

Gregory S. Felzien, MD, AAHIVS  
Diplomat: Internal Medicine and Infectious Disease Georgia Department of Public Health Medical  
Advisor Division of Health Protection/IDI-HIV  
2 Peachtree St., NW, Suite 15-228  
Atlanta, GA 30303-3142  
Tel: 404-651-7372 Fax: 404-463-0126  
[Gregory.Felzien@dph.ga.gov](mailto:Gregory.Felzien@dph.ga.gov)

## **HIV Adherence & Resistance to Medications**

When we look at the current guidelines, several sections make mention of the importance of adherence:  
<http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>

“The optimal initial ARV regimen for a treatment-naive patient consists of two NRTIs in combination with a drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir (RTV), or an INSTI. As shown in clinical trials and by retrospective evaluation of cohorts of patients in clinical care, this strategy has resulted in HIV RNA decreases and CD4 T lymphocyte (CD4) cell increases in most patients.” (1, 2)

We also must be cognizant of interpreting other statements in the guidelines, such as; “Achieving viral suppression requires the use of ARV regimens with at **least two**, and preferably three, active drugs from two or more drug classes. (3)”

Clients started on HAART should receive 3 active drugs from 2 or more classes of drugs since multiple studies looking at dual therapy do not offer long-term HIV viral suppression. In addition, all of the recommended regimens in the guidelines contain 3 medications from at least 2 classes of HIV medications and do not recommend mono or dual therapy.

“All currently Recommended and Alternative regimens consist of two NRTIs plus a third active drug. This strategy, however, may not be possible or optimal in all patients. In some situations it may be necessary to avoid both TDF and ABC, such as in the case of a patient with pre-existing renal disease who is HLA B\*5701 positive or at high risk of cardiovascular disease. Based on these concerns, several clinical studies have evaluated strategies using initial regimens that avoid 2 NRTIs or the NRTI drug class altogether. Some of these studies were not fully powered to permit comparison with established regimens and one was a single-arm study using only a historical standard-of-care regimen as a control. At this point, the Panel does not recommend any of these strategies for initial therapy except in patients in whom both TDF and ABC are contraindicated.”

“In summary, the aggregate results from most of the studies with NRTI-sparing regimens—with the exception of the NEAT ANRS 143 study, which has not yet been published—demonstrate that these initial strategies either have lower efficacy or more side effects than their standard-of-care treatment comparators without affording the benefit of reduced pill burden or dosing frequency. An additional concern is that the two most favorable outcomes in studies thus far were seen with twice-daily LPV/r based regimens (in the PROGRESS and GARDEL trials); LPV/r is not considered a Recommended initial regimen because of its unfavorable lipid, tolerability and pill burden characteristics as compared to ATV/r and DRV/r. PI/r monotherapy has been studied as an NRTI-sparing strategy, but mainly in the setting of regimen simplification in patients who have achieved viral suppression on an initial combination ART regimen.” (4-10)

When looking at adherence, we come across several issues.

1. There will be times when short-term interruption is necessary.

“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” But stopping medications for more than 2 days can place the client at risk for developing resistance when each component of the regimen, as seen with regimens containing Efavirenz, are metabolized at a different rate. Thus, “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]). “ (3)

A more detailed discussion concerning this issue is as follows;

“The optimal interval between stopping Efavirenz (EFV), Etravirine (ETR), or Nevirapine (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. (11-12) 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. (12-13) 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%. (14) 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. (15) 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. (16) 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.”

2. Further issues with Adherence to Antiretroviral Therapy

“Strict adherence to antiretroviral therapy (ART) is key to sustained HIV suppression, reduced risk of drug resistance, improved overall health, quality of life, and survival,(17,18) as well as decreased risk of HIV transmission. (19) Conversely, poor adherence is the major cause of therapeutic failure. Achieving adherence to ART is a critical determinant of long-term outcome in HIV infected patients. For many chronic diseases, such as diabetes or hypertension, drug regimens remain effective even after treatment is resumed following a period of interruption. In the case of HIV infection, however, loss of virologic control as a consequence of non-adherence to ART may lead to emergence of drug resistance and loss

of future treatment options. Many patients initiating ART or already on therapy are able to maintain consistent levels of adherence with resultant viral suppression, CD4+ T-lymphocyte (CD4) count recovery, and improved clinical outcomes. Others, however, have poor adherence from the outset of ART and/or experience periodic lapses in adherence over the lifelong course of treatment. Identifying those with adherence-related challenges that require attention and implementing appropriate strategies to enhance adherence are essential roles for all members of the treatment team.

Recent data underscore the importance of conceptualizing treatment adherence broadly to include early engagement in care and sustained retention in care. The concept of an HIV “treatment cascade” has been used to describe the process of HIV testing, linkage to care, initiation of effective ART, adherence to treatment, and retention in care. The U.S. Centers for Disease Control and Prevention estimates that only 36% of the people living with HIV in the United States are prescribed ART and that among these individuals, only 76% have suppressed viral loads. (20) Thus, to achieve optimal clinical outcomes and to realize the potential public health benefit of treatment as prevention, attention to each step in the treatment cascade is critical. (21) Therefore, provider skill and involvement to retain patients in care and help them achieve high levels of medication adherence are crucial.”

“Therefore, skipping medications makes it easier for drug resistance to develop by allowing HIV to multiply. HIV can become resistant to the anti-HIV medications in a person’s current regimen or to other, similar anti-HIV medications not yet taken, and thereby limiting options for successful HIV treatment. And drug-resistant strains of HIV can be transmitted to others, too. In addition, nonadherence has also been associated with increased rate of hospitalization (22, 23) and longer hospital stays. (22)”

To further illustrate this issue, we can see that there is high variability in the half-life of HIV medications. This results in different rates of metabolism and when a client stops HAART, this results in functional mono and dual therapy and the more rapid development of resistance. (24, 25)

<u>Medication</u>	<u>Half-life (hours)</u>	<u>Medication</u>	<u>Half-life (hours)</u>
Retrovir	1.5 to 2	Zerit	1 to 1.5
Viread	17 (ABC: 1-2)	Evir	5 to 7 (FTC: 10)
Efavirenz	40 – 55	Nevirapine	25 - 45
Nelfinavir	4 - 5	Ritonavir	3 - 5
Saquinavir	12	Atazanavir	7
Isentress	19	Tivicay	15
Selzentry	13		
Indinavir	1 - 3 (Prolonged in hepatic disease)		
Prezista	4 to 5 (unboosted)	19 (boosted)	

Conclusion: Therefore, missing a single dose of medication is not going to result in the development of rapid resistance, but non-adherence due to multiple factors can result in both resistance and cross-resistance to HIV medications. This results in more complicated regimens, further decreased adherence and the potential for more office visits, ER/Urgent care visits, hospitalizations, and greater mortality.

# HIVdb: Genotypic Resistance Interpretation

<http://sierra2.stanford.edu/sierra/servlet/JSierra>

## Drug Resistance Interpretation:

**PI Major Resistance Mutations: M46I, L90M**    **PI Minor Resistance Mutations: K20M, A71V**

### Protease Inhibitors

<b>lopinavir/r (LPV/r)</b>	Low-level resistance	<b>saquinavir/r (SQV/r)</b>	Intermediate
<b>atazanavir/r (ATV/r)</b>	Intermediate resistance	<b>nelfinavir (NFV)</b>	High-level
<b>fosamprenavir/r (FPV/r)</b>	Intermediate resistance	<b>darunavir/r (DRV/r)</b>	Susceptible
<b>indinavir/r (IDV/r)</b>	Intermediate resistance	<b>tipranavir/r (TPV/r)</b>	Susceptible

### PI: Major

- M46I/L are nonpolymorphic PI-selected mutations that reduce susceptibility to IDV, NFV, FPV, LPV and ATV when present with other mutations. M46L also reduces susceptibility to TPV.
- L90M is a nonpolymorphic mutation selected primarily by SQV, NFV, IDV and LPV. It reduces susceptibility to each of the PIs except TPV and DRV.

### PI: Minor

- K20M/V are rare, relatively nonpolymorphic PI-selected mutations that have not been well studied.
- A71T/V are polymorphisms that occur in 2-3% of untreated persons. They increase in prevalence in persons receiving PIs. A71I/L are nonpolymorphic mutations that occur in viruses with multiple PI-resistance mutations.

**NRTI Resistance Mutations: T215CSY**    **NNRTI Resistance Mutations: K101E, K103N**

### Nucleoside RTI

<b>abacavir (ABC)</b>	Low-level resistance
<b>didanosine (DDI)</b>	Low-level resistance
<b>tenofovir (TDF)</b>	Low-level resistance
<b>zidovudine (AZT)</b>	Intermediate resistance
<b>stavudine (D4T)</b>	Intermediate resistance
<b>lamivudine (3TC)</b>	Susceptible
<b>emtricitabine (FTC)</b>	Susceptible

### Non-Nucleoside RTI

<b>etravirine (ETR)</b>	Low-level resistance
<b>rilpivirine (RPV)</b>	Intermediate resistance
<b>efavirenz (EFV)</b>	High-level resistance
<b>nevirapine (NVP)</b>	High-level resistance

### NRTI

- T215Y is a TAM which causes intermediate/high-level resistance to AZT and d4T and low-level resistance to ABC, ddi, and TDF.
- T215Y/F cause intermediate/high-level resistance to AZT and d4T and low-level resistance to ABC, ddi and TDF. T215S/C/D/E/I/V/N/A/L do not reduce NRTI susceptibility but arise from viruses that once contained T215Y/F. The presence of one of these revertant mutations suggests the possibility that the patient may have once harbored a majority virus population with T215Y/F.

### NNRTI

- K101E is a nonpolymorphic mutation that causes intermediate resistance to NVP (~5-fold reduced susceptibility) and low-level resistance (~2-fold reduced susceptibility) to EFV, ETR and RPV. It has a weight of 1.0 in the Tibotec ETR genotypic susceptibility score. In combination with M184I it reduces RPV susceptibility by about 5-fold.
- K103N is a nonpolymorphic mutation that causes high-level resistance to NVP (~50-fold reduced susceptibility) and EFV (~20-fold reduced susceptibility).

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