Patient Preference and Adherence

Dovepress
open access to scientific and medical research

Open Access Full Text Article

EXPERT OPINION

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

This article was published in the following Dove Press journal:
Patient Preference and Adherence
23 December 2011
Number of times this article has been viewed

Jean B Nachega[1–3]
Bernd Rosenkranz[4]
Paul A Pham[5]

[1]Department of International Health, [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [3]Department of Medicine and Centre for Infectious Diseases, [4]Division of Pharmacology, Department of Medicine, Faculty of Health Sciences, University of Stellenbosch, Capetown, South Africa; [5]Department 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.[1] 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).[2] 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.[3–8] 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.[9] The key objectives of this strategy are to reduce the

Correspondence: Jean B Nachega
Johns Hopkins University, Bloomberg School of Public Health, Department of International Health, Global Disease Epidemiology and Control Program, 615 N Wolfe St, Suite W5031, Baltimore, MD 21205, USA
Tel +1 410 955 2378
Fax +1 410 502 6733
Email jnachega@jhsph.edu

Table 1 Antiretroviral fixed-dose combinations

FDA-approved	Type
AZT/3TC	Dual NRTI
d4T/3TC*	Dual NRTI
ABC/3TC	Dual NRTI
TDF/FTC	Dual NRTI
TDF/3TC*	Dual NRTI
AZT/3TC/NVP*	NNRTI + dual NRTI
d4T/3TC/NVP*	NNRTI + dual NRTI
AZT/3TC/ABC	Triple NRTI
TDF/FTC/EFV	NNRTI + dual NRTI
TDF/3TC/EFV*	NNRTI + dual NRTI
LPV/r	Boosted PI
RPV/TDF/FTC	NNRTI + dual NRTI
Under study	
Dolutegravir/ABC/3TC	Integrase inhibitor + dual NRTI
Elvitegravir/cobicistat/TDF/FTC	Boosted integrase inhibitor + dual NRTI
ATV + RTV (coblister)	Boosted PI

Note: *Fixed-dose combinations not available in the United States.
Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RPV, rilpiverine; RTV, ritonavir; TDF, tenofovir.

overall pill burden (from >2–5 daily to one 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 a once-daily fixed-dose combination regimen (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® XR™) 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 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 that patients with HIV-RNA < 50 copies/mL on a twice-daily or three times-daily regimen were switched to a 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 copies/mL).[24] The treatment outcome difference of −5.7% (95% CI: −10.7%, −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 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[28] and "off-label" use of nevirapine immediate-release (2 × 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, I47V, I50V, I54L, I54M, 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[41]	Randomized trial to evaluate safety and antiviral activity of ENF QD versus BID	ENF-naïve, 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 QD: n = 30 BID: n = 31	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[19]	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 QD: = 213 BID+: n = 107	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
Maitland et al[16]	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	BID vs QD: treatment compliance 99.2% (90.7%–100%) versus 96.6% (60.0%–100%) ($P = 0.017$); dosing compliance 97.1% (64.3%–100%) versus 91.9% (33.3%–100%) ($P = 0.016$); and timing compliance 95.5% (53.8%–100%) versus 86.3% (4.3%–100%) ($P = 0.006$) Treatment satisfaction increased significantly at week 4 with ABC/3TC QD: 92% (82%–99%) versus 85% (75%–93%) ($P = 0.004$)
Zajdenverg et al[27]	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	Through 24 weeks, QD dosing of LPV/r resulted in higher treatment compliance than BID dosing; <50 copies/mL and 100% <400 copies/mL
De Jesus et al[23]	Randomized controlled trial comparing EFV/TDF/FTC QD versus BID versus TID	ARV-naïve adults initiating ART	567	Adherence as measured by pill counts	6 months	Improved adherence with STR of EFV/TDF/FTC with QD versus BID or TID ($P < 0.01$, all comparisons)
Airoldi et al[22]	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	1 month after switch to FDR, adherence increased to 96.1% (baseline, 93.8%) ($P < 0.01$) 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^3 ($P < 0.0001$)
Bangsberg et al[12]	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	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%; $P = 0.02$)

						No difference in viral suppression after controlling for adherence
Gathe et al[21]	Randomized, double-blind, double-dummy study comparing efficacy and safety of NVP XR versus IR	ARV-naïve adults initiating ART	1011	Adherence as measured by pill counts	48 weeks	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; NPV, nevirapine inhibitor; PI, protease inhibitor; QD, once daily; QOL, quality of life; STR, single tablet regimen; TDF, tenofovir; VL, viral load; XR, extended-release.

of once-daily antiretroviral regimen, but they need to include social support,[32] side effect management,[33] substance abuse management, depression management, adherence support toolkits (eg, pillbox organizers),[34] and other targeted interventions if needed.[35]

An emerging perspective is that better adherence associated with once-daily fixed-dose combination regimens or other antiretroviral simplification strategies may reduce HIV transmission. Indeed, pre-exposure prophylaxis studies in men who have sex with men who received tenofovir + emtricitabine found a 44% overall reduction of HIV transmission; and as one would expect, the efficacy was higher in adherent patients with detectable antiretroviral plasma concentrations.[36] Likewise, in the CAPRISA 004 trial, which was designed to evaluate the effectiveness and safety of tenofovir gel for the prevention of HIV infection in women, application of 1% tenofovir vaginal gel reduced HIV incidence by 39% and by 45% with high-level gel adherence (defined as >80%).[37]

In the era of pay-for-patient-performance initiatives, rigorous cost-benefit analysis of regimen simplification studies will be important. Using this approach will bring added value to the underlying medical knowledge base, policy makers, and stakeholders if once-daily regimens with directly observed therapy are cost-effective when compared with the total health care costs for patients who are not virologically suppressed on self-administered twice-daily regimens. A key concern that is generating interest from both patients and payers is the overall cost associated with once-daily versus twice-daily dosing regimens, especially in the life-long treatment for chronic HIV infection. With lamivudine coming off patent soon, the drug cost of a once-daily dosing of lamivudine, tenofovir, and efavirenz will likely be lower compared with once-daily dosing of a fixed-dose combination of efavirenz, emtricitabine, and tenofovir (Atripla®). Payer and governmental agencies will need to decide if the benefits of fixed-dose combinations are worth the higher drug cost. Have the impact on antiretroviral adherence and virologic outcomes as well as the direct and indirect costs associated with each treatment paradigm been rigorously compared? Not to our knowledge, and such research is critically needed to guide clinical and policy decision-making. Of note, a recent evaluation of the effect of antiretroviral regimen adherence on direct health care costs demonstrated that high adherence to antiretroviral regimens was associated with lower mean monthly costs of direct health care, with the greatest savings seen in hospitalization costs.[38]

On a global scale, country-specific pharmacoeconomic analyses should address the cost-effectiveness of interventions to improve antiretroviral regimen adherence. These analyses

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,[38] and the cost-effectiveness of simple, reliable, and validated interventions to improve antiretroviral regimen adherence.[39,40] Taken together, these analyses will allow the comprehensive costs of current antiretroviral regimens to be compared with the comprehensive patient costs associated with simplified antiretroviral regimens, facilitating evidence-based decision-making for individual countries and patient groups.

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.

Acknowledgments

JBN receives research supported from the United States National Institutes for Allergy and Infectious Disease, Division of AIDS (K23AI 068582-01), the US PEPFAR Grant Award (T84HA21652-01-00) for Medical Education Partnership Initiative, the European Developing Countries Clinical Trial Partnership Senior Fellowship Award (TA-08-40200-021), and the Wellcome Trust Southern Africa Consortium for Research Excellence (WT087537MA).

Disclosure

In the last 12 months, JBN has received consulting fees or participated in scientific advisory boards for Gilead Sciences and is a speaker bureau member for GlaxoSmithKline, Merck Inc, and Gilead Sciences. PAP declares that he has no competing financial interests. BR declares that he has no competing financial interests. Editorial assistance was provided by José L Walewski of Envision Scientific Solutions, which was contracted by Boehringer Ingelheim Pharmaceuticals Inc, for these services. The authors received no compensation related to the development of the manuscript.

References

1. Moreno S, Lopez Aldeguer J, Arribas JR, et al. The future of antiretroviral therapy: challenges and needs. *J Antimicrob Chemother*. 2010;65:827–835.
2. 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;5:357–367.
3. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*. 2000;14:357–366.
4. Bartlett JA, Fath MJ, Demasi R, et al. An updated systematic overview of triple combination therapy in antiretroviral-naive HIV-infected adults. *AIDS*. 2006;20:2051–2064.
5. 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;146:564–573.
6. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis*. 2009;48:484–488.
7. Pulido F, Ribera E, Moreno S, et al. Once-daily antiretroviral therapy: Spanish Consensus Statement. *J Antimicrob Chemother*. 2005;56:808–818.
8. 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;139:810–816.
9. Negredo E, Molto J, Munoz-Moreno JA, et al. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. *Antivir Ther*. 2004;9:335–342.
10. Barrios A, Negredo E, Domingo P, et al. Simplification therapy with once-daily didanosine, tenofovir and efavirenz in HIV-1-infected adults with viral suppression receiving a more complex antiretroviral regimen: final results of the EFADITE trial. *Antivir Ther*. 2005;10:825–832.
11. 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;7:229–236.
12. 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(18):2835–2840.

13. Macha S, Yong CL, Darrington T, et al. In vitro-in vivo correlation for nevirapine extended release tablets. *Biopharm Drug Dispos*. 2009;30:542–550.
14. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed September 1, 2011.
15. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363:1253–1263.
16. 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;9:667–672.
17. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358:2095–2106.
18. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr*. 2004;36:1011–1019.
19. 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;9:164–176.
20. Klein R, Struble K. Approval of Viramune XR (nevirapine) 400 mg extended release tablet. FDA announcement of Viramune XR approval. Available from: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm248800.htm. Accessed September 12, 2011.
21. Gathe J, Andrade-Villanueva J, Santiago S, et al. Efficacy and safety of nevirapine extended-release once daily versus nevirapine immediate-release twice-daily in treatment-naive HIV-1-infected patients. *Antivir Ther*. 2011;16:759–769.
22. Airoldi M, Zaccarelli M, Bisi L, et al. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Prefer Adherence*. 2010;4:115–125.
23. DeJesus E, Pozniak A, Gallant J, et al. Improvement in fasting lipids but minimal recovery of limb fat were seen 96 weeks after switching from lamivudine/zidovudine plus efavirenz to fixed-dose efavirenz/emtricitabine/tenofovir DF in HIV-infected patients. Paper presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12–15, 2009, San Francisco, CA.
24. Eron J, Rockstroh J, Andrade-Villanueva J, Madruga J. QDMRK, a phase III study of the safety and efficacy of once-daily vs twice-daily RAL in combination therapy for treatment-naive HIV-infected patients. Paper presented at the 18th Conference on Retroviruses and Opportunistic Infections, February 27–March 3, 2011, Boston, MA.
25. Jayaweera D, Dejesus E, Nguyen KL, Grimm K, Butcher D, Seekins DW. Virologic suppression, treatment adherence, and improved quality of life on a once-daily efavirenz-based regimen in treatment-naive HIV-1-infected patients over 96 weeks. *HIV Clin Trials*. 2009;10:375–384.
26. Johnson MA, Gathe JC Jr, Podzamczer D, et al. A once-daily lopinavir/ritonavir-based regimen provides noninferior antiviral activity compared with a twice-daily regimen. *J Acquir Immune Defic Syndr*. 2006;43:153–160.
27. 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*. 2011;54:143–151.
28. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. *J Antimicrob Chemother*. 2004;53:4–9.
29. Clotet B. Once-daily dosing of nevirapine in HAART. *J Antimicrob Chemother*. 2008;61:13–16.
30. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS*. 2009;23:1679–1688.
31. 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.
32. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *J Behav Med*. 2006;29:377–387.
33. Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. *J Acquir Immune Defic Syndr*. 2009;51:65–71.
34. 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;45:908–915.
35. 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–S35.
36. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587–2599.
37. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329:1168–1174.
38. Bishai D, Colchero A, Durack DT. The cost effectiveness of antiretroviral treatment strategies in resource-limited settings. *AIDS*. 2007;21:1333–1340.
39. Nachega JB, Leisegang R, Bishai D, et al. Association of antiretroviral therapy adherence and health care costs. *Ann Intern Med*. 2010;152:18–25.
40. Purdum AG, Johnson KA, Globe DR. Comparing total health care costs and treatment patterns of HIV patients in a managed care setting. *AIDS Care*. 2004;16:767–780.
41. 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(2):73–82.