the discussion.

Forth, 46% (111/241) of patients refused to participate after the study presentation for various reasons, which were collected in the Case Report Forms (CRFs) in 103/111 patients and are presented in Fig. 8.

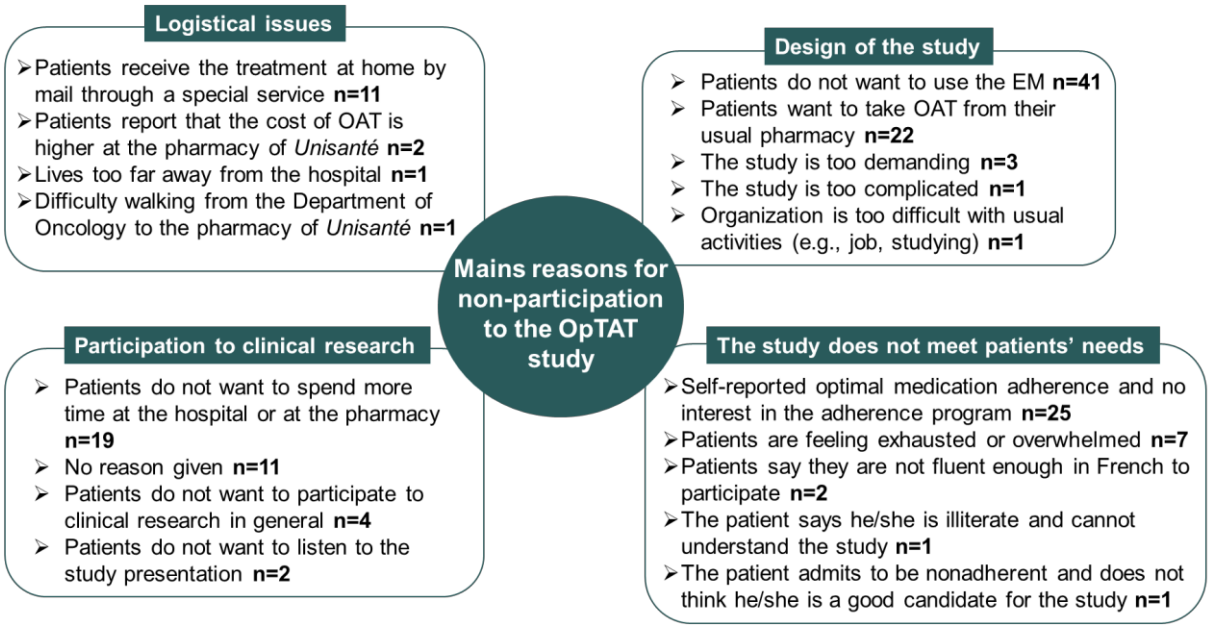


Figure 8 : Main reasons for non-participation reported by 103/111 patients who refused to participate

NB: some patients provided several reasons for non-participation. EM=electronic monitor; OAT=oral anticancer therapies

Fifth, even if some patients agreed to participate, some of them could not be included, mainly due to clinical or administrative reasons. Among them: i) the OAT was stopped before inclusion because of cancer progression, adverse effects or toxicity; ii) the health insurance did not provide a confirmation for the reimbursement of the OAT prescribed, leading to a treatment change before inclusion; iii) patients had a particular medical insurance contract, which prevents the reimbursement of their medications delivered at the community pharmacy of *Unisanté* –the predefined pharmacy specified in the patient's contract must deliver their medications; iv) patients were not eligible anymore to participate (e.g., if the patient had been included in another clinical trial before inclusion) and v) the patient died before inclusion.

Finally, we envisioned to implement the OpTAT study in another hospital site (i.e., the hospital of Bellinzona (TI)) to increase the sample of eligible patients. However, the translation of the study outside the CHUV was not possible due to the lack of time and resources to train healthcare providers (HCPs), develop documentation in Italian, implement and lead the intervention on-site and organize a secure transfer of data. Thus, the OpTAT study remained monocentric with improvements of the recruitment process.

Strategies implemented to improve the recruitment process

Based on the identification of the challenges to recruit eligible patients, innovative strategies were developed from April 2019 to optimize the recruitment process. The impact of the *implementation* of the strategies on the inclusion rate was regularly reported to the research and the clinical teams.

First, flyers depicting the study aims and procedures were hung up in the different meeting rooms of the oncology wards to nudge HCPs to screen eligible patients (Appendix 2). Moreover, investigators were often present in the wards and regularly met the oncologists informally during their routine clinical practice.

Second, in collaboration with the research and the clinical teams, one oncologist from each of the nine oncology clinics was defined as responsible for the recruitment in his/her clinic. This oncologist was the main point of contact for the research team to encourage recruitment in his/her clinic. He/she was asked to inform the clinical interprofessional team (i.e., interns, specialist nurses, dieticians, psychologists) to detect eligible patients during their consultations and to promote the study among the collaborators of the clinic.

Third, the investigators promoted the study at the weekly oncology staff meeting to introduce formally the study to new interns after each biannual rotation: the OpTAT study was presented on January 14 and June 17, 2019, and February 10 and August 17, 2020.

Forth, to coordinate the study, the investigators and study collaborators (e.g., study nurses, PhD student, data managers) met every trimester to analyze the recruitment process and to develop new strategies to increase the recruitment. For instance, investigating reasons for non-participation reported by patients helped to better anticipate and address the questions of patients. Hence, the study procedures were made more flexible to answer patients' needs while ensuring the fidelity to the intervention. Investigators regularly updated the procedures for patients' recruitment and inclusion to the pharmacy team during dedicated meetings (i.e., those presentations took place on February 14, May 9, July 11, September 12 and November 28, 2019, on February 27, July 30 and October 22, 2020, and on February 25, 2021).

Fifth, the data science research team of the CHUV developed an algorithm to scrutinize patients' electronic medical records to detect eligible patients who had not already been screened by oncologists. While this process allowed including more patients, it also allowed decreasing a potential selection bias, as oncologists might have reported eligible patients that they have defined as good candidates for the study. Thus, the study was offered to a more diverse population (e.g., including non-native French speaker, older and younger patients, patients with social vulnerability). Moreover, from April 2019, eligible patients were also

identified directly by the investigator by attending the tumor board meetings during which patients' clinical cases were discussed.

Sixth, we developed new collaborations with HCPs from the Department of Oncology, such as an oncology clinical pharmacist and specialist nurses who routinely met patients with solid tumors. While collaborating with them, we identified two other solid cancer types for which patients could be treated with OAT (i.e., gynecologic and brain cancers). Thus, from July 2019, the OpTAT study was introduced to HCPs from the gynecologic and the neurology clinics. While several patients with gynecologic cancers were included, no patient with brain cancer accepted to participate.

Seventh, as patients participating to the OpTAT study had to spend additional time attending the pharmacy visit after their medical appointments, a collaboration with the Department of Oncology allowed participants to have a discount access to the parking of the CHUV. This discount access was explained during the recruitment, which might have facilitated patient participation.

Finally, we collaborated with health insurances to allow the reimbursement of OAT delivered by the community pharmacy of *Unisanté* for patients having subscribed to a specific insurance contract, which prevented them from obtaining their medications from another pharmacy than the one stated in their insurance contract.

The challenges and strategies of patient recruitment in the OpTAT study were described in a poster at the annual ESPACOMP congress in 2019 (Appendix 3). This poster allowed some discussions with other participants, among whom Dr Xiomara-Skrabal Ross, a researcher who was conducting a study to support patient adherence to OAT in Adelaide (Australia). As we shared the same difficulties to recruit patients, we decided to work together remotely from 2019 to 2021 to confront our perspectives on the lessons learned and strategies to improve patient recruitment and the *implementation* of medication adherence monitoring. We published our observations in a commentary in *Supportive Care in Cancer* in January 2022, entitled "*Interventions to support adherence to oral anticancer therapies: research challenges, lessons learned, and strategies to overcome them from Australia and Switzerland*".
This paper involved the School of Pharmaceutical Sciences (University of Geneva) and the Lausanne University Hospital (CHUV), Dr Xiomara Skrabal Ross from the Cancer Research Institute, University of South Australia (Adelaide, Australia) and her research and clinical teams.
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COMMENTARY

Interventions to support adherence to oral anticancer therapies: research challenges, lessons learned, and strategies to overcome them from Australia and Switzerland

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Abstract

Not monitoring adherence to oral anticancer therapies (OAT) can lead to poor clinical outcomes, including premature death as reported by Foulon et al. (Acta Clin Belg 66(2):85–96, 2011) and Greer et al. (Oncologist 21(3):354–76, 2016). Barriers to the implementation of supportive cancer care interventions in medication adherence occur with multiple hospital sites, cancer diagnoses, and numerous healthcare professionals. This commentary describes challenges and strategies from two OAT adherence trials in Australia and Switzerland to assist researchers in the design and implementation of future interprofessional trials.

Keywords Neoplasms · Patient selection · Implementation science · Clinical trials · Medication adherence · Oral anticancer therapies, Antineoplastic agents

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Context of the studies

The Australian study was a non-randomized, multi-site proof-of-concept trial of a smartphone short message service (SMS) intervention for 10 weeks to support adherence to OAT, where 22 participants (diverse cancer diagnoses and stages) were recruited in 1 year from six hospitals (one hematology and five oncology clinics) [1].

The Swiss study (Optimizing Targeted Anticancer Therapies) has a 1:1 randomized controlled trial design and aims to improve adherence to protein kinase inhibitors (PKI) in patients with solid tumor cancer (diverse cancer diagnoses) [2]. Most of them are initiating PKI for a palliative care for metastatic cancer. The target is of 202 participants in 4 years from one University hospital and eight disease types. The intervention consists of monthly motivational interviewing sessions, patient to pharmacist for 12 months.

Both studies assessed patients' adherence to OAT through an electronic monitor (EM, MEMS™), one of the most reliable adherence measures, frequently used as a standard for validation of other adherence measurement tools, especially self-report [3]. However, it is indirect because opening the EM bottle does not prove drug swallowing.

Challenge 1: Multiple hospital sites and diverse cancer diagnoses

More participants were recruited when using multiple hospital sites. However, the identification of one oncologist in each site as the main contact for accrual did not facilitate recruitment as expected — most of the potential participants were not identified and referred by them.

Both studies included patients with diverse cancer diagnoses. They are prescribed OAT and face similar therapeutic challenges [4]. This strategy helped to investigate adherence to the same OAT across various cancers but was a challenge in the Swiss study, as the pharmacist needed to adapt the intervention to patients' therapeutic journeys. The Australian study tailored the intervention to OAT type but did not consider participants' cancer stages and history of OAT use.

Barriers to OAT adherence may differ across OAT users. They include differences in the severity of side effects [4] and longer history of OAT use, which may affect adherence [5, 6]. OAT adherence intervention trial designs should be tailored to the individual disease, treatment, and pathways (initiating, implementing, or discontinuing a treatment [7]). Table 1 summarizes the challenges and strategies for recruitment and research implementation from the two studies.

Challenge 2: Slow recruitment

The Swiss study only recruited 101 participants over 5 years (07/2015–03/2020). The Australian study target of 22 participants required recruitment from six different hospitals (04/2019–01/2020).

General barriers to the implementation of health interventions which applied to the 2 studies included as follows: hospitals staff's workload, resource limitations [8, 9], and short consultation times [10–12]. The latter can be addressed by hiring dedicated staff (e.g., research coordinator) or integrating the research team into hospital-based services [8, 13]. Adjusting to each hospital and cancer clinic system (e.g., work dynamics) is a key facilitator of implementation of hospital-based interventions [8].

Although the Australian and Swiss research teams performed most of the hospital-based research activities, the identification of potential participants relied primarily on hospital staff (oncologists, oncology pharmacists, and nurses), with no reimbursement programs for these activities. Previous adherence trials show that physicians are more willing to help with trials that require little time commitment and high reimbursement [14].

In both studies, the research teams promoted recruitment by regularly visiting hospital staff, engaging with new staff (oncology pharmacists), and issuing reminders. In the Swiss study, data managers regularly identified potential participants through hospital databases.

Although time consuming, these strategies improved accrual. However, without institutional policies about systematic referral of patients from hospital staff to clinical trials, accrual will continue to be difficult.

Other barriers such as staff's attitudes to and understanding of the intervention should also be considered in trial design [8, 15].

Challenge 3: Patients' reluctance to adopt new routines

Participation in medical cancer clinical trials stands at 8–11% [10]. Reasons for refusal included unwillingness to spend more time at the hospital for research purposes (Switzerland = 17/94) or to change established routines around OAT self-management (Australia = 5/12, Switzerland 22/94). Some eligible patients (Australia = 2/12, Switzerland = 35/94) agreed to the studies but did not enroll because they did not want to store their OAT in EM devices. Although the bulkiness of the EM bottles is often cited as a motive, other reasons should be investigated [16]. Some eligible participants were unwilling to receive text messages from the research team (Australia = 3/12) or

Table 1 Summary of research-related challenges and strategies to overcome them

Challenges	Strategies that improved recruitment or implementation	Strategies that did not improve recruitment or implementation and why
1. Multiple hospital sites and diverse cancer diagnoses	Inclusion of multiple recruitment hospital sites (AU) and diverse cancer diagnoses (AU, CH)	Identification of one oncologist in each hospital site as the main point of contact for recruitment did not improve accrual as eligible patients were not all identified and referred
2. Slow recruitment	Independence of the investigator to find eligible patients through an electronic database or tumor boards' case lists (CH) Involvement of the research team in hospital cancer multi-disciplinary meetings (AU) or regular meetings in all oncology clinics (CH) Building and maintaining positive relations with hospital staff, with frequent physical presence in the cancer clinics and providing frequently reminders about the studies (AU, CH) Collaboration with oncology pharmacists (AU, CH)	Dedicated presentations and team meetings to design recruitment strategies and study processes tailored to the work dynamics and staff availability in each hospital were not successful (AU, CH) Providing oncologists the ability to present the study to the patient themselves: leads to increased workload and this was not implemented, although offered (CH)
3. Patients' reluctance to adopt new routines	N/A	N/A
4. Using EM devices	Negotiation between the research team, hospital outpatient pharmacists, and oncologists to allow the provision of treatment that lasted until the next medical appointment in the hospital (AU, CH) Flexibility around the use of EM. For some exceptions, some participants were offered not to carry the EM with them for particular situations (e.g., holidays, special events) if they felt uncomfortable doing so. This was reported in the Case Report Forms (CH)	N/A
5. Communication between research and hospital staff	One hospital designed a process for communication of OAT stops and dose changes between clinicians, pharmacists, and the research team (AU) Immediate phone calls were established between the hospital staffs and the outpatient pharmacy in case of regimen or OAT changes (CH)	Pharmacists and clinicians were asked to immediately notify the research team about participants' drug stops and changes. They did not notify all changes to the team (AU) Oncologists were asked to deliver a prescription for each OAT regimen change. However, the pharmacy often did not receive these prescriptions (CH)

AU Australia, *CH* Switzerland

believed that their OAT adherence was already well managed (Switzerland = 20/94). Patients with longer stories of OAT and comorbidities may have developed a medication taking routine they feel comfortable with and may be less willing to explore new approaches than those who are newly prescribed OAT. Engaging OAT users in trial co-design and citing patients' experiences may help reduce these challenges in future studies [17].

Challenge 4: Using EM devices

OAT should be kept in their blister packaging in the EM bottles. The professional pharmacy handling for EM is costly, although less costly than suboptimal adherence [3]. In both countries, most of the community pharmacies were not prepared to implement EM handling, and participants had to travel to the hospital outpatient pharmacy for their monthly re-fills, unless there was specific negotiation, say for rural patients.

Challenge 5: Communication between research and hospital staff

Side effects often lead to OAT postponements or dose adjustments [18, 19]. In the Swiss study, this challenged pharmacists to constantly adapt OAT orders and EM filling. Participants were encouraged to communicate dose adjustments directly to pharmacists but without prescriptions, an immediate phone call to the clinical team was essential to deliver the correct OAT regimen.

In both studies, hospital staff, pharmacists, and participants were instructed to immediately communicate to the researchers when OAT was stopped (e.g., due to toxicity, cancer progression, or holidays) so it was not interpreted as non-adherence, but this was rarely reported by hospital staff.

Conclusion

This is the first paper that focuses on the challenges in recruitment and implementation of OAT adherence across countries with different healthcare systems and potential strategies to overcome them. Evidence on the challenges faced by adherence trials in oncology settings is scarce. Future studies should mount an exhaustive literature review focused on supportive cancer care and identify further strategies to improve recruitment and implementation of these types of trials.

Author contribution All authors contributed to research design and implementation, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Data availability The main authors have control of all primary data (each for one of the studies) and agree to allow the journal to review our data if required.

Code availability N/A.

Declarations

Findings reported in this manuscript have not been previously published and the manuscript is not being simultaneously submitted elsewhere.

Ethics approval The Swiss study was approved by the local ethics committee (Vaud, Switzerland) named "Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD)," ID: 65/15. Trial registration number: Clinicaltrials.gov n° NCT04484064. The Australian study was approved by the following Human Research Ethics Committees: The Women's and Children's Hospital (ID: HREC/18/WCHN/146), Calvary Health Care Adelaide (ID:18 CHREC F010), and The University of South Australia (ID: 201826). Trial registration number: ACTRN12618001987257p.

Consent to participate Written informed consent was obtained from all participants included in both studies.

Consent for publication All participants consented for non-identifiable findings of both studies to be published.

Conflict of interest The authors declare no competing interests.

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2. Patient Recruitment in the PANDIA-IRIS study

Eligible patients included in the PANDIA-IRIS study were adults with diabetes type 2, type 1, latent autoimmune diabetes in adults (LADA) or corticoid-induced diabetes, with an impaired renal function (eGFR<60mL/min/1.73m^2)[237]. Patients were recruited at the Service of Endocrinology, Diabetes and Metabolism and at the Service of Nephrology and Hypertension of the CHUV, and at the medical policlinic of *Unisanté*[237]. The targeted sample size was 72 patients (36 in each group)[237]. The recruitment of patients lasted 4.5 years (i.e., from April 2016 to October 2020). To note, due to the COVID-19 pandemic, the recruitment was interrupted between March and June 2020. In total, the PANDIA-IRIS study was offered to 275 patients, of whom 202 refused to participate and 73 patients were included (34 were recruited from the Service of Endocrinology, Diabetes and Metabolism, 26 from the Service of Nephrology and Hypertension and 13 from the medical policlinic of *Unisanté*). The refusal rate was high (202/275=73.5%), but the targeted sample size was reached. The cumulative number of patients included in the PANDIA-IRIS study is presented in Fig. 9.

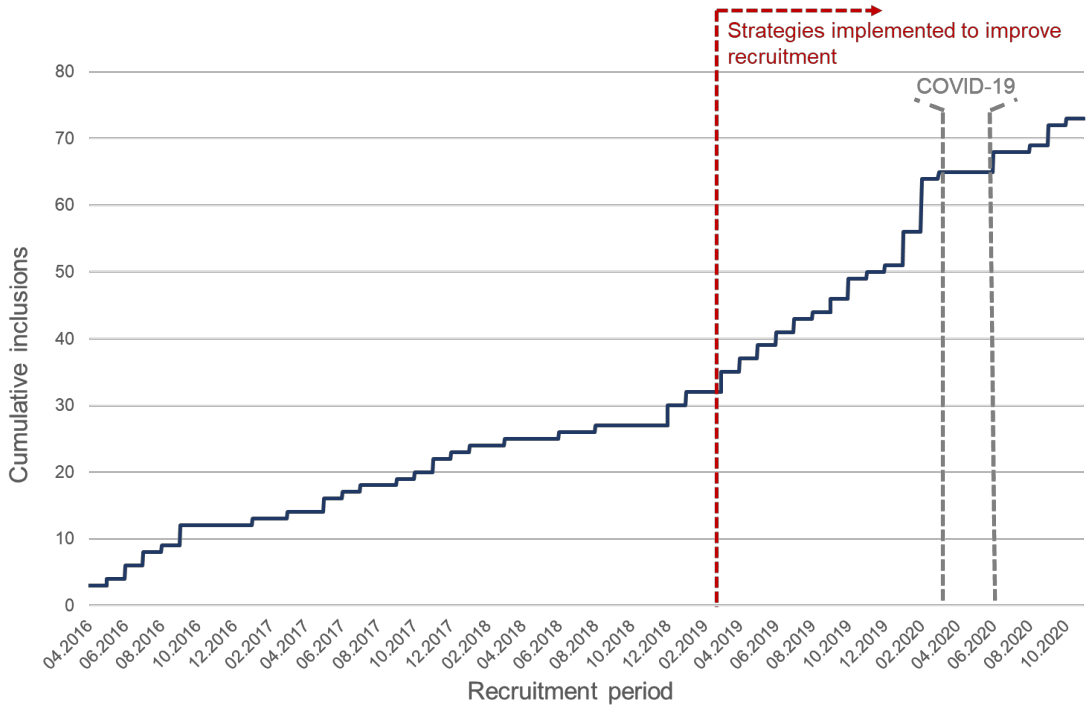


Figure 9: Recruitment of patients in the PANDIA-IRIS study

NB: the dotted red line represents the date from which the strategies to improve the recruitment process were implemented. The period between the dotted grey lines represents the COVID-19 lockdown in Switzerland, during which the recruitment was interrupted.

Recruitment process prior to *implementation* of recruitment strategies

HCPs were asked to provide the identification of eligible patients to the investigators. To identify more eligible patients, the investigator screened weekly two different databases built and regularly updated by the study nurse; these databases listed patients with type 2 diabetes and renal impairment who consulted the Service of Endocrinology, Diabetes and Metabolism and the Service of Nephrology and Hypertension of the CHUV. Each week, eligible patients who would meet their providers in the next week were listed. Providers were contacted by email and invited to introduce the study briefly to the patient during the consultation, so that the investigator could explain the study in-depth after the consultation. If the physician did not respond to the email, the investigator considered that the physician would not introduce the study to the patient and therefore, the investigator did not plan to meet the patient.

Challenges: the recruitment was slower than expected

In January 2019, 31 patients were included, whereas the investigators planned to recruit 72 patients. Barriers were encountered during the recruitment process.

First of all, an important number of patients identified in the databases were not eligible due to the following reasons: i) the patient was already included in the routine IMAP; ii) the patient was involved in complex care (i.e., he/she was dialyzed, had a recent renal replacement therapy); iii) the patient was included in another interventional study; iv) the patient was not followed on a regular basis at the CHUV; v) the patient presented exclusion criteria, such as a new diagnosis of cancer, cognitive impairments or the patient did not self-manage his/her medications; vi) the patient was not fluent in French and an interpreter was not available to translate the study presentation. Moreover, whereas the providers should have reported the identification of eligible patients to the investigator, most of them did not take the time to do it on a systematic basis.

Second, communication about the study was challenging, as the stakeholders involved in the recruitment were numerous: the interprofessional team included nephrologists, endocrinologists, general practitioners (GPs), nurses, dieticians and psychologists. Thus, some stakeholders were not aware that the recruitment for the PANDIA-IRIS study took place in their departments. As a matter of fact, most of the HCPs did not answer the email indicating that some of their patients were eligible to the study. Furthermore, the recruitment was implemented in three medical departments located at three different hospital sites, which made it difficult for the investigators to introduce the study to different patients who had a consultation at the same time.

Third, the proportion of patients who refused to participate was higher than expected (73.5%). Reasons as well as factors for non-participation were further investigated as part of the study "Participation to PANDIA-IRIS" (PART-PANDIA study), the results of which are presented in Chapter 8.

Strategies implemented to improve the recruitment process

Strategies to include more patients were regularly discussed during meetings between investigators and the interprofessional team, and were implemented since March 2019.

First, a consensus between HCPs allowed optimizing the recruitment process. To decrease the workload of HCPs, the investigator met all eligible patients after their medical consultation, even if the provider had not responded to the email inviting them to briefly introduce the study to the patient. The investigator notified the providers that she would come directly at the end of the consultation to discuss with the patient about his/her possible participation to the PANDIA-IRIS study. If the provider agreed, the investigator introduced the study to the patient in the waiting room or in an office, according to the patient's preferences. This daily face-to-face communication between the investigator and the providers strengthened the collaborations and promoted the study within the departments, therefore facilitating the recruitment process. As a result, the study was offered to all consecutive eligible patients screened, which allowed including significantly more patients since March 2019. Moreover, we decided that after each medication adherence interview, the adherence report would be sent not only to the physicians, but also to all HCPs in charge of the patient (e.g., nurses, dieticians and psychologists). Sharing the adherence report favoured common knowledge between HCPs on patients' medication self-management. Based on the adherence report, HCPs could reinforce, in their own consultations with the patient, the medication adherence strategies that have been agreed.

Second, to promote the study among patients with diabetes, new posters and flyers (Appendix 4) presenting the PANDIA-IRIS study were posted in the different waiting rooms in the medical departments. To promote the study outside of the hospital site, flyers have also been posted at the headquarters of *Diabète Vaud*, an association of diabetic patients in the canton of Vaud. Moreover, the PANDIA-IRIS study was presented to HCPs in the departments after each biannual rotation of new interns. The meetings took part in collaboration with other researchers recruiting smokers with type 2 diabetes as part of the Diabetes and Smoking Cessation: a Gender-Oriented (DISCGO) study[238]. The screening of eligible patients for both the PANDIA-IRIS and the DISCGO studies was shared between the research teams. Ultimately, the updated process for patient recruitment and inclusion was regularly communicated to the pharmacy team during dedicated meetings. The strategies to include patients in clinical trials

were also discussed between HCPs and researchers as part of the monthly research meeting of *Unisanté* (Table 2).

Table 2: Presentations of the PANDIA-IRIS study in each department

NB: the medical policlinic of Unisanté is composed of four groups of GPs (blue, orange, green and red groups).

Medical Departments	Dates of the presentations
Service of Endocrinology, Diabetes and Metabolism	In 2019: February 7th, September 26th
Service of Nephrology and Hypertension	March 19, 2019
Medical policlinic of *Unisanté*	In 2019: January 24th (blue group), June 11th*, June 24th (orange group), June 25th (green group), July 18th (blue group), December 5th (blue group), December 9th (orange group), December 10th (green group) In 2020: February 7th (red group), July 23rd (blue group)
Community pharmacy of *Unisanté*	In 2019: February 14th, May 9th, July 11th, September 12th, November 28th In 2020: February 27th, July 30th, October 22nd In 2021: February 25th
Research Department of *Unisanté*	November 5, 2019

*Presentation of the PANDIA-IRIS study during a weekly general meeting for collaborators at *Unisanté,* attended by most HCPs.

Third, the collaboration developed as part of the OpTAT study with the CHUV Data Science Research team to screen eligible patients through algorithms in electronic medical records was extended to allow the screening of eligible patients for the PANDIA-IRIS study as well. This strategy allowed screening new eligible patients not previously listed in the databases built by the research nurse.

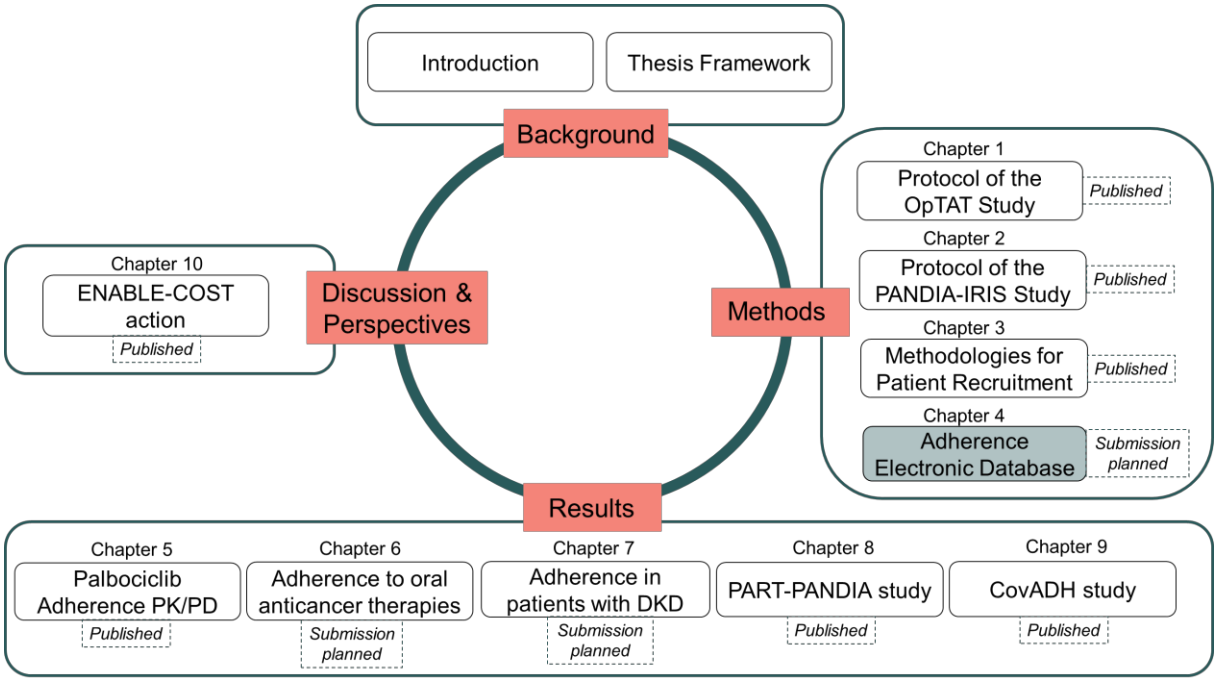
Forth, from June to September 2019, the screening of eligible patients was extended to the emergency departments of the CHUV, thanks to a collaboration built with the DISCGO research team. Each day, two study nurses screened the eligible patients registered in the

emergency departments and informed the research teams. Even if this strategy allowed introducing the study to 35 additional eligible patients, this process did not succeed in including any single patient to the PANDIA-IRIS study. For example, 14/35 were excluded because they were unavailable at recruitment time (e.g., they were receiving care or were isolated from any contact because of a transmissible infection). Based on these inconclusive results and due to the important workload and the time spent on this specific recruitment, the investigators decided to stop the recruitment in the emergency departments in September 2019, i.e., after more than two months of collaboration. Nevertheless, this unsuccessful recruitment process allowed us to understand that the pre-existing trust between the patient, his/her physician and the investigator plays an important role in the patient's decision to participate. Indeed, most of the patients the investigator met at the emergency departments were not followed at the CHUV and the PANDIA-IRIS study was unknown by their usual HCPs. On the contrary, this relationship between the patient, the HCPs and the investigator was strong and valorised during the ongoing recruitment at the Service of Nephrology and Hypertension, the Service of Endocrinology, Diabetes and Metabolism and at the medical policlinic of *Unisanté* (i.e., the investigator and the HCP met the patient shortly together before the investigator introduced the study in-depth to the patient).

Fifth, to increase the sample size and to optimize the recruitment process, an amendment of the PANDIA-IRIS study protocol was submitted to the local ethics committee. The amendment was accepted, and allowed to extend the eligibility criteria to patients with type 1, cortico-induced diabetes or LADA with nephropathy. In addition, patients with type 2 diabetes who had an eGFR >60mL/min/1.73m^2 that had declined rapidly over time (≥5ml/min/year) or who were hospitalized at least twice in the last five years for acute renal failures were eligible to participate[237]. Moreover, after the screening of potential eligible patients, the investigator was authorized to have access to their medical records to check the eligibility criteria before introducing the study to the patients, thereby avoiding unnecessary study presentation to patients who would be excluded afterwards.

Finally, based on the collaboration previously established as part of the OpTAT study with health insurances, patients with a specific medical insurance contract preventing them from obtaining their medications from other pharmacies than those listed in their contract were allowed to participate.

CHAPTER 4: PREPARATION AND ANALYSIS OF ADHERENCE ELECTRONIC MONITORING DATABASE



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

In the last 20 years, digital technologies —such as mobile-phone applications, electronic monitors (EM), ingestible sensors, weekly electronic pillboxes, blister pack technologies, electronic patient self-report diary or insurance claim database[239]— have been increasingly used to measure real-time components of adherence (i.e., initiation, implementation, persistence[37]). However, we currently lack guidance on the methodology to collect, manage, clean and analyze adherence electronic monitoring database.

Chapter 4 presents the methodology developed and used in the OpTAT, PANDIA-IRIS, and CovADH studies to: i) clean and enrich EM adherence data using the CleanADHdata.R script developed in close collaboration with a statistician from the *Département Epidémiologie et Systèmes de Santé* (DESS) at *Unisanté*, and ii) perform the statistical analysis to provide adherence outcomes based on a clean longitudinal EM adherence database.

1. The CleanADHdata.R Script

A tutorial was developed to guide users of the open-source CleanADHdata.R script and the manuscript will be submitted in the first trimester of 2023. We presented the script at the ESPACOMP Adherence Data Analysis workshops in 2021 and 2022, and as a virtual poster presentation during the annual ESPACOMP congress in 2021 (online congress)[240].

A semi-automated procedure to clean electronic adherence monitoring data: a tutorial to use the R script CleanADHdata.R

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I. Abstract

Patient adherence to medications can be assessed by digital technology such as electronic monitors (EM). However, changes in the treatment regimen and deviations from EM use over time must be characterized to establish the real level of medication adherence. The computer script CleanADHdata.R was developed to clean raw EM adherence data. This tutorial aimed at guiding future users of the script. In addition to raw EM data (date and time of each pill-bottle opening), we collected adherence start & stop monitoring dates, we identified the prescribed regimens, the expected number of EM openings per day based on the prescribed regimen, EM use deviations, and patients' demographic data. The CleanADHdata.R script (https://github.com/jpasquier/CleanADHdata) formats the data longitudinally and calculates medication implementation at each day. We provided a simulated dataset for 10 patients, for which 15 different EMs were used during a median period of 187 days (IQR 135-342). Median patient implementation before and after EM raw data cleaning using CleanADHdata.R was respectively 83.3% (IQR 71.5-93.9) and 97.3% (IQR 95.8-97.6), Δ+14%. This difference is important enough to consider EM data cleaning, to avoid data misinterpretation and to provide a cleaned dataset for the analysis of adherence in terms of implementation and persistence, whenever necessary. The development of a semi-automated procedure increases standardization and reproducibility.

Keywords: medication adherence, digital technology, digital pharmacy, electronic adherence monitoring, data management, data cleaning, research methodology, algorithms

II. Introduction

Patient adherence to medication may be suboptimal, as it is estimated that only 50-70% of patients take their medications regularly as prescribed[1]. Medication nonadherence leads to poor clinical outcomes[1-3], additional hospitalizations[4] and increased healthcare costs[1]. Medication adherence is defined by the extent to which a patient takes the medication as prescribed by the provider, ideally based on a shared decision-making process. It is characterized by the initiation (i.e., the patient takes the first dose), the implementation (i.e., the extent to which the patient takes the prescribed regimen according to the recommended dose, timing and regimen) and the discontinuation (i.e., the patient stops taking the treatment earlier than planned by/with the prescriber)[5]. Persistence to treatment is characterized by the time elapsed between initiation and discontinuation.

Medication adherence can be assessed through measurement methods that are subjective (i.e., patient self-report questionnaires) or objective (i.e., medication refill, interactive digital technology such as electronic monitoring (EM))[6, 7].

EM has been considered as one of the gold standards to measure medication implementation[8, 9]. As example of EM, the MEMS (Medication Event Monitoring System, MEMS and MEMS AS, AARDEX Group, Sion, Switzerland) is a pill-bottle with a chip located in the EM cap, registering the date and time of each EM opening; each opening is considered as a proxy of the date and time of each consecutive medication intake. A MEMS pill-bottle contains a medication and a patient can use one or several MEMS at a time. Despite the advantages of using the EM (i.e., provides longitudinal patterns of adherence over time, allows giving an electronic adherence feedback to the patient in interventions aiming at improving adherence[10]), some methodological challenges are to be considered when analysing EM data. Indeed, the EM can be misused (i.e., the patient can open the EM without swallowing the drug, known as “curiosity checks”, the patient can take the drug without opening the EM, known as “pocket doses”), or the patient may not use the EM during specific periods (e.g., during holidays or hospitalizations). In addition, the patient’s treatment regimen can be modified during the monitoring period, such as change of dose or regimen; temporary interruptions of the treatment and alternative medication may be prescribed [11]. If these events are not rigorously collected and reported in EM raw datasets before analysis, patients’ actual level of adherence tends to be underestimated[12]. Thus, data cleaning improves the accuracy of the EM raw dataset before analysis and decreases data misinterpretation.

In the past decade, the quality of adherence data analysis has increased thanks to guidelines on operational adherence definitions[13], advanced statistical analysis[14, 15] and semi-automated procedures to analyse adherence healthcare database (e.g., the Adhere-R package[16]). However, to date, the research community lacks guidance on the methodology

for managing and cleaning EM adherence datasets, whereas it is known that heterogeneous data management impacts adherence outcomes[17].

Some authors attempted to provide guidelines to manually clean EM adherence dataset, as inserting pocket-doses , deleting excessive EM openings and censoring the EM data in periods during which the patient did not use the EM [17-19]. Rotzinger et al. presented a step-by-step procedure to clean manually EM adherence datasets based on pill-count data when available, and proposed to manually add pocket-doses and non-monitored periods if they were validated[20]. However, manual EM data cleaning is prone to errors and lack of reliability, and is time consuming. To date, no semi- nor automated procedure exists in the literature to rigorously clean EM adherence datasets.

We developed a script in the statistical software R® (The R Foundation for Statistical Computing)[12], named CleanADHdata.R, to clean and enrich EM raw datasets before implementation and persistence analysis by using the EM raw data from the 130 patients included in the Optimizing Targeted Anticancer Therapies (OpTAT) study[21]. This tutorial aims at guiding future users of the script.

III. Methods

1. Ethical considerations

To develop the R script, we used the EM adherence dataset of patients included in OpTAT, treated with oral anticancer therapies (OAT) –cyclic or continuous regimen- for solid cancers[21]. The OpTAT study was approved by the local ethics committee in 2015 (ID 65/15). Prospective data collection lasted until May 2022.

2. EM raw data extraction in the required format to use CleanADHdata.R

In order to prepare the EM adherence dataset for cleaning and enrichment, patients EM raw data are extracted using the dedicated software (e.g., the MedAmigo^{TM} software, MEMS and MEMS AARDEX, Switzerland) into a text (CSV) or Excel® file. Three columns entitled “PatientCode”, “Monitor” and “Date” are to be indicated in the first row in the required format to be read by the CleanADHdata.R R script. Data in columns PatientCode and Monitor must be in an alphanumeric format and the data in column Date must be in a proper datetime format or a well formated date character string. The filenames of patients’ EM raw data have to contain the “eventslist” character string and the files are to be registered all together in the same file folder. The “dailyadherence” format (i.e., adherence score at each day) is accepted, but an additional column entitled “RecordedOpenings” needs to be added.

To allow users practicing using the script, we provide blurred EM raw dataset for 10 patients, available online at https://github.com/jpasquier/CleanADHdata.

3. Choosing the relevant variables to collect for cleaning and enriching EM raw data

The level of accuracy of EM data cleaning and enrichment must be adapted to the sample size of each study, to its design and to the treatment monitored. It may not be relevant to insert pocket-doses if their occurrence represents less than 5% of all doses of a monitored period or if the sample size is very large, i.e. >500 patients (estimation), as their impact on the adherence outcomes is limited.

Investigators need to choose in advance which relevant variables to collect to clean and enrich the EM dataset (e.g., regimen changes, hospitalization dates, periods of EM non-use, pocket-dosing) depending on the operational definition of adherence[13], the planned statistical analysis and the information sources available (e.g., patient-reported outcomes/experiences, medical, pharmaceutical, administrative databases). Whenever possible, 2 different sources should be consulted to confirm medication regimen and obtain the best possible medication history[22]. In case of discordant information between the different sources, the investigators have to establish a procedure and document the information in a reproducible and reliable way.

In the OpTAT study, the variables chosen to be collected were the dates of treatment interruptions due to side effects and toxicity as well as hospitalization dates. We also collected the side effects and their grade at each medical visit, the changes in the OAT regimen and doses[8, 14], and the discrepancies in EM use reported by patients (e.g., periods of EM non-use during holidays, non-monitored periods in case of hospitalization or when the patient did not use the EM for any documented reason, or taking pocket-doses[13].
A “Timing pocket-dosing” is defined when the patient took one or several doses out of the EM in advance to be swallowed later on the same day (i.e., day x). Timing pocket-dosing only matters if timing adherence is considered in the analysis. When one or several doses are prepared in advance to be taken on the day after (i.e., day x+1, 24 hours later), we consider the days without any EM openings as a period of EM non-use, e.g., a non-monitored period. The extra-EM openings (e.g., by a physician, a pharmacist or by the patient to check the number of pills left) could also be reported whenever necessary. In order to inserted pocket-doses, delete extra-EM openings or set a non-monitored period, the EM deviations must be carefully documented and reported by the patient before showing him/her the electronic monitoring adherence feedback and must be validated by pill-count.

4. Gathering the relevant variables into a predefined Excel® file format

The collected variables described above have to be gathered into an Excel® file -called "AuxiliaryData" using a predefined format. This Excel® file is composed of seven different sheets: **EMInfo** and **Regimen** are sheets to be filled for running the script (Table 1) while **PatientCovariables, EMCovariables, AddedOpenings, NonMonitoredPeriods** and **AdverseEvents** are optional sheets (Table 2).

In each sheet, the first row contains the predefined variable names (e.g., PatientCode, Monitor, ExpectedOpenings) (Tables 1 and 2). Except for the sheets PatientCovariables and EMCovariables, if other variables are inserted, they will be ignored by the R script (e.g., columns "comment" can be added in the different sheets to help the investigator during data preparation in the AuxliliaryData file).

An example of an "AuxiliaryData" Excel® file is available online at https://github.com/jpasquier/CleanADHdata; the variables inserted will allow cleaning and enriching the blurred EMs raw dataset.

Table 1: Description of the mandatory sheets to be filled in the AuxiliaryData Excel® file

	Mandatory variables in the Excel® sheet, each of them filled in separated sheets	
Sheets	**EMInfo**	**Regimen**
Description of each variable as a header of a row to be filled in the required format	**PatientCode** is the identifier of the patient. **Monitor** is the identifier of each EM used by the patient (one EM per line). **StartDate**: for each EM, start date of use. **EndDate**: for each EM, end date of use.	**PatientCode** is the identifier of the patient. **Monitor** is the identifier of each EM used by the patient (one EM per line). **ExpectedOpenings** (non-negative integer) is the number of expected EM opening(s) per day based on prescribed treatment regimen in the period of time specified between StartDate and EndDate. For each regimen change, a new line is created, associated with the period of time for which the regimen applies. **StartDate**: start date of the period for which the number of daily expected opening applies **EndDate**: end date of the period for which the number of daily expected opening applies **On** (positive integer): in case of a cyclic regimen, number of days during the ON phase during which at least one EM opening is to be expected. This variable is to be left empty in case of a continuous regimen. **Off** (positive integer): in case of a cyclic regimen, number of days during the OFF phase in which the treatment is paused. This variable is to be left empty in case of a continuous regimen.
Comments	The cleaned dataset is truncated by the start and end date of each EM use.	On and Off variables: the cycle begins with the number of expected opening(s) during the consecutive days of the On variable and is followed by 0 expected opening during the number of days of the Off variable. If both columns “On” and “Off” are empty, the R script will consider a continuous daily regimen. If only one of the two On or Off variables is filled, the R script will indicate an error.

Table 2: Description of the optional tables to be filled in the AuxiliaryData file Excel® file

Optional variables in the Excel® sheet					
Sheets	**PatientCovariables**	**EMCovariables**	**AddedOpenings**	**NonMonitoredPeriods**	**AdverseEvents**
Description of each variable as a header of a row to be filled in the required format	**PatientCode** is the identifier of the patient. **Start date** is the start of a period for which a patient covariable applies (e.g. the patient was included in several phases in a study) **End date** is the end of a period for which a patient covariable applies.	**PatientCode** is the identifier of the patient. **Monitor** is the identifier of each EM used by the patient (one EM per line) **Start date** is the start of a period for which a EM covariable applies **End date** is the end of a period for which a EM covariable applies.	**PatientCode** is the identifier of the patient. **Monitor** is the identifier of the EM for which an added or deleted opening is to be inserted at a specific date (one EM per line) **Date** is the date during the monitoring on which a specific number of EM opening (indicated in AddedOpenings variable) is to be added **AddedOpenings** (positive or negative number integer) is the number of EM opening(s) that need to be added (+x), e.g. in case of a pocket-dose, or deleted (-x), e.g., in case of an extra EM opening without	**PatientCode** is the identifier of the patient. **Monitor** is the identifier of the EM for which a non-monitored period was reported (one EM per line) **StartDate** is the start of a period during which the EM was not used but treatment was taken (e.g., in case of hospitalization or holidays, with clear documentation) **EndDate** is the end of a period during which the EM was not used but treatment was taken.	**PatientCode** is the identifier of the patient. **Date** is the date on which the adverse event was reported. **AdverseEvent** (any character string) is the description of the adverse event. **AdverseEventGrade** (any character string) is the grade of the adverse event, representing the severity of the adverse event (e.g., grade 1=adverse

			intake, on the specific date indicated in the variable Date.		effect bearable, grade 4=high toxicity).
Comments	Any relevant patient co-variable can be inserted by adding as many extra columns as needed (e.g., presence of treatment discontinuation, randomization group, gender, age, phase of a study)	Any relevant EM co-variable can be inserted by adding as many extra columns as needed (e.g., international non-proprietary name of the drug monitored, dose, number of tablet(s) to be taken per EM opening)	This sheet allows amending the EM dataset based on patients' EM use. To be noted, the number of pocket-doses reported by the patients can be checked with pill count (i.e., the difference between the number of pills delivered and returned between two consecutive pharmacy visits).	The implementation component of adherence is not calculated during non-monitored periods and data are considered as missing during the analysis.	In this sheet, the adverse effect is added at a specific date. In case of several EM and drugs, the adverse effects are applied to the date of each EM, as it is assumed that the investigator cannot determine the causality between a drug and an adverse event.

5. Using the R script

Once the raw data has been extracted and the AuxiliaryData Excel sheet has been completed, the CleanADHdata.R script can be run. The R script is available online at https://github.com/jpasquier/CleanADHdata.

When the script is run in the statistical software R, a window allows selecting the AuxiliaryData Excel file. Once the latter has been selected, a second window opens up to select the folder that contains the EM raw data. After the end of processing, the R script generates the cleaned and enriched EM dataset, called “implementation.xlsx”, with 2 log files located in the same file folder as the AuxiliaryData Excel sheet.

The log file entitles “errors” will show critical errors that affect implementation calculation and will lead to a wrong implementation calculation (e.g., dates inserted with the wrong format or missing data in the AuxiliaryData Excel® sheet). The log file entitled “warnings” indicates certain inconsistencies in the Auxiliary data file. They do not necessarily imply a miscalculation of the implementation but should be reviewed by the investigator (e.g., no data was found for a patient who appears in the Auxiliary Data file). Based on the errors and warnings listed, the investigator can correct the content of the Auxiliary Data file or the EM raw data file. After all errors and warnings are resolved, the cleaned and enriched EM dataset presented in “implementation.xlsx” is ready for analysis.

The implementation file is divided into 4 sheets: by monitor, by patient, summary by monitor and summary by patient. See https://github.com/jpasquier/CleanADHdata for the presentation of the cleaned and enriched EM dataset (i.e., the implementation.xlsx file) obtained after using CleanADHdata.R. The codebook of this Excel® implementation file is provided in Appendix 1.

6. Operational definition of implementation

The operational calculation for medication implementation can be found in the section “implementation calculation” in the script CleanADHdata.R.

In the first sheet by monitor, the medication implementation for the monitor is considered optimal (=1) at each day if the number of corrected EM openings is at least equal to the number of expected EM openings. Implementation is suboptimal (=0) otherwise. In case of a non-monitored period at a day x, implementation is not calculated at this day x (i.e., depicted with an empty cell), as recommended in the literature(9).

In the second sheet by patient, the medication implementation for the patient is calculated at each day by the product of the implementation outcome of each patient’s EM. In case of a suboptimal implementation (=0) at a given day x for at least one EM monitored, the patient implementation at that day x will be suboptimal (=0). In case of a non-monitored period at a

given day x for at least one EM monitored, the patient implementation at that day x will not be calculated and will be considered as a non-monitored day (i.e., depicted with an empty cell).

In the third and fourth sheets, medication implementation is presented as a summary by monitor and a summary by patient. In the summary by monitor, the implementation rate is calculated based on the number of days with an optimal implementation (=1) for the EM over the number of monitored days for each EM (i.e., non-monitored periods are excluded). In the summary by patient, the implementation rate is calculated based on the number of days with an optimal implementation for all EM used by the patient (=1) over the number of monitored days (i.e., non-monitored periods are excluded).

IV. Results

We used CleanADHdata.R to clean the blurred EM raw data of 10 patients according to variables collected in the AuxiliaryData file to obtain the cleaned and enriched EM dataset entitled “implementation.xlsx” available online.

The EM raw data of 10 patients included in OpTAT were blurred as follows: i) the implementation.xlsx file presenting longidata was scrambled with an R-script (i.e., age, gender, side effects, length of monitoring periods and implementation outcomes were mixed up), providing implementation2.xlsx; ii) an AuxiliaryData file was built based on implementation2.xlsx and variables were randomly modified (e.g., periods of monitoring, date of EM openings, number of added openings, added or deleted non-monitored periods, change of regimen, added or deleted side effects, identification of patients and EM were blurred); iii) based on this Auxiliary data file, the CleanADHdata.R script was run to provide the new implementation3.xlsx. The EM raw data were built based on implementation3.xlsx.

Patients’ characteristics have been inserted in the PatientCovariables sheet of the AuxiliaryData file: median age was 63 years (IQR 50-68), 4/10 (40%) patients were women and 1/10 (10%) patient discontinued the treatment.
The OAT International Nonproprietary Names and the type of the regimen (i.e., continuous or cyclic) were introduced in the EMCovariables sheet. Eight different OAT (i.e., pazopanib, trametinib, dabrafenib, palbociclib, everolimus, alectinib, imatinib and erlotinib) were prescribed. Among them, palbociclib is prescribed with a cyclic regimen scheme (i.e., 21 days on treatment followed by a treatment interruption of 7 days) and imatinib was prescribed with an alternate off-label cyclic regimen (i.e., two different imatinib dosage strengths delivered in two EM are prescribed alternatively, one day over two). Patient B, C, H, I and J used 2 EMs. In total, 15 different EMs were used, during a median period of 187 days (IQR 135-342). Fatigue was the most commonly reported adverse event, mostly reported as grade 1.
Median patient implementation using the blurred EM raw dataset before and after cleaning

with CleanADHdata.R was respectively 83.3% (IQR 71.5-93.9) and 97.3% (IQR 95.8-97.6), Δ+14%. In the clean dataset, the summary of implementation by monitor shows that implementation was <90% for 1/15 (6.6%) EM monitored and 1/10 (10%) patient had an implementation <90% over the monitored period.

V. Discussion

Main results

This tutorial presents a semi-automated procedure to clean and enrich raw EM adherence data by using the CleanADHdata.R script, to provide a dataset ready for analysis along with a first overview of implementation results at both the EM and the patient levels. First, EM raw data are extracted in a predefined format. Then, an Excel® sheet is filled in the predefined format to clean and enrich the EM dataset with the following mandatory variables: start and end dates of each EM used by each patient and the expected number of daily EM openings during the monitored periods. Then, the investigators need to define relevant variables that will allow cleaning and enriching the EM dataset according to study aims and procedures. These variables are collected upon several reliable sources and are inserted in the optional Excel® sheet in the predefined required format. The R script will use both raw data and the Excel® sheet completed with the variables to provide the cleaned and enriched EM dataset, entitled “implementation.xlsx” longidata file. By using blurred EM raw data, we showed that the difference of absolute implementation (Δ+14%) between the raw and the cleaned EM dataset is important enough to consider a systematic EM data cleaning in all studies that plan monitoring adherence with EM to avoid data misinterpretation.

Future developments of a R script to analyse EM data

The use of automated procedures to prepare and analyze large datasets is increasingly being promoted and accessible to the research community, particularly through the interdisciplinary collaborations of healthcare researchers, statisticians and computer scientists. Following EM adherence data cleaning, our team aims at developing an R script to increase the standardization of EM data analysis. Based on the cleaned adherence dataset, the future R script will allow using Kaplan-Meier curves for persistence analysis and generalized estimated equation (GEE) model for the analysis of implementation and adherence. Indeed, the possibilities of analyzing adherence in presence of censoring times to avoid biased results have been recently developed and will be included in the future script[14].

Strengths, challenges and limitations

Using CleanADHdata.R allows researchers to achieve reliable and repeatable EM raw data cleaning. Standardizing and describing the procedures for EM dataset preparation are

necessary in adherence research to allow investigators comparing results provided on a homogeneous method across studies. The script CleanADHdata.R, available online, can be adapted according to study aims and designs (e.g., the calculation of treatment implementation can be revised in the dedicated coding section). Moreover, by providing blurred datasets, we allow users to practice with CleanADHdata.R. Users can then improve the script by giving feedback directly on the GitHub platform, so that the script can be updated upon needs.

A challenge is to be considered when using CleanADHdata.R. Indeed, the investigator needs to carefully fill the variables in the Excel® sheet in the predefined format, which requires time and resources. We would then recommend collecting those data and fill the Excel® sheet progressively at each patient interview, at each new prescription and notification in the medical record. Defining patient's daily expected EM openings based on the drug regimen information from several sources (e.g., the providers, patient and carers, electronic medical and pharmaceutical files) can be challenging, as discrepancies can occur across sources. The investigator needs to define the most reliable information to collect according to the definition of medication adherence components. In order to allow consistency across adherence studies, these decisions need to be documented and clearly depicted in the methodology of the publications.

Our blurred dataset provides EM data for a limited number of 10 patients, which is a small sample size that only allows providing an estimation of the difference between implementation according to a raw and clean datasets. However, when using real EM data from 58 EM used by 40 patients included in the OpTAT study, confirms a significant difference of implementation using the raw and clean datasets (respectively 69% versus 92%, +Δ 23%)[23]. More studies with larger sample sizes should explore the difference of implementation outcomes between raw and clean datasets.

VI. Conclusions

The development of a semi-automated procedure to clean and enrich electronic monitoring adherence dataset saves time, decreases data handling errors and increases reproducibility. Investigators and statisticians worked together to develop the CleanADHdata.R script and described its use in this tutorial to guide future users. Consistent use of this script across research teams will increase the quality and the standardization of EM dataset management as well as the comparability of results across studies monitoring medication adherence with EM.

Supplementary materials

Appendix 1: Codebook of the cleaned EM dataset "implementation.xlsx"

By monitor
PatientCode: patient identification **Monitor** : identification of the EM used by the patient **Date**: date during the monitored period **RecordedOpenings**: number of recorded EM opening(s) at each date, not corrected **AddedOpenings**: number of EM openings added (+x) or deleted (-x) for each day **CorrectedOpenings**: corrected number of EM openings according to the compilation of RecordedOpenings with the number of added or deleted EM openings –indicated in the variable "AddedOpenings" **ExpectedOpenings:** number of EM expected openings at each date according to the drug regimen **NonMonitored:** non-monitored periods are indicated by "TRUE" at each date they occurred. **Implementation**: patient treatment implementation at each date for the considered EM. **RelativeDate**: count of monitored days from the first to the last day of the monitoring period for each EM used. **AdverseEvents**: adverse events reported at each day, separated by a comma. The corresponding grade for each adverse effect is added into brackets. The next variables presented are the EM covariables from the AuxiliaryData file.
By patient
PatientCode: patient identification **Date**: date during the monitored period **MonitorsNb** : for each date, the number of EM for which data are collected to calculate patient implementation **Implementation**: patient treatment implementation based on implementation for all EM used by the patient.

RelativeDate: count of monitored days from the day of the first EM used to the last day of the last EM used. **AdverseEvents**: adverse events reported at each day, separated by a comma. The corresponding grade for each adverse effect is added into brackets. The next variables presented are the patient covariables from the AuxiliaryData file.
Summary by monitor
PatientCode: patient identification **Monitor**: identification of the EM used by the patient **Implementation**: the implementation rate is calculated based on the number of days with an optimal implementation (=1) for the EM over the number of monitored days for each EM (i.e., non-monitored periods are excluded).
Summary by patient
PatientCode: patient identification **Implementation**: the implementation rate is calculated based on the number of days with an optimal implementation for all EM used by the patient (=1) over the number of monitored days (i.e., non-monitored periods are excluded).

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Author Contributions

JP developed the CleanADHData.R script according to feedback regarding EM adherence data monitoring and analysis from CB. Conceptualization, CB, JP, MPS ; Methodology, CB, JP, MPS and IL; Software, JP; Validation, CB, JP, MPS; Formal Analysis, CB, JP;

Investigation, CB, JP, MPS, IL; Writing – Original Draft Preparation, CB and JP; Writing – Review & Editing, MPS and IL; Visualization JP; Project Administration, CB, JP, MPS; Funding Acquisition, MPS

Institutional Review Board Statement

This tutorial has been built based on EM adherence data from the OpTAT study. The OpTAT study was approved by the local ethics committee (Vaud, Switzerland). This tutorial provides blurred datasets and does not contain any real patient information.

Informed Consent Statement

NA

Data Availability Statement

The CleanADHdata.R script and all blurred data are available at https://github.com/jpasquier/CleanADHdata.

Conflicts of interest

The authors have no conflicts of interest to declare.

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2. Statistical Analysis of Longitudinal Medication Adherence Data

For a decade, Dr Isabella Locatelli and Pr Marie P. Schneider have been developing the statistical analysis of medication implementation, persistence and adherence measured by electronic monitors (EM). The methodology has been published elsewhere[44, 241].

2.1. Implementation Analysis

Definition: Medication implementation is a component of medication adherence defined by Vrijens et al[37]. Medication implementation is defined by the extent to which the patient takes the medication as prescribed by the provider, i.e., the correspondence between the dosing history and the medical recommendation.

Outcome: The daily medication intake is characterized in each patient by a binary variable (correct intake =1; incorrect intake =0) at each day x of the monitoring period. This binary variable is defined by the concordance between the number of observed EM daily opening(s) (i.e., patients' medication intake monitored by EM) and the number of expected EM daily opening(s) (i.e., as established on the medical prescription). For instance, in case of one dose prescribed in the morning and one dose in the evening, the number of daily expected EM openings will be 2.

- At each day x, if the number of observed EM opening(s) is equal or superior to the number of expected EM opening(s), the daily medication intake is considered correct and the outcome is "1" at that day x.
- At each day x, if the number of observed EM opening(s) is less than the number of expected EM opening(s), the daily medication intake is considered incorrect and the outcome is "0" at that day x.

To note, these definitions do not allow evaluating over-medication dosing intake, which is considered by the given definition as a correct medication intake. To differentiate an over-medication intake to an exact medication intake, the medication intake can be defined as correct if the number of observed EM opening(s) equals the number of expected EM opening(s).

Statistical analysis: Based on longitudinal medication intake outcomes (0/1), empirical implementation is defined by the proportion of patients with a correct medication intake (proportion of outcomes =1) at each day x of the monitoring period, among patients still participating in the study at that day x. This calculation allows an estimation of the probability of an optimal medication implementation at each day x.

Table 3 shows a simulated EM dataset for five patients included in a 14-day adherence study, as well as the calculation of the empirical implementation at each day of the monitoring period.

Table 3: Simulated EM dataset and calculation of the empirical implementation at each day of the monitoring period.

	Days													
Included patients	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Patient A	1	1	0	0	0	1	1	0	1	0	0	0	1	1
Patient B	1	1	1	0	1									
Patient C	0	1	1	1	1	1	1							
Patient D	1	0	1	0	1	1	1	1	1	1				
Patient E	0	0	1	1	1	0	1	1	1	0	1	0	1	
Empirical Implementation	0.60	0.60	0.80	0.40	0.80	0.75	1.00	0.66	1.00	0.33	0.50	0	1.00	1.00

Based on the daily medication intake outcomes (0/1), the generalized estimating equation (GEE) model allows an estimation of the trend of medication implementation over time, taking into account the interdependence of repeated measures for each patient. Fig. 10 shows empirical implementation (blue line), implementation modelled by GEE (black line) and its 95% confidence intervals (95%CI) (black dotted lines), and the number of participants over time (orange line) processed in the statistical software R version 4.0.2. To note, as the number of participants decreases over time, the variance increases in the empirical implementation as well as the 95%CI around the GEE model.

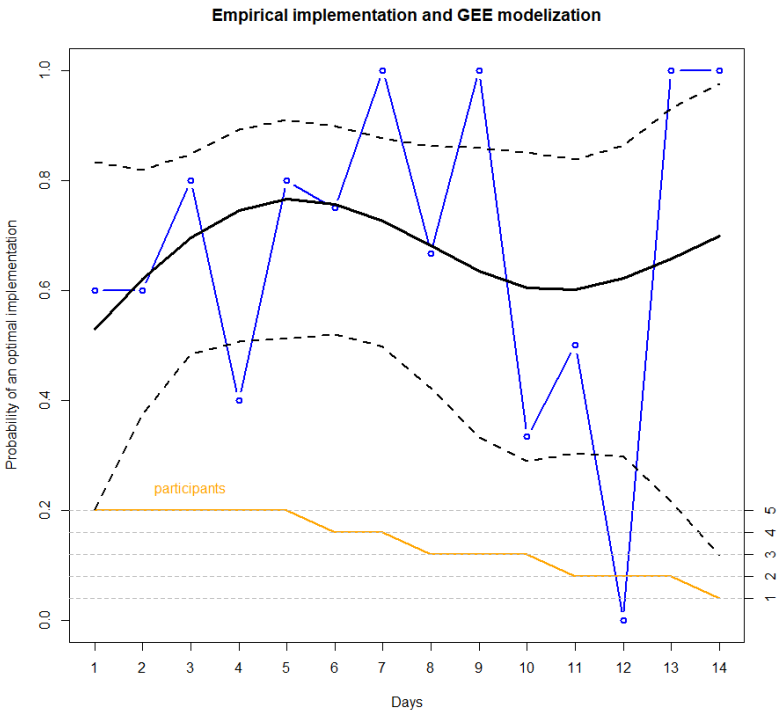


Figure 10: Empirical implementation and GEE model based on the simulated EM dataset ($n_{patients}$=5)

2.2. Persistence Analysis

Definition: Medication persistence is defined by the distribution of individual times until medication discontinuation. Thus, two components are characterized: i) the presence of an event, which is the discontinuation of the medication (i.e., when the patient takes the last dose of the medication earlier than prescribed) or the presence of censoring times (i.e., when a medication discontinuation did not occur during the monitoring period) and ii) the time between medication initiation and discontinuation.

Before starting the analysis, the investigator must clearly define the reasons for a medication discontinuation and censoring times. For instance, in the OpTAT study, we considered a discontinuation when patients prematurely stopped the medication because of the symptoms experienced due to adverse effects or for any other patients' personal reasons. Censoring times were considered in all other reasons for the medication premature stop (i.e., medication stop because of clinical reasons other than side effects) or in case of study interruption without medication discontinuation.

Outcome: In survival analysis, it is considered that the event (e.g., death of a patient, or in persistence analysis, the medication discontinuation; outcome=1) will occur in all patients over time. If the event is not observed during the monitoring period, the patient's EM data are censored (outcome=0). To note, the event is always considered from the day after it occurred (i.e., if a patient took the last dose of the medication because of side effects at day 7, the discontinuation is considered at day 8). In the analysis of persistence, each patient contributes

by the time (in days) between medication initiation and discontinuation and by the presence of discontinuation or censoring times (0, 1).

Statistical analysis: Kaplan-Meier survival analysis estimates the probability of medication persistence, taking into account the censored durations, at each day of the monitoring period.

The investigator has to complete the dataset to indicate the presence of a medication discontinuation or censoring time for each patient, based on the chosen definitions. In this dataset, we simulated that patient C and E decided to stop prematurely the medication because of side effects, which was characterized by a discontinuation. Based on the simulated EM adherence dataset, Table 4 shows, for each patient, the probability of medication persistence at each day of the monitoring period using the Kaplan-Meier estimator.

Table 4: Discontinuation, censoring times and probability of medication persistence in the simulated EM dataset.

NB: the empty red cells represent the day from which the medication discontinuation is considered.

	Days														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Discontinuation (1) Censoring times (0) ***
Patient A	1	1	0	0	0	1	1	0	1	0	0	0	1	1	0
Patient B	1	1	1	0	1										0
Patient C	0	1	1	1	1	1	1								1
Patient D	1	0	1	0	1	1	1	1	1	1					0
Patient E	0	0	1	1	1	0	1	1	1	0	1	0	1		1
Persistence	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.75	0.75	0.75	0.75	0.75	0.75	0.38	

*This information is provided by the investigator.

The Kaplan-Meier curve shows the probability of medication persistence during the monitoring period (Fig. 11). Jumps occur at the time points of a medication discontinuation. Censoring times are represented by the sticks on the line. The 95%CI around the probability of persistence are represented by the dotted green lines. The orange line represents the number of participants over time.

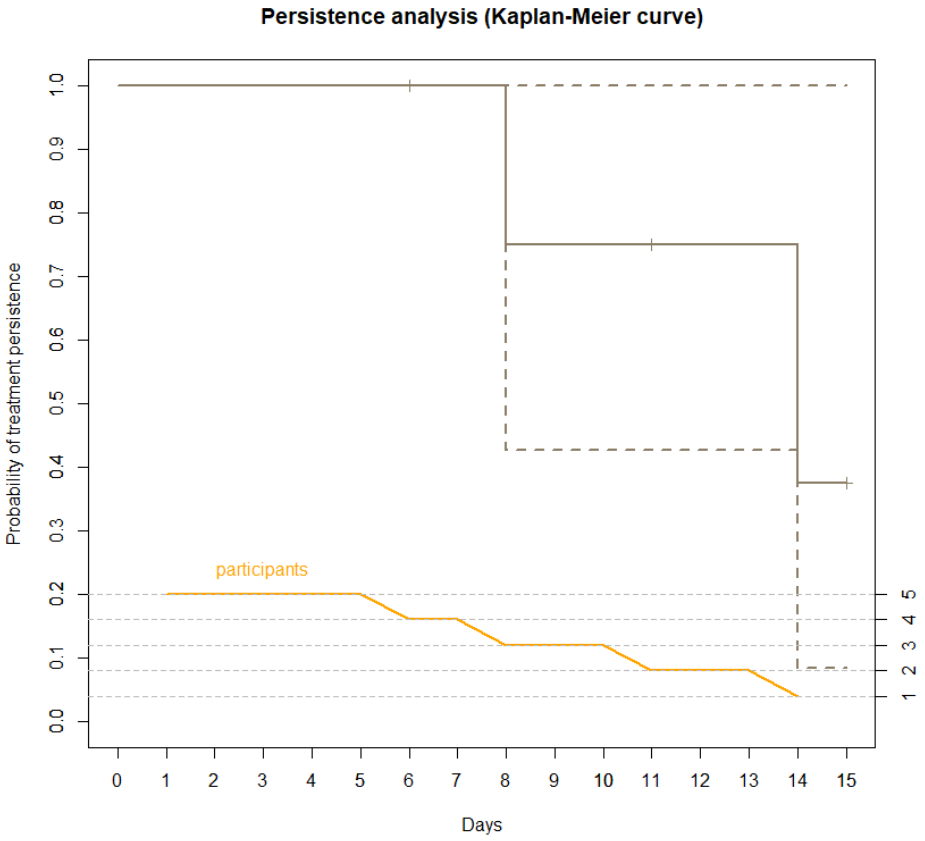


Figure 11: Kaplan-Meier curve showing the probability of medication persistence over time ($n_{patients}$=5)

2.3. Adherence Analysis

Definition: An optimal medication adherence is defined by the extent to which the patient has an optimal adherence regarding his/her medication, i.e., implements the medication optimally and is persistent in taking the medication.

Outcome: Empirical medication adherence is characterized by the proportion of patients with a correct medication intake (proportion of outcomes =1) at each day of the monitoring period, among all patients initially included in the study, i.e., including patients who discontinued the medication before that day. Empirical adherence corresponds to the product between the probability of medication implementation and the Kaplan Meier estimate of persistence at each day of the monitoring period.

Before proceeding to the longitudinal adherence analysis, the EM dataset needs to be completed until the end of the follow-up according to the presence of discontinuations or censoring times. In case of a censoring time at day x, medication implementation is not monitored anymore from that day, so the implementation outcome is missing, and the EM dataset is completed by "NA" from day $(x + 1)$ until the end of the monitoring period. In case

of a discontinuation at day x, it is considered that the medication implementation is suboptimal from that day and the EM dataset is completed by the value 0 from day $(x + 1)$ until the end of the monitoring period.

Statistical analysis: Based on the simulated EM adherence dataset, Table 5 shows both probabilities of medication implementation and persistence, and the probability of empirical adherence at each day of the monitoring period.

Table 5: Calculation of empirical adherence based on the probabilities of medication implementation and persistence

	Days														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Discontinuation (1) Censoring times (0)**
Patient A	1	1	0	0	0	1	1	0	1	0	0	0	1	1	0
Patient B	1	1	1	0	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	0
Patient C	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1
Patient D	1	0	1	0	1	1	1	1	1	1	NA	NA	NA	NA	0
Patient E	0	0	1	1	1	0	1	1	1	0	1	0	1	0	1
Empirical implementa-tion	0.60	0.60	0.80	0.40	0.80	0.75	1.00	0.66	1.00	0.33	0.50	0	1.00	1.00	
Persistence	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.75	0.75	0.75	0.75	0.75	0.75	0.38	
Empirical adherence	0.60	0.60	0.80	0.40	0.80	0.75	1.00	0.50	0.75	0.25	0.38	0	0.75	0.38	

The GEE model shows an estimation of the trend of medication adherence over time, based on the predefined methodology[241]. Figure 12 shows empirical adherence (red line), the GEE model (black line) and its 95%CI (black dotted lines) and the number of participants over time (orange line).

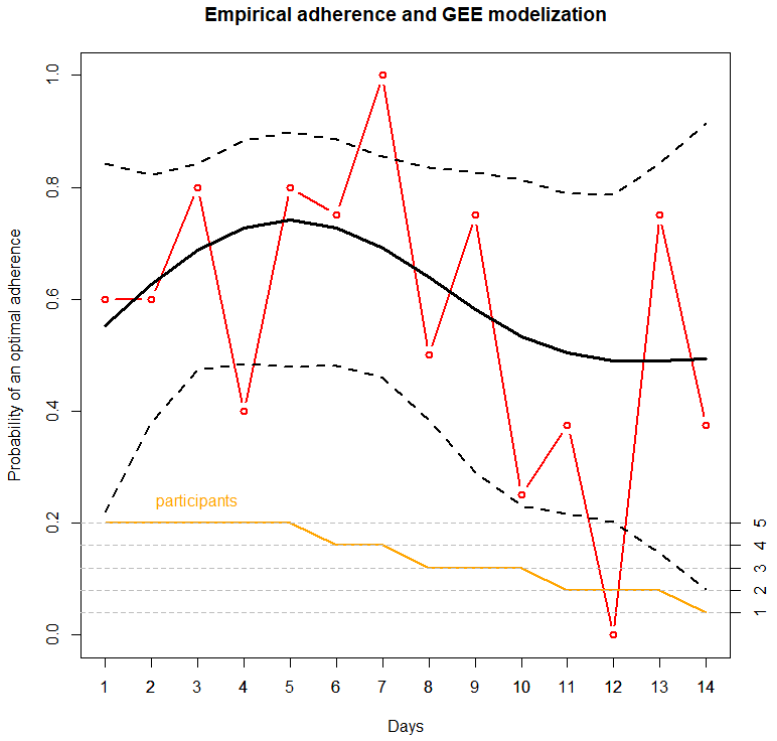
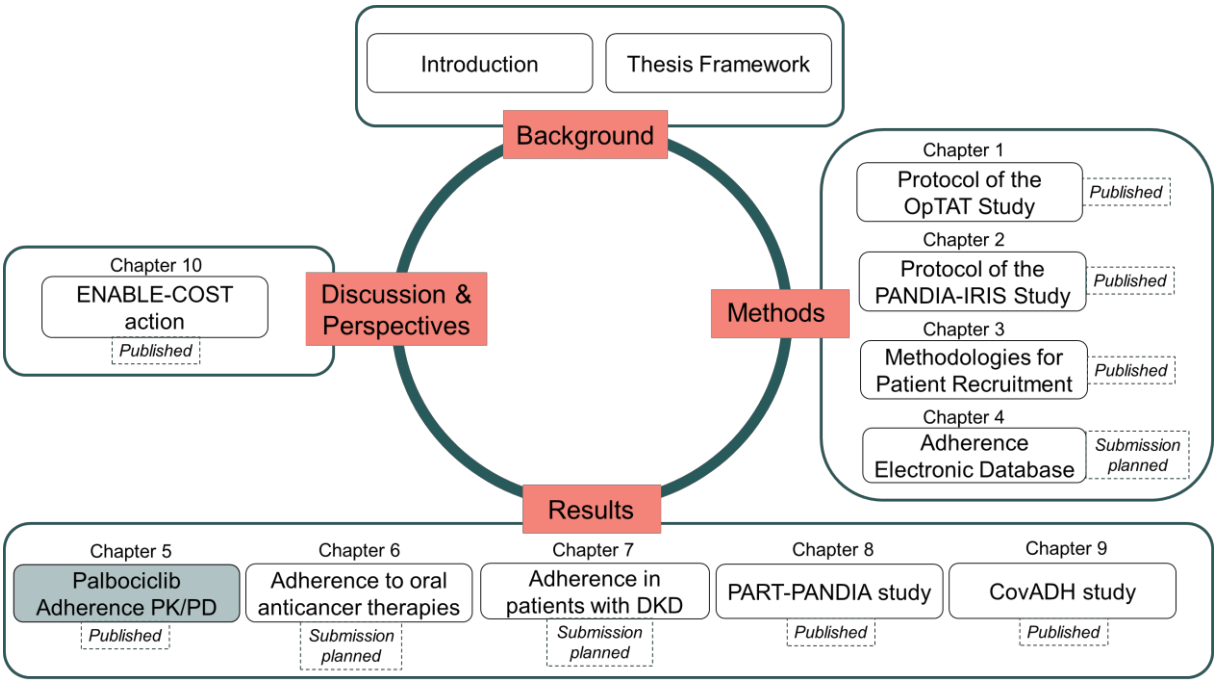


Figure 12: Empirical adherence and GEE model based on the simulated EM dataset ($n_{patients}$=5)

These definitions, outcomes and statistical analyses for medication implementation, persistence and adherence based on longitudinal EM adherence data were used in the OpTAT, PANDIA-IRIS and CovADH study.

CHAPTER 5: ADHERENCE TO PALBOCICLIB AND OMISSION OF DOSE MANAGEMENT AS PART OF THE OPTAT STUDY



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

Chapter 5 presents the article published in *MPDI Cancers*, which describes adherence to palbociclib, a cyclic cyclin-dependent kinase 4 and 6 inhibitor prescribed in advanced breast cancer, in a subgroup of patients included in the OpTAT study. This paper presents the impact of adherence on palbociclib pharmacokinetics (i.e., drug concentrations) and pharmacodynamics (i.e., neutrophil profiles). This study involved the School of Pharmaceutical Sciences (University of Geneva), the Center for Primary Care and Public Health *Unisanté*, the Precision Oncology Centre, the Department of Oncology, the Center for Research and Innovation in Clinical Pharmaceutical Sciences and the Service of Clinical Pharmacology from the Lausanne University Hospital (CHUV).

The results of this study were presented as an oral presentation at the annual ESPACOMP congress in November 2022 (Berlin, Germany)[242].

cancers

MDPI

Article

Adherence to the CDK 4/6 Inhibitor Palbociclib and Omission of Dose Management Supported by Pharmacometric Modelling as Part of the OpTAT Study

Carole Bandiera [1,2,3], Isabella Locatelli [3], Perrine Courlet [4,5], Evelina Cardoso [1,2,4], Khalil Zaman [6], Athina Stravodimou [6], Ana Dolcan [6], Apostolos Sarivalasis [6], Jean-Philippe Zurcher [6], Veronica Aedo-Lopez [6], Jennifer Dotta-Celio [3], Solange Peters [6], Monia Guidi [4,7], Anna Dorothea Wagner [6], Chantal Csajka [1,2,4] and Marie P. Schneider [1,2,*]

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Simple Summary: Medication adherence to CDK4/6 inhibitors such as palbociclib, prescribed as a cyclic oral anticancer therapy in women diagnosed with advanced breast cancer, may be suboptimal. We evaluated adherence to palbociclib and its impact on pharmacokinetic and pharmacodynamic (PK-PD) profiles. Patients included in the OpTAT study used an electronic monitor to register each drug intake event and were randomized into the intervention (i.e., interprofessional medication adherence program) or control group (i.e., usual care). Patients in the intervention group (n = 19) had a higher and more stable adherence than control patients (n = 19). The intervention had a larger effect on patients older than 65 and in patients with longer treatment and disease experience. The PK-PD analysis showed that catching up on a missed dose at the end of the cycle increases the risk of severe neutropenia in the next cycle. The interprofessional healthcare team should closely monitor patients' cycle management to improve prescriptions and decrease toxicity.

Abstract: The cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) palbociclib is administered orally and cyclically, causing medication adherence challenges. We evaluated components of adherence to palbociclib, its relationship with pharmacokinetics (PK), and drug-induced neutropenia. Patients with metastatic breast cancer (MBC) receiving palbociclib, delivered in electronic monitors (EM), were randomized 1:1 to an intervention and a control group. The intervention was a 12-month interprofessional medication adherence program (IMAP) along with monthly motivational interviews by a pharmacist. Implementation adherence was compared between groups using generalized estimating equation models, in which covariates were included. Model-based palbociclib PK and neutrophil profiles were simulated under real-life implementation scenarios: (1) optimal, (2) 2 doses omitted and caught up at cycle end. At 6 months, implementation was slightly higher and more stable in the intervention (n = 19) than in the control (n = 19) group, 99.2% and 97.3% (Δ1.95%, 95% CI 1.1–2.9%), respectively. The impact of the intervention was larger in patients diagnosed with MBC for >2 years (Δ3.6%, 95% CI 2.1–5.4%), patients who received >4 cycles before inclusion (Δ3.1%, 95% CI 1.7–4.8%) and patients >65 (Δ2.3%, 95% CI 0.8–3.6%). Simulations showed that 25% of patients had neutropenia grade ≥3 during the next cycle in scenario 1 versus 30% in scenario 2. Education and monitoring of patient CDK4/6i cycle management and adherence along with therapeutic drug monitoring can help clinicians improve prescription and decrease toxicity.

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Keywords: CDK4/6 inhibitor; palbociclib; neutropenia; medication adherence; electronic adherence monitoring; motivational interviewing; oral anticancer therapy; pharmacists; interprofessionality

1. Introduction

1.1. Background

With 2.3 million new cases and 685,000 deaths in 2020, breast cancer (BC) is the most frequently diagnosed cancer worldwide [1]. In Switzerland, 6300 female patients are diagnosed with BC, and 1400 die from this disease each year [2]. Despite an increased incidence in the last 30 years, mortality has decreased partly due to systemic therapies, including new therapeutic agents such as oral anticancer therapies (OAT) [3]. Although potentially more convenient for patients thanks to self-management [4], the absence of direct medical supervision raises concerns about medication adherence and adverse effect management [5]. Medication adherence is characterized by initiation (i.e., the patient takes the first dose), implementation (i.e., the extent to which a patient takes the medicine as prescribed) and discontinuation (i.e., the patient stops taking the treatment earlier than prescribed) [6]. Persistence of treatment refers to the time between initiation and discontinuation [6]. A recent systematic review showed that adherence to various OAT varies from 23% to almost 100% [7]. This wide range of estimation is mainly due to the variety of methods to measure medication adherence, from patient self-report to pill-count and electronic monitoring, which makes comparison of results difficult. It has been shown that suboptimal adherence influences measured drug plasma concentrations (i.e., pharmacokinetic (PK) profiles) and is significantly associated with poor clinical outcomes [8–10].

It is estimated that 30–60% of BC patients are nonadherent to endocrine therapies, which has a direct impact on their survival [11,12]. Resistance to endocrine therapies has led to the development of new therapeutic options, such as cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i). Palbociclib and ribociclib are two examples of this newer drug class. Approved in 2015, palbociclib became the most common new CDK4/6i prescribed in patients with endocrine-sensitive advanced or metastatic breast cancer (MBC) and human epidermal growth factor receptor 2-negative (HR+/HER2−) tumors, in combination with aromatase inhibitors, tamoxifen or fulvestrant [13,14]. The PALOMA-1/2/3 and Monaleesa-2/3/7 studies showed improved progression-free survival with palbociclib and ribociclib, respectively, prescribed in combination with endocrine therapies [15–20]. Palbociclib and ribociclib medication management is a challenge for patients and providers as these two drugs are administered in a cycle mode: once daily for 21 consecutive days (= ON phase) followed by 7 days of treatment break (= OFF phase) [14,21]. In addition, neutropenia is the most commonly reported adverse effect, resulting in frequent dose reductions and extension of OFF-treatment periods to avoid severe neutropenia [22,23].

In this context, we initiated the randomized controlled trial "Optimizing Targeted Anticancer Therapies" (OpTAT) at the Center for Primary Care and Public Health Unisanté and the Lausanne University Hospital (CHUV), Lausanne, Switzerland [24], to evaluate patient adherence to OAT and its relationship with PK and pharmacodynamics (PD).

1.2. Objectives

The first objective of this study was to evaluate and compare adherence to palbociclib, a cyclic CDK4/6i, with a special focus on implementation and 12-month persistence, in patients included in the intervention group versus those in the control group. The second objective was to simulate palbociclib PK and neutrophil profiles to describe the impact of adherence on drug concentrations and neutropenia.

1.3. Outcomes

The main outcome is medication implementation, described as a binary variable measured for each patient each day over time (1 = the observed number of electronic monitor

(EM) openings is exactly as expected; 0 = the number of observed EM openings diverges from the expected number of EM openings). Medication implementation is defined, at each day t, as the proportion of patients correctly taking the medication (proportion of outcome = 1) among patients still under observation that day.

1.4. Hypothesis

We hypothesized that patients included in the intervention group would implement and persist better on palbociclib and that suboptimal implementation would influence palbociclib PK (i.e., drug exposure) and the risk of neutropenia.

2. Methods

2.1. Ethical Considerations and Guidelines

The OpTAT study was approved by the local ethics committee (Vaud, Switzerland) in 2015 (ID 65/15) and was conducted in accordance with the Declaration of Helsinki principles. We reported findings following the ESPACOMP Medication Adherence Reporting Guideline (EMERGE) [25] and the Consolidated Standards of Reporting Trials (CONSORT) [26].

2.2. OpTAT Medication Adherence Study

2.2.1. Study Design and Participants' Enrolment

The protocol of the OpTAT study has been published elsewhere [24]. Briefly, the OpTAT study was divided into two parts: (1) an open 12-month one-centre 1:1 randomized controlled adherence study and (2) an OAT PK-PD relationship study.

Patients were eligible if they were adults with an OAT prescription for solid cancer. Patients were excluded from the adherence study if their treatment was not self-managed (e.g., home caregivers, medical care services or nursing homes, under tutelage) or if they were diagnosed with cognitive disorders. Patients could either participate in the medication adherence study, the PK-PD study or both by signing a specific informed consent form. In total, 130 patients were included in the medication adherence part of the OpTAT study. In this paper, we analysed a subgroup of MBC patients (n = 38) treated with palbociclib.

2.2.2. Procedures for the Medication Adherence Study

Patient randomization was stratified by cancer type and time since OAT initiation (i.e., more or less than 30 days). Patients were randomized after a baseline period of EM use of at least 21 days. The date of the randomization was determined based on the "per-protocol" statement, i.e., the date of the first intervention delivered. Indeed, because of the coronavirus disease COVID-19 pandemic, the first intervention did not always coincide with randomization and could happen some weeks later. Patients who left the study at any moment before randomization were considered control patients (i.e., they used the EM during baseline but did not receive any intervention).

Patients randomized to the intervention group attended the routine Interprofessional Medication Adherence Program (IMAP). It is a theory-based intervention (information-motivation-behavioural skills model of Fisher [27]) developed to support chronically ill patients with their medication management since 1995 at the community pharmacy of Unisanté [28–30]. All enrolled patients used the electronic monitor (EM, MEMS and MEMS AS; AARDEX Group, Sion, Switzerland), which registers the date and hour of each EM opening. An LCD screen on the top of the EM informed the patient of the number of EM daily openings. At each monthly 15- to 20 min medication adherence interview, a temporal graph representing the daily medication intake was discussed between the patient and the pharmacist. Based on motivational interviewing, the pharmacist explored the patient's needs in terms of information, motivation in medication taking and daily behavioural skills (e.g., medication and adverse effect management) [27]. In addition to EM adherence feedback, pharmacy technicians performed pill counts to calculate the difference between the number of pills delivered and the number of pills that should have been taken by the patient during each intervisit monitored period [31]. To promote interprofessionality, the

pharmacist emailed a report on the intervention to the patient's oncologist and health care providers (HCPs) after each visit [24].

Patients randomized in the control group used the EM but did not have any feedback on their medication intake. Control patients visited the pharmacy only for EM refill. EM data were blinded to patients, clinicians, including the pharmacy team and researchers. Pharmacy technicians only counted the number of pills returned to the pharmacy at each intervisit monitored period so that the concordance of treatment implementation between pill count and EM adherence feedback could be verified at the end of the study.

At each visit, patients in both groups were asked to state any EM deviation use during the last monitored period without (in control patients) and before (in intervention patients) seeing the temporal graph representing medication intake (e.g., pocket doses taken outside of the EM for later use, nonmonitored periods in case of hospitalization or EM nouse during holidays) [31]. Deviations were reported in a case report form (CRF).

2.3. Database Construction

2.3.1. Patients' Sociodemographic and Clinical Data

Patient data were extracted from patients' electronic medical records (Soarian®, Cerner) at enrolment and were registered in the secure data depository RedCap (Research Electronic Data Capture, Vanderbilt University) [32]. This includes sociodemographic (i.e., age, civil status, ethnicity) and clinical data (i.e., time since primary BC diagnosis, time since MBC diagnosis, cancer stage, presence of visceral metastases, palbociclib line of treatment for MBC, previous treatments for MBC if any, combined anticancer therapy in addition to palbociclib, number of received palbociclib cycles before inclusion, time since palbociclib initiation, previous oncologic therapies since BC diagnosis, number of oral prescribed chronic nononcologic treatments at inclusion).

2.3.2. EM Database

The number of observed EM daily openings was reconciled rigorously and manually with pill counts and patient reports about EM deviation use. Both the ON and OFF phases were monitored: one EM opening is expected during the ON phase, and no EM opening is expected during the OFF phase. The end date of the monitoring is defined as the date when the EM is returned or the last day of the last 15-day period with an implementation of >50% if EM has not been used in the last period, as previously performed in adherence research [31].

Palbociclib cycle dates were determined based on three different information levels: (1) the electronic medical record reports and the prescription sheet written by the oncologist, (2) the regimen labelled on the EM pill bottle at each pharmacy dispensation and (3) the patient's report. In the case of discrepancies between these three sources, the cycle dates were established based on the congruency of two sources. Otherwise, the patient's report was considered the most updated information, as the cycle dates in the electronic medical record are not always updated according to the last blood cell count results.

Main reasons for prescribing treatment transient interruptions or cycle start deferrals (i.e., EM expected opening = 0) were classified as follows: (1) toxicity or adverse effects, (2) alternate treatment (e.g., radiotherapy) and (3) intercurent infection (e.g., SARS-CoV-2). Transient interruptions may also be caused by the healthcare system (e.g., insurance reimbursement confirmation pending) or upon patients' requests (e.g., the patient asked the oncologist to delay the new cycle start after her holidays).

Implementation was considered optimal (= 1) if the EM daily observed opening was equal to the expected EM opening and was considered suboptimal (= 0) otherwise. Each reason for a suboptimal implementation was coded with a specific code, which allowed us to describe reasons for nonimplementation (e.g., a specific code for a missed tablet and another code in case of double intake of the drug during the day). Codes were also attributed to each reason for the cycle start deferral (e.g., a code in case of neutropenia

and another code in case of intercurent infection), transient palbociclib interruptions and discrepancies of cycle dates notification in the electronic medical record.

2.4. Statistical Analysis

2.4.1. Descriptive Analysis

Demographic and clinical variables are presented with proportions in both groups; quantitative variables are presented as medians and interquartile ranges (IQR). Clinical, administrative or patients' personal events that altered the palbociclib cycle dates are described with proportions. Chi-squared or Fisher exact tests were performed to compare the proportions of events that occurred during the palbociclib cycle between groups. A statistically significant test result is considered if $p < 0.05$.

2.4.2. Implementation

The underlying overall implementation was estimated by applying a generalized estimating equation (GEE) model on the daily 0/1 data with an autoregressive correlation structure and a linear and quadratic time effect.

Since all patients started baseline in the control group and some of them moved to the intervention group upon randomization after a varying number of days, the group variable was introduced into the model as two time-dependent variables, representing at each follow-up time t (1) the time spent in the control group and (2) the time spent in the intervention group (linear and quadratic terms). This allowed a different time pattern to be estimated for a patient always staying in the control group or a patient switching to the intervention at a given time point (i.e., at 21 days). The result is summarized by the difference in implementation (95% confidence intervals, 95% CI) between these two hypothetical patients at 6 months, when the intervention is fully effective, and enough patients are still participating.

Patient age, time since MBC diagnosis and number of palbociclib cycles received at inclusion were entered one by one as covariates into the model. The covariates were dichotomized using the median of the variable as the threshold (65 years old, 2-year time span since MBC diagnosis and 4 palbociclib cycles received before inclusion). The results are summarized by the difference in implementation (95% CI) between the intervention and control groups at 6 months for each covariate category.

The effect of the treatment phase (ON or OFF) on implementation is estimated in a separate model, where the phase is represented by two time-dependent variables: time spent in ON and OFF phases, both considered in linear and quadratic forms.

All statistical analyses were performed with the R statistical package [33].

2.4.3. Persistence

Treatment discontinuation was defined based on previously published criteria [34], i.e., when a patient stops the treatment by herself for any reason (e.g., side effects, pill fatigue) or when the treatment is stopped based on a shared patient-oncologist decision because of side effects or other personal reasons. Any other premature treatment stops (e.g., due to cancer progression) or premature cessation of the study (i.e., patient drop-out) were considered censoring times. Persistence is usually analysed by Kaplan–Meier curves.

2.4.4. Pharmacokinetic Modelling

The population PK-PD model previously developed with data from the OpTAT study [35] was used to evaluate the influence of medication implementation on palbociclib PK and neutropenia. We used different medication implementation scenarios based on real-life patients' implementation schemes retrieved from our database: (A) optimal implementation (i.e., one dose taken during 21 days followed by 7 days of treatment break); (B1) during the 21 days in phase ON, one dose is omitted at day 18, and is not caught up at cycle end (i.e., the OFF phase is initiated for 7 days from day 22); (B2) during the 21 days in phase ON, one dose is omitted at day 18, which is caught up at cycle end at day 22

(i.e., the OFF phase is initiated from day 23 for 6 days, leading to a shorter OFF period before the next cycle start); (C) during the 21 days in phase ON, the 2 first doses are omitted at day 1 and 2, which are caught up at cycle end at day 22 and 23 (i.e., the OFF phase is initiated from day 24 for 5 days, leading to a shorter OFF period before the next cycle start). Based on these implementation scenarios, we simulated palbociclib plasma concentration (ng/mL) and absolute neutrophil count (G/L) over 3 palbociclib cycles in 1000 patients receiving the standard dosage regimen (125 mg once daily for 21 days followed by 7 days of treatment break).

The population median prediction and the 95% prediction intervals (95% PI) for palbociclib plasma concentrations and absolute neutrophil count as a function of time were derived. For visual interpretation of the impact of real-life implementation scenarios on palbociclib PK, we superimposed to the simulated concentration-time profiles the real palbociclib plasma concentrations measured in one patient receiving a standard palbociclib dosage regimen who generally had an optimal palbociclib implementation (scenario A) but who missed a dose at Day 18 once (scenario B).

3. Results

3.1. Included Patients

The demographic and clinical variables of the 38 patients are presented in Table 1. In the intervention group, face-to-face motivational interviews lasted an average of 18 min; the same additional duration was needed to complete the adherence report for the oncologist. In the control group, the meetings at the pharmacy counter with patients lasted 8 min on average, and the pharmacists spent a median time of 4 min completing the CRF.

Figure 1 describes the flow of patient enrolment and follow-up from inclusion to data analysis. The EM data of one control patient were not analysed, as the patient did not use the EM device. In the intervention and control groups, 12 and 8 participants left the study prematurely due to treatment stopping because of cancer progression or side effects, respectively; 4 patients dropped out in each group.

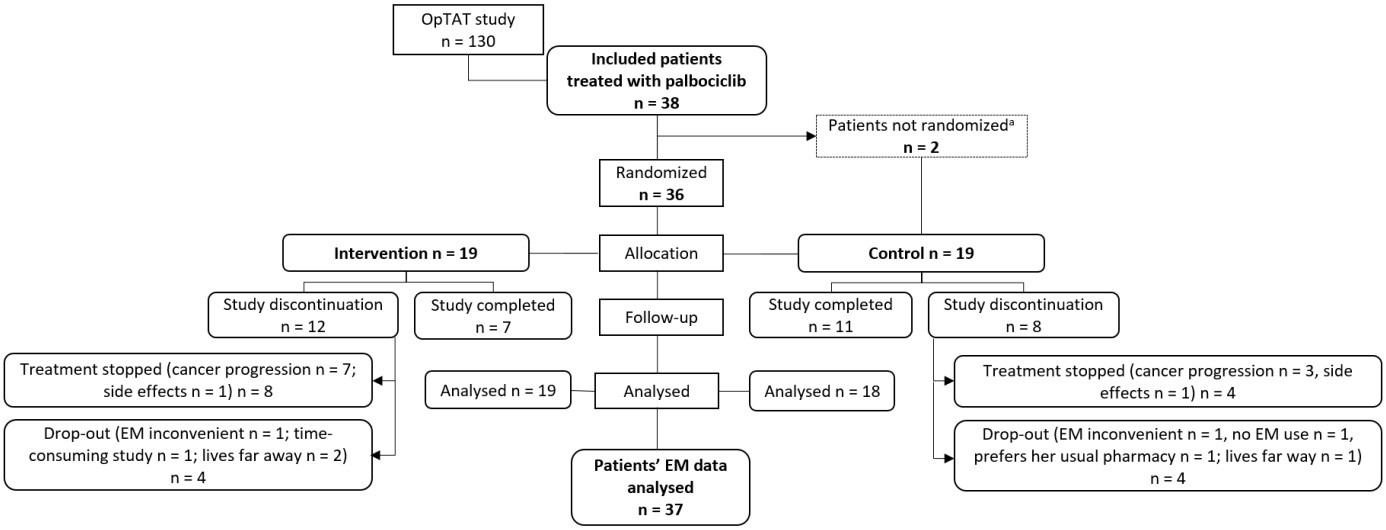


Figure 1. Flow of patient enrollment and follow up from inclusion to data analysis. [a] study discontinuation before randomization; NB: EM = electronic monitor.

Table 1. Demographic and clinical data of patients treated with palbociclib in the OpTAT study (n = 38).

	Intervention (n = 19)	**Control (n = 17) + Not Randomized [c] (n = 2)**
Demographic Data		
Age (years), median (IQR)	62 (52–73)	64 (55–75)
Marital civil status [a], n (%)	10 (52.6)	11 (57.9)
Caucasian ethnicity [b], n (%)	19 (100)	17 (89.5)
Clinical data		
Time since primary BC diagnosis (years), median (IQR)	7.5 (4.5–16.9)	7.3 (3.1–12.8)
Time since MBC diagnosis (years), median (IQR)	1.8 (0.8–3.0)	1.6 (0.5–3.4)
Cancer stage IV, n (%)	19 (100)	19 (100)
Visceral metastases, n (%)	16 (84.2)	10 (52.6)
Palbociclib line of treatment for MBC, n (%)	1st line: 6 (31.6) 2nd line: 3 (15.8) >= 3rd line: 10 (52.6)	1st line: 5 (26.3) 2nd line: 6 (31.6) >= 3rd line: 8 (42.1)
Previous treatment for MBC (if palbociclib is $\geq$ 2nd treatment for MBC), n (%)	Endocrine therapy: 11 (84.6) Chemotherapy: 2 (15.4)	Endocrine therapy: 7 (50) Chemotherapy: 7 (50)
Combined anticancer therapy in addition to palbociclib at inclusion, n (%)	Aromatase inhibitor: 7 (36.8) Fulvestrant: 11 (57.9) Goserelin, leuprorelin: 2 (10.5)	Aromatase inhibitor: 6 (31.6) Fulvestrant: 13 (68.4) Goserelin, leuprorelin: 2 (10.5)
Number of palbociclib cycles received before inclusion, n (%)	0–4 cycle(s): 11 (57.9) >4 cycles: 8 (42.1)	0–4 cycle(s): 10 (52.6) >4 cycles: 9 (47.4)
Time since palbociclib initiation (days), median (IQR)	97 (14–230)	83 (28–228)
Previous oncologic therapies since BC diagnosis, n (%)	Tumor surgery: 19 (100) Aromatase inhibitor: 17 (89.5) IV chemotherapy: 14 (73.7) Radiotherapy: 11 (57.9) Fulvestrant: 4 (21.0) Goserelin, leuprorelin: 4 (21.0) Trastuzumab: 0 (0) Bevacizumab: 4 (21.0) Everolimus: 3 (15.8) Capecitabine: 2 (10.5)	Tumor surgery: 19 (100) Aromatase inhibitor: 17 (89.5) IV chemotherapy: 12 (63.2) Radiotherapy: 15 (79.0) Fulvestrant: 3 (15.8) Goserelin, leuprorelin: 1 (5.3) Trastuzumab: 1 (5.3) Bevacizumab: 5 (26.3) Everolimus: 2 (10.5) Capecitabine: 3 (15.8)
Number of oral prescribed chronic nononcologic treatments at inclusion time, median (IQR)	3 (1–4)	3 (1–3)
Adherence study		
Time spent in the adherence study (days), median (IQR)	209 (133–363)	366 (171–392)

NB: IQR = Interquartile range; BC = breast cancer, MBC = metastatic breast cancer; IV = intravenous. [a] The other patients are separated, divorced, widowed or single. [b] The other patients are African or Hispanic. [c] Patients not randomized left the study before randomization.

3.2. Palbociclib Implementation and Persistence

In total, 155 cycles were monitored and analysed in the 19 intervention patients and 184 cycles in the 18 control patients.

Figure 2a presents palbociclib implementation estimated by our model for patients staying in the control group after the baseline period of 21 days versus patients switching to the intervention. Two discontinuations due to side effects occurred: one in the intervention group at day 111 and one in the control group at day 355. At 6 months, implementation was slightly higher and more stable in the intervention group than in the control group (99.2% and 97.3%, Δ1.95%, 95% CI 1.1–2.9).

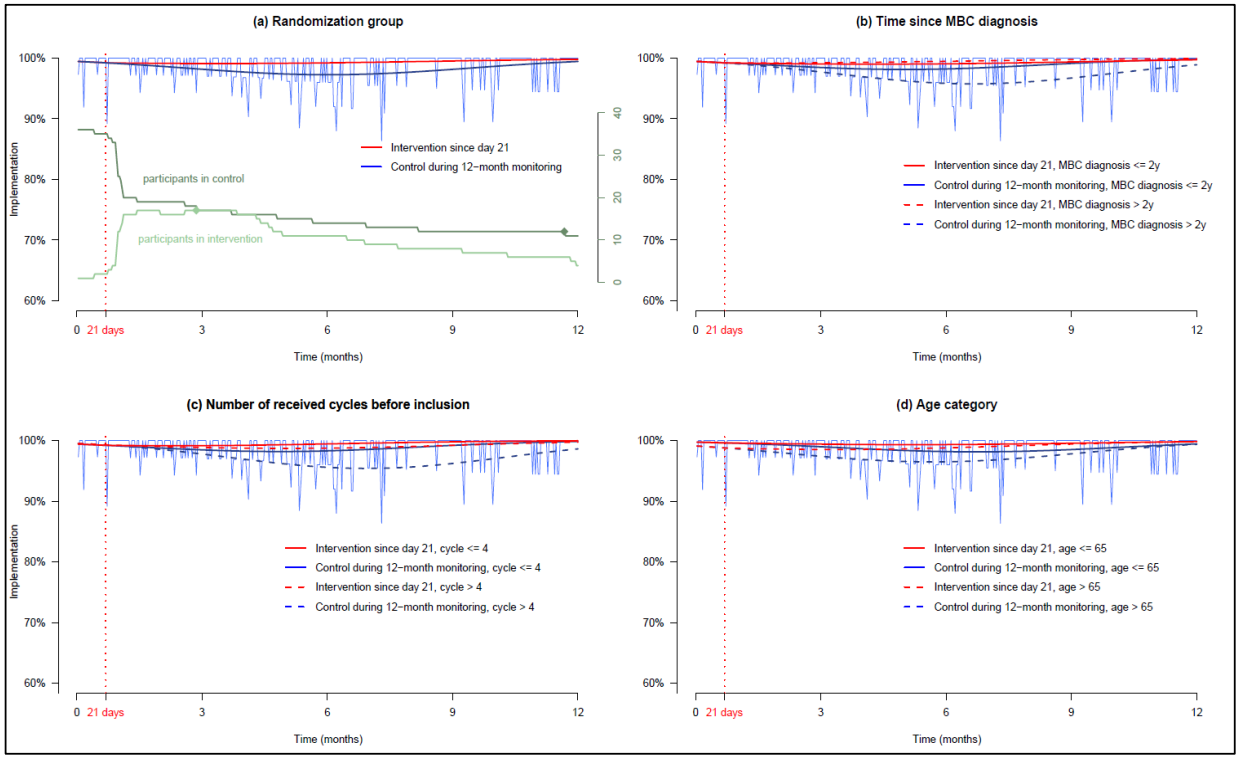


Figure 2. GEE models estimating patient implementation (the vertical red dotted line indicates the randomization at day 21, date on which the intervention starts—i.e., after the baseline period). (**a**) Patients' palbociclib implementation in each randomized group, (**b**) dichotomization in each group according to time since MBC diagnosis, (**c**) dichotomization in each group according to the number of palbociclib cycle received before inclusion, and (**d**) dichotomization in each group according to age. NB: In (**a**), the two discontinuations are represented by dots in the green curves depicting the number of participants over time.

In the control group, patients older than 65 years, patients diagnosed with MBC for more than 2 years and patients who received more than 4 cycles of palbociclib before inclusion had a lower implementation, whereas in the intervention group, these covariates did not impact implementation. Thus, the impact of the intervention on implementation was larger in patients diagnosed with MBC for more than 2 years in the intervention and control groups, 99.5% and 95.9% (Δ3.6%, 95% CI 2.1–5.4%) (Figure 2b), in patients who received more than 4 cycles of palbociclib before inclusion in the intervention and control groups 98.7% and 95.6% (Δ3.1%, 95% CI 1.7–4.8%) (Figure 2c) and in patients older than 65 in the intervention and control groups, 98.8% and 96.5% (Δ2.3%, 95% CI 0.8–3.6%), respectively (Figure 2d). The results are detailed in Appendix A.

The analysis of ON and OFF phases of all participants—regardless of the randomized group–estimated that implementation decreased over time during ON phases but remained stable in OFF phases during the first 6 months (Appendix B). Equations of the GEE models are presented in Appendix C.

Figure 3 describes the reasons for treatment discontinuation and censoring times. As only two discontinuations occurred in our sample (represented in the implementation graph in Figure 2a), we decided not to formally analyse persistence by Kaplan–Meier curves.

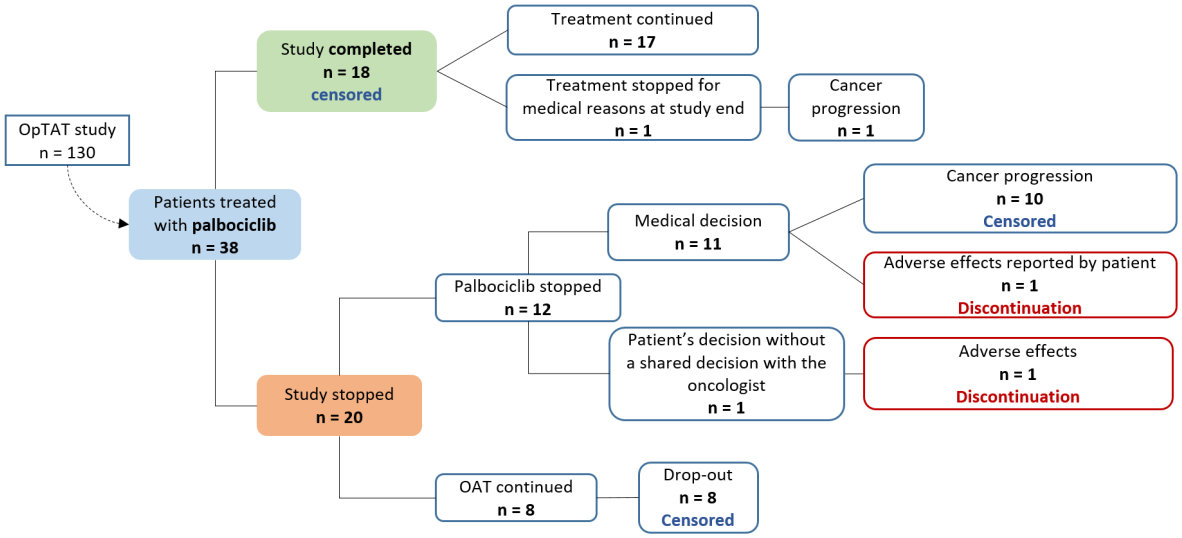


Figure 3. Discontinuation and censoring times algorithm.

3.3. Recommendations for CDK4/6i Cycle Management

3.3.1. Missed Dose Management Recommendation Supported by Pharmacometric Modelling

Forgetting a dose was not uncommon in our population. Significantly more control patients versus intervention missed at least one dose during the monitoring (15/18, 83% and 10/19, 53%, $p = 0.046$), and more cycles were impacted by a missed dose in control versus intervention patients (44/184, 24%, 18/155, 12%, $p = 0.004$) (Table 2). In patients who missed at least one dose, a comparable proportion of patients in both groups caught up these missed doses (7/10, 70% in the intervention and 10/15, 67% in the control group, $p = 1.000$). In the case of a missed dose, some patients did not behave consistently; they caught up the missed dose in some cycles but did not in others (patients who behaved inconsistently in case of a missed dose were 3/10, 30% in intervention versus 7/15, 47% in control group, $p = 0.679$). Some OFF phases were shortened to 6 instead of 7 days in the intervention and control groups, respectively, because a dose was caught up (2/11, 18% and 5/15, 33%, $p = 0.658$) (Table 2). Few patients experienced a dose reduction due to neutropenia (3/19, 16% in the intervention and 2/18, 11% in the control group, $p = 1.000$), and none of these dose reductions were caused by a reduced length of the OFF phase due to the catch-up of missed doses.

Table 2. Patients' palbocilib management behaviour; clinical, administrative or patients' personal events that occurred during the monitored period.

	Intervention Group ($n_{patients}$ = 19; n_{cycles} = 155)	**Control Group** ($n_{patients}$ = 18; n_{cycles} = 184)	***p*-Value**
Patients' Behaviour When a Dose is Missed			
Patients who missed at least one dose, n (%)	10/19 (53)	15/18 (83)	**0.046**
Number of cycles impacted by a missed dose (%)	18/155 (12)	44/184 (24)	**0.004**
Number of ON cycles extended because a missed dose was caught up, n (%)	11/18 (61)	15/44 (34)	0.050
Number of cycles—among those with a caught up dose-in which the OFF phase was shortened from 7 to 6 days, n (%)	2/11 (18)	5/15 (33)	0.658
Number of patients—among those who missed at least one dose-who **caught up** at least one missed dose, n (%)	7/10 (70)	10/15 (67)	1.000
Number of patients—among those who missed at least one dose-who caught up a missed dose **in some cycles and did not caught up in the other cycles**, n (%)	3/10 (30)	7/15 (47)	0.679

Table 2. *Cont.*

	Intervention Group ($n_{patients}$ = 19; n_{cycles} = 155)	Control Group ($n_{patients}$ = 18; n_{cycles} = 184)	*p*-Value
Transient interruptions of palbociblib during the phase ON			
Number of patients who experienced at least one transient interruption of palbociclib during the ON phase, n (%)	6/19 (32)	3/18 (17)	0.447
Number of cycles impacted by an interruption in phase ON, n (%)	10/155 (6)	4/184 (2)	**0.049**
Number of cycles—among those which were interrupted-that were **resumed** after the interruption, n (%)	4/10 (40)	2/4 (50)	1.000
Number of phases ON—among those with an interruption-interrupted because of infection, n (%)	5/10 (50)	2/4 (50)	1.000
Number of phases ON—among those with an interruption-interrupted because of surgery, n (%)	2/10 (20)	1/4 (25)	1.000
Number of phases ON—among those with an interruption-interrupted because of side effects, n (%)	1/10 (10)	1/4 (25)	0.506
Number of phases ON—among those with an interruption-interrupted because of synchronization with the fulvestrant cycle or with previous palbociclib cycles, n (%)	2/10 (20)	0/4 (0)	1.000
Cycle start deferrals			
Number of patients who experienced at least one cycle deferral, n (%)	13/19 (68)	15/18 (83)	0.447
Number of cycles impacted by a deferral, n (%)	40/155 (26)	36/184 (20)	0.170
Number of patients who experienced a cycle deferral due to neutropenia, n (%)	9/19 (47)	7/18 (39)	0.603
Number of cycles deferred because of neutropenia, n (%)	20/155 (13)	11/184 (6)	**0.028**
Number of patients who experienced a cycle deferral due to radiotherapy sessions, n (%)	2/19 (11)	0/18 (0)	0.487
Number of patients who experienced a cycle deferral due to infection, n (%)	3/19 (16)	3/18 (17)	1.000
Number of patients who experienced a cycle deferral due to prevent the risk of SARS-COV-2 infection during the COVID-19 pandemic, n (%)	0/19 (0)	1/18 (6)	0.487
Number of patients who experienced a cycle deferral due to a medical appointment set too late (oncologist not available or PET-scan results pending), n (%)	5/19 (26)	7/18 (39)	0.414
Number of patients who experienced a cycle deferral due to insurance reimbursement decision pending, n (%)	0/19 (0)	1/18 (6)	0.487
Number of patients who experienced a cycle deferral due to the delayed order of the treatment at the external pharmacy, n (%)	1/19 (5)	0/18 (0)	1.000
Number of patients who asked their oncologist to defer the start of at least one cycle for personal reasons (e.g., holidays), n (%)	4/19 (21)	4/18 (22)	1.000
Dose reduction			
Patients who experienced a dose reduction due to neutropenia [a], n (%)	3/19 (16)	2/18 (11)	1.000
Discrepancies of cycle dates notification in the electronic medical record or in the prescription sheet compared to the actual cycles dates			
Number of patients impacted by at **least one discrepancy** in the cycle dates compared to the actual cycle dates, n (%)	10/19 (53)	11/18 (61)	0.603
Number of patients—among those impacted by a discrepancy-for which the prescription was not modified by pharmacists (i.e., the phase OFF was shortened or extended) [b], n (%)	4/10 (40)	5/11 (45)	1.000

[a] The dose was reduced from 100 mg to 75 mg in three intervention patients and one control patient at cycle 5, 10, 20 and 3; as well as from 125 mg to 100 mg in one control patient at cycle 14. This suggests that doses adjustment can occur anytime from treatment initiation. [b] the discrepancies of the cycle dates from the electronic medical record was adapted in the prescription sheet by the oncologist, or the prescription sheet was adapted by the pharmacist according to patients' report and the calculation of cycle dates following the previous cycle.

As a reminder, the simulated scenarios of palbociclib implementation were (A) optimal implementation, (B1) one dose is omitted at day 18, which is not caught up at cycle end, 7 days of treatment break are initiated from day 22, (B2) one dose is omitted at day 18, which is caught up at cycle end at day 22, 6 days of treatment break are initiated from day 23 (C) the 2 first doses are omitted at day 1 and 2 and are caught up at cycle end at day 22 and 23, 5 days of treatment break are initiated from day 24.

Model-based PK-PD simulations showed that missing one (scenarios B1 and B2) or two doses (scenario C) occasionally resulted in a decrease in the palbociclib plasma concentration-time profile compared to optimal implementation (scenario A) immediately after the missed dose(s), as expected. As shown in the real patient palbociclib plasma concentration represented by the blue dot in Figure 4a scenario B1 vs. the green dots in scenario A, the plasma concentration can even drop below the 95% PI after the missed dose at Day 18. However, compared to an optimal implementation (scenario A), missing a dose in a cycle without catching it up at cycle end (Figure 4a, scenario B1) has no consequence on the recovery from neutropenia (Figure 4b, scenario B1). Conversely, omitting a dose and catching it up at the end of the cycle (Figure 4a, scenario B2) shortens the length of the OFF phase, which may decrease the recovery time and, as a consequence, increase the risk of severe neutropenia during the next cycle (Figure 4b, scenario B2). This risk is even more pronounced when the number of doses omitted and caught up increases, as does the catching-up at the end of the cycle of two doses omitted at the beginning of the cycle (scenario C in Figure 4c,d). Indeed, model-based simulations showed that 25% of patients had neutropenia grade ≥3 during the next cycle in scenario A versus 30% in scenario C.

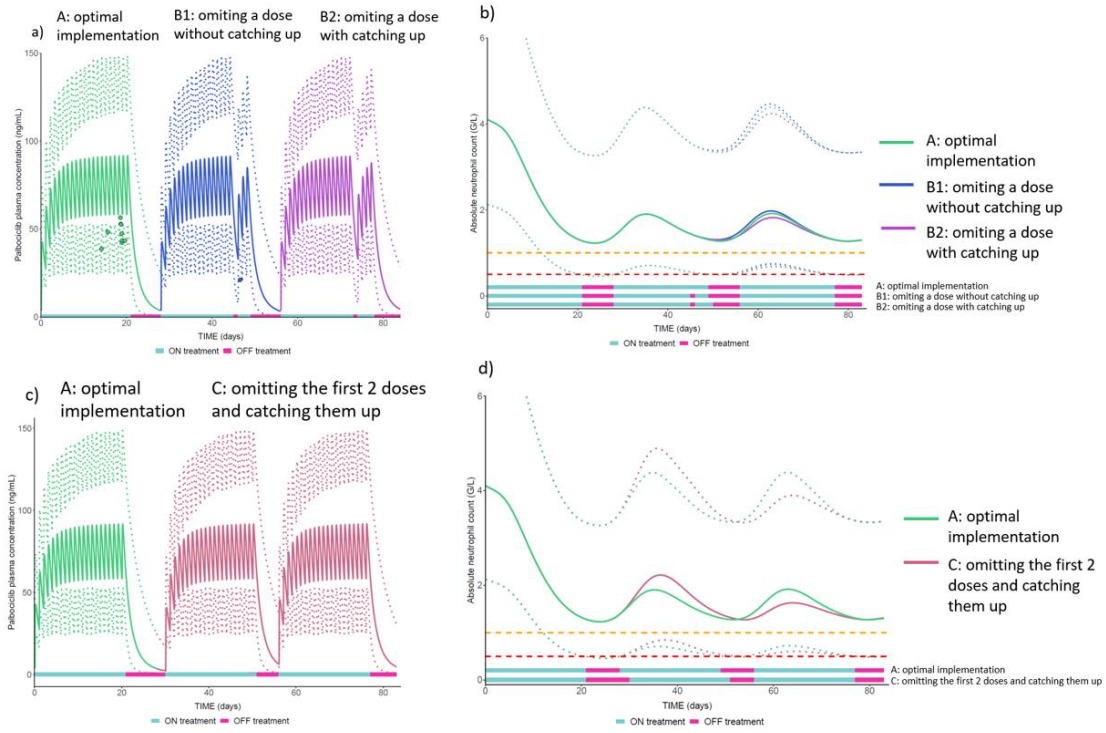


Figure 4. Population median prediction of palbociclib plasma concentrations profiles–solid lines in (**a**,**c**)—and absolute neutrophil count–solid lines in (**b**,**d**)—and their 95% prediction intervals–dotted lines. Orange and red dotted lines represent, respectively the threshold for neutropenia grade ≥3 and ≥4. NB: the dots in (**a**) represent the observed plasma palbociclib concentrations in a real patient included in the OpTAT study in both A and B1 scenarios. In scenario A, the concentrations are lower than the median observed in the simulated patients. This observation is consistent over this patient's cycles and could be attributed to several extrinsic factors potentially increasing palbociclib elimination for this patient (e.g., co-administration of proton-pump inhibitors in fasting conditions [35], increase in creatinine clearance or decrease in alkaline phosphatase [36]).

3.3.2. Transient Interruption during the ON Phase, Cycle Deferrals and Discrepancies of Cycle Dates in the Electronic Medical Record and the Prescription Sheet

At least one transient interruption of palbociclib during the ON phase was experienced in 6/19 (32%) patients in the intervention group and 3/18 (17%) in the control group ($p = 0.447$) (Table 2), with more cycles impacted in the intervention group than in the control group (10/155, 6% vs. 4/184, 2%, $p = 0.049$). Half of the interruptions occurred because of an infection. Other reasons reported were surgery, side effects and synchronization with the fulvestrant cycle or synchronization with previous palbociclib cycles. Among the cycles interrupted, the number of cycles that were resumed after the interruption was 4/10 (40%) in the intervention group and 2/4 (50%) in the control group ($p = 1.000$), whereas the other cycles were stopped for at least 7 days before starting another cycle.

Most patients (13/19, 68% in the intervention and 15/18, 83% in the control group, $p = 0.447$) experienced at least one cycle start deferral due to clinical reasons (e.g., neutropenia, radiotherapy sessions, infections), administrative reasons (e.g., medical appointment set too late, insurance decision for reimbursement pending, delayed order of the treatment at the external pharmacy) or patient's personal reasons (e.g., more than 20% of patients in each group asked their oncologist to delay the start of the new cycle for personal reasons as holidays) (Table 2).

These frequent transient palbociclib interruptions and deferrals of cycle start are probably the cause of discrepancies in the cycle dates notification in patients' electronic medical record and prescription sheets (Table 2).

4. Discussion

4.1. Main Results

In the OpTAT study, patients taking OAT for solid cancer were randomized to the Interprofessional Medication Adherence Program (IMAP) versus controls. In this paper, we present the impact of this intervention in the subgroup of patients treated with palbociclib for MBC. The IMAP, offered to patients in the intervention group, allowed maintaining a higher and more stable palbociclib implementation compared to control patients. The intervention had a larger effect in patients older than 65 years, those diagnosed with MBC for more than 2 years and patients who received more than 4 cycles of palbociclib before inclusion. The intervention did not impact persistence to palbociclib. Model-based PK-PD simulations showed that catching up missed doses at the end of the ON phase, followed by a shortening of the OFF phase, leads to a higher risk of severe neutropenia during the following cycle. Our results show that cycles start deferral occurred due to neutropenia, but also administrative reasons or patients' personal requests. The interprofessional health care team should closely monitor patients' cycle management to update cycle dates in the prescription sheets and electronic medical record.

4.2. Impact of IMAP on Palbociclib Implementation

Overall, patient implementation was high (>95%) at 6 months in both randomized groups, which indicates efficient treatment self-management. Facilitators for adherence may have been the frequent medical appointments (i.e., usually once per month), sometimes coupled with other consultations from the interprofessional health care team (i.e., nurses, clinical pharmacists, psychologists) to help the patient cope with treatment and disease self-management. Such added consultations to the medical appointments are not offered systematically but according to the patient's request and needs. Supporting medication adherence is not the core of these interventions and is not embedded in any theoretical framework. Interestingly, our population is not polymedicated (i.e., less than 5 chronic nononcologic treatments are prescribed per day) [37], which may be a facilitator for treatment adherence compared to polymedicated patients. The largest difference in implementation between groups was found between patients diagnosed with MBC for more than 2 years (i.e., +3.6% at 6 months in the intervention group). We hypothesize that patients at a longer distance from the diagnosis may benefit more from the intervention,

whereas the usual support from the healthcare team has decreased. A longer time since diagnosis has previously been reported as a determinant of nonadherence to OAT [5,38,39], which may be caused by treatment fatigue [40], a lower perceived need for OAT over time and a lower perceived susceptibility to the disease. Furthermore, the impact of +3.6% of increased implementation on clinical outcomes, such as progression-free survival, needs to be further investigated.

4.3. Patient Empowerment to Self-Manage CDK4/6i

Even if patients with BC describe OAT as convenient to use compared to intravenous chemotherapy [41], the numerous dose adjustments, cycle deferrals or interruptions represent a treatment burden, which may impact patient adherence. To better understand patients' cycle management and avoid any confusion in cycle dates, strategies must be reinforced in daily practice to collect the accurate dates of each cycle start and stop in the electronic medical record, the prescription sheet and on the patient educational written or e-documentation (e.g., "Take one pill per day from 1st January 2022 to 20th January 2022 included, followed by 7 days of treatment break"). In this regard, patients acknowledge the role of pharmacists in providing them education about the treatment [42].

In our study, various behaviours were observed in the same patients after a missed dose, which highlights that consensual education provided by HCPs to self-manage a missed dose might not be sufficient. If oncologists are not aware of patient missed doses and end-of-cycle catching-up behaviours, a low neutrophil blood count can be misinterpreted, leading (i) to unnecessary dose reductions, (ii) treatment interruptions, (iii) next cycle start deferral, and so on to desynchronization with concomitant cyclic treatments, e.g., fulvestrant injections. Interprofessional partnerships are to be strengthened and better defined to synergistically improve patient adherence to palbociclib.

4.4. Electronic Adherence Monitoring Databases for Cyclic Regimens

In this study, implementation was monitored in OFF phases (i.e., daily implementation = 1 when observed EM opening = 0), even though the patient's effort to reach an optimal implementation during the ON phase (i.e., the patient takes a pill once per day) is higher than in the OFF phase. Indeed, we showed that implementation during the ON phases decreased with increasing cycles, whereas it was stable in the OFF phases. Notably, extended OFF phases (e.g., during several weeks for radiotherapy sessions) must be considered differently (e.g., intermittent discontinuation). Further scientific methodologies to characterize the implementation of treatment with cyclic regimens must be investigated (e.g., based on the number of completed cycles over the year with minimal regimen deviation). Data cleaning is of particular importance when numerous prescribed treatment interruptions are monitored to avoid misinterpreting EM nonopenings. As automated and robust methodologies to clean EM databases are needed, we are currently developing a script in the statistical software R to clean and reconcile EM data according to patient's report and patient's electronic medical record.

Finally, some patients actively participate in shared decision-making about their treatment management (e.g., asking clinicians for cycle deferral during their holidays). The way to consider them needs to be defined before analysing medication implementation (and adherence) either by considering it as a treatment nonimplementation as it deviates from the recommended regimen or as an optimal treatment implementation as the new regimen relies on a shared-decision process.

4.5. Strengths and Limitations

This study has several strengths. First, medication adherence was evaluated by EM, which is considered one of the gold standard methods to measure adherence and especially implementation [43–45]. Although patients feeling observed may improve their adherence, this Hawthorn effect fades away within 40 days of monitoring [46–49]. Second, EM data were reconciled with pill counts [44,49,50]. Third, the database was cleaned rigorously,

and the cycle dates were reconciled based on patient reports, medical and pharmaceutical records and prescription sheets. Advanced longitudinal statistical analysis including covariates was performed, which allows estimating patterns of adherence over time [34] by considering the impact of covariates on the implementation trajectories. Last, to the best of our knowledge, the catching-up behaviour was not previously reported in patients taking palbociclib, and the consequences on PK and PD properties are not investigated yet. Indeed, while official instructions for palbociclib stipulate not to catch up a missed dose during the same day, no information is provided on the possibility to catch up a missed dose at cycle end [51].

Some limitations should be acknowledged. First, palbociclib implementation in control patients seems to increase towards the study end. This phenomenon was already observed in a study depicting patient implementation to antiretrovirals in patients with human immunodeficiency virus (HIV) [52] and was defined as a data artefact associated with the decreased number of patients over time. Second, our sample size (n = 38) was relatively small. However, this subgroup represents the largest proportion of patients treated with the same OAT (i.e., palbociclib) among all patients included in the OpTAT study (n = 38/130, 29% of the total sample size). Our robust methodology (i.e., 12-month longitudinal repeated, real-time measures) allows us to provide a solid internal validity of the results. Yet, the external validity needs confirmation with larger multi-center studies. Last, the control group may have been polluted by the implementation of the intervention group at the pharmacy: (i) the exact cycle dates were written in the EM labels at study initiation in both groups, which is not frequent in standard of care if the cycle dates are not written in the prescription sheet; (ii) during the implementation of the OpTAT study at the pharmacy, community pharmacists have improved their scientific knowledge and expertise about OAT, which might have influenced the professional attitude with the control patients; (iii) for ethical reasons, patients in both groups were recalled if they did not show up after a missed appointment for the intervention or a missed date for refill in control patients, respectively, in the next 24 h for intervention patients and after 72 h for control patients, which does not happen in usual care; (iv) participation in the OpTAT study and EM use might have raised awareness of the importance of medication adherence in control patients; (v) to avoid EM misuse, control patients were asked to report their deviation of EM use at each refill visit.

5. Conclusions

The interprofessional medication adherence program shows that the intervention had a larger effect in patients older than 65 and those with longer treatment and disease experience. Various clinical, administrative or patients' personal events can alter the dates of ON and OFF phases. OFF-period reduction due to missed doses that are caught up at cycle end increases the risk of severe neutropenia in the next cycle, which may lead to inappropriate dose reduction. Currently, two CDK4/6i are administered cyclically, palbociclib and ribociclib. Well-designed education programs and monitoring of patient cycle management by an interprofessional team along with PK-piloted dose reduction in case of side effects can help clinicians improve prescriptions and better prevent toxicity. The impact of adherence on CDK4/6i effectiveness should be further investigated.

Author Contributions: C.B. wrote the manuscript, revised by M.P.S., P.C., K.Z. and I.L. followed by all co-authors. E.C., A.D.W., C.C. and M.P.S. contributed to the conception and design of the OpTAT study. C.B., E.C., J.D.-C. and M.P.S. implemented the study within the Interprofessional Medication Adherence Program (IMAP) at the community pharmacy of Unisanté. C.B., E.C., K.Z., A.S. (Athina Stravodimou), A.D., A.S. (Apostolos Sarivalasis), J.-P.Z. and V.A.-L. identified the eligible patients and K.Z., A.S. (Athina Stravodimou), A.D., A.S. (Apostolos Sarivalasis), J.-P.Z. and V.A.-L. followed the patient clinically. S.P. supported and facilitated the implementation of the OpTAT study in the Department of Oncology by co-organizing meetings with oncologists and nurses. C.B. extracted and cleaned EM data. C.B., E.C., K.Z., M.P.S. and I.L. analysed the results. P.C., E.C., M.G. and C.C. developed the PK-PD population approach model and performed the model-based simulations. I.L.

performed the statistical analysis. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The OpTAT study was approved by the local ethics committee of the county of Vaud, Switzerland "La Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD)" in 2015 (ID 65/15) and was conducted in accordance with the Declaration of Helsinki principles.

Informed Consent Statement: Any Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical reasons.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

BC	Breast Cancer
CDK4i and CDK6i	Cyclin-dependent kinases 4 and 6 inhibitors
CI	Confidence interval
CHUV	Lausanne University Hospital
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus Disease
CRF	Case Report Form
EMERGE	ESPACOMP Medication Adherence Reporting Guideline
GEE	Generalized estimating equation
HCPs	Health care providers
HR+/HER2−	Endocrine-sensitive and human epidermal growth factor receptor 2 negative
HIV	Human Immunodeficiency Virus
IMAP	Interprofessional Medication Adherence Program
IQR	Interquartile ranges
EM	Electronic monitor
MBC	Metastatic breast cancer
OAT	Oral anticancer therapies
OpTAT	Optimizing Targeted Anticancer Therapies study
PK-PD	Pharmacokinetics/pharmacodynamics
PI	Prediction Interval

Appendix A

Table A1. Palbociclib implementation at 6 months in the different GEE models.

At 6 Months	Implementation (%)				
	Intervention	Control	Difference	95%CI	
	99.20	97.25	1.95	1.11	2.87
Number of received palbociclib cycles at inclusion ≤4	99.43	98.28	1.15	0.40	1.96
Number of received palbociclib cycles at inclusion >4	98.74	95.62	3.12	1.69	4.75
Time since MBC ≤2 years	99.04	98.19	0.85	−0.04	1.72
Time since MBC >2 years	99.45	95.85	3.60	2.06	5.36
Age ≤65 years old	99.33	98.19	1.14	0.36	2.09
Age >65 years old	98.78	96.49	2.28	0.83	3.63

CI = Confidence interval.

Appendix B Patients' Implementation in ON and OFF Phases

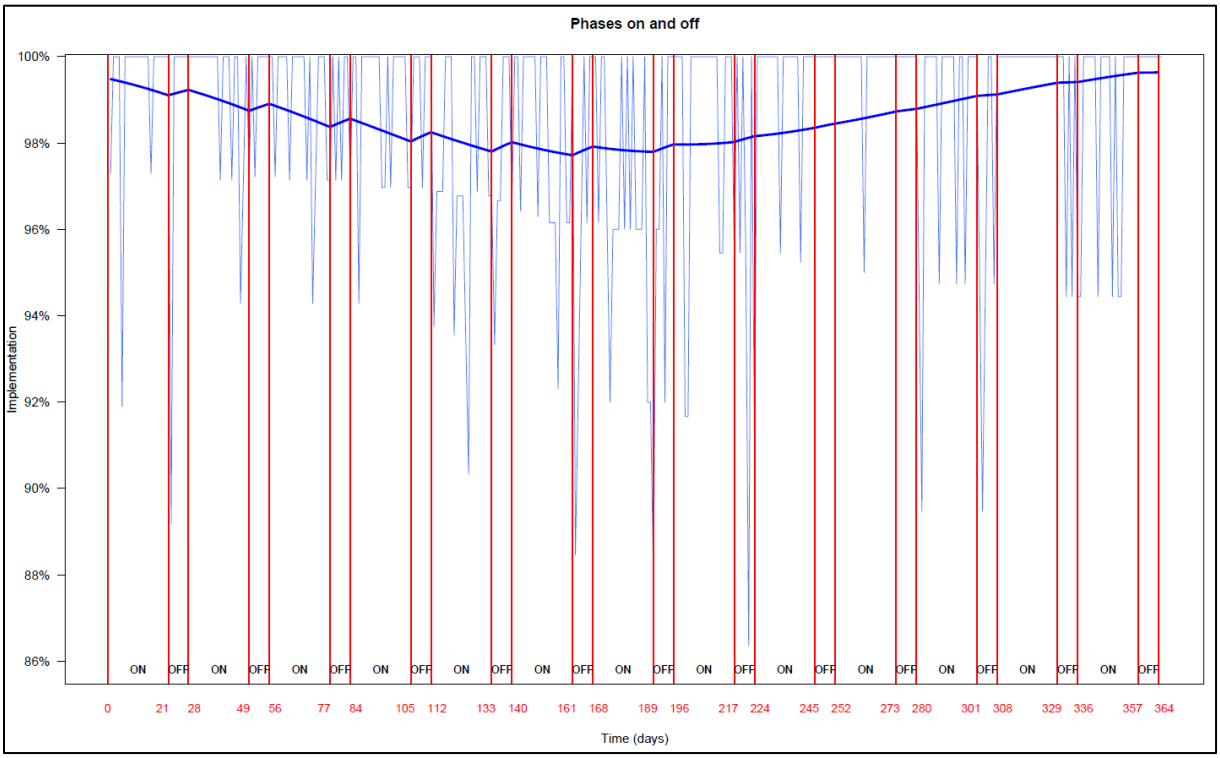


Figure A1. NB: The end of each ON (21 days) and OFF phase (7 days) is represented in red lines and numbers. Empirical implementation is represented with the light blue curves, GEE modelisation is represented with the thick blue curve in each ON and OFF phase.

Appendix C

Table A2. Equations of GEE models.

Models	Equations							
Total sample	logit(imp) = 5.2	$+3.4 \times 10^{-5}$ t	$+4.4 \times 10^{-5}$ t^2					
Group	logit (imp) = 5.2	-1.8×10^{-2} t_0	$+ 4.8 \times 10^{-5}$ t_0^2	-3.6×10^{-3} t_1	$+ 2.2 \times 10^{-5}$ t_1^2			
Group + Cycle	logit (imp) = 5.1	$+2.3 \times 10^{-1}$ (cycle > 4)	-1.5×10^{-2} t_0	-6.6×10^{-3} t_0* (cycle > 4)	$+5.2 \times 10^{-5}$ t_0^2	-3.3×10^{-3} t_1	-5.6×10^{-3} t_1* (cycle > 4)	$+3.4 \times 10^{-5}$ t_1^2
Group + Age	logit (imp) = 5.9	$-1.2 \times 10^{+00}$ (age > 65)	-1.9×10^{-2} t_0	$+3.1 \times 10^{-3}$ t_0* (age > 65)	$+4.7 \times 10^{-5}$ t_0^2	-8.4×10^{-3} t_1	$+3.5 \times 10^{-3}$ t_1* (age > 65)	$+3.1 \times 10^{-5}$ t_1^2
Group + t.MBC	logit (imp) = 5.2	$+7.2 \times 10^{-2}$ (t.MBC > 2)	-1.6×10^{-2} t_0	-5.1×10^{-3} t_0* (t.MBC > 2)	5.2×10^{-5} t_0^2	-4.8×10^{-3} t_1	$+3.8 \times 10^{-3}$ t_1* (t.MBC > 2)	$+2.2 \times 10^{-5}$ t_1^2
phase	logit (imp) = 5.3	-3.0×10^{-2} $t.on$	$+9.8 \times 10^{-5}$ $t.on^2$	$+2.2 \times 10^{-2}$ $t.of$	-1.1×10^{-4} $t.of^2$			

NB: imp = implementation, MBC = metastatic breast cancer. t_0 = time in control; t_1 = time in intervention; $t.on$ = time in phase ON; $t.of$ = time in phase OFF.

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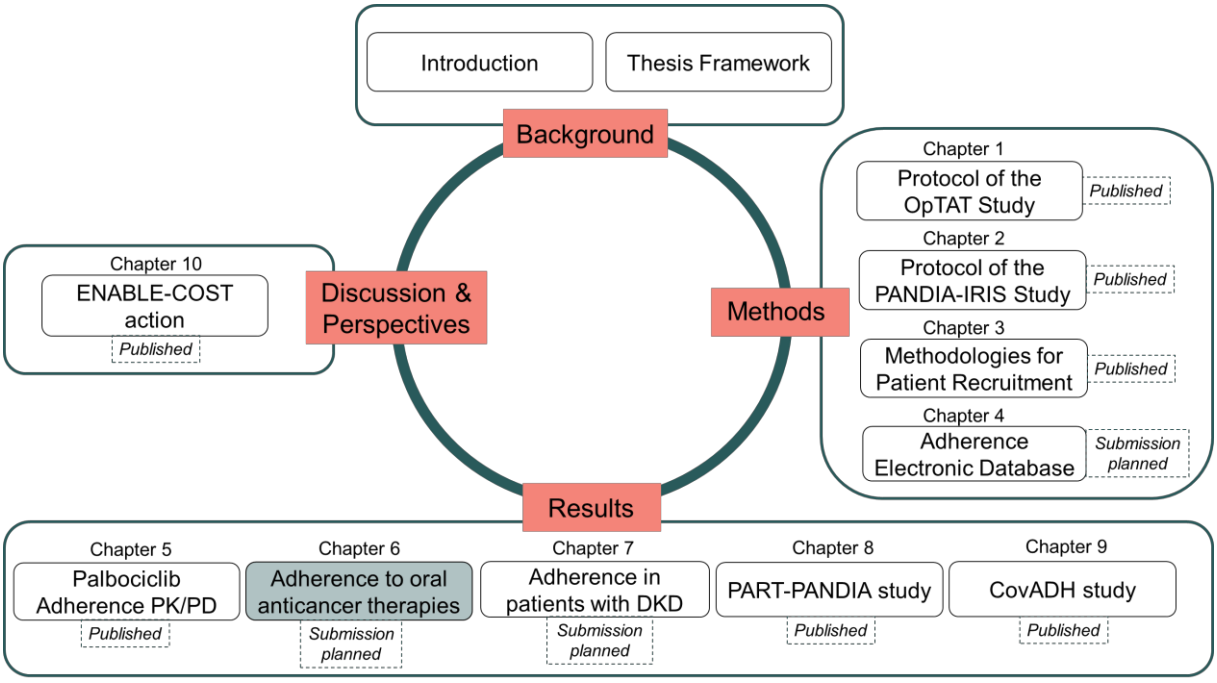
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CHAPTER 6: ADHERENCE TO ORAL ANTICANCER THERAPIES (OPTAT STUDY)



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

Chapter 6 presents the results of the adherence part of the OpTAT study (i.e., the impact of the interprofessional medication adherence program on components of adherence, beliefs about medicines and quality of life in patients taking oral anticancer therapies). The paper is in preparation and co-authors have not yet reviewed the article.

The main results of this study were presented as a poster presentation (Appendix 5) at the annual ESPACOMP congress in November 2022 (Berlin, Germany)[243]. The poster was awarded with the *Jean-Michel Metry Poster Prize* for the best poster presentation (Appendix 6).

A pharmacist-led interprofessional medication adherence program improved adherence to oral anticancer therapies: the OpTAT randomized controlled trial[1]

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[1] Co-authors have not yet reviewed the article.

I. Abstract

Background Oral anticancer therapies such as protein kinase inhibitors (PKIs) are increasingly prescribed in cancer care. We aimed to evaluate the impact of a pharmacist-led interprofessional medication adherence program (IMAP) on patient implementation, persistence and adherence to 27 PKIs prescribed in different types of solid cancers, as well as the impact on patients' beliefs about medicines (BAM) and quality of life (QoL).

Methods Patients were randomized 1:1 in two parallel arms. All PKIs were delivered in electronic monitors (EM). During the 12-month educational, behavioral and affective intervention, pharmacists supported patient adherence through monthly electronic and motivational feedback; the control arm received standard care plus EM without intervention. Medication implementation and adherence were compared between groups using generalized estimating equation models, in which relevant covariables were included; persistence was compared with Kaplan-Meier curves. Questionnaires to evaluate BAM and QoL were completed in patients who refused to participate and those who accepted at inclusion, 6- and 12-month post-inclusion.

Results PKI implementation was constantly higher in the intervention (n=58) than in control arm (n=60), 98.1% and 94.9% (Δ3.2%, 95%CI 2.6%; 3.7%) at 6 months. The probabilities of persistence and adherence were comparable between groups, as well as BAM and QoL scores – no difference in BAM or QoL were found in patients who refused versus those who participated. The intervention benefited most to men (Δ5.4%, 95%CI 4.2; 6.5), those who initiated PKI for more than 60 days (Δ4.6%, 95%CI 3.7; 5.5), patients without a diagnosis of metastasis (Δ4.6%, 95%CI 3.4; 5.7), those aged less than 60 years old (Δ4.1%, 95%CI 3.3; 4.9) and those who had never used any adherence tools (Δ4.1%, 95%CI 3.4; 4.7). Oncologists prescribed regular treatment interruptions to help patients recover from side effects; this information was compiled in the implementation and adherence analyses.

Conclusions The IMAP, led by pharmacists in interprofessional collaboration, supports adherence, specifically implementation, to PKIs in solid cancers. Patients struggle with side effects, forcing oncologists to prescribe off-label regimens. Longer-term medication adherence interventions, embedded in routine care, should provide results on the impact on progression-free survival.

Trial registration ClinicalTrials.gov NCT04484064

Keywords medication adherence, electronic adherence monitoring, oral anticancer therapy, protein kinase inhibitors, adherence interventions, interprofessionality, digital technology, digital pharmacy

II. Introduction

1. Background

New cancer cases were diagnosed in 19.3 million people worldwide in 2020, and 10.0 million patients died from this disease[1]. Despite an increasing incidence of cancer cases, mortality is decreasing in developed countries, thanks to early diagnosis and advanced cancer treatments, such as oral anticancer therapies (OAT)[2]. OAT include a large variety of therapeutic agents, such as cytotoxic and immunomodulatory drugs, hormonal antagonists and targeted agents that complement or substitute intravenous (IV) chemotherapy. Targeted agents include protein kinase inhibitors (PKIs), which are antagonists of mutated protein kinases; these kinases favour the signalling pathways of uncontrolled cancer cell growth and spread[3]. In 2001, the PKI imatinib was launched in the pharmaceutical market and revolutionized cancer care by showing significant clinical benefit and prolonged survival in patients with chronic myeloid leukemia (CML)[4]. Since then, an increasing number of OAT have been marketed for a wide variety of cancers –as many as 11 compounds have been approved by the United Stated Food and Drug Administration (FDA) in 2020[5]. Patients often prefer being prescribed OAT compared to IV chemotherapy, as the oral administration route is more convenient, less invasive and no hospitalization is required[6]. Although OAT increase patient autonomy, patient responsibility in self-managing the treatment at home is extensive and the oncology healthcare team cannot directly supervise medication adherence and side effect management.

Medication adherence is defined by the extent to which a patient takes the treatment as prescribed, ideally following a shared decision-making process with the healthcare team. Medication adherence is characterized by three interrelated and quantifiable phases: treatment initiation (i.e. first dose taken), treatment implementation (i.e., the extent to which the patient's dosing history corresponds to the prescription –according to the correct dosing regimen, the correct timing and other specific requirements) and discontinuation (i.e., the patient stops taking the treatment prematurely)[7]. The persistence to treatment is the time between the first and the last dose taken[7]. Achieving an optimal adherence is paramount to reach targeted clinical outcomes[8], as nonadherence to OAT increases drug resistance, leads to treatment failure[9, 10] and decreases survival[11-13]. Overall, it is estimated that one quarter to one third of patients do not implement or persist to OAT[14, 15], due to a large variety of clinical, personal and contextual determinants (i.e., intolerance, toxicity, regimen complexity, low perceived need for OAT at distance from diagnosis, forgetfulness, high out-of-pocket costs in some countries)[16-18]. To address these determinants, interventions to improve adherence to OAT have been increasingly reported in the last decade, but their evaluation and evidence on the improvement of adherence

and clinical outcomes remain limited. However, multifactorial interventions tailored to patients' needs (i.e., education, counselling, behavioral interventions), such as pharmacist-led programs, have shown promising results[19-22]. While the majority of the studies monitored adherence to endocrine therapies in patients with breast cancer or adherence to PKIs in CML, little is known about adherence to other PKIs prescribed in solid tumors.

The Interprofessional Medication Adherence Program (IMAP), implemented for more than 20 years at the community pharmacy of the Center of Primary Care and Public Health *Unisanté* (Lausanne, Switzerland)[23, 24], supports adherence and retention in care in chronically ill patients[25, 26]. In a prior study, even if medication implementation was high and stable among 43 patients included in IMAP treated with endocrine therapies and cytotoxic agents, 15% had discontinued their medication at 12 months[22]. In this context, the randomized and controlled Optimizing Targeted Anticancer Therapies (OpTAT) study was implemented at the community pharmacy of *Unisanté* and at the Lausanne University Hospital, located in the same hospital complex[27].

2. Objectives

The first objective of the OpTAT study was to evaluate the longitudinal impact of a pharmacist-led IMAP (=intervention group) on implementation, persistence and adherence to PKIs over 12 months, compared to the standard of care (=control group). We also aimed to evaluate the impact of the IMAP on patients' beliefs about medicines (BAM) and their quality of life (QoL) at study inclusion, 6 and 12 months in both groups, and to compare BAM and QoL between patients who accepted and those who refused to participate. The second objective was to evaluate the impact of patients' clinical and demographic covariables on implementation to PKIs in both groups. The third objective was to describe patient implementation longitudinally by considering adaptations of the PKI prescriptions by the oncologists (i.e., prescriptions of PKI interruptions, off-label decreased regimens), compared to the labelled regimen marketed by pharmaceutical industries.

3. Outcomes

We considered a daily medication intake outcome, defined as a longitudinal binary variable (correct intake=1; incorrect intake =0) measured for each patient at each day of the monitoring period. The medication intake was considered as correct (=1) a given day *t* when the patient took at least all the prescribed drug doses for each EM that day, being incorrect (=0) otherwise. Empirical implementation was defined by the proportion of patients with a correct medication intake (proportion of outcomes =1) among patients still participating in the study that day.

A second continuous outcome was the individual time between study inclusion and treatment discontinuation.

Treatment adherence was defined at each day *t* by the proportion of patients with a correct medication intake among all patients initially included in the study, including patients having discontinued before time *t*.

4. Hypothesis and Research Questions

We hypothesized that PKI implementation, persistence and adherence in patients included in the intervention group (i.e., benefiting from the IMAP) would be improved and would stay stable over time compared to control patients. We further hypothesized that improvement in adherence would also result in a better QoL of patients in the intervention group and these patients would perceive fewer prejudices and concerns about taking PKI. We hypothesized that PKI implementation would be affected by demographic (age, gender) and clinical determinants (time since PKI initiation, presence of metastases), and previous use of adherence tools. PKI implementation would be significantly lower if the off-label regimen adaptations prescribed by oncologists would not be considered in the calculation instead of the on-label regimens as prescribed at PKI initiation.

III. Methods

1. Ethical considerations and guidelines

The OpTAT study was approved by the local ethics committee "*Commission cantonale d'éthique de la recherche sur l'être humain*" (Vaud, Switzerland, ID 65/15) in 2015. All included patients signed an informed consent form to participate. The study was conducted in accordance with the declaration of Helsinki. Both the ESPACOMP Medication Adherence Reporting Guidelines (EMERGE)[28] and Consolidated Standards of Reporting Trials (CONSORT) guidelines[29] were used to report findings.

2. The OpTAT medication adherence study

Design of the OpTAT study

The OpTAT protocol has been published elsewhere[27]. The OpTAT study is monocentric, open, and composed of two parts: i) the randomized and controlled medication adherence study and ii) a combined PKI pharmacokinetic and pharmacodynamic analysis based on the collection of patients' blood samples. While partial results were reported in a subgroup of patients included in OpTAT and treated with palbociclib –a PKI prescribed in metastatic breast cancer–[30], this paper presents the results of the medication adherence part in all patients included in OpTAT.

Eligible patients were adults treated with an oral PKI for solid cancers. Patients were excluded if

they did not self-manage their treatment (i.e., benefited from home care services, caregivers or under tutelage) or if they were diagnosed with major cognitive impairments. Patients' reasons for refusal to participate in the study were collected in Case Report Forms (CRF). The PKI was delivered in electronic monitor(s) (EM, Medication Event Monitoring System, MEMS and MEMS AS, AARDEX Group, Sion, Switzerland) in all included patients. The EM is an interactive digital technology, composed of a pill-bottle and a cap, in which a chip records the time and date of each EM opening, considered as a proxy for drug intake. A Liquid Cristal Display (LCD) screen on top of the EM cap informs the patient on the number of daily EM openings (i.e., from 3:00 am to 2:59 am the next day). Baseline medication adherence was monitored by EM for 21 days, after which patients were randomized 1:1 in two parallel arms (intervention or control) (see Fig. 1, adapted from Bandiera et al[27]). In order to distribute equitably cancer types and PKI experience between groups, randomization was stratified per cancer type and time since PKI initiation (i.e., more or less than 30 days).

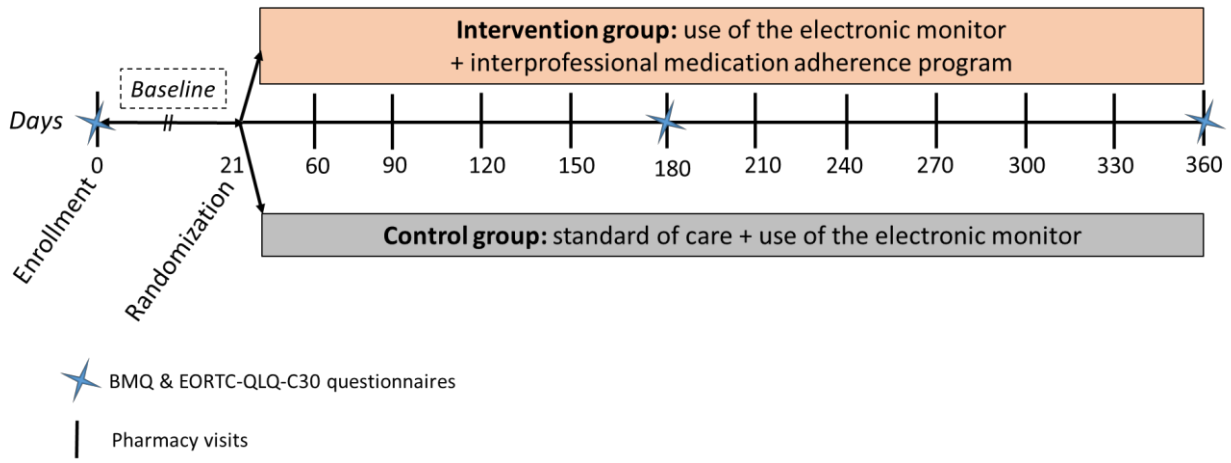


Figure 1: Design of the adherence part of the OpTAT study adapted from Bandiera et al[27]

NB: BMQ= Beliefs about Medicines Questionnaire; EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, version 3.0

Intervention group: the IMAP

The intervention group benefited from the IMAP, which consists in a monthly 15-minute face-to-face patient-pharmacist interview, in an interview room; medication adherence feedback is provided to the patient using the spirit and techniques of motivational interviewing, guided by the theoretical model of Fisher et al. "Information-Motivation-Behavioral skills"[31]. In a non-

judgmental way, the pharmacist investigated the patient's needs in terms of information on medication and medication behavior, the patient's motivation and readiness to take the treatment, and explored the patient's daily medication and side effects management. If medication adherence was suboptimal, the pharmacist explored the patient's willingness and capacity to change his/her behavior. BAM and QoL were also explored and addressed whenever needed. After the intervention, the pharmacist sent a structured adherence report summarizing the content of the intervention to the healthcare team (e.g., oncologist, nurses), which strengthened interprofessional collaborations. To note, during the coronavirus disease (COVID)-19 pandemic lockdown, interviews were conducted by phone calls and pill boxes were sent by mail so that patients could refill their EM at home[32].

Medication adherence feedback is provided based on sharing the EM chronology plot to the patient (i.e., a graph representing, day-by-day, the occurrence and timing of each EM opening since the last interview). Importantly, before showing the chronology plot as feedback to the patient, the pharmacist asked patients to report i) the estimated perceived number of missed doses since the last interview; ii) the non-monitored periods during which the EM was not used (e.g., during hospitalizations); iii) the use of pocket-doses (i.e., when the patient opened the EM to take the pill more than 24 hours later) or curiosity checks (i.e., EM openings without drug intake). In addition, pharmacy technicians performed a pill count to calculate an aggregated percentage of medication intake since the last refill. The pill count allowed pharmacists to reconcile EM and pill count data to strengthen the methodology, especially in case of multiple tablets per intake.

Control group: use of the EM in addition to the standard of care

Patients included in the control group used the EM but did not benefit from the IMAP. EM adherence data were blinded to the patient, the pharmacy, the clinical and the research teams. The patient came to the pharmacy after each medical consultation to fill the EM with the prescribed PKI. At each pharmacy visit, the pharmacist asked predefined questions to the patient at the pharmacy counter to report any deviation from the expected EM use (e.g., pocket doses, non-monitored periods), which were reported in a CRF. The pharmacy technicians counted the number of pills returned to the pharmacy without calculating the aggregated percentage of medication intake.

Questionnaires

In both groups, patients were asked to fill a set of questionnaires validated in French with good psychometric properties at inclusion, 6- and 12-month post-inclusion: i) the validated French version of the Beliefs about Medicines Questionnaires (BMQ)[33] developed by Horne et al.[34],

which evaluates perceived necessity, beliefs, concerns and prejudices about the treatment, and ii) the validated French version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30, version 3.0)[35], which evaluates QoL through patients functioning, symptoms and global health status. Patients who refused to participate in the study were also invited to fill both questionnaires anonymously.

3. Database construction

Collection of patients' clinical and sociodemographic data and questionnaires

At study inclusion, patients' sociodemographic (i.e., age, gender, civil status, ethnicity) and clinical data (i.e., oncology clinic, time since primary and metastasis cancer diagnosis, presence of metastases, PKI treatment objective –if palliative, number of palliative lines–, time since PKI initiation, actual oncology treatment –name of actual PKI, number of PKIs monitored and combined anticancer treatments–, previous oncology treatments, number of oral prescribed chronic non-oncologic treatments, use of adherence tools and if yes, adherence tools used) were retrieved from the electronic medical and administrative records (Soarian, Oracle Cerner, USA) of the Lausanne University Hospital.

Patient-reported data regarding adherence was collected in CRFs (i.e., reasons for drop-out, attendance to the IMAP after study end). Patients completed the BMQ and EORTC-QLQ questionnaires on paper. All data were gathered in the secure web platform REDCap™ version 6.13.3 (Vanderbilt University)[36].

EM adherence database

The raw EM database was cleaned and enriched using a semi-automated procedure developed in the statistical software R by our research team (i.e., the CleanADHdata.R script available on https://github.com/jpasquier/CleanADHdata). For each patient, we truncated the EM adherence database by the actual start and end dates of EM use, we adapted the number of expected EM openings based on the prescription sheets; we considered all adaptations over time (i.e., dosage and regimen changes and transient interruptions) by exploring and reconciling all available sources: patient medical record, pharmacy record and patient report. In case of EM non-openings, if a patient reported pocket-doses and if the pill count confirmed that the doses were indeed taken, we corrected the number of EM non-openings by inserting the number of pockets-doses reported by the patient. We set non-monitored periods as the periods during which the patient did not use the EM (e.g., hospitalizations), for which the implementation outcome was missing. We enriched the EM adherence database with patient covariables (e.g., age, group of randomization, presence of treatment discontinuation or censoring times), EM covariables (e.g., international

nonproprietary name, dosing strengths) and adverse effects reported by patients at each medical visit.

To answer our first and second objectives, in case of off-label PKI interruptions prescribed by the oncologist, the number of expected EM opening was 0, leading necessarily to an optimal implementation according to our definition. On the contrary, to answer our third objective, the off-labelled PKI interruptions prescribed by oncologists were considered as a deviation from the official regimen recommendations provided by the pharmaceutical industry. Therefore, all off-labelled EM expected openings of 0 were replaced by the number of EM expected openings based on the usual PKI regimen recommended by the pharmaceutical industry.

4. Statistical analysis

a. Descriptive analysis

In both groups, sociodemographic and clinical variables were presented as proportions for categorical variables and in median and interquartile ranges (IQR) for continuous variables.

b. Implementation

For each EM used by the patient, the medication intake was considered correct (=1) if the number of observed EM openings was at least equal to the number of expected EM openings defined based on the prescription of the oncologist; medication intake was considered incorrect otherwise (=0). At each day of the monitoring period, empirical implementation was defined by the proportion of patients with a correct medication intake (proportion of outcomes=1) among patients still participating in the study that day[22].

From study inclusion to 12 month-post inclusion, longitudinal implementation was then described by a generalized estimating equation (GEE) model on the daily medication intake 0/1, with an autoregressive correlation structure and a polynomial time effect.

Since patients experienced a baseline period before being randomized either to stay in the control group or to be included in the intervention group, the group variable was introduced in the GEE model with two time-dependent variables representing at each day *t* the time spent in the intervention and the time spent in the control group until *t*. The model estimate of implementation was presented at 6-month post-inclusion (i.e., when the impact of the intervention can be best evaluated, e.g. with most patients still participating in the study) in a representative patient remaining in the control group after randomization and in a representative patient switching to the intervention group after the baseline period of 21 days. The difference (Δ) of treatment

implementation and the 95% confidence intervals (95%CI) between the two representative patients at 6 months were also presented.

Patient age, gender, use of adherence tools, time since PKI initiation and the presence of metastases were included as covariables one at the time into the GEE model. Continuous variables were dichotomized at their median value.

c. Persistence and adherence

We defined a PKI discontinuation as a premature PKI stop for adverse effects (i.e., symptoms experienced by the patient), based (or not) on a shared decision-making between the patient and the oncologist, or for any other patients' personal and unilateral reasons. Other reasons of premature PKI stop (i.e., clinical reasons other than side effects, cancer progression or toxicity for which no symptoms were experienced by the patient), or study interruptions without discontinuing PKI were considered as censoring times. Treatment persistence was characterized by the distribution of the continuous outcome defined as the individual times until treatment discontinuation, and it was estimated by Kaplan Meier survival curves, allowing to account for censored durations[22].

Empirical adherence was defined at each day by the proportion of patients with a correct medication intake (outcome=1) among all patients initially included in the study[22], corresponding to the product between the probabilities of PKI implementation and persistence at each day of the monitoring period[37]. Adherence was then compared between study groups using GEE model, using a predefined methodology[37]. The baseline period was excluded from this analysis (i.e., data are included from the randomization date) and the monitoring period was considered until 340 days (i.e., approximately 12 months minus the 21 days of the baseline period). The model estimate of adherence was presented at 6-month post-randomization in both groups, as well as the difference (Δ) between groups with 95%CI.

d. Questionnaires

i) BMQ

The BMQ is composed of 18 questions rated on a 5-point Likert scale from 1 "Strongly agree" to 5 "Strongly disagree". The questionnaire evaluated four scales of BAM: specific beliefs, among which the perceived necessity for the treatment (5 questions) and the concerns about the treatment (5 questions); and the general beliefs, among which the perception of over-prescribing (4 questions) and the perceived prejudices of the treatment (4 questions). For each scale, a total score was calculated by adding the reverse scores of the questions, which ranged from 5 to 25

for perceived necessity and concerns, and from 4 to 20 for perceived over-prescribing and prejudices[33]. Higher scores indicate stronger beliefs[33].

ii) EORTC-QLQ-C30

The EORTC-QLQ-C30 questionnaire is composed of 30 questions, exploring patients' functional status (15 questions) and patients' symptoms (13 questions), rated on a 4-point Likert scale from 1 "Not at all" to 4 "Very much"; and perceived global health status (2 questions) rated on a 7-point Likert scale from 1 "Very poor" to 7 "Excellent". Each scale was scored as follows: the mean of the score per question (RawScore, RS) was linearly transformed to a 0-100 score (S) as defined by the guidelines (i.e., for the functional scale, S=(1-(RS-1)/3)x100; for the symptom scale, S=((RS-1)/3)x100 and for the global health status, S=((RS-1)/6)x100)[35, 38]. A high score for the functional scale indicates a healthy level of functioning, a high score for the global health status indicates high QoL and a high score in the symptom scale indicates a high level of symptomatology[38].

For each scale of both questionnaires, the mean scores and their standard deviation were reported in patients who refused to participate and completed the questionnaire at the enrollment date, and in patients who accepted to participate and completed the questionnaire at study inclusion. The mean scores and their standard deviation were also reported in patients included in the intervention and in the control groups, at 6-month and 12-month post-inclusion. Welch's t-tests were performed to compare scores between groups; a statistically significant difference was considered if $p<0.05$. Missing values were clearly depicted.

IV. Results

1. Included patients

The study was offered to 241 eligible patients, of whom 111 refused to participate. In total, 130 patients were included, of whom 12 left the study during the baseline period. Among them, 3 patients did not use the EM. The median time spent in the adherence study was 184 (IQR 108; 359) days among patients included in the intervention group versus 247 (135; 375) in the control group. To note, after study completion, 5 patients in the intervention group decided to keep attending the IMAP and 4 patients in the control group decided to start attending the IMAP.

EM data of 127/130 (97.7%) patients were analyzed. The sociodemographic and clinical variables of these 127 patients (intervention group n=58, control group n=60; not randomized n=9) are presented in Table 1. In total, 27 PKIs or association of PKIs were monitored, of which 4 PKIs

were prescribed as a cyclic regimen. Most patients were diagnosed with a gastrointestinal cancer or breast cancer. The majority of patients were diagnosed with metastasis and the PKIs were mainly prescribed with a palliative objective. Even if patients were not polymedicated (i.e., less than 5 chronic daily treatments prescribed[39]), approximately a quarter of the patients in both groups had used adherence tools in their therapeutic itinerary, which was in most cases a weekly pill-box.

Table 1: Patients' demographic and clinical data at study inclusion

	Intervention (n=58)	**Control (n=60) + not randomized (n=9)**
Demographic data at inclusion		
Age (years), median (IQR)	61 (53.0-70.7)	61 (52.2 ; 68.4)
Female gender, n patients (%)	37 (63.8)	38 (55.1)
Marital civil status[a], n patients (%)	30 (51.7)	40 (58.0)
Caucasian, n patients (%)	55 (94.8)	61 (88.4)
Clinical and pharmaceutical data at inclusion		
Oncology clinic, n patients (%)	Breast cancers 21 (36.2) Gastrointestinal cancers 17 (29.3) Melanoma 5 (8.6) Sarcoma 4 (6.9) Urologic cancers 4 (6.9) Oral cancers 3 (5.2) Gynaecologic cancers 3 (5.2) Lung cancers 1 (1.7)	Gastrointestinal cancers 22 (31.9) Breast cancers 21 (30.4) Melanoma 6 (8.7) Gynaecologic cancers 6 (8.7) Sarcoma 5 (7.3) Urologic cancers 4 (5.8) Lung cancers 4 (5.8) Oral cancers 1 (1.4)
Time since primary cancer diagnosis (years), median (IQR)	4.2 (1.7-8.0) Missing data n=2	2.1 (0.9-5.8)
Presence of metastases (cancer stage IV), n patients (%)	50 (86.2)	53 (76.8)
Time since metastasis diagnosis (years) among patients with metastasis, median (IQR)	1.9 (0.8-2.9) Patients without metastases n=8	1.6 (0.6-2.4) Patients without metastases =16

Treatment objective of the first PKI monitored, n patients (%)	Palliative 46 (79.3) Adjuvant 8 (13.8) Neo-adjuvant 4 (6.0)	Palliative 58 (84.1) Neo-adjuvant 9 (13.0) Adjuvant 2 (2.9)
If palliative objective, palliative line, n patients (%)	1st line 19 (41.3) >=3rd line 17 (37.0) 2nd line 10 (21.7) No observation n=12	1st line 24 (41.4) >=3rd line 22 (37.9) 2nd line 12 (20.7) No observation=11
Time (days) between initiation of monitored PKI and study enrollment, median (IQR)	57 (18-207)	63 (20-177)
Name of the anticancer molecule monitored, n patients (%)[b]	Palbociclib 19 (32.8) Regorafenib 7 (12.1) Pazopanib 6 (10.3) Imatinib 5 (8.6) Sorafénib 4 (6.9) Everolimus 3 (5.2) Lenvatinib 3 (5.2) Trametinib/Dabrafenib 3 (5.2) Axitinib 2 (3.4) Olaparib 2 (3.4) Cobimetinib 1 (1.7) Erdafitinib 1 (1.7) Erlotinib 1 (1.7) Niraparib 1 (1.7) Trametinib 1 (1.7) Trametinib/olaparib 1 (1.7) Vémurafenib 1 (1.7) Cabozantinib 1 (1.7) Binimetinib 0 (0) Alectinib 0 (0) Cobimetinib/Vémurafenib 0 (0) Encorafenib 0 (0) Lapatinib 0 (0) Osimertinib 0 (0) Ribociclib 0 (0) Sunitinib 0 (0) Neratinib 0 (0)	Palbociclib 18 (26.1) Imatinib 14 (20.3) Trametinib/Dabrafenib 5 (7.2) Pazopanib 4 (5.8) Regorafenib 4 (5.8) Sorafénib 3 (4.3) Sunitinib 3 (4.3) Axitinib 3 (4.3) Alectinib 2 (2.9) Everolimus 2 (2.9) Niraparib 2 (2.9) Olaparib 2 (2.9) Binimetinib 1 (1.4) Cobimetinib/Vémurafenib 1 (1.4) Encorafenib 1 (1.4) Lapatinib 1 (1.4) Lenvatinib 1 (1.4) Osimertinib 1 (1.4) Ribociclib 1 (1.4) Trametinib 1 (1.4) Neratinib 1 (1.4) Cabozantinib 0 (0) Cobimetinib 0 (0) Erdafitinib 0 (0) Erlotinib 0 (0) Trametinib/olaparib 0 (0) Vémurafenib 0 (0)

Number of monitored PKI per patient, median (IQR)	1 (1-1)	1 (1-1)
Previous oncologic treatments since cancer diagnosis, n patients (%)	Tumor surgery 44 (75.9) Chemotherapy iv 30 (51.7) Radiotherapy or radiofrequency 29 (50.0) Endocrine therapy 19 (32.8) Immunotherapy 10 (17.2) Anti-VEGF (Avastin, Bevacizumab) 8 (13.8) Oral chemotherapy (Xeloda, capécitabine) 6 (10.3) Oral PKI 5 (8.6) Hormonal iv (Fulvestrant) 5 (8.6) Goserelin (Zoladex) or leuprorelin (Lucrin) 4 (6.9) m-TOR inhibitors (everolimus) 3 (5.2) Radioembolisation 3 (5.2) Chemoembolisation 3 (5.2) Cryoablation 2 (3.4) Thermal ablation 1 (1.7) Radiosurgery 0 (0) Anti-HER-2 (Kadcyla, Herceptin, trastuzumab) 0 (0) No previous anticancer treatments n=4 (6.9)	Tumor surgery 43 (62.3) Chemotherapy iv 29 (42.0) Radiotherapy or radiofrequency 28 (40.6) Endocrine therapy 19 (27.5) Immunotherapy 10 (14.5) Previous anti-VEGF (Avastin, Bevacizumab) 13 (18.8) Oral PKI 8 (11.6) Oral chemotherapy (Xeloda, capécitabine) 6 (8.7) Hormonal iv (Fulvestrant) 3 (4.3) Anti-HER-2 (Kadcyla, Herceptin, trastuzumab) 3 (4.3) m-TOR inhibitors (everolimus) 2 (2.9) Chemioembolisation 2 (2.9) Cryoablation 2 (2.9) Radiosurgery 1 (1.4) Radioembolisation 1 (1.4) Thermal ablation 1 (1.4) Goserelin (Zoladex) or leuprorelin (Lucrin) 1 (1.4) No previous anticancer treatments n=13 (18.8)
Combined anticancer treatment in addition to PKI at inclusion, n patients (%)	Hormonal iv (Fulvestrant) 11 (19.0) Endocrine therapy 9 (15.5) Chemotherapy iv 1 (1.7) Radiotherapy 2 (3.4) Goserelin (Zoladex) or leuprorelin (Lucrin) 2 (3.4) Anti-VEGF (Avastin, Bevacizumab) 1 (1.7) Immunotherapy 0 (0) No concomitant anticancer treatment n=45 (77.6)	Hormonal iv (Fulvestrant) 12 (17.4) Endocrine therapy 8 (11.6) Immunotherapy 2 (2.9) Radiotherapy 2 (2.9) Goserelin (Zoladex) or leuprorelin (Lucrin) 2 (2.9) Chemotherapy iv 0 (0) Anti-VEGF (Avastin, Bevacizumab) 0 (0) No concomitant anticancer treatment n=35 (50.7)

Number of oral prescribed chronic non-oncologic treatments at inclusion, median (IQR)	3 (1-5)	2 (1-4)
Patients having used previous adherence supporting tools, n patients (%)	14 (25.0) Missing data n= 2	17 (25.0) Missing data n= 1
Adherence personal tools used, n patients (%)	Weekly pill-box 13 (22.4) Other personal tools 1 (1.7) Electronic monitor 0 (0)	Weekly pill-box 16 (23.2) Electronic monitor 1 (1.4) Other personal tools 0 (0)

NB: PKI=protein kinase inhibitors, IQR=interquartile ranges; IMAP=Interprofessional Medication Adherence Program. [a]The other patients are divorced, single, widowed, separated or other; [b]Some patients were monitored with more than one PKI.

Face-to-face interviews with patients in the intervention group lasted a median of 18 minutes (IQR 11; 25), and pharmacists wrote the adherence report in 20 minutes (IQR 15; 25). The pharmacist met control patients during a median time of 5 minutes (IQR 5; 10), and the pharmacists took another 5 minutes (IQR 2; 5) to fill in the CRF.

Fig. 2 describes patient enrollment from inclusion to data analysis. In the intervention group, 15/58 (26%) patients completed the 12-month study. Among patients who discontinued the study, 35/43 (81%) of patients left the study due to clinical reasons and 8/43 (19%) patients dropped out. In the control group, 30/60 (50%) patients completed the 12-month study and among patients who discontinued the study, 25/30 (83%) left the study due to clinical reasons and 5/30 (17%) patients dropped out. In both groups, the main reasons for PKI premature stops were cancer progression, side effects or toxicity. Two patients in the control group died during the study.

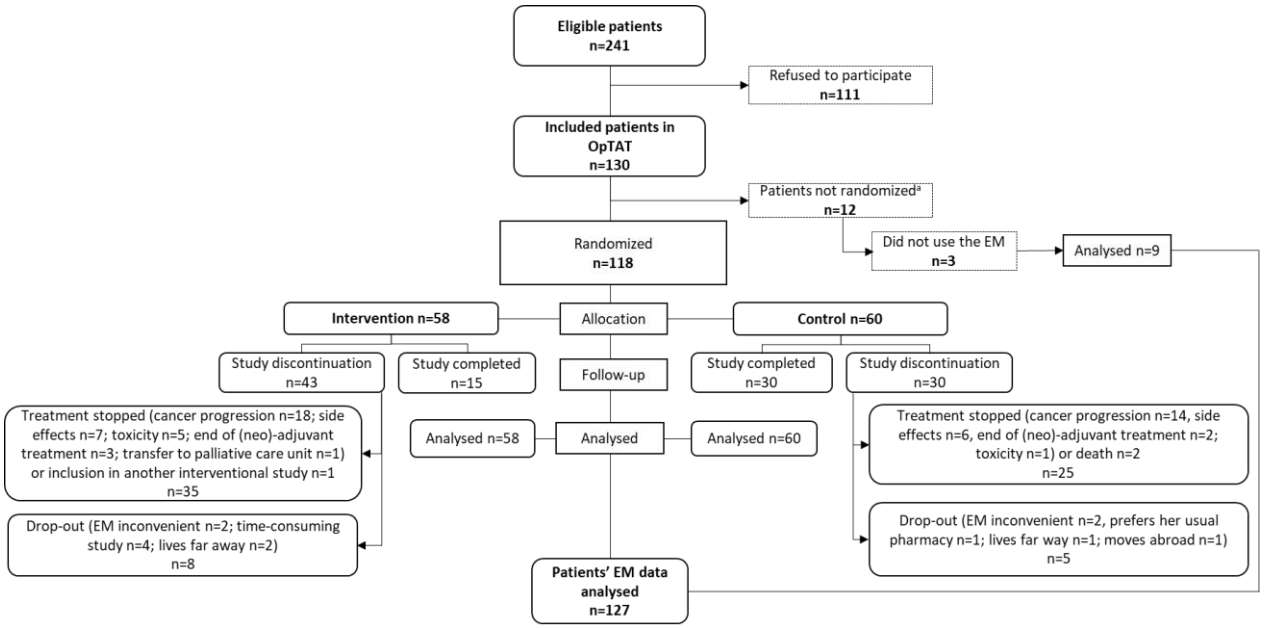


Figure 2: Flow of patient enrollment from inclusion to data analysis.

NB: [a]patients left the study during the baseline period before randomization.

2. PKI implementation

Treatment implementation is presented in Fig. 3 for a representative patient randomized in the intervention group at day 21 (red line) versus a representative patient who stayed in the control group after randomization (blue line). Implementation to PKI improved in patients included in the intervention group since the first interview at 21 days and was constantly higher and more stable during the 12-month monitoring period compared to control patients. At 6 months, the estimation of the probability of PKI implementation in the intervention versus the control group was respectively of 98.1% and 94.9% (Δ3.2%, 95%CI 2.6; 3.7). Fig. 4 shows the impact of covariables on PKI implementation in both groups. Implementation decreased in control patients, especially in men (at 6 months, Δ5.4%, 95%CI 4.2; 6.5), those who, at study inclusion, had initiated PKI more than 60 days ago (Δ4.6%, 95%CI 3.7; 5.5), patients who did not have any metastasis (Δ4.6%, 95%CI 3.4; 5.7), those aged less than 60 years old (Δ4.1%, 95%CI 3.3; 4.9) and those who had never used any adherence tools before inclusion (Δ4.1%, 95%CI 3.4; 4.7).

Table 2 shows the estimation of PKI implementation in both groups by the GEE models and the difference of implementation between groups and its 95%CI.

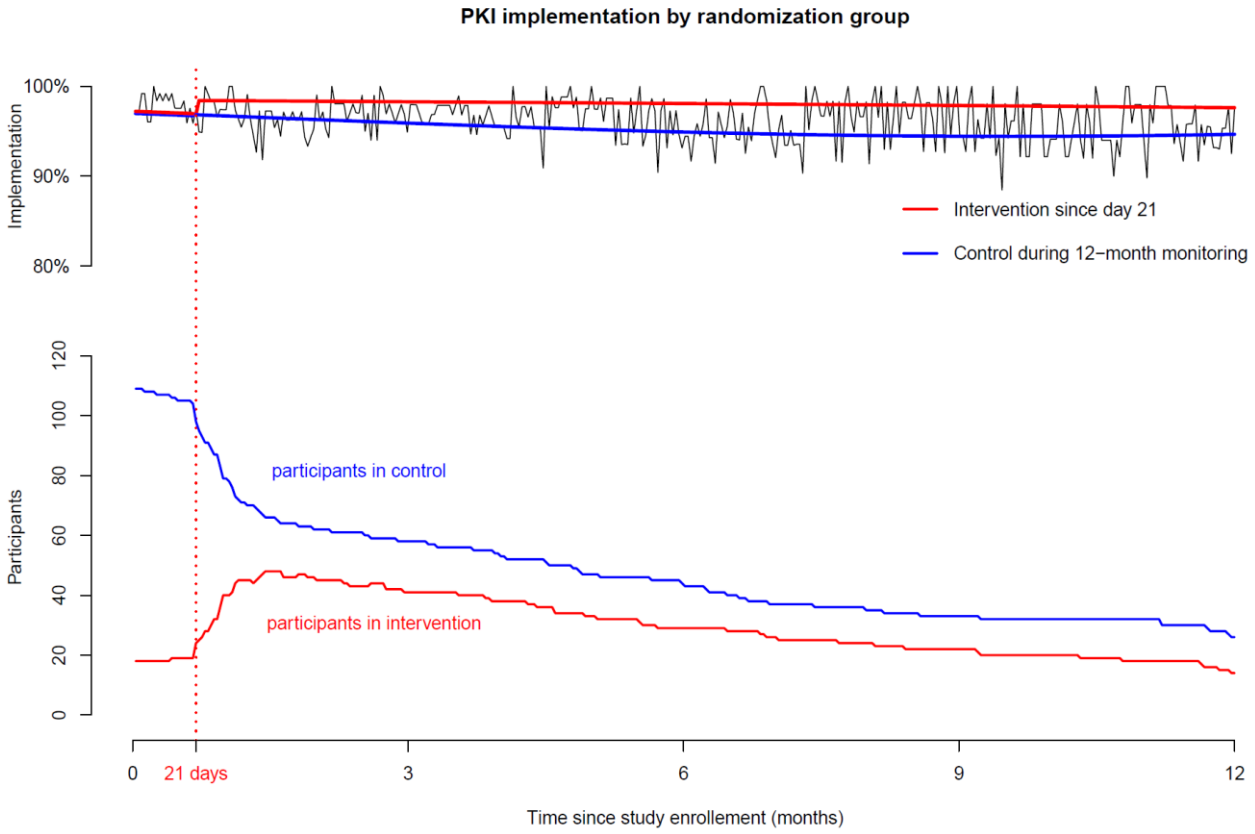


Figure 3: GEE model showing PKI implementation during the 12-month monitoring period for a representative patient randomized in the intervention group since day 21 (red line) versus a representative control patient who stayed in the control group at randomization (blue line).

NB: the black lines on the background show empirical implementation in the total sample. The red and blue lines on the bottom of the figure represent the number of participants over time in the intervention and control group respectively.

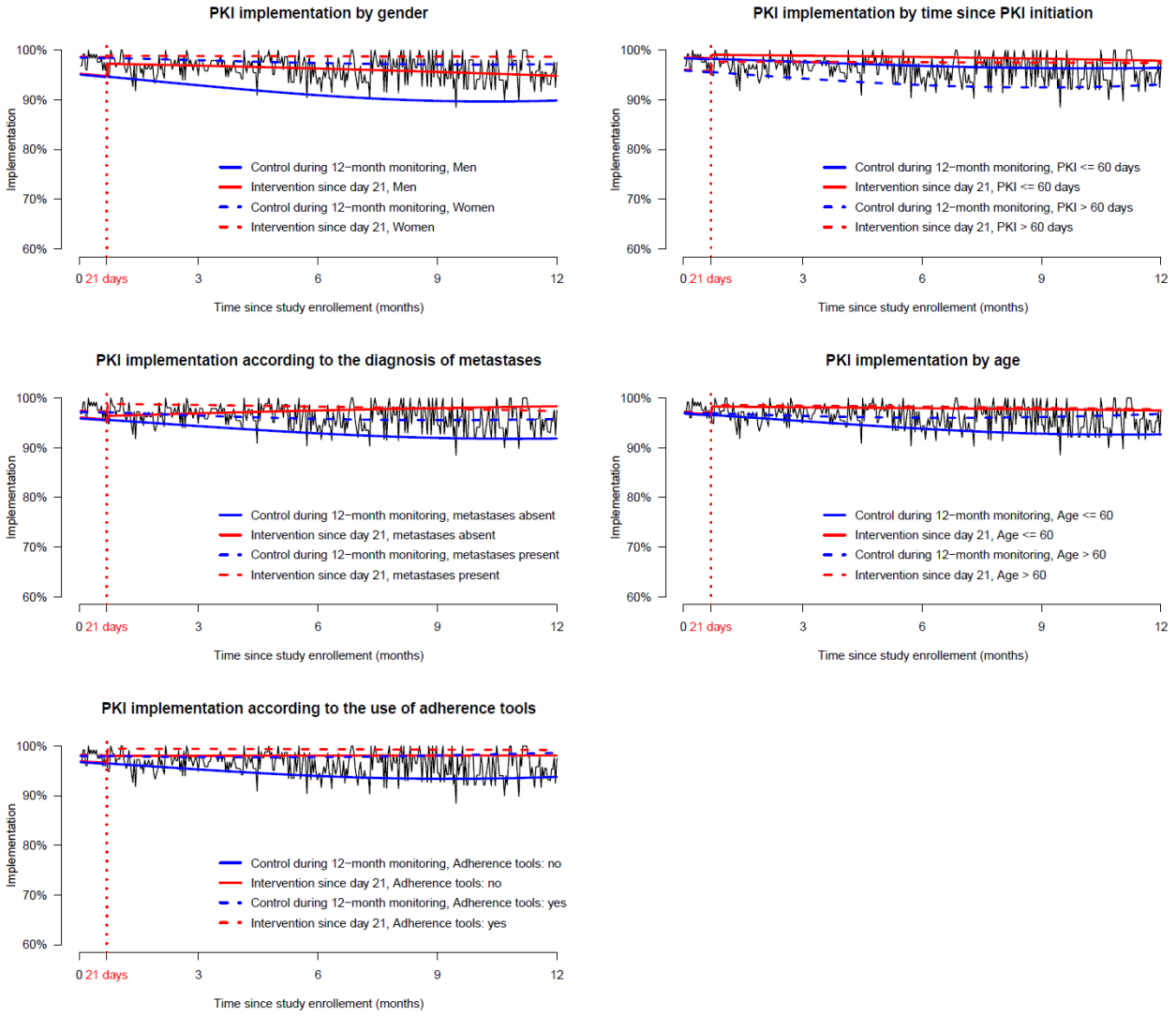


Figure 4: GEE models showing PKI implementation during the 12-month monitoring period for two representative patients randomized in the intervention group since day 21 (continued and dotted red lines) versus two representative control patients who stayed in the control group at randomization (continued and dotted blue lines); a: PKI implementation according to gender, b: according to the time since PKI initiation, c: according to the diagnosis of metastasis, d: according to patients' age, e: according to the use of adherence tools.

NB: the black lines on the background show empirical implementation in the total sample.

Table 2: Probabilities of PKI implementation in representative patients randomized in the intervention and control groups estimated by the GEE models

At 6 months	Intervention	Control	Difference (Δ)	95%CI	
Total implementation	96.27			94.46	97.5
implementation between groups	98.09	94.93	3.16	2.60	3.74
Implementation in men	96.32	90.97	5.35	4.20	6.49
Implementation in women	98.78	97.42	1.36	0.91	1.82
Implementation in patients <= 60 years old	97.96	93.86	4.09	3.30	4.92
Implementation in patients > 60 years old	98.27	96.04	2.23	1.60	2.87
Implementation in patients with a time since diagnosis <= 3y	96.17	95.30	0.88	0.01	1.71
Implementation in patients with a time since diagnosis > 3y	99.04	94.11	4.93	4.22	5.69
Implementation in patients who have never used any adherence tools	98.05	93.98	4.06	3.40	4.73
Implementation in patients who have used adherence tools	99.34	97.75	1.59	0.92	2.29
Implementation in patients without a diagnosis of metastasis	97.49	92.92	4.56	3.44	5.68
Implementation in patients diagnosed with a metastasis	98.28	95.83	2.45	1.89	3.03
Implementation in patients with a time since PKI initiation <= 60 days	98.64	96.85	1.79	1.22	2.35
Implementation in patients with a time since PKI initiation > 60 days	97.57	93.00	4.57	3.72	5.45
Adherence between groups since randomization	88.85	87.42	1.43	-11.36	12.49
Persistence between groups since randomization	91.24	91.67	-0.43	-12.02	11.17
Total implementation according to on-label prescription analysis (i.e., recommendation of the pharmaceutical industry)	88.53			84.19	91.8

3. Persistence and adherence to PKI

In total, 7 patients in the intervention group and 6 in the control group discontinued the treatment due to side effects. Fig. 5 shows the Kaplan Meier survival curves for treatment persistence during the 12-month monitoring period, as well as the estimation of the probability of PKI adherence by the GEE model. At 6 months, the probabilities for treatment persistence and adherence were comparable between groups: in the intervention and control groups respectively, persistence was 91.2% and 91.7% (Δ-0.4%, 95%CI -12.0%; 11.2%) and adherence was respectively 88.9% and 87.4% (Δ 1.4, 95%CI -11.4%; 12.5%).

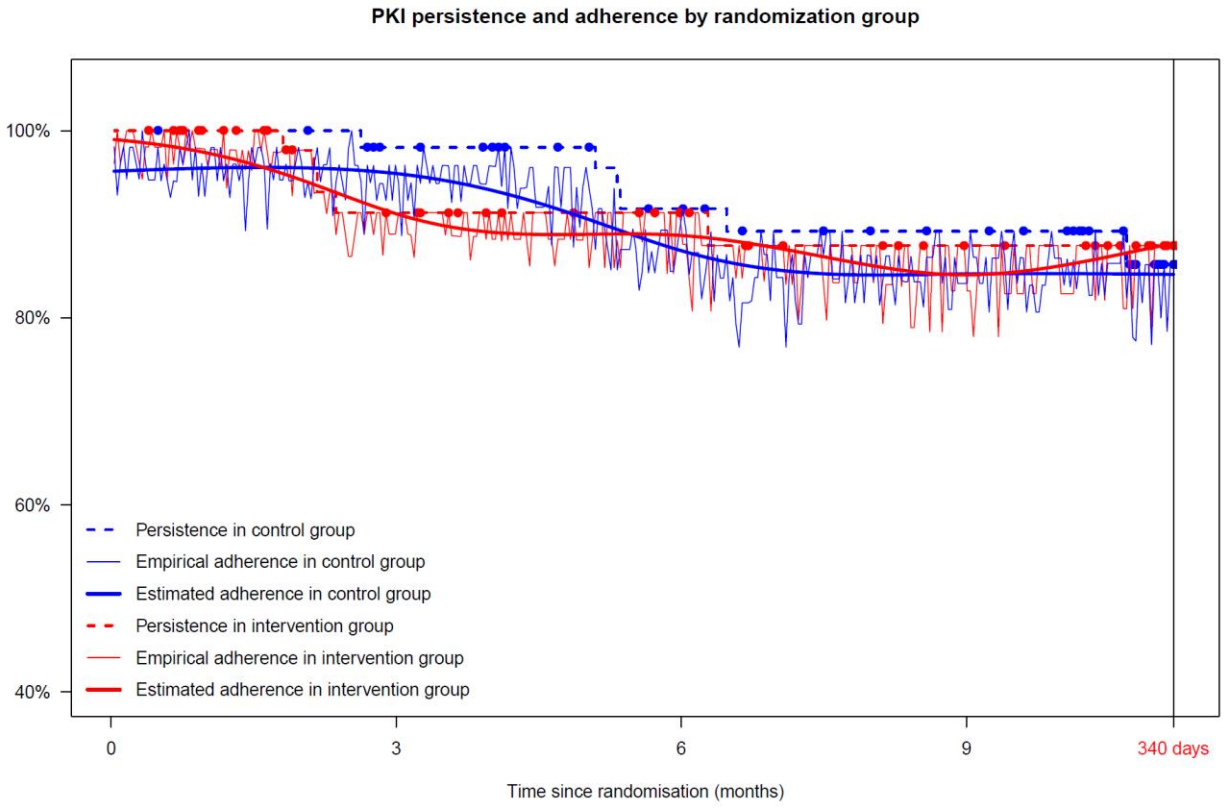


Figure 5: Kaplan Meier curves showing PKI persistence (censoring times are represented with dots on the dotted lines) and GEE model showing PKI adherence in the intervention group (red line) and control group (blue line) since randomization.

NB: the red and blue lines on the background show empirical adherence in the intervention and control groups respectively.

4. **Comparative analysis of PKI implementation between the prescription of PKI interruptions by the oncologist (off-label) and the official recommended regimen by pharmaceutical industries (on-label)**

In all patients included (intervention and control patients), Fig. 6 shows i) implementation to PKI considering the prescribed PKI interruptions by oncologists in the analysis (off-label) and ii) considering the official regimen recommendation provided by pharmaceutical industries (on-label). Patient implementation to PKI would be lower (-7.8%) if the transient interruptions prescribed by the oncologists during the study would not be considered in the analysis: at 6 months, implementation was 96.3% (95%CI 94.5; 97.5) considering the transient interruptions in the analysis versus 88.5% (95%CI 84.2; 91.8%) if the transient interruptions would not have been considered in the analysis.

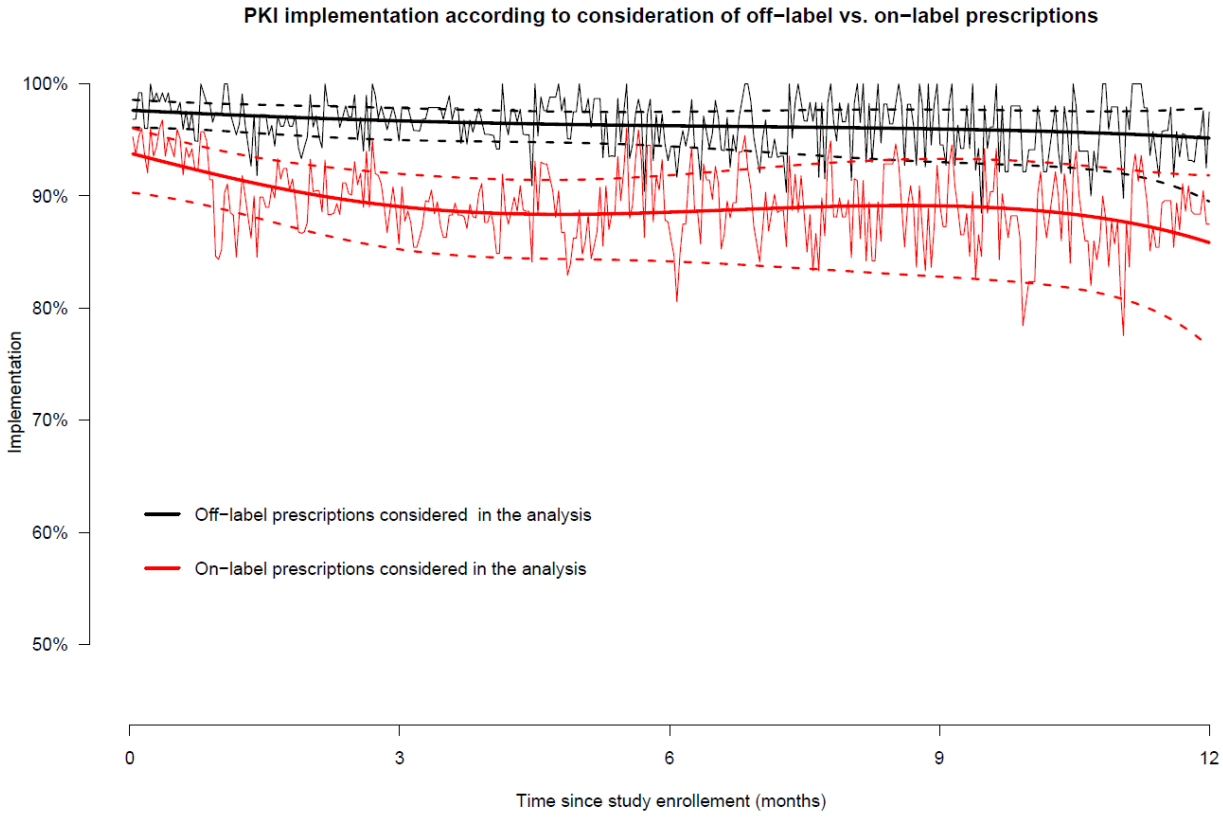


Figure 6: GEE model showing PKI implementation during the 12-month monitoring period in the total sample, considering off-label prescriptions (i.e., following oncologists' prescriptions, black lines) and on-label prescriptions (i.e., the official recommended regimens from the pharmaceutical industry, red lines) and its 95%CI (dotted black and red lines).

NB: the black and red lines on the background show empirical implementation in the total sample considering off-label (black lines) or on-label (red lines) prescriptions.

5. BMQ and EORTC-QLQ-C30 questionnaires

The scores for BAM (i.e., perceived treatment necessity, concerns, prejudices and overprescribing) and for QoL (i.e., in terms of functioning, symptoms and global health status) were comparable in any dimensions of the questionnaires between groups at 6- and 12-month post-inclusion (Appendix 1). Moreover, no difference was found in both questionnaires between patients who refused and those who accepted to participate (Appendix 2). To note, scores for perceived concerns, prejudices and overprescribing were in the upper half of the scale in patients at inclusion, 6-month and 12-month post-inclusion and in patients who refused to participate, which indicates relatively high negative beliefs.

V. Discussion

1. Main results

The IMAP, led by pharmacists in interprofessional collaborations, improved patient implementation to PKI during the 12-month monitoring period, whereas no impact was found on persistence and adherence, nor on BAM and QoL. Regarding medication implementation, the intervention benefited most to men, patients with a longer PKI experience, patients without a diagnosis of metastasis, younger than 60 years old and patients who had never used any adherence tools in their therapeutic itinerary. As oncologists often prescribed PKI interruptions to help patients recover from side effects, such adaptations needed to be considered in the analysis to avoid underestimating implementation and thus adherence.

2. Clinical outcomes, quality of life and beliefs about PKI

While the IMAP increased treatment implementation by 3.2% at 6 months in the intervention group compared to the control group, the impact of such an improvement on clinical outcomes (e.g., progression-free survival, tumor size) needs to be further investigated. In the OpTAT study, we were not able to perform such analysis with a robust methodology because of numerous confounders (e.g., time since cancer diagnosis, time since PKI initiation, PKI prescription objective, PKI palliative line, concomitant oncologic treatment). Future multi-centric studies should consider monitoring medication adherence post-intervention along with progression-free survival and mortality in the cohort of included patients 1- to 5-year post-intervention. Indeed, such data is missing in the literature[8]. The impact of the intervention on patient-reported outcomes and experiences should also be further explored during and post-intervention. Our population reported a low symptomatology and a high level of functioning in both groups since study inclusion, but the perceived global health status was around 6/10 (i.e., showing relatively low perceived QoL). Our

questionnaire data did not show an improvement in QoL in the patients included in the intervention. Patients expressed an unfavorable balance between PKI harm versus necessity, which was not reversed during the intervention.

3. Determinants of implementation

In our study, implementation varied according to covariables. First, control patients without a diagnosis of metastasis, who were prescribed a PKI as neo-adjuvant or adjuvant treatment implemented their PKI less; the perceived disease severity may be lower in these patients than patients with a diagnosis of metastasis, and the PKI may be prescribed in these patients for a longer period of time than for a palliative purpose. As previously reported in the literature and confirmed by our results, a longer treatment experience may be a factor for suboptimal PKI implementation[16, 17]. We also showed that patients who have never used any tools to support medication adherence implemented their PKI less, suggesting that patient past involvement in their care is a determinant of actual PKI implementation that is worth scrutinizing at the start of the IMAP intervention. More women were included as our larger subgroup of patients were patients with breast cancers. The fact that men implemented less their PKI in the control group was not previously reported in the literature and further studies should explore the influence of sociodemographic determinants on adherence to PKI.

4. Side effects related to PKI impact persistence to treatment and force oncologists to adapt prescription

In our study, similarly in each group, more than 20% of patients discontinued their PKI because of side effects (i.e., 7/34 in the intervention and 6/23 in the control group). Oncologists prescribed frequent PKI transient interruptions so that patients could recover from side effects. If such interruptions would not be prescribed, patients would certainly struggle to implement their PKI optimally. Our results show that the PKI dosing recommendation provided by pharmaceutical industries often leads to severe adverse effects and toxicity unbearable for patients in routine care. A systematic review also reported that alterations in PKI regimens such as off-label and alternate-day dosing, dose reductions or repeated dose interruptions are common with the prescription of OAT, and the impact on clinical outcomes is to be further investigated[40], as well as on patient anxiety. Besides, in order to refine official PKI dosage recommendations, rigor in adherence monitoring to OAT in oncology clinical trials with accurate measure should be reinforced (i.e., EM instead of pill count), as only 20% of trials reported adherence to OAT in their documentation for market authorization[41, 42]. To better adapt the PKI regimen to individual needs, a larger panel of dose strengths should be marketed along with systematic collection of patient-reported experience and outcomes[5] and routine pharmacokinetic/pharmacodynamic profiling[43]. As

already pointed out in the literature[20], training pharmacists on PKI objectives, lines of treatment, alternative and off-label regimens, side-effects and toxicity related to PKI, and drug-drug interactions are paramount to better inform patients and support them with their medication management.

5. Limitations and strengths of the study

The OpTAT study has strengths. First, the OpTAT study explored adherence to PKI in advanced solid cancers, a vulnerable population of patients underinvestigated in the literature. Second, the OpTAT study was implemented in a busy routine practice, as part of a semi-structured intervention, which has been implemented in routine care for more than 20 years. Medication implementation was improved in the intervention group versus the control group every consecutive day during 12 months although the improvement might be perceived as modest (see limitations). Third, we used the EM to objectively and longitudinally monitor different components of patient behavior towards medication management (i.e., implementation, persistence and adherence) over time. The rigorous cleaning and enrichment of the electronic adherence database allowed us to provide accurate measures of treatment components of adherence in cancer care, where multiple treatment adjustments are “the norm”. We decreased the risk of misinterpreting and overestimating nonpersistence and nonimplementation in both groups. Forth, statistical analysis performed on the EM adherence database is robust and validated[22, 37], and the inclusion of covariables in the GEE models allowed us to detect relevant determinants explaining differential PKI implementation. Our population included patients treated with a diversity of PKIs for different solid cancers.

Some limitations are to be acknowledged. First, the implementation of an educational and behavioral intervention in an RCT can contaminate the control group, in the sense that the control group will indirectly benefit from the intervention, leading to an underestimation of the real impact of the intervention[44-46]. In the OpTAT study, the control group may have been polluted by the intervention group in several ways: i) control patients used the EM with the LCD screen indicating the daily number of EM openings and time elapsed since the last opening, which helps preventing forgetfulness. We decided to do so to mimic some original PKI packaging, which provides tools such as daily or weekly blisters, in order not to deprive patients from existing tools; ii) pharmacists were specifically trained in oncology clinical pharmaceutical care, and the discussion at the counter with control patients may have been more informative than in usual community pharmacies; iii) for ethical reasons, patients in the control group were recalled 72 hours after a missed appointment (versus immediately after the missed appointment in patients in the intervention group) to fix another appointment for EM refill, which does not happen in the standard

of care because patient attendance at the pharmacy is not monitored. This process could have increased treatment persistence in control patients; iv) in case of cyclic regimen, the exact cycle dates were transmitted in writing to the patients in both groups, and cross-checked with the patient and the oncologist in case of discrepancies. This professional attitude emerged from the pharmacists with the implementation of the OpTAT study, which might have increased adherence to PKI with cyclic regimen in both groups and v) control patients were also asked to fill the questionnaires regarding their BAM and QoL at inclusion, 6 months and at study end, which could have led to specific thoughts impacting indirectly their adherence to PKI. Second, the attrition rate is consequent in our study, however, it is known that attrition rates are high in oncology trials[47]. Indeed, numerous patients dropped out due to cancer progression, as also reported in the literature[48]. Other reasons for attrition are related to the burden of the study. For example, to lower patient burden to attend the intervention, the frequency of pharmacy visits was scheduled on patients' medical appointments with the oncologist. Importantly, some patients did want to continue to attend the IMAP after the end of the study, showing a real interest in long-term medication adherence support.

Most patients had a baseline period before being randomized, but 34 patients were randomized at inclusion rather than after the baseline period (i.e., 18 patients in the intervention group and 16 in the control group). We cannot exclude that the knowledge of being included in the intervention group may have impacted medication adherence in these patients during the baseline period although the intervention was not provided at study inclusion but at the next visit. Indeed, the visit at study inclusion was dedicated to explain the study procedures and the use of the EM to the patient. Finally, while our study showed no impact of the intervention on patients' BAM and QoL, a significant number of missing data (i.e., non-responders to questionnaires) limited the interpretation of the results. However, patients were frequently recalled to fill the questionnaires (i.e., the questionnaires were sent by mail, reminders were provided by phone calls and during the pharmacy visits).

VI. Conclusions

The pharmacist-led interprofessional medication adherence program consistently improved patient implementation to PKI during the 12-month monitoring period. The increase in patient implementation between groups might be seen as marginal as implementation was high in both groups, probably due to the pollution of the control group by the intervention. Men, patients younger than 60, those who had never used any adherence tools before inclusion, patients without a diagnosis of metastasis and patients who initiated the PKI more than 60 days before inclusion benefited most from the intervention. Oncologists frequently prescribed PKI dosage adaptations and transient interruptions to help patients cope with side effects, showing that the official dosing recommendation from pharmaceutical industries often needs to be adapted in routine clinical practice. Further cohort studies in solid cancers should explore the impact of interventions to support adherence to PKI on clinical outcomes and patient-reported experiences and outcomes in the middle and long terms.

Abbreviations

BAM	Beliefs about medicines
BMQ	Beliefs about medicines questionnaires
CI	Confidence interval
CML	Chronic myeloid leukemia
CONSORT	Consolidated standards of reporting trials
COVID	Coronavirus disease
CRF	Case report form
EM	Electronic monitor
EMERGE	ESPACOMP medication adherence reporting guidelines
EORTC-QLQ-C30	European organization for research and treatment of cancer quality of life questionnaire
GEE	Generalized estimating equation
HCP	Health care providers

IMAP	Interprofessional medication adherence program
IQR	Interquartile ranges
IV	Intravenous
LCD	Liquid cristal display
OAT	Oral anticancer therapies
OpTAT	Optimizing targeted anticancer therapies study
PKIs	Protein kinase inhibitors
QoL	Quality of life
RS	Raw score

Appendix

Appendix 1: Questionnaire scores in patients included in the intervention versus control groups at 6- and 12-month post-inclusion

A. BMQ and EORTC-QlQ-C30 scores at 6-month post-inclusion in both groups

Variables, at 6-month post-inclusion	**Control (n=60, 50.8%)**	**Intervention (n=58, 49.2%)**	**p-value (Welch's t-test)**
BMQ_necessity_6m	10.1 (±3)	9.7 (±4.3)	0.758
missing values	45	45	
BMQ_concerns_6m	14.9 (±4.1)	15.6 (±4.6)	0.666
missing values	45	44	
BMQ_prejudices_6m	15.5 (±3.2)	15.3 (±2.5)	0.819
missing values	45	47	
BMQ_overprescribing_6m	14.3 (±2.7)	14.3 (±2.3)	0.979
missing values	45	45	
EORTC_funtioning_6m	81.7 (±13.7)	83.9 (±12.4)	0.677
missing values	46	46	
EORTC_symptoms_6m	24.1 (±14)	24.1 (±22.1)	0.995
missing values	45	46	
EORTC_global_health_6m	66.7 (±17.5)	60.9 (±20.2)	0.432
missing values	45	45	

B. BMQ and EORTC-QlQ-C30 scores at 12-month post-inclusion in both groups

Variables, at 12-month post-inclusion	Control (n=60, 50.8%)	Intervention (n=58, 49.2%)	p-value (Welch's t-test)
BMQ_necessity_12m	9.7 (±3.5)	9.9 (±4)	0.791
missing values	19	24	
BMQ_concerns_12m	14.3 (±4.6)	15.8 (±4.8)	0.174
missing values	22	26	
BMQ_prejudices_12m	14 (±3)	14.1 (±3.1)	0.962
missing values	20	24	
BMQ_overprescribing_12m	14.2 (±2.9)	14.1 (±3)	0.839
missing values	20	24	
EORTC_functioning_12m	74.8 (±16.9)	73.7 (±18.9)	0.822
missing values	33	36	
EORTC_symptoms_12m	25.3 (±16.6)	28.4 (±19.9)	0.563
missing values	35	35	
EORTC_global_healt_12m	67.6 (±16.7)	56.7 (±23.2)	0.060
missing values	33	33	

Appendix 2: Questionnaire scores between patients who refused (at the enrollment date) and those who accepted to participate (at the study inclusion) in the OpTAT study

Variables at the enrollment date or at study inclusion	Patients who refused (n=103, 46.6%)	Patients who accepted (n=118, 53.4%)	p-value (Welch's t-test)
BMQ_necessity_0m	10.1 (±3.4)	9.2 (±3.6)	0.162
missing values	62	19	
BMQ_concerns_0m	15.1 (±5)	15.2 (±4.6)	0.890
missing values	67	15	
BMQ_prejudices_0m	14.5 (±2.8)	14.7 (±2.7)	0.658
missing values	62	18	
BMQ_overprescribing_0m	14.1 (±3.2)	13.8 (±3.1)	0.696
missing values	63	14	
EORTC_functioning_0m	75.6 (±16.2)	79.7 (±15.4)	0.271
missing values	74	59	
EORTC_symptoms_0m	26.8 (±13.4)	24.9 (±17.1)	0.580
missing values	74	61	
EORTC_global_health_0m	59.9 (±18.4)	66.1 (±20.2)	0.143
missing values	72	55	

Acknowledgments

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VII. References

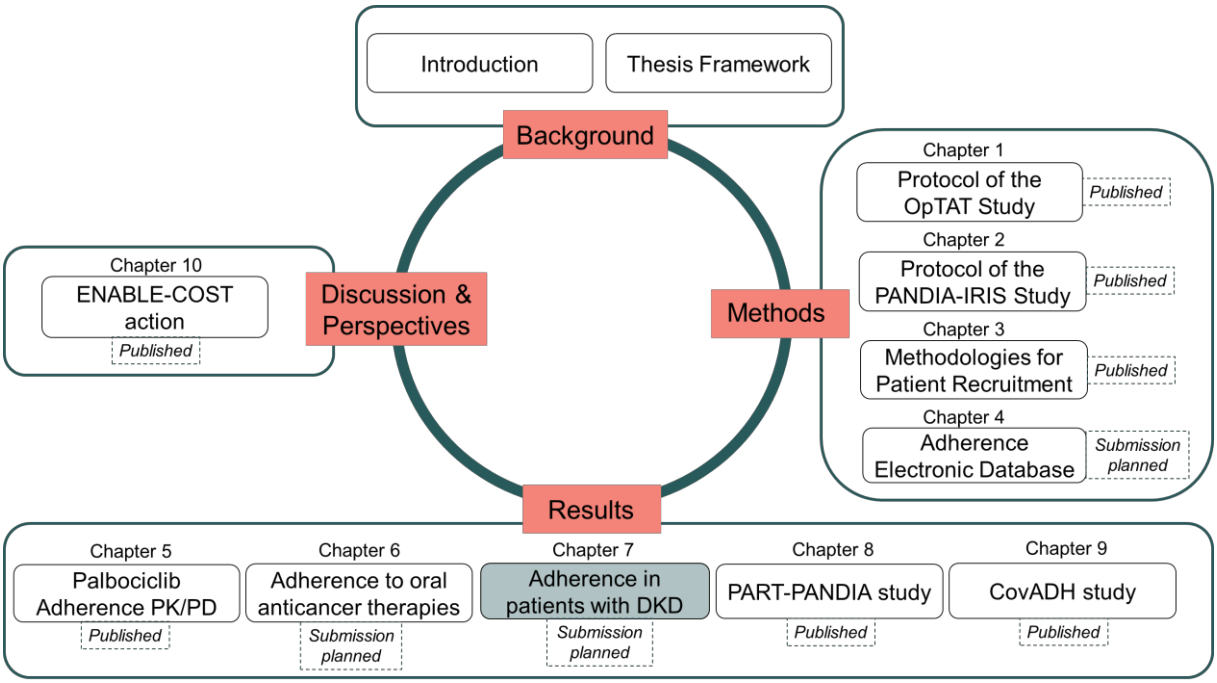
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CHAPTER 7: ADHERENCE TO ANTIDIABETICS, ANTIHYPERTENSIVE DRUGS AND STATINS IN PATIENTS WITH DIABETIC KIDNEY DISEASE (PANDIA-IRIS STUDY)



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

Chapter 7 presents the results of the PANDIA-IRIS study (i.e., the longitudinal differential impact of a 6-month versus 12-month duration of the interprofessional medication adherence program on adherence to antidiabetics, antihypertensive drugs and statins in patients with diabetic kidney disease). The paper is in preparation and co-authors have not yet reviewed the article.

The differential impact of a 6- versus 12-month pharmacist-led interprofessional medication adherence program on medication adherence in patients with diabetic kidney disease: the randomized PANDIA-IRIS study[1]

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[1] Co-authors have not yet reviewed the article.

I. Abstract

Background Forty percents of patients with diabetes will develop a diabetic kidney disease (DKD) over time. This diabetes complication may be due to a history of nonadherence to their prescribed medications. We aimed to evaluate the differential impact of a 6- versus 12-month pharmacist-led interprofessional medication adherence program (IMAP) on components of adherence (i.e., implementation and discontinuation) in patients with DKD, during and after the intervention.

Methods All included patients benefited from the IMAP, which consists in face-to-face regular motivational interviews between the patient and the pharmacist based on the adherence feedback from electronic monitors (EMs), in which the prescribed treatments were delivered. Adherence reports were available to prescribers to be considered in their intervention. Patients were randomized 1:1 into two parallel arms: a 12-month IMAP intervention in group A, versus a 6-month intervention in group B. Adherence was monitored continuously during 24 months post-inclusion during the consecutive intervention and follow-up phases. In the follow-up phase post-intervention, EM data were blinded. The repeated measures of daily patient medication intake outcomes (1/0) to antidiabetics, antihypertensive drugs and statins were modelled longitudinally by generalized estimated equation in both groups, and in both the intervention and the follow-up phases.

Results EM data of 72 patients were analyzed (34 in group A, 38 in group B). Patient implementation to antidiabetics and antihypertensive drugs increased during the IMAP intervention phase and decreased progressively during the follow-up period. At 12 months, implementation to antidiabetics in group A versus B was respectively of 93.8% and 86.8% (Δ7.0%, 95%CI 5.7%; 8.3%); implementation to antihypertensive drugs was respectively of 97.9% and 92.1% (Δ5.8%, 95%CI 4.8%; 6.7%). At 24 months, implementation to antidiabetics in group A versus B was respectively of 88.6% and 85.6% (Δ3.0%, 95%CI 1.7%; 4.4%); implementation to antihypertensive drugs was respectively of 94.4% and 85.9% (Δ8.5%, 95%CI 6.6%; 10.7%). Implementation to statins was comparable at each time point between groups. Three patients discontinued at least one treatment; they were all in group B.

Conclusions The IMAP supports adherence to chronic medications in patients with DKD. The longer the patients benefit from the intervention, the more the implementation increases over time, and the more the effect lasts after the end of the intervention. A 12-month rather than a 6-month program should be provided as a standard of care to support medication adherence in this population. The impact on clinical outcomes needs to be investigated.

Trial registration Clinicaltrials.gov NCT04190251_PANDIA IRIS.

Keywords medication adherence, electronic adherence monitoring, adherence interventions, diabetes complication, diabetic kidney disease, nephropathy, interprofessionality, digital technology, digital pharmacy

II. Introduction

1. Background

The pandemic of diabetic disease keeps growing worldwide. While in 2021, 537 million adults were diabetic and 6.7 million died from this disease, it is expected that 783 million patients will be diagnosed with diabetes by 2045[1]. The global health economic burden of adult patients with diabetes keeps rising, reaching USD 966 billion worldwide in 2021[1]. Thus, diabetes is an urgent public health concern and an important economic burden for the healthcare systems. Several types of diabetes exist, all characterized by hyperglycemia. An uncontrolled hyperglycemia severely degrades tissues and organs, leading to microvascular (i.e., retinopathy, kidney disease, neuropathy) and macrovascular complications (i.e., atherosclerosis)[2]. Among these complications, diabetic kidney disease (DKD) is characterized by a progressive decrease of the estimated Glomerular Filtration Rate (eGFR) over time[3] and an increased albumin urinary elimination[4]. DKD is the leading cause of End Stage Renal Disease (ESRD)[5, 6] defined as an eGFR of less than 15mL/min/1.72m^2[7]. It is estimated that 40% of patients with diabetes will develop a DKD over time[4, 8].

The goal of pharmacological treatments in diabetes is to slow down the progression of the renal impairment, prevent cardiovascular events and complications by intensively controlling the urine albumin-creatinine ratio, the blood pressure, lipid and glycemic blood levels. As a consequence, patients with DKD are polymedicated, which contributes to treatment nonadherence.

Medication adherence is described by three interrelated and quantifiable phases, following ideally a shared decision-making process regarding prescribing: initiation (i.e., first dose taken), implementation (i.e., the extent to which the patient takes the treatment as prescribed), and discontinuation (i.e., the patient stops taking the treatment earlier than planned by the prescriber)[9]. Treatment persistence is the time between initiation and discontinuation[9]. Literature reports that 40% of patients with DKD are not adherent to their medications[10-12], while medication nonadherence leads to poor clinical outcomes and increases mortality[13-15]. Medication adherence must become a priority for interprofessional healthcare teams. However,

studies evaluating interventions aiming to improve adherence in patients with DKD are scarce, and their impact on adherence and clinical outcomes remains limited[12, 16, 17].

The PANDIA-IRIS (*Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique*) study was developed at the community pharmacy of *Unisanté* to support medication adherence in patients with DKD. The intervention consists in a pharmacist-led Interprofessional Medication Adherence Program (IMAP), implemented since 1995 at the community pharmacy of *Unisanté*, aiming to support medication adherence in chronically ill patients[18].

2. Objectives

The main objective of the PANDIA-IRIS study was to evaluate the differential impact of a 6-month versus 12-month pharmacist-led IMAP on implementation and persistence to antihypertensive drugs, antidiabetics and statins in patients with DKD at different time points, i.e., at 6, 12, 18 and 24-month post-inclusion.

3. Outcomes

The medication intake is a binary variable (1= correct intake; 0= incorrect intake) measured with each electronic monitor (EM) in each patient at each day of the monitoring period. To be considered as optimal, the medication intake has to be correct (=1) for each EM used. On each day, medication implementation is the proportion of patients with a correct medication intake among patients still under observation on that day. Persistence to treatment is characterized by the time between study initiation and treatment discontinuation (=1) for each patient.

4. Hypothesis and research questions

We hypothesized that patients in both groups would benefit from the IMAP, yet the impact of the intervention on medication adherence, i.e. implementation and persistence, would be higher and would last longer post-intervention in participants included in the IMAP for 12 months (group A) compared to patients who benefited from the IMAP during 6 months (group B). We hypothesized that during the follow-up period post-intervention, patients included in group A would maintain a higher implementation compared to patients included in group B.

III. Methods

1. Ethical considerations and guidelines

The PANDIA-IRIS study was approved by the local ethics committee "*Commission cantonale d'éthique de la recherche sur l'être humain*" (Vaud, Switzerland, ID 2016-01674). All patients signed an informed consent form to participate. The study was conducted in accordance with the declaration of Helsinki. Both the ESPACOMP Medication Adherence Reporting Guidelines (EMERGE)[19] and Consolidated Standards of Reporting Trials (CONSORT) guidelines[20] were used to report findings.

2. Design of the PANDIA-IRIS medication adherence study

The protocol of the PANDIA-IRIS study has been published elsewhere[21]. The PANDIA-IRIS study was monocentric, open and randomized. Patients were recruited from the Service of Nephrology and Hypertension, the Service of Endocrinology, Diabetes and Metabolism of the Lausanne University Hospital (*Centre Hospitalier Universitaire Vaudois*, CHUV) and at the policlinic of the Center for Primary Care and Public health *Unisanté,* located in the same hospital complex. Eligible patients were adults with a diagnosis of diabetes type 2 or type 1, a Latent Autoimmune Diabetes in Adults (LADA) or a glucocorticoid-induced diabetes with renal failure (eGFR of less than 60mL/min/1.73 m^2). Patients were excluded if they did not self-manage their treatments (i.e., home care services, nursing homes) or had cognitive disorders. Patients who were pregnant or had an active cancer were also excluded. Enrolled patients were randomized at inclusion into two parallel arms, each lasting 24 months. Participants in the first arm received the intervention for 12 months (Group A) versus 6 months (Group B) in the second arm (Fig. 1 adapted from Bandiera et al.[21]). To stratify randomization according to the risk of nonadherence due to the adverse effects of statins or the complexity of drug regimen, four randomization groups were created (i.e., patients monitored with at least a statin, patients monitored with a least one medication with multi-dose regimen, patients with both of the former conditions and patients with none of the former conditions)[21].

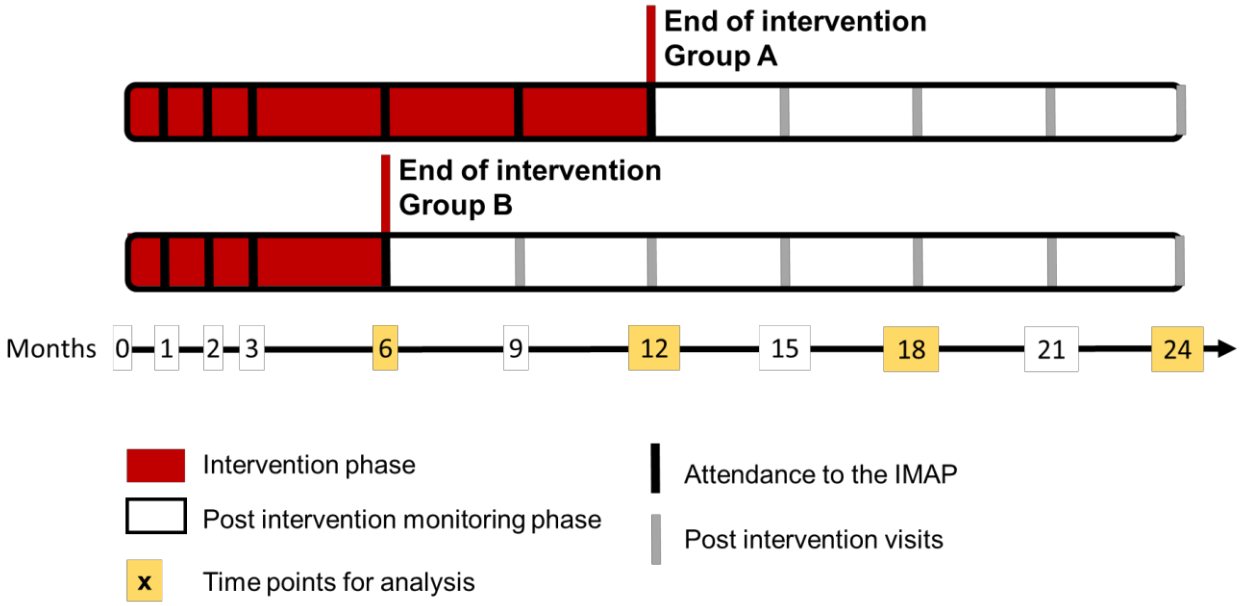


Figure 1: Design of the PANDIA-IRIS study, adapted from Bandiera et al.[21]

IMAP= Interprofessional Medication Adherence Program

Intervention phase: the Interprofessional Medication Adherence Program (IMAP)

As part of the IMAP[18], all included patients used at least one electronic monitor (EM, Medication Event Monitoring System, MEMS and MEMS AS, AARDEX Group, Sion, Switzerland), an interactive digital technology, to monitor their medication adherence. Each EM contained one oral prescribed chronic treatment. Monitoring priority was determined as follows for each consecutive patient: 1) antidiabetics, 2) antihypertensive drugs, diuretics, beta- and alpha-blockers, calcium antagonists, 3) statins and 4) aspirin. Before randomisation, while investigators offered patients to monitor all eligible medications in EM, patients' preferences on the number of EM to be used were taken into consideration so as not to burden their medication management habits. On the top of the EM cap, a liquid-crystal display (LCD) screen indicated the number of EM opening(s) during 24 hours from 3:00 am to 2:59 am the day after. The EM registers the date and time of each EM opening, which is considered as a proxy for the timing of drug intake. By reading EM data, the MedAmigo™ software (AARDEX Group, Sion, Switzerland) establishes a chronology graph of medication intake during the current inter-visit intervention period. At each pharmacy visit, the pharmacist investigated EM deviation use by asking the patient to report i) non-monitored periods during which the medication was taken without opening the EM (i.e., during hospitalizations, holidays); ii) the use of pocket-doses (i.e., when the patient took a tablet outside of the EM to

swallow it more than 24 hours later) and curiosity checks (i.e., when the patient opened the EM without taking the dose) and iii) the usual time between EM openings and the medication intake. Besides, pharmacy technicians calculated an aggregated value of days covered by pill count for conciliation with EM data. Any significant discrepancy was immediately investigated during the interview by the pharmacist.

The intervention consisted in face-to-face 15 to 20-minute motivational interviews between the patient and the pharmacist based on the electronic adherence feedback presented in the form of a chronology plot. The intervention was built upon Fisher et al's socio-cognitive theoretical framework "information-motivation-behavior"[22]. Pharmacists and patients investigated together the patient's habits and skills in self-managing medication and side effects. The pharmacist explored the patient's own beliefs, preferences and motivation to take the treatment, and delivered information according to the patient's needs. If necessary, goals for improving medication adherence were set collaboratively by the patient with the pharmacist, according to patient engagement, from one interview to the next one. After the end of the interview, the pharmacist sent a report summarizing the content of the intervention to the healthcare team (i.e., endocrinologist, nephrologist, general practitioner, diabetes specialist nurses, psychologists, dieticians).

Post-intervention (follow-up) monitoring phase

After the end of the intervention phase, medication adherence was continuously monitored by EM until the end of the study (i.e., 24-month post-inclusion). During the post-intervention phase, the patient did not receive any intervention. EM data were blinded to the patient, the pharmacy team, the medical team and the researchers. At each follow-up pharmacy visit, the pharmacist evaluated EM use deviations through the same set of questions as during the intervention phase and reported the answers in a Case Report Form (CRF). Besides, pharmacy technicians counted pills left in the EM without calculating any adherence rate.

At each visit during both the intervention and the follow-up phase, pharmacists measured patients' systolic and diastolic blood pressure, and heart rate. They measured and reported patients' abdominal circumference every 6 months. In order to prevent patients from coming to the pharmacy during the lockdown enforced by the coronavirus disease (COVID)-19 pandemic (from March to June 2020), the medications were sent by mail so that patients could fill their EMs at home[23]. The motivational interviews were delivered by phone, yet without EM feedback[23] for patients in the intervention phase. In order to guarantee homogeneity of the interventions between patients, the intervention phase was extended for 3 months after the lockdown in all patients (n=15), who were in the intervention phase.

3. Database construction

Collection of patients' clinical and sociodemographic data

Patients' demographic data (age, gender, marital status, ethnicity, education level) and clinical data at inclusion (type of diabetes, time since diabetes diagnosis, body mass index (BMI), abdominal circumference, diagnosis of retinopathy, presence of atrial fibrillation, systolic and diastolic blood pressure and heart rate, eGFR decline per year, current or past diagnosis of depression or anxiety, smoking status, number of chronic treatments prescribed, patient use of adherence support tools) were collected in patients' electronic medical and administrative records. The following clinical variables were collected for each patient as the mean of the values measured in the 12 months prior to study inclusion: glycated hemoglobin (HbA1c), eGFR, creatinine blood concentration and low-density lipoprotein (LDL)-cholesterol. Missing data were clearly depicted. All data were collected on the secure web platform REDCap™ version 6.13.3 (Vanderbilt University)[24].

EM adherence database

Patients' EM raw data were cleaned and enriched using the CleanADHdata.R script (available on https://github.com/jpasquier/CleanADHdata), developed by our research team. The script truncates the EM database from the first to the last date of each EM use. The periods during which the EM was not used but the medication was taken (e.g. during holidays or hospitalizations) were set as non-monitored periods, and implementation was not calculated during these non-monitored periods. Covariables were inserted in each EM (e.g., the international nonproprietary name of the molecule monitored and its dose strength) and for each patient (e.g., randomization group, phase of the study, gender, age).

4. Statistical analysis

a. Descriptive analysis

Continuous sociodemographic and clinical variables were described by medians and interquartile ranges (IQR) and qualitative data by proportions of patients in each group.

b. Implementation and discontinuation

For each electronic monitor (EM) used by the patient, the medication intake is considered correct (=1) a given day if the number of observed EM opening(s) is at least equal to the number of expected EM opening(s) based on the regimen provided in the prescription sheet; and is considered incorrect otherwise (=0). For each patient at each day of the monitoring period, an overall optimal medication intake (=1) was defined by the product of each EM medication intake

outcome: the medication intake needs to be correct (=1) for all EM monitored in each drug class (i.e., antidiabetics, antihypertensive drugs and statins) to consider a global correct medication intake for that day. Empirical medication implementation is then expressed as the proportion of patients with a global correct medication intake (proportion of outcomes=1) at each day of the monitoring period, among patients still participating in the study at that day.

From study inclusion to the end of the intervention (6 versus 12 months) and in the follow-up phase until 24 months post-inclusion, longitudinal implementation was described by generalized estimating equation (GEE) model on the daily medication intake 0/1. Implementation was then estimated by the model for two representative patients: one who benefited from the intervention during 12 months (a patient from group A) versus one who benefited from the intervention during 6 months (a patient from group B). Implementation was estimated in three different GEE models, showing respectively implementation to antidiabetics, antihypertensive drugs and statins. The probability of treatment implementation was estimated for each drug class at 6, 12, 18 and 24 months for both representative patients A and B. The difference of implementation between both representative A and B patients (Δ) was presented with the 95% confidence interval (95%CI).

A discontinuation was defined when a patient stopped taking at least one of his/her treatment earlier than planned by the prescriber, due to side effects or for any other patients' unilateral and personal reasons. Other reasons for premature treatment stop (i.e., clinical reasons other than side effects) or study interruption without treatment discontinuation were considered as censoring times. We represented graphically the moments of discontinuation in each model.

IV. Results

1. Included patients

The PANDIA-IRIS study was offered to 275 patients, of whom 73 accepted to participate. The main reasons for non-participation were investigated as part of the "Participation to the PANDIA-IRIS" study (PART-PANDIA study), the results of which have been published elsewhere[25]. The sociodemographic and clinical variables[2] of the 73 included patients at baseline (group A n=35, group B n=38) are presented in Table 1. Most of the patients were male, caucasian, diagnosed with Type 2 diabetes and had a basic- to intermediate-level schooling. Patients were polymedicated and most of them already used a weekly pillbox to manage a median of 9 chronic prescribed

[2] Main clinical outcomes are described in this article at baseline. Systolic blood pressure will be analyzed longitudinally later as part of the final publication.

treatments. More than one third of patients in each group were current smokers at study inclusion. The eGFR decline (-2.4 mL/min/1.73m^2/year in both groups) is faster in patients included in our study compared to patients with type 2 diabetes in the Swiss ambulatory care (-1.2 mL/min/1.73m^2/year (standard deviation (SD) 0.05) in men, -1.0 mL/min/1.73m^2/year (SD 0.06) in women[26]).

Table 1: Baseline demographic and clinical characteristics of patients included in the PANDIA-IRIS study

	Group A (n=35) **12-month intervention**	**Group B (n=38)** **6-month intervention**
Demographic data		
Age (years), median (IQR)	66.3 (58.9 ; 70.9)	62.0 (56.0 ; 69.2)
Female gender, n patients (%)	4 (11.4)	8 (21.1)
Marital civil status[a], n patients (%)	16 (45.7)	16 (42.1)
Caucasian, n patients (%)	29 (82.9)	33 (86.8)
Education level, n patients (%)	Without training after mandatory school 11 (31.4) Professional training 17 (48.6) General training 3 (8.6) Higher education 2 (5.7) Universities 2 (5.7)	Without training after mandatory school 6 (15.8) Professional training 21 (55.3) General training 1 (2.6) Higher education 4 (10.5) Universities 6 (15.8)
Clinical data		
Type 2 diabetes[b], n patients (%)	34 (97.1)	34 (89.5)
Time since diabetes diagnosis (years), median (IQR)	9.6 (4.7 ; 16.3) Missing data n=1	9.1 (4.3 ; 18.8)
BMI, median (IQR)	31.3 (27.6 ; 33.1) Missing n=3	31.9 (28.1 ; 34.7) Missing n=3
Abdominal circumference (cm), median (IQR)	115 (105-122)	113 (100-119)
Diagnosis of retinopathy, n patients (%)	8 (22.9)	17 (44.7)

Presence of atrial fibrillation, n patients (%)	2 (5.7)	5 (13.2)
Systolic blood pressure (mmHg), median (IQR)	135 (125 ; 152)	133 (121 ; 143)
Diastolic blood pressure (mmHg), median (IQR)	71 (62 ; 80)	77 (69 ; 84)
Heart rate, median (IQR)	72 (62 ; 79)	78 (65 ; 86)
HbA1c (%), median (IQR)	7.6 (6.8; 8.2) Missing data n=4	7.2 (6.8 ; 8.2) Missing data n=9
eGFR (mL/min/1.73m2), median (IQR)	40 (34.2; 42.5) Missing data n=19	43 (37.5; 52.6) Missing data n=18
eGFR decline per year (mL/min/1.73m^2/year), median (IQR)	-2.4 (-4.42 ; -0.29)	-2.4 (-4.27 ; -0.84)
Creatinine blood concentration (µmol/L), median (IQR)	128 (88.0 ; 154.5)	120 (97.5; 147.1)
LDL-cholesterol (mmol/l), median (IQR)	2.2 (1.85 ; 2.65) Missing data n=7	2.2 (1.50 ; 2.60) Missing data n=9
Current or past diagnosis of depression or anxiety, n patients (%)	11 (31.4)	6 (15.8)
Current smoker, n patients (%)	11 (31.4)	14 (36.8)
Number of prescribed chronic medications, median (IQR)	9 (7-12)	9 (7-12)
Previous use of adherence tools, n patients (%)	21 (60.0)	19 (50.0)
Adherence personal tools used among those who had used an adherence tool, n patients (%)	Electronic pillbox 6 (28.6) Weekly pillbox 19 (90.5) Personal items 2 (9.5) No adherence tools used n=14	Electronic pillbox 5 (26.3) Weekly pillbox 14 (73.7) Personal items 3 (15.8) No adherence tools used n=19

Stratification list, n patients (%)	Statins n=10 Multi-dose regimen n=8 Statins and multi-dose regimen n=12 No statin nor multi-dose regimen n=5	Statins n=11 Multi-dose regimen n=10 Statins and multi-dose regimen n=12 No statin nor multi-dose regimen n=5
Number of EMs dispensed, n patients (%)	1 EM n =5 (14.3) 2 EM n =9 (25.7) 3 EM n =11 (31.4) 4 EM n =8 (22.9) 5 EM n =1 (2.9) 6 EM n =1 (2.9)	1 EM n =4 (10.5) 2 EM n =15 (39.5) 3 EM n =5 (13.2.) 4 EM n =10 (26.3) 5 EM n =3 (7.9) 6 EM n =1 (2.6)
Number of EMs used per patient, median (IQR)	3 (2-4)	2.5 (2-4)

NB: EM=electronic monitor, IQR=interquartile ranges, BMI= body mass index, LDL= low-density lipoprotein, HBA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate.
[a]The other patients are in partnership, separated, divorced, widow or single.
[b]The other patients have diabetes type 1, Latent Autoimmune Diabetes in Adults, post-transplantation or glucocorticoid-induced diabetes. From October 2019, the eligibility criteria were expanded to include other types of diabetes than type 2, which explains the low proportion of patients in these categories.

Fig. 2 describes patient enrolment and follow-up in the study. In groups A and B respectively, 20 and 26 patients dropped out, mainly due to logistical reasons or because the study was perceived as an additional burden in their care. Patients in groups A and B spent respectively a median time of 539 days (IQR 124; 747) and 366 (IQR 145; 740) in the study. The EM data of one patient included in group A was not analyzed as the patient used a weekly pillbox instead of the EM. After completion of the study, 4 versus 3 patients in group A and B respectively decided to continue attending the routine IMAP.

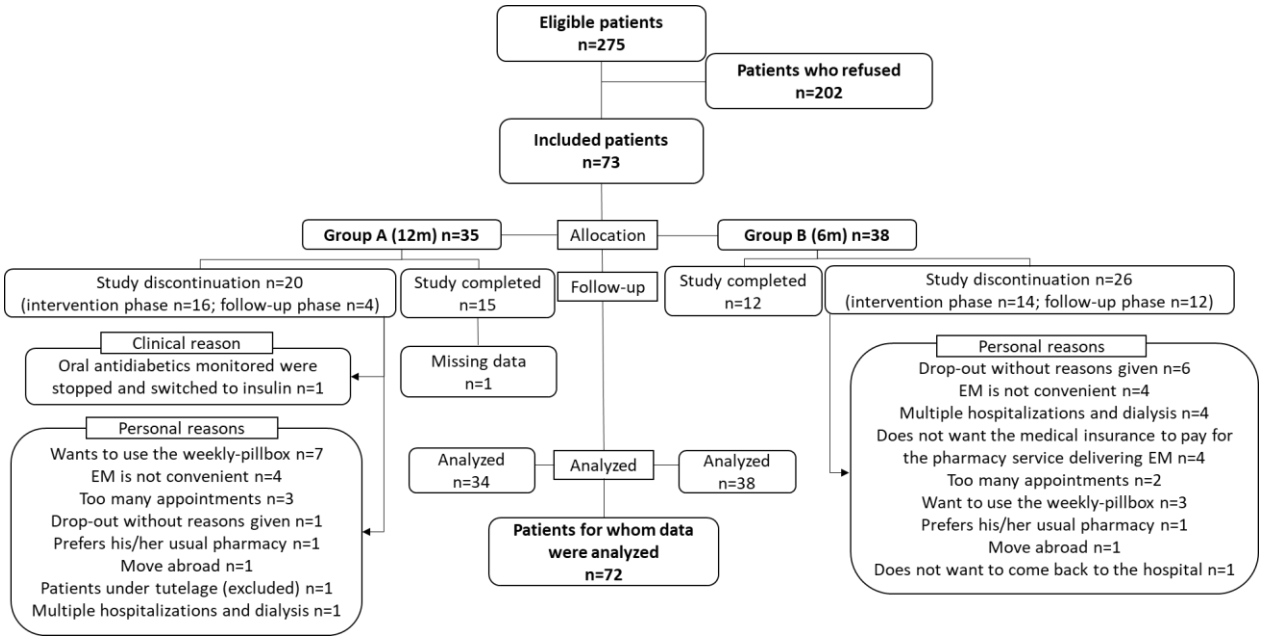


Figure 2: flow of patients from enrolment to data analysis in the PANDIA-IRIS study. EM=electronic monitor.

2. **Medication implementation by drug classes**

i) Implementation to antidiabetics and antihypertensive drugs

Empirical implementation to antidiabetics and antihypertensive drugs is presented in patients who were prescribed antidiabetics (n=57) in Figure 3 and antihypertensive drugs (n=57) in Figure 4. The GEE models represent implementation for a representative patient participating in the intervention during 12 months (red curve) or 6 months (blue curve). Patient implementation to antidiabetics and antihypertensive drug increases steadily during the intervention period. At the end of the intervention (at 6- and 12-month post-inclusion), the model shows that implementation drops and then gradually decreases over time during the follow-up phase. In this follow-up phase, patients who benefited from the intervention during 12 months maintained a higher implementation than patients who received the intervention during 6 months. At 6, 12, 18 and 24 months, implementation to antidiabetics and antihypertensive drugs in patients who benefited from the intervention for 12 months was continuously higher than in patients who received the intervention for 6 months.

At 12 months, the implementation to antidiabetics in a patient completing the 12-month intervention (patient A) and in a patient having completed the 6-month intervention 6 months earlier (patient B) was respectively of 93.8% and 86.8% (Δ7.0%, 95%CI 5.7%; 8.3%) (Table 2). At 12 months,

implementation to antihypertensive drugs in a patient A versus B was respectively of 97.9% and 92.1% (Δ5.8%, 95%CI 4.8%; 6.7%).

At 24 months, implementation to antidiabetics in a patient A versus B was respectively of 88.6% and 85.6% (Δ3.0%, 95%CI 1.7%; 4.4%) and implementation to antihypertensive drugs was respectively of 94.4% and 85.9% (Δ8.5%, 95%CI 6.6%; 10.7%) (Table 2).

Table 2: Implementation to antidiabetics, antihypertensive drugs and statins at 6, 12, 18 and 24-month post-inclusion

	Time since inclusion, months	Number of patients	Implementation in group A (intervention lasted 12m)	Implementation in group B (intervention lasted 6m)	Difference (Δ)	95%CI	
Antidiabetics	6 m	37	92.5%	87.4%	5.1%	3.7%	6.5%
	12 m	31	93.8%	86.8%	7.0%	5.7%	8.3%
	18 m	24	89.1%	86.2%	2.9%	1.7%	4.1%
	24 m	21	88.6%	85.6%	3.0%	1.7%	4.4%
Antihypertensive drugs	6 m	34	95.9%	94.2%	1.7%	0.7%	2.8%
	12 m	30	97.9%	92.1%	5.8%	4.8%	6.7%
	18 m	23	95.9%	89.5%	6.5%	5.4%	7.6%
	24 m	20	94.4%	85.9%	8.5%	6.6%	10.7%
Statins	6 m	31	95.4%	96.4%	-1.1%	-1.8%	-0.2%
	12 m	25	95.0%	95.4%	-0.4%	-1.7%	0.7%
	18 m	18	95.1%	94.2%	0.9%	0.1%	1.8%
	24 m	14	93.7%	92.6%	1.1%	0.1%	2.4%

NB: CI=confidence interval

No patient of group A versus three of group B discontinued at least one of their monitored treatments. The moments of treatment discontinuation are shown in figures 3 and 4 by the blue dots on the green curve showing the number of participants over time.

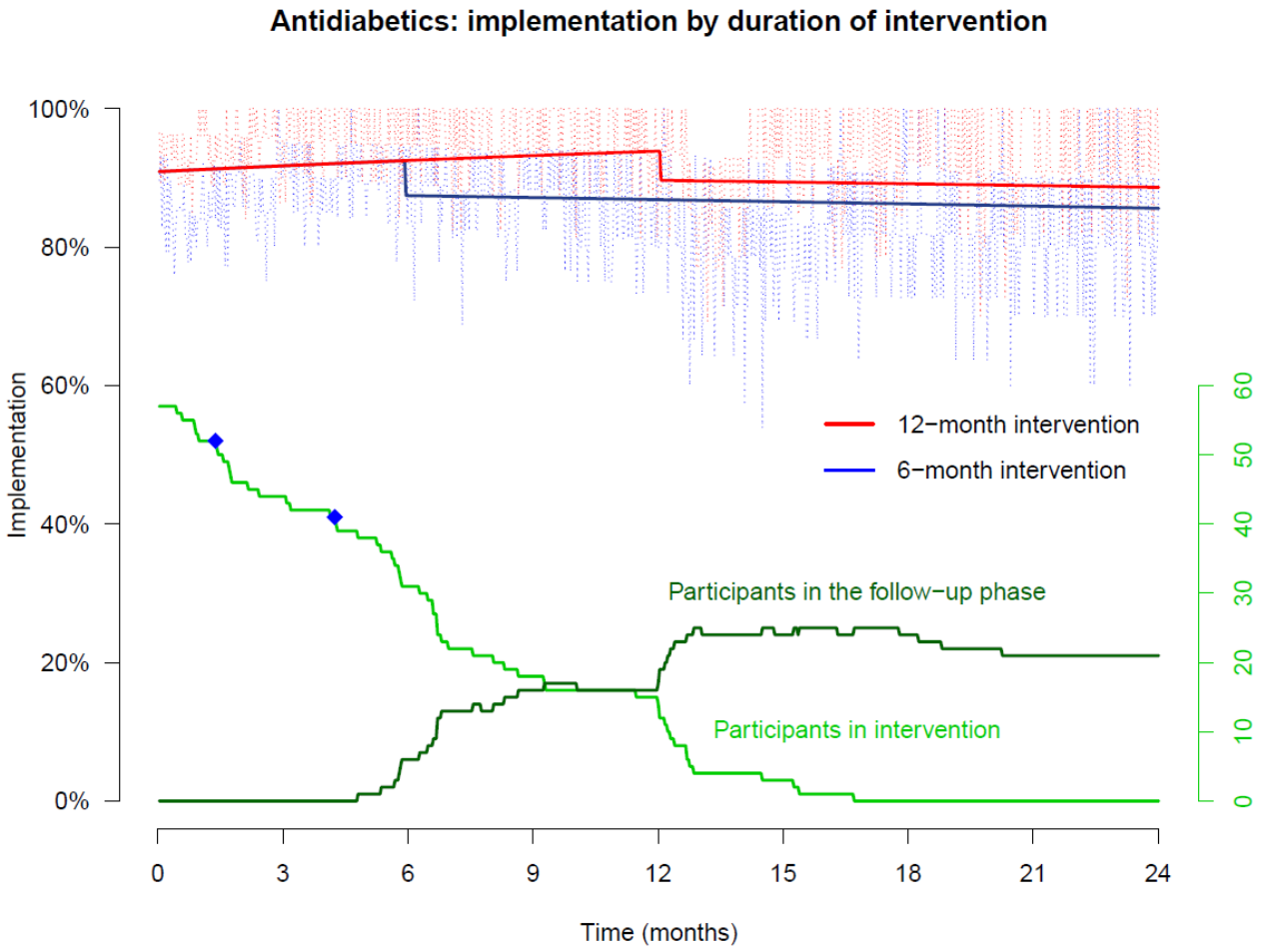


Figure 3: implementation to antidiabetics in representative patients of groups A and B throughout the study.

NB: the light red and blue curves show empirical implementation, the thick red and blue lines represent implementation to antidiabetics modelled by GEE. The green curves represent the number of participants over time in the intervention and the follow-up phases, the blue dots on the green curve show the moment when a patient discontinued at least one of his/her antidiabetic.

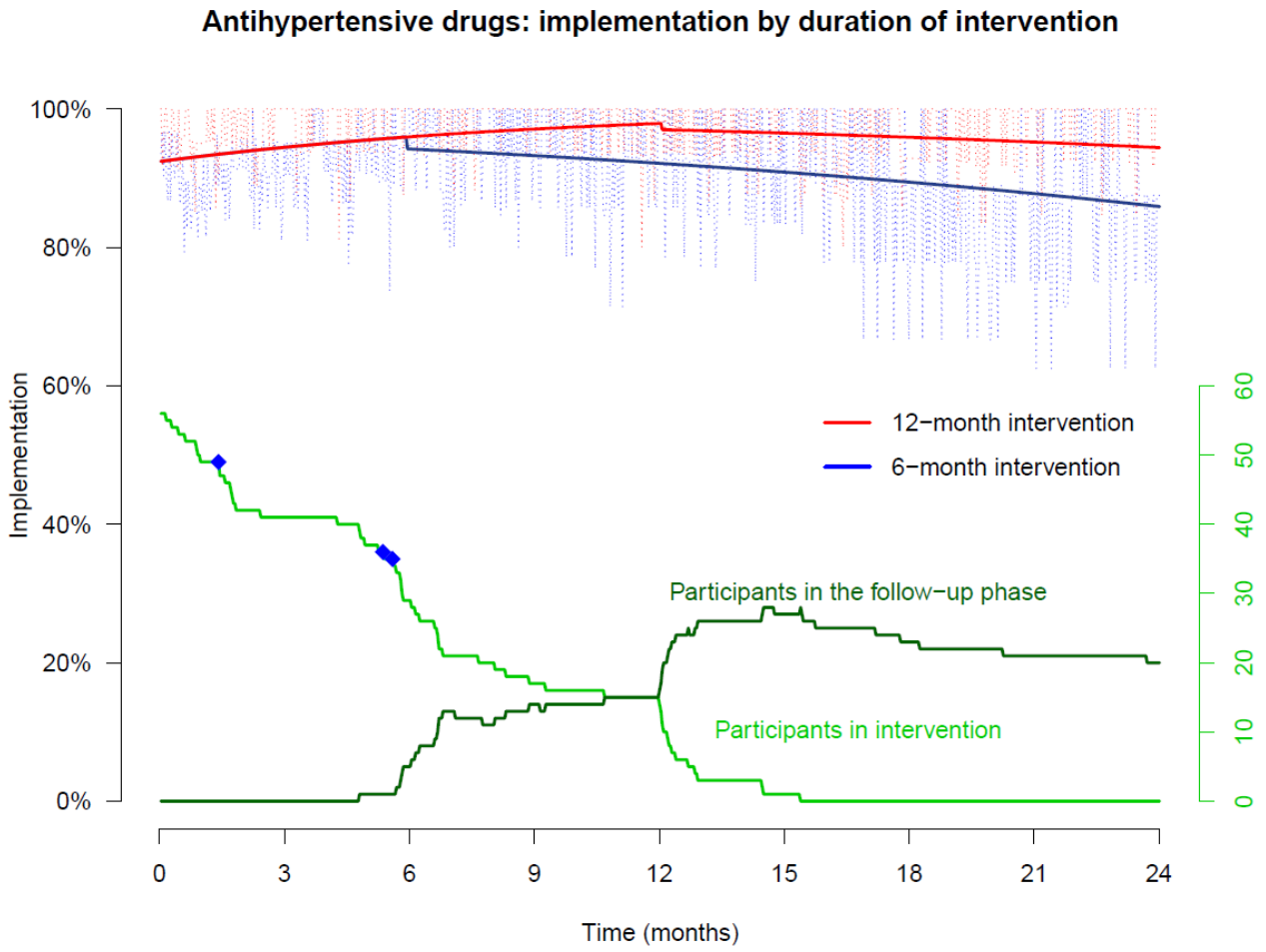


Figure 4: implementation to antihypertensive drugs in representative patients of groups A and B throughout the study.

NB: the light red and blue curves show empirical implementation, the thick red and blue lines represent implementation to antihypertensive drugs modelled by GEE. The green curves represent the number of participants over time in the intervention and the follow-up phases, the blue dots on the green curve show the moment when a patient discontinued at least one of his/her antihypertensive drug.

ii) Implementation to statins

Empirical implementation in patients who were prescribed statins (n=44) and implementation to statins modelled by GEE are presented in Figure 5. Implementation remained stable during the intervention until 12 months. At the end of the intervention at 6- and 12-month post-inclusion, implementation increases slightly and then decreases steadily in the follow-up phase. At 12 months, implementation to statins in a representative patient of group A versus B was respectively of 95.0% and 95.4% (Δ -0.4%, 95%CI -1.7%; 0.7%). At 24 months, implementation to statins was comparable between both representative patients: implementation was respectively of 93.7% in patient A and 92.6% in patient B (Δ 1.1%, 95%CI 0.1%; 2.4%).

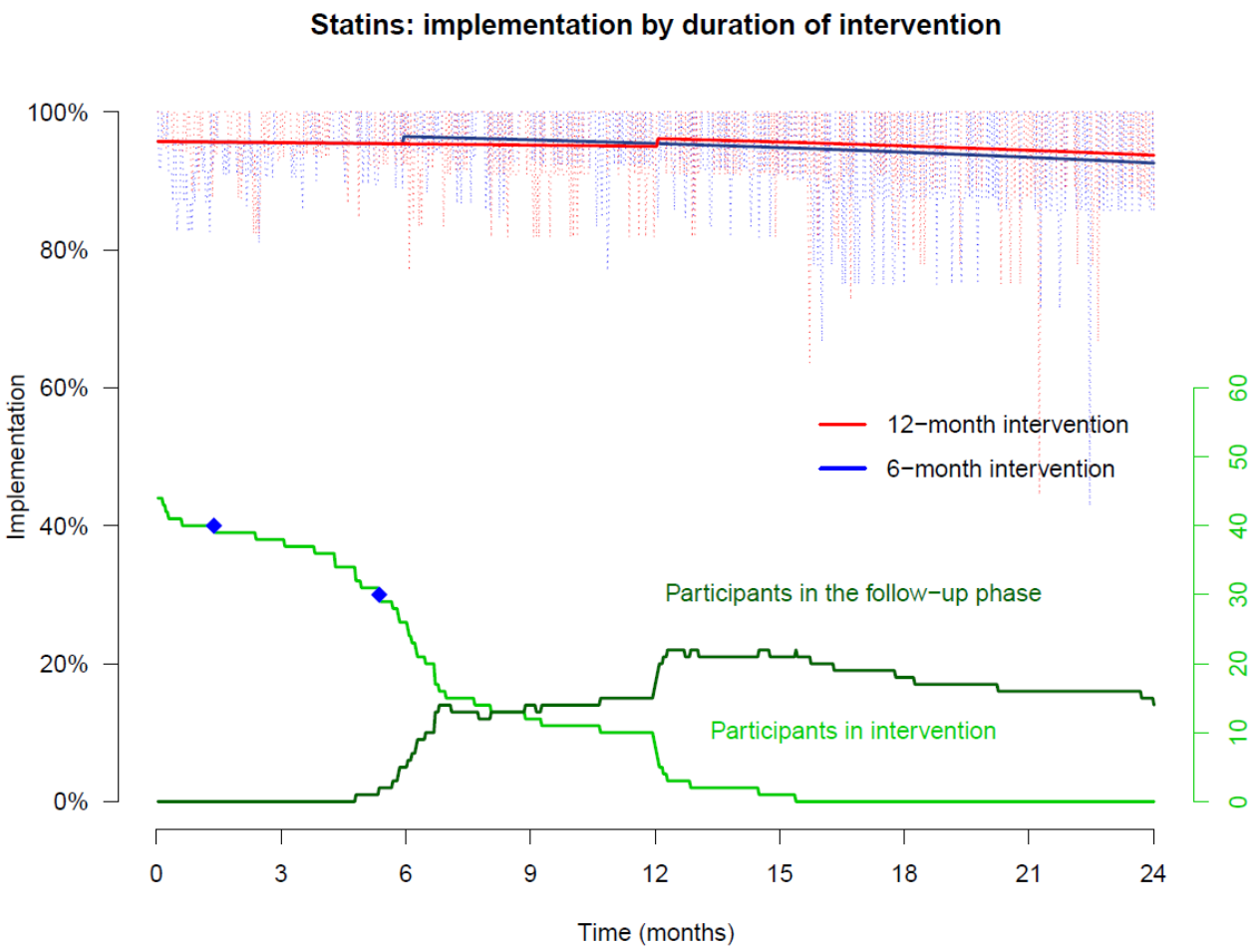


Figure 5: implementation to statins in representative patients of groups A and B throughout the study.

NB: the light red and blue curves show empirical implementation, the thick red and blue lines represent implementation to statins modelled by GEE. The green curves represent the number of participants over time in the intervention and the follow-up phases, the blue dots on the green curve show the moment when a patient discontinued the statin.

V. Discussion

1. Main results

The pharmacist-led interprofessional medication adherence program improved implementation to antidiabetics and antihypertensive drugs but not to statins in patients with DKD and the effect persisted 24-month after inclusion. Therefore, the duration of the intervention seems to be crucial to ensure a lasting effect on the maintenance of medication implementation: the longer patients benefit from the intervention, the more the implementation increases over time and the more the effect lasts after the end of the intervention. The impact of the IMAP on implementation to statins needs to be investigated further with a larger sample size. The ongoing analysis will determine the

longitudinal impact of medication adherence on clinical outcomes (e.g., systolic blood pressure) at each time point.

2. The impact of the IMAP on implementation to statins

The impact of the IMAP on implementation to statins is unclear, which can be explained by several hypotheses. First, antidiabetics and antihypertensive drugs are often prescribed with a more complex regimen than statins (i.e., multiple drug intakes per day), whereas statins are mostly prescribed with a once-daily regimen. In addition, drug, dose and regimen changes occurred more often with antidiabetics and antihypertensive drugs than with statins. These factors may contribute to the difficulty for patients to adhere optimally to antidiabetics and antihypertensive drugs compared to statins, and the room for improvement of treatment implementation may be larger in these drug classes than with statins. Patients were used to take their statin for several years and there was no major complaint on usual statin side effects. Second, as the implementation to statins was already high (>95%) at study start in both groups, pharmacists focused the discussion on antidiabetics and antihypertensive drugs during the motivational interviews and less on statins (based on qualitative study monitoring data).

3. Definition of treatment implementation

Our definition of treatment implementation states that a patient needs to implement optimally all his/her medications monitored at a day x in order to have an overall optimal medication implementation at that day x. This definition has been commonly used in previous research[27, 28]. However, patients with DKD are polymedicated, and patients included in the PANDIA-IRIS study often used more than one EM. Each additional EM used reduced the probability to have a daily optimal overall implementation. For instance, in a patient who used 5 EMs and implemented optimally 4 of them, the overall implementation will depend on the implementation of the 5th treatment, leading to an underestimation of the actual treatment implementation. As the number of EM used per patient is distributed evenly in our sample, probably reinforced by the stratification of the randomization, our analysis is valid. Additionally, we analysed medication implementation by drug classes to limit the risk. Nevertheless, the definition of treatment implementation monitored through EM with the binary variable 1/0 needs to be better adapted for polymedicated patients. The probability of an optimal implementation could be calculated according to the number of treatments for which the patient has an optimal implementation over the total number of treatments monitored (i.e., at a day x, if the patient has an optimal implementation to 4/5 of his/her medications, the probability of an optimal implementation at that day x would be of 80%). Our research raises the

point that the operational definitions of implementation should be evaluated further and the statistical methodology developed in polymedicated patients.

4. Impact of the study on clinical practice

Patients were overall satisfied about the IMAP[25]. A consequent number of patients left the study during the intervention phase, mainly due to personal reasons (i.e., 46% (16/35) of patients in the 12-month intervention vs. 37% (14/38) of patients in the 6-month intervention). This important number of drop-outs shows the difficulty of conducting behavioral interventions in routine practice. In order to improve retention in the intervention while limiting the inclusion bias, intervention such as the IMAP should be considered as an integral component of the standard of care for polymedicated patients. Including all consecutive chronically ill patients to the IMAP would allow a prospective evaluation of the impact of the IMAP on clinical outcomes. For example, polymedicated patients would be invited to experience the IMAP for 12 months early in their therapeutic itinerary to co-construct their medication adherence with healthcare providers (HCPs), tailored to their individual needs, before deciding whether they would benefit from continuing the intervention or repeating it later based on defined clinical outcomes, personal experiences and indicators[25]. The interprofessional collaborations between patients, pharmacists, physicians, nurses and other HCPs should be strengthened in order to synergistically promote the IMAP to patients and to better define the roles and responsibilities of each HCP in supporting medication adherence.

5. Limitations and strengths of the study

The PANDIA-IRIS study has strengths. First, the IMAP is a proven, theory-based, semi-structured intervention program implemented in routine practice. As part of the intervention, pharmacists i) explore patients' capability to acquire knowledge and skills to strengthen their self-efficacy, ii) explore and participate in the development of patients' motivation to take the treatment and iii) explore opportunities in patients' environment that encourage a behavioral change to improve or maintain their medication adherence. These three components impact patient health behaviors and are the main components of the Behavior Change Wheel model designed by Michie et al. to lead effective interventions[29]. Second, the design of the PANDIA-IRIS study is innovative as it provides an analysis of the duration of an intervention, which is insufficiently studied in the literature, by comparing a 6- to 12-month intervention. To our knowledge, this is also the first time that medication adherence was monitored during an extended period of time (24 months), including the post-intervention period in order to understand the durability of the intervention. Our results suggest that medication adherence interventions should be delivered on long periods of time based on patients' needs by adapting the level of the intervention to short-, middle- and long-term objectives.

Our experience with the IMAP in routine care shows that some chronic patients stay in the program for years while others leave it after a semester, and sometimes return afterwards. Third, we reported findings through a robust methodology. We used electronic monitoring during 24 months, a method that is considered the most robust methodology to measure objectively and longitudinally medication implementation over time. The statistical analysis processed on repeated adherence electronic monitoring measures was previously developed and validated[28, 30] and the analysis of the implementation to the different drug classes allowed to provide the differential impact of the IMAP on implementation to antidiabetics, antihypertensive drugs and statins.

Some limitations are to be acknowledged. First, even if the targeted sample size was reached, a considerable number of patients either refused inclusion or dropped out during the study. Inclusion refusal was addressed in another paper[25]. Regarding drop-outs, we cannot exclude that patients who left the study had a different medication adherence than those who completed the study. This needs further exploration. Second, patients used the EM during the follow-up period, which could have been a supportive tool in their medication management. Indeed, the LDC screen on the top of the EM cap indicated the number of daily EM opening(s), which can help prevent forgetfulness. Furthermore, patients had to refill their EMs at the pharmacy every three months, and they were recalled by phone calls if they missed the appointment, which is not the standard of care. Pharmacists had to check EM use deviation at each follow-up visit for methodological reasons, which may have raised patient awareness on medication adherence during the follow-up period. In addition, the blood pressure and the abdominal circumference measured by pharmacists during the follow-up phase may have influenced patient medication adherence. Thus, medication adherence measured during the follow-up period might have been higher than in the standard of care. Third, due to the low prevalence of treatment discontinuation, we did not analyse medication persistence. We would need a larger database with a larger sample size to evaluate carefully the impact of the IMAP on medication persistence in patients with DKD after the intervention. Finally, as the frequency of the laboratory tests differed from a patient to another, numerous clinical outcomes data were missing at the different time points (e.g., eGFR, LDL-cholesterol), which prevented us from analysing the impact of medication adherence on these clinical outcomes. However, blood pressure was systematically collected at each patient visit, and this analysis is ongoing to investigate the impact of the IMAP on systolic blood pressure.

VI. Conclusions

The interprofessional medication adherence program (IMAP) supports adherence in terms of implementation to chronic medications in patients with diabetic kidney disease. The longer the patients benefit from the intervention, the more the implementation increases over time and the more the effect lasts after the end of the intervention. The IMAP should be recommended for at least 12 months, or even longer on a schedule of decreasing intensity depending on the needs of patients, to have a positive and sustained effect on treatment implementation in patients with diabetic kidney disease. The impact on clinical outcomes needs to be further investigated.

Abbreviations

BMI	Body Mass Index
CHUV	*Centre Hospitalier Universitaire Vaudois*
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus disease
CRF	Case Report Form
DKD	Diabetic Kidney Disease
eGFR	estimated Glomerular Filtration Rate
EMs	Electronic monitors
EMERGE	ESPACOMP Medication Adherence Reporting Guidelines
ESRD	End Stage Renal Disease
GEE	Generalized estimating equation
HbA1c	Glycated hemoglobin
HCPs	Health care providers
IMAP	Interprofessional Medication Adherence Program
IQR	Interquartile ranges

LADA	Latent Autoimmune Diabetes in Adults
LCD	Liquid-crystal display
LDL	Low-density lipoprotein
PANDIA-IRIS	*Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique*
PART-PANDIA	Participation to the PANDIA-IRIS study
SD	Standard deviation

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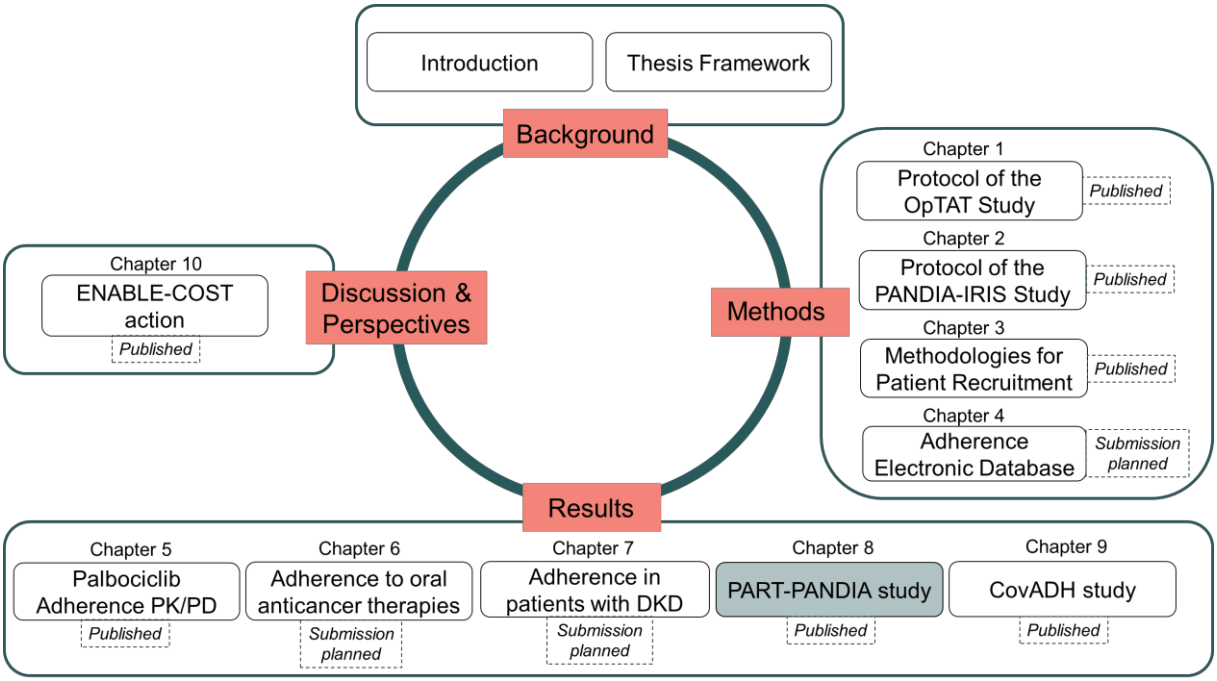
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CHAPTER 8: THE "PARTICIPATION TO PANDIA-IRIS" (PART-PANDIA) STUDY



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

Chapter 8 presents the article published in *BMC Diabetology & Metabolic Syndrome* in September 2022, which described the results of the study “Participation to the PANDIA-IRIS study” (PART-PANDIA). This paper involved the School of Pharmaceutical Sciences (University of Geneva), the Center for Primary Care and Public Health *Unisanté*, the Service of Nephrology and Hypertension and the Service of Endocrinology, Diabetes and Metabolism of the Lausanne University Hospital (CHUV).

The preliminary results of this study were presented as a virtual poster presentation at the annual ESPACOMP congress in November 2020 (online congress)[244]. The definitive results were presented as a poster presentation at the Pharmaceutical Care Network in Europe (PCNE) congress in February 2022 (Lisbon, Portugal)[245] and at the *Société Suisse de Médecine Interne Générale (SSMIG)* congress in June 2022 (Lausanne, Switzerland) (Appendix 7).

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RESEARCH

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Understanding reasons and factors for participation and non-participation to a medication adherence program for patients with diabetic kidney disease in Switzerland: a mixed methods study

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Abstract

Background: An interprofessional medication adherence intervention led by pharmacists, combining motivational interviews and feedback with electronic monitor (EM) drug assessment, was offered to all consecutive patients with diabetic kidney disease (DKD) (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) visiting their nephrologist or endocrinologist. Approximately 73% (202/275) of eligible patients declined to participate, and the factors and reasons for refusal were investigated.

Methods: Sociodemographic and clinical data of included patients and those who refused were collected retrospectively for those who had previously signed the general consent form. Multivariate logistic regression analysis was performed to identify independent variables associated with non-participation. Patients who refused or accepted the adherence study were invited to participate in semi-structured interviews. Verbatim transcription, thematic analysis, and inductive coding were performed.

Results: Patients who refused to participate were older (n = 123, mean age 67.7 years, SD:10.4) than those who accepted (n = 57, mean age 64.0 years, SD:10.0, p = 0.027) and the proportion of women was higher among them than among patients who accepted it (30.9% vs 12.3%, p = 0.007). The time from diabetes diagnosis was longer in patients who refused than in those who accepted (median 14.2 years IQR 6.9–22.7 vs. 8.6 years, IQR 4.5–15.9, p = 0.003). Factors associated with an increased risk of non-participation were female sex (OR 3.8, 95% CI 1.4–10.0, p = 0.007) and the time from diabetes diagnosis (OR 1.05, 95% CI 1.01–1.09, p = 0.019).

The included patients who were interviewed (n = 14) found the interprofessional intervention useful to improve their medication management, support medication literacy, and motivation.

Patients who refused to participate and who were interviewed (n = 16) explained no perceived need, did not agree to use EM, and perceived the study as a burden and shared that the study would have been beneficial if introduced

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earlier in their therapeutic journey. Other barriers emerged as difficult relationships with healthcare providers, lack of awareness of the pharmacist's role, and negative perception of clinical research.

Conclusions: Investigating the factors and reasons for participation and non-participation in a study helps tailor intervention designs to the needs of polypharmacy patients. Patients who refused the adherence intervention may not be aware of the benefits of medication management and medication literacy. There is an urgent need to advocate for interprofessional outpatient collaborations to support medication adherence in patients with DKD.

Trial registration Clinicaltrials.gov NCT04190251_PANDIA IRIS.

Keywords: Medication adherence, Electronic adherence monitoring, Patient selection, Patient satisfaction, Patient preference, Diabetes mellitus, Diabetic nephropathies, Chronic renal insufficiency, Interventions, Qualitative research, Interprofessional program, Pharmacists

Background

Context

In 2021, one in 10 adults worldwide was diagnosed with diabetes of any kind, representing 537 million adults [1]. Preventive measures should be adopted to slow down the pandemic, as it is estimated that 10.2% of the world's population will be diabetic by 2030. In Switzerland, 500,000 people have diabetes, representing 6% of the Swiss population [2, 3].

Among people diagnosed with diabetes, 30–40% develop chronic kidney disease over time, making it one of the first causes of end-stage renal disease (ESRD) in the occidental world. Treating diabetic kidney disease (DKD) is complex and requires an interprofessional team of healthcare providers (HCP) to improve prognosis, slow down the decline in renal function, and prevent cardiovascular events [4, 5].

Optimal medication adherence is essential to achieve these goals. Medication adherence refers to the extent to which a patient takes a treatment as prescribed. It is characterized by the initiation (first dose of the treatment taken), implementation (dose taken at the right time, with the right regimen, and according to specific requirements), and absence or presence of discontinuation (the patient stopped taking the drug before the end of the prescription). More than 700 determinants characterize medication adherence, including patient-, condition-, treatment-, socioeconomic and health care system-related factors (e.g., patients' relationship with their HCP) [6, 7].

The risk of ESRD declines if the patient's adherence to antihypertensive medication is higher than 80% (hazard ratio (HR) 0.67, IC 95% 0.54–0.83) [8]. Although up to 40% of DKD patients encounter medication implementation issues during their care itinerary [9], medication nonadherence is often not addressed by HCPs. Finally, it is estimated that increasing medication adherence in patients with diabetes would lead to annual cost savings of at least US$661 million in the USA [10].

The randomized and controlled PANDIA-IRIS study (*Patients Diabétiques et Insuffisants Rénaux: un programme interdisciplinaire de soutien de l'adhésion thérapeutique*) aimed at monitoring—and if necessary improving— medication adherence among patients diagnosed with DKD who consulted the diabetes and renal outpatient clinics at the Lausanne University Hospital (*Centre Hospitalier Universitaire Vaudois*, CHUV, Lausanne, Switzerland). The intervention included patients in the local Interprofessional Medication Adherence Program (IMAP) at the community pharmacy of the Primary Care and Public Health *Unisanté* (Lausanne, Switzerland) [11]. The program consists of regular motivational face-to-face interviews between the patient and pharmacist to explore patients' medication management monitored by electronic monitors (EMs) (MEMS and MEMS AS, AARDEX Group, Sion, Switzerland) that capture each date and time the EM is opened by the patient. The protocol has been previously described [12]. This study approached 275 eligible DKD patients, but 73% of the patients declined to participate. This low recruitment success rate seems to be recurrent in the scientific literature; for example, in another study recruiting Type 1 diabetes patients for a randomized controlled trial (RCT), 71% of the patients refused to participate [13]. In another RCT recruiting type 2 diabetes patients, 51% of the patients refused to participate [15]. Such frequent, high levels of patient non-participation and attrition alter the study power and reliability of interventional studies.

Few studies have explored patient factors and reasons for non-participation in interventional programs to promote diabetes self-management education [14–17]. Among the predominant factors cited, the relationship between the patients and their HCP plays a key role in the decision to participate to self-management programs [16]. None of the studies have explored participation in interventions to support medication adherence in patients with DKD.

Objectives

The primary objective of the PART-PANDIA (*PARTicipation in PANDIA-IRIS*) study was to compare the population of patients with DKD who refused versus accepted to participate in the PANDIA-IRIS study according to their sociodemographic and clinical variables.

The secondary objective was to understand in depth the reasons for non-participation, the patients' actual medication management process, their relationship with their HCP, and their perception of the role of interprofessional teams, including the pharmacist. The results were put into perspective with qualitative interviews led with patients with DKD included in the PANDIA-IRIS study, to explore their reasons for participation, their perception of the intervention and their reasons for drop-out if any. Recommendations to adapt the study design were provided upon participants' feedback.

Methods

Ethical considerations

The local ethics committee (Vaud, Switzerland) approved the PANDIA-IRIS study in April 2016 (project ID 2016-01674) and the PART-PANDIA study in February 2021 (project-ID 2020-02540).

The randomized and controlled PANDIA-IRIS study

Aim and design of the PANDIA-IRIS study

The PANDIA-IRIS study was a randomized, controlled, and open trial. Enrolled patients were adults diagnosed with diabetes and renal impairment (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2). The included patients were randomized into two arms, each lasting for 24 months—participants in the first arm received IMAP intervention for 6 months vs 12 months in the second arm [12]. During the intervention phase, the patient and pharmacist together explore patients' medication management habits and skills, patients' beliefs, preferences and motivation to take the treatment, and patient needs for information regarding the treatment and medication adherence; they investigate the presence of side effects and their management, and they set stepped goals, if necessary, from one interview to the next. The IMAP program is built upon the information-behavior-motivation model of Fisher et al. [11, 18] and contributes to improve patients' self-management and medication literacy. After the intervention phase (i.e., the follow-up phase), medication adherence was monitored electronically in a blinded manner, without any motivational interviews or feedback. The aim of the PANDIA-IRIS study was to compare medication adherence in both groups to determine the impact of IMAP duration on 24-month medication adherence [12].

Patients' recruitment in the PANDIA-IRIS study

Recruitment began in April 2016, and ended in October 2020. The study recruited 275 eligible patients consecutively (i.e., regardless of the patient's mother tongue, socioeconomic background, relationship with the HCP, or regularity of attendance to medical appointments). The investigators (JDC and CB) recruited outpatients at the end of their medical consultation at the diabetes and renal outpatient clinics of the Lausanne University Hospital (*Centre Hospitalier Universitaire Vaudois*, CHUV) and at the Center of Primary Care and Public Health *Unisanté*. The physician usually presented the study briefly to the patients before JDC and CB explained the study procedures to the patients in depth. No incentive (e.g., financial) was offered to participants. In total, only 73/275 (27%) patients agreed to participate and were included in the PANDIA-IRIS study.

The quantitative and qualitative PART-PANDIA study

Design of the PART-PANDIA study

The PART-PANDIA study was an observational study with a quantitative and a qualitative part (see Fig. 1). The main ethical and methodological difficulties involved retrieving data from patients who refused to participate. The local ethics committee (Vaud, Switzerland) required that patients who refused participation could be included in the quantitative analysis solely if they had previously agreed to participate and signed the General Consent Form (GCF) of the CHUV. The GCF was offered to all patients who had attended at least one medical appointment at the CHUV. The patient's agreement with the GCF enables researchers to use their health data as coded (no direct patient identification) for any kind of research project initiated at the CHUV. The ethics committee also agreed to the use of coded health data of deceased patients who did not disagree with the GCF when they were alive. The coded health data of patients who refused to participate in the PANDIA-IRIS study and did not sign the GCF but agreed to sign the specific consent form to participate in the qualitative interview (which specified the use of their health data as coded for this specific study) were also included in the quantitative analysis.

Quantitative analysis of sociodemographic and clinical variables

Sociodemographic data (age, sex, civil status, nationality, and patient residence) were collected at the PANDIA-IRIS study proposal date in each patient's administrative

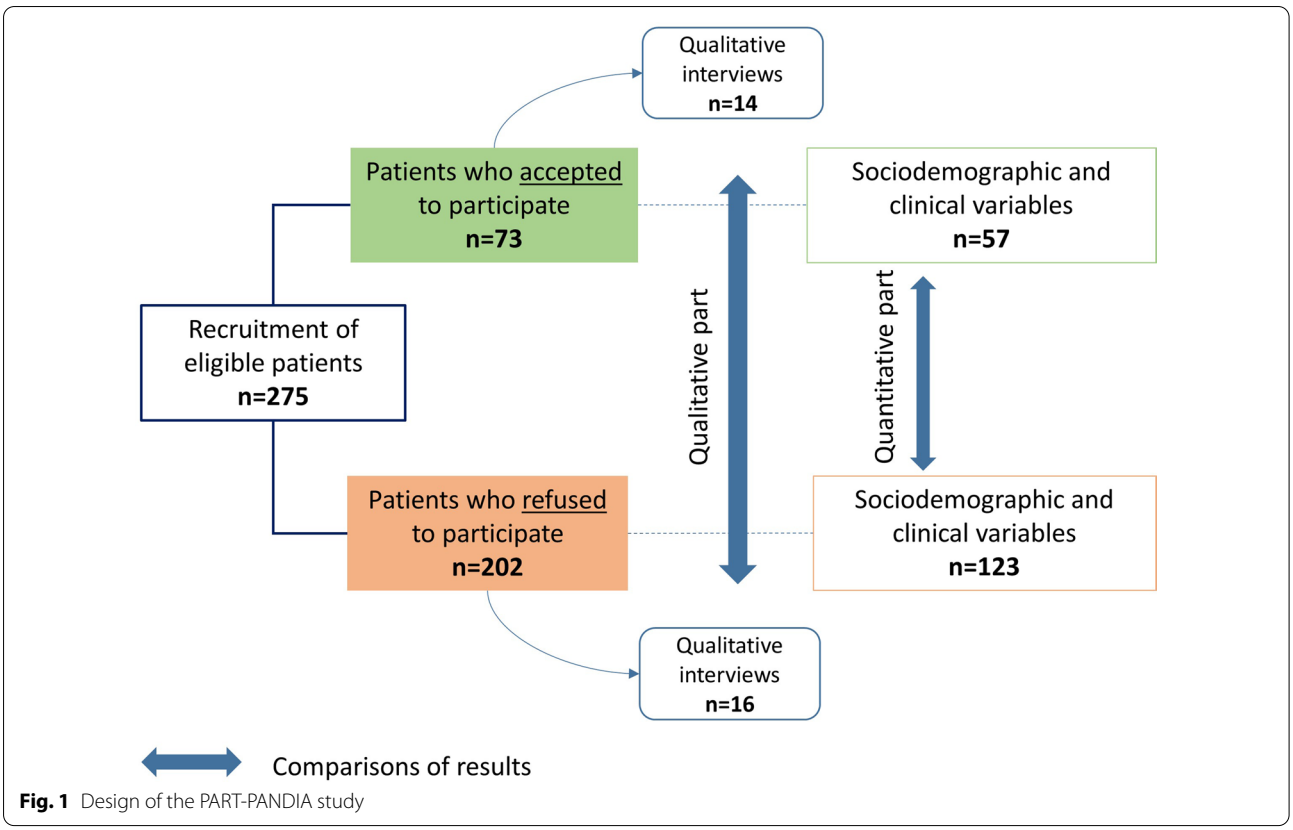


Fig. 1 Design of the PART-PANDIA study

hospital record. All of the following clinical values measured during the 12 months preceding the PANDIA-IRIS study proposal date were extracted from the patient's medical record (Soarian®, Cerner) by a data manager through an algorithm for extracting specified data from coded or free-text fields: body mass index (BMI), creatinine blood concentration, eGFR, glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, and systolic and diastolic blood pressure. Each variable was expressed as the 12-month mean value per patient to decrease the risk of outlier values as the frequency of medical appointments—and thus the collection of clinical variables—varies from a patient to another within a year. In case of missing data, discrepancies, or inconsistencies in the database, data were checked individually by the investigator in the patient's medical record. If no data were available within this timeframe, they were labelled as missing.

The clinical variables collected were used to characterize the population. These variables were also identified as possible risk factors for nonadherence or non-participation to adherence interventions. The following variables were retrieved from patients' medical records at the medical appointment closest to the recruitment date: diabetes type, number of chronic treatments, time from diabetes diagnosis, cardiovascular events, depression or anxiety diagnosis, smoking status, alcohol or drug addiction, and disability. The missing data were clearly identified. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed to report quantitative data [19].

Calculation of the eGFR decline per year

Because renal function declines when diabetes and blood pressure remain uncontrolled [20], we planned to verify if the eGFR decline was different between the included participants and patients who refused inclusion. On the basis of the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, rapid renal function decline is defined as an eGFR decline of more than 5 mL/min/1.73 m^2/year [21]. To calculate the patient's eGFR decline rate per year, all patients' blood creatinine concentrations available from 2000 to 2021 were extracted from the patients' medical records. eGFR was calculated according to the Modification of Diet in Renal Disease (MDRD) or, when available, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, including sex and race adjustments [22]. If the time span was less than 720 days between the first and last blood creatinine

values [23] or if less than four creatinine values were available, the patient was excluded from the analysis.

If a patient received a kidney or any other organ transplant or had undergone a nephrectomy prior to recruitment, patients' creatinine values were included starting one year post-transplantation or post-nephrectomy and onwards (the kidney function varies significantly during the year following a transplant or nephrectomy). If the transplant or nephrectomy occurred after the recruitment date, or if a patient underwent Renal Replacement Therapy (RRT) or dialysis, patients' creatinine values were included only until the surgery, RRT, or dialysis date.

Linear regression of eGFR values according to time was performed for each patient [24]. The value of the slope of the linear regression represents the change in eGFR per day, which is multiplied by 365 (number of days in a non-leap year) to obtain the patient's eGFR decline per year (mL/min/1.73 m^2/year) (= a). If $a \geq 0$, kidney function is stable or increases over time; if $a < 0$, kidney function decreases.

Linear regression was performed using Microsoft Excel® 32 bites (Microsoft Corporation, Washington) with built-in functions.

Statistical analysis

If continuous variables were distributed normally, data were presented as means and standard errors, and Student's t-test was performed to compare data between groups. If continuous variables were not distributed normally, data were presented as medians and interquartile ranges, and the Wilcoxon-Mann-Whitney test was used to compare data between groups. Categorical variables were presented as numbers and percentages and were compared between groups using the chi-squared test or the Fisher exact test when any expected frequency was less than or equal to 5.

Multivariate logistic regression included only variables showing an association with non-participation in the univariate comparisons ($p < 0.2$), with a maximum of six variables included (standard rule of thumb—at least 10 events per independent variable in the smallest group size to reduce the risk of overfitting data). The linearity of each continuous variable on the logit scale was tested using the Box-Tidwell test. Statistical analyses were performed using the software for statistics and data science (Stata 17 64 bit) [25].

Qualitative interviews with included participants and with patients who refused to participate to the PANDIA-IRIS study

One-to-one interviews with a representative subset of participants were conducted from July 2017 to August 2020. One-to-one post hoc interviews were conducted with a subset of persons with DKD who refused to participate in the PANDIA-IRIS study but accepted the interview afterwards from March to May 2021.

All participants who attended a 30-min interview signed a specific consent form and were compensated with 20 Swiss francs to cover associated costs, such as transport and parking. The interviews were conducted face-to-face at the Lausanne University Hospital, either by JDC or CB. They led the interviews with a semi-structured guide which enabled the investigators to ask planned questions and the patients to explain themselves in depth as well as to address relevant yet unplanned subjects.

The guide for the interviews with PANDIA-IRIS participants was structured with questions exploring patients' reasons for participation, IMAP intervention sessions with the pharmacist, patients' perceived positive and negative aspects of the PANDIA-IRIS intervention, and their relationship with HCPs (pharmacists, physicians, and nurses) during the intervention phase.

The interview guide with persons who refused to participate was structured with questions about the history of medication (self-)management (present and past), reasons for study refusal, patient's relationship with the HCPs, patient's perceived usefulness and uselessness of the PANDIA-IRIS study, and clinical research in general.

The interviews were audio-recorded and transcribed verbatim using Microsoft Office Word® software. Verbatims were coded by CB and LL using the MaxQDA software® (version 2018). A thematic analysis was performed, and coding was performed using an inductive approach (i.e., codes are driven from raw data to enable the possible emergence of new codes that do not necessarily fit the researcher code preconception) [26]. Themes and categories emerge from the coding process. Each code was compared, and discrepancies were discussed between the investigators to reach a consensus. Data saturation (i.e., no emergence of new codes) was achieved.

To interview a heterogeneous population of patients who agreed to participate, patients from both PANDIA-IRIS arms were interviewed, some of whom had just finished the intervention phase but were pursuing the follow-up phase, some completed the 24-month follow-up, whereas others dropped out prematurely for personal reasons. We included patients with different levels of

medication adherence (based on the results of electronic monitoring), sex, and age.

Recruitment of patients who refused to participate was intentionally heterogeneous regarding age, sex, marital status, and renal impairment level (eGFR > or < 50 ml/min/1.73 m^2). This study followed the Standards for Reporting Qualitative Research (SRQR) guidelines [27].

Results

Quantitative part: comparison of sociodemographic and clinical variables of patients who refused versus agreed to participate in PANDIA-IRIS

Among the 275 patients to whom the PANDIA-IRIS study was presented, 169 (61.5%) patients had signed the GCF, six patients died and did not disagree with the GCF while they were alive, and five patients signed the specific consent form allowing data retrieval and participated in the qualitative interview. In total, the sociodemographic and clinical data of 180 patients (123 patients who refused and 57 who accepted) were included in the quantitative analysis. According to their GCF endorsements, patients included in the PANDIA-IRIS study were more willing to participate in research projects (57/73, 78%) than those who refused participation in PANDIA-IRIS (112/202, 55%), p = 0.0007.

The sociodemographic and clinical variables of the patients who refused versus agreed to participate in the PANDIA-IRIS study are presented in Table 1. Patients who refused to participate were older (mean age 67.7 years, SD:10.4) than those who accepted (64.0 (SD:10.0), p = 0.027). The percentage of women was higher among patients who refused than among those who accepted it (30.9% vs 12.3%, p = 0.007). The time from diabetes diagnosis was longer in patients who refused than in those who accepted (median 14.2 years, IQR 6.9–22.7 vs 8.6 years, IQR 4.5–15.9, p = 0.003) (Table 1). In the multivariable logistic regression analysis, factors associated with an increased risk of non-participation were female sex (OR 3.8, 95% CI 1.4–10.0, p = 0.007) and the time from diabetes diagnosis (OR 1.05, 95% CI 1.01–1.09, p = 0.019) (Table 2).

Patients who agreed to participate took a mean of 9 (SD:4) chronic treatments, whereas patients who refused took 10 (SD:3) treatments (Table 1).

For the included patients, the eGFR decline was calculated based on the mean time span between blood creatinine values of 3030 days (min 729 days, max 4353 days) and the mean number of creatinine values per patient of 65 (min 5; max 192). In patients who refused to participate, the mean time span was 3204 days (min 960 days; max 4342 days), and the mean number of creatinine values per patient was 62 (min 7; max 263). The eGFR decline per year was not significantly different between patients who refused and those who accepted (respective median −1.8 mL/min/1.73m^2/year (IQR: −4.2; −0.5) vs −2.4mL/min/1.73m^2/year (IQR −4.2; −0.7) (Table 1). The results show that patients are faster decliners than the average found in type 2 diabetes patients in Swiss ambulatory care (i.e., −1.2 mL/min/1.73m^2/year (SD 0.05) in men, −1.0 mL/min/1.73m^2/year (SD 0.06) in women [28]).

Qualitative part: Interviews on satisfaction with patients included in the PANDIA-IRIS study

Data saturation was achieved after 12/14 interviews. Based on the transcribed verbatim from the 14 interviews, 1182 segments were coded and gathered into the following main themes: (i) reasons for participation, (ii) usefulness of the PANDIA-IRIS intervention and (iii) adaptations of the intervention.

Why did patients accept to participate to the PANDIA-IRIS study?

Patients were willing to participate to "improve" medical and clinical knowledge, and therefore "help" other patients (P01, P06, P10, P11, P13). They also wanted to benefit from the intervention to improve their medication management and knowledge about their medicines (P02, P14, P07). Some patients accepted to participate following the recommendation of their endocrinologist or nephrologist (P03, P04, P08, P09, P12).

> *"I participated because the nephrologist told me that it would be useful for me. It should reassure the doctors that I'm taking my medication regularly." (P09).*

Moreover, patients participated as they were reassured by being monitored clinically throughout the study, in addition to the usual medical appointments (i.e., blood pressure was controlled at each pharmacy visit) (P10, P05, P13). Meeting the pharmacist regularly allows the patient to refer to suspicious symptoms without waiting for the next medical appointment.

> *"I had a better follow-up [by being included in the study]. It allows us to free ourselves from our health worries." (P13).*

How do the participants perceive the usefulness of the PANDIA-IRIS intervention?

- The intervention allows participants to reflect on their own medication management

  The interviewees explained that the intervention was useful and well designed (EM refill, interviews with

Table 1 Sociodemographic and clinical variables of patients with diabetic kidney disease eligible to the PANDIA-IRIS study

	Patients who accepted n = 57	Patients who refused n = 123	p-value
Sociodemographic variables			
Age (years), mean (SD)	64.0 (10.0)	67.7 (10.4)	P = 0.027
Female, n (%)	7 (12.3)	38 (30.9)	P = 0.007
Married/partnership civil status[a], n (%)	26 (45.6)	66 (53.7)	P = 0.315
Swiss nationality, n (%)	35 (61.4)	91 (74.0)	P = 0.087
Patients living in the Lausanne center or surroundings (maximal distance of 20 km), n (%)	39 (68.4)	88 (71.5)	P = 0.669
Clinical variables			
Type 2 diabetes[b], n (%)	54 (94.7)	108 (87.8)	P = 0.149
Body Mass Index (BMI), median (IQR)	31 [28–34]	29 [26–32]	P = 0.101
Creatinine blood concentration (μmol/l), median (IQR)	128.7 (100.7–154.5)	123.4 (95.5–157.5)	P = 0.465
eGFR (mL/min/1.73m^2), median (IQR)	49.0 (37.0–60.0)	48.8 (34.3–61.0)	P = 0.876
eGFR decline per year (mL/min/1.73m^2/year), median (IQR)	−2.4 (−4.2; −0.7)	−1.8 (−4.2; −0.5)	P = 0.431
HbA1c (%), median (IQR)	7.1 (6.7–8.0)	7.4 (6.8–8.3)	P = 0.228
LDL-cholesterol (mmol/l), mean (SD)	2.1 (0.7)	1.9 (1.0)	P = 0.263
Systolic blood pressure (mmHg), mean (SD)	135.8 (15.5)	137.8 (15.3)	P = 0.415
Diastolic blood pressure (mmHg), mean (SD)	76.9 (8.8)	74.2 (9.5)	P = 0.065
Number of oral prescribed chronic treatments at the time of recruitment, mean (SD)	9 [4]	10 [3]	P = 0.228
Time from diabetes diagnosis (years), median (IQR)	8.6 (4.5–15.9)	14.2 (6.9–22.7)	P = 0.003
Current or past cardiovascular event(s)[c], n (%)	12 (21.1)	32 (26.0)	P = 0.471
Depression or anxiety diagnosis, n (%)	11 (19.3)	18 (14.6)	P = 0.428
Current smoker at the time of recruitment, n (%)	9 (15.8)	16 (13.0)	P = 0.616
Current or past alcohol addiction, n (%)	17 (29.8)	33 (26.8)	P = 0.676
Current or past drug addiction, n (%)	1 (1.8)	3 (2.4)	NA
Disability or amputation or handicap, n (%)	3 (5.3)	15 (12.2)	P = 0.149

NB1: Pearson's chi-squared test was used for the following variables; Female sex, Married/partnership civil status, Swiss nationality, Patients living in the Lausanne center or surroundings, Type 2 diabetes, Current or past cardiovascular event(s), Depression or anxiety diagnosis, Current smoker at the time of recruitment, Current or past alcohol addiction, Disability or amputation or handicap; Fischer's exact test was used for current or past drug addiction; T-Student test was used for: age, LDL-cholesterol, Systolic and diastolic blood pressure, Number of oral prescribed chronic treatments; Mann–Whitney test was used for: BMI, Creatinine blood concentration, eGFR, eGFR decline per year, HbA1c, Time from diabetes diagnosis

NB2: among patients who refused participation, missing data were: 2 BMI values, 6 creatinine blood concentrations, 6 eGFR values, 5 eGFR decline per year values, 34 HbA1c values, 39 LDL-cholesterol values and 10 values for the time from diabetes diagnosis. In patients who accepted, missing data were 11 HbA1c values and 14 LDL-cholesterol values

NA="not applicable"; statistical test not applicable as the number of patients is too small

[a] The other patients are separated, divorced, widowed or single

[b] The other category includes patient diagnosed with diabetes type 1, glucocorticoid-inducted, post-transplantation or post-pancreatectomy diabetes or Latent Autoimmune Diabetes in Adults (LADA). The eligibility criteria were expanded from October 2019 to include other types of diabetes than type 2, which explains the low proportion of patients in these categories

[c] Stroke, ST elevation myocardial infarction (STEMI) or Non-ST elevation myocardial infarction (NSTEMI), transient ischemic attacks (TIAs), cardiopulmonary arrest

pharmacists, EM feedback, and adherence reports sent to the physician).

"*I am very glad I participated, it helped me in my daily medication management (…) I better understand if I take the medication or not or if I take it twice or if I take the right one; so it allows me to be aware. (…) It allowed me to try to adapt, to take it [the medication] better in fact. (…) So I paid more attention to what I had to do.*" (P11).

Feedback on medication adherence was provided to the patients at each encounter through EM chronology graph-based interviews. Patients explained that the repeated feedback components, based on communication and monitoring, increase their self-reflection and awareness of the way they self-manage their medication (e.g., shed light on forgetfulness and confusion). It decreases the medication burden (e.g., "*If we have an interview, we can talk about it [medi-*

Table 2 Multivariate logistic regressions including maximum 6 variables associated with non-participation in the univariate comparisons (p < 0.2)

	OR	95% CI		p-value
Age (years)	1.03	0.99	1.06	0.161
Sex female	3.80	1.44	10.01	0.007
Swiss nationality	1.46	0.69	3.06	0.320
Diastolic blood pressure (mmHg)	0.99	0.95	1.03	0.490
Time from diabetes diagnosis (years)	1.05	1.01	1.09	0.019
BMI	0.96	0.90	1.03	0.236

cation intake] directly, openly, instead of keeping everything in your head" (P13)).

The electronic monitors are memory aids to check daily drug intake through a liquid–crystal display (LCD) screen on top of the bottle cap. On study completion, some patients decided to pursue the IMAP intervention in order to continue using EM and to benefit from an interview with the pharmacist.

"Before using the electronic monitors, I used to take my medication at 11:00 a.m. and sometimes at 8:00 a.m. When I use the electronic monitor, I am more careful. It makes me aware that I have to be careful. I take them [the medications] more regularly now [since the inclusion in the study]. (…) I have control over my medication intake. Besides, I better understand the role of each medication." (P13).

"Having a double check of the correct medication taking was useful. It's a relief. (…) I can see what was really done. And I like to see the graph. (…) I realized that I would really like to keep using the electronic monitor [at study completion]" (P11).

In addition, after the intervention phase (i.e., during the follow-up phase when the patient used EM without any feedback or intervention), some patients were disappointed not to attend the motivational interviews.

"[In the follow-up period], I missed that [the graphic]! Having a discussion and getting feedback and being able to explain our behavior was missing. I think everyone needs feedback." (P13).

In contrast, some patients did not perceive a significant impact of the intervention on their medication routine as they reported managing their medication well.

"*I don't think [the study] had a huge influence [on the medication management]. It was interesting to see the graph together [with the pharmacist], to analyze if I had forgotten a dose and why and what happened. But I don't think it had a strong impact on how I took them [the medications]."* (P14).

"I still took the same medicines, at the same frequency, in the morning, in the evening. It [the intervention] did not make any difference to me. They [pharmacists] never asked me to change my behavior. (…) An electronic pillbox is practical." (P05).

- Included patients acquired knowledge about their medication

Pharmacists' active listening allowed patients to ask their questions about their treatments or disease and to gain additional knowledge (e.g., taking the drug in a fasting condition or not, what to do in the case of a missed dose). The patients appreciated the quality and relevance of the information provided, in addition to the information provided by the physician. The support and clinical skills of pharmacists were appreciated.

"Sometimes, we don't precisely know what medication we are taking… We talk about this with the pharmacist during the interviews, we can ask questions about medications, what their effects or side effects are." (P14).

The newly acquired knowledge complements personal beliefs, which keep conveying ambivalence in certain patients, for example, about the usefulness of treatments in case of frequent changes ("*My medication changes too much. (…) In the long term, a medication is no longer efficient*" (P12)). Some discussed their own use of alternative medicines ("*… nux-vomica, which drains the substrates of the drugs*." (P08)).

- The adherence report promotes interprofessionnality

Sharing the adherence report with different HCPs was appreciated by the patients. One patient pointed out that it helps to harmonize decisions (e.g., "*My physician agrees with what my pharmacist does*" (P04)). The adherence report is the starting point for physicians to adjust the treatment based on the patient's adherence. One patient

(P04) reported that his relationship with his physician improved by participating in the study, as his physician did not have confidence in his medication management before study inclusion.

"To my mind, the more information the doctor has, the better he can figure it out. Every person is different, every person reacts differently, especially with diabetes. You can't make a general rule." (P14).

According to participants, what are the intervention adaptations and improvements to be made to the PANDIA-IRIS study design?

The study burden should be as low as possible. Flexibility in the frequency of appointments should be considered (e.g., especially for full-time employed patients) (P03, P04, P10, P14). Patients were already busy managing their medical appointments and felt overwhelmed by adding other pharmacy visits to their routine clinical care (P04, P06, and P10).

Developing interventions in the patients' usual pharmacies would have been appreciated by some patients (P06, P08). Considering flexibility and adaptations regarding the use of the adherence monitor (i.e., another tool than the EM, as an electronic weekly pill-organizer) may lead to improve recruitment. Indeed, the plurality of treatments requires the use of several EM (P05), and frequent changes in treatments require additional pharmacy visits to adapt EMs' content (P12), which was reported as a reason for drop-out. In some cases, the use of EM in parallel with a weekly pillbox (P01, P13) disrupts the usual medication management routine and was also a reason for drop-out.

Nevertheless, the 14 patients interviewed unanimously recommended the PANDIA-IRIS study to other patients.

Qualitative part: interviews with patients who refused to participate

Among the 202 patients who refused to participate, 26 were invited to participate in the qualitative interview and 16 agreed (62%). The main reasons for refusal were a lack of interest in the research and living too far from the hospital to attend the interview.

Data saturation was achieved after 13/16 interviews. Based on the transcribed verbatim from the 16 interviews, 1830 segments were coded and grouped into the following main themes: (i) main reasons for non-participation in the PANDIA-IRIS study, (ii) current and past treatment management at home, (iii) relationship with HCPs, and (iv) perceived HCPs' roles.

Main reasons for non-participation in the PANDIA-IRIS study

The reasons for refusal were complex and multifactorial; they involved both patients and their relatives.

- Patients who refused did not feel the need to participate in a medication adherence study, and they did not perceive a sense of medication adherence support.

Patients were confident about their medication management and felt that they would not benefit from such support and were not interested in learning more about their treatment. Some did not even understand the purpose and usefulness of such a support program to the point that they did not consider it at all. Most patients indicated that the intervention program could be useful for more vulnerable or older people (patients with poor knowledge, suffering from cognitive disorders, or depression).

> *"As long as I'm not totally senile, I think I'm responsible enough to take all the medications prescribed to me without forgetting any." (P15).*

"For me that's useless to talk about that [treatment management]. (…) I think [the doctor] has other things to worry about than hearing my whining about my medication management (…). I prefer to discuss my illness with the doctor, a more serious thing than my medication management." (P08).

- The electronic monitor (EM) was rejected by many patients

Patients did not want to change their medication management habits as they were used to other adherence tools that they chose (e.g., weekly pillboxes, boxes, bags, kits, and small cups), which were perceived as reliable, useful, and convenient. Some patients explained that the EM was too bulky, not easy to carry along, and not suited to manual dexterity impairments. Moreover, some patients explained that they were not confident about the use of electronic tools.

"It's a routine, every Saturday morning, after breakfast, we [the patient and his wife] prepare the weekly pillbox for the coming week, and there is no problem." (P03).

"Not practical for travelling because […] I will need 7 [electronic monitors], which are still much more cumbersome than if I take my small weekly pillbox to move around." (P02).

- The design of the intervention was a burden for patients

Intervention was perceived as an additional burden on patients' busy medical care. Although scheduled on the same day as the visit to the physician, most of the patients felt overwhelmed by the frequency of appointments at the pharmacy (monthly during the first 3 months, then once every three months). The fact that the intervention could be delivered only in a single academic pharmacy was a barrier to participation, as patients were bound to their usual pharmacy located at a short distance from home, where they were familiar with the staff.

"There is a logistical issue: I don't live in the city so I don't want to come to the city once per month." (P15).

"The pharmacist in my city is very competent. When I have a new prescription, he explains to me how to take it well. He has become a friend because I have been going to his pharmacy for so many years. It's valuable." (P12).

- A negative perception of clinical research

Some patients had negative representations of clinical research (e.g., linked to the business generated by pharmaceutical companies (P04)), which affected their decision to participate in all kinds of research projects.

"*There is a lot of money in [research] (…). So I say to myself it's money, money and money*." (P08).

How do patients who refused to participate in the PANDIA-IRIS study explain the way they manage their treatments at home?

- A rigorous medication management as described by patients at interview initiation…

All patients mentioned a well-established and ritualized medication management routine. Medication was often associated with daily activities (e.g., after getting up, mealtime, coffee time, and bedtime). Medications were stored in a dedicated place, and preparation of the weekly pillbox became routine. Some patients had implemented personal tools or techniques to avoid forgetting or taking their medication twice (e.g., notes, alarms, reminders from their partner, putting the medication in the jacket when going out, putting the medication box in a different place after taking them). Retired or nonworking patients reported fewer constraints to taking their medications compared to the time when they were employed full-time.

"*What at first seemed so huge to me… It has calmed down, it has become easier. But it takes time anyway. I've been doing it [the weekly pillbox] for years and it suits me a lot. (…) I had my list, it was very complicated really, and little by little you get used to it, then you do it almost with your eyes closed" (P05).*

Self-confidence, known role, perceived needs, and importance of each drug have been reported as the main sources of motivation to adhere to treatment. Some patients reported a journey toward resilience and acceptance of long-term treatment. Some patients referred to their responsibility to take treatment, associated with a desire to live, and the fear of deterioration of the disease.

"*My life depends on [the medication]. My kidneys are still functioning, but I don't know how long for (…). Preventing them [the kidneys] from declining motivates me to take my medication. Well, you can also live with dialysis but… if I can avoid it, I will do everything possible. (…) I want to be alive and I will take my medication in order to keep myself fit.*" (P06).

The interviewees were actively engaged in the management of their disease and described themselves as self-determined and empowered. Most of them read the medication leaflets, looked for information on the internet, or asked their physician, and sometimes their pharmacist, about side effects or medication interactions.

"I'm a pro now. (…) Before I had to be more careful. I've always been able to manage it. (…) I'm autonomous, I manage my medication, I manage my illnesses, I think I know my body pretty well, I'm not a doctor but I know myself pretty well. And that's a lot." (P13).

Support from relatives also played an important role in this process. If a family caregiver was in charge of the patient's medication, he/she was systematically contacted to obtain his or her opinion on participation in a study. Among the interviewed patients, female spouses were often in charge of managing their husbands' medication (e.g., filling the weekly pillbox or refilling medication at the pharmacy).

"So I don't manage them [the medications], my wife does the work (…) Patient's wife*: "And he wouldn't be able to prepare the weekly pillbox by himself."* (P04).

- However, when asking open-ended questions throughout the interview, the patients had detailed difficulties in managing their treatment.

Interestingly, while the interview proceeded with open-ended questions about possible forgetfulness or misuse of medication, some patients expressed denial of their illness and banalization of nonadherence.

Patients reported a few instances of unintentional forgetting, delayed intakes, or voluntary omissions, which occasionally occurred because of a disrupted routine (e.g., appointments, social encounters). Episodes of

confusion were described in the cases of medication or regimen changes. Some patients also explain that the high cost of treatment was a risk factor for nonadherence.

"If I'm invited to a friend's house or if I go to a restaurant, it's true that I don't always take my insulin syringe (…). So I skip the [insulin] shot. (…) I can see that the blood sugar rises a bit more than usual, but well." (P02).

The transition from forgetting once in a while to not taking the treatment at all happens sometimes unintentionally, for example, in relation to a personal burden, as explained by the patient below:

"It annoys me if one day I forget because I am so busy helping my husband (…) I remind him but nobody reminds me (…) My husband is also ill and under heavy treatment and he can't prepare his weekly pillbox alone, and I have to do everything. In addition to mine, it is a tsunami, it's a lot (…). The mental load of women has nothing to do with the mental load of men." (P05, caregiver burden).

When moving forward with the interview, patients were invited to talk about their medication and disease management throughout their therapeutic journey. The patients explained their concerns about the constant increase in the number of prescribed medications. Some participants talked about a "*cocktail*" of medications that was not easy to accept (P14, P15).

"Over the years I finally resigned myself, I accepted it. At first, I was a bit upset every time my physician added a medication… I found it difficult to accept. However, I got used to the cocktail. (…) Well, I accepted it of course, but I thought it was a lot, adding one extra pill every eight or ten months. Well… I trusted him [the physician]." (P15).

Hence, a few patients described their personal beliefs, ambivalence about their treatments, and fear of adverse effects.

"We have more and more pills… We don't know the role of each of them. This is frustrating that we don't know if a pill interacts with another." (P04).

"Diabetes has always been a problem for me. (…) At the beginning, I didn't take care of [the diabetes]. I didn't manage it properly. (…) I was taking my medication but there were a lot of things I couldn't stand (…) So it's true that I didn't really pay attention to that [the diabetes], and (…) my [blood sugar] levels were high." (P13).

"I am against medication, of course I don't like to take medication for anything. (…) Of course I'd like not to take them (…). It's like a laboratory [when preparing the weekly pillbox]." (P05).

"I've been through this before two years ago. Yeah, it was boring, it was almost a constraint (…). I was pretty rebellious about the whole stinging thing and everything because, I think I've had enough" (P09).

Patients described their emotions during their therapeutic journey as stress (P05, P09), fear (P05, P13), concern about disease degradation (P02, P03, P04, P06, P13), feeling overwhelmed about the disease burden and treatment complexity (P03, P04, P05, P09, P10, P12, P13), frustration in case of treatment ineffectiveness (P02, P11), and shame for not being able to manage the disease efficiently (P13).

What is the relationship between patients who refused to participate and their HCPs?

The relationships between the patient and HCPs were either complete trust or a difficult relationship. Some interviewees were engaged in regular shared-decision processes with their physicians (e.g., they asked for regimen adjustments according to efficacy and side effects).

"I sometimes suggest my physician to change my medicines. For instance, I can't stand the medicines "Co-Lisinopril [lisinopril + hydrochlorothiazide]" in summer because I tend to sweat more and it causes low blood pressure! In winter, I could take the "Co-Lisinopril" and the "simple Lisinopril" in summer. I suggested this to my physician who accepted the proposal." (P02).

On the other hand, physicians' lack of time and empathy were perceived as barriers to sharing information about medication management. Two patients explained that a breach of trust with the physician led to nonadherence, expressed either as a discontinuation of their treatment for several months or voluntary defective treatment implementation. Another barrier is physician turnover, which frequently occurs in university hospitals. This prevents patients from sharing their medication management if the relationship is renewed.

"I had a problem with endocrinologists. (…) When we begin the consultation, they tell us: "show me your booklet!" I hate this booklet. I have it with me but I say I don't have it. I'm so afraid, because when we have high blood sugar concentrations, they say "you didn't pay attention" whereas I did. (…)" (P13).

How do patients who refused to participate perceive the role of their HCPs about medication management support?

Patient confidence in physicians, pharmacists, and nurses is unequal. Physicians occupy a privileged place in the minds of patients to discuss medication management. For many patients, this was reinforced by accessibility of their medical records. According to one patient, nurses were too overloaded to talk about medication management, while another patient explained being less confident about talking to a nurse compared to a pharmacist or a physician. A patient's wife (P04) believed that home

care nurses were paramedical staff and could not be trusted.

"*Some people may have more difficulty to confide in a nurse compared to a physician because of their social status.*" (P06).

The patient's perception of the pharmacist's role was dichotomous. On the one hand, patients explained that the skills and availability of their pharmacists were appreciated and reassuring. The usefulness of pharmacy services, such as the preparation of weekly pillboxes, was praised (e.g., "*Making a weekly pillbox for them [patients who need it] is already a precious help*". (P05)).

On the other hand, the pharmacist's role seemed to be often perceived as technical (e.g., the role of the pharmacist is only to "*control*" the treatment. (P06)). Pharmacy is still perceived as a point of sale rather than a place of pharmaceutical care. The lack of confidentiality and the stand-up position at the pharmacy made the exchange less comfortable than in the doctor's office (P14). The concept of continuity of care and interprofessionality was absent in most patients' speech, and this influenced patients' decisions to participate in the pharmacist-led intervention study.

"I expect the pharmacist to advise me and to inform me about the compatibilities of the medicines. It will always be difficult for a pharmacist to replace the doctor, as he/she [the pharmacist] does not have access to the medical file, he/she does not know the case." (P02).

"I never thought about pharmacists [to discuss about medication taking]. (…) My doctor tells me what to take."(P07).

"The pharmacist can only repeat the doctor's recommendations." (P08).

"[My pharmacist] does not understand anything, we cannot discuss. I come to take my medicines to the pharmacy and that's all, goodbye. This is totally different from my previous usual pharmacy, where we could discuss, laugh, it was nice. But now it is not the case anymore." (P08).

Discussion

Main results

This study addressed a common yet under-investigated issue—patients' refusal to participate in an interprofessional medication adherence intervention study. Taken together, our PART-PANDIA results showed that more women than men refused to participate, and patients who refused had a longer diabetes experience than those who accepted. However, patients in both groups were clinically at risk, as their renal function continued to decrease over time at a faster rate than the usual diabetic population. More patients who accepted the PANDIA-IRIS study signed the GCF compared to patients who refused, showing that the included patients were more willing, available, and interested in research than non-participants. The participants also stressed the importance of tailoring the adherence program to fit their busy medical schedules and needs. The included patients found the intervention useful to improve their medication and disease management and sharpen their knowledge. They felt reassured by close monitoring and emerging interprofessional collaboration, especially through the adherence report shared between HCPs. By contrast, patients who refused did not see the point of being part of such an intervention, which they perceived to be a burden. Even though they described rigorous medication management, they also described adherence difficulties.

Benefits of the intervention

By participating, the included patients discovered the usefulness of the intervention and became active partners. They described that improving their treatment management was a complex process, based on knowledge, learning attempts, individual efforts, and a safe environment to explore their beliefs about medication [29–31]. The common emotional burden of polymedicated patients is a theme shared by participants and non-participants, which should be addressed by interprofessional interventions.

For ethical reasons, few studies have compared medication adherence in adherence interventions among non-participants and participants. Therefore, it is difficult to understand if the level of medication adherence and acceptance of participation are correlated. Based on self-reports, non-participants reported significantly higher diabetes self-management compared to participants in an educational diabetes intervention [15]. Another study reported no difference in adherence between participants and non-participants to an adherence intervention for cardiovascular risk management, but only 36% were considered highly adherent in both groups [32]. A RCT including patients with type 1 diabetes aimed at defining optimal treatment to prevent nephropathy and retinopathy complications. Patients who reported a high study burden had a lower adherence during the first year and a lower study retention compared to patients who reported lower barriers to participation [13].

Patients at risk of non-participation

More women refused to participate than men. Even though the women described themselves during

recruitment as autonomous in managing their treatment, they could trivialize their need for support, which may impact their own medication adherence (e.g., women reporting caregiving involvement and burden [13, 33, 34]). It is unclear whether gender is a risk factor for non-adherence as many other covariates are involved (e.g., perceived treatment side effects, age, and comorbidities) [35–39].

Patients who benefit from strong support from family caregivers are at risk of non-participation if an informal caregiver is absent when the study is presented to the patients. Such caregivers are essential to ensure optimal medication adherence [40] and special attention should be paid to this dyad during study presentations. Importantly, a supportive medication adherence program must be presented early enough during the care itinerary so that patients can get the full benefit of the intervention to reinforce their autonomy before having to rely on a family caregiver.

Patient recruitment in diabetes education programs is often low, whereas such programs are strongly recommended to achieve clinical outcomes and increase quality of life [41, 42]. The patients' decision to participate in an intervention depends on multiple complex factors [17, 43], including logistical reasons or lack of personal interest [13, 17, 44]. Patients who refuse may not consider or understand the positive impact of the intervention on their medication management, medication literacy, and quality of life. Literature shows that this aspect has been encountered and cited as the "don't know" factor and was a key barrier to participation in an educational program for patients with type 2 diabetes [14].

The intervention should be offered sooner in patients' therapeutic journey

The patients who refused to participate had a longer history of diabetes. These patients had a long treatment experience and may have acquired habits and self-confidence about their disease and treatment management over the years, which they relied on and felt reluctant to discuss. In our study, non-participants tended to be older than participants. In the study by Thoolen et al., patients treated intensively were more likely to participate in the first year after diabetes diagnosis than 2–3 years after [15]. Offering interventions for patients newly diagnosed with diabetes could increase the inclusion rate. In a meta-analysis including 771 adherence studies, the effects of the interventions on medication adherence outcomes seem to be smaller in older patients compared to younger [45]. Adherence interventions must be presented to patients at the right time according to a predefined shared plan to allow patients to actively participate in the decision with HCPs. Indeed, medication adherence is a dynamic process which can drastically evolves over time, especially after major clinical or personal events (e.g., hospitalization, moving, giving birth, death of a close relative). Outside of a trial context, polypharmacy patients should first experience the IMAP for some months to obtain a reliable evaluation of their medication adherence before deciding whether they need to pursue an intervention or not. This would allow to make patients aware of the existence of such adherence programs so that they could participate upon their own perceived needs during their care itinerary. Based on the recruitment experience, we noticed that patients who refused could have been less at ease in discussing their treatment management difficulties and may have needed time to decide to participate. This should be taken into consideration when introducing the intervention step by step. To increase access to effective medication adherence interventions, patient participation should be planned in advance based on a shared-decision model.

New models of care and interprofessionnality

The PART-PANDIA study demonstrated that a trusted relationship between the patient and HCPs plays an important role in patients' decision to participate in an intervention, reinforcing what has already been described in the literature [14, 16, 46]. Many patients refuse to participate in medication adherence interventions that are not yet nested into routine care; such interventions may be perceived as extra-curricular, optional, and sometimes confronting. In our study, non-participants did not understand the role of the pharmacist in supporting medication adherence, showing a lack of information on the many interventions that the pharmacist can provide to support medication management. In addition, they prioritized their physician as the main contact person and the leader of their care, although the responsibility was shared interprofessionally between pharmacists and nurses. Patients may hierarchize HCPs through personal and social representations. The shared decision-making process with pharmacists is not well established; however, it is increasingly acknowledged between physicians and patients [47]. Therefore, patients should be better informed of the plurality of the roles and responsibilities of each HCP in monitoring medication management. This transition of care toward interprofessional collaborations, including the patient as a partner, may help improve medication adherence.

Potential room for improvement of the adherence intervention

Patients' reasons for refusal were often similar to the barriers cited by patients who left the study prematurely

(e.g., too many appointments and EM being bulky). To overcome this problem, efforts must be undertaken to adapt interventions to patients' needs (e.g., implementing tele-consultation to prevent disabled patients from coming regularly to the intervention site, adapting the tool to measure adherence). In addition, clinical research should be made more accessible and attractive, especially for vulnerable patients or those with low health literacy (e.g., those with low retention in care).

Strengths and limitations

This study had several strengths, especially the robustness of its mixed quanti-quali methodologies. All sociodemographic and clinical variables were extracted from patients' medical records -the most reliable information source- with few missing data. According to an adjusted multivariate analysis, we could identify that participants and non-participants differed in sex and time from diabetes diagnosis. The calculation of the eGFR decline is based on a rigorous methodology, which is clearly explained. This calculation is scarce in the current literature whereas it allows to characterize renal decline in DKD patients.

This study had some limitations. First, eligible patients recruited in the PANDIA-IRIS study who rejected GCF were not included in the quantitative analysis. We cannot exclude the possibility that patients who refused GCF differed from those who signed it. Nevertheless, two-thirds of the eligible patients were included in the PART-PANDIA study, providing a substantial database for analyzing demographic and clinical variables in both groups. Second, the patient's education level was not available in the patient's record, whereas literature shows that there could be a differential education level among participants compared with non-participants [15]. Third, as interviews with non-participants were hold several months after the recruitment date, a recall bias about their reasons for refusal cannot be excluded. However, this bias was limited as at the beginning of the interview, the investigator reminded the patients about the context of the recruitment, showed them the EM, and explained them again the study procedures and design. Forth, patients who refused to participate in the qualitative interviews would have brought up other themes, even though the recruitment was sufficiently heterogeneous to limit selection bias.

Conclusions

To our knowledge, this is the first study to compare factors and reasons for participation and non-participation in a medication adherence intervention in patients with DKD using a mixed methods approach. Patient recruitment in educational diabetes programs is a difficult task, and patients who refuse to participate may not be aware of the benefits they could gain from their medication management, medication literacy, and quality of life. Understanding systematic factors and reasons for non-participation helps tailor intervention designs to the needs of such polypharmacy patients to facilitate their engagement in medication adherence interventions. Information on specific support in medication management that pharmacists can provide within an interprofessional healthcare team must be better promoted among chronically ill patients.

Abbreviations

BMI: Body Mass Index; CHUV: *Centre Hospitalier Universitaire Vaudois*, Lausanne University Hospital; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration formula; DKD: Diabetic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; EM: Electronic Monitor; ESRD: End stage Renal Disease; GCF: General Consent Form; HbA1c: Glycated Haemoglobin; HCP: Healthcare Provider; IQR: Interquartile Range; IMAP: Interprofessional Medication Adherence Program; KDIGO: Kidney Disease Improving Global Outcomes guidelines; LADA: Latent Autoimmune Diabetes in Adults; LCD: Liquid–crystal display; LDL: Low Density Lipoprotein; MDRD: Modification of Diet in Renal Disease; NSTEMI: Non-ST Elevation Myocardial Infarction; PANDIA-IRIS: *Patients Diabétiques et Insuffisants Rénaux: un programme interdisciplinaire de soutien de l'adhésion thérapeutique*; PART-PANDIA: PARTicipation to PANDIA-IRIS; RCT: Randomized Controlled Trial; RRT: Renal Replacement Therapy; SD: Standard Deviation; SRQR: Standards for Reporting Qualitative Research guidelines; STEMI: ST Elevation Myocardial Infarction; STROBE: STrengthening the Reporting of OBservational studies in Epidemiology guidelines; TIAs: Transient Ischemic Attacks; USA: United States of America.

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Author contributions

CB, MPS and AZ designed the PART-PANDIA study; CB, JDC, DD, GW, MP and AZ were implicated in patients' recruitment; DD, GW, MP and AZ followed the patient clinically; CB, LL, IL, AZ and MPS analysed and interpreted the data. CB wrote the manuscript, reviewed by MPS. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to ethical reasons but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The local ethics committee (Vaud, Switzerland) approved the PANDIA-IRIS study in April 2016 (project-ID 2016–01674) and the PART-PANDIA study in February 2021 (project-ID 2020–02540). All participants gave specific or general consent to participate to the study. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

Specific and general consent forms ensure that the authors have the permission to publish research findings.

Competing interests

The authors declare that they have no competing interests.

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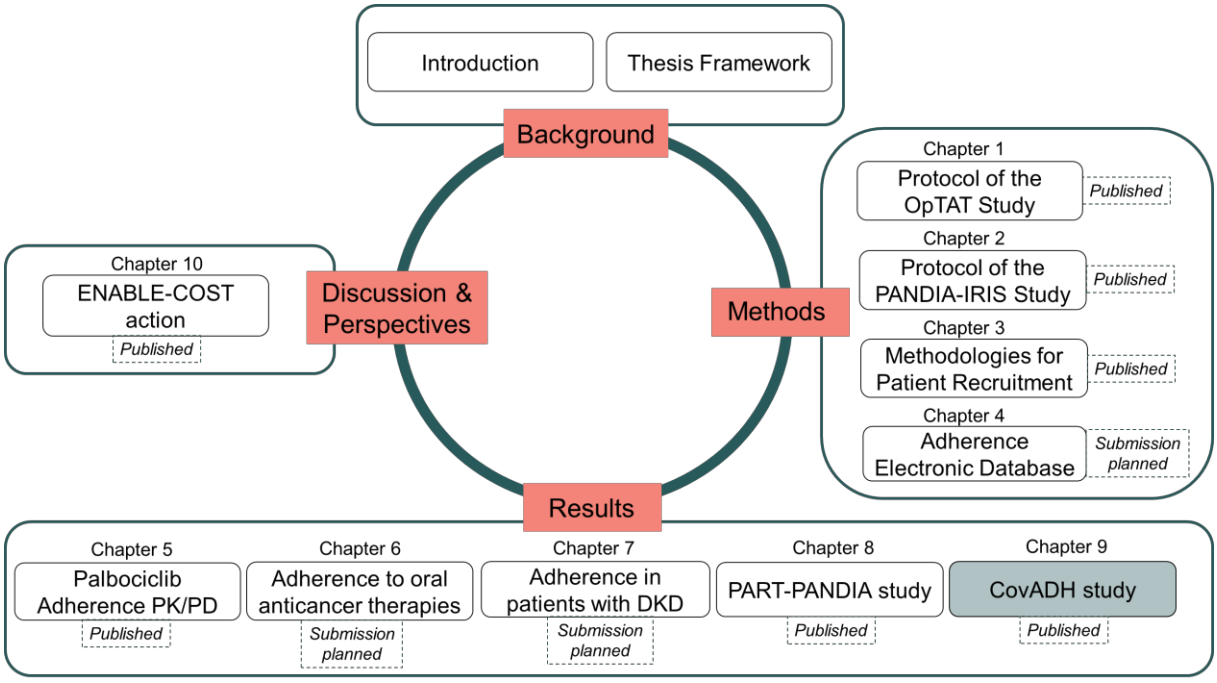
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CHAPTER 9: THE COVID-19 AND ADHERENCE (COVADH) STUDY



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

Chapter 9 presents the article published in *Patient Preference and Adherence* in August 2022, which described the results of the "Covid-19 and Adherence" (CovADH) study. This paper involved the School of Pharmaceutical Sciences (University of Geneva), the Center for Primary Care and Public Health *Unisanté*, the Center for Research and Innovation in Clinical Pharmaceutical Sciences, the Service of Nephrology and Hypertension, the Service of Endocrinology, Diabetes and Metabolism, the Service of Oncology, the Service of Infectious Diseases of the Lausanne University Hospital (CHUV) as well as the Service of Infectious Diseases of the Bern University Hospital.

The results of the CovADH study were presented as a poster at the International Pharmaceutical Federation (FIP) congress in July 2022 (Utrecht, The Netherlands)[246] (Appendix 8).

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ORIGINAL RESEARCH

Medication Adherence Evaluated Through Electronic Monitors During the 2020 COVID-19 Pandemic Lockdown in Switzerland: A Longitudinal Analysis

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Background: During the 2020 COVID-19 lockdown, patients included in the Interprofessional Medication Adherence Program (IMAP) in Switzerland continued to use electronic monitors (EMs) that registered daily drug-dose intake. We aimed to understand to what extent patients' medication implementation (ie, the extent to which the patient took the prescribed medicine), measured with EMs, was impacted by the lockdown.

Methods: Patients participating in the IMAP were diagnosed with diabetic kidney disease (DKD), solid cancer, human immunodeficiency virus (HIV) and miscellaneous long-term diseases (MLTD). Patient implementation was defined through a proxy: if all patient EMs were opened at least once daily, implementation was considered active (=1), and no implementation was considered (=0) otherwise. Implementation before (from December 2019 to March 2020), during (March to June 2020) and after (June to September 2020) the lockdown was compared. Subanalyses were performed according to the patients' diseases. Subanalyses were performed in patients who used at least one EM in 2018–2019 during the same periods (defined as winter, spring and summer). The logistic regression models used to estimate medication implementation according to the period were fitted using generalized estimating equations.

Results: In 2020, patient implementation (n = 118) did not differ significantly before versus during (OR = 0.98, 95% CI: 0.84–1.15, p = 0.789) and before versus after (OR = 0.91, 95% CI: 0.79–1.06, p = 0.217) the lockdown. These findings remained stable when separately analyzing the implementation of patients with HIV (n = 61), DKD (n = 25) or MLTD (n = 22). Too few patients with cancer were included (n = 10) to interpret the results. In 2019, the implementation of 61/118 (51.7%) patients was significantly lower during summertime versus wintertime (OR = 0.73, 95% CI: 0.60–0.89, p = 0.002).

Conclusion: Medication implementation remained steady before, during and after the lockdown in 2020. The IMAP before, during and after the lockdown may have supported the adherence of most patients, by ensuring continuity of care during periods of routine disturbances.

Keywords: SARS-CoV-2, COVID-19, medication adherence, patient compliance, implementation adherence, electronic adherence monitoring, interprofessional adherence intervention

Introduction

Medication nonadherence in patients with chronic diseases is a major economic and public health concern.[1] Medication adherence is the extent to which a patient manages a prescription, whether the medication is prescribed according to shared decision-making or not. It is characterized by initiation (whether the patient

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takes the first dose), implementation (daily treatment intake) and discontinuation (prematurely stopping the treatment).[2] Persistence describes the time between initiation and discontinuation. Adherence can be affected by more than 700 determinants,[3] including social support, access to medication,[4] communication with health care providers (HCPs), and socioeconomic or employment status, which were impacted by the lockdown due to the Coronavirus disease (COVID)-19 pandemic.

Indeed, during the COVID-19 lockdown in Switzerland, from March to June 2020, the Swiss authorities strongly recommended that the population stay at home: working from home was mandatory; schools, social and cultural places were closed; social gatherings were prohibited, including in nursing homes; only essential shops were accessible; and Swiss frontiers were closed for nonworkers.

Literature about patients' medication adherence during this period is scarce and often measured by retrospective self-reports.[5–7] Adherence during lockdown varied according to the monitored treatment, the disease and the patient's perceived risk: in a German study, 84% of patients with inflammatory rheumatic diseases treated with immunomodulatory therapies reported that they continued the treatment, and only 3% discontinued treatment. Patients' behaviour towards medication management remained stable before, during and after the lockdown.[8] The adherence of patients with asthma and chronic obstructive pulmonary disease in the USA, evaluated through electronic monitors (EM) during the first 7 days of January 2020 and compared to the last 7 days of March 2020, increased from 54% to 62%.[9] In India, patients who missed their medical appointments in a glaucoma clinic during the lockdown answered a questionnaire by phone call regarding their medication adherence. In total, 57% were considered non-adherent. Barriers to adherence were medicine supply issues, financial difficulties and no perceived effectiveness of the antiglaucoma medications.[10] To our knowledge, no longitudinal adherence data are available on patients' adherence in Switzerland during the lockdown.

The aim of the CovADH (Covid and ADHerence to medication) study is to analyze EM data of patients included in the Interprofessional Medication Adherence Program (IMAP)[11] to describe patients' medication implementation before, during and after the 2020 lockdown. We hypothesized that medication implementation was impacted during and after the lockdown compared to before the lockdown.

Methods

The CovADH study is a retrospective analysis that combines the anonymous databases of several prospective studies and cohorts from the IMAP. The local ethics committee (Vaud, Switzerland) authorized the CovADH study to be run after the anonymization of the databases. All included patients signed either the IMAP-specific informed consent form or the Swiss HIV (Human Immunodeficiency Virus) cohort study (SHCS)-specific informed consent form, which allows researchers to use patients' adherence data for research purposes.

The IMAP runs routinely at the outpatient community pharmacy of the Center for Primary Care and Public Health (Unisanté, Lausanne, Switzerland)[11] and at the Department of Infectious Diseases of the University Hospital in Bern (Inselspital, Bern, Switzerland). Patients included are mostly adults, able to manage their treatment on their own (ie, do not receive home care services) and without any major cognitive impairment. The IMAP consists of repeated one-on-one motivational interviews between a patient and an HCP to support medication self-management and adherence.[12,13] Patients included in IMAP use at least one EM (MEMS and MEMS AS; AARDEX Group, Sion, Switzerland), each of which contains a patient's medication. EMs register the date and hour of each opening in real time as a proxy of drug intake. During the lockdown, the IMAP organization was adapted to avoid patients coming to the pharmacy (eg, medications were mailed, interventions were delivered by phone or in person to patients known to have adherence issues).[14]

The following IMAP participants were included in the CovADH database: patients with diabetic kidney disease (DKD) from the PANDIA-IRIS study,[15] patients with solid cancer from the OpTAT study,[16] participants of the SHCS and patients with miscellaneous long-term diseases (MLTD) (eg, hypertension, diabetes, heart diseases, renal failure). To be eligible for inclusion, participants had to use one or more EMs during the lockdown (the minimum monitored period was 47 days).

As the combined database is anonymous, patient daily regimens and the expected number of daily EM openings were not known. Thus, patients' implementation was defined through a proxy: if all EMs used by a patient were opened at least once daily, medication implementation was considered as active (=1) and no implementation was considered (=0) otherwise. EM data with an oral chemotherapy cyclic regimen were excluded from the analysis. Hence, implementation was expressed as the number of days where a patient opened each EM at least once divided by the number of monitored days during the monitored period.

Patient implementation was compared among three periods: before (December 1, 2019 to March 15, 2020), during (March 16 to June 7, 2020) and after (June 8 to September 30, 2020) the lockdown. The implementation of subgroups of patients diagnosed with solid cancer, HIV, DKD or MLTD was compared.

Implementation of the same patients who also used one or more EMs during Spring 2019 (the minimum monitored period was 74 days) during the same time frame, defined as winter (December 1, 2018 to March 15, 2019), spring (March 16 to June 7, 2019) and summer (June 8 to September 30, 2019), served to compare variation within a year.

To obtain a clean database, all consecutive EM nonopenings equal to or more than 6 consecutive days (arbitrary choice of length established upon database observations) were set as nonmonitored periods to prevent misinterpretations of EM nonopenings (eg, hospitalization, prescribed treatment interruptions, treatment use without an EM). In the case of initiation of EM use after the 1st of December or stopping EM use before September 30 of the following year, the label "missing data" was imputed between December 1st and EM initiation or from EM stopping until September 30, respectively. This EM data cleaning process prepared the database, named the "clean EM database", for implementation analysis in both 2019 and 2020.

In total, analyses were performed on three different databases, including 2019 and 2020 EM data: the main analysis was processed with the clean EM database, and two sensitivity analyses were performed to confirm its validity. The first sensitivity analysis, called "A", was performed on the "Raw database" (ie, the unclean database without any nonmonitored periods). The second sensitivity analysis, called "B", was performed on the "Restricted database", a clean database including only the EM data of patients who used their EM during the entire period of interest (ie, from December 1 to September 30 of the following year).

A logistic regression model was used to estimate the implementation according to the period, using "before the lockdown" in the 2020 analysis ("winter" in the 2019 analysis) as the reference. The models were fitted using Generalized Estimating Equations (GEE) because of the unknown correlation between the repeated observations of the patients (each patient was observed multiple times, ie, once per day). The level of statistical significance was set at $p < 0.05$. EM database cleaning and statistical analysis were performed using R statistical software.[17]

Results

Of the 118 patients (10 patients with cancer, 25 with DKD, 61 with HIV and 22 with MLTD) included in the 2020 implementation analysis, 61 (51.7%) (1 patient with cancer, 6 with DKD, 41 with HIV, 13 with MLTD) were also included in the 2019 implementation analysis.

Sensitivity analysis A (ie, using the raw database) included the same number of patients. Sensitivity analysis B (ie, including only patients who used EMs during the entire period) included 60/118 (50.8%) patients from the 2020 clean database and 31/61 (50.8%) patients from the 2019 clean database.

In 2020, the probability of active implementation was 90.3% before, 90.1% during and 89.5% after the lockdown. Patient implementation did not differ before versus during (OR = 0.98, 95% CI: 0.84–1.15, p = 0.789) and before versus after (OR = 0.91, 95% CI: 0.79–1.06, p = 0.217) the lockdown (Table 1). Figure 1 depicts the empirical implementation and the GEE modelisations within each period, respectively, in 2020 (a) and 2019 (b) using the clean database. The results of sensitivity analyses A (Supplementary Materials 1 and 2) and B (Supplementary Materials 3 and 4) were similar.

In 2019, the probability for active implementation was 92.2% in the winter, 90.9% in the spring and 89.5% in the summer. Patient implementation was significantly lower during summertime than during wintertime (OR = 0.73, 95% CI: 0.60–0.89, p = 0.002) (Table 1, Figure 1). Again, the results were similar in sensitivity analysis A (Supplementary Materials 1 and 2). In sensitivity analysis B, implementation was significantly lower in the summer and spring compared

Table 1 Patient Medication Implementation in 2020 and 2019 Using the Clean Database

EM Database 2020 (n = 118)							
All Patients (n = 118)							
Periods	**Implementation**			**Odds Ratio**			
	Estimate	**95% CI**		**Estimate**	**95% CI**		**p-value**
Before[a]	0.903	0.869	0.929	NA			
During[b]	0.901	0.863	0.929	0.979	0.835	1.147	0.789
After[c]	0.895	0.856	0.923	0.911	0.787	1.056	0.217
Patients with cancer (n = 10)							
Before[a]	0.964	0.889	0.989	NA			
During[b]	0.962	0.891	0.987	0.945	0.755	1.182	0.619
After[c]	0.942	0.821	0.983	0.610	0.512	0.726	<0.001[g]
Patients with diabetic kidney disease (n = 25)							
Before[a]	0.972	0.948	0.985	NA			
During[b]	0.962	0.931	0.979	0.731	0.485	1.100	0.133
After[c]	0.960	0.932	0.977	0.701	0.462	1.063	0.094
Patients with HIV (n = 61)							
Before[a]	0.892	0.842	0.928	NA			
During[b]	0.905	0.853	0.939	1.146	0.959	1.368	0.133
After[c]	0.893	0.840	0.930	1.008	0.822	1.237	0.938
Miscellaneous patients (n=22)							
Before[a]	0.861	0.765	0.922				
During[b]	0.828	0.706	0.907	0.781	0.534	1.140	0.200
After[c]	0.835	0.713	0.911	0.818	0.633	1.056	0.124
EM database 2019 (n = 61)							
All patients (n = 61)							
Periods	**Implementation**			**Odds Ratio**			
	Estimate	**95% CI**		**Estimate**	**95% CI**		**p-value**
Winter[d]	0.922	0.894	0.942	NA			
Spring[e]	0.909	0.873	0.936	0.852	0.706	1.029	0.097
Summer[f]	0.895	0.860	0.923	0.728	0.596	0.891	0.002

Notes: [a]From December 1, 2019 to March 15, 2020; [b]From March 16 to June 7, 2020; [c]From June 8 to September 30, 2020; [d]From December 1, 2018 to March 15, 2019; [e]From March 16 to June 7, 2019; [f]From June 8 to September 30, 2019; [g]This result is not interpretable as only 5/10 (50%) patients with cancer were still using the EM on September 30, 2020.
Abbreviation: NA, not applicable (reference period).

with the winter (Supplementary Materials 3 and 4). In 2020, the probability for active implementation of the 61 patients who used their EM both in 2019 and 2020 was stable across the periods: implementation was 87.6% before, 86.6% during and 86.2% after the 2020 lockdown (Supplementary Materials 5 and 6).

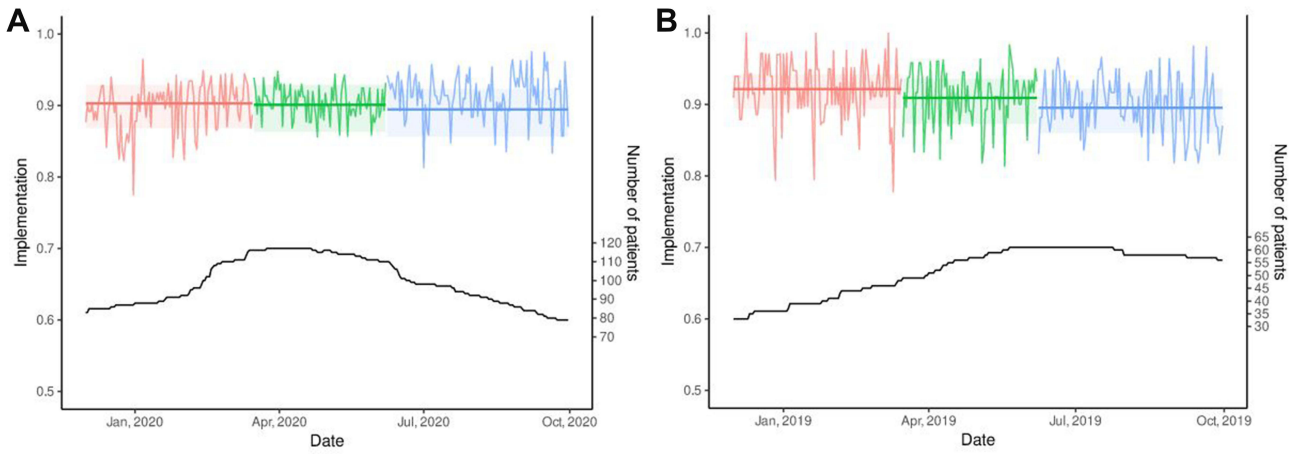


Figure 1 Empirical implementation and GEE modelisations in 2020 (**A**) and 2019 (**B**) using the clean database. (**A**) Period Before During After. (**B**) Period Winter Spring Summer.

Subgroups of Patients in 2020

The implementation of patients with HIV, DKD or other MLTD did not differ significantly among the periods in 2020 (there were too few patients with cancer at the end of the monitoring period to allow for analysis) (Table 1). Both sensitivity analyses showed some changes in implementation among periods according to the disease: for instance in sensitivity analysis A, patients with HIV implemented their treatment better during the lockdown (+3%), and the implementation of patients with MLTD decreased during (−10%) and after (−6%) the lockdown compared to before the lockdown (Supplementary Material 1).

Discussion

Our results do not support our hypothesis, as medication implementation remained steady before, during and after the lockdown in 2020, and the results were similar across patient subgroups.

On the one hand, implementation may have been positively impacted by the lockdown, eg, many patients slowed down their activities, traveled less, and were more cautious in managing their chronic treatment due to the fear of developing disease complications in a difficult sanitary context. On the other hand, implementation may also have been negatively impacted by social isolation and the loss of workday routines. We hypothesize that both tendencies could have counterbalanced each other. Moreover, during the pandemic, continuity of care was ensured by medical teleconsultations and phone calls between patients and their HCPs. Pharmacists mailed medications to patients' homes and led interviews by phone calls with patients included in the IMAP. Despite fewer medical and pharmacist face-to-face consultations, adherence was not impaired.

When analyzing subgroups of patients, implementation was quite similar across groups except for the group of patients diagnosed with MLTD, whose implementation rate was lower. These patients came from different medical backgrounds, and probably had less threatening diseases than patients in the other subgroups. The sample size was relatively small, and caution must be taken when interpreting the results.

In 2019, medication adherence decreased during the summertime, but this phenomenon did not occur after the lockdown in the summer 2020; this is potentially linked to the fact that the population had just emerged from the lockdown with much uncertainty about the evolution of the pandemic.

The main strengths of this study rely on the longitudinal, electronic monitoring of medication implementation before, during and after the lockdown and on the sensitivity analyses, which strengthen the results.

The main limitation of this study is the evaluation of medication implementation through a proxy. This proxy, which considered all regimens as QD (once-daily) regimens, might have overestimated adherence in patients who were prescribed a more frequent regimen, such as a BID (twice-daily) regimen. In contrast, adherence might have been underestimated if implementation was low for one drug but adequate for others. Nevertheless, the same proxy was used to evaluate implementation across the various periods (before, during and after the lockdown), which allowed us to analyze the change

in implementation between periods rather than the implementation rate itself. Second, some patients were prescribed cotreatments that were not monitored by EMs, and their implementation could have differed from those that were monitored. However, the monitored medications were among the most relevant medications that our participants were taking. Third, although only half (61/118; 52%) of the participants in 2020 were taking part in the IMAP in 2019, the sample remained quite substantial to provide a comparative overview of the change of implementation across periods in 2019. Finally, the timing of drug intake could have been shifted during the lockdown due to the dismantling of routines, but due to ethical requirements, we were not allowed to investigate this dimension, as unusual timing could enable the identification of some patients. Also, because of ethical requirements linked to the anonymization of the database, we were not allowed to provide sample characteristics (eg, age, gender, education). Further studies should investigate the sociodemographic determinants of adherence during the 2020 COVID-19 lockdown.

Conclusions

Medication implementation remained steady before, during and after the lockdown in 2020. According to our results, it is unlikely that medication adherence was negatively impacted by the lockdown. The IMAP may have contributed to supporting the medication adherence of patients throughout the pandemic. Interprofessional adherence programs that are tailored to patients' needs, ensure continuity of care and avoid gaps in medication supply by the regular mailing of treatment contribute to supporting patients during periods of routine disturbances such as lockdowns in a pandemic context.

Abbreviations

BID, Twice-daily regimen; CovADH, Covid and ADHerence to medication study; COVID, COronaVIrus Disease; DKD, Diabetic Kidney disease; EM, Electronic Monitor; GEE, Generalized Estimating Equations; HCPs, Health Care Providers; HIV, Human Immunodeficiency Virus; IMAP, Interprofessional Medication Adherence Program; MLTD, Miscellaneous Long-Term Diseases; QD, Once-daily regimen; SHCS, Swiss HIV Cohort Study; USA, United States of America.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The local ethics committee (Comité d'éthique de la Recherche du canton de Vaud, Switzerland) authorized the CovADH study to be run after anonymization of the databases. All included patients signed an IMAP or SHCS-specific informed consent form, which allows researchers to use EM data of patients for research purposes. The study was performed in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

Prof. Dr. Grégoire Wuerzner reports consultancy and/or advisory board from Aktiia, Bayer, Servier and AstraZeneca, outside the submitted work. Prof. Dr. Gilles Wandeler reports grants, Speaker and advisory board fees paid to their institution from Gilead Sciences and MSD, grants from Roche Diagnostics, advisory board fees paid to their institution from ViiV, outside the submitted work. Dr Anna Dorothea Wagner reports personal fees, non-financial support from Merck, personal fees from Lily, personal fees from Pierre-Fabre Pharma, is coordinating investigator of EORTC trial 1203 "INNOVATION", which is supported by an educational grant to EORTC from Hoffmann La Roche, personal fees from Sanofi, personal fees from Daiichi Sankyo, personal fees from Dragonfly Therapeutics, personal fees from Servier, personal fees from Bristol-Myers Squibb, personal fees from Astellas Pharma, outside the submitted work.

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Supplementary materials

Supplementary material 1: Sensitivity analysis A using the raw database

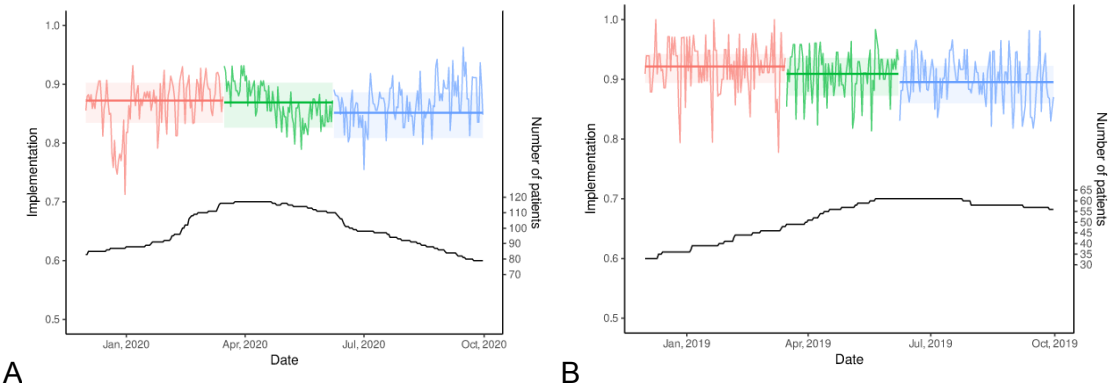
EM raw database 2020 (n=118)							
All patients (n=118)							
Periods	Implementation			Odds ratio			
	Estimate	**95% CI**		**Estimate**	**95% CI**		**p-value**
Before[a]	0.872	0.834	0.903	NA			
During[b]	0.869	0.826	0.903	0.972	0.784	1.206	0.796
After[c]	0.852	0.809	0.886	0.840	0.693	1.017	0.074
Patients with cancer (n=10)							
Before[a]	0.950	0.838	0.986	NA			
During[b]	0.909	0.754	0.971	0.527	0.196	1.418	0.204
After[c]	0.847	0.706	0.928	0.291	0.117	0.719	0.008[g]
Patients with diabetic kidney disease (n=25)							
Before[a]	0.926	0.867	0.960	NA			
During[b]	0.929	0.868	0.963	1.033	0.643	1.661	0.892
After[c]	0.899	0.804	0.950	0.705	0.456	1.090	0.116
Patients with HIV (n=61)							
Before[a]	0.846	0.784	0.893	NA			
During[b]	0.880	0.817	0.923	1.334	1.060	1.678	**0.014**
After[c]	0.851	0.787	0.898	1.035	0.797	1.344	0.796
Miscellaneous patients (n=22)							
Before[a]	0.855	0.755	0.918	NA			
During[b]	0.754	0.625	0.849	0.522	0.318	0.855	**0.010**
After[c]	0.795	0.674	0.879	0.659	0.493	0.882	**0.005**
EM raw database 2019 (n=61)							
All patients (n=61)							
Periods	Implementation			Odds ratio			
	Estimate	**95% CI**		**Estimate**	**95% CI**		**p-value**
Winter[d]	0.902	0.862	0.931	NA			
Spring[e]	0.888	0.843	0.921	0.860	0.673	1.099	0.229
Summer[f]	0.869	0.829	0.901	0.723	0.546	0.956	**0.023**

NA= Not Applicable (reference period)

[a]From December 1, 2019 to March 15, 2020; [b]From March 16 to June 7, 2020; [c]From June 8 to September 30, 2020; [d]From December 1, 2018 to March 15, 2019; [e]From March 16 to June

7, 2019; [f]From June 8 to September 30, 2019; [g]This result is not interpretable as only 5/10 (50%) patients with cancer were still using the EM on September 30, 2020.

Supplementary material 2: empirical implementation and GEE modelisations in 2020 (A) and 2019 (B) using the raw database



A B

Legend Figure A Supplementary Material 2: Period — Before — During — After

Legend Figure B Supplementary Material 2: Period — Winter — Spring — Summer

Supplementary material 3: Sensitivity analysis B using the restricted database

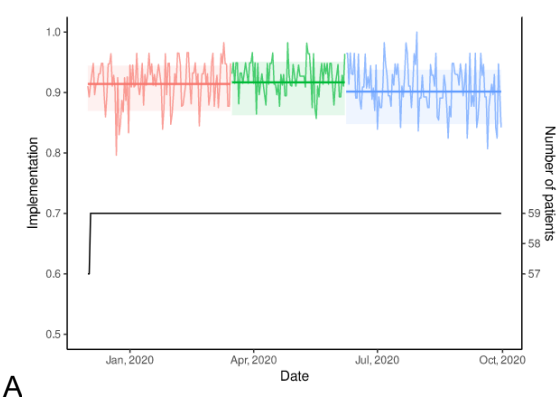
EM database 2020 (n=60)							
All patients (n=60)							
Periods	Implementation			Odds ratio			
	Estimate	**95% CI**		**Estimate**	**95% CI**		**p-value**
Before[a]	0.914	0.870	0.945	NA			
During[b]	0.917	0.862	0.951	1.035	0.837	1.281	0.751
After[c]	0.902	0.848	0.938	0.859	0.712	1.037	0.114
Patients with cancer (n=2)							
Before[a]	NA[g]						
During[b]							
After[c]							
Patients with diabetic kidney disease (n=11)							
Before[a]	0.986	0.973	0.993	NA			
During[b]	0.972	0.948	0.985	0.496	0.295	0.834	**0.008**
After[c]	0.972	0.952	0.984	0.504	0.292	0.868	**0.014**
Patients with HIV (n=36)							

Before[a]	0.920	0.890	0.943	NA			
During[b]	0.932	0.899	0.955	1.188	0.901	1.566	0.222
After[c]	0.916	0.878	0.943	0.949	0.715	1.258	0.715
Miscellaneous patients (n=11)							
Before[a]	0.892	0.743	0.960	NA			
During[b]	0.874	0.629	0.966	0.837	0.558	1.256	0.391
After[c]	0.854	0.637	0.951	0.707	0.553	0.904	**0.006**
EM database 2019 (n=31)							
All patients (n=31)							
Periods	Implementation			Odds ratio			
	Estimate	**95% CI**		**Estimate**	**95% CI**		**p-value**
Winter[d]	0.927	0.888	0.953	NA			
Spring[e]	0.907	0.847	0.945	0.769	0.618	0.956	**0.018**
Summer[f]	0.906	0.856	0.940	0.759	0.603	0.956	**0.019**

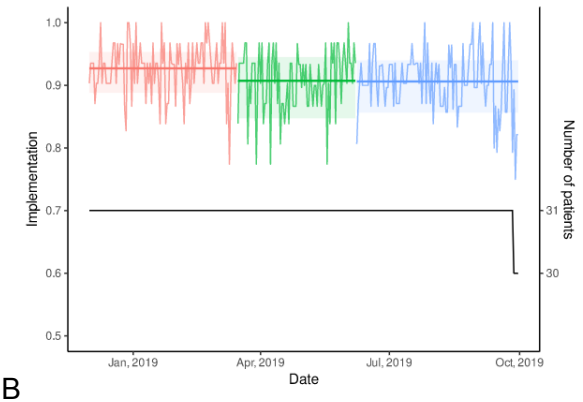
NA= Not Applicable

[a]From December 1, 2019 to March 15, 2020; [b]From March 16 to June 7, 2020; [c]From June 8 to September 30, 2020; [d]From December 1, 2018 to March 15, 2019; [e]From March 16 to June 7, 2019; [f]From June 8 to September 30, 2019; [g]This result is not interpretable as only 2 patients were included.

Supplementary material 4: empirical implementation and GEE modelisations in 2020 (A) and 2019 (B) using the restricted database



A



B

Legend Figure A Supplementary Material 4:



Legend Figure B Supplementary Material 4:



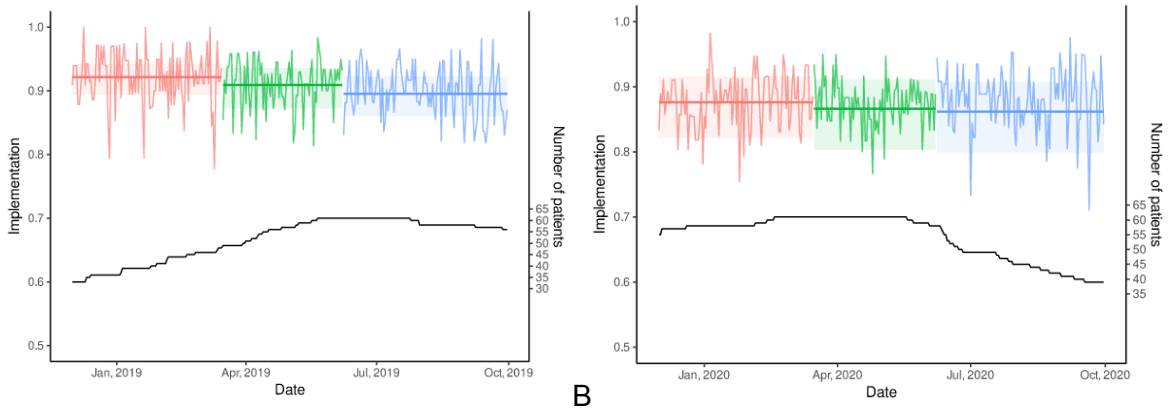
Supplementary material 5: In 2020, medication implementation of the 61 patients who used their EM both in 2019 and 2020 using the clean database

EM database 2020							
Patients who used their EM both in 2019 and 2020 (n=61)							
Periods	Implementation			Odds ratio			
	Estimate	**95% CI**		**Estimate**	**95% CI**		**p-value**
Before[a]	0.876	0.821	0.916	NA			
During[b]	0.866	0.803	0.911	0.916	0.758	1.105	0.359
After[c]	0.862	0.799	0.907	0.882	0.740	1.051	0.160

NA= Not Applicable (reference period)

[a]From December 1, 2019 to March 15, 2020; [b]From March 16 to June 7, 2020; [c]From June 8 to September 30, 2020

Supplementary material 6: Empirical implementation and GEE modelisations of the 61 patients who used their EM in 2019 (A) and 2020 (B) using the clean database



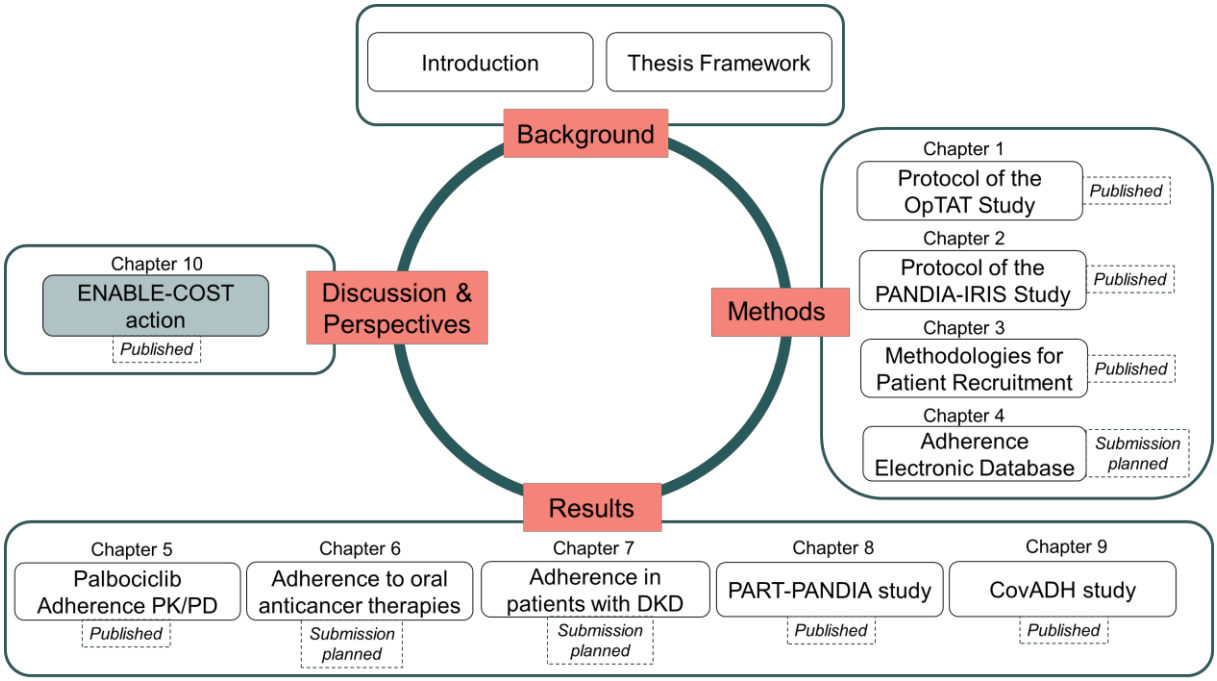
A B

Legend Figure A Supplementary Material 6: Period — Winter — Spring — Summer

Legend Figure B Supplementary Material 6: Period — Before — During — After

NB: If a patient is not monitored at a given day x (e.g., hospitalization), then this patient is not included in the implementation estimates on that day x, leading to a daily variation of patients in the database.

CHAPTER 10: DISCUSSION AND PERSPECTIVES



PK=pharmacokinetic; PD=pharmacodynamic; DKD=diabetic kidney disease

1. Main Findings and Implications for the Practice

Medication nonadherence is prevalent in the population of chronically ill patients. This high prevalence is the result of multifactorial determinants that impact patient self-care behavior, medication self-management and self-efficacy. The Interprofessional Medication Adherence Program (IMAP) is an intervention implemented in routine care at the community pharmacy of *Unisanté*, aiming at supporting patient adherence by addressing determinants of adherence throughout the patients' therapeutic journey. The global aim of this thesis was to evaluate the impact of the IMAP on medication adherence in patients with solid cancer (the OpTAT study) and patients with diabetic kidney disease (DKD) (the PANDIA-IRIS study), by exploring each population's medication management habits and skills, adverse effects management skills, knowledge on the disease and treatment, motivation to take the treatment, and other specific determinants of adherence.

This thesis showed that the IMAP supported, improved and sustained medication implementation in patients with solid cancer and in patients with DKD in comparison to patients who did not benefit from the program. Moreover, medication implementation remained stable during the COVID-19 pandemic in a large population of chronically ill patients attending the IMAP, showing that medication adherence teleinterventions hold promise in a future where the use of telehealth will increase to face provider shortage. In the PANDIA-IRIS study, we were able to show the differential impact of the IMAP on antihypertensive and antidiabetic drugs versus statins. For the first time, we were able to investigate the evolution of patient adherence after the end of the intervention in the PANDIA-IRIS study, and we showed that the longer the patients participated to the IMAP (i.e., at least 12 months), the higher the level of medication implementation was maintained in the post-intervention period.

While conducting the OpTAT and PANDIA-IRIS studies, we highlighted that recruiting patients and retaining them in educational behavioral adherence interventions are *implementation* projects in themselves. As these tasks are complex and challenging, they require the involvement of the interprofessional healthcare team to adapt the intervention and to elaborate the strategies to overcome barriers to patient recruitment and retention. While no difference was found in terms of beliefs about medicines and quality of life between included patients and non-participants in the OpTAT study, we showed that women and patients with a longer time since diabetes diagnosis were less willing to participate to the PANDIA-IRIS study. This thesis provided key elements to optimize the process of patient recruitment, reduce selection bias (e.g., including ethnically diverse populations, different populations in terms of age, gender, comorbidities) and prevent drop-outs, which will make adherence programs such as the IMAP more adjusted and, ultimately, more attractive for future participants. To conduct large cohort studies in multiple populations of patients and to increase the number of patients who may

benefit from educational and behavioral adherence interventions, these kinds of programs should be offered to all consecutive patients in a standardized way as close as possible to the standard of care.

Throughout this thesis, we explored two populations of chronically ill patients with similar needs (i.e., clarifying the treatment plan especially after treatment adaptations, supporting the emotional burden related to the disease management), but also different adherence determinants (i.e., management of drug-related side effects impacting quality of life in the OpTAT study, and polypharmacy and polymorbidity in the PANDIA-IRIS study). This thesis studied several determinants of adherence in patients with solid cancer. We showed that medication implementation was influenced by age, gender and timing. Indeed, an increase in the time since diagnosis and treatment initiation was associated with a lower medication implementation, whereas the previous use of adherence supporting tools was associated with higher adherence. This analysis confirmed the importance of assessing and supporting medication adherence regularly as early as possible from diagnosis.

Patients with cancer were not polymedicated and had an excellent medication adherence at baseline. Thus, the intervention was mainly focused on side effect management, reviewing the treatment plan and clarifying the complex regimen (e.g., cyclic regimen), helping the patient to cope with the frequent adaptations of the prescriptions, delivering information on the disease and the treatment objectives. In addition, emotional support was paramount in this population, especially after a medical consultation during which patients were told that the treatment did not improve clinical outcomes. Thus, a consultation with cancer specialist nurses or psychologists immediately after the medical consultation would help patients to cope with their emotional burden. Moreover, to train pharmacists to communicate with patients with empathy and professionalism in case of emotional burden, we developed a specific communication training[247-249]: the pharmacist was advised to explore and verbalize the patient's emotions, to identify their own emotions as healthcare professionals (HCPs) and then, to adjust the delivery of the medication adherence intervention to the patient's emotional condition. In other words, they were encouraged to keep a right therapeutic distance to support patients with their treatment management by acknowledging their emotions without overwhelming them with information on medication adherence and oral anticancer therapies that they would not need at this moment. Besides, the emotions were described and addressed in the medication adherence report for consideration by the oncology team.

On the contrary, patients with DKD were polymedicated and most of them were already using a weekly pillbox to manage their medications. These patients were followed clinically by

multiple specialists, and the interview with the pharmacist was an additional and new intervention in their therapeutic itinerary. The IMAP was an opportunity to clarify the understanding of the treatment plan, regimen changes or new medications prescribed. Patients with DKD often reported their anxiety about drug-drug interactions and long-term side effects of polypharmacy, the latter being called a “cocktail” of medications by some of the patients. Thus, the intervention was mainly focused on addressing cognitive behavioral components (i.e., providing information about the aim of each medication, providing adherence support tools to manage polypharmacy outside the home) to help patients to cope with polypharmacy, while strengthening their knowledge on the disease and medications. Moreover, pharmacists supported patients and their emotions associated with the burden of their care, such as feeling overwhelmed by the medication management or by the stress associated with polymorbidity and fear of disease deterioration.

Thus, this thesis brings new perspectives on when, how, from whom and why chronically ill patients should benefit from the IMAP. While the IMAP was previously known to be an educational, behavioral and motivational intervention, the emotional support that pharmacists delivered to patients has not yet been well described in the literature, whereas paramount to strengthen the therapeutic relationship and essential to consider during the shared decision-making process for promoting behavior changes[57, 250]. The role of pharmacists in supporting medication adherence goes beyond a medication review and encompasses cognitive, behavioral and affective support approaches to answer the needs of each patient. Better training of the interprofessional team in behavioral health, and better definitions of roles and responsibilities are needed.

2. Strengths and Limitations of the Thesis

The strengths of this thesis lie in the conduct of two randomized and controlled adherence studies, which were funded and implemented in a busy routine practice over several years (6 years for the OpTAT study and 4.5 years for the PANDIA-IRIS study). The IMAP involved many stakeholders in interprofessional teams in the care of two populations of chronically ill patients (i.e., pharmacists, pharmacy technicians, oncologists, nephrologists, endocrinologists, general practitioners (GPs), nurses, dieticians and psychologists). This research is based on the careful design, conduct and *implementation* of the IMAP in routine care, in an area where the evaluation of theoretical-based cognitive behavioral adherence programs is rarely reported in the literature.

This research was supported by robust and innovative methodologies: i) the protocols of both the OpTAT and PANDIA-IRIS randomized controlled studies were published, to ensure transparent reporting of findings; ii) the recruitment process was scrutinized to decrease

selection bias; iii) the measure of medication adherence was based on longitudinal and repeated data with electronic monitors (EM), considered as the gold standard to assess medication implementation; iv) the CleanADHdata.R script was developed to clean EM adherence database to allow the use of a common methodology to standardize data preparation in adherence studies; v) the advanced statistical analysis used were previously developed and validated; vi) pharmacokinetic/pharmacodynamic methods were used to investigate the relationship between adherence, drug concentrations and toxicity in an innovative way; vii) the triangulation of mixed quantitative-qualitative analysis allowed the findings to be deepened.

While our findings did show an improved medication implementation in patients benefiting from the IMAP in both the OpTAT and the PANDIA-IRIS studies compared to those who did not, the significance of this improvement needs to be discussed. Unfortunately, we did not reach a 10% difference in medication implementation between groups in the OpTAT and PANDIA-IRIS studies. However, we have to acknowledge that the groups of patients who did not benefit from the intervention (i.e., control group in the OpTAT study, follow-up period post-intervention in the PANDIA-IRIS study) attended –because of the trial– planned visits at the community pharmacy of *Unisanté*, which is known to be an excellent academic center in triage, validation of prescriptions and support of patient self-management. Thus, patients who did not benefit from the intervention had access to the best practice of pharmaceutical care, which is better than usual care. Moreover, contamination of the intervention on the control group cannot be excluded[251]. For example, whatever the group the patients were assigned to, i) all patients used the EM, ii) appointments at the pharmacy were planned from one visit to the next one, iii) patients were asked to report any deviation of EM use, iv) they completed questionnaires in the OpTAT study, v) the blood pressure was monitored at each visit in the PANDIA-IRIS study.

The IMAP remains one of the few programs that are implemented as part of routine practice, is evidence-based to support patient adherence and recognized internationally as a breakthrough intervention thanks to the numerous findings reported over the years in patients with HIV[48, 57, 115, 116, 252, 253], renal transplant recipients[254], diabetes[255], hypertension[117] or multiple sclerosis[118, 256]. This thesis provides further results in the population of patients with solid cancer[236, 257, 258] and diabetic kidney disease[195, 222, 237]. The chronic illness diversity of the populations attending the IMAP has increased, which is crucial to provide relevant information for scaling up the intervention in the community by using *implementation* science.

Some limitations need to be acknowledged. First, we cannot exclude a selection bias during recruitment as included participants were willing to share their medication self-management

habits with a pharmacist and a research team by accepting to be part of a clinical trial. While, among patients who refused, some could have had an optimal medication implementation as a legitimate reason for refusal, others could on the contrary be more vulnerable with a high risk of suboptimal implementation and thus could benefit from the intervention. Medication adherence interventions should be investigated as part of the standard of care, for example, in non-academic community pharmacies. Our results provide a solid internal validity but the external validity should be confirmed in multi-center studies.

Second, the impact of the IMAP on clinical outcomes needs to be further investigated. This analysis is ongoing in the PANDIA-IRIS study. Although medication implementation is a robust surrogate endpoint to estimate the impact of an intervention on clinical outcomes, the increment in adherence achieved in the OpTAT intervention group could be perceived as limited without reaching significance. We hypothesize that the difference would be larger if compared to actual usual care. Eventually, the long-term impact of the adherence intervention on clinical outcomes should be evaluated in the cohort of patients for one to five years post-intervention.

Last, through the results of the OpTAT and PANDIA-IRIS studies, we highlighted that persistence to treatment was high. Persistence was influenced in the intervention and control groups by the monthly appointment scheduled at the pharmacy and the rescheduling of missed appointments by phone calls. Even if improving medication implementation and addressing determinants of adherence reduce ultimately the probability of a premature treatment discontinuation, we would need larger database, longer follow-up periods and an adapted methodology (i.e., using electronic healthcare database[259] instead of the EM) to further investigate medication persistence after the intervention has stopped.

3. Future Research Directions and Perspectives

This thesis confirms that the IMAP is evidenced-based and provides important insights for scaling up a medication adherence program in routine care for chronically ill or long-term patients. The *implementation* of the IMAP in routine practice at the community pharmacy of *Unisanté* is solid, as implemented for almost 30 years in routine practice, however fragile, as still not considered as a standard of care. *Implementation* science gives the methodology for translating and sustaining educational and behavioral adherence programs in routine care, allowing larger populations of patients to benefit from the intervention[260, 261]. *Implementation* science includes the measure of determinants, processes and outcomes to describe the *implementation* pathway and to understand “what, why and how evidence-based interventions work in the real world”[262]. There is a growing interest for *implementation* science worldwide. *Implementation* theories, models and frameworks are regularly developed

and updated to reduce the 15- to 17-year time lag in translating knowledge from clinical trials to routine practice[263-270]. In Switzerland, *implementation* science has been emerging –the first Swiss *Implementation* Science Network (IMPACT) conference was launched in 2020[271, 272]. While barriers and facilitators to implement interprofessional adherence programs are poorly reported in the literature, a recent Swiss study showed that influencing factors for scale up are pharmacists' skills and fidelity in providing a medication adherence intervention and pre-existing local interprofessional collaborations[255].

Interprofessional collaborations between patients, physicians, nurses and pharmacists should be further developed and strengthened within the IMAP[273] to support patient adherence on the three interrelated contexts: before and during the prescription process (i.e., at the clinic), at the medication delivery (i.e., at the pharmacy) and/or at the patient's home (i.e., home care services, nurse home care)[274]. Defining roles and responsibilities, developing complementary competencies in clinical and behavioral sciences, and sharing knowledge between HCPs contribute to building a relationship of trust to support patient adherence. Interprofessionality in the ambulatory setting and primary care should be further evaluated in order to increase patient safety and quality of care, as detailed in a policy brief edited in 2021 by the Swiss Federal Health Office[275]. Some recommendations were described, e.g., developing electronic platforms to share information and knowledge between HCPs, and elaborating a sustainable economic model of care to foster interprofessionality by revising remuneration systems that currently hamper a collaborative work[275]. While the young generations of pharmacy, nursing and medical students have been trained in collaborative practice for some years now at the University of Geneva[276], interprofessional postgraduate training should be developed as part of the continuing education of HCPs. The strengthening of interprofessional practices will allow bridging the gap between behavioral and clinical sciences to improve patients' health outcomes and continuity of care, which will ultimately help to contain health care costs.

Along with their pharmacological and pharmaceutical backgrounds, pharmacists must integrate behavioral health skills to support patients' behavior changes, establish an emotional connection with patients and share a goal attainment to improve clinical outcomes[277]. Pharmacists should be encouraged to participate in continuing education in behavioral health as the synergy of behavioral and clinical skills is required to improve the impact of medication adherence interventions. For instance, the University of Geneva offers a Certificate of Advanced Studies (CAS) for psychologists in behavioral sciences applied to health promotion, in which HCPs could attend too. The international society for medication adherence (ESPACOMP) education initiative aims at offering workshops to teach international HCPs and researchers best medication adherence knowledge.

Switzerland takes part, among 39 European countries, in the 2020-European Network to Advance Best practices & technoLogy on medication adherencE (ENABLE), a Cooperation in Science and Technology (COST) Action, which aims to develop and implement medication adherence-enhancing technologies into clinical practice across Europe. Indeed, digital technologies (e.g., mobile apps, telehealth, artificial intelligence) will speed up development, feasibility and uptake of adherence interventions and patient involvement in their care in partnership with their providers. To facilitate the *implementation* of digital medication adherence-enhancing programs in Switzerland and beyond, health policies should be informed and encouraged to raise awareness of medication nonadherence in the population while promoting medication adherence programs as a standard of care.

In March 2022, as part of the ENABLE-COST Action, the University of Basel and the University of Geneva collaborated synergistically to organize an online conference to lead scientific reflections with stakeholders on the strategies to translate interprofessional adherence interventions into the Swiss routine practice in the next 5 to 10 years. Close to complete our PhD thesis on medication adherence research, Janette Ribaut (University of Basel) and myself collaborated to describe the recommendations and perspectives that emerged from the ENABLE-COST conference on the Swiss priority setting to foster the *implementation* of medication adherence-enhancing technology interventions into practice, in a commentary published in the *International Journal of Public Health* in August 2022. The policy brief developed based on this commentary is presented in Appendix 9.

Important stakeholders were involved: the School of Pharmaceutical Sciences (University of Geneva, Switzerland), the Nursing Science Department of Public Health (University of Basel, Switzerland), the Research and Development Unit of the Institut de Recerca Sant Joan de Déu (Barcelona, Spain), the Department of Pharmaceutical Sciences (University of Basel, Switzerland), the Centre for International Health, Swiss Tropical and Public Health Institute (University of Basel, Switzerland), the Patient-as-Partner Project (University of Geneva, Switzerland), Innosuisse (Bern, Switzerland), Real World Data Strategy and Innovation, Novartis Pharma AG (Basel, Switzerland), the Faculty of Biology and Medicine (University of Lausanne, Switzerland), the Department of Clinical Pharmacy and Pharmacology (University Medical Center Groningen, the Netherlands), the European Center of Pharmaceutical Medicine (University of Basel, Switzerland), the Federal Department of Home Affairs, Federal Office of Public Health Division (Bern, Switzerland), the Department of Health Services, Policy and Practice (Brown University School of Public Health, USA), the Academic Center for Nursing and Midwifery and the Department of Public Health and Primary Care, KU Leuven (Leuven, Belgium).

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COMMENTARY
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Swiss Priority Setting on Implementing Medication Adherence Interventions as Part of the European ENABLE COST Action

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INTRODUCTION

Medication non-adherence, i.e., patients not taking medications as prescribed, diminishes clinical outcomes and quality of life. This phenomenon is endemic, leading to an estimated 200,000 premature deaths and 125 billion Euros of excess healthcare costs each year in Europe alone [1].

Medication adherence (MA) consists of three interrelated phases: initiation (first dose taken), implementation (daily regimen management) and discontinuation (last dose taken) [2]. In Switzerland, half of the population aged 15 years and older takes at least one medication per week [3]. Worldwide, studies showed that most patients (69–96%) initiate their prescribed treatments correctly, but 30–50% do not implement them optimally. Within 2 years of their first prescription, more than 50% of patients discontinue use of their prescribed medication [1].

The high prevalence and consequences of medication non-adherence have attracted considerable attention over the past 30 years. Researchers, clinicians and policymakers search for improved methods to assess this phenomenon and its determinants, along with effective MA-enhancing multifaceted interventions tailored to patients' needs [4].

In 2011, the UK's National Health Service (NHS) introduced the largest-ever national evidence-based MA intervention: the New Medicine Service (NMS) [5]. After certain new medications are prescribed, NHS pharmacists identify and assess any adherence problems and their causes. While increasing quality-adjusted life-years per patient, the NMS has led to reduced costs compared with standard care [6].

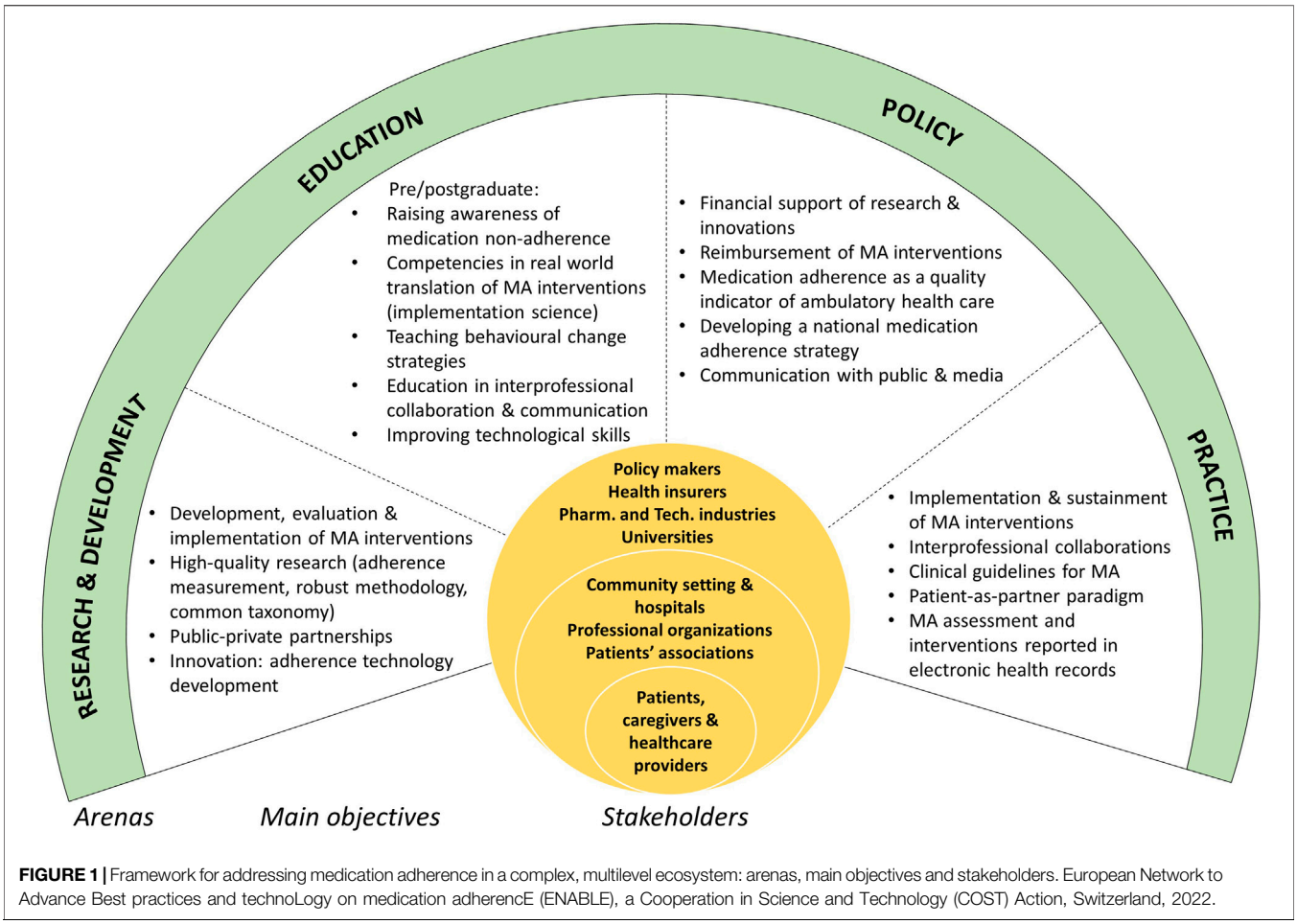


FIGURE 1 | Framework for addressing medication adherence in a complex, multilevel ecosystem: arenas, main objectives and stakeholders. European Network to Advance Best practices and technoLogy on medication adherencE (ENABLE), a Cooperation in Science and Technology (COST) Action, Switzerland, 2022.

While evidence on addressing medication non-adherence is available, translation of that evidence into real-world clinical practice remains challenging. In Switzerland, no adherence-focused national programs or guidelines have been developed, implemented or evaluated [7].

Therefore, the launch of the European Network to Advance Best practices and technoLogy on medication adherencE (ENABLE), a Cooperation in Science and Technology (COST) Action (https://www.cost.eu/actions/CA19132/) in 2020 was well-timed [8]. Linking stakeholders across 39 European countries, including Switzerland, ENABLE aims to drive the implementation of MA-enhancing technologies into clinical practice.

LAUNCH OF THE SWISS COST ENABLE NETWORK

On March 18th, 2022 Switzerland's ENABLE country group launched a pioneering initiative to set priorities for implementing MA interventions in real-world settings. An online conference was held to: 1) connect Swiss and international stakeholders; and 2) initiate MA priority-setting, particularly regarding implementation of MA interventions and technologies.

Seventy-five participants including researchers, clinicians, healthcare industry delegates and one policymaker, from 34 countries took part. Keynote lectures and an interprofessional roundtable highlighted the state-of-the-art MA understanding regarding the place for digital technology in real-world settings, alongside strategies to address non-adherence. Priorities to move toward a more favourable, multilevel ecosystem for developing, implementing and maintaining MA interventions in Switzerland were discussed. While the highest priority was identified as support to the implementation of MA interventions in real-world settings, education, research and policy measures were also highlighted (**Supplementary File S1**).

The ideas discussed were organized into a framework (**Figure 1**)—partly for a systematic elaboration of strategies to address MA at a national level, partly to move towards an integrated, patient-as-partner healthcare system.

PRIORITY SETTING TO IMPLEMENT MA INTERVENTIONS IN SWITZERLAND

While MA is a major public health concern that warrants high-priority treatment by health authorities, it remains absent from Swiss policymakers' agendas. As a first step, raising awareness for

MA and promoting research are needed to change the mindset and attitudes of the population, health care professionals (HCPs), and all other stakeholders.

Prerequisites for MA Intervention Implementation

Multilevel Ecosystem

To achieve synergies, stakeholders must work interprofessionally, fine-tuning their actions, and engaging their responsibilities to collaboratively monitor and maximize MA in the ecosystem. Connecting innovative ecosystems in Switzerland (e.g., funding agencies, start-up incubators) and public-private-partnerships will foster further MA development (e.g., new MA technologies).

While reimbursement of MA interventions -by health insurers- will enhance adoption of these interventions in clinical practice, the scientific basis to support reimbursement should go beyond demonstration of MA improvement. A clear value statement is needed in which the effects of MA interventions guarantee favorable clinical outcomes [9].

Patient-As-Partner

Along with shared decision-making and therapeutic education, the patient-as-partner paradigm is critical to raise MA awareness and for mutual learning.

However, efforts should not only target the individual level. Building trusting partnerships and communication across all HCPs and patients reinforces MA by decreasing conflicting information and ensuring continuity of care. Emphasizing MA interventions, behavioural training and interprofessional competencies should be integrated within the training curricula of all involved HCPs (i.e., including physicians, nurses, psychologists, pharmacists) to develop competencies vital to MA management in clinical practice. Integrated care models powered by digitalization provide fertile ground for these efforts and innovations.

Monitoring Medication Adherence

Measuring MA and its determinants in routine practice enables researchers to know when patients have MA difficulties or underlying non-adherence risk factors and provides an informed basis for clinical decision-making. In routine practice, adherence should be treated both as a patient's fifth vital sign and as a system-level indicator of quality of care. Technology (e.g., smartphone apps, electronic adherence monitors) can be helpful, but must be designed to match patients' and HCPs' preferences.

Investing in Translation From Research to Real-World Settings

Internationally, research evidence underscores the value of multilevel interventions, monitoring and equipping HCPs to address MA [1, 4]. However, in Switzerland, implementation of MA interventions in clinical practice is limited. Assisting the uptake of research evidence into clinical practice will require a systematic implementation science approach [10].

Next Steps to Support the Translation of MA Interventions into Swiss Clinical Practice

First, key interprofessional cross-sectoral stakeholders need to be identified to address MA in the multilevel ecosystem and to determine contextually appropriate multilevel MA interventions. Every step will need to fit within a national Swiss MA strategy.

Second, efforts towards coordinated care models must be strengthened and tailored to facilitate MA management. Technology-based innovations and digital health infrastructure (e.g., electronic medical records, teleconsultation) and use of new technologies (e.g., digital pill boxes, smart inhalers) and methodologies (e.g., artificial intelligence) have the potential to facilitate or contribute directly to interventions. Importantly, technology literacy needs to be concurrently enhanced at the patient and HCP levels.

Third, contextually appropriate implementation strategies (e.g., development of clinical guidelines, patient/consumer involvement) need to be integrated using a multilevel approach.

Fourth, research funding schemes must be adapted to provide opportunities for MA research (e.g., MA is prioritized by the Innovative Medicines Initiative, an EU public-private-partnership). Researchers should be encouraged to expand their foci from traditional efficacy/effectiveness research to include evaluation of implementation strategies for MA interventions in real-world settings.

Finally, to maximize impact, the synergies between bottom-up and top-down approaches, public/private initiatives and interprofessional collaborations are required to power much-needed change.

Conclusion: A Framework for Change

The Swiss COST ENABLE conference built on its participants' critical knowledge, competencies and experience of interprofessional dynamics to define priorities to tackle MA as a major public health issue. One point was clear: translating MA-relevant evidence into real-world outcomes demands multilevel approaches.

Through the Swiss ENABLE conference, diverse presenters and participants committed to raising MA awareness. Regarding the knowledge and practice gap, an initial consensus was reached on three early steps: provide the foundations for MA-supportive ecosystems, translate effective interventions into clinical practice and promote research into MA-enhancing technologies. The Swiss strategies discussed here will potentially inform research activities, policies and implementation of MA interventions across Europe.

AUTHOR CONTRIBUTIONS

SDG and MS conceptualized and organized the conference. After the conference, all authors discussed the main themes to be included in the manuscript. CB and JR drafted the paper and SDG, MS, and AD reviewed it. All authors gave feedback on the draft. All authors agreed upon the final version of the paper.

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AUTHOR DISCLAIMER

The statements in this commentary represent the personal view of DA, it does not engage the position and commitment of the Federal Department of Home Affairs, Federal Office of Public Health Division, Switzerland.

CONFLICT OF INTEREST

Author MO was employed by the company Novartis Pharma AG.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.ssph-journal.org/articles/10.3389/ijph.2022.1605204/full#supplementary-material

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Appendix 1: Article published in the *Revue Médicale Suisse* in June 2020 "*Adhésion thérapeutique et collaboration médecin-pharmacien. L'exemple du patient avec néphropathie diabétique*"

Adhésion thérapeutique et collaboration médecin-pharmacien. L'exemple du patient avec néphropathie diabétique

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La polypharmacie concerne de nombreux patients avec une maladie chronique. Elle est appropriée lorsque chaque médicament a été prescrit dans un but thérapeutique spécifique discuté avec un patient motivé et capable de gérer ses médicaments. Elle peut cependant être inappropriée lorsque le traitement devient trop complexe pour une personne fragile. Le risque est une non-adhésion au traitement, dont découle souvent une intensification de la thérapie en raison d'objectifs thérapeutiques non atteints. La collaboration médecin-pharmacien est donc primordiale pour l'accompagnement éducatif du patient complexe dans la gestion de ses médicaments. Dans cet article, nous revoyons les études examinant l'adhésion thérapeutique chez le patient diabétique avec une atteinte rénale lors d'une collaboration médecin-pharmacien.

Medication adherence and physician-pharmacist collaboration. Focus on the patient with diabetic nephropathy

Polypharmacy is common in patients with a chronic disease. It is appropriate when both the patient and the physician discuss the goal of each prescribed medication with a motivated patient capable of managing his/her medication. It can however be inappropriate when treatment becomes too complex for the frail patient. The risk is non-adherence to therapy, which often results in an intensification of treatment due to unmet therapeutic goals. Collaboration between physicians and pharmacists is therefore essential for the educational support of patients with polypharmacy. In this article, we review the studies examining the impact of a physician-pharmacist collaboration on the medication adherence of diabetic patients with renal impairment.

COMPLEXITÉ ET POLYPHARMACIE

La polymorbidité et la prescription de plusieurs médicaments (polypharmacie) sont communes et leur prévalence augmente avec l'âge des patients. Malgré cela, il n'y a pas de définition consensuelle de la polypharmacie. Elle est fondée sur des seuils arbitraires, comme la prescription concomitante de plus de 3 ou 4 médicaments.[1] Cette définition est limitée par le fait qu'elle ne distingue pas la polypharmacie appropriée de la polypharmacie inappropriée. La polypharmacie peut s'avérer bénéfique, comme dans la prise en charge du diabète avec néphropathie ou en présence de facteurs de risque cardiovasculaires. Pour être bénéfique, chaque médicament devrait être prescrit pour un objectif thérapeutique spécifique, discuté avec le patient; les objectifs thérapeutiques devraient être atteints ou s'en approcher raisonnablement, le traitement devrait être optimisé afin de minimiser la survenue d'effets indésirables et le patient devrait être motivé et capable de gérer son traitement. En revanche, la polypharmacie est inappropriée si toutes les conditions précédentes ne sont pas remplies, lorsqu'elle devient trop complexe à gérer pour le patient, ou encore si celui-ci est fragile ou très âgé. À ce stade, le traitement doit être réévalué et les médicaments inappropriés (*potentially inappropriate medication* (PIM)) progressivement retirés. La pertinence de la polypharmacie est à documenter dans les différentes étapes clés que sont la prescription, la dispensation et l'administration des médicaments. L'établissement de cette pertinence implique une bonne communication et écoute du patient, et une bonne collaboration interprofessionnelle (médecin, pharmacien et infirmière).

Les conséquences délétères de la polypharmacie inappropriée sont, entre autres, la survenue d'effets indésirables, une adhésion thérapeutique suboptimale, des erreurs de médication ou une rupture de confiance thérapeutique patient-professionnel de la santé. La non-adhésion induite par la polypharmacie peut être volontaire ou involontaire. Dans certaines situations, elle est étroitement associée à des effets indésirables/symptômes ressentis par le patient ou à la complexité du traitement.

Dans le diabète, il a été montré que la complexité du traitement (médicaments multiples, doses multiples, exigences diététiques et temporelles de prises) altère l'adhésion. D'une part, la complexité du traitement augmente le risque de non-adhésion, mais, d'autre part, un historique de non-adhésion peut conduire le prescripteur à intensifier et complexifier le traitement. La relation de causalité est donc difficile à déterminer. Il est important que le professionnel y soit sensible.

À ce jour, la littérature scientifique n'a pas démontré d'amélioration de l'adhésion thérapeutique par réduction de la polypharmacie, bien que les premiers résultats avancent cette hypothèse.[2] Des études confirmatoires sont donc nécessaires. En présence de polypharmacie, deux aspects cruciaux s'imposent. Premièrement, il est important de prescrire des traitements nécessaires et efficaces avec des modalités d'administration

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simples dans la mesure du possible, sans enfreindre l'efficacité (par exemple, une prise journalière unique peut être inefficace chez les métaboliseurs rapides). Deuxièmement, les patients, en faisant partie intégrante de la démarche thérapeutique, doivent être invités autant que possible à participer au mieux à la décision. Ils doivent pouvoir bénéficier d'un accompagnement éducatif interprofessionnel afin de renforcer leur littératie en santé et leur autogestion des médicaments.

L'EXEMPLE DE LA NÉPHROPATHIE DIABÉTIQUE

La néphropathie diabétique est une complication microvasculaire du diabète qui touche environ un tiers des patients diabétiques; elle est actuellement la première cause de dialyse. L'objectif du soignant sera d'accompagner le patient diabétique avec une atteinte rénale dans la gestion de ses multiples comorbidités avec une prise en charge non pharmacologique (activité physique, tabac, nutrition) et pharmacologique, comme le traitement antidiabétique, antihypertenseur et hypolipémiant. À des stades plus avancés de la néphropathie diabétique, s'ajoute le traitement de l'hyperkaliémie, de l'acidose et de l'anémie. Le patient doit gérer une grande quantité de médicaments, dont l'utilité n'est pas toujours bien comprise en raison de pathologies souvent silencieuses.

En Suisse, la prévalence d'un débit de filtration glomérulaire estimé (DFGe) < 60 ml/min/1,73 m^2 est de 22,4% dans un échantillon de 1359 patients diabétiques de type 2 suivis chez leur médecin de premier recours.[3] Dans cette étude, seuls 2,2% ont atteint tous les objectifs de contrôle tensionnel, glycémique et lipidique.[4] Les causes sont certes multiples (inertie dans l'introduction et l'adaptation du traitement, manque de temps du médecin, non-adhésion aux visites), mais la non-adhésion au traitement pharmacologique est certainement une cause importante qui doit être recherchée.

BARRIÈRES À UNE GESTION OPTIMALE DE LA MALADIE

Les barrières à une bonne gestion de la maladie les plus fréquemment rapportées par les patients sont notamment la faible continuité des soins, des propos discordants et une communication pauvre entre les spécialistes.[5] Les patients rapportent également une mauvaise compréhension de la maladie rénale, engendrant un stress, surtout dû à la possibilité de devoir débuter une dialyse. Le faible soutien familial ou amical était également rapporté comme un facteur défavorable.

Ces barrières sont à explorer chez les patients diabétiques avec atteinte rénale afin de les atténuer le plus possible. Il a d'ailleurs été montré que la forte implication de ces patients dans la gestion de leur maladie était associée à une meilleure qualité de vie.

ADHÉSION THÉRAPEUTIQUE DES PATIENTS ATTEINTS DE NÉPHROPATHIE DIABÉTIQUE

La non-adhésion aux antidiabétiques oraux atteint 40% chez les patients avec néphropathie diabétique.[6] Elle est associée à un risque plus élevé de développer une insuffisance rénale terminale. Or, les évaluations de programmes de soutien de l'adhésion médicamenteuse destinés aux patients avec néphropathie diabétique sont rares; elles démontrent néanmoins une amélioration des paramètres de contrôle métabolique et tensionnel avec une amélioration des activités d'autosoin.[7] La majorité des programmes d'intervention est menée en collaboration interprofessionnelle avec des pharmaciens ou des infirmières spécialisées. Du fait de leurs expertises différentes, leurs rôles dans le soutien de l'adhésion se complètent.[8]

Dans ces programmes, l'adhésion médicamenteuse est peu investiguée. Figurant uniquement dans les objectifs secondaires des études d'intervention, l'estimation de l'adhésion résulte souvent d'une méthodologie faible. Des questionnaires autorapportés sont généralement utilisés,[9] la qualité d'administration de ces questionnaires et l'intervention de soutien à l'adhésion sont peu détaillées. D'autre part, un faible taux de patients éligibles participe à ces études. Elles sont donc composées de petits effectifs avec parfois un taux d'attrition non négligeable, diminuant la validité externe des résultats.

Une étude observationnelle de 24 mois chez 160 patients comparant une prise en charge structurée médecin-pharmacien à une prise en charge standard a montré que la prise en charge structurée ralentit le déclin de la fonction rénale. Dans cette étude interprofessionnelle, le pharmacien évaluait l'adhésion médicamenteuse en questionnant les patients sur leur prise médicamenteuse, les accompagnait et émettait des recommandations thérapeutiques au médecin. Cependant, l'aspect subjectif de l'estimation de l'adhésion n'a pas permis de corréler l'amélioration de l'adhésion et le ralentissement du déclin rénal.[10]

L'amélioration de l'adhésion n'a pas non plus été démontrée dans une étude qui consistait à la remise d'un plan de médication, au visionnage d'un DVD d'éducation thérapeutique et à des entretiens motivationnels téléphoniques réguliers réalisés par une infirmière spécialisée. Dans cette étude, les auteurs rapportent la difficulté d'évaluer l'adhésion par le comptage des comprimés et concluent que des méthodes plus rigoureuses accessibles aux chercheurs sont nécessaires. Finalement, une autre étude a montré une amélioration tensionnelle suite à un programme de soutien mensuel par une infirmière communautaire spécialisée avec une évaluation de l'adhésion par un questionnaire. Le processus du soutien n'est cependant pas décrit, ni les domaines de compétences en adhésion médicamenteuse soutenus par l'infirmière.[11]

PROGRAMME DE SOUTIEN DE L'ADHÉSION POUR DIABÉTIQUES AVEC ATTEINTE RÉNALE (PANDIA IRIS)

Dès 1995, la Pharmacie d'Unisanté (Lausanne) a implémenté, en collaboration interprofessionnelle, un programme d'adhésion thérapeutique pour les patients chroniques (*Interprofessional Medication Adherence Program* (IMAP)).[12,13] Une cohorte de 300 patients-année atteints d'une maladie chronique y est suivie. Depuis 2019, la consultation d'adhésion existe également à Pharma24, pharmacie académique ambulatoire sise dans les bâtiments des HUG (Genève). L'intégration de la

consultation d'adhésion dans un concept d'accompagnement des patients chroniques (*chronic care management*) est en cours à l'échelle des pharmacies suisses (exemple: programme SISCARE).[14,15] La consultation d'adhésion est assurée par les pharmaciens en coordination avec les équipes médicale et infirmière afin de soutenir l'adhésion thérapeutique et promouvoir la continuité des soins.

Afin de combler les faiblesses méthodologiques des études publiées dans la littérature, un programme de soutien à l'adhésion médicamenteuse des patients diabétiques et insuffisants rénaux a été développé et implémenté à la pharmacie d'Unisanté en 2016 (programme PANDIA IRIS), en collaboration avec les services d'endocrinologie, diabétologie et métabolisme, et de néphrologie du CHUV. Ce programme interprofessionnel, toujours en cours, combine la mesure objective de l'adhésion médicamenteuse par le pilulier électronique à des entretiens motivationnels brefs mais répétés qui engagent le patient activement et à son rythme dans l'autogestion de son traitement (*cf.* encadré).

Exemple d'une patiente diabétique avec atteinte rénale présentant une adhésion suboptimale (participant au programme PANDIA IRIS)

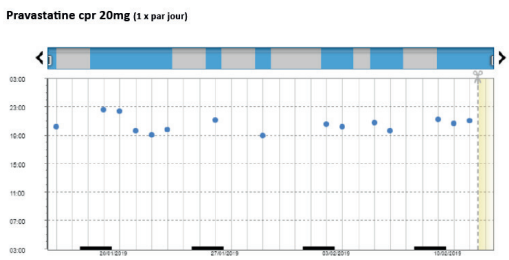
Une patiente diabétique de 63 ans présente une insuffisance rénale chronique développée sur une néphropathie diabétique. Elle travaille de nuit et exprime sa difficulté à avoir un rythme régulier de prise de ses 6 médicaments.

FIG 1 **Ouvertures quotidiennes du pilulier électronique**

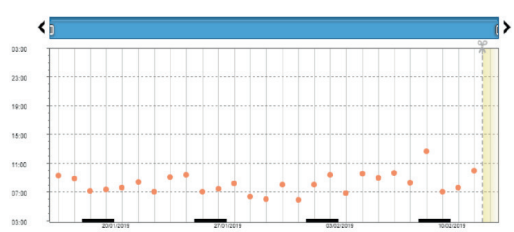
Chaque point représente une ouverture du pilulier (les jours sur l'axe des abscisses et les heures sur l'axe des ordonnées).

A

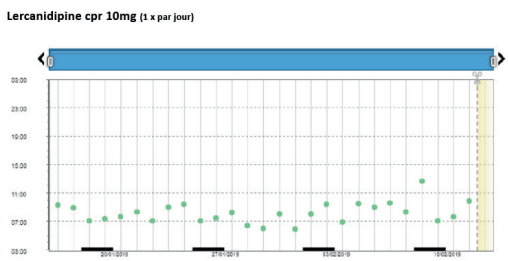
Adhésion$_{pravastatine}$ = 60%



Adhésion$_{olmésartan}$ = 100%

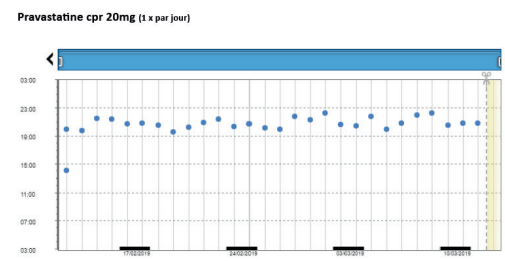


Adhésion$_{lercanidipine}$ = 100%

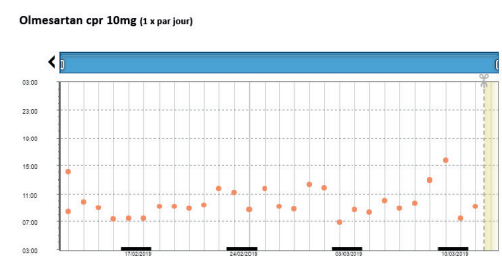


B

Adhésion$_{pravastatine}$ = 100%



Adhésion$_{olmésartan}$ = 100%



Lors de la lecture du graphique représentant les ouvertures quotidiennes du pilulier électronique, la pharmacienne s'aperçoit que la prise de la statine est suboptimale (60%) alors que l'adhésion aux deux antihypertenseurs est excellente (partie A de la **figure 1**). Durant l'entretien d'adhésion, la patiente indique avoir régulièrement des vertiges qui diminuent sa qualité de vie au quotidien; elle a parfois «du mal à marcher droit». La tension moyenne mesurée lors de l'entretien est de 125/77 mm Hg, la fréquence cardiaque est de 78 bpm. Elle attribue cet effet indésirable à la prise de la statine et a donc décidé par elle-même de ne pas avaler quotidiennement ce médicament.

S'apercevant de la confusion, la pharmacienne revoit, avec l'accord de la patiente, l'indication des traitements et lui indique que les vertiges sont probablement dus aux antihypertenseurs. Elle détaille son intervention dans le rapport d'adhésion pour le médecin qui décide d'interrompre la lercanidipine.

Lors de l'entretien suivant, l'adhésion à la statine et à l'olmésartan est optimale (partie B de la **figure 1**). Suite à l'arrêt de la lercanidipine, la patiente ne présente plus de vertiges.

Ainsi, l'arrêt de la lercanidipine, décidé de manière interprofessionnelle et selon un décours temporel favorable, a permis d'améliorer significativement la qualité de vie de la patiente. Un tel exemple illustre l'importance de la collaboration et de la communication patient-médecin-pharmacien pour soutenir la gestion médicamenteuse complexe des patients diabétiques avec atteinte rénale.

Les résultats de PANDIA IRIS donneront les lignes directrices pour:

1. Mieux définir la plus-value d'une approche interprofessionnelle de l'adhésion thérapeutique et définir le rôle de chaque professionnel dans ce contexte.
2. Mieux définir la population de patients cibles (diabétiques avec prémisses d'insuffisance rénale).
3. Optimiser la durée du programme d'intervention sur l'adhésion thérapeutique.

CONCLUSION ET PERSPECTIVES

Malgré un arsenal thérapeutique efficace et consensuel, un tiers des patients diabétiques développe une néphropathie diabétique. La majorité de ces patients sont polymédiqués de longue date, leurs parcours thérapeutiques sont pluriels et leurs besoins d'accompagnement évoluent avec le temps. Le médecin joue un rôle clé pour questionner régulièrement la pertinence de chaque traitement selon les guidelines cliniques mais également selon les possibilités individuelles du patient, afin d'ancrer au mieux l'adhésion thérapeutique de ce dernier. L'adhésion thérapeutique du patient devrait ensuite être renforcée au travers d'une approche interprofessionnelle médecin-pharmacien-infirmier assurant la continuité des soins et des messages thérapeutiques, et capitalisant sur le patient comme membre à part entière de l'équipe. Les professionnels de la santé ont urgemment besoin de guidelines interprofessionnelles afin de définir comment mieux accompagner le patient diabétique à long terme et ralentir le déclin de la fonction rénale. Les programmes interprofessionnels sont une réelle opportunité de mieux soigner ces patients, il est temps de les mettre sur pied au travers d'études d'interventions de bonne qualité méthodologique.

Conflit d'intérêts: Les auteures n'ont déclaré aucun conflit d'intérêts en relation avec cet article. L'étude PANDIA IRIS est soutenue par le Fonds qualité et recherche de santésuisse, curafutura et pharmaSuisse (fonds sans restriction).

IMPLICATIONS PRATIQUES

- La néphropathie diabétique touche environ un tiers des patients diabétiques
- L'adhésion thérapeutique fluctue au cours du temps, les professionnels de santé doivent donc s'en soucier dès le début et tout au long du suivi, particulièrement en cas de polymédication, afin de préserver au mieux la fonction rénale des patients diabétiques
- Le médecin doit réévaluer la liste des traitements régulièrement avec le patient afin d'en vérifier la pertinence et le pharmacien complète la prise en charge en identifiant les facteurs influant sur l'adhésion pour offrir un soutien individuel de la gestion médicamenteuse
- L'accompagnement interprofessionnel et individualisé entre médecins, pharmaciens et infirmières spécialisées a le potentiel d'améliorer les résultats cliniques des patients; ce potentiel doit être vérifié dans des études adaptées aux besoins des patients et bien menées méthodologiquement

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* **à lire**
** **à lire absolument**

Appendix 2: Flyer presenting the OpTAT study

OpTAT: Optimization of Targeted Anticancer Therapies

Introduction

La majorité des inhibiteurs de protéine kinase (Protein Kinase Inhibitors - PKIs) sont prescrits à une posologie standard malgré une variabilité de **leurs concentrations plasmatiques** entre individus. Cela pourrait favoriser une progression tumorale (en cas de concentrations médicamenteuses sous-thérapeutiques) ou le développement d'effets indésirables (en cas de sur-exposition médicamenteuse).
De plus, **l'adhésion médicamenteuse** est un déterminant majeur à la réponse thérapeutique.

Personnes de contact

ARC, Equipe translationnelle CTE : Saskia Wehrli (62617), Marzio Bergomi (61374)
Pharmacie d'Unisanté : Carole Bandiera (63244)

Populations d'étude

PKIs

- **Palbociclib**
- **Trametinib/ Dabrafenib** (combinés ou non)
- **Imatinib**
- **Sorafenib**
- **Regorafenib**
- **Pazopanib**

Cliniques

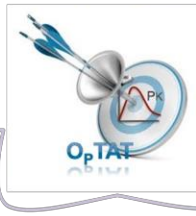
- SEN
- GI
- URO
- THOR
- SARC
- MEL
- ORL
- NEURO
- GYN

Étude en 3 parties

Partie 1 : Pharmacocinétique (PK)
- 1 prélèvements de 10 ml en même temps qu'une prise de sang standard
- 8 prélèvements au total

Partie 2 : PK approfondie (en pharmacologie clinique) -> optionnel

Partie 3 : Adhésion thérapeutique (à la pharmacie d'Unisanté)



Procédures de la partie 1

Médecins
- Identification des patients
- Prévenir **Saskia ou Marzio** du potentiel patient

Prescription prise de sang pour OpTAT

ARC

Présentation et collecte du consentement original

- Suivi des patients inclus
- Mise à jour de la liste patients
- Rappel aux médecins des pds à faire

Feuille de prescription

Infirmiers

Prise de Sang
- Utilisation des pochettes « OpTAT » apportées par l'ARC ou stockées au desk des prises de sang (Vacutainer 10 ml + papillon + Formulaire de demande de Labo)
- Indication de l'heure du prélèvement sanguin et signature sur Formulaire de demande de Labo
- Appel au laboratoire CTE (**60 765**) pour récupérer et traiter les échantillons

Investigateurs principaux de l'étude:
- Pr Chantal Csajka: Chantal.Csajka@chuv.ch, 66 046 (Pharmacologie clinique)
- Pr Marie Schneider: marie.schneider@unige.ch (Université de Genève)

26.03.2021

Appendix 3: Challenges and strategies of patient recruitment in the OpTAT study; poster presented at the annual ESPACOMP congress in November 2019 (Porto, Portugal)

How to recruit more patients? In the study: Optimizing Targeted Anticancer Therapies (OpTAT)

Carole Bandiera[1] ; Saskia Wehrli[2] ; Evelina Cardoso[1] ; Dorothea Wagner[2] ; Chantal Csajka[1] ; Marie Paule Schneider[1]
[1]: Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Switzerland.
[2]: Department of Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland.

Introduction

For the last decade, there has been a **shift in cancer care** from injectable chemotherapy **to oral treatment.** This leads to:

- ✓ Home-manageable chronic diseases
- × Expensive treatment, adverse effects and suboptimal adherence

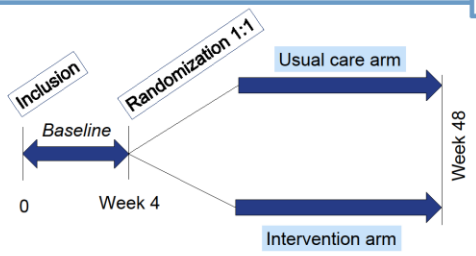
Randomised Controlled Trial: to evaluate the impact of an adherence intervention for patients taking protein kinases inhibitors (PKI) compared to usual care.

- Aim: enrol in total **202 patients** by December 2020.
- From July 2015 to October 2019, **88 patients** have been included.

Key issues :

- **Recruitment is slower than expected.**
- **Oncologists do not declare all eligible patients**

Design



Usual care arm: use of MEMS

Monthly usual care visit:
No feedback with the pharmacist, data blinded to the patient, all healthcare providers and researchers

Intervention arm: use of MEMS + interviews

Monthly adherence intervention:
Feedback, information and support provided to facilitate adherence to PKI, side effect investigation

Methods: recruitment strategies

Core strategies

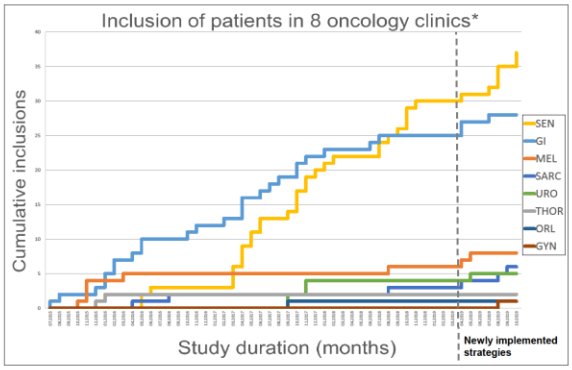
- **Active communication** in the oncology clinics
- **OpTAT flyer** is posted in the different clinics
- **Oncologists identify eligible patients**
- All the investigators **meet** every four months
- Provide **study advancements** to residents, chief doctors and nurses during regular staff meetings and through emails

Newly implemented strategies since March 2019

- **Algorithms** scrutinising patients' medical files
- Identify patients to which a PKI is delivered in the **community pharmacy**
- **The reports** of all Tumour-Boards are read to detect eligible patients
- Collaboration with an **oncology clinical pharmacist**
- Facilitation of administrative work with **health insurances** to allow patients with particular contracts to enter OpTAT

Results

Newly implemented strategies increased inclusions.



*Breast (SEN) and gastrointestinal (GI) cancers, melanoma (MEL), sarcoma (SARC), urologic (URO), thoracic (THOR), ORL and gynaecologic (GYN) cancers

Investigators face **barriers** when recruiting patients taking PKI:

Reasons why 74 patients were not included

Before introducing the study to the patient	Between signature of consent and inclusion
Treatment stopped** n=32	Treatment stopped** n=8
Patients excluded*** n=14	Health insurance does not reimburse the drug n=1
Patients died n=11	Patients died n=2
Participation in another interventional study n=4	Participation in another interventional study n=2

**Main reasons: adverse effects, cancer progression
***Main reasons: non-French speaker, patients do not manage their treatment alone (nursing home, home health care nurse, carers)

Conclusion

At study mid-term, new strategies have been implemented to **enable investigators to identify eligible patients**.
Key presence of a research member in the clinical team as well as **strategic collaborations** increase patient inclusions.

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Appendix 4: Flyer presenting the PANDIA-IRIS study

unisanté

Centre universitaire de médecine générale
et santé publique · Lausanne

PROGRAMME
PANDIA IRIS

Pour les patient·e·s
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Aidez-nous à améliorer votre prise en charge médicamenteuse : participez à notre programme de soutien !

curafutura
pharmaSuisse
santésuisse

Fonds de qualité et de recherche RPB IV / 1

PROGRAMME
PANDIA IRIS

CHUV

POUR PARTICIPER :

- Renseignez-vous à l'accueil ou auprès de la pharmacie d'Unisanté au 5e étage
- Des flyers sont à votre disposition dans les salles d'attente
- Pour plus d'informations, appelez le 079 556 32 44

Appendix 5: Results of the OpTAT study; poster presented at the annual ESPACOMP congress in November 2022 (Berlin, Germany)

A pharmacist-led interprofessional medication adherence program improved adherence to oral anticancer therapies

Carole Bandiera[1,2,3], Evelina Cardoso[4], Isabella Locatelli[3], Antonia Digklia[5], Khalil Zaman[5], Antonella Diciolla[5], Valérie Cristina[5], Athina Stravodimou[5], Aedo-Lopez Veronica[5], Ana Dolcan[5], Apostolos Sarivalasis[5], Hasna Bouchaab[5], Aikaterini Liapi[5], Angela Orcurto[5], Jennifer Dotta-Celio[3], Solange Peters[5], Laurent Decosterd[6], Nicolas Widmer[1,2,6,7], Dorothea Wagner[5], Chantal Csajka[1,2,4], Marie P. Schneider[1,2]

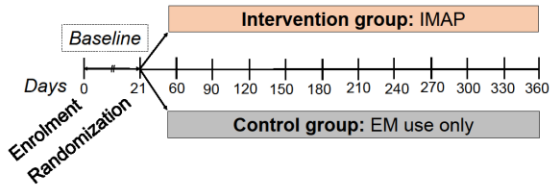
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Aim

To evaluate the impact of an **interprofessional medication adherence program (IMAP)** on patients' implementation and persistence to protein kinase inhibitors (PKI) in solid cancers

Design of the OpTAT study

- The OpTAT study is a 1:1 randomized controlled and open trial
- Eligibility criteria: adult patients treated with PKI (cyclic or continuous regimen) for solid cancers



INTERVENTION: ~ Once per month
- ✓ Electronic based feedback
- ✓ Face-to-face motivational interview (Information-Motivation-Behavioural skills) between patient and pharmacist
- ✓ Adherence report describing the intervention shared with the interprofessional team



CONTROL:
Use of electronic monitor (EM) only without any feedback



Methods

- Implementation is considered **optimal** if the number of observed EM opening is **at least equal** to the number of EM expected opening.
- **Operational definition of implementation**: proportion of patients with an optimal implementation at each day of the monitored period.
- The EM database was **rigorously cleaned**, as the numerous PKI premature stops, altered regimens and interruptions due to intolerance or toxicity could have led to data misinterpretation.
- **Implementation** to PKI was compared between groups, using a **generalized estimating equation** (GEE) model.
- Relevant covariables were included in the GEE model ; age was dichotomized according to the median value in the sample size.
- **Persistence** was assessed in both groups using Kaplan-Meier curves.

Results

In total, **130 patients** were included, of whom 12 left the study during the baseline period (Table 1).

Implementation

The PKI implementation was constantly higher in intervention (n=58) than in control group (n=60), respectively 98.1% and 94.9% at 6 months (Δ3.2%, 95%CI: 2.6-3.7%) (Fig 1).

The intervention benefited most to (implementation at 6 months):

- **Male gender**: 96.3% in the intervention and 91.0% in the control group (Δ5.3%, 95%CI: 4.2-6.5%) (Fig 2)
- Patients **younger than 60**: 97.9% in the intervention and 93.9% in the control group (Δ4.1%, 95%CI: 3.4-4.9%) (Fig 3)
- Patients who have never used any **adherence tools in their therapeutic journey:** 98.1% in the intervention and 94.0% in the control group (Δ4.1%, 95%CI: 3.4-4.7%) (Fig 4).

Persistence

Persistence was comparable between intervention & control group at 6m: 91.2% and 91.7% (Δ-0.5%, 95%CI: -12.0; +11.2%).

	Intervention (n=58)	Control (n=60)
Age (years), mean (CI)	60.5 (57.3-63.7)	59.6 (56.1-63.1)
Female gender, n (%)	37 (63.8)	34 (56.7)
Caucasian, n (%)	55 (94.8)	55 (91.7)
Adherence tools use, n (%)	14 (25.0) Missing data n=2	14 (23.7) Missing data n=1

Table 1: Randomized patients' characteristics (n=118)

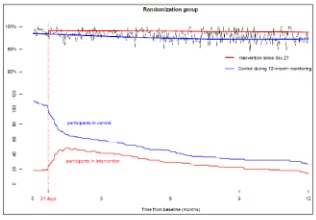


Fig 1: randomization group

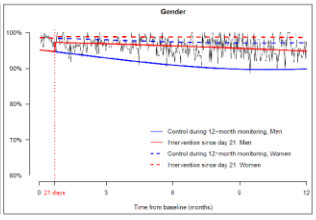


Fig 2: gender

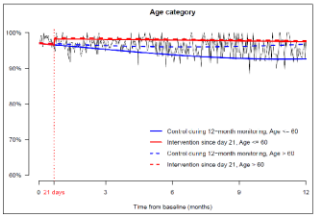


Fig 3: age category

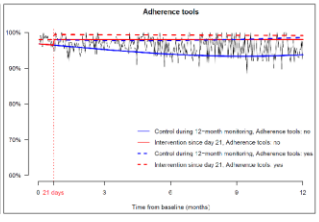


Fig 4: adherence tools use

Conclusions

The IMAP, led by pharmacists within interprofessional collaborations, **supports the implementation** to OAT. **Men, patients younger than 60 and those who have never used any adherence tools** in their therapeutic journey benefited most from the intervention.
The impact on clinical outcomes has to be evaluated.

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Appendix 6: *Jean-Michel Metry Poster Prize* for the best poster presentation (ESPACOMP congress 2022)



Jean-Michel Métry Poster Prize

Winner 2022

Carole Bandiera

for the poster presentation entitled:

An Interprofessional Medication Adherence Program to Optimize Adherence to Oral Anticancer Therapies: A Randomized Controlled Trial

ON BEHALF OF THE ORGANIZING COMMITTEE

TODD RUPPAR

ESPACOMP

www.espacomp.eu

Appendix 7: Results of the PART-PANDIA study; poster presented at the Pharmaceutical Care Network in Europe (PCNE) congress in February 2022 (Lisbon, Portugal) and at the *Société Suisse de Médecine Interne Générale (SSMIG)* congress in June 2022 (Lausanne, Switzerland)

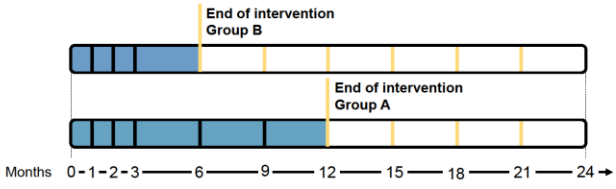
What are the factors and reasons for non-participation to an adherence program among patients with diabetic kidney disease?

Carole Bandiera[1,2,3], Liliane Lam[1], Jennifer Dotta-Celio[3], Dina Duarte[4], Gregoire Wuerzner[4], Menno Pruijm[4], Anne Zanchi[4,5], Marie P. Schneider[1,2]

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PANDIA-IRIS adherence program: 73% (202/275) patients refused to participate

- The PANDIA-IRIS study is a 1:1 randomized controlled and open trial
- Aim: to determine the impact of the duration of the interprofessional adherence program (6m vs. 12m) on long-term adherence
- Eligibility criteria: patients with diabetic kidney disease (eGFR ≤60 ml/min/1.73m²) visiting their nephrologist or endocrinologist at the Lausanne University Hospital (Switzerland)



Design of the PANDIA-IRIS study

INTERVENTION:
✓ Electronic based feedback
✓ Face-to-face interview between patient and pharmacist

FOLLOW-UP:
Blinded use of electronic monitor (EM) only

Medication adherence visit | Post intervention visit (refill)

Aim

1) To **describe** patients who refused vs. accepted to participate to the PANDIA-IRIS study
2) To **understand,** in-depth, reasons for non-participation in patients who refused, and perceived usefulness in patients who accepted

Methods

1) A **quantitative** comparison of sociodemographic and clinical variables (eligibility: patients who signed the general consent)
2) **Qualitative** interviews with patients who refused (n=16) and accepted (n=14) to participate

Results

1) Patients who refused are **older** and diagnosed **for a longer duration** than patients who accepted.
More women refused to participate compared to men.

	Patients who accepted n=57	Patients who refused n=123	p-value
Age (years)	64.0 (SD: 10.0)	67.7 (SD: 10.5)	**P=0.024**
Gender	Male: 50 (87.7%) Female: 7 (12.3%)	Male: 85 (69.1%) Female: 38 (30.9%)	**P=0.007**
Diabetes types	Type 2: 54 (94.7%) Type 1: 1 (1.8%) Other*: 2 (3.5%)	Type 2: 108 (87.8%) Type 1: 2 (1.6%) Other*: 13 (10.6%)	P=0.194
Time from diabetes diagnosis (years)	Median: 9 (IQR 4-16)	Median : 15 (IQR 7-23) Missing data: 11 patients	**P=0.002**
eGFR decline per year (mL/min/1.72m²/year)**	Median: -2.5 (IQR -4.1 ; -0.9)	Median: -1.8 (IQR -4.2 ; -0.5) Missing data: 5 patients	P=0.405
HbA1C (%)	Median: 7.1 (IQR 6.7-8.0) Missing data: 11 patients	Median: 7.4 (IQR 6.8-8.3) Missing data: 34 patients	P=0.228
Number of chronic treatments	Median: 8 (IQR 6-11)	Median: 9 (IQR 7-12)	P=0.228

*Type 1, glucocorticoid-induced, post-transplantation, post-pancreatectomy diabetes or Latent Autoimmune Diabetes in Adults (LADA)
**eGFR: estimated Glomerular Filtration Rate

2) The decision to participate to an interventional study is **complex and multifactorial,** it involves the patients and their relatives.

I participated

- ✓ EM feedback **useful** to prevent forgetfulness
- ✓ Medication **literacy** improved and **motivation** increased
- ✓ **Reassured** by the interprofessional intervention

I won't participate

- **Do not feel the need** of an adherence support program
- **Did not agree** to use the EM
- **Study design** is perceived as a **burden**
- Described a **well-established medication routine** but the study **could have been beneficial if introduced earlier** in their therapeutic journey
- Other barriers: **difficult relationship** with healthcare providers, **lack of awareness** of pharmacist's role in supporting adherence, **negative perception** of clinical research

Conclusions

There is an urgent need to advocate for **interprofessional outpatient collaborations** between physicians, pharmacists and nurses **to support medication adherence in patients with diabetic kidney disease.**

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Financial support for this study was provided by the LOA IV fund, managed by curafutura, pharmaSuisse and santésuisse, Switzerland

Appendix 8: Results of the CovADH study; poster presented at the International Pharmaceutical Federation (FIP) congress in July 2022 (Utrecht, The Netherlands)

The Interprofessional Medication Adherence Program (IMAP) supported patients' medication adherence during the COVID-19 lockdown in Switzerland

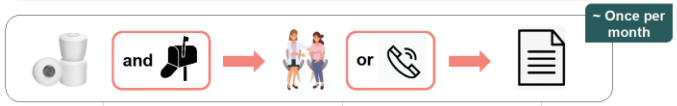
Carole Bandiera[1,2,3], Jérôme Pasquier[3], Isabella Locatelli[3], Anne Niquille[2,3], Grégoire Wuerzner[4], Jennifer Dotta-Celio[3], Anna Hachfeld[5], Gilles Wandeler[5], Dorothea Wagner[6], Chantal Csajka[1,2,7], Anne Zanchi[4,8], Matthias Cavassini[9], Marie P. Schneider[1,2]

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Question

To what extent **medication adherence** was impacted by the COVID-19 lockdown in patients included in the Interprofessional Medication Adherence Program (IMAP)?

The IMAP worked routinely during the Covid-19 pandemic



Patients with **diabetic kidney disease (DKD), solid cancer, HIV, miscellaneous long-term diseases** used **electronic monitor(s) (EMs)** which register daily doses intake

Adherence intervention:
- **Electronic based feedback**
- **Face-to-face motivational interviews** with a pharmacist

Adherence report sent to the patient's health care providers

During the lockdown: medicines were sent by mail

During the lockdown: interviews were hold by phone calls

Methods

Patients' implementation (i.e., the extent to which the patient takes the prescribed medicine) was defined through a proxy: if all EMs used by a patient were opened at least once daily, implementation was considered optimal (=1); and suboptimal (=0) otherwise.

Implementation was **compared** around the Swiss lockdown periods:
- **Before**: from December 1, 2019 to March 15, 2020
- **During**: March 16 to June 7, 2020
- **After**: June 8 to September 30, 2020

To compare variations across a year, patients' implementation within the same periods in 2018-2019 (winter, spring, summer) were analysed.

Statistical Analysis

A **logistic regression** model estimated implementation **according to the period.** Reference: "before the lockdown" or "winter".

The models were fitted using **generalized estimating equations.**

Sensitivity analyses were performed to ensure the quality of results.

Results

Empirical patients' implementation and GEE modelisations in 2020 (Fig. 1) and 2019 (Fig. 2)

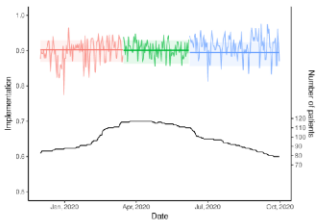


Fig. 1

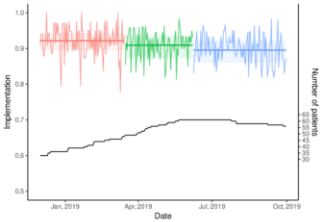


Fig. 2

EM database 2020, all patients (n=118)							
Periods	Implementation			Odds ratio			
	Estimate	95% CI		Estimate	95% CI		p-value
Before	0.903	0.869	0.929	Reference			
During	0.901	0.863	0.929	0.979	0.835	1.147	0.789
After	0.895	0.856	0.923	0.911	0.787	1.056	0.217
EM database 2019, all patients (n=61)							
Periods	Implementation			Odds ratio			
	Estimate	95% CI		Estimate	95% CI		p-value
Winter	0.922	0.894	0.942	Reference			
Spring	0.909	0.873	0.936	0.852	0.706	1.029	0.097
Summer	0.895	0.860	0.923	0.728	0.596	0.891	0.002

Table 1. Patients' implementation across the periods in 2020 and 2019

Conclusions

Medication implementation remained **steady** before, during and after the lockdown in **2020**, whereas a **decrease in implementation** was observed during summertime in **2019**.

IMAPs that are tailored to patients' needs, ensure **continuity of care** and **avoid gaps in medication supply** by the regular mailing of treatment contribute to supporting patients during periods of **routine disturbances** such as **lockdowns** in a pandemic context.

Financial support for this study was provided by the LOA IV fund, managed by curafutura, pharmaSuisse and santésuisse, Switzerland

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Appendix 9: Policy brief “Swiss Priority Setting on Implementing Medication Adherence Interventions –the European ENABLE COST Action”

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ISPSO INSTITUT DES SCIENCES PHARMACEUTIQUES DE SUISSE OCCIDENTALE

Universität Basel
Medizinische Fakultät
Departement Public Health

Policy brief

Swiss Priority Setting on Implementing Medication Adherence Interventions –the European ENABLE COST Action



While medication adherence is a major public health concern that warrants high priority by all stakeholders in the healthcare system, it remains absent from Swiss policymakers' agendas.

This policy brief summarizes key recommendations to implement interventions to support patients' medication adherence in Switzerland.
Public health media campaigns would raise public awareness about medication non-adherence. Funding agencies are encouraged to invest in medication adherence research and innovations. Health insurance companies are advised to develop innovative models of financial contributions to promote the development and implementation of medication adherence interventions in daily clinical practice (i.e., screening, monitoring and facilitating patients' medication adherence). A new model of remuneration for healthcare providers facilitating patients' medication adherence would foster an integrated model of care through inter-professional collaborations. Concurrent development of teaching resources to be integrated in pre-, post-graduate and in-service training would ensure that the latest findings about medication adherence are rapidly scaled up into practice with cost-effective public health benefits.

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Context

Definition of medication adherence

Medication adherence is "the process by which patients take their medications as prescribed" [2]. This process follows the prescribing process, where, ideally, shared decision-making supports the choice of the best treatment in partnership with the patient, family and carers.

Medication adherence consists of three phases: *initiation, implementation* and *discontinuation.*

Initiation occurs when the patient takes the first dose of a prescribed medication.

Implementation is the extent to which a patient's actual dosing corresponds to the prescribed regimen, from initiation until the last dose.

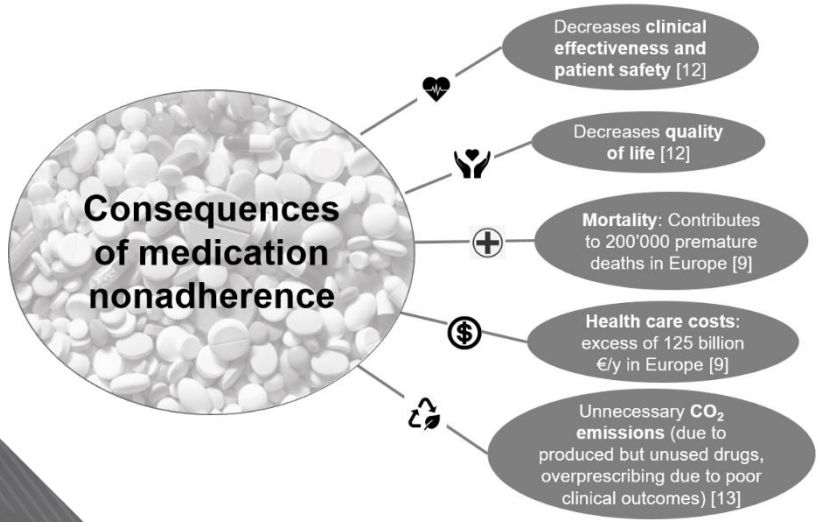
Discontinuation occurs when the patient stops taking the prescribed medication earlier than planned, for whatever reason(s) [2].

In Switzerland, 50% of the population ≥15 yrs. takes at least one medication each week [4]. About 17% of the adult Swiss population is polymedicated (i.e., using ≥5 medications chronically) [5]. Among the population aged 65-80 yrs, 45% is polymedicated, which rises to 65% in people aged 81-92 yrs [8].



Volume of tablet blisters prescribed over a year for a single kidney transplant patient [1]

Medication non-adherence (i.e., not taking the medication as prescribed) is endemic. Although three quarters of the patients initiate their prescribed long-term treatments, 30-50% do not implement them correctly. Additionally, more than 50% of patients discontinue their prescribed medication within two years after treatment initiation [9]. Insurance companies estimate that enhancing medication adherence would decrease health care costs by a factor four [10, 11].



Evidence on addressing medication non-adherence exists [3] (e.g., effective multi-level interventions), but is often not translated into real-world settings, preventing patients and public health from benefitting from scientific knowledge [6, 7]. To date, there are no adherence-focused national programs, nor have guidelines been developed, implemented or evaluated in Switzerland [6].

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The ENABLE COST Action

The European Network to Advance Best practices & technoLogy on medication adherencE (ENABLE), a Cooperation in Science and Technology (COST, https://www.cost.eu/actions/CA19132/) action, links relevant stakeholders across 40 European countries, including Switzerland, to work collaboratively towards implementation of medication adherence enhancing technologies into daily clinical practice.

The Swiss ENABLE COST network

In March 2022, the Swiss ENABLE COST country group initiated an online conference 1) to network national and international stakeholders, and, 2) to initiate priority setting for medication adherence, particularly with regard to the implementation of adherence interventions and technologies in real-world settings. This was funded by ENABLE Cost Action (19132) and the Swiss National Science Foundation (IZSEZ0_208877).

Moving toward a more enabling ecosystem for improving the translation of adherence interventions into practice in Switzerland: a framework for change

Seventy-five participants (i.e., researchers, clinicians, healthcare industry delegates, and one policy maker) from 34 countries met to discuss the main actions needed to create an enabling ecosystem to implement adherence interventions in Switzerland. The ideas discussed were organized into a framework for change (Fig. 1) to describe stakeholders, arenas and main objectives - on the one hand, for a systematic elaboration of strategies to address medication adherence at the national level, and, on the other hand, to move towards an **integrated, patient-as-partner healthcare** system.

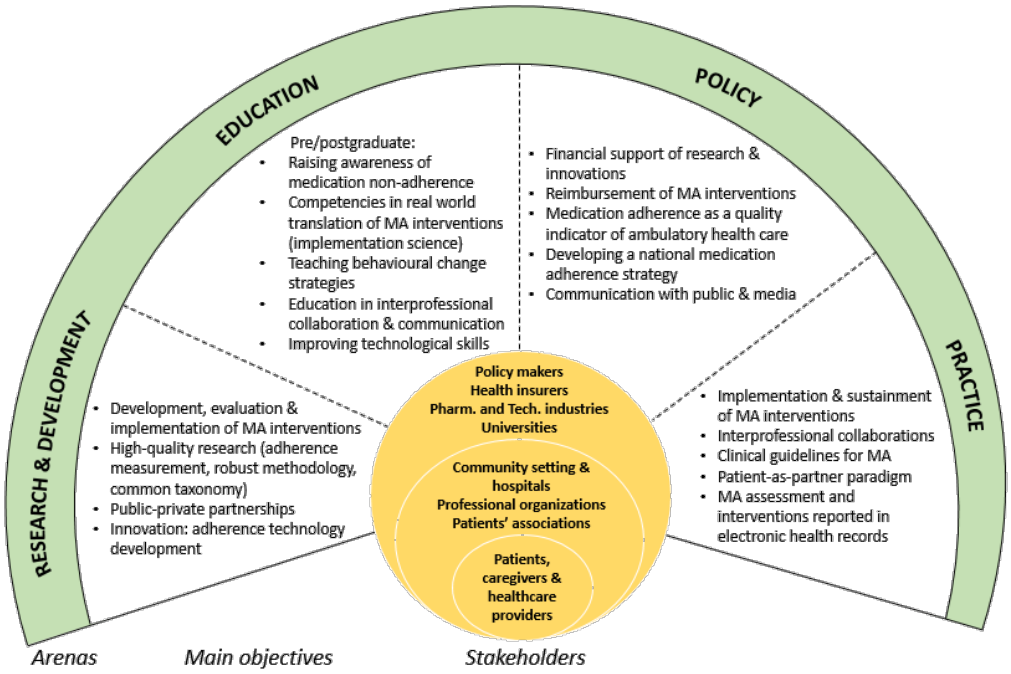


Figure 1: Framework for addressing medication adherence in a multilevel ecosystem: stakeholders (in yellow circle), arenas (in green ribbon) and main objectives (in white wedges).

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Priorities for creating a more enabling ecosystem for the development, implementation and sustainment of adherence interventions



Changing the mindset and attitudes of patients and the population overall, health care professionals (HCPs), health care organizations and other stakeholders:

- **Raising awareness** on the health and social benefits of sharing objectives on medication adherence
- Promoting medication adherence **research and funding**

Preparing a multilevel ecosystem, involving patients, relatives, HCPs and other stakeholders



- **Synergies:** Enabling stakeholders to work inter-professionally and coordinate their actions to jointly support, monitor and maximize medication adherence
- **Innovative ecosystems:** Connecting funding agencies, start-up incubators, and public-private-partners to foster development of medication adherence enhancing technology innovations
- **Financial support:** Negotiation with health insurers to develop reimbursement models to facilitate the implementation of evidence-based interventions in clinical practice

Strengthening the patient-as-partner paradigm as the basis for shared decision-making and therapeutic awareness-raising



- **Tailoring interventions:** Supporting medication adherence based on the patients' individual needs, preferences and possibilities
- **Developing trust, partnerships and communication channels across all HCPs and patient groups:** Reducing conflicting information and ensuring continuity of care
- **Training of HCPs:** Capacity-building behavior change and inter-professional competencies
- **Integrated care models powered by digitalization:** Providing fertile ground for development of innovations (e.g., improved computerization in healthcare settings)

Monitoring medication adherence and its determinants in routine practice as an informed basis for clinical decision-making



- **Routine practice:** Medication adherence to be considered as a patient's 5th vital sign
- **System-level:** Medication adherence as an indicator of quality of care
- **Technology:** Designed to match patients' and HCPs' needs and preferences



Investing in **translation from research to real-world settings**

- **Effective multi-level and multi-sectoral medication interventions.**
- **Implementation science:** Assisting the uptake of research evidence into clinical practice [14]

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Recommendations to expand medication adherence efforts to all health care system professions, consistent with the Swiss *Health2030* strategy [15]

1

Key inter-professional **stakeholders** need to be **identified and connected** to address medication adherence in the multi-level ecosystem and to determine contextually appropriate medication adherence interventions as well as long-term quality indicators.

2

Efforts to develop and implement **coordinated care models** must be strengthened and tailored to facilitate medication adherence management.

Technology-based innovations (e.g., electronic health records, teleconsultation), new technologies (e.g., digital pill boxes) and methodologies (e.g., artificial intelligence) should be adapted to facilitate interventions.

Technology literacy needs to be enhanced at all levels, including the patient and HCPs.

3

To support the translation of medication adherence evidence into Swiss clinical practice, contextually appropriate **implementation strategies** (e.g., patient involvement) need to be integrated using a multi-level approach.

4

Research funding programs that support medication adherence research are needed. Funding options should be devised to enable and encourage researchers to broaden their foci from efficacy / effectiveness research to **evaluate implementation and implementation strategies** for medication adherence interventions in real-world settings.

5

Synergies between **bottom-up and top-down** approaches, public and private initiatives as well as inter-professional collaborations are needed to maximize impact and drive change.

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Conclusions

This policy brief builds on evidence, expert knowledge and inter-professional experience to define priorities for addressing medication adherence as a major public health problem. Multi-level approaches are necessary to allow translation of evidence to implement medication adherence interventions into real-world practice.

Three first steps are needed to raise medication adherence awareness:

- **Laying the foundations for health ecosystems to support medication adherence;**
- **Translating effective medication adherence interventions into daily clinical practice;**
- **Promoting research into technologies to improve medication adherence.**

These strategic first steps are needed to inform research activities, policies and implementation of medication adherence interventions in Switzerland.

COST is supported by the Horizon 2020 Framework Programme of the European Union

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COST is supported by the Horizon 2020 Framework Programme of the European Union