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

P.G. Clay, PharmD, S. Nag, PhD, C.M. Graham, PhD, and S. Narayanan, MS, MHS

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 = 0.003; 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.

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.2 ART is recommended by the World Health Organization (WHO) as an effective treatment for HIV disease progression and prevention.3 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.4

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.5–8 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...
>90% adherence when compared with MTR. Therefore, several guidelines urge providers to use STR and MTR containing FDCs when choosing regimens of similar efficacy and tolerability for their patients. STRs may provide long-term durability, allowing for continued immunological recovery, leading to increased life expectancy. Further, STRs appear to generate improved adherence, higher perceived quality of life (QoL), and lower costs to the healthcare system. 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 comparisons 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 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. A critical appraisal was conducted for the OS included in the meta-analysis, using the Critical Appraisal Skills Programme (CASP), United Kingdom checklist, 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. Heterogeneity was evaluated using the Chi-squared test and quantified using the I² statistic. Alpha < 0.05 was used to determine statistical significance. I² 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 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), 13 were RCT, and 4 were EM-based studies. 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-naïve 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...
| Study          | Study Type | Intervention                | Comparator                  | Population                  | Sample Size | Outcomes Assessed                                                                 | Included in Meta-Analysis? |
|---------------|------------|-----------------------------|-----------------------------|-----------------------------|-------------|-----------------------------------------------------------------------------------|----------------------------|
| Arribas et al | RCT        | EVG/COBI/TDF/FTC            | TDF/FTC plus RTV-boosted PI | Treatment experienced       | 438         | Adherence, efficacy, safety/tolerability                                            | Yes (efficacy, safety/tolerability) |
| Cohen et al   | RCT        | EVG/COBI/TDF/FTC            | EFV/FTC                     | Treatment naïve             | 71          | Efficacy, safety/tolerability                                                     | No                          |
| Cohen et al   | RCT        | RVP/TDF/FTC                 | EVP/TDF/FTC                 | Treatment-naive             | 799         | Adherence, efficacy, safety/tolerability                                            | No                          |
| Dejesus et al | RCT        | EFV/TDF/FTC                 | PI (with or without RTV boosting) + at least 2 NRTIs | Treatment experienced | 306         | Adherence, efficacy, safety/tolerability                                            | Yes (efficacy, safety/tolerability) |
| Landman et al | RCT        | EFV/TDF/FTC                 | TDF/FTC + NVP, TDF + LPV/r | Treatment-naive             | 120         | Adherence, efficacy, safety/tolerability                                            | No                          |
| NCT00112047   | RCT        | EFV/TDF/FTC                 | CBV + EFV                   | Treatment-naive             | 511         | Efficacy, safety/tolerability                                                     | No                          |
| NCT01403051   | RCT        | EFV/TDF/FTC                 | EVP/FTC/TDF/TDF plus vitamin D3 and calcium carbonate | Treatment-naive            | 167         | Efficacy, safety/tolerability                                                     | No                          |
| Palella et al | RCT        | EVP/COBI/TDF/FTC            | RTV-boosted PI + 2 NRTIs    | Treatment experienced       | 482         | Adherence, efficacy, safety/tolerability                                            | Yes (efficacy, safety/tolerability) |
| Pozniak et al | RCT        | EVP/COBI/TDF/FTC            | NNRTI (EFV and non-EFV) + TDF/FTC | Treatment experienced | 439         | Adherence, efficacy, safety/tolerability                                            | Yes (efficacy, safety/tolerability) |
| Rockstroh et al | RCT      | EVP/COBI/TDF/FTC            | RTV/ATV + TDF/FTC           | Treatment-naive             | 715         | Adherence, efficacy, safety/tolerability                                            | No                          |
| Sax et al     | RCT        | EVP/COBI/TDF/FTC            | EVP/FTC                     | Treatment-naive             | 707         | Adherence, efficacy, Safety/tolerability                                            | No                          |
| Sax et al     | RCT        | EVP/COBI/TDF/FTC            | EVP/COBI/FTC/TDF            | Treatment-naive             | 171         | Adherence, efficacy, safety/tolerability                                            | No                          |
| Walmsley et al | RCT    | EVP/COBI/TDF/FTC            | EVP/FTC                     | Treatment-naive             | 844         | Adherence, efficacy, safety/tolerability                                            | No                          |
| Airoldi et al | OS         | EVP/COBI/TDF/FTC            | Switched from 3TC/TDF or TFC/TDF FDCs (or combination of separate pills) | Treatment experienced | 212         | Adherence, efficacy                                                               | No                          |
| Bangsberg et al | OS       | EVP/FTC                     | EVP/FTC/TDF/TDF + 3TC/TDF   | Treatment naïve and experienced | 118         | Adherence, efficacy                                                               | Yes (adherence)              |
| Beck et al    | OS         | EVP/FTC                     | TDF/FTC + EVP, TDF + EFV, TDF + 3TC + EVP | Treatment-naive            | 1448        | HRU/costs, adherence                                                             | No                          |
| Buscher et al | OS         | EVP/FTC                     | Any cART (incl. FDCs) with >1 pills | Treatment-naive            | 184         | Adherence, efficacy                                                               | Yes (adherence)              |
| Cohen et al   | OS         | EVP/FTC                     | Any cART (incl. FDCs) with >1 pills | Treatment-naive and experienced | 7381        | HRU/costs, adherence                                                             | No                          |
| Colombo et al | OS         | EVP/FTC                     | EFV + TDC + FTC, ATV/r + TDF, DRV/r + TDF + FTC, LPV/r + TDF + FTC | Treatment-naive and experienced | 474         | Costs                                                                               | No                          |
| Engsig et al  | OS         | EVP/FTC                     | TDF+3TC + EFV                | G1: treatment experienced, G1I: 167, G1I: 868 | 553         | Adherence, efficacy                                                               | Yes (adherence)              |
| Fabbiani et al | OS       | EVP/FTC                     | EFV + NRTI backbone (incl. TDF/FTC, AZT/3TC) | Treatment experienced | 553         | Adherence, efficacy                                                               | Yes (adherence)              |
| Grimes et al  | OS         | EVP/FTC                     | ATZ/r + TDF/FTC, DRV/r + TDF/FTC, RAL + TDF/FTC, EFV + ABC/3TC, DRV + ABC/TDF/3TC, etc. | Treatment-naive and experienced | NA         | Costs                                                                               | No                          |
| Hanna et al   | OS         | EVP/FTC                     | Multiple-tablet regimen of any type | Treatment experienced | 1727        | Adherence, efficacy                                                               | No                          |
| Hill et al    | OS         | EVP/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   | OS         | EVP/FTC                     | PI or NRTI-based cART with individual components | Treatment experienced | 225         | HRU/costs                                                             | No                          |
| Juday et al   | OS         | EVP/FTC                     | PI- or NNRTI-based cART with at least 2 NRTIs | Treatment experienced | 461         | HRU, adherence                                                              | No                          |
| Juday et al   | OS         | EVP/FTC                     | LPV/r-containing, ATV/r-containing, other PI-containing regimen with TDF/FTC, AZT/3TC, etc. | Treatment-naive and experienced | 2460        | Persistence                                                              | No                          |
| Pujari et al  | OS         | EVP/FTC                     | NA                         | Treatment-naive             | 141         | Adherence, efficacy, safety/tolerability                                            | No                          |
| Scourfield et al | OS    | EVP/FTC                     | NA                         | Treatment-naive             | 472         | Adherence, efficacy, safety/tolerability                                            | No                          |
| Skwara et al  | OS         | EVP/FTC                     | Any cART (incl. FDCs) with >1 pills | Treatment experienced | 95          | Adherence, efficacy, safety/tolerability                                            | Yes (adherence)              |
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 \(^1,4,38,59,61\) 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; \(P = 0.0001\)).

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 be 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 was 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).
| References | Study Period | Country | Treatment Regimen | N | Age, Median (Range) | Female, n (%) | BL CD4, Count/mL (Mean ± SD) | Median Viral Load (log), copies/mL (Mean ± SD) | Median Duration Since First Positive HIV-1 Test (yr), Mean (SD) | Prior Treatment, n (%) | Comorbidities, n (%) |
|------------|--------------|---------|-------------------|---|-------------------|-------------|---------------------------|-----------------------------------------------|--------------------------|----------------------|---------------------|
| Arribas et al | 2011–2012, 96 wk | Europe and North America | EVG/COB/H/FTC | 293 | 41 yr (33–46) | 40 (15) | Mean: 604 (SD = 251) | NR | 6 (4–8) | NA | Atazanavir: 123 (42); darunavir: 113 (39); lopinavir: 49 (17); fosamprenavir: 6 (2); saquinavir: 2 (1) | Positive HBsAg: 10 (31); positive HCV antibody: 19 (7) |
| Bangsberg et al | 1996–2008, 6 mo | USA | EFV/TDF/FTC | 47 | Mean (SD): 47.2 (8.2) | 10 (21.3) | NR | NR | 34 | | ART: 25 (53.2) |
| Buscher et al | 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/mm³ (36, 271) | 5.32 (4.90, 5.73) | NR | 29 | Not applicable |
| DeJesus et al | 2006, 48 wk | USA and Puerto Rico | EFV/TDF/FTC | 203 | 43 (37–47) | 114 (56) | 517 (567–630) | <50%: 96%; 50 to <200: 2%; 200 to <500: 1% | 35 (36.5) | 61 (63.5) |
| Pozniak et al | 2011–2012, 96 wk | Australia, Europe, and North America | EVG/COB/H/FTC | 291 | 43 (34–49) | 23 (8) | Mean: 586 (SD = 210) | NR | Mean: 6 (SD = 4.3) | NA | Efavirenz: 232 (90); coformulated efavirenz, emtricitabine, and tenofovir: 222 (76); nevirapine: 47 (16); rilpivirine: 9 (3); coformulated rilpivirine, emtricitabine, and tenofovir: 7 (2); emtricitabine: 3 (1) | Positive for surface antigens of the HBV: 5 (2); positive for HCV antibody: 11 (4) |
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.\(^\text{58,41,52–53}\) While all 4 studies reported reasons for discontinuation, 2 reported protocol-defined SAEs,\(^\text{58,53}\) 3 reported Grade 3 to 4 AEs,\(^\text{38,52–53}\) 2 reported Grade 3 to 4 laboratory abnormalities,\(^\text{38,52}\) and 2 reported mortality.\(^\text{38,53}\)

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.

Toleration (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,\(^\text{10–11,30–31,44,47}\) and 4 model-based studies,\(^\text{49,50,61}\)) but none were included in the meta-analysis. In terms of HRU, 1 study\(^\text{10}\) 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\(^\text{31}\) reported substantially lower total cost per day for the FDC regimen (including economic evaluations\(^\text{10–11,30–31,44,47}\) and 4 model-based studies) compared with the other regimen. A fourth\(^\text{44}\) reported insignificantly lower average wholesale prices for STR (vs MTR). Two studies\(^\text{30,53}\) reported statistically significantly lower total HRU costs per month (\(P = 0.0001\)) 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\(^\text{61}\) whereas a second reported statistically significantly lower annual cost associated with STR (\(P = 0.0001\)) both comparing to MTR. The sixth\(^\text{37}\) 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.\(^\text{37}\)

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.\(^\text{39}\)

**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 |
| | Risk of bias | Yes | Yes | Yes | Yes |
| | Missing data handling | Yes | No | Yes | Yes |
| | Risk of bias | Yes | Yes | Yes | Yes |
| Attrition bias | Were there any unexpected imbalances in drop-outs between groups? | No | No | No | No |
| | Risk of bias | Low | Unclear | Low | Low |

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

| CASP Section | Question | Fabbiani et al [43] | Skwara et al [49] | 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 | Cannot tell | Cannot tell |
What are the results of this study? STR found to be associated with good adherence and viral suppression compared to MTR. However, the difference was not significant for STR vs MTR (P < 0.0001). Further, STR resulted in statistically significant higher medication adherence using "pill count" (P < 0.0001). This aligns with historical meta-analyses and reinforces observations 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. Highly associated with failure to adhere are unfavorable health outcomes beyond HIV such as cardiovascular and cerebrovascular disease, autoimmune disease, and mental illness. 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.

Economically supporting the clinical findings, STR lowered resource utilization in comparison to patients on MTR. Mean costs (annual, bi-annual, monthly, or per-diem) were found to be lower for the STR group compared with multiple tablets and deemed cost-effective as a function of lower ICER. 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. 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.
simplifying and standardizing ART regimens. 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. Wide-spread 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.

**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 2.** Adherence 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 copies/mL), fewer Grade 3 to 4 lab abnormalities and better adherence compared with patients on MTR—all critical to long-term ART goals. 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.

ACKNOWLEDGMENTS

The authors would like to thank the team at Capita India Pvt Ltd for their database searches and analytic support, and Helen Pan for her help with supplemental literature reviews.

REFERENCES

1. WHO. HIV/AIDS Factsheet Number 360. 2014. Available http://www.who.int/hiv/pub/factsheets/fs360/en/

2. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. June 30, 2013. Available http://www.who.int/hiv/pub/guidelines/arv2013/en/

3. Astuti N, Maggiolo F. Single-tablet regimens in HIV therapy. Infect Dis Ther. 2014;3:1–17.

4. Frishman WH. Importance of medication adherence in cardiovascular disease and the value of once-daily treatment regimens. Cardiol Rev. 2007;15:257–263.

5. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2006;23:577–585.

6. Lafeber M, Grobbee DE, Schrover IM, et al. Comparison of a morning polypill, evening polypill and individual pills on LDL-cholesterol, ambulatory blood pressure and adherence in high-risk patients: a randomized crossover trial. Int J Cardiol. 2014;181C:193–199 [Epub ahead of print].

7. Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. Clin Infect Dis. 2014;58:1297–1307.

8. Parienti JJ, Bangsberg DR, Verdon R, et al. Better adherence with once-daily antiretroviral regimens: a meta-analysis. Clin Infect Dis. 2009;48:484–488.

9. Buscher A, Hartman C, Kal len MA, et al. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, HAART naïve, HIV patients. Int J STD AIDS. 2012;23:351–355.

10. Cohen CJ, Meyers JL, Davis KL. Association between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US Medicaid population with HIV. BMJ Open. 2013;3:e003028.

11. Juday T, Gupta S, Grimm K, et al. Factors associated with complete adherence to HIV combination antiretroviral therapy. HIV Clin Trials. 2011;12:71–78.

12. Nachega JB, Mugavero MJ, Zeier M, et al. Treatment simplification in HIV-infected adults as a strategy to prevent toxicity, improve adherence, quality of life and decrease healthcare costs. Patient Prefer Adherence. 2011;5:357–367.

13. Airoldi M, Zaccarelli M, Bisi L, et al. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. Patient Prefer Adher. 2010;4:115–125.

14. Bangsberg DR, Ragland K, Monk A, et al. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. AIDS. 2010;24:2835–2840.

15. Department of Health and Human Services (DHHS). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. November 2014. Available http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

16. EACS. European AIDS Clinical Society Guidelines Version 7.1. November 2014. Available http://www.eacsociety.org/files/guideline-files/English_71_141204.pdf

17. Panel of Experts of GESIDA & Spanish Secretariat for the National Plan on AIDS. Executive summary. Consensus document of GESIDA and SPNS (Spanish Secretariat for the National Plan on AIDS) regarding combined antiretroviral treatment in adults infected by the human immunodeficiency virus. Enferm Infec Microbiol Clin. 2012;30:315–324.

18. Gunthard HF, Aberg JA, Er on JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA. 2014;312:410–425.

19. Hoen B, Bonnet F, Delaugerre C, et al. French 2013 guidelines for antiretroviral therapy of HIV-1 infection in adults. J Int AIDS Soc. 2014;17:e19034.
20. Marrazzo JM, del Rio C, Holgrave DR, et al. HIV prevention in clinical care settings: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA. 2014;312:390–409.

21. Raffi F, Reyes J. Antiretroviral treatment French guidelines 2013: economics influencing science. J Antimicrob Chemother. 2014;69:1158–1161.

22. Rouleau D, Fortin C, Trottier B, et al. Antiretroviral therapy for adults infected with HIV: guidelines for health care professionals from the Quebec HIV care committee. Can J Infect Dis Med Microbiol. 2011;22:52–60.

23. South African National AIDS Council. The South African Antiretroviral Treatment Guidelines 2010. Available http://www.uj.ac.za/EN/Corporate Services/ihoa/Document/Document/ART%20Guideline.pdf

24. Sungkanuparp S, Tchesahith W, Utaipiboon C, et al. Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010. Asian Biomed. 2010;4:515–528.

25. Williams I, Churchill D, Anderson J, et al. British HIV Association guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012 (updated November 2013). HIV Med. 2014;15(Suppl 1):1–85.

26. Deeks ED, Penny CM. Efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Atripla): a review of its use in the management of HIV infection. Drugs. 2010;70:2315–2338.

27. Cohen C, Elion R, Ruane P, et al. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. AIDS. 2011;25:F7–F12.

28. Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? Curr Med Res Opin. 2014;30:89–97.

29. Colombo GL, Di Matteo S, Antinori A, et al. Economic evaluation of initial antiretroviral therapy for HIV-infected patients: an update of Italian guidelines. Clinicoecon Outcomes Res. 2013;5:489–496.

30. Colombo GL, Castagna A, Di Matteo S, et al. Cost analysis of initial highly active antiretroviral therapy regimens for managing human immunodeficiency virus-infected patients according to clinical practice in a hospital setting. Ther Clin Risk Manag. 2014;10:9–15.

31. Beck EJ, Mandalia S, Sangha R, et al. Lower healthcare costs associated with the use of a single-pill ARV regimen in the UK, 2004–2008. PLoS ONE. 2012;7:e47376.

32. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

33. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (updated September 2009). The Cochrane Collaboration 2008. Available www.cochrane-handbook.org

34. Critical Appraisal Skills Programme (CASP) Systematic Review Checklist 31.05.13. Available http://media.wix.com/ugd/dded87_37491d0241aa488af3d4ae17c694972.pdf

35. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clinicoecon Outcomes Res. 2003;5:59–68.

36. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–1558.

37. Angeletti C, Pezzotti P, Antinori A, et al. Antiretroviral treatment-based cost saving interventions may offset expenses for new patients and earlier treatment start. HIV Med. 2014;15:165–174.

38. Arribas JR, Paoloux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. Lancet Infect Dis. 2014;14:581–589.

39. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. AIDS. 2014;28:989–997.

40. Colombo GL, Di Matteo S, Maggiolo F. Antiretroviral therapy in HIV-infected patients: a proposal to assess the economic value of the single-tablet regimen. Clinicoecon Outcomes Res. 2013;5:59–68.

41. DeJesus E, Young B, Morales-Ramirez JO, et al. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate versus unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. J Acquir Immune Defic Syndr. 2009;51:163–174.

42. Engsig FN, Gerstoft J, Helleberg M, et al. Effectiveness of antiretroviral therapy in individuals who for economic reasons were switched from a once-daily single-tablet regimen to a triple-tablet regimen. J Acquir Immune Defic Syndr. 2014;66:407–413.

43. Fabbiani M, Zaccarelli M, Grima P, et al. Single tablet regimens are associated with reduced Efavirenz withdrawal in antiretroviral therapy naive or switching for simplification HIV-infected patients. BMC Infect Dis. 2014;14:26.

44. Grimes RM, Shenouda TA. Using cost as a consideration for antiretroviral regimen selection: an example using average wholesale prices. AIDS Care. 2013;25:1380–1384.

45. Hanna DB, Hessol NA, Golub ET, et al. Increase in single-tablet regimen use and associated improvements in adherence-related outcomes in HIV-infected women. J Acquir Immune Defic Syndr. 2014;65:587–596.

46. Hill S, Kavookjian J, Qian J, et al. Effects of pill burden on discontinuation of the initial HAART regimen in minority female patients prescribed 1 pill/day versus any other pill burden. AIDS Care. 2014;26:595–601.

47. Homar F, Lozano V, Martinez-Gomez J, et al. Cost analysis of HIV treatment and drug-related adverse events when fixed-dose combinations of antiretrovirals (FDCs) were stopped, versus continuation with FDCs. Health Econ Rev. 2012;2:1–9.

48. Juday T, Grimm K, Zoe-Powers A, et al. A retrospective study of HIV antiretroviral treatment persistence in a commercially insured population in the United States. AIDS Care. 2011;23:1154–1162.

49. Landman R, Koulla-Shiro S, Sow PS, et al. Evaluation of four tenofovir-containing regimens as first-line treatments in Cameroon and Senegal: the ANRS 12115 DAYANA trial. Antivir Ther. 2014;19:51–59.

50. NCT00112047. A phase 3, randomized, multicenter study of the treatment of antiretroviral-naive HIV-1 infected subjects comparing tenofovir disoproxil fumarate and emtricitabine in combination with efavirenz vs combivir (lamivudine/zidovudine) and efavirenz. Gilead Sciences. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 (cited 2014DEC10). Available https://clinicaltrials.gov/ct2/show/study/NCT00112047 NLM Identifier: NCT00112047. (accessed November 12, 2014)

51. NCT01403051. A prospective, randomized, double-blind phase II trial of high-dose vitamin D and calcium for bone health in HIV-infected individuals initiating highly active antiretroviral therapy (HAART). AIDS Clinical Trials Group. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 (cited 2014DEC10). Available https://clinicaltrials.gov/ct2/show/NCT01403051 NLM Identifier: NCT01403051 (accessed November 12, 2014)

52. Palella FJ Jr, Fisher M, Tебa P, et al. Simplification to rilpivirine/ emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS. 2014;28:335–344.
53. Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis*. 2014;14(5):590–599.

54. Pujari S, Dravid A, Gupu N, et al. Effectiveness and safety of generic fixed-dose combination of tenofovir/emtricitabine/efavirenz in HIV-1-infected patients in western India. *MedGenMed*. 2008;10:196.

55. Rockstroh JK, Dejesus E, Henry K, et al. A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr*. 2013;62:483–486.

56. Sax PE, Dejesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379:2439–2448.

57. Sax PE, Zoïlo A, Brar I, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr*. 2014;67:52–58.

58. Scourfield A, Zheng J, Chinthapalli S, et al. Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals. *AIDS*. 2012;26:1399–1401.

59. Skwara P, Bociaga-Jasik M, Kalinowska-Nowak A, et al. Adherence to single-tablet versus multiple-tablet regimens in the treatment of HIV infection: a questionnaire-based survey on patients satisfaction. *HIV AIDS Rev*. 2014;13:95–99.

60. Sterrattino G, Santoro L, Bartolozzi D, et al. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. *Patient Prefer Adherence*. 2012;6:427–433.

61. Walensky RP, Sax PE, Nakamura YM, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med*. 2013;158:84–92.

62. Walmsey SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369:1807–1818.

63. Cohen C, Davis K, Meyers J. Association of partial adherence (PA) to antiretroviral therapy with hospitalizations and healthcare costs in an HIV population [Abstract]. *J Int AIDS Soc*. 2012;15(Suppl 4):18060.

64. Connor J, Rafter N, Rodgers A. Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review. *Bull World Health Organ*. 2004;82:935–939.

65. Molassiotis A, Nahas-Lopez V, Chung WY, et al. Factors associated with adherence to antiretroviral medication in HIV-infected patients. *Int J STD AIDS*. 2002;13:301–310.

66. Chesney MA. The elusive gold standard. Future perspectives for HIV adherence assessment and intervention. *J Acquir Immune Defic Syndr*. 2006;43(Suppl 1):S149–S155.

67. 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.

68. WHO. Adherence to long term therapies—evidence for action. 2003; Geneva. Available http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf

69. Sun K, Zhou S, Chen RY, et al. Recent key advances in human immunodeficiency virus medicine and implications for China. *AIDS Res Ther*. 2010;7:12.

70. Vitoria M, Ford N, Doherty M, et al. Simplification of antiretroviral therapy: a necessary step in the public health response to HIV/AIDS in resource-limited settings. *Antivir Ther*. 2014;19 (Suppl 3):31–37.

71. De Vera MA, Bhole V, Burns LC, et al. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78:684–698.

72. Phan K, Gomez YH, Elbaz L, et al. Statin treatment non-adherence and discontinuation: clinical implications and potential solutions. *Curr Pharm Des*. 2014;20:6314–6324.

73. Shin S, Jang S, Lee TJ, et al. Association between non-adherence to statin and hospitalization for cardiovascular disease and all-cause mortality in a national cohort. *Int J Clin Pharmacol Ther*. 2014;52:948–956.

74. Morken G, Wilden JH, Grawe RN. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenics. *BMC Psychiatry*. 2008;8:32.

75. Ernst & Young. Progressions: Navigating the payer landscape. *Global Pharmaceutical Report* 2014. Available http://www.euy.com/Publication/vwLUAssets/EY_-_Progressions_2014_-_Navigating_the_payer_landscape/SFile/EY-progressions-2014.pdf

76. Daemmrich A, Mohanty A. Healthcare reform in the United States and China: pharmaceutical market implications. *J Pharmac Policy Pract*. 2014;7:9.

77. Kanavos P, Nicod E, van den Aardweg S, et al. The impact of health technology assessments: an international comparison. *Euro Observer*. 2010;12:1–17.

78. Permpalung N, Putcharoen O, Avihingsanon A, et al. Treatment of HIV infection with once-daily regimens. *Expert Opin Pharmacother*. 2012;13:2301–2317.

79. Siregar AYM, Pitriyan P. Increasing access to HIV treatment/ART through scaling-up ART in West Java. *Working Papers in Economics and Development Studies* 2013; No. 201302. Available http://lp3e.fe.unpad.ac.id/wopeds/201302.pdf

80. Satyanarayana K, Srivastava S. Patent pooling for promoting access to antiretroviral drugs (ARVs)—a strategic option for India. *Open AIDS J*. 2010;4:41–53.

81. WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach—2010 revision. Available http://wwwlpibdoc.who.int/publications/2010/9789241599764_eng.pdf

82. WHO. Antiretroviral treatment working group treatment white paper. 2010. Available http://www.who.int/hiv/pub/arv/treatment_white_paper.pdf?ua=1

83. UNAIDS. Access to antiretroviral therapy in Africa: Aatus report on progress towards the 2015 targets. UNAIDS report 2013; Geneva. Available http://www.unaids.org/sites/default/files/media_asset/20131219_AccessARTAfricaStatusReportProgress2015 Targets_en_0.pdf

84. Resch S, Korenromp E, Stover J, et al. Economic returns to investment in AIDS treatment in low and middle income countries. *PLoS ONE*. 2011;6:e25310.

85. UNAIDS. Treatment 2015. UNAIDS report 2014; Geneva. Available at: http://www.unaids.org/sites/default/files/media_asset/JC2484_treatment-2015_en_1.pdf