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Systematic review and meta-analysis: Patient and programme impact of fixed-dose combination antiretroviral therapy

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Abstract

OBJECTIVES To compare the advantages to patients and to programmes between fixed-dose combination (FDC) antiretroviral therapy and separate tablet regimens.

METHODS Three electronic databases and two conference abstract sites were searched from inception to 01 March 2013 without geographical, language or date limits. Studies were included if they reported data on clinical outcomes, patient-reported outcomes and programme-related outcomes that could be related to pill burden for adult and adolescent patients on ART. For the primary outcomes of adherence and virological suppression, relative risks and 95% confidence intervals were calculated, and these were pooled using random effects meta-analysis.

RESULTS Twenty-one studies including information on 27 230 subjects were reviewed. Data from randomised trials showed better adherence among patients receiving FDCs than among patients who did not (relative risk 1.10, 95%CI 0.98–1.22); these findings were consistent with data from observational cohorts (RR 1.17, 95% CI 1.07–1.28). There was also a tendency towards greater virological suppression among patients receiving FDCs in randomised trials (RR 1.04, 95%CI 0.99–1.10) and observational cohort studies (RR 1.07, 95% CI 0.97–1.18). In all studies reporting patient preference, FDCs were preferred. The overall quality of the evidence was rated as low.

CONCLUSIONS Fixed-dose combinations appear to offer multiple advantages for programmes and patients, particularly with respect to treatment adherence.

keywords adherence, antiretrovirals, fixed-dose combinations, virological suppression

Introduction

Successful antiretroviral therapy (ART) depends critically on adherence, and suboptimal adherence is the most common reason why the benefits of ART are not sustained (Wood *et al.* 2003; Kalichman *et al.* 2010). Among numerous solutions proposed to improve adherence to ART, fixed-dose combination (FDC) therapy, which combines two or more active drugs in a single pill, is a favoured approach. The first FDC to be marketed as part of anti-HIV therapy was the combination of zidovudine and lamivudine, as both compounds were produced by the same company. Triple-combination FDCs as single tablets became the standard of care in resource-limited settings from early 2000, as the combination of three generic antiretrovirals – stavudine, lamivudine and nevirapine. The subsequent development of other, potentially useful, FDCs has been conditioned by the extent to which different patent holders are willing to work together and produce combination therapy.

The use of FDCs in HIV therapy has been suggested to provide benefits to both patients and programmes. Patients have reported improved adherence and quality of life (Mosen *et al.* 2010; Sterrantino *et al.* 2012), and programmes can benefit through simplified supply chain and prescribing (Calmy *et al.* 2006). On the other hand, there is concern that FDCs may limit patient management options by preventing single drug substitutions or dosage adaptation (Llibre *et al.* 2011). We conducted this review to assess the patient and programme impact of FDC antiretroviral therapy.

Methods

This review followed the PRISMA guidelines for reporting of systematic reviews (Moher *et al.* 2009).

Search strategy and study selection process

We searched three electronic databases (MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews) from inception to 01 March 2013. No geographical, language or date limits were applied. Keywords for terms such as 'HIV' and 'fixed-dose combination', and related terms were used to identify relevant studies. A detailed description of the search terms is provided in the review protocol (Appendix S1). Conference abstracts from the databases of International AIDS Society Conferences (up to July 2012) and the Conference on Retroviruses and Opportunistic Infections (up to March 2013) were also searched**.** Titles and abstracts were screened for eligibility independently and in duplicate by two reviewers (RR, NF). Bibliographies of all included and other relevant articles were handsearched to identify further studies, as well as bibliographies of previously published studies assessing the efficacy of once-daily regimens (Nachega *et al.* 2014) to seek further potential inclusions and determine the extent to which this variable could influence outcomes of this review.

Inclusions and exclusions

We sought studies reporting clinical outcomes, patient-reported outcomes and programme-related outcomes that could be related to pill burden for adult and adolescent patients on ART. To assess clinical outcomes, comparative studies were sought. Partial FDCs (where two pills are combined) and full FDCs (single tablet regimens) were eligible for inclusion provided the comparator regimen comprised a greater number of pills, regardless of the dosing schedule. We excluded any comparison regimens that were considered clinically non-equivalent such that any differences in outcomes could be attributed to characteristics other than pill burden (e.g. differences in efficacy or tolerability). Only regimens for which there were no *a priori* expected differences in virological efficacy were included. For patient-reported and programme-related outcomes such as quality of life or supply chain management, non-comparative studies were also considered. Switch studies, where patients started on one regimen were subsequently switched to a different regimen once virological suppression had been achieved, were included. Case reports, case series <10 patients, and pharmacokinetic and bioequivalence studies were excluded. Children (defined as age ≤15 years) were excluded because their ART dose must be adjusted as they grow and because of differing limitations of drug use owing to toxicity concerns; both issues complicate the evaluation of FDCs for children.

Clinical outcomes assessed were adherence (as defined by the studies), virological response (as defined by the studies), immunological response (CD4 gain), mortality and incidence of opportunistic infections. Where studies reported multiple thresholds for virological suppression, the lowest threshold was used for analysis. Patient-reported outcomes of interest included quality of life and patient preferences and satisfaction (as defined by the studies). Programme-level outcomes of interest included drug stock-outs and supply chain management.

Data synthesis and analysis

Using data extraction templates, we extracted data on study characteristics, patient characteristics, details about the intervention and comparators, and outcomes; data were extracted by one reviewer (RR) and verified by a second reviewer (NF). When clarification or further information was required, study authors were contacted. Conference abstract first authors were contacted regarding availability of a corresponding full text paper. Studies that were similar in setting and cohort size were checked to avoid duplication, and in case of uncertainty, study authors were contacted for confirmation. A set of 12 criteria was developed in order to rate the methodological quality. Summary scores were not generated as these provide misleading estimates of risk of bias by treating all criteria as equal (Juni *et al.* 2001).

For the primary outcomes of adherence and virological suppression, relative risks and 95% confidence intervals were calculated and these were pooled using random effects meta-analysis (Fleiss 1993). These outcomes were reported separately according to study design (randomised trial or observational cohort), and for the randomised trials, subgroup analyses were undertaken to assess potential differences in virological outcomes according to definition of virological failure applied and whether studies were switch studies. Statistical heterogeneity was assessed by the I^2 statistic. All *P*-values were two-sided with a *P*-value of <0.05 considered significant. All statistical analyses were carried out in Stata (version 12.0; StataCorp LP, College Station, TX, USA)

Results

Study characteristics

Of 1707 titles screened, 663 conference abstracts retrieved, 53 studies were reviewed in full and 22 papers

reporting outcomes from 21 studies (one study reported clinical outcomes and patient preferences in two separate reports (Sterrantino *et al.* 2006, 2012) were taken forward for review; these studies provided information on 27 230 subjects were taken forward for review (Figure 1). Study size ranged from 12 (Rosso *et al.* 2012) to 15 933 patients (Cocohoba *et al.* 2012). There were 6 randomised trials (Eron *et al.* 2000; Fischl *et al.* 2003; Sosa *et al.* 2005; Lamarca *et al.* 2006; Maitland *et al.* 2008; Hodder *et al.* 2010), 10 prospective cohort studies (Clotet *et al.* 2004; Sanchez *et al.* 2006; Sterrantino *et al.* 2006; Rutland and Mani 2009; Airoldi *et al.* 2010; Pasquet *et al.* 2010; Manfredini *et al.* 2011; Homar *et al.* 2012; Rosso *et al.* 2012; Hull *et al.* 2013) and 5 retrospective cohort studies (Legorreta *et al.* 2005; Willig *et al.* 2008; Juday *et al.* 2011; Cocohoba *et al.* 2012; Keiser *et al.* 2007). Publication date ranged from 1999 to 2013 and reporting periods span 1995 to 2012. Most studies were carried out in high income settings, with the largest number of studies originating from the United States (nine studies) and Italy (five studies). None of the clinical studies comparing fixed-dose regimens against separate tablet regimens differed in terms of daily dosing.

The most common FDC studied was efavirenz+emtricitabine + tenofovir, which was assessed by 13 studies (mostly observational studies), followed by abacavir + lamivudine, which was assessed by eight studies (mostly randomised trials). Full FDCs were assessed by 16 studies, and partial FDCs were assessed by seven studies.

Six studies reported coinfection. Hepatitis C was most frequently reported (five studies) followed by hepatitis B (two studies). It was not clear, however, whether these patients were receiving concurrent medication. Study characteristics are summarised in Table 1.

Overall, the quality of included studies was rated as low. The majority of the included studies were non-randomised observational studies, including five retrospective cohort studies. Among the RCTs, only one adequately described method of allocation concealment

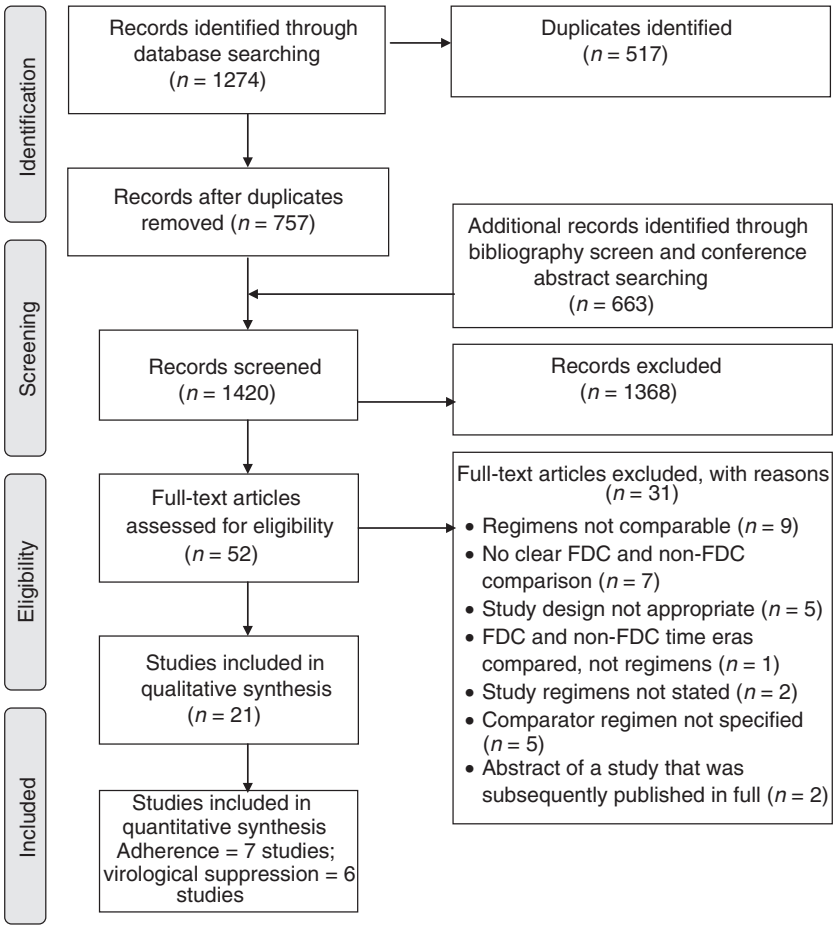

Figure 1 Study selection process.

Table 1 Study characteristics

Study ID	Reporting Period	Study Design	Country	Patient Population	Average Age	Proportion of female	Baseline CD4 (cells/μL)	Coinfection	FDC regimens	Comparator regimens	Outcome Measures
Randomised controlled trials											
Hodder *et al.* (2010)	August 2006–November 2006	Randomised comparative switch study	United States and Puerto Rico	Patients on stable ART, virologically suppressed (<200 copies/ml) for >3 months	43 years for both the FDC and non-FDC groups	11% and 14% for the FDC and non-FDC groups, respectively	517 and 515 for the FDC and non-FDC groups, respectively	7% and 1% HBV or HCV coinfection in the FDC and non-FDC groups, respectively	Full FDC EFV/FTC/TDF	PI or NNRTI-based therapy	Quality of life, perceived ease of the regimen, preference of medication
Maitland *et al.* (2008)	N/S	Randomised comparative switch study	England	Virologically suppressed patients (<50 RNA copies/ml)	47.1 and 46.5 years for the FDC and non-FDC groups, respectively	8.5% and 8.5% for the FDC and non-FDC groups, respectively	474 and 525 for the FDC and non-FDC groups, respectively	N/S	Partial FDC 3TC/ABC + any ARV drug	Separate-pill 3TC + ABC + any ARV drug	Adherence, patient satisfaction
Lamarca *et al.* (2006)	N/S	Randomised controlled trial	Europe and North America	Virologically failing patients (>1000 copies/ml), with <3 NRTI mutations	38 and 39 years for the FDC and non-FDC groups, respectively	29% and 19% for the FDC and non-FDC groups, respectively	309 and 304 for the FDC and non-FDC groups, respectively	N/S	Partial FDC 3TC/ABC + TDF + NNRTI or PI	Separate-pill 3TC/ABC + TDF + NNRTI or PI	Adherence, change in CD4 cell count, viral resistance, Virological response
Sosa *et al.* (2005)	September 2002–May 2003	Randomised comparative switch study	United States, Panama, Costa Rica and Puerto Rico	Virologically suppressed patients (<400 copies/ml) for >3 months	38 and 38 years for the FDC and non-FDC groups, respectively	20% and 16% for the FDC and non-FDC groups, respectively	565 and 549 for the FDC and non-FDC groups, respectively	N/S	Partial FDC 3TC/ABC + PI or NNRTI	Separate-pill 3TC + ABC + PI or NNRTI	Adherence, change in CD4 cell count, virological response
Fischl *et al.* (2003)	November 1999–January 2001	Randomised 'before-after' switch study	United States	ART-experienced patients	38 and 35 years for the FDC and comparator groups, respectively	23% and 26% for the FDC and comparator groups, respectively	612.3 and 594.3 in the FDC and comparator groups, respectively	N/S	Full FDC 3TC/ABC/AZT	Partial FDC 3TC/AZT + ABC	Adherence, virological response

(continued)

Table 1 (*Continued*)

Study ID	Reporting Period	Study Design	Country	Patient Population	Average Age	Proportion of female	Baseline CD4 (cells/μL)	Coinfection	FDC regimens	Comparator regimens	Outcome Measures
Eron *et al.* (2000)	May 1997–June 1998	Randomised controlled trial	United States and Puerto Rico	ART- experienced patients, VL <10 000 copies/ml receiving treatment for >10 weeks immediately prior to the study	39.7 and 40.2 years for the FDC and non-FDC groups, respectively	16% and 13% for the FDC and non-FDC groups, respectively	543 and 545 for the FDC and non-FDC groups, respectively	N/S	Single-pill, fixed-dose 3TC/AZT + a PI	Separate-pill 3TC + AZT + a PI	Adherence, change in CD4 cell count, virological response
Cohort studies											
Cocohoba *et al.* (2012)	May 2007–August 2009	Retrospective cohort study	United States	Patients with >30 days of ART prescription claims	47.1 years for both FDC and non-FDC groups	9% and 13% for the FDC and non-FDC groups, respectively	N/S	N/S	*Full FDC:* 3TC/ABC/AZT/, EFV/FTC/TDF or LPV/r *Partial FDC:* 3TC/AZT, 3TC/ABC, FTC/TDF,	NNRTI-based regimen, NRTI-based regimen, PI-based regimen	Adherence
Homar *et al.* (2012)	June 2010–July 2011	Prospective cohort, comparative switch study	Spain	ART-experienced patients, with controlled HIV-1 infection	46 and 44 years in the FDC and non-FDC groups, respectively	25% and 24% in the FDC and non-FDC groups, respectively	542 and 573 in the FDC and non-FDC groups, respectively	39% and 40% HCV coinfection in the FDC and non-FDC groups, respectively	*Full FDC:* 3TC/ABC/AZT, EFV/FTC/TDF *Partial FDC:* 3TC/ABC,3TC/AZT, FTC/TDF,	Equivalent separate-pill regimens (FTC replaced with 3TC)	Cost analysis, virological response
Rosso *et al.* (2012)	December 2008–June 2009	Prospective cohort, 'before-after' switch study	Italy	Virologically suppressed adolescents (<50 copies/ml) on ART for >6 months	16 years	58.3%	808.7	N/S	Full FDC FTC/TDF/EFV	Separate-pill 3TC or FTC + TDF + EFV	Patients preferences
Sterrantino *et al.* (2012)	December 2010–January 2012	Prospective cohort study	Italy	Patients on ART for at least 3 months	47.7 years	22.8%	602	20.4% HCV coinfection	Full FDC TDF/FTC/EFV	Regimens containing ritonavir-boosted PI, NNRTI, raltegravir, and maraviroc	Adherence

(continued)

Table 1 (*Continued*)

Study ID	Reporting Period	Study Design	Country	Patient Population	Average Age	Proportion of female	Baseline CD4 (cells/μL)	Coinfection	FDC regimens	Comparator regimens	Outcome Measures
Hull *et al.* (2013)	January 2000–April 2010	Prospective cohort study	Canada	ART-naïve patients initiating treatment	Mean of 41 years	16%	204	71% HCV infection	*Full FDC:* 3TC or FTC/EFV/TDF *Partial FDC:* 3TC/ABC, 3TC or FTC/TDF	Separate-pill ABC + 3TC, 3TC or FTC + TDF and 3TC or FTC + TDF + EFV)	Regimen switch, Virological response
Juday *et al.* (2011)	January 2003–June 2008	Retrospective cohort study	United States	ART-naïve patients initiating treatment	N/S	N/S	N/S	N/S	EFV/FTC/TDF	EFV + FTC + TDF	Regimen discontinuation
Manfredini *et al.* (2011)	N/S	Prospective cohort, 'before-after' switch study	Italy	Virologically suppressed adolescents (<50 copies/ml)	Range of 14–25 years	N/S	N/S	N/S	Full FDC EFV/FTC/TDF	Separate-pill 3TC + EFV + TDF	Patient satisfaction, quality of life
Airoldi *et al.* (2010)	March 2008 – April 2009	Prospective cohort, 'before-after' switch study	Italy	Patients on ART, VL <50 copies/ml	45.8 years	22.6%	556	N/S	Full FDC EFV/FTC/TDF	Separate-pill 3TC or FTC, + EFV + TDF	Patient preferences, quality of life
Pasquet *et al.* (2010)	February 2006–June 2007	Prospective cohort study	Cote d'Ivoire	ART-naïve patients initiating treatment	35 years	73.4%	136	N/S	N/S	N/S	Drug stock-outs, Interruption in care or death
Sanchez *et al.* (2006)	N/S	Prospective cohort study	Spain	ART-naïve patients initiating treatment	Mean of 37.4 years in FDC group	3% in FDC group	291 in FDC group	6% HCV coinfection in FDC group	Full FDC EFV/FTC/TDF	Partial FDC FTC/TDF + EFV	Change in CD4 cell count, Virological response
Rutland and Mani (2009)	July-October 2008	Prospective cohort, 'before-after' switch study	England	ART-experienced patients	N/S	N/S	N/S	N/S	Full FDC EFV/FTC/TDF	Partial FDC FTC/TDF + EFV	Patient satisfaction
Sterrantino *et al.* (2012)	N/S	Prospective cohort, 'before-after' switch study	Italy	ART-experienced patients, VL <50 copies/ml	N/S	N/S	N/S	N/S	Full FDC EFV/FTC/TDF	Partial FDC FTC/TDF + EFV	Patient preferences

(continued)

Table I (*Continued*)

Study ID	Reporting Period	Study Design	Country	Patient Population	Average Age	Proportion of female	Baseline CD4 (cells/μL)	Coinfection	FDC regimens	Comparator regimens	Outcome Measures
Willig *et al.* (2008)	January 2000–July 2007	Retrospective cohort study	United States	ART-naïve patients initiating treatment	37.9 years	23.1%	31% <50 26% 50–199 21.5% 200–350 21.5% >350	N/S	95% use of fixed-dose combination ART	77% use of fixed-dose combination ART	Initial regimen duration, Regimen discontinuation
Keiser *et al.* (2007)	N/S	Retrospective cohort study	N/S	ART-naïve patients initiating treatment	N/S	N/S	N/S	N/S	Full FDC EFV/FTC/TDF	Separate-pill EFV + FTC + TDF	Adherence
Legorreta *et al.* (2005)	1995–2001	Retrospective cohort study	United States	ART-naïve patients initiating treatment	40.16 and 43.36 years for the FDC and non-FDC groups, respectively	47.84% and 39.06% for the FDC and non-FDC groups, respectively	N/S	0.59% and 1.56% HBV infection in the FDC and non-FDC groups, respectively	Partial FDC 3TC/AZT	Separate-pill 3TC + AZT	Adherence
Clotet *et al.* (2004)	N/S	Prospective cohort, 'before-after' switch study	Spain	Patients with VL <400 copies/ml	Mean of 41 years	24%	N/S	N/S	Full FDC 3TC/ABC/AZT	Any standard ART (2 NRTIs + 1 or 2 PIs, or 2 NRTIs + 1 NNRTI)	Patient satisfaction, quality of life

3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; ARV, antiretroviral; AZT, zidovudine; CMV, cytomegalovirus; d4T, stavudine; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; HIV, human immunodeficiency virus; N/S, not stated; HBV, hepatitis B; HCV, hepatitis C; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PCP, pneumocystis pneumonia; PI, protease inhibitor; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; US, United States.

and randomisation (Maitland *et al.* 2008). Ten studies received industry support (Table S1).

Clinical outcomes

Virological suppression. Seven studies evaluated virological suppression, with varying thresholds and durations of follow-up. Four of these studies reported a larger proportion of subjects achieving virological suppression in the FDC group than in the non-FDC group (Eron *et al.* 2000; Fischl *et al.* 2003; Hull *et al.* 2013; Homar *et al.* 2012).

Six studies, comprising four RCTs (806 patients) and two observational cohorts (311 patients), contributed to the meta-analysis of virological suppression (one study reported outcomes on virological suppression but data could not be disaggregated for inclusion in the meta-analysis, and authors were unable to provide clarification (Hull *et al.* 2013)). For the RCTs, the relative risks ranged from 0.98 (95% CI 0.87–1.11) to 1.16 (95% CI 1.01–1.33), and overall there was a tendency towards greater virological suppression among patients receiving FDCs than among those who did not, with a borderline significant relative risk of 1.04 (95% CI 0.99–1.10) (Figure 2). Heterogeneity was low (I^2 = 9.3%). One of the two observational cohort studies was excluded due to no events in either arm; the relative risk for the remaining study was 1.07 (95% CI 0.97–1.18). In subgroup analysis, outcomes did not differ according to definition of virological suppression applied, or whether studies were switch studies or not.

Adherence. Ten studies assessed adherence, and eight of these reported results favouring FDCs (Eron *et al.* 2000; Fischl *et al.* 2003; Legorreta *et al.* 2005; Keiser *et al.* 2007; Hull *et al.* 2013; Maitland *et al.* 2008; Manfredini *et al.* 2011; Cocohoba *et al.* 2012; Sterrantino *et al.* 2012). One RCT reported a statistically significant benefit of FDCs in terms adherence to taking the medication (99.2% *vs.* 96.6%, P = 0.017), correct dosing (97.1% *vs.* 91.9%, P = 0.006) and correct timing (95.5% *vs.* 86.3%, P = 0.006) (Maitland *et al.* 2008). A study that compared a two-pill regimen (emtricitabine/tenofovir + efavirenz) to the equivalent three-pill regimen found adherence to be significantly higher in the FDC group for emtricitabine and tenofovir (87% *vs.* 74%, $P < 0.01$) as well as for efavirenz (87% *vs.* 84%, P = 0.026) (Keiser *et al.* 2007). Of the remaining four studies (Fischl *et al.* 2003; Sosa *et al.* 2005; Lamarca *et al.* 2006; Homar *et al.* 2012), all reported higher adherence in the FDC group, but two studies did not find this difference to be significant and two studies did not provide information about statistical significance.

Five RCTs (873 patients) contributed to the meta-analysis of adherence, and the relative risks ranged from 1.04 (95% confidence interval 0.97–1.12) to 1.31 (95% CI 0.95–1.82). Overall, there was a tendency towards better adherence among patients receiving FDCs than among those that did not, with a relative risk of 1.10 (0.98–1.22). There was substantial heterogeneity (I^2 = 66.2%). For the two observational cohorts contributing to the meta-analysis (1721 patients), relative risks were 1.13 (95% CI 0.98–1.31) and 1.20 (95% CI 1.06–

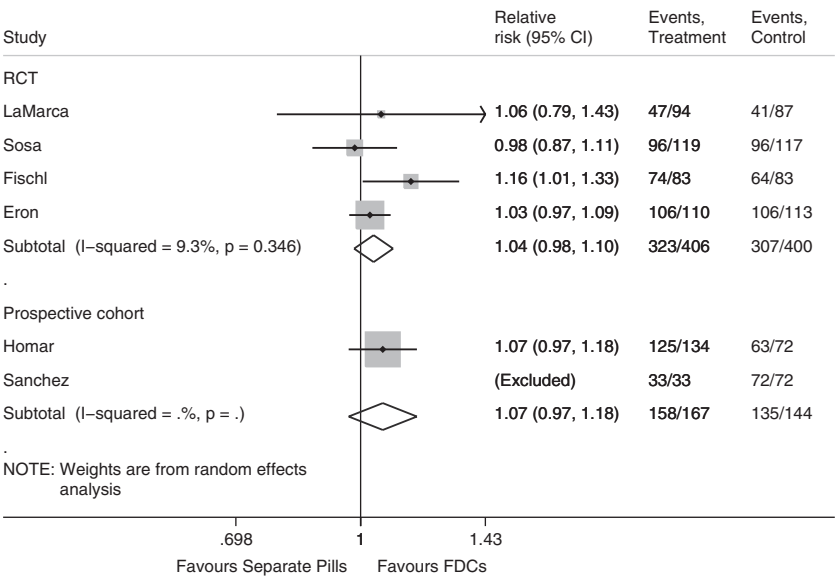

Figure 2 Pooled analysis of virological suppression comparing FDCs and separate tablet regimens.

1.35); pooling these two studies gave a statistically significant relative risk of 1.17 (95% CI 1.07–1.28). There was no statistical heterogeneity (I^2 = 0%) (Figure 3).

One prospective cohort study (Willig *et al.* 2008), from the United States, provided indirect evidence for adherence benefit by comparing time periods before and after the introduction of FDCs. Regimen discontinuation was significantly lower in the post-FDC period than the pre-FDC period (14% *vs.* 6%, $P < 0.02$). Additionally, duration of initial ART was measured according to these time periods and according to the regimen pill burden; the initial regimen duration was higher in the post-FDC period (1043 days *vs.* 780 days) and higher as the number of pills decreased (340 days for ≥6 pills, 766 days for 4–5 pills and 1218 days for ≤3 pills) (Cocohoba *et al.* 2012).

Other clinical outcomes. Five studies reported a CD4 cell count increase in the FDC group over the follow-up period. Three reported increases greater in the FDC relative to the non-FDC group, one study reported this increase to be significant ($P < 0.005$), another reported no significance and the remaining study did not provide information about statistical significance; in the remaining two studies, the CD4 gain was lower in the FDC group. Only one study reported data on resistance mutations by arm (Lamarca *et al.* 2006). 4 K65R mutations were reported in the FDC arm and three in the separate-pill arm; L74V mutations were reported in one subject per arm, and Y115F mutations were reported in two subjects in the FDC arm and one subject in the separate-pill group. Finally, one study evaluated retention in care and found that subjects who were still on ART had a greater likelihood of receiving this as FDC than those who were not (58% and 46%, respectively; $P < 0.01$) (Pasquet *et al.* 2010).

Patient-reported outcomes

Four studies evaluated quality of life, and all reported it to be consistently higher for subjects taking FDCs than for those taking separate-pill treatment. Hodder *et al.* (2010) reported a statistically significant difference for physical quality of life score between patients taking FDCs and non-FDCs (54.9% *vs.* 52.9%, $P = 0.01$). Airoldi *et al.* (2010) reported an improvement in four indicators of mental quality of life following the switch from non-FDC to FDC and statistically significant increases for overall quality of life score (increase of 3.92/10, $P = 0.042$); this study also provided evidence of an association between adherence and quality of life. The third study reported a statistically significant increase in overall quality of life score (increase of 3.4/10, $P = 0.02$, respectively) (Clotet *et al.* 2004). Manfredini *et al.* (2011) assessed quality of life using a depression score (decrease of 2.2/30 post-switch) and self-perceived psychological fatigue (decrease in score of 2.2/10 post-switch), both of which showed significant improvement.

Five studies, including three switch studies, measured patient satisfaction, and all reported a statistically significant increase in patient satisfaction favouring FDCs (Clotet *et al.* 2004; Watson *et al.* 2004; Rutland and Mani

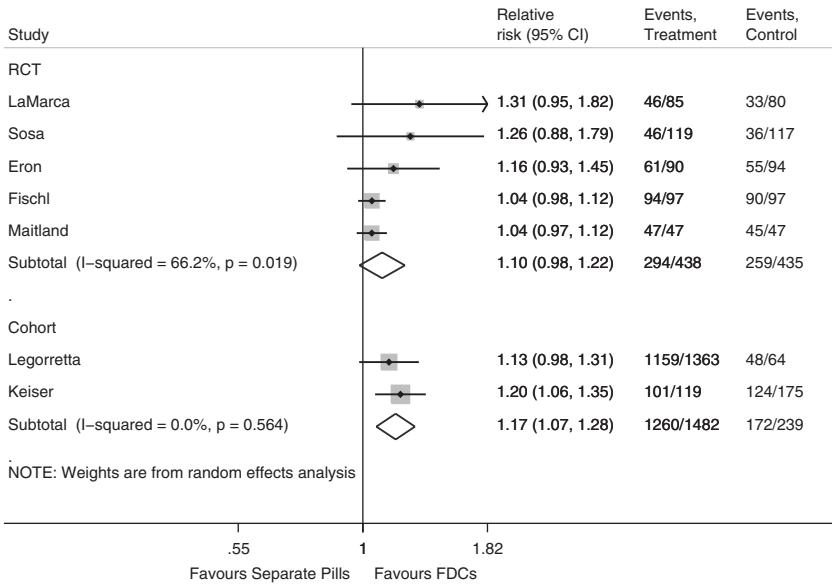

Figure 3 Pooled analysis of adherence to ART comparing FDCs and separate tablet regimens.

2009; Manfredini *et al.* 2011). Similarly, four studies evaluated patient preferences, and all reported results in favour of FDCs (Willig *et al.* 2008; Airoldi *et al.* 2010; Hodder *et al.* 2010; Rosso *et al.* 2012). Two studies reported on convenience, and this outcome was also found to favour FDCs. Finally, one study assessed perceived ease of regimen use using a questionnaire with a 4-point scale (Hodder *et al.* 2010). At the end of follow-up, 97% of FDC subjects perceived their regimen to be 'very easy' compared to 81% of non-FDC subjects ($P < 0.0001$); 94% of patients reported their reason for opting to switch to a FDC was a desire to simplify their current regimen. Patient-reported outcomes are summarised in Tables S2 and S3 (online only).

Programme-related outcomes

One study provided information on stock-outs (Pasquet *et al.* 2010). Overall, 11% of subjects in this study experienced prolonged regimen discontinuation or therapy modification as a result of drug stock-outs. In 27% and 51% of cases, stock-outs included nevirapine and zidovudine + lamivudine, respectively. In contrast, the most commonly used FDC regimen, stavudine + nevirapine + lamivudine, did not encounter any stock-outs during the follow-up period.

Discussion

Medication adherence is widely recognised as a challenging and widespread concern that can negatively affect patient outcomes and incur substantial cost to healthcare programmes. In the United States, it has been estimated that up to half of all adults are non-adherent to long-term medications leading to an estimated $100 billion in preventable costs annually (Marcum *et al.* 2013).

Fixed-dose combinations have been widely promoted as an intervention to improve adherence to treatment among people living with HIV/AIDS and for other major infectious (TB, malaria) or non-infectious diseases such as hypertension (Anonymous 2003). The World Health Organization has long supported the use of FCDc as part of simplification and scale up, and as part of the Treatment 2.0 Strategy to optimise ART in support of the UN target to reach 15 million people on ART by 2015, promotes the use of effective, affordable and simple therapy, including FDCs as a priority intervention (Anonymous 2011).

Overall, this systematic review found that fixed-dose antiretroviral therapy appears to improve rates of adherence and possibly virological suppression compared to separate-pill regimens. While the adherence benefit is not large, it is line with benefits derived from other adherence interventions. The use of community support (food provision and home care) and text messaging are both accepted as interventions that work and the reported effect sizes of these interventions are within the range of the improvements found in this review (Barnighausen *et al.* 2011). Unlike other adherence support interventions which themselves require a degree of adherence, FDCs require no further action on the part of the patient or provider as the intervention is an indivisible characteristic of the treatment.

These findings are supported by the benefits reported by patients in terms of improvements in quality of life and satisfaction with treatment. Several other studies identified by this review process that did not meet the eligibility criteria indicate further possible benefits: one study, from the USA, reported improved treatment outcomes for homeless and marginalised people taking FDCs (Bangsberg *et al.* 2010). Another study, from South Africa, suggested that FDCs may improve adherence among mobile migrant workers. Several studies also reported that FDCs are cost-effective compared to separate tablet regimens (Matambo *et al.* 2012). While intuitively reducing pills would decrease the risk of drug stock-outs and improve supply chain management, the lack of reporting of these outcomes could be a publication bias consequent to few studies reporting logistical outcomes in the medical literature.

The findings of this review are supported by evidence from several RCTs and evidence from a range of different settings reporting a variety of outcomes including both objective (viral load) and subjective (patient preferences) measures. A notable weakness of the evidence base is the use of different outcome measures and measurement tools used by different studies, with differing levels of reliability, including questionnaires with limited attention paid to reducing bias. One study only reported outcomes up to 8 weeks (Maitland *et al.* 2008); we chose to include this study as early adherence has been found to be predictive of longer-term virological outcomes (Ford *et al.* 2010). In particular, there is a lack of data on impact in terms of drug resistance development, with only one study reporting this outcome. Finally, despite efforts to identify as many studies applicable to this review as possible, there is always the possibility that relevant studies, particularly in the grey literature, may have been overlooked.

This review included switch studies (in which only patients with a suppressed viral load are included), which may result in bias due to both patient selection and modification of some of the patient's treatment regimen. Nonetheless, we decided to include these studies as they reflect decisions made in practice: in April 2013, South

Africa changed policy to recommend FDCs as the preferred first line and consequently many patients are being switched from separate-pill therapy. Finally, an alternative explanation for some of the positive results was the fact that some FDCs also provide benefit in terms of reducing daily dosing (Parienti *et al.* 2009). For the primary outcome analyses of adherence and virological suppression in which all drug regimens were clearly described, this was assessed and no difference in dosing schedule was observed.

Assessment of evidence in the field of FDC is a challenge as few studies have been designed explicitly to directly compare the same regimens as separate pills and fixed-dose. Nevertheless, the results of most studies point in the same direction of modest benefit favouring FDCs. From a programme perspective, FDCs may reduce the risk of dosing error and therefore support task shifting of ART prescribing to lesser trainer healthcare workers (Morris *et al.* 2009; Llibre *et al.* 2011) and could potentially simplify supply chain management and reduce the risk of drug stock-outs, although again the evidence base is weak. Despite these potential advantages, not all regimens are available as FDCs, and company interests and patent restrictions, rather than public health considerations, for the most part explain which individual antiretroviral drugs get combined into FDCs and which do not. These considerations are particularly relevant a time where generic antiretrovirals are beginning to enter the European and American markets, and trade-offs may need to be made between pill burden and cost (Walensky *et al.* 2013).

In conclusion, the evidence base for clinical advantages of FDCs over separate pills is limited, but the findings of most studies included in this review point in the same direction of benefit, with no evidence of harm. Programmes should consider adopting FDCs in preference to further support scale up and sustain treatment benefits, provided costs are similar.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Methodological Quality Assessment Table.

Appendix S1. Search Terms.

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