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SYSTEMATIC REVIEW AND META-ANALYSIS (PRISMA COMPLIANT)

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Meta-Analysis of Studies Comparing Single and Multi-Tablet Fixed Dose Combination HIV Treatment Regimens

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Abstract: Availability of a single source review of once-daily fixed-dose single tablet regimen (STR) and multiple tablet fixed-dose regimen (MTR) would optimally inform healthcare providers and policy makers involved in the management of population with human immunodeficiency virus (HIV).

We conducted a meta-analysis of published literature to compare patient adherence, clinical, and cost outcomes of STR to MTR.

Published literature in English between 2005 and 2014 was searched using Embase, PubMed (Medline in-process), and ClinicalTrials.Gov databases. Two-level screening was undertaken by 2 independent researchers to finalize articles for evidence synthesis. Adherence, efficacy, safety, tolerability, healthcare resource use (HRU), and costs were assessed comparing STR to MTR. A random-effects meta-analysis was performed and heterogeneity examined using meta-regression.

Thirty-five articles were identified for qualitative evidence synthesis, of which 9 had quantifiable data for meta-analysis (4 randomized controlled trials and 5 observational studies). Patients on STR were significantly more adherent when compared to patients on MTR of any frequency (odds ratio [OR]: 2.37 [95% CI: 1.68, 3.35], $P < 0.001$; 4 studies), twice-daily MTR (OR: 2.53 [95% CI: 1.13, 5.66], $P = 0.02$; 2 studies), and once-daily MTR (OR: 1.81 [95% CI: 1.15, 2.84], $P = 0.01$; 2 studies). The relative risk (RR) for viral load suppression at 48 weeks was higher (RR: 1.09 [95% CI: 1.04, 1.15], $P = .0003$; 3 studies) while RR of grade 3 to 4 laboratory abnormalities was lower among patients on STR (RR: 0.68 [95% CI: 0.49, 0.94], $P = 0.02$; 2 studies). Changes in CD4 count at 48 weeks, any severe adverse events (SAEs), grade 3 to 4 AEs, mortality, and tolerability were found comparable between STR and MTR. Several studies reported significant reduction in HRU and costs among STR group versus MTR.

Study depicted comparable tolerability, safety (All-SAE and Grade 3–4 AE), and mortality and fewer Grade 3 to 4 lab abnormalities and better viral load suppression and adherence among patients on FDC-containing STR versus MTR; literature depicted favorable HRU and costs for STRs.

These findings may help decision makers especially in resource-poor settings to plan for optimal HIV disease management when the choice of both STRs and MTRs are available.

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Abbreviations: AE = adverse event, ART = antiretroviral therapy, cART = combination antiretroviral therapy, CASP = Critical Appraisal Skills Programme, CD4 = cluster of differentiation 4, CI = confidence intervals, EM = economic models, FDCs = fixed-dose combinations, HIV = human immunodeficiency virus, HRU = healthcare resource use, ICER = incremental cost-effectiveness ratio, MTR = multiple tablet fixed-dose combination regimen, OR = odds ratio, OS = observational studies, PICOS = patient, intervention, comparator outcome and study design, PRISMA = preferred reporting items for systematic reviews and meta-analyses, QALYs = quality-adjusted life-years, QoL = quality of life, RCT = randomized controlled trials, RR = risk ratio, SAE = severe adverse event, SD = standard deviation, STR = single tablet regimen, UNAIDS = Joint United Nations Programme on HIV and AIDS, WHO = World Health Organization.

INTRODUCTION

In 2013, there were approximately 35 million people living with and 1.5 million people dying from human immunodeficiency virus (HIV) worldwide.[1] About 12.9 million people living with HIV were receiving antiretroviral therapy (ART) globally, including 11.7 million in low- and middle-income countries.[1] ART is recommended by the World Health Organization (WHO) as an effective treatment for HIV disease progression and prevention.[1] Both the Joint United Nations Programme on HIV and AIDS (UNAIDS) and WHO recommend initiating combination antiretroviral therapy (cART) containing a ''backbone'' of 2 nucleoside reverse transcriptase inhibitors along with a ''base'' consisting of either a non-nucleoside reverse transcriptase inhibitor, a ''boosted'' protease inhibitor, or an integrase inhibitor.[2]

Medical providers continually seek regimen simplification to help achieve and maintain HIV treatment adherence. Fixed-dose combination (FDC) ART medications combine elements of backbone and base medications into fewer dosing units and offer simplified regimen options to HIV patients. Single tablet regimens (STR) incorporate FDC into a single dosing unit that is administered once daily; multiple tablet regimens (MTR) incorporate FDC and require multiple dosing times or units per day. Regardless of disease being treated, adherence rates tend to be higher when simpler, once-daily regimens are combined with lower pill burden.[3–8] Studies have suggested that HIV patients treated with once-daily fixed-dose STR are more adherent compared to patients on ≥2 pills per day regimens,[9–12] and that patients on STR were better at achieving

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SNarayanan and PGC designed the research and formulated the objectives and outcome measures. SNarayanan and SNag conducted literature searches, abstract/article screenings and selected the final articles for qualitative and quantitative evidence synthesis. All authors contributed to the interpretation of the results and creation of first draft, provided comments on the following drafts, and approved the final version.
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>90% adherence when compared with MTR.[13,14] Therefore, several guidelines urge providers to use STR and MTR containing FDCs when choosing regimens of similar efficacy and tolerability for their patients.[2,15–25]

STRs may provide long-term durability, allowing for continued immunological recovery, leading to increased life expectancy.[26–27] Further, STRs appear to generate improved adherence, higher perceived quality of life (QoL), and lower costs to the healthcare system.[3,10,28–31] To confirm these hypotheses, formal investigation is required. At present, there are no literature reviews or meta-analyses comparing STR to MTR using randomized controlled trials (RCT), observational studies (OS), and economic models (EM) encompassing patient adherence, clinical outcomes, and economic outcomes. Availability of a single-source review of single-tablet compared with multi-tablet HIV regimens containing FDCs would optimally inform healthcare providers and policy makers involved in the management of HIV populations amidst increasingly scarce resources.

METHODS

Search Strategy and Study Selection

A literature review and meta-analysis of published scientific articles, focusing on STR compared with MTR for the management of HIV was completed employing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[32] and ''PICOS principle'' (Patient, Intervention, Comparator, Outcome, and Study design) based on an internal study protocol (available upon request). Research followed a 2-level screening process conducted independently by 2 reviewers. Databases were searched from November to December 2014 and included Embase, PubMed (Medline in-process), and ClinicalTrials.gov. Articles published in English, beginning in 2005, when STR Atripla was first introduced, to December 2014 were considered for the analyses. The search criteria used in this research is depicted in the Supplemental Content accompanying this manuscript, http://links.lww.com/MD/A444.

Data sought included published or publicly available RCT and observational study results on human subjects which included: patient adherence, clinical efficacy, safety, resource utilization, and cost outcomes. The methodological quality of RCT was assessed independently using a checklist that assessed the risk of bias across 5 different categories (selection, performance, detection, reporting, and attrition), according to the Cochrane handbook for systematic reviews.[33] A critical appraisal was conducted for the OS included in the meta-analysis, using the Critical Appraisal Skills Programme (CASP), United Kingdom checklist,[34] assessing the validity of the results from each study. The first-pass screening of bibliographic details, titles, and abstracts of all citations retrieved by the literature search eliminated citation duplicates. Studies found eligible and presenting relevant data were included for data extraction. Only studies with outcome measures in evaluable format (n/N, mean, standard deviation, N, or median and inter-quartile range) with a clear comparison between STR and MTR were included for meta-analysis. Because only secondary/published literature was considered for this research and no human subjects were approached or included in this research in any manner, an internal peer review process was adopted for review of the study documents; an external independent institutional review board (IRB) approval was not considered necessary.

Meta-Analysis

A random-effects meta-analysis with forest plots was carried out to investigate the parameters of interest from the included studies using Review Manager (RevMan 5.1.7) software (The Nordic Cochrane Centre, Copenhagen, Denmark). The primary endpoints were reported for adherence outcomes based on either achieving a specific threshold measure (yes/no) or based on pill count or percentage of drugs used; efficacy outcomes based on either percentage achieving viral load suppression (<50 copies/mL) at 48 weeks or changes in mean CD4 counts from baseline at 48 weeks; safety outcomes based on percentage having any severe adverse event (SAE) at 48 weeks, any grade 3 to 4 clinically significant event at 48 weeks, or any grade 3 to 4 lab abnormalities at 48 weeks; and tolerability outcomes based on the percentage of patients discontinuing their STR or MTR HIV treatment for any reason. The adherence outcomes were also assessed based on the frequency of MTR regimen (subject to data availability), as prespecified in the study protocol. The qualifying economic studies are not included in the meta-analyses since the data were not in an analyzable format. The studies are retained and summarized in the review; however, in keeping with 1 of the study objectives (provide a single-source review of STR compared with MTR for HIV to inform healthcare providers and policy makers amidst increasingly scarce resources).

Inverse variance methods were used in a random-effects model to analyze both dichotomous and continuous data and to assess heterogeneity.[35] Heterogeneity was evaluated using the Chi-squared test and quantified using the I^2 statistic.[36] Alpha < 0.05 was used to determine statistical significance. I^2 values of 25%, 50%, and 75% correspond to low, medium, and high levels of heterogeneity, respectively. Summary statistics were calculated for each study to describe observed treatment effects; mean and standard deviation values were calculated where studies reported median and inter-quartile range. A pooled treatment effect estimate was then calculated as the weighted average of the treatment effects estimated in the individual studies. Each study was weighted as the inverse of the variance of the effect estimate (ie, 1 over the square of its standard error). Larger studies with smaller standard errors were given more weight than smaller studies with larger standard errors. For the studies which had multiple MTR arms, data from the MTR arms were first pooled within the trials and then between the trials. Dichotomous outcomes were evaluated by making an adjustment to the study weights according to the extent of variation, or heterogeneity, among the treatment effects.

Values for dichotomous outcomes (adherence [based on a threshold measure; yes/no], viral load suppression, safety events, and tolerability) were presented as n/N, where n = subset of sample size; N = total sample size, and the odds ratio (OR) or risk ratio (RR) with 95% confidence intervals (CI) were calculated. Values for continuous outcomes (CD4 cell counts and adherence [based on pill count or percentage of drug(s) used]) were presented as mean, standard deviation (SD), and N (sample size), with calculated standardized mean differences. For economic evaluations where studies reported healthcare resource use (HRU), the direct medical costs and Incremental Cost-Effectiveness Ratio (ICER) values were summarized.

RESULTS

Literature searches from all databases yielded 3681 citations, of which 158 were duplicates and discarded, resulting in 3523 unique citations. Following the first review of the

abstracts, 165 potentially relevant studies were identified. Two additional relevant studies were identified from hand searching of bibliographies. Thereafter, following a detailed examination of the 167 full-text articles, 124 articles did not meet the inclusion criteria and 8 were identified as secondary publications, thus linked to the primary publications. Consequently, a total of 35 studies[9–11,13–14,27,29–31,37–62] were included for qualitative evidence synthesis. The PRISMA flow of the review process is shown in Figure 1.

Of the 35 publications, 18 were OS (which included prospective and retrospective designs covering adherence, clinical and health resource use/cost-effectiveness outcomes),[9–11,13–14,30–31,42–48,54,58–60] 13 were RCT,[27,38–39,41,49,50,51–53,55–57,62] and 4 were EM-based studies.[29,37,40,61] Twenty-four studies reported efficacy outcomes, 20 reported adherence outcomes, 16 had measured safety/tolerability outcomes, 6 focused on economic evaluations, 4 were EM-based studies, and 1 reported treatment persistence. Seventeen studies (RCT: 9, OS: 6, and EM: 2) included only treatment-naïve patients, 9 (RCT: 4 and OS: 5) included only treatment-experienced patients, and 9 (OS: 7 and EM: 2) included both treatment-experienced and treatment-naive patients. Most studies were from the years 2014 (n = 14) and 2013 (n = 7); years 2012, 2011, and 2010 had 6, 3, and 3 studies, respectively. Only 1 study qualified from each of the years 2009 and 2008, and no eligible studies were found in 2007, 2006, or 2005. Key characteristics of the 35 studies are depicted in Table 1. Of these studies, only 9 studies were found eligible for meta-analyses, as they had outcome measures in evaluable format (n/N, mean, standard deviation, N, or median and inter-quartile

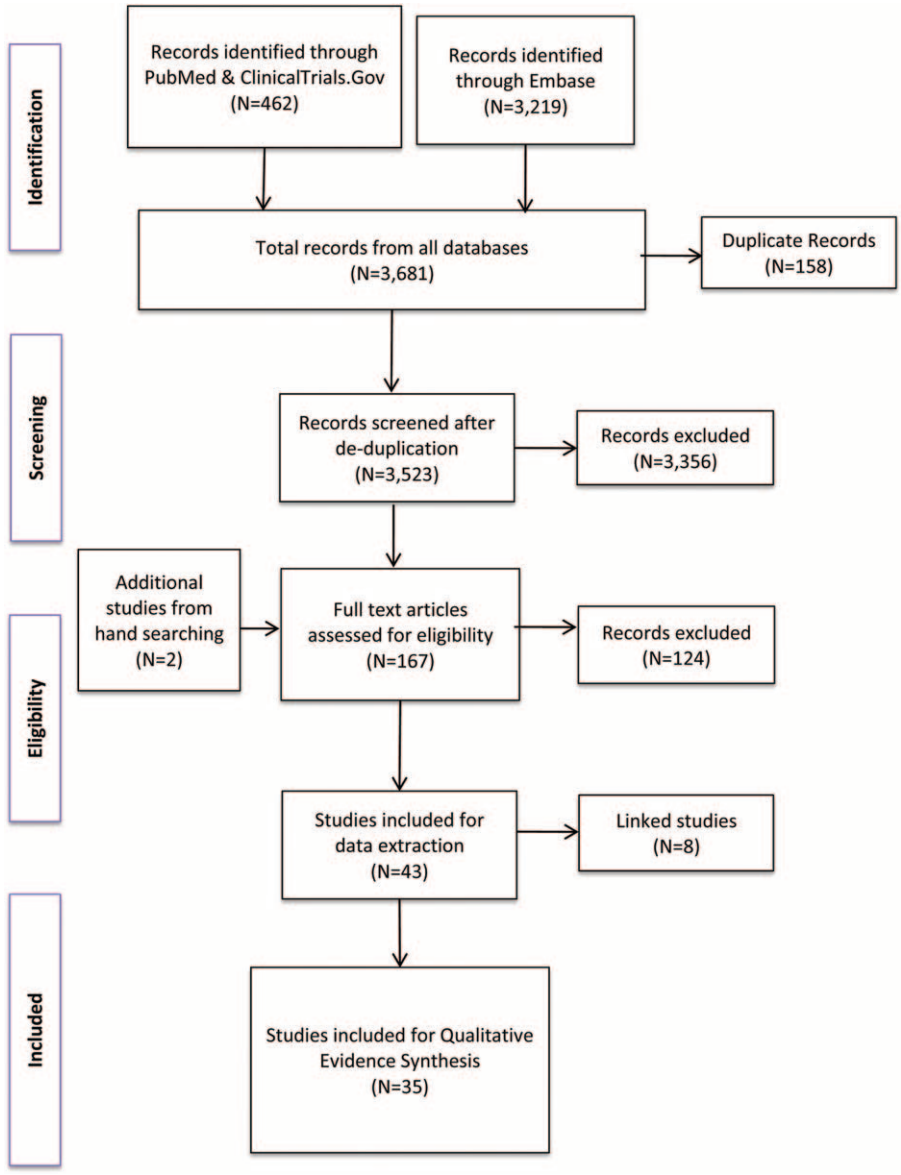

FIGURE 1. PRISMA flow diagram for literature search and study selection.

TABLE 1. Characteristics of Studies Included in Qualitative Evidence Synthesis

Study	Study Type	Intervention	Comparator	Population	Sample Size	Outcomes Assessed	Included in Meta-Analysis?
Arribas et al[38]	RCT	EVG/COBI/TDF/FTC	TDF/FTC + RTV-boosted PI (ATV or DRV or LPV or FPV or SQV	Treatment experienced	438	Adherence, efficacy, safety/tolerability	Yes (efficacy, safety/tolerability)
Cohen et al[27]	RCT	EVG/COBI/TDF/FTC	EFV/TDF/FTC	Treatment naïve	71	Efficacy, safety/tolerability	No
Cohen et al[39]	RCT	RVP/TDF/FTC	RVP/TDF/FTC	Treatment-naive	799	Adherence, efficacy, safety/tolerability	No
Dejesus et al[41]	RCT	EFV/TDF/FTC	PI (with or without RTV boosting) + at least 2 NRTIs; or NNRTI + at least 2 NRTIs	Treatment experienced	306	Adherence, efficacy, safety/tolerability	Yes (efficacy, safety/tolerability)
Landman et al[49]	RCT	EFV/TDF/FTC	TDF/FTC + NVP; TDF + LPV/r; TDF/FTC + AZTC	Treatment-naive	120	Adherence, efficacy, safety/tolerability	No
NCT00112047[50]	RCT	EFV/TDF/FTC	CBV + EFV	Treatment-naive	511	Efficacy, safety/tolerability	No
NCT01403051[51]	RCT	EFV/TDF/FTC	EFV/FTC/TDF plus vitamin D3 and calcium carbonate	Treatment-naive	167	Efficacy, safety/tolerability	No
Palella et al[52]	RCT	RVP/TDF/FTC	RTV-boosted PI + 2 NRTIs	Treatment experienced	482	Adherence, efficacy, safety/tolerability	Yes (safety/tolerability)
Pozniak et al[53]	RCT	EVG/COBI/TDF/FTC	NNRTI (EFV and non-EFV) + TDF/FTC	Treatment experienced	439	Adherence, efficacy, safety/tolerability	Yes (efficacy, safety/tolerability)
Rockstroh et al[55]	RCT	EVG/COBI/TDF/FTC	RTV/ATV + TDF/FTC	Treatment-naive	715	Adherence, efficacy, safety/tolerability	No
Sax et al[56]	RCT	EVG/COBI/TDF/FTC	EFV/TDF/FTC	Treatment-naive	707	Adherence, efficacy, Safety/tolerability	No
Sax et al[57]	RCT	EVG/COBI/FTC/TAF	EVG/COBI/FTC/TDF	Treatment-naive	171	Adherence, efficacy, safety/tolerability	No
Walmsley et al[62]	RCT	Dolutegravir + ABC/3TC	EFV/TDF/FTC	Treatment-naive	844	Adherence, efficacy, safety/tolerability	No
Airoldi et al[13]	OS	EFV/TDF/FTC	Switched from 3TC/TDF or TFC/TDF FDCs (or combination of separate pills)	Treatment experienced	212	Adherence, efficacy	No
Bangsberg et al[14]	OS	EFV/TDF/FTC	RTV-boosted PI or NNRTI + 2 NRTIs	Treatment naïve and experienced	118	Adherence, efficacy	Yes (adherence)
Beck et al[31]	OS	EFV/TDF/FTC	TDF/FTC + EFV; TDF + FTC + EFV; TDF + 3TC + EFV	Treatment-naive	1448	HRU/costs	No
Buscher et al[9]	OS	EFV/TDF/FTC	Any cART (incl. FDCs), with >1 pills	Treatment-naive	184	Adherence, efficacy	Yes (adherence)
Cohen et al[10]	OS	EFV/TDF/FTC	Any cART (incl. FDCs), with >1 pills	Treatment-naïve and experienced	7381	HRU/costs, adherence	No
Colombo et al[30]	OS	EFV/TDF/FTC	EFV + TDC + FTC, ATV/r + TDF + FTC, DRV/r + TDF + FTC, LPV/r + TDF + FTC	Treatment-naive	474	Costs	No
Engsig et al[42]	OS	TDF+3TC+EFV	EFV/TDF/FTC	GI: treatment-naïve; GII: treatment experienced	GI: 167; GII: 868	Efficacy	No
Fabbiani et al[43]	OS	EFV/TDF/FTC	EFV + NRTI backbone (incl. TDF/FTC, AZT/3TC)	Treatment naïve and experienced	553	Adherence, efficacy	Yes (adherence)
Grimes et al[44]	OS	EFV/TDF/FTC	ATZ/r + TDF/FTC, DRV/r + TDF/FTC, RAL + TDF/FTC, EFV + ABC/3TC, DRV + ABC/3TC, etc.	Treatment-naïve and experienced	NA	Costs	No
Hanna et al[45]	OS	EFV/TDF/FTC, EVG/COBI/TDF/FTC, RPV/TDF/FTC	Mutiple-tablet regimen of any type	Treatment experienced	1727	Adherence, efficacy	No
Hill et al[46]	OS	EFV/TDF/FTC	LPV/r + TDF/FTC, LPV/r + AZT/3TC, Nevirapine + AZT/3TC, Nelfinavir + AZT/3TC, etc.	Treatment naïve and experienced	115	Efficacy	No
Homar et al[47]	OS	EFV/TDF/FTC, AZT/3TC, ABC/3TC, ABC/AZT/3TC, TDF/FTC	PI or NNRTI-based cART with individual components	Treatment experienced	225	HRU/costs	No
Juday et al[11]	OS	EFV/TDF/FTC	Pi- or NNRTI-based cART with at least 2 NRTIs	Treatment experienced	461	HRU, adherence	No
Juday et al[48]	OS	EFV/FTC/TDF, EFV-contaning regimen, other NNRTI-containing regimen	LPV/r-containing, ATV/r-containing, other PI-containing regimen with TDF/FTC, AZT/3TC, etc.	Treatment-naïve	2460	Persistence	No
Pujari et al[54]	OS	EFV/TDF/FTC	NA	Treatment-naive	141	Adherence, efficacy, safety/tolerability	No
Scourfield et al[58]	OS	EFV/TDF/FTC	NA	Treatment-naive	472	Efficacy, safety/tolerability	No
Skwara et al[59]	OS	EFV/TDF/FTC, RVP/TDF/FTC	Any cART (incl. FDCs), with >1 pills	Treatment experienced	95	Adherence, efficacy, safety/tolerability	Yes (adherence)

Study	Study Type	Intervention	Comparator	Population	Sample Size	Outcomes Assessed	Included in Meta-Analysis?
Sterrantino et al[60]	OS	PI-based and NNRTI-based regimen, with NRTI backbone (incl. FDCs)	EFV/TDF/FTC	Treatment-naïve and experienced	427	Adherence, efficacy	Yes (adherence)
Angeletti et al[37]	EM	NNRTI-based STR	RTV-boosted PI-based monotherapy or triple regimen	Treatment-naïve and experienced	NA	Costs	No
Colombo et al[29]	EM	RPV/TDF/FTC	TDF/FTC + RPV, TDF/FTC + EFV, ABC/3TC + EFV, TDF/FTC + ATV/r, ABC/3TC + ATV/r, TDF/FTC + DRV/r, TDF/FTC + RAL	Treatment-naive	NA	Cost, QALYs, ICER	No
Colombo et al[40]	EM	EFV/TDF/FTC	TDF/FTC + EFV	Treatment-naive	NA	Costs, QALYs, ICER	No
Walensky et al[61]	EM	No ART; EFV + 3TC + TDF	EFV/TDF/FTC	Treatment-naïve and experienced	NA	Cost, QALYs, ICER	No

x/y notation indicates single co-formulated drug containing both x and y; x + y notation indicates 2 separate drugs taken together.''2 NTRIs'' usually included FDCs such as TDF/FTC, AZT/3TC, or ABC/3TC. 3TC = lamivudine; ABC/3TC = Kivexa; ABC/AZT/3TC = Trizivir; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; AZT/3TC = Combivir; AZT = zidovudine; COBI = cobicistat; d4T = stavudine; DLT + ABC + 3TC = Triumeq; DLT = dolutegravir; DRV/r = darunavir/ritonavir; EFV/TDF/FTC = Atripla; EFV = efavirenz; EVG/COBI/TDF/FTC = Stribild; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; NA = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTIs = nucleoside reverse-transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RVP/TDF/FTC = Complera/Eviplera; SQV = saquinavir; TDF/FTC = Truvada; TDF = tenofovir.

range) and/or at consistent time points, with a clear comparison between STR and MTR. Demographic characteristics of the studied population depicted in these 9 studies are shown in Table 2. For the 9 studies included in the meta-analyses, RCT were assessed for quality measures per the Cochrane handbook for systematic reviews and OS were assessed using the CASP checklist. For the RCT, a low risk of bias was observed, with unclear observations for blinding in treatment allocations; for OS, 2 were rated as medium and 3 as satisfactory. The detailed assessments are presented in Table 3A and B.

Adherence Outcomes

While 20 of the 35 studies reported patient adherence outcomes, only 5 studies reported quantifiable or analyzable data for meta-analysis. Four (of 35) studies[14,43,59–61] reported patient quantity found to be adherent (per protocol definition; a dichotomous outcome) for STR and MTR and 2 studies[9,14] reported data to calculate the standardized mean difference in medication adherence based on pill count.

In the dichotomous adherence outcome analysis, 75.9% (range: 58.0% to 85.4%) patients were adherent in the STR group versus 65.6% (range: 53.0% to 74.5%) in the MTR group. Correspondingly, patients on STR were found to be statistically significantly more adherent according to their respective study-defined adherence goals when compared to patients on once or twice daily MTR regimens (OR: 2.37 [95% CI: 1.68–3.35], $P < 0.0001$). Minimal heterogeneity was observed ($Chi^2 = 2.78$; $i^2 = 0\%$) (Fig. 2A). In the subanalyses of STR versus twice daily MTR, 84.0% (range: 82.6% to 85.4%) in the STR group were adherent versus 67.3% (range: 60.7% to 73.9%) in the twice-daily MTR group, and the odds of adherence were found to be statistically significantly higher for the STR group (OR: 2.53 [95% CI: 1.13–5.65]) compared with twice daily MTR group ($P = 0.02$; Figure 2A). Comparing STR to once daily MTR, adherence favored STR (84.0% [range: 82.6% to 85.4%] compared with once daily MTR (75.1% [range: 75.0% to 75.1%]), and the odds of adherence were statistically significantly higher for the STR group (OR: 1.81 [95% CI: 1.15–2.84]) compared with the once daily MTR group ($P = 0.01$; Fig. 2A). Similarly, medication adherence based on ''pill count'' was higher in the STR group (92.1% [range: 86.0% to 98.3%]) compared with 84.8 % (range: 73.6% to 95.9%) in the collective MTR groups. The standardized mean difference comparing medication adherence was also statistically significantly in favor of the STR group (SMD: 0.68 [95% CI: 0.40–0.97], $P < 0.0001$) in these analyses (Fig. 2B).

Efficacy Outcomes

Twenty-four of the 35 studies reported efficacy data for viral load suppression and CD4 count. After excluding studies that reported data time points other than 48 weeks and/or parameters not in a quantifiable format, 3 studies[38,41,53] provided analyzable data for viral load suppression (<50 copies/mL) at 48 weeks comparing STR to MTR and the same 3 studies[38,41,53] reported change in CD4 cell count at 48 weeks for the analysis. The viral load suppression at 48 weeks was found to significantly better for STR cohorts in comparison to MTR cohorts (RR: 1.09 [95% CI: 1.04–1.15], $P = 0.0003$); no heterogeneity between the studies were observed (Fig. 3A). The standardized mean difference in CD4 cell count between STR and MTR was not statistically significant at 48 weeks (SMD: −0.01 [95% CI: −0.14 to 0.11], $P = 0.83$), and no heterogeneity between the studies was observed (Fig. 3B).

TABLE 2. Characteristics of Study Population Included in the Meta-Analysis

References	Study Period	Country	Treatment Regimen	N	Age, Median (Range)	Female, n (%)	BL CD4, Count/μL, n (%) Mean (SD), Median (Range)	BL Viral Load (log), copies/mL	Median Duration Since First Positive HIV-1 Test (yr), Mean (SD)	Prior Treatment, n (%)		BL Comorbidity, n (%)
										Naïve	Experienced	
Arribas et al[38]	2011–2012, 96 wk	Europe and North America	EVG/COBI/TDF/FTC	293	41 yr (33–48)	43 (15)	Mean: 604 (SD = 275)	NR	6 (4–8)	NA	Atazanavir: 123 (42); darunavir: 113 (39); lopinavir: 49 (17); fosamprenavir:6 (2); saquinavir: 2 (1)	Positive HBsAg: 10 (3); positive HCV antibody: 19 (7)
			TDF/FTC + RTV-boosted PI (ATV or DRV or LPV or FPV or SQV)	145	40 yr (35–47)	19 (14)	Mean: 624 (SD = 270)	NR	5 (3–6)	NA	Atazanavir: 51 (37); darunavir: 60 (43); lopinavir: 23 (16); Fosamprenavir: 5 (4); saquinavir: 0	Positive HBsAg: 3 (2); positive HCV antibody: 10 (7)
Bangsberg et al[14]	1996–2008, 6 mo	USA	EFV/TDF/FTC	47	Mean (SD): 47.2 (8.2)	10 (21.3)	NR	NR	NR	NR	ART: 25 (53.2)	NR
			RTV-boosted PI + 2 NRTIs	57	Mean (SD): 44.3 (7.3)	19 (33.3)	NR	NR	NR	NR	ART: 11 (19.3)	NR
			NNRTI + 2 NRTIs	14	Mean (SD): 43.6 (8.6)	21.4 (22)	NR	NR	NR	NR	ART: 6 (42.9)	NR
Buscher et al[9]	18 mo	USA	EFV/TDF/FTC	34	<30 yr old: 22 (22); 30–39 yr old: 35 (35); 40–49 yr old: 24 (24); 50 and above: 18 (18)	27 (27)	135 K/mm^3 (36, 271)	5.32 (4.90, 5.73)	NR	29	Not applicable	NR
			>1 pill, once daily regimen	36						34		
			>1 pill, twice daily regimen	29						36		
Dejesus et al[41]	2006, 48 wk	USA and Puerto Rico	EFV/TDF/FTC	203	43 (37–47)	114 (56)	517 (367–670)	<50: 96%; 50 to <200: 3%; ≥200: 1%	NR	NA	PI: 108 (53); NNRTI: 95 (47)	NR
			PI (with or without RTV boosting) + at least 2 NRTIs or NNRTI + at least 2 NRTIs	97	43 (38–50)	11 (11)	515 (377–649)	<50: 98%; 50 to <200: 2%; ≥200: 0%	NR	NA	PI: 52 (54); NNRTI: 45 (46)	NR
Fabbiani et al[43]	1999–2012	Italy	EFV + (TDF + FTC/3TC)	96	42 (32–47)	29 (30.20)	Median (IQR): 430 (322–573)	Median (IQR): 4.8 (4.1–5.3)	Median (IQR): 3.0 (1.4–7.6)	35 (36.5)	61 (63.5)	
			EFV + (TDF + FTC/3TC) or EFV + (ABC + 3TC) or EFV + (AZT + 3TC) or EFV + (other)	457	38 (33–45)	133 (29.10)	Median (IQR): 275 (185–433)	Median (IQR): 4.8 (4.6–5.3)	Median (IQR): 2.5 (0.5–7.4)	248 (54.3)	209 (45.7)	
Palella et al[52]	2010–2012, 48 wk	Europe and North America	RVP/TDF/FTC	317	42 (35–48)	44 (13.9)	Median: 576 (SD: 236.6)	NR	NR	NA	Atazanavir: 122 (38.5); lopinavir: 97 (30.6); darunavir:63(19.9); fosamprenavir: 25 (7.9); saquinavir: 6 (1.9); amprenavir: 1 (0.3)	NR
			RTV-boosted PI + 2 NRTIs	159	43 (36– 49)	15 (9.4)	Median: 600 (SD: 258.8)	NR	NR	NA	Atazanavir: 54 (34.0); lopinavir: 58 (36.5); darunavir:33(20.8); fosamprenavir: 12 (7.5); Saquinavir: 2 (1.3); amprenavir: 0 (0)	NR
Pozniak et al[53]	2011–2012, 96 wk	Australia, Europe, and North America	EVG/COBI/TDF/FTC	291	43 (34–49)	23 (8)	Mean: 586 (SD: 210)	NR	Mean: 6 (SD = 4.3)	NA	Efavirenz: 232 (80); coformulated efavirenz, emtricitabine, and tenofovir: 222 (76); nevirapine: 47 (16); rilpivirine: 9 (3); coformulated rilpivirine, emtricitabine, and tenofovir: 7 (2); etravirine: 3 (1)	Positive for surface antigen of the HBV: 5 (2); positive for HCV antibody: 11 (4)

References	Study Period	Country	Treatment Regimen	N	Age, Median (Range)	Female, n (%)	BL CD4, Count/μL, n (%) Mean (SD), Median (Range)	BL Viral Load (log), copies/mL	Median Duration Since First Positive HIV-1 Test (yr), Mean (SD)	Prior Treatment, n (%)		BL Comorbidity, n (%)
										Naïve	Experienced	
			NNRTI (EFV and non-EFV) + TDF/FTC	147	39 (32–48)	9 (6)	Mean: 593 (SD: 225)	NR	Mean: 5 (SD = 2.9)	NA	EFV: 106 (74); EFV/TDF/FTC: 100 (70); nevirapine: 27 (19); rilpivirine: 10 (7); coformulated rilpivirine, emtricitabine, and tenofovir: 9 (6); etravirine: 0	Positive for surface antigen of the HBV: 3 (2); positive for HCV antibody: 2 (1)
Skwara et al[59]	2013, 6 mo	Poland	EFV/TDF/FTC, RVP/TDF/FTC	31	40	6 (19)	NR	NR		NR	NR	NR
			Any cART (incl. FDCs), with >1 pills	64	37.5	12 (19)	NR	NR		NR	NR	NR
Sterrantino et al[60]	2010–2012	Italy	EFV/TDF/FTC and PI-based and NNRTI-based regimen, with NRTI backbone (incl. FDCs)	372	47.7 (42.1–54.5)	85 (22.8)	Median (IQR): 602 (423.5–825.0)	<50 copies/mL: 334 (89.8)	NR	53 (14.2)	Overall duration of ART (months), median (IQR): 123 (55.2–173.0); duration of current cART (months), median (IQR): 19.2 (11.0–36.4)	HCV positive: 76 (20)

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; AZT/3TC = combivir; AZT = zidovudine; d4T = stavudine; DRV/r = darunavir/ritonavir; EFV = efavirenz; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; LPV/r = lopinavir/ritonavir; NA = not applicable; NNRTI = non-nucleoside reversetranscriptase inhibitor; NR = not reported; NRTIs = nucleoside reverse-transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = rilpivirine; TDF/FTC = truvada; TDF = tenofovir.

Safety and Tolerability Outcomes

Of the 35 studies, 16 reported safety outcomes with data relevant to adverse events (AEs), laboratory abnormalities, mortality, and tolerability (treatment discontinuation). Four RCT studies reported analyzable data for the safety outcome parameters.[38,41,52–53] While all 4 studies reported reasons for discontinuation, 2 reported protocol-defined SAEs,[38,53] 3 reported Grade 3 to 4 AEs,[38,52–53] 2 reported Grade 3 to 4 laboratory abnormalities,[38,52] and 2 reported mortality.[38,53]

Meta-analyses of SAEs, grade 3 to 4 AEs and mortality revealed no statistically significant differences between STR and MTR (Fig. 3C). Risk Ratio (RR) of any SAEs (RR: 1.00 [95% CI: 0.55–1.82], $P = 0.99$), Grade 3 to 4 AEs (RR: 0.77 [95% CI: 0.50–1.67], $P = 1.20$), and mortality (RR: 0.49 [95% CI: 0.05–4.65], $P = 0.53$) was minimal. No heterogeneity was observed among the studies. A statistically significantly lower RR for Grade 3 to 4 laboratory abnormalities appeared for the STR group compared with the collective MTR groups (RR: 0.68 [95% CI: 0.49–0.94], $P = 0.02$), with no heterogeneity in the studies.

Tolerability (treatment discontinuations due to any reason) were also similar among the STR and MTR groups (RR: 0.67 [95% CI: 0.40–1.11], $P = 0.12$) (Fig. 3D). High heterogeneity was observed in the tolerability studies ($chi^2 = 8.63$, $i^2 = 65\%$), potentially due to variation in study design/population.

Economic Summary

Ten economic studies were critically evaluated (6 economic evaluations[10–11,30–31,44,47] and 4 model-based studies),[29,37,40,61] but none were included in the meta-analysis. In terms of HRU, 1 study[10] reported lower inpatient and outpatient services, number of prescriptions, and total healthcare encounters per month for patients on STR in comparison with 2 or more pills per day. Similarly, a second[31] reported substantially lower inpatient service use among both non-AIDS and AIDS patients on STR versus those on MTR and other regimens while also finding comparable costs/patient/year at 6 and 12 months. A third[47] study reported marginally, but not statistically significantly, lower total cost per day for the FDC regimen (including STR) compared with the other regimen. A fourth[44] reported insignificantly lower average wholesale prices for STR (vs MTR). Two studies[30,63] reported statistically significantly lower total HRU costs per month ($P = 0.0001$) and lower mean annual cost ($P = 0.0001$) in STR patients compared with MTR. The only available mathematical model-based studies offer conflicting outcomes in that 1 reported higher annual cost/person and higher ICER for branded STR in comparison to generic alternatives[61] whereas a second reported statistically significantly lower annual cost associated with STR ($P = 0.0001$),[40] both comparing to MTR. The sixth[37] reported only marginal cost savings associated with switching from any cART to STR; this study also projected annual average HRU-related cost decreases of 0.6% to 6.1% and 0.9% to 8.6% for overall HRU-related costs and ART treatment only, respectively, when considering impact of ART generics in the 2012 to 2016 time period.[37] Lastly, 1 study found STR to be the most cost-effective owing to higher quality-adjusted life-years (QALYs) and the corresponding lower ICER compared with MTR.[29]

DISCUSSION

This meta-analysis found 1 of the efficacy outcomes (change in CD4 cell count at 48 weeks), tolerability

TABLE 3. Quality of Studies

A: Quality of RCT Included in Quantitative Evidence Synthesis (Meta-Analysis)

RCT		Arribas et al[38]	Dejesus et al[41]	Palella et al[52]	Pozniak et al[53]
Selection bias	Was randomization carried out appropriately?	Yes	Unclear	Yes	Yes
	Risk of bias	Low	Unclear	Low	Low
	Was the concealment of treatment allocation adequate?	Yes	Unclear	Yes	Yes
	Risk of bias	Low	Unclear	Low	Low
Performance bias	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	Yes	Yes
	Risk of bias	Low	Low	Low	Low
	Were the care providers, participants, and outcome assessors blind to treatment allocation?	No	No	No	No
	Risk of bias	High	High	High	High
Reporting bias	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
	Risk of bias	Unclear	Low	Low	Low
Detection bias	Did the analysis include an intention-to-treat analysis?	Yes	Yes	Yes	Yes
	Appropriate?	Yes	Yes	Yes	Yes
	Missing data handling	Yes	No	Yes	Yes
	Risk of bias	Low	Unclear	Low	Low
Attrition bias	Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
	Were they explained or adjusted for?	Yes	Yes	Yes	Yes
	Risk of bias	Low	Low	Low	Low

B: Quality of Observational Studies Included in Quantitative Evidence Synthesis (Meta-Analysis)

CASP Section	Question	Fabbiani et al[43]	Skwara et al[59]	Buscher et al[9]	Bangsberg et al[14]	Sterrantino et al[60]
Are the results of the study valid?	Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
	Was the cohort recruited in an acceptable way?	Yes	Cannot tell	Yes	Yes	No
	Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes	Cannot tell	Yes
	Was the outcome accurately measured to minimize bias?	Yes	No	Yes	Yes	No
	Have the authors identified all important confounding factors?	Yes	No	Yes	Cannot tell	Yes
	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Cannot tell	Yes	Yes	No
	Was the follow up of subjects complete enough?	Yes	Yes	Yes	Cannot tell	Cannot tell
	Was the follow up of subjects long enough?	Yes	Yes	Yes	Yes	Cannot tell

B: Quality of Observational Studies Included in Quantitative Evidence Synthesis (Meta-Analysis)

CASP Section	Question	Fabbiani et al[43]	Skwara et al[59]	Buscher et al[9]	Bangsberg et al[14]	Sterrantino et al[60]
What are the results?	What are the results of this study?	STR found to be associated with higher adherence, lower virological failure and low CNS toxicity compared to MTR	STR was associated with improved adherence, quality of life and efficacy compared to MTR	STR showed better adherence compared to MTR (twice daily) in both overall and ART naive population. However, the difference was not significant for STR vs MTR (>1 pill regimen) for all population	One-pill per day STR was associated with good adherence and viral suppression in a challenging population	Nonadherence was lower in the STR as compared to multi-tablet regimen
	How precise are the results?	Results appear precise as confidence intervals were not so wide	Results were not presented with the variance	The study findings were precise as inter quartile ranges were found to be narrow	Precision was unclear as study did not report results with the confidence intervals	The study results were precise enough
	Do you believe the results?	Cannot tell; uncontrolled bias can occur in the retrospective studies	Cannot tell	Yes	Yes	Yes
Will the results help locally?	Can the results be applied to the local population?	Yes	Yes	Yes	Yes	No
	Do the results of this study fit with other available evidence?	Yes	Yes	No	Yes	Yes
	What are the implications of this study for practice?	There was difference in baseline characteristics between the treatment groups so the results should be considered cautiously	The results should be considered cautiously as the treatment duration was longer in patients using multi-tablet regimens	The study results could not be generalized as patients, who did not receive HAART during the study, died or was not followed up	Simplification of therapy represents an important step forward in supporting adherence and treatment success	The study overestimates the adherence, as patients were on steady cART; also self reporting may overestimate the level of adherence
	Overall quality	Medium	Satisfactory	Medium	Satisfactory	Satisfactory

(discontinuation due to any reason), and select safety outcomes (any SAEs, grade 3 to 4 AEs and mortality) to be comparable between STR and MTR. The incidence of Grade 3 to 4 laboratory abnormalities was found to be statistically significantly lower in the STR group ($P = 0.02$) while the viral load suppression (at 48 weeks) was found to be statistically significantly higher in the STR group ($P = 0.0003$), in comparison to the MTR group. An additional body of evidence identified in the qualitative evidence synthesis further depicted STR to have impact on maintaining virologic and immunologic efficacy and was found to be generally tolerable with lower AEs, while resulting in better adherence, in comparison to MTR.[13,27,45,58,64] Collectively, these data portray STR as durable once initiated without sacrificing treatment goals. Theoretically, as STR prohibits splitting of agents into individual components, providers' assurance is heightened that patients are receiving the correct dose of all prescribed medications.

Another important finding in this meta-analysis is the confirmation of adherence-related benefits associated with STR. The odds of adherence associated with STR was found to be 2.37 times higher than MTR ($P < 0.0001$), and the odds remained in favor of STR irrespective of whether MTR was administered once ($P = 0.01$) or twice daily ($P = 0.02$). Further, STR resulted in statistically significant higher medication adherence using ''pill count'' ($P < 0.0001$). This aligns with historical meta-analyses[7,8] and reinforces observations[48] of patients on STR to be 2.1 times more likely to have complete antiretroviral adherence.

ART adherence is critical to not only better health but also to improved QoL, HIV prevention, HIV viral load suppression, drug resistance prevention, and ultimately survival.[3,7,10,15,27,65–70] Highly associated with failure to adhere are unfavorable health outcomes beyond HIV such as cardiovascular and cerebrovascular disease,[4,71–73] auto-immune disease,[5] and mental illness.[74] It is established that there are statistically significant effects of reduction in pill burden on improving adherence correlated to improved patient QoL when switched from individual components to an STR.[13]

Economically supporting the clinical findings, STR lowered resource utilization in comparison to patients on MTR.[10,31] Mean costs (annual, bi-annual, monthly, or per-diem) were found to be lower for the STR group compared with multiple tablets[30,40,44,47,63] and deemed cost-effective as a function of lower ICER.[29] These observations may have important implications for patients and their healthcare systems. Currently, several national and regional payers across the world are exercising fiscal management of healthcare expenditures, putting pressure on healthcare providers to adhere to standard clinical treatment guidelines and to document evidence for improved health outcomes and resource savings, which supports continued reimbursement of costly medicines.[75–77] Since HIV is managed as a chronic disease, demonstrated savings in HRU and associated costs may help healthcare systems to spare resources to expand the safety net for the HIV population in need of care. This effect is even more pronounced in resource-poor settings, where the stakeholders are sometimes forced to make choices between treatment efficacy/safety and cost. Both policymakers and providers are focused on the rapid scale-up of affordable and effective healthcare interventions to provide timely access to care and to further reduce the spread of HIV.[3,15,28,78–79] The WHO has advised countries to consider in-country cART costs and has encouraged implementation of public health approaches to scaling up quality HIV care and treatment and

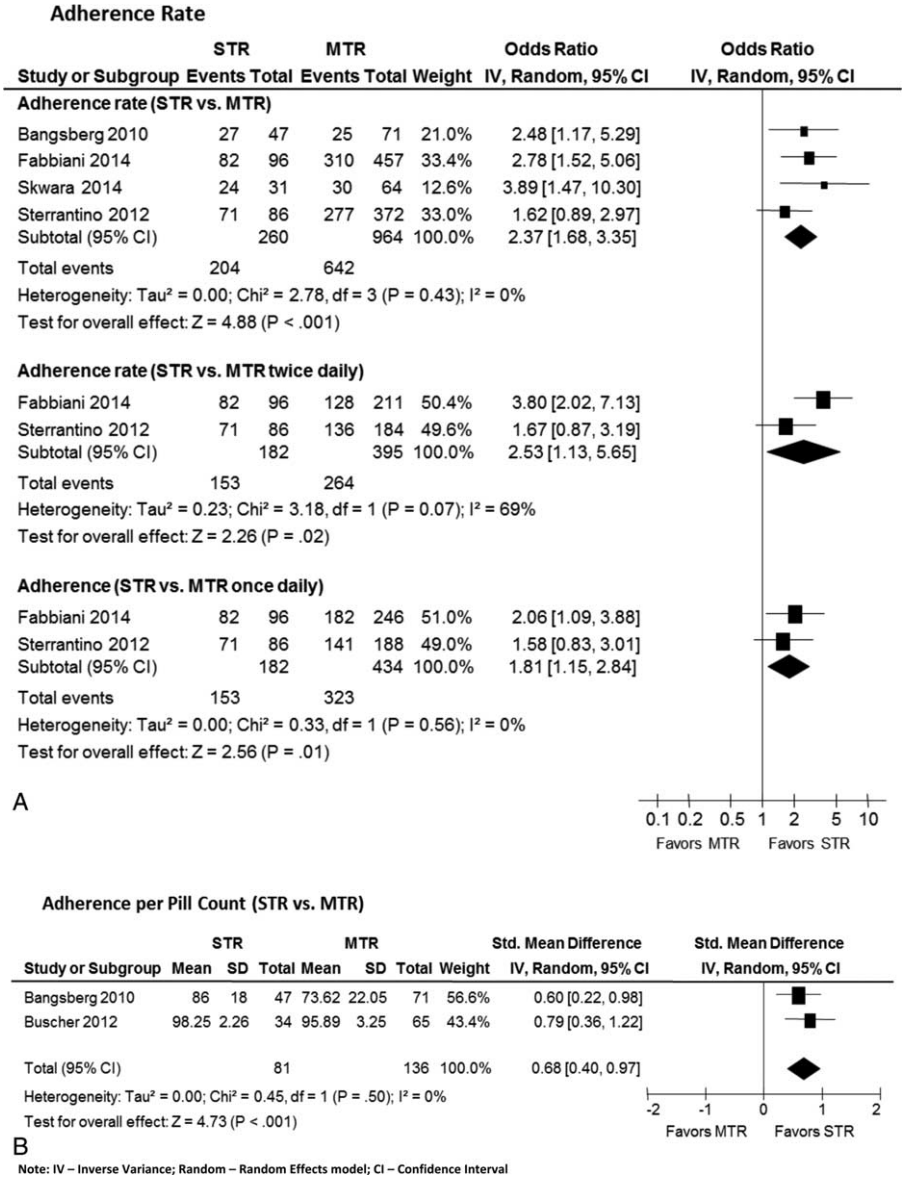

FIGURE 2. Adherence outcomes. CI = confidence interval; IV = inverse variance; Random = random effects model.

simplifying and standardizing ART regimens.[69,77,80–82] In such scenarios, access to STR may prove valuable for patients, physicians, and healthcare systems over the long term. Recent updates on guidelines from WHO, UNAIDS, and various countries support the use of FDC regimens, and many particularly mention STR as 1 of the primary recommended treatments in the management of HIV across the world.[2,15–25,83] Widespread use of ARTs (including STRs) may initially increase the ART-specific budget for resource-limited settings, but could also lower overall HRU in the long-term and facilitate achievement of public health goals.[84,85]

STUDY STRENGTHS AND LIMITATIONS

The strengths of this review include a search strategy with explicit inclusion and exclusion criteria and the use of a random-effects model to assess pooled estimates extracted from RCT and OS, minimizing the risk of outliers in the accompanying heterogeneity analyses. Since the focus of this analysis was to specifically compare FDC-containing STR to MTR, a large number of studies were excluded on the basis of analyzable data with accurate and quantifiable measurement of outcomes of interest. Efficacy results were reported at several time-points across the included studies; however, only 48-week outcomes data were included in the analyses for consistency. Variations in the patient population characteristics at baseline were also noted and assumed to contribute to heterogeneity in the analytic results in some instances. Finally, dosing scheme may just be 1 of the differences between the regimens when examining these particular health and economic outcomes.

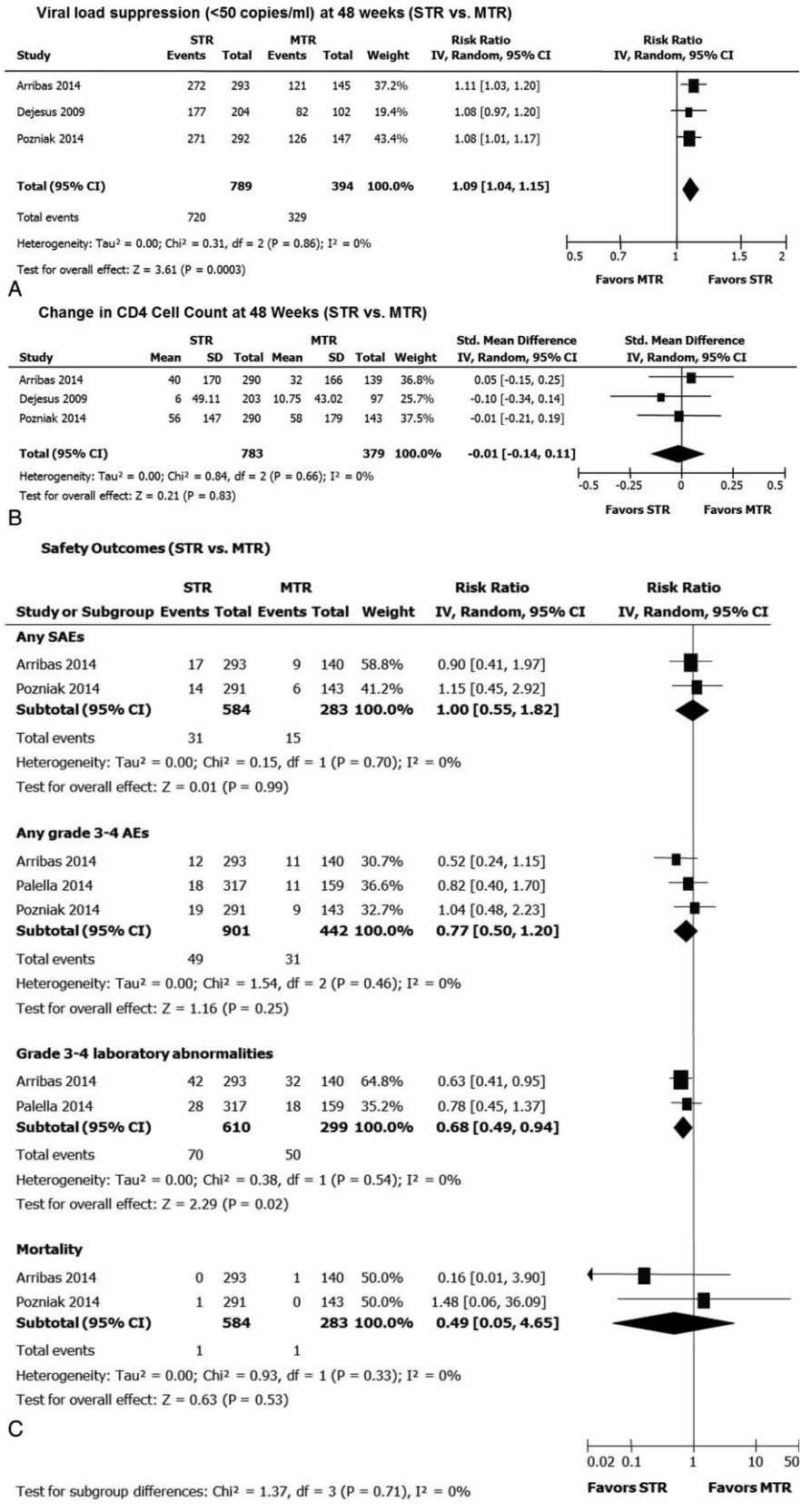

FIGURE 3. Efficacy, safety, and tolerability outcomes. CI = confidence interval; IV = inverse variance; Random = random effects model.

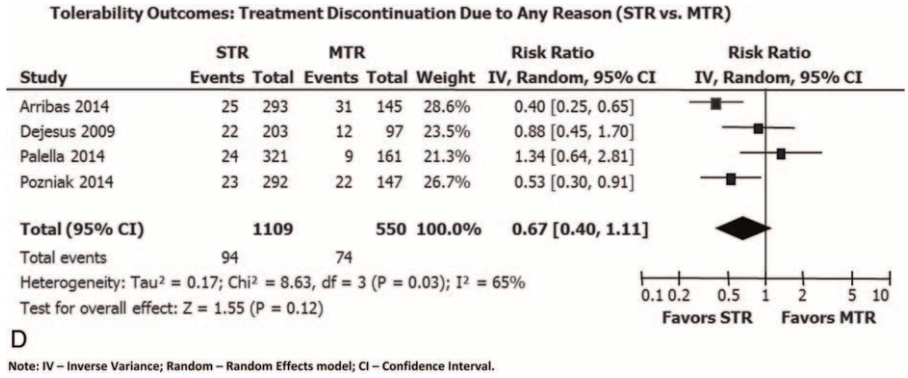

FIGURE 3. Efficacy, safety, and tolerability outcomes. CI = confidence interval; IV = inverse variance; Random = random effects model.

CONCLUSIONS

The findings from this literature review and meta-analysis depicted comparable tolerability, safety (all SAE and Grade 3–4 AE), mortality results and changes in CD4 cell counts between patients on FDC-containing STR and MTR. However, patients on STR have statistically significantly better viral load suppression (<50 copes/mL), fewer Grade 3 to 4 lab abnormalities and better adherence compared with patients on MTR—all critical to long-term ART goals.[15,27,66,67] Additionally, these analyses discovered potentially reduced treatment and HRU and costs in patients taking STR in comparison to MTR. To the best of our knowledge, this study represents the most up-to-date and comprehensive evidence on FDC-containing STR versus MTR, encompassing both clinical and economic outcomes.

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