



Article scientifique

Editorial

2018

Published version

Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

---

## Mathematical modelling to inform 'treat all' implementation in sub-Saharan Africa: a scoping review

---

Kimmel, April D; Bono, Rose S; Keiser, Olivia; Sinayobye, Jean D; Estill, Janne Anton Markus; Mujwara, Deo; Tymejczyk, Olga; Nash, Denis

### How to cite

KIMMEL, April D et al. Mathematical modelling to inform "treat all" implementation in sub-Saharan Africa: a scoping review. In: Journal of Virus Eradication, 2018, vol. 4, n° Suppl 2, p. 47–54.

This publication URL: <https://archive-ouverte.unige.ch/unige:115707>

# Mathematical modelling to inform ‘treat all’ implementation in sub-Saharan Africa: a scoping review

April D Kimmel<sup>1\*</sup>, Rose S Bono<sup>1</sup>, Olivia Keiser<sup>2</sup>, Jean D Sinayobye<sup>3</sup>, Janne Estill<sup>2,4</sup>, Deo Mujwara<sup>1</sup>, Olga Tymejczyk<sup>5,6</sup> and Denis Nash<sup>5,6</sup>

<sup>1</sup> Department of Health Behavior and Policy, Virginia Commonwealth University, Richmond VA, USA

<sup>2</sup> Institute of Global Health, University of Geneva, Switzerland

<sup>3</sup> Research and Clinical Education Division, Rwanda Military Hospital, Kigali, Rwanda

<sup>4</sup> Institute of Mathematical Statistics and Actuarial Science, University of Bern, Switzerland

<sup>5</sup> Institute for Implementation Science in Population Health, City University of New York, NY, USA

<sup>6</sup> School of Public Health, City University of New York, NY, USA

## Abstract

**Objective:** Despite widespread uptake, only half of sub-Saharan African countries have fully implemented the World Health Organization’s ‘treat all’ policy, hindering achievement of global HIV targets. We examined literature on mathematical modelling studies that sought to inform scale-up and implementation of ‘treat all’ in sub-Saharan Africa.

**Methods:** We conducted a scoping review, a research synthesis to assess emerging evidence and identify gaps, of peer-reviewed literature, extracting study characteristics on ‘treat all’ policies and assumptions, setting, key populations, outcomes and findings. Studies were narratively summarised and potential gaps characterised.

**Results:** We identified 16 studies examining ‘treat all’ alone ( $n=12$ ) or with expanded testing ( $n=7$ ) and/or care continuum improvements ( $n=6$ ). Twelve studies examined ‘treat all’ for Southern African countries, while none did so for Central Africa. Four included the role of resistance; one evaluated any key population. A range of health and economic outcomes were reported, although fewer studies formally assessed budget impact. Fourteen studies involved co-authors with any in-country affiliation; one study also had co-authors with local government affiliation. Overall, ‘treat all’ improves health outcomes and is cost-effective compared to deferred HIV treatment; ‘treat all’ with expanded testing or care continuum improvements may provide further health benefits. However, studies generally used optimistic assumptions about the implementation of expanded testing or care continuum improvements.

**Conclusions:** The modelling literature demonstrates improved health and economic benefits of ‘treat all’. Using mathematical modelling to inform real-world implementation of ‘treat all’ requires realistic assumptions about expanded testing and care continuum interventions across a wide range of settings and populations.

**Keywords:** HIV, mathematical modelling, treat all, sub-Saharan Africa

## Introduction

In September 2015, the World Health Organization recommended ART initiation for all people living with HIV (PLWH), regardless of CD4 cell count [1]. This ‘treat all’ policy is a cornerstone for achieving subsequent UNAIDS 90-90-90 targets [2], that is, 90% of PLWH aware of their status, 90% of individuals with known status receiving ART, and 90% of individuals receiving ART achieving viral suppression by 2020. This, together with evidence-based prevention efforts, can end the global HIV epidemic. In sub-Saharan Africa, where nearly 70% of PLWH world-wide reside [3], ‘treat all’ has been adopted formally in most countries [4].

However, approximately half of sub-Saharan African countries have had limited or delayed ‘treat all’ implementation [4]. Questions remain on local scale-up and potential challenges, such as late presentation to care [5] or health workforce constraints [6]. Consequently, the local health outcomes that can be achieved through ‘treat all’ – and the policy’s value and affordability for specific settings or populations – are uncertain.

Insights into the future outcomes of ‘treat all’ can be gained through mathematical modelling. Mathematical modelling offers a means to use existing evidence to make formal, timely policy evaluations. Model-based analyses allow synthesis of health and/

or economic data from multiple sources and permit decision-makers to extrapolate beyond evidence from a single clinical trial, target population, or geographical setting. They also offer a framework for managing uncertainty in the data informing the model and model assumptions, providing a plausible range of potential outcomes.

In 2009, a ground-breaking modelling analysis of ART scale-up in South Africa suggested that the transmission-prevention effects of ART, when implemented in the context of universal HIV testing and immediate ART, could nearly eliminate HIV transmission in a generalised epidemic [7]. While findings depended on optimistic policy scenarios (e.g. 100% annual uptake of voluntary HIV testing), this work ignited policy discussion on the recommendation and implementation of ‘treat all’ policies. The current study aims to summarise the breadth of the mathematical modelling literature seeking to inform ‘treat all’ scale-up, including implementation challenges, in sub-Saharan Africa.

## Methods

We conducted a scoping review of peer-reviewed literature using mathematical modelling to examine the scale-up, implementation challenges, and research gaps of ‘treat all’ in sub-Saharan Africa. Scoping reviews provide a broad overview of a particular field of study and identify gaps in knowledge [8,9]. After specifying search terms (Box 1), we identified candidate studies by searching PubMed/MEDLINE, by examining candidate article references, and through co-author recommendation [9]. One analyst identified studies in July/August 2017 and March 2018, and two

\*Corresponding author: April D Kimmel, 830 E Main Street, 9<sup>th</sup> floor, Richmond, VA 23298, USA  
Email: [adkimmel@vcu.edu](mailto:adkimmel@vcu.edu)

**Box 1.** Database search specifications

**PubMed/MEDLINE search term:**

("Africa"[Mesh] OR "low income countries" OR "middle income countries" OR "low and middle income countries" OR "sub-Saharan Africa" OR hyperendemic) AND (HIV OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency") AND ("test and start" OR "test and treat" OR universal OR "treat all" OR "early initiation" OR regardless OR "combination prevention" OR "multiple intervention\*" OR eligib\* OR threshold OR expand\* OR "fast-track" OR "treatment as prevention") AND (mathematic\* OR simulation OR dynamic\* OR compartment\* OR "agent-based" OR systems\* OR stochastic OR deterministic OR epidemic OR epidemiologic\* OR transmission OR cost\* OR model\* OR modeling OR modelling)

**Filters:**

English language; publication dates 01/01/2009 to 03/31/2018

analysts extracted data in March/April 2018; the first author reviewed a sub-sample of studies to ensure accuracy in study identification and data extraction.

This review defines 'treat all' as provision of ART immediately after HIV diagnosis, regardless of CD4 cell count. 'Treat all with expanded testing' is defined as provision of ART immediately after HIV diagnosis, regardless of CD4 cell count, with additional efforts to diagnose HIV cases. We considered 'treat all with care continuum improvements' as immediate ART, regardless of CD4 cell count, with additional efforts to improve care continuum outcomes (e.g. improvements in linkage, retention or adherence), with or without expanded HIV testing. We defined these terms, since the literature uses terms such as 'treat all', 'test-and-treat', and 'universal treatment' inconsistently.

Included studies met all of the following pre-specified criteria: use of a mathematical model to project outcomes over time; assessment of any 'treat all' policy; a study objective to examine 'treat all' scale-up or implementation; study population including, but not limited to, adults; sub-Saharan African setting; and published in English by 31 March 2018. We excluded studies examining 'treat all' primarily as a strategy to prevent HIV transmission (alone or in combination with other prevention interventions), since they do not directly address 'treat all' implementation challenges, the focus of the current study. We excluded studies assessing 'treat all' as a component of other infectious disease control strategies, studies examining 'treat all' in the context of clinical trial design or mathematical modelling methods assessment, and studies that did not model a 'treat all' policy for a specific country or countries, although we assigned a country if one was not specified and most data came from a particular locale. No restrictions were made based on type of mathematical model, 'treat all' policy or policies evaluated, outcomes examined, or specific key populations modelled or assessed.

Data were extracted on: 'treat all' policies assessed and their definitions, assessment of implementation challenges and constraints, policy assumptions (e.g. HIV testing frequency and coverage), other model assumptions, country, region within sub-Saharan Africa [10], and health and/or economic outcomes assessed. We also extracted data on gender and key population(s), which we defined broadly as any vulnerable, under-served, or hard-to-reach population (e.g. female sex workers). We examined involvement of local stakeholders, reporting the number of studies with a co-author having any documented affiliation in the country for which a 'treat all' policy was assessed and the number with a co-author having any local government affiliation, including Ministry of Health. Finally, we extracted data on model type,

level (e.g. individual, population), inclusion of transmission dynamics, reduced infectivity due to ART, model structural decisions (e.g. age- and/or sex-stratification), and evidence of uncertainty analysis and model performance assessment.

We identified commonalities among studies, summarised commonalities using narrative synthesis, and highlighted potential knowledge gaps to articulate research priorities.

## Results

### Study characteristics

Sixteen studies met eligibility criteria [11–26] (Figure 1). Fifteen were identified using the database search [11,12,14–26] and one through co-author recommendation [13]. Of the 16 studies, seven have been published since 2015 [12,19,20,22–24,26]. Table 1 shows key study characteristics.

We found wide variation in how 'treat all' implementation was evaluated. 'Treat all' alone was considered in 12 studies [11,12,15–17,19–24,26]. 'Treat all with expanded testing' only was examined in seven studies [13,14,18,19,22,24,25], while 'treat all with care continuum improvements' was assessed in six [14,16,17,22,24,26].

Across the seven studies examining 'treat all with expanded testing', testing coverage for the general adult population was assumed to be 90% [18,19] or 100% [25] annually, with two studies assuming 90% testing coverage less frequently at every 2 [14] or 4 years [24], another assuming lower testing coverage at 20% and 50% annually [13], and one assuming testing rates were doubled [22].

Studies modelling 'treat all with care continuum improvements' did so individually and in combination. Examples included: increasing rates of linkage to care [17]; improving rates of linkage to care and ART re-initiation, while reducing drop-out rates [22]; and improving rates of linkage, re-entry into pre-ART care, and retention on ART, as well as use of point-of-care CD4 testing (routinely and during testing) [24]. Rate adjustments assessed at all steps along the care continuum largely did not appear to be based on empirical estimates from the literature; rather, rates were increased or decreased by a multiplier, e.g. linkage rates doubled or dropout halved.

Few studies examined 'treat all' implementation challenges, such as late diagnosis [13,17,24,26] and/or delayed ART initiation [23,26], although two considered 'treat all' with explicit resource constraints, resulting in limited treatment slots [19,26]. Additional policy responses – such as task-shifting or international competition to lower drug prices [23], or no availability of more costly viral load monitoring or second-line ART [26] – were also assessed when resources are constrained.

'Treat all' implementation was assessed for multiple countries (Figure 2), with most studies reporting outcomes for the overall population in a given setting. Three of four sub-Saharan African regions were represented; 12 studies assessed 'treat all' in Southern Africa [12–14,16–21,23,25,26], six in East Africa [12,15,19,20,22,24], four in West Africa [11,12,19,26] and none in Central Africa. Twelve studies either examined 'treat all' in the context of South Africa or used primarily South African data [12,13,17–21,23,25,26]. 'Treat all' was not assessed sub-nationally in any study. While many models are age- and/or sex-structured, no studies reported outcomes separately by age group (e.g. adolescents) and only one study reported outcomes separately by sex [13]. Similarly, while some studies explicitly incorporated key populations in the model structure, no studies

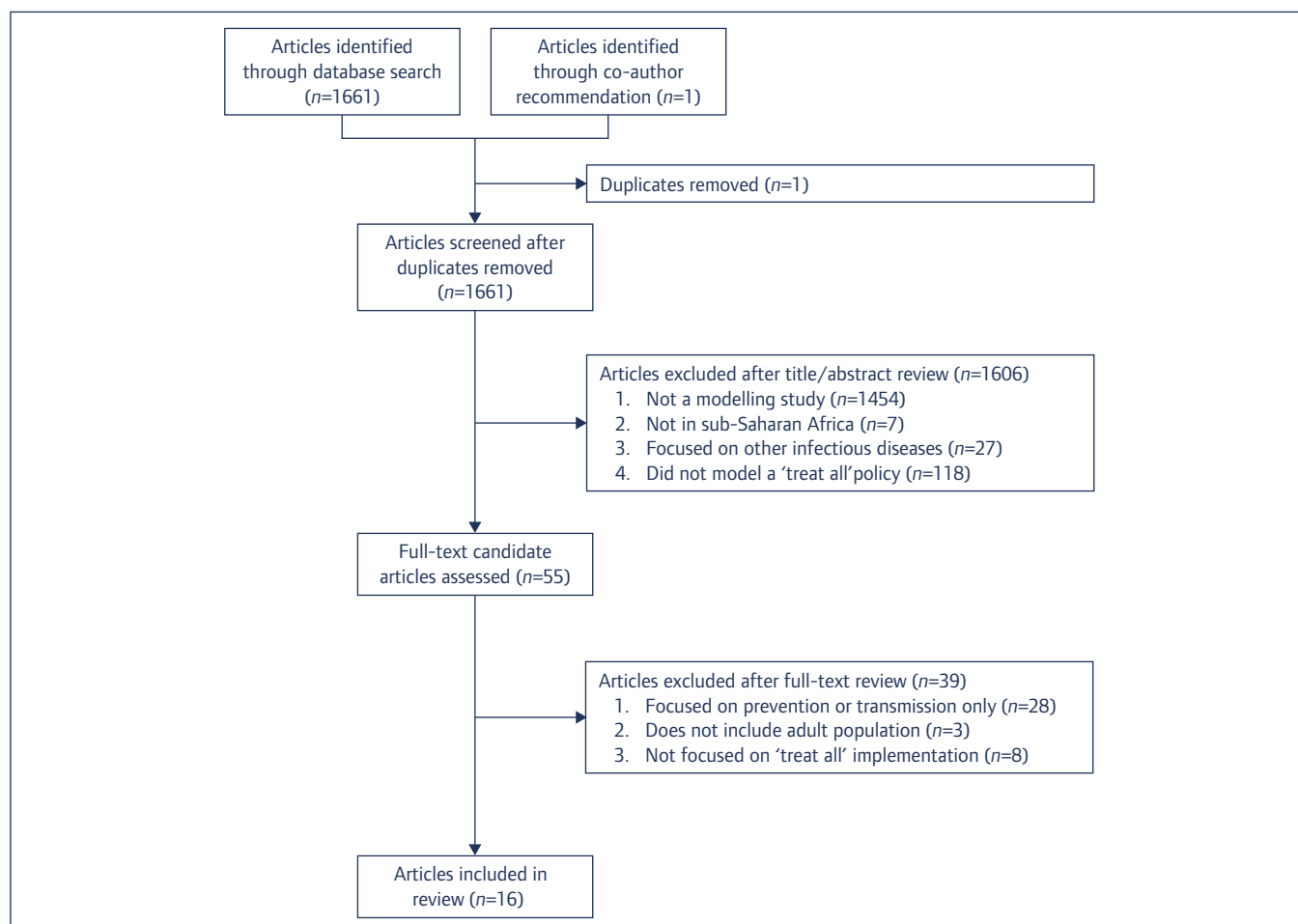


Figure 1. Flowchart for study identification.

examined 'treat all' implementation and outcomes specifically in key populations, although one study examined outcomes for individuals with HIV and hepatitis C and/or B co-infection [21].

Across studies, four reported only health outcomes, one reported only economic outcomes, and 11 reported both. For the 15 studies reporting health outcomes, types of health outcomes included: intermediate health outcomes (e.g. change in CD4 cell count), treatment-related outcomes (e.g. ART coverage) and long-term health outcomes (e.g. number of deaths, life expectancy). Three studies reported modelling of increasing resistance [15,16,25], and one both modelled and reported accumulation of drug resistance and its impact on first- and second-line ART outcomes [16]. Twelve studies reported on any HIV transmission-related outcome (e.g. prevalence [14,18], incidence or new infections [13–20,22,24–26]), although transmission-related outcomes were not the focus of this review.

Among the 12 studies reporting economic outcomes, the type of economic outcome reported also varied. These included: total or cumulative costs, cost-effectiveness (e.g. cost per disability-adjusted life year [DALY] averted), net monetary benefit, optimal set of health interventions under a budget constraint, and other economic outcomes related to affordability (e.g. financing or investment needs). Among studies reporting economic outcomes, cost-effectiveness was most frequently represented; few studies formally examined budget impact.

Studies used a variety of model structures, including single-cohort state-transition models, single- and multi-cohort individual-level microsimulations, and population-level dynamic compartmental models. Fifteen studies modelled HIV transmission and accounted

for reduced infectivity due to ART. Analytic time horizons varied from 5 years to lifetime, although were most commonly 20–40 years. Eleven studies reported any uncertainty analysis, while 10 reported any model performance assessment.

Fourteen studies included co-authors with any in-country affiliation. All 14 studies had authors affiliated with universities or research units [11–20,22–24,26]; one of these studies also had a co-author with local government affiliation [23].

## Synthesis of findings

### Health outcomes

Studies found that implementation of 'treat all' increases life expectancy [14,15,21] and saves lives [13,14,19,21,26] versus deferred ART initiation. There appeared to be consensus that 'treat all with expanded testing' or 'care continuum improvements' – in particular earlier diagnosis and/or linkage to care – further improves health outcomes compared to 'treat all' alone. However, there was little consistency in the composition of additional interventions, and their levels, that are required for successful 'treat all' implementation and achievement of national or global targets. For example, Bacaër *et al.* found that while 'treat all with expanded testing' saves lives and averts new HIV infections compared to ART initiation at a CD4 cell count of <200 cells/mm<sup>3</sup>, annual testing may not be necessary to end the South African HIV epidemic [13]. However, Olney *et al.* asserted that combining 'treat all' with multiple other strategies that improve linkage, utilise point-of-care CD4 cell count testing including upon diagnosis, and improve pre-ART retention, will avert more DALYs than 'treat all with expanded testing' only [24].

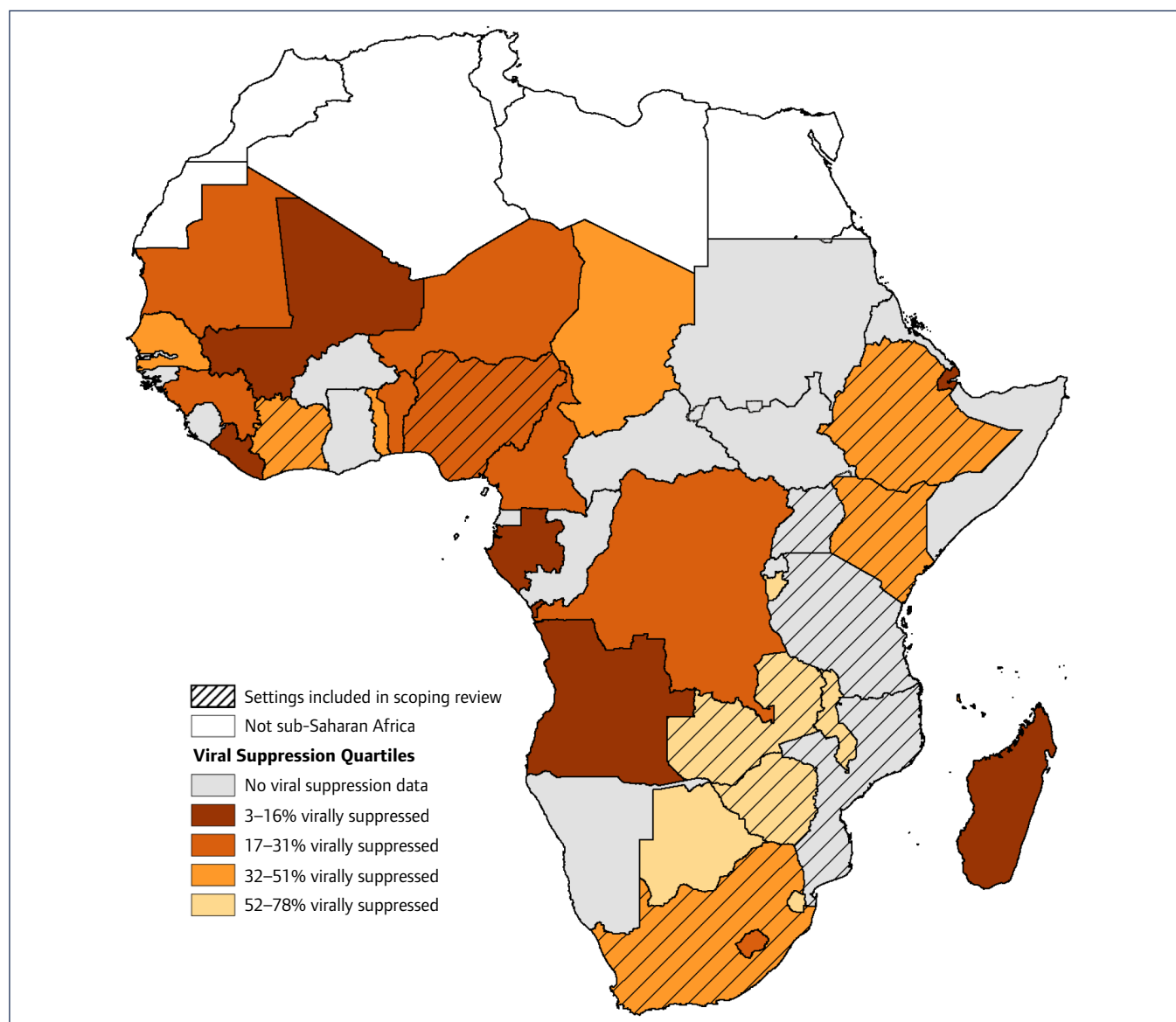
**Table 1.** Key characteristics of ‘treat all’ studies meeting eligibility criteria\*

Author [Ref]	Setting	‘Treat all’ policy			‘Treat all’ policy definitions	Key population(s)†		Outcomes	
		TA	TA+ET	TA+CC		Model structure	Policy assessment	Health	Economic
Anglaret [11]	Côte d’Ivoire	Yes	–	–	–	–	–	CD4 cell count change; cumulative risk of other diseases; mortality	–
Atun [12]	Ethiopia, Kenya, Malawi, Nigeria, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	Yes	–	–	–	FSW, MSM, PWID	–	–	Total annual costs; present value of future public financing needs 2015; debt-to-GDP ratios
Bacaër [13]	South Africa	–	Yes	–	20% or 50% of population tested annually	–	–	New infections averted; lives saved; person-years on ART	–
Bendavid [14]	South Africa	–	Yes	Yes	90% of population tested every 2 years; 67% or 100% of diagnosed linked to care; 80% or 100% retained in care	–	–	LMs gained; number and rates of death; new infections; prevalence; population growth	–
Braithwaite [15]	Kenya, Uganda	Yes	–	–	–	FSW	–	Total discounted LYs and QALYs; AIDS deaths; new infections	Total discounted cost; per-person annual costs; incremental cost per QALY gained
Cambiano [16]	South Africa	Yes	–	Yes	80% of ART-eligible in care; 92% retained in care 1 year after ART initiation	–	–	Number on/off ART, by regimen; incidence; number and % with NNRTI-resistant virus; % with transmitted drug resistance	–
Eaton [17]	South Africa, Zambia	Yes	–	Yes	Increased HIV testing and linkage so that 80% of ART-eligible in care	–	–	Annual incidence per 100 PYs; % new infections averted	Total incremental costs; incremental cost per DALY averted
Granich [18]	South Africa	–	Yes	–	90% of adults tested annually	–	–	Number (%) on ART; PYs on ART; deaths; DALYs; new infections; prevalence	Total costs; cost savings; incremental cost per DALY averted
Hontelez [19]	Ethiopia, Kenya, Malawi, Mozambique, Nigeria, South Africa, Tanzania, Uganda, Zambia and Zimbabwe	Yes	Yes	–	90% of adults tested annually	–	–	Number with HIV; new infections; number on ART; LYs saved	Annual investment needs; cost per LY saved
Kuznik [20]	Nigeria, South Africa, Uganda	Yes	–	–	–	–	–	Threshold for relative risk reduction in HIV transmissions; DALYs averted per patient	Cost per patient; incremental cost per DALY averted
Martin [21]	South Africa	Yes	–	–	–	HBV- or HCV-co-infected	HBV- or HCV-co-infected	PYs on ART; life expectancy; discounted DALYs averted; HIV or hepatitis deaths; HIV, vertical hepatitis B/C transmissions	–
McCreesh [22]	Uganda	Yes	Yes	Yes	HIV testing rates doubled; drop-out rates halved; ART restart rates doubled; linkage doubled	–	–	DALYs averted; HIV incidence	Incremental cost per DALY averted; net monetary benefit
Meyer-Rath [23]	South Africa	Yes	–	–	–	Children <13 years	–	Number initiating ART; number on ART	Total cost
Olney [24]	Kenya	Yes	Yes	Yes	90% testing coverage every 4 years; 30% linked if not previously diagnosed/40% linked if previously diagnosed	–	–	DALYs averted; % deaths averted	Total incremental costs; incremental cost per DALY averted; strategies maximising health gains given a budget constraint
Wagner [25]	South Africa	–	Yes	–	100% of adults tested every 6 months to 4 years	–	–	Testing and treatment needed to eliminate transmission; number on ART; number in need of ART, by regimen; reductions in incidence; new infections averted	Annual and cumulative treatment costs
Walensky [26]	Côte d’Ivoire, South Africa	Yes	–	Yes	Initial mean CD4 cell count 160–199 cells/mm <sup>3</sup> ; 92% retained in care at 1 year and 70% at 5 years	–	–	HIV transmission; deaths; years of life lost	Total costs; budget savings

Abbreviations: ART: antiretroviral therapy; DALY: disability-adjusted life-year; FSW: female sex worker; HBV: hepatitis B virus; HCV: hepatitis C virus; MSM: men who have sex with men; PWID: people who inject drugs; TA: ‘treat all’ alone; TA+ET: ‘treat all with expanded HIV testing’; TA+CC: ‘treat all with care continuum improvements’; PY: person-year; QALY: quality-adjusted life-year.

\* Entries of ‘–’ indicate that no information was reported on a given study characteristic.

† Key population was defined broadly as any vulnerable, underserved or hard-to-reach population.



**Figure 2.** Geographical settings represented in eligible studies, by viral suppression quintile. This figure shows the geographical settings represented in ‘treat all’ studies meeting eligibility criteria, by country-level viral suppression quintile (<http://aidsinfo.unaids.org>). Hatch marks indicate a country for which a ‘treat all’ implementation study was identified. We consider the settings represented in the context of viral suppression achievement, with lower levels of viral suppression shown in darker shades of brown and higher levels of viral suppression shown in lighter shades of brown. Overall, countries in Central and West Africa are under-represented among studies evaluating ‘treat all’ implementation. Using national viral load suppression rates as an indicator, countries in Central and West Africa are among the countries in greatest need of evaluation of ‘treat all’ and related policies (UNAIDS AIDSinfo database [27]).

Studies highlighted circumstances under which ‘treat all’ policies may result in suboptimal or unintended outcomes. For example, Anglaret and colleagues found that compared to deferred ART initiation at a CD4 cell count of 350 cells/mm<sup>3</sup>, ‘treat all’ improves survival, but this finding may not hold if on-ART retention and treatment adherence is low [11]. Wagner and Blower further suggested that ‘treat all with expanded testing’ may increase drug resistance, increasing the need for more costly second-line ART regimens, compared to universal access to treatment for those meeting lower CD4 cell count eligibility thresholds [25]. Projections from Cambiano *et al.* concurred, indicating that ‘treat all’ with expansions in diagnosis and retention would increase the number of PLWH with non-nucleoside reverse-transcriptase inhibitor drug resistance by approximately 25% compared to ‘treat all’ without such improvements [16].

#### Economic outcomes

Studies suggested that ‘treat all’, with or without expanded testing, increases per-person costs compared to deferred ART initiation [12,13,15,25,26], is cost-effective at conventional thresholds

[17–20,22,24], and may decrease annual population-level economic costs in the longer term [18,23]. These findings were consistent across studies, which relied on different model structures but which all appeared to incorporate assumptions regarding reduced infectivity due to HIV viral suppression while on ART. In optimal conditions – such as high ART adherence and no costs associated with HIV counselling and testing – ‘treat all’ may have lifetime individual cost savings, assuming an annual discount rate of 3% [20]. Under similarly optimistic assumptions of annual HIV counselling and testing at 90% coverage, Granich and colleagues found that the upfront societal investment of expanding ART to all HIV-infected individuals is offset by cost savings of prevented HIV infections in 10 years or more when costs are discounted at 3% annually [18]. Atun *et al.* further found that upfront investments in ART will reduce costs in the long term, from \$5 billion annually in 2015 to \$1.8 billion by 2050 [12], when using annual discount rates of 3%.

Multiple studies indicated that simultaneous implementation of improvements along the care continuum may be necessary to efficiently employ limited resources. For example, while Eaton



and colleagues found that ‘treat all with care continuum improvements’ is cost-effective over 20 years [17], the priority with which ‘treat all’ should be implemented changes depending on current ART coverage. That is, in settings with lower ART coverage, efficiency gains are greater when expanding HIV testing and linkage to care and maintaining a deferred, CD4 cell count threshold-based ART initiation policy; in settings with higher ART coverage, expanding ART eligibility is more efficient [17]. Similarly, Olney *et al.* suggested that a combination of care continuum improvements, but without expanded HIV testing, averts more DALYs for the same cost than ‘treat all with expanded testing’ only [24].

Emerging work examined ‘treat all’ in the context of affordability or explicit budgetary and health system constraints. Atun and colleagues suggested the resources required to scale up HIV services, including ‘treat all’, in sub-Saharan Africa cannot be met with domestic financing alone [12]. Hontelez *et al.* modelled ‘treat all’ under different scale-up scenarios, including constraints on the number of individuals able to receive ART, and found that while ‘treat all’ is cost-effective compared to ART initiation at CD4 cell count <500 cells/mm<sup>3</sup> under most scenarios, extreme supply-side constraints could result in a net health loss if healthier individuals crowd out less healthy individuals [19], assuming no policy that prioritises treatment for those with more advanced disease. Meyer-Rath and colleagues suggested that increases in costs under ‘treat all’ can be offset under different health system constraints, such as allowing for task-shifting and international competition for drug pricing [23]. Finally, Walensky *et al.* found that in South Africa and Côte d’Ivoire, CD4 cell count-based treatment eligibility criteria instead of a ‘treat all’ policy, which could occur with potential cutbacks in foreign aid, saves approximately \$60 million across both countries over 10 years, but substantially increases HIV transmissions and deaths [26].

## Discussion

A growing mathematical modelling literature from sub-Saharan Africa finds that the implementation of ‘treat all’ improves both individual- and population-level health, is cost-effective, and can reduce long-term population-level costs compared to deferred treatment initiation. While the knowledge base is strongest for ‘treat all’ alone, expanded HIV testing and other improvements along the HIV care continuum are likely required to achieve the full health and economic benefits of ‘treat all’.

The gaps in this literature highlight opportunities to gain further insights into the effective and efficient implementation of ‘treat all’ (Table 2). Despite broad consensus that earlier diagnosis and linkage improve individual and population health [7,28,29], we found little agreement on additional intervention composition or levels, which in many cases were defined optimistically, sometimes with unrealistically frequent testing, high coverage, high levels of retention and rapid ART initiation. Importantly, UNAIDS 90-90-90 targets do not directly address timely diagnosis and/or subsequent ART initiation, which ultimately reduce the time to viral suppression, driving reduced morbidity, mortality and onward transmission. Assumptions in the studies reviewed here largely did not reflect the realities of advanced disease stage at enrolment or the fact that previous ART eligibility expansions, despite resulting in significant increases in timely ART initiation at the original site of enrolment, generally did not achieve full uptake among eligible patients [30]. Similarly, few studies quantified unintended consequences and real-world challenges of ‘treat all’, including development of resistance [31], supply chain challenges [32], the unlikely possibility for crowd-out [30,33], and health system and other resource constraints [34,35]. Modelling studies

**Table 2.** Key gaps in the mathematical modelling literature seeking to inform scale-up and implementation of ‘treat all’ in sub-Saharan Africa

- Limited incorporation of unintended consequences and real-world challenges of ‘treat all’, such as late diagnosis, late ART initiation, resource constraints, development of drug resistance, and supply chain disruptions
- Inadequate use of realistic assumptions for interventions along the care continuum, such as HIV testing coverage and frequency, that are necessary in addition to ‘treat all’ to achieve 90-90-90 targets
- Lack of assessment of the role of timely diagnosis and/or timely ART initiation in not only achieving 90-90-90 targets, but accelerating the time to viral suppression and reducing morbidity, mortality and onward transmission
- Little to no examination of ‘treat all’ in Central, East, and West Africa
- Nearly absent assessment of ‘treat all’ implementation for men versus women, different age groups, and hard-to-reach or key populations
- No sub-national examination of tailored interventions for implementing ‘treat all’
- Limited involvement of Ministry of Health, other government officials or additional key in-country stakeholders, beyond academia

from South Africa have addressed these issues most comprehensively, although not routinely and rarely in combination. The contextual relevance of future modelling studies would benefit from collaborative involvement not only by in-country researchers, who are largely represented in these studies, but also by local government officials (e.g. Ministry of Health) and other stakeholders who do not regularly conduct research.

Also notable are the settings and populations that remain unaddressed. A minority of studies assessed ‘treat all’ implementation for East and West Africa and none in Central Africa. Despite relatively low HIV prevalence in West and Central Africa, fewer than half of PLWH in these regions know their status, resulting in rates of ART coverage, retention and viral suppression (see Figure 2) that are among the lowest, and AIDS-related deaths among the highest, globally [36]. A greater absence in this literature is seen in assessment of ‘treat all’ by gender, age group and hard-to-reach populations – a concerning finding given that barriers to achieving UNAIDS targets are among the highest for men, adolescents and young adults, and key populations that may require differentiated care [36]. Finally, we found no sub-national ‘treat all’ assessments, which may require tailored interventions and greater country-level coordination [36].

This work complements two previous reviews. Ying *et al.* reviewed how principles of implementation science can be integrated into mathematical models of HIV prevention to improve universal access to ART [37], while Mikkelsen *et al.* called for inclusion of health-system constraints in cost-effectiveness analyses on ART scale-up [38]. While our review differs in its focus on modelling of ‘treat all’ implementation, findings are similar: to develop a more nuanced understanding of ‘treat all’ implementation, inclusion of real-world challenges and constraints is warranted but as yet unaddressed in the current modelling literature.

This review also complements a rich literature on modelling studies focusing on the transmission effects of ‘treat all’ or that include ‘treat all’ in prevention packages. The projected transmission effects of ‘treat all’ have been well studied, with a systematic comparison of 12 independent mathematical models finding that ART can reduce new infections when access and adherence are

high, although longer-term projected outcomes and the efficiency with which ART reduces new infections varies [39]. This comparison adds to empirical evidence from a systematic review finding that ART reduces HIV transmission risk in sero-discordant couples [40]. Similar to our study, this literature confirms that improvements along the care continuum, and specific interventions and implementation strategies that could bring such improvements, are required to achieve the optimal health outcomes and full preventive benefits of ART [39,41]. Results corroborate findings from recent randomised trials: in eSwatini, ‘treat all’ implementation dramatically increased viral suppression [42], a necessary precursor for ART to reduce transmissions, but in South Africa, a test-and-treat intervention did not reduce HIV incidence, probably because early diagnosis, linkage to care, and CD4 cell count at ART initiation were sub-optimal [43]. Myriad other modelling work from sub-Saharan Africa has examined the role of ‘treat all’ in combined prevention packages, alongside interventions like pre-exposure prophylaxis and condom distribution [44–49].

## Limitations

First, we searched a single database and only reviewed articles in English. Second, we found substantial heterogeneity in the terms used to refer to ‘treat all’ policies, and despite refining our search strategy iteratively to include new terms [8,9], we may not have captured all relevant studies. Third, by excluding studies primarily examining transmission benefits of ‘treat all’, we cannot draw conclusions about the impact of ‘treat all’ on HIV transmission. However, a systematic comparison of 12 independent mathematical models finds that ART reduces new infections, assuming high antiretroviral access and adherence [40]. In this review, we expand on this comparison to understand how mathematical modelling studies have sought to address real-world challenges and constraints across settings and populations in order to scale-up and fully implement ‘treat all’. Fourth, projected outcomes were difficult to compare across studies, given varying model structures, assumptions and timeframes, as well as differing approaches and reporting regarding model performance. Finally, we did not include non-peer-reviewed grey literature.

## Conclusions

Mathematical modelling studies can inform the scale-up and implementation of ‘treat all’ policies. While studies have confirmed that ‘treat all’ improves health and is cost-effective, questions surrounding ‘treat all’ implementation remain. Useful analyses will require realistic assumptions and more complete integration of health consequences and constraints, including real-world budgets. Development of country-specific models that address ‘treat all’ implementation sub-nationally and among different sub-populations is critical to ongoing policy assessment and achievement of global targets.

## Acknowledgements

This research was supported in part by the National Institutes of Health (award numbers U01AI096299 and R13AI134393) and a professorship grant from the Swiss National Science Foundation (award number 163878). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

## References

- World Health Organization. *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. Switzerland: September 2015. Available at: <http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/> (accessed July 2017).
- UNAIDS. 90-90-90: *An ambitious treatment target to help end the AIDS epidemic*. Geneva: Joint United Nations Programme on HIV/AIDS; 2017. Available at: [www.unaids.org/en/resources/documents/2017/90-90-90](http://www.unaids.org/en/resources/documents/2017/90-90-90) (accessed April 2018).
- UNAIDS. *Fact Sheet - World AIDS Day 2017*. Geneva: UNAIDS; 2017. Available at: [www.unaids.org/sites/default/files/media\\_asset/UNAIDS\\_FactSheet\\_en.pdf](http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf) (accessed April 2018).
- World Health Organization. *Treat all: policy adoption and implementation status in countries*. Geneva: World Health Organization; November 2017. Available at: <http://apps.who.int/iris/bitstream/handle/10665/259532/WHO-HIV-2017.58-eng.pdf?sequence=1> (accessed April 2018).
- Hoffman S, Wu Y, Lahuerta M *et al*. Advanced disease at enrollment in HIV care in four sub-Saharan African countries: change from 2006 to 2011 and multilevel predictors in 2011. *AIDS* 2014; **28**: 2429–2438.
- Rasschaert F, Philips M, Van Leemput L *et al*. Tackling health workforce shortages during antiretroviral treatment scale-up – experiences from Ethiopia and Malawi. *J Acquir Immune Defic Syndr* 2011; **57 Suppl 2**: S109–112.
- Granich RM, Gilks CF, Dye C *et al*. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373**: 48–57.
- Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Social Res Methodol* 2005; **8**: 19–32.
- Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010; **5**: 69.
- United Nations Statistics Division. *Standard country or area codes for statistical use*. Available at: <https://unstats.un.org/unsd/methodology/m49/> (accessed May 2018).
- Anglaret X, Scott CA, Walensky RP *et al*. Could early antiretroviral therapy entail more risks than benefits in sub-Saharan African HIV-infected adults? A model-based analysis. *Antivir Ther* 2013; **18**: 45–55.
- Atun R, Chang AY, Ogbuoi O *et al*. Long-term financing needs for HIV control in sub-Saharan Africa in 2015–2050: a modelling study. *BMJ Open* 2016; **6**: e009656.
- Bacaer N, Pretorius C, Auvert B. An age-structured model for the potential impact of generalized access to antiretrovirals on the South African HIV epidemic. *Bull Math Biol* 2010; **72**: 2180–2198.
- Bendauid E, Brandeau ML, Wood R, Owens DK. Comparative effectiveness of HIV testing and treatment in highly endemic regions. *Arch Intern Med* 2010; **170**: 1347–1354.
- Braithwaite SR, Nucifora KA, Toohey C *et al*. How do different eligibility guidelines for antiretroviral therapy affect the cost-effectiveness of routine viral load testing in sub-Saharan Africa? *AIDS* 2014; **28 Suppl 1**: S73–83.
- Cambiano V, Bertagnolio S, Jordan MR *et al*. Predicted levels of HIV drug resistance: potential impact of expanding diagnosis, retention, and eligibility criteria for antiretroviral therapy initiation. *AIDS* 2014; **28 Suppl 1**: S15–23.
- Eaton JW, Menzies NA, Stover J *et al*. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. *Lancet Glob Health* 2014; **2**: 23–34.
- Granich R, Kahn JG, Bennett R *et al*. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011–2050. *PLoS One* 2012; **7**: e30216.
- Hontelez JA, Chang AY, Ogbuoi O *et al*. Changing HIV treatment eligibility under health system constraints in sub-Saharan Africa: investment needs, population health gains, and cost-effectiveness. *AIDS* 2016; **30**: 2341–2350.
- Kuznik A, Ilyasu G, Habib AG *et al*. Initiation of antiretroviral therapy based on the 2015 WHO guidelines. *AIDS* 2016; **30**: 2865–2873.
- Martin NK, Devine A, Eaton JW *et al*. Modeling the impact of early antiretroviral therapy for adults coinfected with HIV and hepatitis B or C in South Africa. *AIDS* 2014; **28 Suppl 1**: S35–46.
- McCreesh N, Andrianakis I, Nsubuga RN *et al*. Universal test, treat, and keep: improving ART retention is key in cost-effective HIV control in Uganda. *BMC Infect Dis* 2017; **17**: 322.
- Meyer-Rath G, Johnson LF, Pillay Y *et al*. Changing the South African national antiretroviral therapy guidelines: the role of cost modelling. *PLoS One* 2017; **12**: e0186557.
- Olney JJ, Braitstein P, Eaton JW *et al*. Evaluating strategies to improve HIV care outcomes in Kenya: a modelling study. *Lancet HIV* 2016; **3**: e592–e600.
- Wagner BG, Blower S. Universal access to HIV treatment versus universal ‘test and treat’: transmission, drug resistance & treatment costs. *PLoS One* 2012; **7**: e41212.
- Walensky RP, Borre ED, Bekker L *et al*. Do less harm: evaluating HIV programmatic alternatives in response to cutbacks in foreign aid. *Ann Intern Med* 2017; **167**: 618–629.
- UNAIDS. *AIDSinfo database*. 2018; **167**: 618–629.
- Cohen MS, Chen YQ, McCauley M *et al*. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365**: 493–505.
- The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795–807.
- Tymeczyk O, Brazier E, Yiannoutsos C *et al*. HIV treatment eligibility expansion and timely antiretroviral treatment initiation following enrollment in HIV care: a meta-regression analysis of programmatic data from 22 countries. *PLoS Med* 2018; **15**: e1002534.
- World Health Organization. *HIV drug resistance report 2017*. 2017. Available at: [www.who.int/hiv/pub/drugresistance/hivdr-report-2017/en](http://www.who.int/hiv/pub/drugresistance/hivdr-report-2017/en) (accessed May 2018).
- Jamieson D, Kellerman SE. The 90-90-90 strategy to end the HIV pandemic by 2030: can the supply chain handle it? *J Int AIDS Soc* 2016; **19**: 20917.
- Kluberger SA, Fox MP, LaValley M *et al*. Do ART eligibility expansions crowd out the sickest? Evidence from South Africa. *Conference on Retroviruses and Opportunistic Infections*. February 2016. Boston, MA, USA. Abstract 1012.
- Stop Stockouts. *SSP Stockouts National Survey*. 2016. Available at: [www.groundup.org.za/media/uploads/documents/StopStockoutsSurvey2016.pdf](http://www.groundup.org.za/media/uploads/documents/StopStockoutsSurvey2016.pdf) (accessed May 2018).
- Shubber Z, Mills EJ, Nachega JB *et al*. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. *PLoS Med* 2016; **13**: e1002183.



36. UNAIDS. *Ending AIDS: Progress Towards the 90–90–90 Targets*. 2017. Available at: [www.unaids.org/sites/default/files/media\\_asset/Global\\_AIDS\\_update\\_2017\\_en.pdf](http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf) (accessed May 2018).
37. Ying R, Barnabas RV, Williams BG. Modeling the implementation of universal coverage for HIV treatment as prevention and its impact on the HIV epidemic. *Curr HIV/AIDS Rep* 2014; **11**: 459–467.
38. Mikkelsen E, Hontelez JA, Jansen MP *et al*. Evidence for scaling up HIV treatment in sub-Saharan Africa: a call for incorporating health system constraints. *PLoS Med* 2017; **14**: e1002240.
39. Eaton JW, Johnson LF, Salomon JA *et al*. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med* 2012; **9**: e1001245.
40. Anglemyer A, Rutherford GW, Horvath T *et al*. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Database Syst Rev* 2013; Cd009153.
41. McCreesh N, Andrianakis I, Nsubuga RN *et al*. Improving ART programme retention and viral suppression are key to maximising impact of treatment as prevention – a modelling study. *BMC Infect Dis* 2017; **17**: 557.
42. Khan S, Spiegelman D, Walsh F *et al*. Universal test and treat (UTT) versus standard of care for access to antiretroviral therapy in HIV clients: the MaxART stepped-wedge randomized controlled health systems trial in Swaziland. *22nd International AIDS Conference*. July 2018. Amsterdam, the Netherlands. Abstract WEAX0102LB.
43. Iwuji CC, Orne-Gliemann J, Larmarange J *et al*. Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial. *Lancet HIV* 2018; **5**: e116–e125.
44. Abuelezam NN, McCormick AW, Fussell T *et al*. Can the heterosexual HIV epidemic be eliminated in South Africa using combination prevention? A modeling analysis. *Am J Epidemiol* 2016; **184**: 239–248.
45. Alsallaq RA, Buttolph J, Cleland CM *et al*. The potential impact and cost of focusing HIV prevention on young women and men: a modeling analysis in western Kenya. *PLoS One* 2017; **12**: e0175447.
46. Blaizot S, Maman D, Riche B *et al*. Potential impact of multiple interventions on HIV incidence in a hyperendemic region in western Kenya: a modelling study. *BMC Infect Dis* 2016; **16**: 189.
47. Cremin I, Alsallaq R, Dybul M *et al*. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. *AIDS* 2013; **27**: 447–458.
48. Stover J, Bollinger L, Izazola JA *et al*. What Is required to end the AIDS epidemic as a public health threat by 2030? The cost and impact of the fast-track approach. *PLoS One* 2016; **11**.
49. McGillen JB, Anderson SJ, Hallett TB. PrEP as a feature in the optimal landscape of combination HIV prevention in sub-Saharan Africa. *J Int AIDS Soc* 2016; **19**: 21104.