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## Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials

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# Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials

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**Background.** Contemporary antiretroviral treatment regimens are simpler than in the past, with lower pill burden and once-daily dosing frequency common. We performed a meta-analysis of randomized controlled trials (RCTs) to investigate the impact of pill burden and once-daily vs twice-daily dosing on ART adherence and virological outcomes.

**Methods.** A literature search of 4 electronic databases through 31 March 2013 was used. RCTs comparing once-daily vs twice-daily ART regimens that also reported on adherence and virological suppression were included. Study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Study quality was rated using the Cochrane risk-of-bias tool.

**Results.** Nineteen studies met our inclusion criteria (N = 6312 adult patients). Higher pill burden was associated with both lower adherence rates ( $P = .004$ ) and worse virological suppression ( $P < .0001$ ) in both once-daily and twice-daily subgroups, although the association with adherence in the once-daily subgroup was not statistically significant. The average adherence was modestly higher in once-daily regimens than twice-daily regimens (weighted mean difference = 2.55%; 95% confidence interval [CI], 1.23 to 3.87;  $P = .0002$ ). Patients on once-daily regimens did not achieve virological suppression more frequently than patients on twice-daily regimens (relative risk [RR] = 1.01; 95% CI, 0.99 to 1.03;  $P = .50$ ). Both adherence and viral load suppression decreased over time, but adherence decreased less with once-daily dosing than with twice-daily dosing.

**Conclusions.** Lower pill burden was associated with both better adherence and virological suppression. Adherence, but not virological suppression, was slightly better with once- vs twice-daily regimens.

**Keywords.** randomized controlled trials; ART; fixed-dose combination; once-daily; twice-daily.

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<sup>a</sup>J. B. N. and J.-J. P. contributed equally to this work.

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Among human immunodeficiency virus (HIV)-infected patients, adherence to antiretroviral therapy (ART) is a primary determinant of virological suppression, disease progression, and death [1–3]. ART regimens are now

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simpler than they were in the past, with lower pill burden and dosing frequency; they have also become less toxic and better tolerated [4]. In 2006, tenofovir–emtricitabine–efavirenz became the first approved branded, fixed-dose, single-tablet regimen (STR) [5,6]. Two other STRs were subsequently approved by the US Food and Drug Administration: tenofovir–emtricitabine–rilpivirine and tenofovir–emtricitabine–elvitegravir–cobicistat [7, 8], both of which are currently recommended by the US Department of Health and Human Services [9].

Little is known about the impact of once- vs twice-daily ART and pill burden on adherence and virological outcomes. Indeed, in some patients with suboptimal adherence and/or virological failure, reducing the pill burden may be more important than switching from a twice-daily regimen to a once-daily regimen. Furthermore, governments, third-party payers, and HIV programs may prefer the use of non-coformulated ART generics because they are less expensive than brand name STRs. Therefore, as more generics become available, there is the potential for a paradoxical “desimplification,” with movement away from STR regimens [10, 11].

A 2009 meta-analysis by Parienti and colleagues of 11 randomized trials reported that ART adherence rates were significantly better with once-daily than with twice-daily regimens [12], with a modest effect that was more pronounced at the time of treatment initiation and was not observed in ART-experienced patients. However, that study did not find a significant effect of once-daily vs twice-daily regimens on virological outcome, possibly because of insufficient statistical power [13]. Since 2009, more randomized clinical trials comparing once- vs twice-daily regimens have been published, allowing a pooled meta-analysis with greater power to reinvestigate this question as well as the impact of pill burden [14–26]. Also, these more recent trials investigated better-tolerated, more contemporary regimens that are currently in wide clinical use.

Thus, we conducted an updated meta-analysis to evaluate the impact of pill burden and once- vs twice-daily ART on adherence as well as virological outcomes in both ART-naive and -experienced HIV-infected adults.

## METHODS

### Protocol and Registration

The study background, rationale, and methods were specified in advance and documented in a protocol that was published in the PROSPERO register (CRD42012002515).

### Inclusion Criteria

We included only randomized controlled trials (RCTs) that compared once-daily vs twice-daily regimens in either ART-naive or -experienced patients with objective measures of adherence and measures of virological outcomes.

### Search Strategy

We systematically searched the following databases from their inception until 31 March 2013 (including those years searched by the Parienti meta-analysis): Cochrane CENTRAL, PubMed, Google scholar, and Web of Science. Our search terms included the following: “HIV,” “treatment simplification,” “co-formulation,” “fixed-dose combination,” “QD,” “twice-daily,” “once-daily,” “adherence,” “HAART,” “ART,” “cART,” and “patient preference.” We also searched abstracts from major HIV/AIDS and infectious diseases conferences (from 2008 onward) including Conference on Retrovirus and Opportunistic Infections, International AIDS Conference, International AIDS Society Conference on HIV Treatment, Pathogenesis and Prevention, International Conference on Antimicrobial Agents and Chemotherapy, and Infectious Diseases Society of America Conference. In addition, the bibliographies of relevant review articles, metaanalyses, and selected articles were examined for pertinent studies.

### Study Selection

We evaluated each identified study using the following predetermined selection criteria: open-label RCTs of HIV-infected subjects either ART naive or ART experienced that compared once-daily ART regimens with any twice-daily antiretroviral regimens and assessed both adherence (using objective measures, such as pill count or medication event monitoring system [MEMS]) and viral suppression (percentage of subjects with HIV-1 RNA levels < 50 copies/mL or < 200 copies/mL in the intent-to-treat, missing-equals-failure analysis). Placebo-controlled, blinded trials were excluded because the regimen frequency was identical for the comparator arms (to maintain blinding) and, therefore, the impact of the placebo on adherence could not be measured. We chose to exclude trials that used self-reported adherence as the patients are more likely to overestimate adherence due to social desirability and typically these trials do not reflect true variability in adherence due to a ceiling effect [27–30].

### Validity Assessment

We used the Cochrane Collaboration’s tool for assessing the risk of bias for quality assessment of the included studies [31]. The studies were graded based on the following: sequence generation, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other sources of bias. The other sources of bias considered whether the analysis was intention-to-treat. We summarized the global assessment for each trial as low risk, unclear, or high risk of bias.

### Data Extraction

Three reviewers (O. A. U., J. J. P., and J. B. N.) independently evaluated the eligibility and methodological quality of studies

obtained from the literature search. These same reviewers also independently extracted and compared the data. For each identified study that met the selection criteria, details on study design, study population characteristics, intervention, outcome measures, and study quality were extracted. Discrepancies were resolved by consensus through discussion.

### Summary Measures

The primary measures of treatment effects were weighted mean difference (WMD) with 95% confidence interval (CI) for adherence to treatment and relative risk (RR) with 95% CI for virological suppression. We used the following methods to compute effect sizes, when incompletely reported: contact with the corresponding author; estimation of the standard deviation (SD) on the basis of the sample size, median, and range as suggested by Hozo and colleagues [32] or on the basis of the sample size and *P* value; and imputation of the SD reported in similar studies.

### Statistical Analysis

The Spearman rank correlation coefficient ( $\rho$ ) was used to examine the associations between regimen pill burden (daily number of tablets), length of follow-up period, adherence rates, and virological response.

We used DerSimonian and Laird [33] random effect models to synthesize results across studies due to anticipated heterogeneity resulting from the differences in methodology, population, and ART regimen. Between-study heterogeneity was assessed using the  $I^2$  statistic, which reports the percentage of total variation across studies due to heterogeneity rather than chance [34, 35]. Based on a significant interaction previously found in the meta-analysis by Parienti et al [12], subgroup analyses were prespecified to explore the reasons for heterogeneity. These were based on patient characteristics at baseline, including the following: treatment-naïve individuals initiating their first regimens of ART, treatment-experienced individuals with virological suppression, and treatment-experienced individuals with treatment failure (ie, lack of virological suppression).

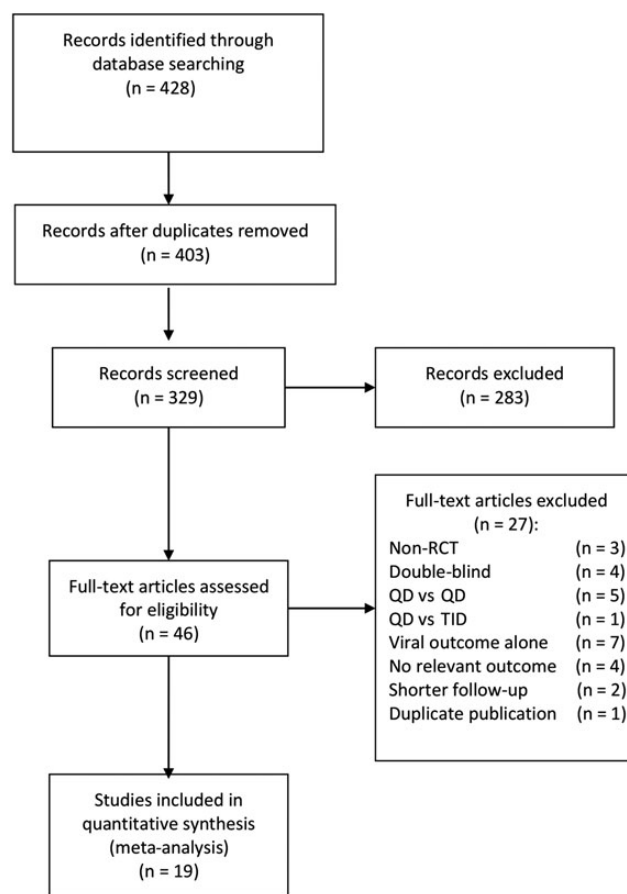
We examined the reliability and conclusiveness of the available evidence using a trial sequential analysis (TSA) [36–39] and the sample size required for a reliable and conclusive meta-analysis. Therefore, we calculated the sample size (ie, the heterogeneity-corrected optimal information size [HOIS]) required to detect or reject a once-daily regimen intervention effect of minimal relevant difference of 2 percentage points in mean adherence and a 10% RR difference in viral suppression. We then used the HOIS to construct Lan-DeMets sequential monitoring boundaries for our cumulative metaanalyses analogous to interim monitoring in an RCT [36–39]. We conducted the TSA with the intention of maintaining an overall 5% risk of a type I error and 20% risk of a type II error.

This review was performed according to the PRISMA recommendations for meta-analyses of RCTs [40]. Stata 12 (Stata Corporation, College Station, TX) and Review Manager 5.2 software (<http://ims.cochrane.org/revman>) were used for meta-analysis; Trial Sequential Analysis Software, version 0.9 beta ([www.ctu.dk/tsa](http://www.ctu.dk/tsa)), was used for the trial sequential analyses.

## RESULTS

### Study Selection and Characteristics

The literature search yielded 428 articles (Figure 1). After review, 46 articles were selected for critical reading. Of the 46 articles, 27 did not meet the inclusion criteria and were excluded. Nineteen studies [5, 17–19, 21, 22, 24, 41–49, 51–53] with useable outcome data involving 6312 individuals met the inclusion criteria and were included. Table 1 shows the characteristics of the included studies. The studies were published between 2004 and 2011; 11 studies with 3029 patients were included in the earlier meta-analysis [12] and 8 additional studies with 3283 patients



**Figure 1.** Study selection flow diagram. Abbreviations: QD, once daily; RCT, randomized controlled trial; TID, three times a day.

**Table 1. Characteristics of Studies Included in a Meta-Analysis of Once-Daily vs Twice-Daily Antiretroviral Therapy Regimens**

Study	Year	Once-Daily Regimen	Twice-Daily Regimen	Population	Follow-up, weeks	Means of Assessing Adherence	Outcomes Reported	Risk of Bias
Benson [41]	2004	FTC, D4T or AZT, and an NNRTI or a PI	3TC, D4T or AZT, and an NNRTI or a PI	Experienced-controlled	48	Pill count	Both	Low
Eron [43]	2004	LPV/r and NRTIs	LPV/r and NRTIs	Treatment-naive	48	MEMS	Both	Low
Sosa [53]	2005	ABC, 3TC, and a PI or NNRTI	ABC, 3TC, and a PI or NNRTI	Experienced-controlled	48	Pill count	Both	Low
Gallant [5]	2006	TDF, FTC, and EFV	AZT, 3TC, and EFV	Treatment-naive	48	Pill count	Both	Low
Kubota [44]	2006	ABC, 3TC, and a third agent	ABC, 3TC, and a third agent	Treatment-naive	12	MEMS	Adherence	Low
LaMarca [45]	2006	ABC/3TC (FDC) + TDF + New NNRTI or PI	ABC + 3TC + TDF + new NNRTI or PI	Experienced-failing	48	Pill count	Both	Low
Portsmouth [51]	2006	D4T XR, 3TC, and EFV	D4T or AZT, 3TC, and EFV	Experienced-controlled	24	MEMS	Both	Low
Ruane [52]	2006	AZT, 3TC, ABC and EFV	AZT, 3TC, ABC and EFV	Experienced-controlled	24	MEMS	Both	Low
Molina [48]	2007	LPV/r, TDF and FTC	LPV/r, TDF and FTC	Treatment-naive	96	MEMS	Both	Low
Parienti [49]	2007	NVP and NRTIs	NVP and NRTIs	Experienced-controlled	16	MEMS	Both	Low
Boyle [42]	2008	D4T XR, 3TC, and EFV	NRTIs and PI or NNRTI	Experienced-controlled	48	MEMS	Both	Low
Maitland [46]	2008	ABC and 3TC	ABC and 3TC	Experienced-controlled	4	MEMS	Both	Low
Molina [47]	2008	ATV/r plus TDF-FTC	LPV/r plus TDF-FTC	Treatment-naive	48	Pill count	Both	High
Campo [24]	2010	EFV plus NRTIs	EFV plus NRTIs	Experienced-controlled	48	Pill count	Both	Low
Flexner [22]	2010	LPV/r and NRTIs	LPV/r and NRTIs	Treatment-naive	48	MEMS	Both	Low
Gonzalez-Garcia [21]	2010	LPV/r, FTC, and TDF	LPV/r, FTC, and TDF	Treatment-naive	96	MEMS	Both	Low
Zajdenverg [19]	2010	LPV/r and NRTIs	LPV/r and NRTIs	Experienced-failing	48	MEMS	Both	Low
Arasteh [18]	2011	NPV XR plus NRTIs	NPV IR plus NRTIs	Experienced-controlled	24	Pill count	Both	Low
Cahn [17]	2011	DRV/r and NRTIs	DRV/r and NRTIs	Experienced-failing	48	Pill count	Both	Low

The generation of the allocation sequence was adequately reported in 8 studies (42%) and inadequately reported in 11 studies (58%). Potential risk of bias likely to be introduced by incomplete data was low in 16 studies (84%), unclear in 2 studies (11%), and high in 1 study [47] (imbalanced loss to follow-up). There was evidence of selective reporting in 3 studies (16%) that reported adherence alone. Most studies used intention to treat analysis (n = 18, 95%).

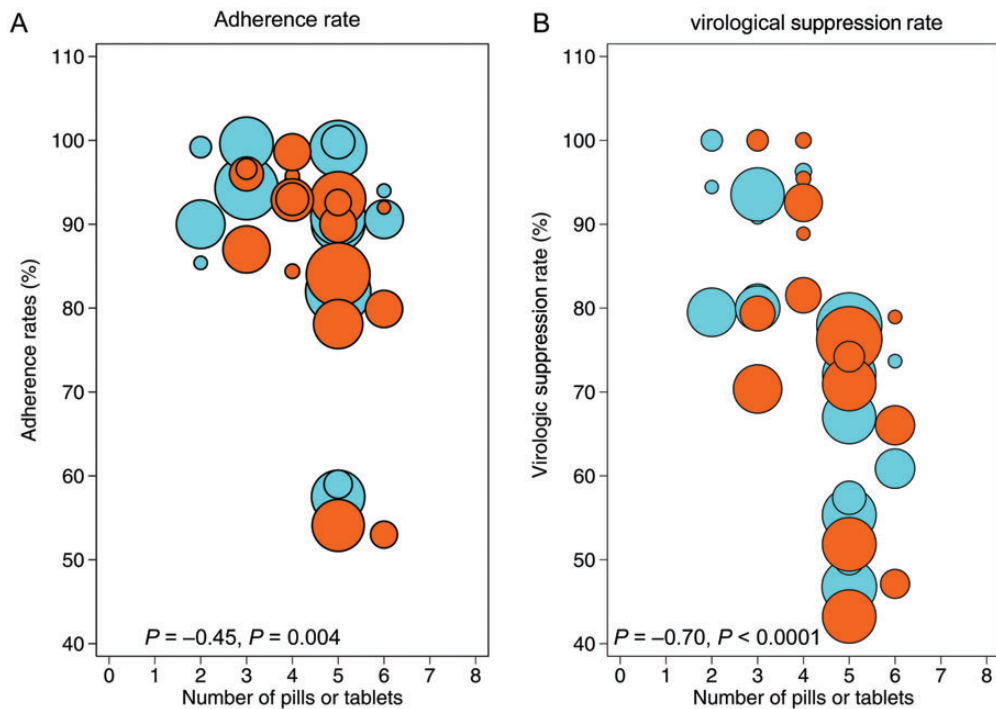
Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; AZT, zidovudine; d4T, stavudine; DRV/r, darunavir/ritonavir; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; MEMS, Medication Event Monitoring System; NA, not applicable; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTIs, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir; XR, extended release.

were identified. Most studies (18/19; 95%) were published in peer-reviewed journals. Seven studies (37%) included treatment-naive patients, 9 (47%) evaluated treatment-experienced patients with suppressed viral loads, and 3 (16%) evaluated treatment-experienced patients with unsuppressed viral loads. The median duration of follow-up was 48 weeks (range, 4–96 weeks). Most studies (N = 17; 89%) reported both adherence and virological suppression. Eleven studies (58%) used MEMS

to measure adherence, and 8 studies used pill count ratio. [Supplementary Table 1](#) shows the characteristics of studies that were excluded from the meta-analysis, and [Supplementary Table 2](#) shows the assessment of bias risk among the included studies.

### Pill Burden

There was a negative and statistically significant association (Figure 2A) between adherence and pill burden (Spearman



**Figure 2.** Antiretroviral therapy adherence rate, virological response, and pill burden. Area of circle is proportional to the sample size. Blue, once-daily regimens; orange, twice-daily regimens.

correlation =  $-0.45$ ; 95% CI,  $-.67$  to  $-.16$ ;  $P = .004$ ) for both once-daily and twice-daily regimens. However, when the analysis was stratified by the regimens, the association between adherence and pill burden was significant in the twice-daily regimens (Spearman correlation =  $-0.67$ ; 95% CI,  $-.86$  to  $-.37$ ;  $P = .001$ ) but not in the once-daily regimens (Spearman correlation =  $-0.22$ ; 95% CI,  $-.60$  to  $.25$ ;  $P = .35$ ). There was also a statistically significant negative association (Figure 2B) between pill burden and virological suppression (Spearman correlation =  $-0.70$ ; 95% CI,  $-.84$  to  $-.49$ ;  $P < .0001$ ), which was significant in both the once-daily (Spearman correlation =  $-0.63$ ; 95% CI,  $-.85$  to  $-.23$ ;  $P = .005$ ) and twice-daily subgroups (Spearman correlation =  $-0.75$ ; 95% CI,  $-.90$  to  $-.44$ ;  $P = .0003$ ).

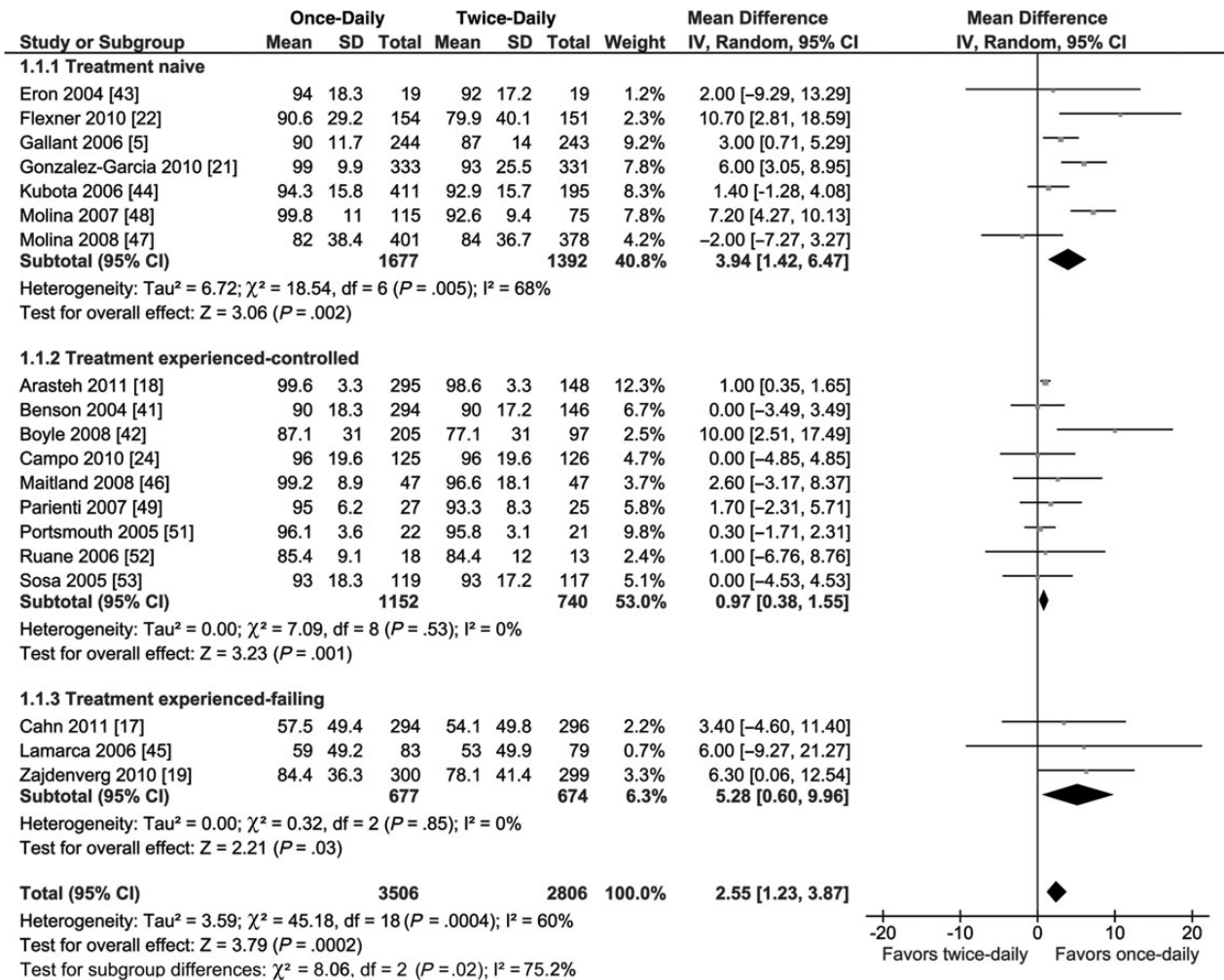
### Once-Daily Dosing

When all populations were combined, mean adherence was slightly higher among participants following once-daily regimens than those following twice-daily regimens (WMD = 2.55%; 95% CI, 1.23–3.87;  $P = .0002$ ; Figure 3). The trial sequential analysis demonstrated that for the regimens evaluated, the meta-analysis was conclusive (Supplementary Figure 1). In prespecified subgroup analyses, the greater average adherence with once-daily vs twice-daily dosing was more pronounced in treatment-naïve patients (WMD = 3.94%; 95% CI, 1.42–

6.47;  $P = .002$ ; Figure 3) and treatment-experienced patients with virological failure switching to once-daily dosing (WMD = 5.28%; 95% CI, .60–9.96;  $P = 0.03$ ; Figure 3) than in treatment-experienced patients who switched (for simplification/convenience) when their viral load was suppressed (WMD = 0.97%; 95% CI, .38–1.55;  $P = 0.53$ , Figure 3). These differences between subgroups were statistically significant ( $P = .02$  for interaction). There was no significant difference in virological suppression among patients following once-daily vs twice-daily regimens (RR = 1.01; 95% CI, .98–1.03;  $P = .57$ ;  $I^2 = 0\%$ , Figure 4). Trial sequential analysis suggested that as of 2007 (after the ninth trial), sufficient evidence had accrued to demonstrate that the likelihood of finding a treatment effect was too low to justify further data collection. We therefore conclude that any possible intervention effect of once-daily regimens vs twice-daily regimens is lower than a 10% RR reduction in virological suppression (the prespecified threshold; Supplementary Figure 2). Furthermore, there was no significant difference between once- and twice-daily regimens in virological suppression in the treatment-naïve or -experienced subgroups (Figure 4).

### Duration of Follow-up and Treatment Effects

Adherence declined significantly over time (Spearman correlation =  $-0.41$ ; 95% CI,  $-.64$  to  $-.11$ ;  $P = .009$ ; Supplementary



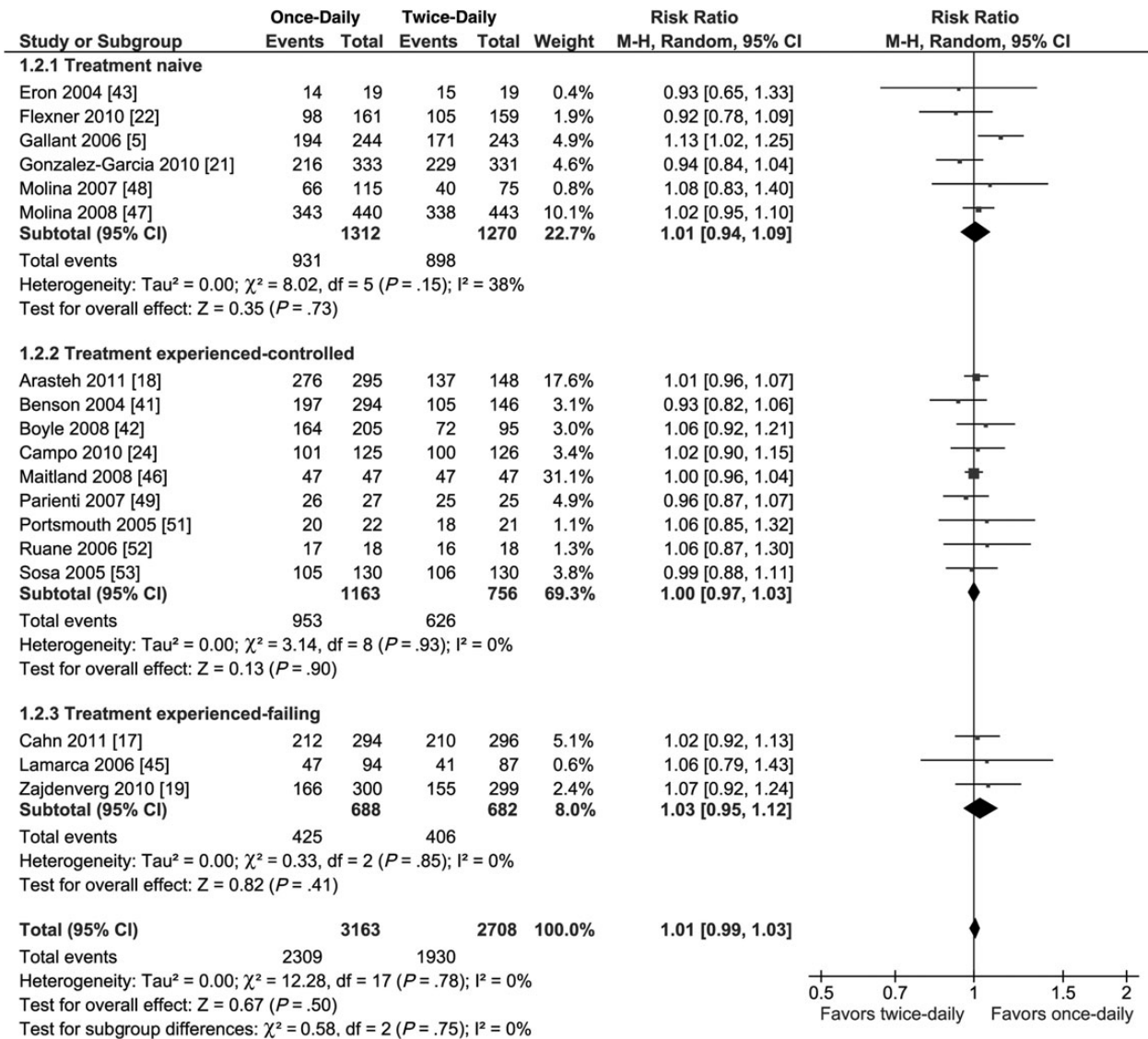
**Figure 3.** Forest plot of the effect of once-daily vs twice-daily antiretroviral regimens on the rate of adherence. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation.

Figure 3A). When the analysis was stratified by dosing regimens, twice-daily remained statistically significant (Spearman correlation = -0.50; 95% CI, -.80 to -.03; *P* = .04), whereas the once-daily was not (Spearman correlation = -0.368; 95% CI, .697 to .088; *P* = .110). Similarly, there was a significant negative association (Supplementary Figure 3B) between virological suppression and duration of follow-up (Spearman correlation = -0.700; 95% CI, -.836 to -.482; *P* < .0001), such that virological suppression declined with longer follow-up. The associations were similar to the overall for both twice-daily (Spearman correlation = -0.692; 95% CI, -.876 to -.333; *P* = .002) and once-daily (Spearman correlation = -0.709; 95% CI, -.833 to -.362; *P* = .001) regimens.

Of note, in a post hoc sensitivity analysis, inclusion of studies with self-reported adherence or virological outcomes only did not materially change our results (data not shown).

## DISCUSSION

This meta-analysis of 19 RCTs which included 6312 patients found that higher pill burden was associated with both lower adherence and worse virological suppression in both twice-daily and once-daily subgroups. In addition, adherence was higher with once-daily ART regimens than with twice-daily regimens when adherence was measured objectively using pill counts and/or MEMS caps. However, this difference was minimal and did not translate into better treatment outcomes. Furthermore, the greater adherence with once-daily dosing was only statistically significant in treatment-naive individuals and in those who switched from twice- to once-daily dosing with virological failure. Adherence did not increase among treatment-experienced patients who switched from twice- to once-daily dosing while virologically suppressed; adherence was likely



**Figure 4.** Forest plot of the effect of once-daily vs twice-daily antiretroviral regimens on virologic suppression (plasma RNA HIV level <50 or <200 copies/mL). Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; M-H, Mantel-Haenszel.

high in these patients prior to the switch. Both adherence and virological suppression decreased with longer follow-up, but the adherence decrease was less pronounced with once-daily dosing than with twice-daily dosing.

Interestingly, none of the included randomized trials directly evaluated the effect of an STR, which we consider an unanswered question for further research. However, in our study, there was a significant negative association between pill burden and virological suppression, suggesting that regimen simplification with STRs may be helpful in select situations. One small observational study conducted among marginally housed individuals and 2 large observational studies conducted found better adherence with STRs (compared with all other regimens,

whether once daily or twice daily) [55, 56, 57], while 2 other observational studies found no difference between STRs and other once-daily regimens among patients starting ART [58] or among those who were switched from STR to multitablet regimens for reasons of cost [59].

There are several possible explanations for the apparent lack of impact of once- vs twice-daily dosing on virological outcomes. First, the impact of once-daily dosing on adherence was relatively small (2.5% absolute increase in adherence); this was possibly too small to result in a clinically meaningful difference in virological suppression. Second, a substantial number of the trials included in this meta-analysis were of relatively short duration. Moreover, volunteers for clinical trials



are likely to be more adherent than their counterparts managed in routine clinical practice, and there may be more resources available to support adherence in clinical trial settings [60]. For these reasons, the difference in virological suppression that we found between once- and twice-daily ART regimens may be underestimated.

These results have several important practical implications. Currently, as all recommended regimens are highly potent, ART combinations should be selected based on factors such as tolerability, potential drug interactions, patient preference for dosing frequency, and pill burden, as well as structural factors (eg, cost, drug availability, access to care, insurance coverage) [61]. Efforts to improve and sustain adherence should not be limited to regimen simplification, but consideration should be given to proven evidence-based interventions to improve adherence such as social support [62], adherence support toolkits (eg, pillbox organizers) [63], use of cell phone and/or text messages, treatment supporters, and other targeted interventions when necessary [64–68].

In a mathematical simulation, Walensky and colleagues showed that the future use of a once-daily regimen that includes generic efavirenz plus generic lamivudine plus branded tenofovir in the United States could yield savings of almost \$1 billion per year to HIV programs [69]. Our results suggest that these savings may be counterbalanced, in part, by worse virological outcomes if an increase in pill burden is required. However, no study, including ours, was specifically designed to directly investigate the impact of desimplification involving switching patients from once-daily STR to once-daily ART regimens containing multiple tablets. Further research is urgently needed to address this question.

Our study has several strengths. We performed a comprehensive search of several databases and sources to identify eligible RCTs that provide the highest quality of evidence. Three authors independently evaluated each study for inclusion and data extraction. Furthermore, we performed a trial sequential analysis; this is an efficient decision-making tool that is used to establish whether firm evidence of effect has been obtained [70]. Regarding limitations, most studies were of good quality with a low risk of bias. However, to the extent that their evidence was potentially biased, those biases are mirrored in our analyses. Notably, the likelihood of attrition bias, with a systematic difference between the 2 regimens in withdrawal rates, was very high in 1 study. While there was no evidence of heterogeneity in assessing virological suppression, the level of heterogeneity between studies in assessing adherence rates was high ( $I^2 > 50\%$ ). Also, by focusing on once-daily vs twice-daily dosing, our analysis may have masked regimen-specific effects (eg, differences in toxicity) that have little to do with the frequency of dosing. Finally, the impact of regimen frequency and pill burden on adherence and virological outcomes in RCTs may not

necessarily generalize to desimplification, in which patients may perceive that their regimen has been reduced in quality. Such a change could adversely affect adherence and/or treatment outcome, and, as noted above, specific studies to investigate this question are needed.

In this meta-analysis of 19 RCTs, we confirmed that once-daily ART regimens increased adherence when compared with twice-daily regimens, but the difference was modest and not associated with a difference in virological suppression. Importantly, we found that higher pill burden was associated with lower rates of virological suppression regardless of dosing frequency. The nonlinear correlation between pill burden and adherence or virological suppression suggests that, while ART desimplification from once-daily STRs to once-daily multitablet regimens may have adverse effects on virological outcomes, separating out STRs and/or fixed-dose combinations into their constituents is not likely to have a major detrimental impact on virological outcomes (provided that the overall pill burden does not increase dramatically). Nevertheless, further research is needed to directly investigate the impact of such a switch, in particular among patients who are virologically suppressed at baseline. In the meantime, our results suggest that pill burden should be a consideration in the selection of an antiretroviral regimen, independent of dosing frequency.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

**Authors' contributions.** J. B. N. and J.-J. P. contributed equally to this work. *Study concept and design:* J. B. N., O. A. U., J.-J. P., and T. P. G. *Acquisition of data:* J. B. N., O. A. U., and J.-J. P. *Analysis and interpretation of data:* All. *Drafting or writing of the manuscript:* O. A. U., J. B. N., J.-J. P., T. P. G., P. E. S., J. E. G., R. G., D. W. D., and M. J. M. *Critical revision of the manuscript for important intellectual content:* All. *Statistical analysis:* O. A. U., J. B. N., J.-J. P., R. G., and E. J. M. *Administrative, technical, or material support:* J. B. N., E. J. M., and O. A. U. *Study supervision:* J. B. N., J.-J. P., and T. P. G. *Access to study data:* J. B. N. and J.-J. P. had full access to all data in the study and had final responsibility for the decision to submit this manuscript for publication.

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## References

- Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* **2001**; 15:1181-3.
- Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Ann Intern Med* **2007**; 146:564-73.
- Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350×10(9) cells/L. *Ann Intern Med* **2003**; 139:810-6.
- Nachega JB, Mugavero MJ, Zeier M, Vitoria M, Gallant JE. 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**; 5:357-67.
- Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *New Engl J Med* **2006**; 354:251-60.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Washington, DC: U.S. Department of Health and Human Services, **2013**.
- Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* **2011**; 378:229-37.
- Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, 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**; 379:2439-48.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Recommendation on Integrase Inhibitor Use in Antiretroviral Treatment-Naïve HIV-Infected Individuals from the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents (October 30, 2013). Department of Health and Human Services. **2013**. Available at: [http://aidsinfo.nih.gov/contentfiles/upload/AdultARV\\_INSTIREcommendations.pdf](http://aidsinfo.nih.gov/contentfiles/upload/AdultARV_INSTIREcommendations.pdf).
- Sax PE. Generic lamivudine has arrived. HIV and ID Observations. WATCH Blogs Web site, **2012**.
- U.S. Food and Drug Administration. Approved Drug Products with Therapeutic Equivalence Evaluations. Silver Spring, MD, USA: Orange Book, **2012**.
- Parietti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis* **2009**; 48:484-8.
- Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. *Clin Epidemiol* **2010**; 2:57-66.
- Molina JM, Lamarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis* **2012**; 12:27-36.
- Maserati R, Brandolini M, Cattelan A, et al. Once-a-day (QD) vs. twice-daily (BID) nevirapine as simplification in PI-treated patients after 2 mos. of BID induction. *Curr HIV Res* **2011**; 9:166-73.
- Eron JJ Jr, Rockstroh JK, Reynes J, et al. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. *Lancet Infect Dis* **2011**; 11:907-15.
- Cahn P, Fourie J, Grinsztejn B, et al. Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. *AIDS* **2011**; 25:929-39.
- Arasteh K, Ward D, Plettenberg A, et al. Twenty-four-week efficacy and safety of switching virologically suppressed HIV-1-infected patients from nevirapine immediate release 200 mg twice daily to nevirapine extended release 400 mg once daily (TRANxITION). *HIV Med* **2012**; 13:236-44.
- Zajdenverg R, Podsadecki TJ, Badal-Faesen S, et al. Similar safety and efficacy of once- and twice-daily lopinavir/ritonavir tablets in treatment-experienced HIV-1-infected subjects at 48 weeks. *J Acquir Immune Defic Syndr* **2010**; 54:143-51.
- Vispo E, Barreiro P, Maida I, et al. Simplification from protease inhibitors to once- or twice-daily raltegravir: the ODIS trial. *HIV Clin Trials* **2010**; 11:197-204.
- Gonzalez-Garcia J, Cohen D, Johnson M, et al. Short communication: Comparable safety and efficacy with once-daily versus twice-daily dosing of lopinavir/ritonavir tablets with emtricitabine + tenofovir DF in antiretroviral-naïve, HIV type 1-infected subjects: 96 week final results of the randomized trial M05-730. *AIDS Res Hum Retroviruses* **2010**; 26:841-5.
- Flexner C, Tierney C, Gross R, et al. Comparison of once-daily versus twice-daily combination antiretroviral therapy in treatment-naïve patients: results of AIDS clinical trials group (ACTG) A5073, a 48-week randomized controlled trial. *Clin Infect Dis* **2010**; 50:1041-52.
- Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naïve subjects with CCR5-tropic HIV-1 infection. *J Infect Dis* **2010**; 201:803-13.

24. Campo RE, Cohen C, Grimm K, Shangguan T, Maa J, Seekins D. Switch from protease inhibitor- to efavirenz-based antiretroviral therapy improves quality of life, treatment satisfaction and adherence with low rates of virological failure in virologically suppressed patients. *Int J STD AIDS* **2010**; 21:166–71.
25. King MS, Lawal AA, Fredrick LM, Rode RA, Podsadecki TJ, Bernstein BM. Improved Treatment Compliance with Once-Daily (QD) Compared to Twice-Daily (BID) Lopinavir/Ritonavir (LPV/r) in HIV-1-Infected, Antiretroviral-Experienced Subjects. In: 12th European AIDS Conference Cologne. Germany, **2009**.
26. Gathe J, da Silva BA, Cohen DE, et al. A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naïve subjects through 48 weeks. *J Acquir Immune Defic Syndr* **2009**; 50:474–81.
27. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. *BMC Med Res Methodol* **2011**; 11:149.
28. Kimmerling M, Wagner G, Ghosh-Dastidar B. Factors associated with accurate self-reported adherence to HIV antiretrovirals. *Int J STD AIDS* **2003**; 14:281–4.
29. Melbourne KM, Geletko SM, Brown SL, Willey-Lessne C, Chase S, Fisher A. Medication adherence in patients with HIV infection: a comparison of two measurement methods. *AIDS Read* **1999**; 9:329–38.
30. Wagner GJ, Rabkin JG. Measuring medication adherence: are missed doses reported more accurately than perfect adherence? *AIDS Care* **2000**; 12:405–8.
31. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **2011**; 343:d5928.
32. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* **2005**; 5:13.
33. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* **1986**; 7:177–88.
34. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *StatMed* **2002**; 21:1539–58.
35. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* **2003**; 327:557–60.
36. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol* **2008**; 61:763–9.
37. Higgins JP, Whitehead A, Simmonds M. Sequential methods for random-effects meta-analysis. *Stat Med* **2011**; 30:903–21.
38. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* **2008**; 61:64–75.
39. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol* **2009**; 9:86.
40. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health-care interventions: explanation and elaboration. *BMJ* **2009**; 339:b2700.
41. Benson CA, van der Horst C, Lamarca A, et al. A randomized study of emtricitabine and lamivudine in stably suppressed patients with HIV. *AIDS* **2004**; 18:2269–76.
42. Boyle BA, Jayaweera D, Witt MD, Grimm K, Maa JF, Seekins DW. Randomization to once-daily stavudine extended release/lamivudine/efavirenz versus a more frequent regimen improves adherence while maintaining viral suppression. *HIV Clin Trials* **2008**; 9:164–76.
43. Eron JJ, Feinberg J, Kessler HA, et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naïve HIV-positive patients: a 48-week randomized clinical trial. *J Infect Dis* **2004**; 189:265–72.
44. Kubota M, Cohen C, Scribner A, et al. Short-Term Safety and Tolerability of ABC/3TC Administered Once-daily (QD) Compared with the Separate Components Administered Twice-daily (BID): Results from ESS101822 (ALOHA). In: The 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). San Francisco, CA, USA, **2006**.
45. Lamarca A, Clumeck N, Plettenberg A, et al. Efficacy and safety of a once-daily fixed-dose combination of abacavir/lamivudine compared with abacavir twice daily and lamivudine once daily as separate entities in antiretroviral-experienced HIV-1-infected patients (CAL30001 Study). *J Acquir Immune Defic Syndr* **2006**; 41:598–606.
46. Maitland D, Jackson A, Osorio J, Mandalia S, Gazzard BG, Moyle GJ. Switching from twice-daily abacavir and lamivudine to the once-daily fixed-dose combination tablet of abacavir and lamivudine improves patient adherence and satisfaction with therapy. *HIV Med* **2008**; 9:667–72.
47. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* **2008**; 372:646–55.
48. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses* **2007**; 23:1505–14.
49. Parienti JJ, Massari V, Reliquet V, et al. Effect of twice-daily nevirapine on adherence in HIV-1-infected patients: a randomized controlled study. *AIDS* **2007**; 21:2217–22.
50. Podsadecki TJ, Rode RA, Naylor C, Cohen DE, Marsh TM. Adherence with lopinavir/ritonavir (LPV/r) tablet and SoftGel (SGC) capsule based antiretroviral regimens and predictors of early treatment compliance. *J Int AIDS Soc* **2008**; 11(Suppl 1):P170.
51. Portsmouth SD, Osorio J, McCormick K, Gazzard BG, Moyle GJ. Better maintained adherence on switching from twice-daily to once-daily therapy for HIV: a 24-week randomized trial of treatment simplification using stavudine prolonged-release capsules. *HIV Med* **2005**; 6:185–90.
52. Ruane P, Lang J, DeJesus E, et al. Pilot study of once-daily simplification therapy with abacavir/lamivudine/zidovudine and efavirenz for treatment of HIV-1 infection. *HIV Clin Trials* **2006**; 7:229–36.
53. Sosa N, Hill-Zabala C, DeJesus E, et al. Abacavir and lamivudine fixed-dose combination tablet once daily compared with abacavir and lamivudine twice daily in HIV-infected patients over 48 weeks (ESS30008, SEAL). *J Acquir Immune Defic Syndr* **2005**; 40:422–7.
54. Gathe J, de Silva B, Loufty M. Study M05–730 primary efficacy results at week 48: phase 3, randomized, open-label study of lopinavir/ritonavir (LPV/r) tablets once-daily (QD) versus twice daily (BID), co-administered with tenofovir DF (TDF) + emtricitabine (FTC) in antiretroviral-naïve (ARV) HIV-1 infected subjects [abstract 775]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). Alexandria, VA: Foundation for Retrovirology and Human Health, **2008**.
55. Bangsberg DR, Ragland K, Monk A, Deeks SG. 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**; 24:2835–40.
56. 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* **2013**.
57. 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:pii:e003028.
58. Buscher A, Hartman C, Kallen MA, Giordano TP. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, HAART naïve, HIV patients. *Int J STD & AIDS* **2012**; 23:351–5.
59. Engsig F, Gerstoft J, Helleberg MK, Ronborg G, Mathiesen L, Obel N. Virological Response in Patients, Who for Economic Reasons Were

- Changed from Atripla to a Multi-tablet cART Regimen. Abstract #579. In: 20th Conference on Retroviruses and Opportunistic Infections. March 3–6, 2013. Atlanta, GA, USA, **2013**.
60. Chesney MA. Factors affecting adherence to antiretroviral therapy. *Clin Infect Dis* **2000**; 30 (Suppl 2): S171–6.
  61. Mills EJ, Nachega JB, Bangsberg DR, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med* **2006**; 3:e438.
  62. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *J Behav Med* **2006**; 29:377–87.
  63. Petersen ML, Wang Y, van der Laan MJ, Guzman D, Riley E, Bangsberg DR. Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis. *Clin Infect Dis* **2007**; 45:908–15.
  64. Barnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *Lancet Infect Dis* **2011**; 11:942–51.
  65. Lester R, Karanja S. Mobile phones: exceptional tools for HIV/AIDS, health, and crisis management. *Lancet Infect Dis* **2008**; 8:738–9.
  66. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS* **2011**; 25:825–34.
  67. Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. *J Acquir Immune Defic Syndr* **2006**; 43 (Suppl 1): S23–35.
  68. Gross R, Bellamy SL, Chapman J, et al. Managed problem solving for antiretroviral therapy adherence: a randomized trial. *JAMA Int Med* **2013**; 173:300–6.
  69. 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.
  70. van der Tweel I, Bollen C. Sequential meta-analysis: an efficient decision-making tool. *Clin Trials* **2010**; 7:136–46.
  71. Shaw AL, Shen G, Wakeford CW, Quinn JB, Rousseau FS. Once-Daily Emtricitabine Compared to Twice-Daily Abacavir Within a HAART Regimen in Antiretroviral Drug-Naive HIV-1-Infected Patients (ODECTA) (Poster 547). In: The 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France, **2003**.
  72. DeJesus E, McCarty D, Farthing CF, et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naive adults with HIV infection: a randomized equivalence trial. *Clin Infect Dis* **2004**; 39:411–8.
  73. Wright D, Rodriguez A, Godofsky E, et al. Efficacy and safety of 48 weeks of enfuvirtide 180 mg once-daily dosing versus 90 mg twice-daily dosing in HIV-infected patients. *HIV Clin Trials* **2008**; 9:73–82.
  74. Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. *Clin Infect Dis* **2009**; 49:1591–601.
  75. Martinez E, Arranz JA, Podzamczar D, et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. *J Acquir Immune Defic Syndr* **2009**; 51:290–7.
  76. Podzamczar D, Olmo M, Sanz J, et al. Safety of switching nevirapine twice daily to nevirapine once daily in virologically suppressed patients. *J Acquir Immune Defic Syndr* **2009**; 50:390–6.
  77. Zajdenverg R, Badal-Faesens S, Andrade-Villanueva J, et al. Lopinavir/ritonavir (LPV/r) tablets administered once-(QD) or twice-daily (BID) with NRTIs in antiretroviral-experienced HIV-1 Infected subjects: results of a 48-week randomized trial (Study M06-802). In: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Cape Town, South Africa, **2009**.
  78. Airolidi 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 Adherence* **2010**; 4:115–25.
  79. Cooper V, Horne R, Gellaity G, et al. The impact of once-nightly versus twice-daily dosing and baseline beliefs about HAART on adherence to efavirenz-based HAART over 48 weeks: the NOCTE study. *J Acquir Immune Defic Syndr* **2010**; 53:369–77.
  80. Musiime V, Kendall L, Bakeera-Kitaka S, et al. Pharmacokinetics and acceptability of once- versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. *Antivir Ther* **2010**; 15:1115–24.
  81. Nelson M, Girard PM, Demasi R, et al. Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data. *J Antimicrob Chemother* **2010**; 65:1505–9.
  82. Clumeck N, Rieger A, Banhegyi D, et al. 96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline. *J Antimicrob Chemother* **2011**; 66:1878–85.
  83. 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:F7–12.
  84. Honda M, Ishisaka M, Ishizuka N, Kimura S, Oka S. Open-label randomized multicenter selection study of once daily antiretroviral treatment regimen comparing ritonavir-boosted atazanavir to efavirenz with fixed-dose abacavir and lamivudine. *Intern Med* **2011**; 50:699–705.
  85. Bunupuradah T, Chetchotisakd P, Ananworanich J, et al. A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: the HIV STAR study. *Antivir Ther* **2012**; 17:1351–61.
  86. Andersson LM, Vesterbacka J, Blaxhult A, et al. Lopinavir/ritonavir, atazanavir/ritonavir, and efavirenz in antiretroviral-naive HIV-1-infected individuals over 144 weeks: An open-label randomized controlled trial. *Scand J Infect Dis* **2013**.
  87. Reynes J, Trinh R, Pulido F, et al. Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study. *AIDS Res Hum Retroviruses* **2013**; 29:256–65.
  88. Bonnet M, Bhatt N, Baudin E, et al. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a randomised non-inferiority trial. *Lancet Infect Dis* **2013**.