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.
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,” “coformulation,” “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.

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 I² 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-naive 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.

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 usable 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.
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

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

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; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir; XR, extended release.
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-naive 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 = .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; I² = 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-naive 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 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.
Figure 3). 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
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 (I² > 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


**Access to study data:** J. B. N. and J.-I. 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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