Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Downloaded from http://aidsinfo.nih.gov/guidelines on 3/17/2013

Management of the Treatment-Experienced Patient

Virologic and Immunologic Failure (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations

- Assessing and managing an antiretroviral (ARV)-experienced patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.
- Evaluation of virologic failure should include an assessment of the severity of the patient's HIV disease, ART history, use of concomitant medications with consideration of adverse drug interactions with ARV agents, HIV RNA and CD4 T-cell count trends over time, and prior drug-resistance testing results.
- Drug-resistance testing should be obtained while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation **(AII)**.
- The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL) **(AI)**.
- To design a new regimen, the patient's treatment history and past and current resistance test results should be used to identify at least two (preferably three) fully active agents to combine with an optimized background ARV regimen **(AI)**. A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, drug-resistance testing, and/or a novel mechanism of action.
- In general, adding a single, fully active ARV in a new regimen is ***not*** recommended because of the risk of rapid development of resistance **(BII)**.
- In patients with a high likelihood of clinical progression (e.g., CD4 count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits **(CI)**.
- For some highly ART-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued **(AI)** with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression.
- Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is ***not*** recommended **(AI)**.
- In the setting of virologic suppression, there is no consensus on how to define or treat immunologic failure.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Virologic Definitions

Virologic suppression: A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

Virologic failure: The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).

Incomplete virologic response: Two consecutive plasma HIV RNA levels >200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response, and some regimens will take longer than others to suppress HIV RNA levels.

Virologic rebound: Confirmed detectable HIV RNA (to >200 copies/mL) after virologic suppression.

Persistent low-level viremia: Confirmed detectable HIV RNA levels that are <1,000 copies/mL.

Virologic blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Causes of Virologic Failure

Virologic failure in a patient can occur for multiple reasons. Data from older patient cohorts suggested that suboptimal adherence and drug intolerance/toxicity accounted for 28%–40% of virologic failure and regimen discontinuations.[1-2] More recent data suggest that most virologic failure on first-line regimens occurred due to either pre-existing (transmitted) drug resistance or suboptimal adherence.[3] Factors associated with virologic failure include:

- Patient characteristics
    - higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
    - lower pretreatment or nadir CD4 T-cell count
    - prior AIDS diagnosis
    - comorbidities (e.g., active substance abuse, depression)
    - presence of drug-resistant virus, either transmitted or acquired
    - prior treatment failure
    - incomplete medication adherence and missed clinic appointments
- ARV regimen characteristics
    - drug side effects and toxicities
    - suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs)
    - food/fasting requirements
    - adverse drug-drug interactions with concomitant medications
    - suboptimal virologic potency
    - prescription errors
- Provider characteristics, such as experience in treating HIV disease
- Other or unknown reasons

Management of Patients with Virologic Failure

Assessment of Virologic Failure

If virologic failure is suspected or confirmed, a thorough work-up is indicated, addressing the following factors:

- change in HIV RNA and CD4 T-cell counts over time
- occurrence of HIV-related clinical events
- ARV treatment history
- results of prior resistance testing (if any)
- medication-taking behavior (including adherence to recommended drug doses, dosing frequency, and food/fasting requirements)

- tolerability of medications
- concomitant medications and supplements (with consideration for adverse drug-drug interactions)
- comorbidities (including substance abuse)

In many cases, the cause(s) of virologic failure will be identified. In some cases, no obvious cause(s) may be identified. It is important to distinguish among the reasons for virologic failure because the approaches to subsequent therapy differ. The following potential causes of virologic failure should be explored in depth.

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) (e.g., difficulties accessing or tolerating medications, depression, active substance abuse) and simplify the regimen if possible (e.g., decrease pill count or dosing frequency). (See Adherence.)
- **Medication Intolerance.** Assess the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can impact adherence. Management strategies for intolerance in the absence of drug resistance may include:
  - using symptomatic treatment (e.g., antiemetics, antidiarrheals)
  - changing one ARV to another within the same drug class, if needed (e.g., change to tenofovir [TDF] or abacavir [ABC] for zidovudine [ZDV]-related toxicities; change to nevirapine [NVP] or etravirine [ETR] for efavirenz [EFV]-related toxicities)[4-5]
  - changing from one drug class to another (e.g., from a non-nucleoside reverse transcriptase inhibitor [NNRTI] to a protease inhibitor [PI], from enfuvirtide [T-20] to raltegravir [RAL]) if necessary and no prior drug resistance is suspected
- **Pharmacokinetic Issues.** Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug Interactions section and tables for common interactions) and make appropriate substitutions for ARV agents and/or concomitant medications, if possible. Therapeutic drug monitoring (TDM) may be helpful if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected. (See also Exposure-Response Relationship and Therapeutic Drug Monitoring.)
- **Suspected Drug Resistance.** Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation if the plasma HIV RNA level is >500 copies/mL **(AII)**. (See Drug-Resistance Testing.) Evaluate the degree of drug resistance and consider the patient's prior treatment history and prior resistance test results. Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account. Routine genotypic or phenotypic testing gives information relevant for selecting nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs. Additional drug-resistance tests for patients experiencing failure on fusion inhibitors and/or integrase strand transfer inhibitors (INSTIs) and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See Drug-Resistance Testing.)

Changing ART

There is no consensus on the optimal time to change therapy for virologic failure. The goal of ART is to suppress HIV replication to a level where drug-resistance mutations do not emerge. However, the specific level of viral suppression needed to achieve durable virologic suppression remains unknown. Selection of drug resistance does not appear to occur in patients with persistent HIV RNA levels suppressed to <48 copies/mL,[6] although this remains controversial.[7]

The clinical implications of HIV RNA in the range of >48 to <200 copies/mL in a patient on ART are controversial. Unlike the case with higher levels of HIV RNA, most, if not all, circulating virus from individuals with this level of HIV RNA results from the release of HIV from long-lived latently infected cells and does not signify ongoing viral replication with the emergence of drug-resistant virus.[8] Although some studies have suggested that viremia at this low level predicts subsequent failure[9] and can be associated with the evolution of drug resistance,[10] a large retrospective analysis showed that using an HIV RNA threshold for virologic failure of <200 copies/mL had the same predictive value as using a threshold of <50 copies/mL.[11]

Newer technologies (e.g., Taqman assay) have made it possible to detect HIV RNA in more patients with low level viremia (<200 copies/mL) than was possible with previous assays. Use of these newer assays has resulted in more confirmatory viral load testing than may be necessary.[12-14]

Persistent HIV RNA levels >200 copies/mL often are associated with evidence of viral evolution and drug-resistance mutation accumulation;[15] this is particularly common when HIV RNA levels are >500 copies/mL.[16] Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should therefore be considered as virologic failure.

Viremia "blips" (e.g., viral suppression followed by a detectable HIV RNA level and then subsequent return to undetectable levels) usually are not associated with subsequent virologic failure.[17]

Management of Virologic Failure

Once virologic failure is confirmed, generally the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations.[18]

Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs on the basis of drug treatment history, resistance testing, or new mechanistic class **(AI)**.[19-27] Some ARV drugs (e.g., NRTIs) may contribute partial ARV activity to a regimen, despite drug resistance,[28] while others (e.g., T-20, NNRTIs, RAL) likely do not provide partial activity.[28-30] Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. In addition, archived drug-resistance mutations may not be detected by standard drug-resistance tests, emphasizing the importance of considering treatment history and prior drug-resistance tests. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Early studies of ART-experienced patients identified factors associated with better virologic responses to subsequent regimens.[31-32] These factors included lower HIV RNA level and/or higher CD4 cell count at the time of therapy change, using a new (i.e., not yet taken) class of ARV drugs, and using ritonavir (RTV)-boosted PIs in PI-experienced patients.

More recent clinical trials support the strategy of conducting reverse transcriptase (RT) and protease (PT) resistance testing (both genotype and phenotype) while an ART-experienced patient is taking a failing ARV regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting at least two and preferably three active drugs for the new treatment regimen.[20-21, 23-24, 33] Higher genotypic and/or phenotypic susceptibility scores (quantitative measures of drug activity) are associated with better virologic responses.[23-24] Patients who receive more active drugs have a better and more prolonged virologic response than those with fewer active drugs in the regimen. Active ARV drugs include those with activity against drug-resistant viral strains, including newer members of existing classes (the NNRTI—ETR, the PIs—darunavir [DRV] and tipranavir [TPV]) and drugs with new mechanisms of action (the fusion inhibitor—T-20, the CCR5 antagonist—maraviroc [MVC] in patients with R5 but not X4 virus, and the INSTI—RAL). Drug-resistance tests for patients experiencing failure on fusion inhibitors (FIs) and/or INSTIs and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See Drug-Resistance Testing.)

Clinical Scenarios of Virologic Failure

- **Low-level viremia (HIV RNA <1,000 copies/mL).** Assess adherence. Consider variability in HIV RNA assays. Patients with HIV RNA <48 copies/mL or isolated increases in HIV RNA ("blips") do not require a change in treatment[13] **(AII)**. There is no consensus regarding how to manage patients with HIV RNA levels >48 copies/mL and <200 copies/mL; HIV RNA levels should be followed over time to assess the need for changes **(AIII)**. Patients with persistent HIV RNA levels >200 copies/mL often select out drug-resistant viral variants, particularly when HIV RNA levels are >500 copies/mL. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as possible virologic failure; resistance testing should be attempted if the HIV RNA level is >500 copies/mL. For individuals with sufficient therapeutic options, consider treatment change **(BIII)**.
- **Repeated detectable viremia (HIV RNA >1,000 copies/mL) and NO drug resistance identified.** Consider the timing of the drug-resistance test (e.g., was the patient off ARV for >4 weeks and/or nonadherent?). Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine whether a resistant viral strain emerges **(CIII)**.
- **Repeated detectable viremia (HIV RNA >1,000 copies/mL) and drug resistance identified.** The goals in this situation are to resuppress HIV RNA levels maximally (i.e., to <48 copies/mL) and to prevent further selection of resistance mutations. With the availability of multiple new ARVs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. In a patient with ongoing viremia and evidence of resistance, some drugs in a regimen (e.g., NNRTI, T-20, RAL) should be discontinued promptly to decrease the risk of selecting additional drug-resistance mutations in order to preserve the activity of these drug classes in future regimens. A new regimen should include at least two, and preferably three, fully active agents **(AII)**.
- **Highly drug resistant HIV.** There is a subset of patients who have experienced toxicity and/or developed resistance to all or most currently available regimens, and designing a regimen with two or three fully active drugs is not possible. Many of these patients received suboptimal ARV regimens (i.e., did not have access to more than one or two of the drugs at the time they became available) or have been unable to adhere to any regimen. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). There is no consensus on how to optimize the management of these patients. It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits.[34] There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, reduces the risk of disease progression.[35] Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL.[36-37] However, these potential benefits all must be balanced with the ongoing risk of accumulating additional resistance mutations.

In general, adding a single, fully active ARV in a new regimen is ***not*** recommended because of the risk of rapid development of resistance **(BII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 cell count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits **(CI)**. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., ARV activity) of using a single active drug in the heavily ART-experienced patient is complicated, and consultation with an expert is advised.

Patients with ongoing viremia and with an insufficient number of approved treatment options to construct a

fully suppressive regimen may be candidates for research studies or expanded access programs, or single-patient access of investigational new drug(s) (IND), as specified in Food and Drug Administration (FDA) regulations: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm163982.htm.

Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 T-cell count and increases the risk of clinical progression.[38-39] Therefore, this strategy is ***not*** recommended **(AI)**. See Discontinuation or Interruption of Antiretroviral Therapy.

- **Prior treatment and suspected drug resistance, now presenting to care in need of therapy with limited information (i.e., incomplete or absence of self-reported history, medical records, or previous resistance data).** Every effort should be made to obtain medical records and prior drug-resistance testing results; however, this is not always possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2–4 weeks to help guide the choice of the next regimen; another strategy is to start two or three drugs known to be active based on treatment history (e.g., MVC with R5 virus, RAL if no prior INSTI).

Immunologic Failure: Definition, Causes, and Management

Immunologic failure can be defined as the failure to achieve and maintain an adequate CD4 response despite virologic suppression. Increases in CD4 counts in ARV-naive patients with initial ARV regimens are approximately 150 cells/mm^3 over the first year.[40] A CD4 count plateau may occur after 4–6 years of treatment with suppressed viremia.[41-45]

No accepted specific definition for immunologic failure exists, although some studies have focused on patients who fail to increase CD4 counts above a specific threshold (e.g., >350 or 500 cells/mm^3) over a specific period of time (e.g., 4–7 years). Others have focused on an inability to increase CD4 counts above pretherapy levels by a certain threshold (e.g., >50 or 100 cells/mm^3) over a given time period. The former criterion may be preferable because of data linking these thresholds with the risk of non-AIDS clinical events.[46]

The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/mm^3 through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/mm^3, 66% in those starting with a CD4 count 200–350 cells/mm^3, and 85% in those starting with a CD4 count >350 cells/mm^3.[41]

A persistently low CD4 count while on suppressive ART is associated with a small, but appreciable, risk of AIDS- and non-AIDS-related morbidity and mortality.[47-48] For example, in the FIRST study,[49] a low CD4 count on therapy was associated with an increased risk of AIDS-related complications (adjusted hazard ratio of 0.56 per 100 cells/mm^3 higher CD4 count). Similarly, a low CD4 count was associated with an increased risk of non-AIDS events, including cardiovascular, hepatic, and renal disease and cancer. Other studies support these associations.[50-53]

Factors associated with poor CD4 T-cell response:

- CD4 count <200/mm^3 when starting ART
- Older age
- Coinfection (e.g., hepatitis C virus [HCV], HIV-2, human T-cell leukemia virus type 1 [HTLV-1], HTLV-2)
- Medications, both ARVs (e.g., ZDV,[54] TDF + didanosine [ddI][55-57]) and other medications.
- Persistent immune activation
- Loss of regenerative potential of the immune system
- Other medical conditions

Assessment of Immunologic Failure. CD4 count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., cancer chemotherapy, interferon, prednisone, ZDV; combination of TDF and ddI), and consideration should be given to substituting or discontinuing these drugs, if possible. Untreated coinfections (e.g., HIV-2, HTLV-1, HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Immunologic Failure. No consensus exists on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 counts <200 cells/mm^3 because patients with higher CD4 counts have a lower risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the ARV regimen. Because ongoing immune activation occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit.[58] Others suggest changing the regimen to another regimen (e.g., from NNRTI-based to PI-based, INSTI-based, or CCR5 antagonist-based regimens), but this strategy has not shown clear benefit.

An immune-based therapy, interleukin-2, demonstrated CD4 count increases but no clinical benefit in two large randomized studies[59] and therefore is not recommended **(AI)**. Other immune-based therapies (e.g., gene therapies, growth hormone, cyclosporine, interleukin-7) are under investigation. Currently, immune-based therapies should not be used unless in the context of a clinical trial **(AIII)**.

References

1. d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS*. 2000;14(5):499-507.
2. Mocroft A, Youle M, Moore A, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS*. 2001;15(2):185-194.
3. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis*. 2010;201(5):662-671.
4. Schouten JT, Krambrink A, Ribaudo HJ, et al. Substitution of nevirapine because of efavirenz toxicity in AIDS clinical trials group A5095. *Clin Infect Dis*. 2010;50(5):787-791.
5. Waters L, Fisher M, Winston A, et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS*. 2011;25(1):65-71.
6. Kieffer TL, Finucane MM, Nettles RE, et al. Genotypic analysis of HIV-1 drug resistance at the limit of detection: virus production without evolution in treated adults with undetectable HIV loads. *J Infect Dis*. 2004;189(8):1452-1465.
7. Shiu C, Cunningham CK, Greenough T, et al. Identification of ongoing human immunodeficiency virus type 1 (HIV-1) replication in residual viremia during recombinant HIV-1 poxvirus immunizations in patients with clinically undetectable viral loads on durable suppressive highly active antiretroviral therapy. *J Virol*. 2009;83(19):9731-9742.
8. Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nat Med*. 2003;9(6):727-728.
9. Eron JJ, Cooper DA, Steigbigel RT, et al. Sustained antiretroviral effect of raltegravir at week 156 in the BENCHMRK studies, and exploratory analysis of late outcomes based on early virologic responses. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 515.
10. Taiwo B, Gallien S, Aga S, et al. HIV drug resistance evolution during persistent near-target viral suppression. *Antiviral Therapy* 2010;15:A38.

11. Ribaudo H, Lennox J, Currier J, et al. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 580.
12. Lima V, Harrigan R, Montaner JS. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. *J Acquir Immune Defic Syndr*. 2009;51(1):3-6.
13. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis*. 2009;48(2):260-262.
14. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr*. 2010;54(4):442-444.
15. Aleman S, Soderbarg K, Visco-Comandini U, et al. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS*. 2002;16(7):1039-1044.
16. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS*. 2004;18(7):981-989.
17. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA*. 2005;293(7):817-829.
18. Hosseinipour MC, van Oosterhout JJ, Weigel R, et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS*. 2009;23(9):1127-1134.
19. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med*. 2008;359(4):355-365.
20. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med*. 2003;348(22):2186-2195.
21. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med*. 2003;348(22):2175-2185.
22. Reynes J, Arasteh K, Clotet B, et al. TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS*. 2007;21(8):533-543.
23. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet*. 2007;369(9568):1169-1178.
24. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. 2008;359(4):339-354.
25. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS*. 2009;23(17):2289-2300.
26. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med*. 2008;359(14):1429-1441.
27. Fatkenheuer G, Nelson M, Lazzarin A, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med*. 2008;359(14):1442-1455.
28. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis*. 2005;192(9):1537-1544.
29. Deeks SG, Lu J, Hoh R, et al. Interruption of enfuvirtide in HIV-1 infected adults with incomplete viral suppression on an enfuvirtide-based regimen. *J Infect Dis*. 2007;195(3):387-391.
30. Wirden M, Simon A, Schneider L, et al. Raltegravir has no residual antiviral activity in vivo against HIV-1 with

resistance-associated mutations to this drug. *J Antimicrob Chemother*. 2009;64(5):1087-1090.

31. Gulick RM, Hu XJ, Fiscus SA, et al. Randomized study of saquinavir with ritonavir or nelfinavir together with delavirdine, adefovir, or both in human immunodeficiency virus-infected adults with virologic failure on indinavir: AIDS Clinical Trials Group Study 359. *J Infect Dis*. 2000;182(5):1375-1384.
32. Hammer SM, Vaida F, Bennett KK, et al. Dual vs single protease inhibitor therapy following antiretroviral treatment failure: a randomized trial. *JAMA*. 2002;288(2):169-180.
33. Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet*. 2006;368(9534):466-475.
34. Murray JS, Elashoff MR, Iacono-Connors LC, et al. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS*. 1999;13(7):797-804.
35. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS*. 2000;14(18):2857-2867.
36. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet*. 2004;364(9428):51-62.
37. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr.* 2004;37(1):1147-1154.
38. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med*. 2001;344(7):472-480.
39. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med*. 2003;349(9):837-846.
40. Bartlett JA, DeMasi R, Quinn J, et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS*. 2001;15(11):1369-1377.
41. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446.
42. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med*. 2003;163(18):2187-2195.
43. Garcia F, de Lazzari E, Plana M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *J Acquir Immune Defic Syndr*. 2004;36(2):702-713.
44. Tarwater PM, Margolick JB, Jin J, et al. Increase and plateau of CD4 T-cell counts in the 3(1/2) years after initiation of potent antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001;27(2):168-175.
45. Mocroft A, Phillips AN, Ledergerber B, et al. Relationship between antiretrovirals used as part of a cART regimen and CD4 cell count increases in patients with suppressed viremia. *AIDS*. 2006;20(8):1141-1150.
46. Lau B, Gange SJ, Moore RD. Risk of non-AIDS-related mortality may exceed risk of AIDS-related mortality among individuals enrolling into care with CD4+ counts greater than 200 cells/mm^3. *J Acquir Immune Defic Syndr*. 2007;44(2):179-187.
47. Loutfy MR, Walmsley SL, Mullin CM, et al. CD4(+) cell count increase predicts clinical benefits in patients with advanced HIV disease and persistent viremia after 1 year of combination antiretroviral therapy. *J Infect Dis*. 2005;192(8):1407-1411.
48. Moore DM, Hogg RS, Chan K, et al. Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response. *AIDS*. 2006;20(3):371-377.

49. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008;22(7):841-848.

50. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. 2008;22(16):2143-2153.

51. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641.

52. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.

53. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis*. 2010;51(4):435-447.

54. Huttner AC, Kaufmann GR, Battegay M, et al. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. *AIDS*. 2007;21(8):939-946.

55. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS*. 2005;19(6):569-575.

56. Lacombe K, Pacanowski J, Meynard JL, et al. Risk factors for CD4 lymphopenia in patients treated with a tenofovir/didanosine high dose-containing highly active antiretroviral therapy regimen. *AIDS*. 2005;19(10):1107-1108.

57. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis*. 2005;41(6):901-905.

58. Hammer S, Bassett R, Fischl MA, et al. Randomized, placebo-controlled trial of abacavir intensification in HIV-1-infect adults with plasma HIV RNA < 500 copies/mL. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 56.

59. Abrams D, Levy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. 2009;361(16):1548-1559.

Regimen Simplification (Last updated January 10, 2011; last reviewed January 10, 2011)

Regimen simplification can be defined broadly as a change in established effective therapy to reduce pill burden and dosing frequency, to enhance tolerability, or to decrease specific food and fluid requirements. Many patients on suppressive antiretroviral therapy (ART) may be considered candidates for regimen simplification, especially if (1) they are receiving treatments that are no longer recommended as preferred or alternative choices for initial therapy; (2) they were prescribed a regimen in the setting of treatment failure at a time when there was an incomplete understanding of resistance or drug-drug interaction data; or (3) they were prescribed a regimen prior to the availability of newer options or formulations that might be easier to administer and/or more tolerable.

This section will review situations in which clinicians might consider simplifying treatment in a patient with virologic suppression. Importantly, this section will not review consideration of changes in treatment for reducing ongoing adverse effects. Regimens used in simplification strategies generally should be those that have proven high efficacy in antiretroviral (ARV)-naive patients (see What to Start) or that would be predicted to be highly active for a given patient based on the individual's past treatment history and resistance profile.

Rationale

The major rationales behind regimen simplification are to improve the patient's quality of life, maintain long-term adherence, avoid toxicities that may develop with prolonged ARV use, and reduce the risk of virologic failure. Systematic reviews in the non-HIV literature have shown that adherence is inversely related to the number of daily doses.[1] Some prospective studies in HIV-infected individuals have shown that those on regimens with reduced dosing frequency have higher levels of adherence.[2-3] Patient satisfaction with regimens that contain fewer pills and reduced dosing frequency is also higher.[4]

Candidates for Regimen Simplification

Unlike ARV agents developed earlier in the HIV epidemic, many ARV medications approved in recent years have sufficiently long half-lives to allow for once-daily dosing, and most also do not have dietary restrictions. Patients on regimens initiated earlier in the era of potent combination ART with drugs that pose a high pill burden and/or frequent dosing requirements are often good candidates for regimen simplification.

Patients without suspected drug-resistant virus. Patients on first (or modified) treatment regimens without a history of treatment failure are ideal candidates for regimen simplification. These patients are less likely to harbor drug-resistant virus, especially if a pretreatment genotype did not detect drug resistance. Prospective clinical studies have demonstrated that the likelihood of treatment failure is relatively low in patients after simplification and, indeed, may be lower than in patients who do not simplify treatment.[5] However, some patients may have unrecognized drug-resistant HIV, either acquired at the time of infection or as a consequence of prior treatment, such as patients who were treated with presumably nonsuppressive mono- or dual-nucleoside reverse transcriptase inhibitor (NRTI) regimens before the widespread availability of HIV RNA monitoring and resistance testing.

Patients with documented or suspected drug resistance. Treatment simplification may also be appropriate for selected individuals who achieve viral suppression after having had documented or suspected drug resistance. Often, these patients are on regimens selected when management of drug resistance, understanding of potentially adverse drug-drug interactions, and understanding of treatment options were relatively limited. Regimen simplification may also be considered for patients on two ritonavir (RTV)-boosted protease inhibitors (PIs). Although successful in suppressing viral replication, this treatment may cause patients to be on regimens that are cumbersome, costly, and associated with potential long-term adverse events. The ability to simplify regimens in this setting often reflects the availability of recently approved agents that have activity against drug-resistant virus and are easier to take without sacrificing ARV activity. Specific situations in which drug simplification could be considered in ART-experienced patients

with viral drug resistance are outlined below. Simplifying regimens in patients who have extensive prior treatment histories is complicated. In such a case, a patient's treatment history, treatment responses and tolerance, and resistance test results should be thoroughly reviewed before designing a new regimen. Expert consultation should be considered whenever possible.

Types of Treatment Simplification

Within-Class Simplifications. Within-class substitutions offer the advantage of not exposing patients to still-unused drug classes, which potentially preserves other classes for future regimens. In general, within-class substitutions use a newer agent; coformulated drugs; or a formulation that has a lower pill burden, a lower dosing frequency, or would be less likely to cause toxicity.

- ***NRTI Substitutions*** *(e.g., changing from zidovudine [ZDV] or stavudine [d4T] to tenofovir [TDF] or abacavir [ABC]):* This may be considered for a patient who has no history of viral resistance on an NRTI-containing regimen. Other NRTIs may be substituted to create a regimen with lower dosing frequency (e.g., once daily) that takes advantage of coformulated agents and potentially avoids some long-term toxicities (e.g., pancreatitis, peripheral neuropathy, lipoatrophy).
- ***Switching of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)*** *(e.g., from nevirapine [NVP] to efavirenz [EFV]):* This may be considered to reduce dosing frequency or to take advantage of coformulated agents.
- ***Switching of PIs:*** This switch can be from one PI to another PI, to the same PI at a lower dosing frequency (such as from twice-daily to once-daily RTV-boosted lopinavir [LPV/r] or RTV-boosted darunavir [DRV/r]) or, in the case of atazanavir (ATV), to administration without RTV boosting.[6] (Unboosted ATV is presently not a preferred PI component and not recommended if the patient is taking TDF or if the patient has HIV with reduced susceptibility to ATV.) Such changes can reduce dosing frequency, pill count, drug-drug or drug-food interactions, or dyslipidemia or can take advantage of coformulation. These switches can be done with relative ease in patients without PI-resistant virus. However, these switches are not recommended in patients who have a history of documented or suspected PI resistance because convincing data in this setting are lacking.

Out-of-Class Substitutions. One common out-of-class substitution for regimen simplification involves a change from a PI-based to an NNRTI-based regimen. An important study in this regard was the NEFA trial, which evaluated substitution of a PI-based regimen in virologically suppressed patients with NVP, EFV, or ABC.[7] Although the baseline regimens in the study are no longer in widespread use, the NEFA findings are still relevant and provide information about the risks and benefits of switching treatment in patients with virologic suppression. In this study, 460 patients on stable, PI-based regimens with virologic suppression (<200 copies/mL for the previous 6 months) were switched to their randomized treatment arms. After 36 months of follow-up, virologic failure occurred more frequently in patients switched to ABC than in patients switched to EFV or NVP. The increased risk of treatment failure was particularly high in patients who had previous suboptimal treatment with mono- and dual-NRTI therapy. This emphasizes the need to consider the potential for drug-resistant virus prior to attempting simplification.[8]

Newer agents that target different sites in the HIV life cycle, such as the integrase strand transfer inhibitor (INSTI) raltegravir (RAL) and the CCR5 antagonist maraviroc (MVC), also offer opportunities for out-of-class substitutions, particularly in patients who have a history of virus resistant to older HIV drugs. Three randomized studies have evaluated replacing a boosted PI with RAL in virologically suppressed patients. In two of these studies,[9-10] the switch to RAL was associated with an increased risk of virologic failure in patients with documented or suspected pre-existing NRTI resistance; a third study did not find this higher risk, possibly due to a longer period of virologic suppression before the change.[11] Overall, these results suggest that in ART-experienced patients, RAL should be used with caution as a substitute for a boosted PI.

This strategy should be avoided in patients with documented NRTI resistance unless there are other fully active drugs in the regimen.

Because enfuvirtide (T-20) requires twice-daily injections, causes injection-site reactions, and is more expensive than other available ARV agents, patients who are virologically suppressed on T-20-containing regimens may wish to substitute T-20 with an active oral agent. Because the majority of patients on T-20 have highly drug-resistant virus, substitution must be with another fully active agent. Data from one randomized trial and one observational study suggest that RAL can safely substitute for T-20 in patients not previously treated with INSTI.[12-13] Although this strategy generally maintains virologic suppression and is well tolerated, clinicians should be aware that any drug substitution may introduce unanticipated adverse effects or drug-drug interactions.[14]

Other newer agents that might be considered as substitutes for T-20 are etravirine (ETR) or MVC. Use of ETR in this setting would optimally be considered only when viral susceptibility to ETR can be assured from resistance testing performed prior to virologic suppression and after carefully assessing for possible deleterious drug-drug interactions (e.g., ETR cannot be administered with several PIs [see Table 16b]). In the ETR early access program, switching from T-20 to ETR showed promise in maintaining viral suppression at 24 weeks, but only 37 subjects were included in this report.[15] MVC is only active in those with documented R5-only virus, a determination that cannot routinely be made in those with undetectable HIV RNA on a stable regimen. Although there is a commercially available proviral DNA assay to assess viral tropism in virologically suppressed patients, there are no clinical data on whether results of this test predict the successful use of MVC as a substitute for another active drug.

Reducing the number of active drugs in a regimen. This approach to treatment simplification involves switching a patient from a suppressive regimen to fewer active drugs. In early studies, this approach was associated with a higher risk of treatment failure than continuation of standard treatment with two NRTIs plus a PI.[16] More recently, studies have evaluated the use of an RTV-boosted PI as monotherapy after virologic suppression with a two-NRTI + boosted-PI regimen.[17-18] The major motivations for this approach are a reduction in NRTI-related toxicity and lower cost. In a randomized clinical trial,[18] low-level viremia was more common in those on maintenance LPV/r alone than on a three-drug combination regimen. Viral suppression was achieved by resuming the NRTIs. Studies of DRV/r monotherapy, both as once- or twice-daily dosing, have reported mixed results.[19-20] In aggregate, boosted-PI monotherapy as initial[21] or as simplification treatment has been somewhat less effective in achieving complete virologic suppression and avoiding resistance. Therefore, this strategy cannot be recommended outside of a clinical trial.

Monitoring After Treatment Simplification

Patients should be evaluated 2–6 weeks after treatment simplification to assess tolerance and to undergo laboratory monitoring, including HIV RNA, CD4 cell count, and markers of renal and liver function. Assessment of fasting cholesterol subsets and triglycerides should be performed within 3 months after the change in therapy. In the absence of any specific complaints, laboratory abnormalities, or viral rebound at that visit, patients may resume regularly scheduled clinical and laboratory monitoring.

References

1. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296-1310.
2. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006;354(3):251-260.
3. 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(12):1505-1514.

4. Stone VE, Jordan J, Tolson J, et al. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *J Acquir Immune Defic Syndr*. 2004;36(3):808-816.
5. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. *Clin Infect Dis*. 2007;44(11):1484-1492.
6. Squires KE, Young B, Dejesus E, et al. Similar efficacy and tolerability of atazanavir compared with atazanavir/ritonavir, each with abacavir/lamivudine after initial suppression with abacavir/lamivudine plus ritonavir-boosted atazanavir in HIV-infected patients. *AIDS*. 2010;24(13):2019-2027.
7. Martinez E. The NEFA study: results at three years. *AIDS Rev*. 2007;9(1):62.
8. Ochoa de Echaguen A, Arnedo M, Xercavins M, et al. Genotypic and phenotypic resistance patterns at virological failure in a simplification trial with nevirapine, efavirenz or abacavir. *AIDS*. 2005;19(13):1385-1391.
9. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet*. 2010;375(9712):396-407.
10. 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(4):197-204.
11. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS*. 2010;24(11):1697-1707.
12. Harris M, Larsen G, Montaner JS. Outcomes of multidrug-resistant patients switched from enfuvirtide to raltegravir within a virologically suppressive regimen. *AIDS*. 2008;22(10):1224-1226.
13. De Castro N, Braun J, Charreau I, et al. Switch from enfuvirtide to raltegravir in virologically suppressed multidrug-resistant HIV-1-infected patients: a randomized open-label trial. *Clin Infect Dis*. 2009;49(8):1259-1267.
14. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. 2008;22(14):1890-1892.
15. Loutfy M, Ribera E, Florence E, et al. Sustained HIV RNA suppression after switching from enfuvirtide to etravirine in the early access programme. *J Antimicrob Chemother*. 2009;64(6):1341-1344.
16. Havlir DV, Marschner IC, Hirsch MS, et al. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. *N Engl J Med*. 1998;339(18):1261-1268.
17. Swindells S, DiRienzo AG, Wilkin T, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA*. 2006;296(7):806-814.
18. Pulido F, Arribas JR, Delgado R, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. *AIDS*. 2008;22(2):F1-9.
19. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS*. 2010;24(2):223-230.
20. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*. 2010;24(15):2365-2374.
21. Delfraissy JF, Flandre P, Delaugerre C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. *AIDS*. 2008;22(3):385-393.

Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations
• Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult **(CIII)**. • TDM may be considered in selected clinical scenarios, as discussed in the text below.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Knowledge of the relationship between systemic exposure (or concentration) and drug responses (beneficial and/or adverse) is key in selecting the dose of a drug, in understanding the variability in the response of patients to a drug, and in designing strategies to optimize response and tolerability.

TDM is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes measured drug concentrations to design dosing regimens to improve the likelihood of the desired therapeutic and safety outcomes. The key characteristic of a drug that is a candidate for TDM is knowledge of the exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Several ARV agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy.[1] The rationale for TDM in managing antiretroviral therapy (ART) derives from the following:

- data showing that considerable interpatient variability in drug concentrations exists among patients who take the same dose;
- data indicating that relationships exist between the concentration of drug in the body and anti-HIV effect and, in some cases, toxicities; and
- data from small prospective studies demonstrating that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities.[2-3]

TDM for ARV agents, however, is not recommended for routine use in the management of the HIV-infected adult (CIII).

Multiple factors limit the routine use of TDM in HIV-infected adults.[4-5] These factors include:

- lack of large prospective studies demonstrating that TDM improves clinical and virologic outcomes. (This is the most important limiting factor for the implementation of TDM at present.);
- lack of established therapeutic range of concentrations for all ARV drugs that is associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions;
- intrapatient variability in ARV drug concentrations;
- lack of widespread availability of clinical laboratories that perform quantitation of ARV concentrations under rigorous quality assurance/quality control standards; and
- shortage of experts to assist with interpretation of ARV concentration data and application of such data to revise patients' dosing regimens.

Exposure-Response Relationships and TDM with Different ARV Classes

Protease Inhibitors (PIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Integrase Inhibitors. Relationships between the systemic exposure to PIs and NNRTIs and treatment response have been reviewed in various publications.[4-7] Although there are limitations and unanswered questions, the consensus among clinical pharmacologists from the United States and Europe is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. However, information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians who use TDM as a strategy to manage either ARV response or toxicities should consult the most current data on the proposed therapeutic concentration range. Exposure-response data for darunavir (DRV), etravirine (ETR), and raltegravir (RAL) are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in Table 9b.

CCR5 Antagonists. Trough maraviroc (MVC) concentrations have been shown to be an important predictor of virologic success in studies conducted in ART-experienced persons.[8-9] Clinical experience in the use of TDM for MVC, however, is very limited. Nonetheless, as with PIs and NNRTIs, the exposure-response data provide a framework for TDM, and that information is presented in these guidelines (Table 9b).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma or intracellular NRTI concentrations for an individual patient largely remains a research tool. Measurement of plasma concentrations, however, is routinely used for studies of drug-drug interactions.

Scenarios for Use of TDM. Multiple scenarios exist in which both ARV concentration data and expert opinion may be useful in patient management. Consultation with a clinical pharmacologist or a clinical pharmacist with HIV expertise may be advisable in these cases. These scenarios include the following:

- Suspect clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities;
- Changes in pathophysiologic states that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- Pregnant women who may be at risk of virologic failure as a result of changes in their pharmacokinetic parameters during the later stage of pregnancy, which may result in plasma concentrations lower than those achieved in the earlier stages of pregnancy and in the nonpregnant patient;
- Heavily pretreated patients experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;
- Use of alternative dosing regimens and ARV combinations for which safety and efficacy have not been established in clinical trials;
- Concentration-dependent, drug-associated toxicities; and
- Lack of expected virologic response in medication-adherent persons.

TDM

- **For patients who have drug-susceptible virus.** Table 9a includes a synthesis of recommendations[2-7] for minimum target trough PI and NNRTI concentrations in persons with drug-susceptible virus.
- **For ART-experienced patients with virologic failure** (see Table 9b). Fewer data are available to formulate suggestions for minimum target trough concentrations in ART-experienced patients who have viral isolates with reduced susceptibility to ARV agents. Concentration recommendations for tipranavir

(TPV) and MVC were derived only from studies in ART-experienced persons. It is likely that use of PIs and NNRTIs in the setting of reduced viral susceptibility may require higher trough concentrations than those needed for wild-type virus. The inhibitory quotient (IQ), which is the ratio of ARV drug concentration to a measure of susceptibility (genotype or phenotype) of the patient's strain of HIV to that drug, may additionally improve prediction of virologic response—as has been shown, for example, with DRV in ART-experienced persons.[10-11] Exposure-response data for DRV, ETR, and RAL are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in Table 9b.

Using Drug Concentrations to Guide Therapy. There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor ARV concentrations in a patient requires multiple steps:

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient's pharmacokinetic characteristics;
- integration of information on patient adherence;
- interpretation of the concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

Guidelines for the collection of blood samples and other practical suggestions can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee.[4]

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical information. In addition, as knowledge of associations between ARV concentrations and virologic response continues to accumulate, clinicians who employ a TDM strategy for patient management should consult the most current literature.

Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs[2-9]	
Fosamprenavir (FPV)	400 (measured as amprenavir concentration)
Atazanavir (ATV)	150
Indinavir (IDV)	100
Lopinavir (LPV)	1000
Nelfinavir[a] (NFV)	800
Saquinavir (SQV)	100–250
Efavirenz (EFV)	1000
Nevirapine (NVP)	3000

[a] Measurable active (M8) metabolite

Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains	
Maraviroc (MVC)	>50
Tipranavir (TPV)	20,500
Median (Range) Trough Concentrations from Clinical Trials[12-14]	
Darunavir (DRV) (600 mg twice daily)	3300 (1255–7368)
Etravirine (ETR)	275 (81–2980)
Raltegravir (RAL)	72 (29–118)

References

1. Spector R, Park GD, Johnson GF, et al. Therapeutic drug monitoring. *Clin Pharmacol Ther*. 1988;43(4):345-353.
2. Fletcher CV, Anderson PL, Kakuda TN, et al. Concentration-controlled compared with conventional antiretroviral therapy for HIV infection. *AIDS*. 2002;16(4):551-560.
3. Fabbiani M, Di Giambenedetto S, Bracciale L, et al. Pharmacokinetic variability of antiretroviral drugs and correlation with virological outcome: 2 years of experience in routine clinical practice. *J Antimicrob Chemother*. 2009;64(1):109-117.
4. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses*. 2002;18(12):825-834.
5. van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. *Curr Opin HIV AIDS*. 2008;3(3):266-271.
6. Boffito M, Acosta E, Burger D, et al. Current status and future prospects of therapeutic drug monitoring and applied clinical pharmacology in antiretroviral therapy. *Antivir Ther*. 2005;10(3):375-392.
7. LaPorte CJL, Back BJ, Blaschke T, et al. Updated guidelines to perform therapeutic drug monitoring for antiretroviral agents. *Rev Antivir Ther*. 2006;3:4-14.
8. Pfizer Inc. Selzentry (maraviroc) tablets prescribing information NY. 2007.
9. McFayden L, Jacqmin P, Wade J, et al. Maraviroc exposure response analysis: phase 3 antiviral efficacy in treatment-experienced HIV+ patients. Paper presented at: 16th Population Approach Group in Europe Meeting; June 2007, 2007; Kobenhavn, Denmark. Abstract P4-13.
10. Molto J, Santos JR, Perez-Alvarez N, et al. Darunavir inhibitory quotient predicts the 48-week virological response to darunavir-based salvage therapy in human immunodeficiency virus-infected protease inhibitor-experienced patients. *Antimicrob Agents Chemother*. 2008;52(11):3928-3932.
11. Sekar V, DeMeyer S, Vangeneugden T, et al. Pharmacokinetic/pharmacodynamic (PK/PD) analysies of TMC114 in the POWER 1 and POWER 2 trials in treatment-experienced HIV-infected patients. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5, 2006, 2006; Denver, CO. Abstract J-121.
12. Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. *J Acquir Immune Defic Syndr*. 2006;43(5):509-515.
13. Kakuda TN, Wade JR, Snoeck E, et al. Pharmacokinetics and pharmacodynamics of the non-nucleoside reverse-transcriptase inhibitor etravirine in treatment-experienced HIV-1-infected patients. *Clin Pharmacol Ther*. 2010;88(5):695-703.
14. Food and Drug Administration (FDA). Prezista (package insert). 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021976s016lbl.pdf.

Discontinuation or Interruption of Antiretroviral Therapy (Last updated January 10, 2011; last reviewed January 10, 2011)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression. Unplanned interruption of ART may become necessary because of severe drug toxicity, intervening illness, surgery that precludes oral therapy, or unavailability of antiretroviral (ARV) medication. Some investigators have studied planned treatment discontinuation strategies in situations or for reasons that include: in patients who achieve viral suppression and wish to enhance adherence; to reduce inconvenience, long-term toxicities, and costs for patients; or in extensively treated patients who experience treatment failure due to resistant HIV, to allow reversion to wild-type virus. Potential risks and benefits of interruption vary according to a number of factors, including the clinical and immunologic status of the patient, the reason for the interruption, the type and duration of the interruption, and the presence or absence of resistant HIV at the time of interruption. Below are brief discussions on what is currently known about the risks and benefits of treatment interruption in some of these circumstances.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or unavailability of drugs. Stopping ARV drugs for a short time (i.e., <1 to 2 days) due to medical/surgical procedures can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Need for Short-Term Interruption

- **When a patient experiences a severe or life-threatening toxicity or unexpected inability to take oral medications**—all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short Term Interruption (> 2–3 days)

- **When all regimen components have similar half-lives and do not require food for proper absorption**—all drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously. All discontinued regimen components should be restarted simultaneously.
- **When all regimen components have similar half-lives and require food for adequate absorption, and the patient cannot take anything by mouth for a sustained period of time**—temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.
- **When the ARV regimen contains drugs with differing half-lives**—stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically a non-nucleoside reverse transcriptase inhibitor [NNRTI]). Options in this circumstance are discussed below. (See Discontinuation of efavirenz, etravirine, or nevirapine.)

Interruption of Therapy after Pregnancy

ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of whether they have indications for ART for their own health. Following delivery, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as for other nonpregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference.

Planned Long-Term Therapy Interruptions

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. Therapy interruptions ***cannot be recommended*** at this time outside of controlled clinical trials **(AI)**.

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression**—the optimal duration of treatment and the consequences of treatment interruption are not known at this time. (See Acute HIV Infection.)
- **In patients who have had exposure to multiple ARV agents, have experienced ARV treatment failure, and have few treatment options available because of extensive resistance mutations**—interruption is ***not recommended*** unless done in a clinical trial setting **(AI)**. Several clinical trials, largely yielding negative results, but some with conflicting results, have been conducted to better understand the role of treatment interruption in these patients.[1-4] The largest of these studies showed negative clinical impact of treatment interruption in these patients.[1] The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit;[5] therefore, interruption of therapy is not recommended.
- **In patients on ART who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 counts were either above or below that recommended threshold**—interruption is also ***not recommended*** unless done in a clinical trial setting **(BI)**. (See discussion below highlighting potential adverse outcomes seen in some treatment interruption trials.)

Temporary treatment interruption to reduce inconvenience, potential long-term toxicity, and/or overall treatment cost has been considered as a strategy for patients on ART who have maintained CD4 counts above those currently recommended for initiating therapy. Several clinical trials have been designed to determine the safety of such interruptions, in which reinitiation is triggered by predetermined CD4 count thresholds. In these trials, various CD4 count levels have been set to guide both treatment interruption and reinitiation. In the SMART study, the largest of such trials with more than 5,000 subjects, interrupting treatment with CD4 counts >350 cells/mm^3 and reinitiating when <250 cells/mm^3 was associated with an increased risk of disease progression and all cause mortality compared with the trial arm of continuous ART.[6] In the TRIVACAN study, the same CD4 count thresholds were used for stopping and restarting treatment.[7] This study also showed that interruption was an inferior strategy; the interventions in both trials were stopped early because of these findings. Data from the DART trial reported a twofold increase in rates of World Health Organization (WHO) Stage 4 events/deaths in the 12-week ART cycling group among African patients achieving a CD4 count >300/mm^3 compared with the continuous ART group.[8] Observational data from the EuroSIDA cohort noted a twofold increase in risk of death after a treatment interruption of >3 months. Factors linked to increased risk of death or progression included lower CD4 counts, higher viral loads, and a prior history of AIDS.[9] Other studies have reported no major safety concerns,[10-12] but these studies had smaller sample sizes. Results have been reported from several small observational studies evaluating treatment interruption in patients doing well with nadir CD4 counts >350/mm^3, but further studies are needed to determine the safety of treatment interruption in this population.[13-14] There is concern that CD4 counts <500 cells/mm^3 are associated with a range of non-AIDS clinical events (e.g., cancer and heart, liver, and kidney disease).[6, 15-16]

Planned long-term therapy interruption strategies ***cannot be recommended*** at this time outside of controlled clinical trials **(BI)** based on available data and a range of ongoing concerns.

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome,

increased risk of HIV transmission, decline of CD4 count, HIV disease progression or death, development of minor HIV-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. Treatment interruptions often result in rapid reductions in CD4 counts.

Prior to any planned treatment interruption, a number of ARV-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz (EFV), etravirine (ETR), or nevirapine (NVP).** The optimal interval between stopping EFV, ETR, or NVP and other ARV drugs is not known. The duration of detectable levels of EFV or NVP after discontinuation ranges from less than 1 week to more than 3 weeks.[17-18] Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs because NNRTIs have much longer half-lives than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphisms may be more common among specific ethnic groups, such as African Americans and Hispanics.[18-19] Some experts recommend stopping the NNRTI but continuing the other ARV drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving 4 or 7 days of zidovudine (ZDV) + lamivudine (3TC) after a single dose of NVP reduced the risk of postnatal NVP resistance from 60% to 10%–12%.[20] Use of nucleoside reverse transcriptase inhibitors (NRTIs) with a longer half-life such as tenofovir (TDF) plus emtricitabine (FTC) has also been shown to decrease NVP resistance after single-dose treatment.[21] The findings may, however, differ in patients on chronic NVP treatment. An alternative strategy is to substitute a protease inhibitor (PI) for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI- to a PI-based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of resuppression of HIV RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the 2-NRTI.[22] The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks, some suggest that the PI-based regimen may need to be continued for up to 4 weeks. Further research to determine the best approach to discontinuing NNRTIs is needed. Clinical data on ETR and treatment interruption is lacking but its long half-life of approximately 40 hours suggests that stopping ETR needs to be done carefully using the same suggestions for NVP and EFV for the time being.
- **Discontinuation and reintroduction of NVP.** Because NVP is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of NVP without a 2-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk of toxicity. Therefore, in a patient who has interrupted treatment with NVP for more than 2 weeks, NVP should be reintroduced with a dose escalation period of 200 mg once daily for 14 days and then a 200 mg twice-daily regimen **(AII)**.
- **Discontinuation of FTC, 3TC, or TDF in patients with hepatitis B virus (HBV) coinfection.** Patients with HBV coinfection (hepatitis B surface antigen [HbsAg] or hepatitis B e antigen [HBeAg] positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation.[23-24] (See Hepatitis B (HBV)/HIV Coinfection.)

References

1. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med*. 2003;349(9):837-846.
2. Ruiz L, Ribera E, Bonjoch A, et al. Role of structured treatment interruption before a 5-drug salvage antiretroviral

regimen: the Retrogene Study. *J Infect Dis*. 2003;188(7):977-985.

3. Ghosn J, Wirden M, Ktorza N, et al. No benefit of a structured treatment interruption based on genotypic resistance in heavily pretreated HIV-infected patients. *AIDS*. 2005;19(15):1643-1647.
4. Jaafar A, Massip P, Sandres-Saune K, et al. HIV therapy after treatment interruption in patients with multiple failure and more than 200 CD4+ T lymphocyte count. *J Med Virol*. 2004;74(1):8-15.
5. Kousignian I, Abgrall S, Grabar S, et al. Maintaining antiretroviral therapy reduces the risk of AIDS-defining events in patients with uncontrolled viral replication and profound immunodeficiency. *Clin Infect Dis*. 2008;46(2):296-304.
6. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.
7. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet*. 2006;367(9527):1981-1989.
8. DART Trial Team DTT. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/microl. *AIDS*. 2008;22(2):237-247.
9. Holkmann Olsen C, Mocroft A, Kirk O, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. *HIV Med*. 2007;8(2):96-104.
10. Maggiolo F, Ripamonti D, Gregis G, et al. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS*. 2004;18(3):439-446.
11. Cardiello PG, Hassink E, Ananworanich J, et al. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. *Clin Infect Dis*. 2005;40(4):594-600.
12. Ananworanich J, Siangphoe U, Hill A, et al. Highly active antiretroviral therapy (HAART) retreatment in patients on CD4-guided therapy achieved similar virologic suppression compared with patients on continuous HAART: the HIV Netherlands Australia Thailand Research Collaboration 001.4 study. *J Acquir Immune Defic Syndr*. 2005;39(5):523-529.
13. Pogany K, van Valkengoed IG, Prins JM, et al. Effects of active treatment discontinuation in patients with a CD4+ T-cell nadir greater than 350 cells/mm^3: 48-week Treatment Interruption in Early Starters Netherlands Study (TRIESTAN). *J Acquir Immune Defic Syndr.* 2007;44(4):395-400.
14. Skiest DJ, Su Z, Havlir DV, et al. Interruption of antiretroviral treatment in HIV-infected patients with preserved immune function is associated with a low rate of clinical progression: a prospective study by AIDS Clinical Trials Group 5170. *J Infect Dis*. 2007;195(10):1426-1436.
15. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. 2008;22(16):2143-2153.
16. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS*. 2008;22(18):2409-2418.
17. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr*. 2005;38(3):283-288.
18. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis*. 2006;42(3):401-407.
19. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS*. 2004;18(18):2391-2400.
20. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med*. 2009;6(10):e1000172.
21. Chi BH, Sinkala M, Mbewe F, et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *Lancet*. 2007;370(9600):1698-1705.

22. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS*. 2008;22(17):2279-2289.
23. Bessesen M, Ives D, Condreay L, et al. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis*. 1999;28(5):1032-1035.
24. Sellier P, Clevenbergh P, Mazeron MC, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. *Scand J Infect Dis*. 2004;36(6-7):533-535.