Twice-daily versus once-daily antiretroviral therapy and coformulation strategies in HIV-infected adults: benefits, risks, or burden?

Jean B Nachega1,3
Bernd Rosenkranz4
Paul A Pham5

1Department of International Health, 2Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; 3Department of Medicine and Centre for Infectious Diseases, 4Division of Pharmacology, Department of Medicine, Faculty of Health Sciences, University of Stellenbosch, Capetown, South Africa; 5Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract: The recent development of once-daily antiretroviral agents and fixed-dose combination formulations has been an important development in antiretroviral regimen simplification. Recent studies indicate that once-daily antiretroviral regimens improve adherence, especially in antiretroviral-naïve patients and in difficult-to-treat populations, such as the homeless or marginally housed. However, there are potential risks with the higher peak and lower trough plasma drug concentrations that may result from certain once-daily formulations. Due to the multifactorial and complex nature of adherence behavior, clinicians’ efforts to improve patient adherence should not be limited to prescribing once-daily regimens, but should also consider social support, side effect management, and adherence support tools, such as pillbox organizers and other targeted interventions. Additional research will clarify the benefits of once-daily and fixed-dose combination regimens on clinical and virologic outcomes. Comprehensive cost-benefit analysis of regimen simplification could help facilitate evidence-based decisions regarding antiretroviral regimen choices.

Keywords: regimen adherence, regimen simplification, health care costs, fixed-dose combination, once-daily antiretroviral drugs

Antiretroviral regimen simplification: a moving target

The simplification of antiretroviral regimens has the potential to improve long-term adherence, virologic efficacy, and clinical outcomes. Simplification strategies that employ antiretroviral agents that are currently approved or under study include use of once-daily dosing regimens, better tolerated or less toxic regimens, fixed-dose coformulations, and induction-maintenance approaches (Table 1). In this brief narrative review, we will focus on the following: results from published clinical studies (both randomized and observational) that directly compare twice-daily versus once-daily regimens; the clinical benefits and possible risks to the patient with once-daily regimens; the costs and benefits associated with better adherence when using once-daily regimens; and the ongoing research agenda for evidence-based improvements to simplified regimens.

Multiple studies have demonstrated that adherence to antiretroviral therapeutic regimens is among the most powerful predictors of sustained virologic suppression, reduced risk of developing drug resistance, limited disease progression, and improved patient survival. Since simpler antiretroviral regimens are considered easier to follow and result in improved patient adherence, over the last decade the trend has been to simplify treatment regimens. The key objectives of this strategy are to reduce the...
Overall pill burden (from 2–5 daily to once daily) and the number of times per day pills must be taken (eg, from three times daily to once daily) while maintaining virologic efficacy and treatment tolerability.10,11

Data from randomized controlled trials are necessary to confirm whether the benefits of these simplified regimens extend beyond improved adherence. Treatment simplification with older antiretroviral regimens (eg, didanosine/tenofovir, abacavir/zidovudine/lamivudine) did not result in improved virologic efficacy.12–14 However, a more recent observational study involving patients with limited social support (eg, homeless or marginally housed patients) found that once-daily fixed-dose combination regimens (efavirenz/emtricitabine/tenofovir) significantly improved adherence (P = 0.006) and viral suppression (human immunodeficiency virus [HIV] RNA < 50 copies/mL: 69.2% vs 46.5%; P = 0.02) when compared with a historical control group using multiple-dose antiretroviral regimens.15 The fixed-dose combination of efavirenz/tenofovir/emtricitabine is a Department of Health and Human Services preferred first-line antiretroviral regimen based on sustained non-inferior virologic efficacy compared with ritonavir (r)-boosted protease inhibitors (eg, darunavir/r, atazanavir/r), and raltegravir-based and maraviroc-based regimens.16–18 The success of efavirenz/emtricitabine/tenofovir in the marketplace has led to the development of other single-pill once-daily coformulated regimens (eg, rilpivirine/emtricitabine/tenofovir and elvitegravir/cobicistat/emtricitabine/tenofovir).

The immediate-release formulation of nevirapine was approved for twice-daily dosing, which is less than ideal if the background regimen is taken on a once-daily basis. Because nevirapine immediate-release has a long half-life, once-daily dosing was initially explored, but this dosing regimen was associated with an increased risk of hepatitis.19

A new extended-release formulation of nevirapine (Viramune® XRTM) has been approved for once-daily dosing by the US Food and Drug Administration,20 based principally on the results of the recent VERxVE study, a double-blind, double-dummy randomized clinical trial comparing the efficacy and safety of nevirapine extended-release (once daily) with nevirapine immediate-release (twice daily) in HIV treatment-naïve adults (n = 1011).21 The nevirapine extended-release formulation was found to have noninferior efficacy compared with the nevirapine immediate-release formulation, (both in combination with tenofovir and emtricitabine).21 The safety and adverse event profiles of the two formulations were also similar.21 The new nevirapine extended-release formulation provides an additional once-daily regimen option for clinicians and their patients, in keeping with once-daily nucleoside reverse transcriptase inhibitor background agents (eg, tenofovir/emtricitabine) that are widely used.

In summary, the development of new antiretroviral formulations that enable simplification of treatment regimens is essential to meet the medical objective of better adherence by utilizing once-daily antiretrovirals.

### Once-daily versus twice-daily dosing regimens

A limited number of studies in the past have addressed improving treatment adherence with once-daily dosing regimens in varied patient populations. In general, these reports agree with the hypothesis that patients demonstrate better adherence when using once-daily regimens. In a meta-analysis of 11 randomized controlled trials involving a total of 3029 subjects, the impact of once-daily regimens on treatment adherence was evaluated. Adherence rates were modestly better with once-daily regimens (+2.9%, 95% confidence interval [CI]: 1.0%–4.8%; P < 0.003) than with twice-daily regimens,11 providing support for the use of once-daily regimens to help improve patient adherence. However, week 48 treatment outcomes as measured by virologic suppression were comparable between once-daily versus twice-daily dosing regimens.
twice-daily regimens (77% vs 76%, respectively; \( P = 0.21 \)). More recent antiretroviral simplification studies comparing once-daily versus twice-daily antiretroviral regimens are summarized in Table 2. Patient adherence to treatment regimens showed improvement in most of these studies with treatment simplification.\(^{13,19,22–27} \) In another study, Airoldi et al reported better antiretroviral adherence after the switch to the fixed-dose combination of efavirenz/emtricitabine/tenofovir and reported better antiretroviral adherence after the switch (93.8% vs 96.1%, respectively; \( P < 0.01 \)).\(^{22} \)

In summary, the overall degree of improvement in antiretroviral adherence in these recent studies (Table 2) varied from modest to significant. Once-daily treatment regimens, especially those that are based on single-tablet fixed-dose combination formulations, confer the major advantages of reduced pill counts and dosing frequencies.\(^{19,22–27} \) Especially for patients who may otherwise find it difficult to follow rigorous dosing schedules, these simplified regimens have been shown to improve regimen adherence, treatment persistence and patient satisfaction in a number of studies. These associated benefits apply to all patients on antiretroviral regimens, but appear to be especially important in patients facing multiple life challenges, such as marginal housing or frank homelessness, and/or active injection drug use.\(^{13} \) A more extensive discussion on the impact of once-daily regimens on treatment adherence and persistence has been published elsewhere.\(^{2} \)

### Risks and burdens with once-daily antiretroviral regimens?

The convenience of a once-daily antiretroviral regimen is appealing, but the pharmacologic consequence of a missed dose is greater with a once-daily formulation than with a twice-daily regimen. Furthermore, there are clinical scenarios where once daily is not recommended. For example, patients with high baseline viral load (\( > 100,000 \)) had lower virologic suppression with once-daily dosing compared with twice-daily dosing of lopinavir/ritonavir.\(^{27} \) Once-daily dosing of lopinavir should be avoided in the third trimester of pregnancy because this may result in lower drug exposure. In patients with genotypic protease inhibitor mutations, twice-daily dosing of boosted protease inhibitor (ie, lopinavir/r, darunavir/r) is recommended due to better virologic outcome.

While initial pharmacokinetic/dynamic parameters suggested that raltegravir may be a once-daily regimen candidate, a randomized study of raltegravir 800 mg once daily compared with raltegravir 400 mg twice daily, each on a background of tenofovir/emtricitabine in 770 antiretroviral-naïve patients, demonstrated that 83.2% taking raltegravir once daily versus 88.9% taking raltegravir twice daily achieved an undetectable viral load (\(< 50 \text{ copies/mL} \)).\(^{24} \) The treatment outcome difference of –5.7% (95% CI: –10.7% to –0.83%) did not meet the criteria for noninferiority. The observed difference was largely driven by patients with high viral load. Among those with a viral load \( > 100,000 \text{ copies/mL} \), 74.3% of the once-daily group versus 84.2% of the twice-daily group had undetectable viral load.\(^{24} \)

Finally, clinicians should be aware that the pharmacokinetic parameters of once-daily dosing may not be adequate. A once-daily treatment regimen is usually associated with higher maximum plasma concentration and lower trough plasma concentrations of the antiretrovirals. The increase in peak concentration may result in higher toxicity, as demonstrated for boosted protease inhibitors\(^{29} \) and “off-label” use of nevirapine immediate-release (2 \( \times 200 \) mg once daily).\(^{29} \) Drugs with a short half-life, such as zidovudine, stavudine, and the non-boosted protease inhibitors (except atazanavir), are not suitable for once-daily administration due to inadequate drug concentrations through needed 24-hour period. On the other hand, once-daily administration of boosted protease inhibitors may not provide adequate trough concentrations when the virus shows reduced susceptibility to the drug, such as during rescue therapy or in patients with protease inhibitor-associated mutations. For example, although daily dosing with darunavir/r (800/100 mg once daily) is noninferior and even superior to lopinavir/r in treatment-naïve patients,\(^{30} \) once-daily darunavir/r is not recommended in patients with more than one darunavir-associated resistance mutation (eg, V11I, V32I, L33F, 147V, 150V, 154L, 154M, T74P, L76V, I84V, and L89V). The enhanced pharmacokinetic profile achieved with twice-daily darunavir/r (600/100 mg twice daily) is required to overcome low level darunavir resistance.

### Way forward and the corresponding research agenda

Antiretroviral nonadherence may result from factors other than pill burden or dosing frequency, including: tolerability and potential drug interactions of regimen; patient factors, such as depression or substance abuse; social factors, such as stigma and discrimination; or structural factors (eg, cost, drug availability, lack of access to and retention in care, lack of insurance coverage).\(^{31} \) Therefore, it is important to re-emphasize that clinicians’ efforts to improve and sustain antiretroviral adherence should not be limited to the choice...
Table 2 Summary of recent studies comparing once-daily with twice-daily or three times daily HIV regimens

| Reference | Study design/aim | Population | n | Adherence end point | Duration | Results |
|-----------|-----------------|------------|---|---------------------|----------|---------|
| Wright et al<sup>11</sup> | Randomized trial to evaluate safety and antiviral activity of ENF QD versus BID | ENF-naive, on an unchanged prestudy regimen for ≥28 days with VL ≥ 5000 copies/mL and prior experience or documented resistance to 3 classes of approved ARVs (PIs, NRTIs, and NNRTIs) | n = 61 | Proportion of patients achieving HIV RNA < 400 copies/mL | 48 weeks | At week 48, 23.3% of QD patients versus 22.6% of BID (P = 0.969) achieved HIV RNA < 400 copies/mL, and 13.3% and 22.6% (P = 0.323), respectively, achieved <50 copies/mL. No significant differences in AEs were noted. Adherence (95% of prescribed doses) was higher with ENF QD (80.0%) versus BID (58.1%). |
| Boyle et al<sup>19</sup> | Open-label, randomized, multicenter, Phase IIIB noninferiority study to evaluate BID+ regimen versus QD regimen | HIV-infected adult patients with VL < 50 copies/mL on a BID or more frequent ARV regimen | n = 320 | Proportion of patients who maintained plasma HIV RNA < 50 copies/mL at week 48 after switching to QD arm versus patients in BID+ arm | 48 weeks | QD arm was noninferior to BID+ arm in primary efficacy measure (proportion of patients who maintained suppression at week 48; QD arm, 80.0% versus BID+ arm, 75.8%). Adherence and treatment satisfaction significantly favored QD arm, in which 91.0% of patients preferred simpler regimen. |
| Maidand et al<sup>16</sup> | Randomized open-label study comparing adherence, efficacy, and safety of immediate versus delayed switching from ABC + 3TC BID to ABC/3TC FDC Q | Single-center, open-label study in HIV-infected patients with VL < 50 copies/mL | 94 | Patient satisfaction measured by HIVTSQ questionnaire; adherence by MEMS caps | 8 weeks | Patient satisfaction increased significantly at week 4 with ABC/3TC QD: 92% (82%–99%) versus 85% (75%–93%) (P = 0.004). Through 24 weeks, QD dosing of LPV/r resulted in higher treatment compliance than BID dosing; <50 copies/mL and 100% <400 copies/mL. |
| Zajdenverg et al<sup>17</sup> | Randomized controlled trial LPV/r tablet QD versus BID + NRTIs in ARV-experienced patients | ARV-experienced adult patients | 599 | Noncompliance (ingestion, correct dose, time of ingestion) | 6 months | Improved adherence with STR of EFV/FTC/TDF with QD versus BID or TID (P < 0.01, all comparisons) |
| De Jesus et al<sup>23</sup> | Randomized controlled trial comparing EFV/TDF/FTC QD versus BID versus TID | ARV-naive adults initiating ART | 567 | Adherence as measured by pill counts | 6 months | I month after switch to FDR, adherence increased to 96.1% (baseline, 93.8%) (P < 0.001) and was 96.2% at 6 months. QOL improved over time from 68.8% to 72.7% (P = 0.042). QOL was significantly associated with adherence (P < 0.0001). During FDR use, mean CD4 count increased from 556 to 605 cells/mm<sup>3</sup> (P < 0.0001). |
| Airoldi et al<sup>22</sup> | ADONE: prospective, multicenter, open-label, comparative study with within-patient analysis | Patients chronically treated with FTC + TDF + EFV or 3TC + TDF + EFV and with HIV-RNA < 50 copies/mL | 202 | Effect of simplification of ARV regimen on adherence | 6 months | Adherence was higher in EFV/FTC/TDF STR regimen compared with multiple-pill regimens (P = 0.006) after controlling for multiple confounders. Viral suppression (HIV RNA < 50 copies/mL) was greater in EFV/FTC/TDF STR than multiple-pill regimens (69.2% versus 46.5%; P = 0.02) |
| Bangsberg et al<sup>21</sup> | Prospective observational study assessing adherence and virologic response to EFV/FTC/TDF as STR | Homeless and marginally housed | 658 | Adherence and viral suppression versus historical controls from same cohort | 6 months | Through 1 year of FDR, adherers maintained a high adherence of ≥95% of the QD regimen. |
No difference in viral suppression after controlling for adherence

Week 48 virological responses were 81.0% (409/505) for NVP XR and 75.9% (384/506) for NVP IR. The adjusted difference in favor of NVP XR was 4.9% (95% CI: 0.1–10.0%). Mean adherence rates were 99.0% for NVP XR, and 97.6% for the NVP IR treatment groups.

**Abbreviations:** 3TC, lamivudine; ABC, abacavir; AE, adverse event; ARV, antiretroviral; ART, antiretroviral therapy; BID, twice daily; BID+, twice daily or greater; CI, confidence interval; EFV, efavirenz; ENF, enfuvirtide; FDC, fixed-dose combination; FDR, fixed daily regimen; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIVSQ, HIV Treatment Satisfaction Questionnaire; IR, immediate release; LPV/r, lopinavir/ritonavir; MEMS, Medication Event Monitoring System; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase; NVP, nevirapine inhibitor; PI, protease inhibitor; QD, once daily; QOL, quality of life; STR, single tablet regimen; TDF, tenofovir; VL, viral load; xR, extended-release.
should include overall global patient costs (ie, not only the actual direct costs of different formulations for each drug), but also related costs associated with lesser adherence to antiretroviral treatment regimens. Total patient costs should include the additional health care costs related to managing adverse consequences resulting from poor regimen adherence (eg, hospitalization with an opportunistic infection) and non-medical costs, such as social services. Finally, this assessment should also include expenses associated with the design of new antiretroviral regimens (eg, new genotypic and phenotypic virologic testing if applicable) if the original regimen fails.

Country-specific pharmacoeconomic analyses should address prospective investigations of the long-term benefits of better antiretroviral regimen adherence, the resulting improvements in overall patient outcomes and associated costs, and the cost-effectiveness of simple, reliable, and validated interventions to improve antiretroviral regimen adherence. Taken together, these analyses will allow the comprehensive and cost-effectiveness of simple, reliable, and validated once-daily antiretroviral dosing strategies in various patient conditions where the virus shows sufficient susceptibility to this strategy is suitable for selected antiretrovirals and under this regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. 

**Conclusion**

Simplification of antiretroviral treatment is evolving and remains an important strategy to improve the long-term management of HIV-infected patients. This can be achieved by the development of once-daily fixed-dose combination formulations and by new drugs with improved pharmacokinetic characteristics. Available evidence demonstrates better treatment adherence with once-daily fixed-dose combination regimens, especially in patient populations who are more likely to be noncompliant with their regimens; however, this strategy is suitable for selected antiretrovirals and under conditions where the virus shows sufficient susceptibility to the specific antiretrovirals in the fixed-dose combination under consideration. Clinicians’ efforts to improve and sustain patient adherence should not be limited to the choice of a once-daily regimen, but also need to be comprehensive in addressing the specific patient’s needs and preferences. Further research will be necessary to establish the benefits of once-daily antiretroviral dosing strategies in various patient populations, including better adherence, reduction of HIV transmission, and comprehensive cost-effectiveness.

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Regimen simplification in HIV infection

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