WHEN AND WHY SWITCH OR INTENSIFY?

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ABSTRACT

Switching or intensifying an antiretroviral regimen is an important aspect of human immunodeficiency virus management. In clinical practice, many initial regimens require replacement of one or more agents or the addition of another agent. Reasons for switching or intensifying therapy include drug toxicity, intolerance, incomplete viral suppression in the early stages of treatment, and rebound viremia that occurs later.

Factors that should be assessed before changing an antiretroviral regimen that suppresses viremia but is not well tolerated include hypersensitivity reactions, adverse effects, flare in comorbid conditions, and inconvenience associated with adhering to the regimen. Factors that should be assessed before intensifying a regimen that may be well tolerated but does not suppress viremia completely include time (some regimens take 6 months to be effective, especially in those with a high baseline viral load), adherence, drug interactions, absorption problems, and resistance selection. Except for additional time, these factors should also be assessed if there is rebound viremia.

Lipodystrophy—particularly lipoatrophy or fat wasting—is the most troublesome side effect of antiretroviral therapy for many patients. However, lipid changes and other metabolic abnormalities are also associated with antiretroviral therapy and are an area of concern because they are cardiovascular risk factors. Switching strategies are definitely recommended for fat wasting and visceral fat accumulation when these side effects appear. However, because there is little optimism that these strategies will result in dramatic improvement if instituted at this point, questions have arisen regarding preemptive switching before these signs appear. By comparison, recent studies and reports on switching strategies to control dyslipidemia have shown that switching is beneficial.


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suppression in the initial regimen may be due to transmitted or therapy-related resistance, inadequate regimen potency, or poor adherence to therapy. Viral rebound may be due to drug interactions, malabsorption, or nonadherence to therapy.

Because the reasons for adjusting therapy are varied, there are many different approaches to switching or intensifying regimens that reflect, in large part, the variation in selection and tolerability of the initial regimen. The approaches fall into 3 broad categories: adequate viral suppression but poor tolerability or serious toxicity; inadequate viral suppression but acceptable tolerability; and viral rebound after initial viral suppression.

**Switching Therapy Because of Lipodystrophy**

**Video Commentator:** One of the major issues we're dealing with at this time is how to manage patients who have signs of lipodystrophy. Should we change treatment or should we continue with the treatment the patient is on? What benefit could a treatment switch provide for the patient?

Switching and salvage therapy rely as much on the art of HIV medicine as on the science. Managing a patient who has developed morphologic changes on highly active antiretroviral therapy (HAART) is not as clear-cut as previously thought and certainly more complex than the schematic representation of the metabolic and morphologic changes associated with the lipodystrophy phenotype shown in Figure 1.

Although Figure 1 illustrates the contributions of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) only, nonnucleoside reverse transcriptase inhibitors (NNRTIs) also contribute to lipid changes and other metabolic abnormalities. Some of these changes, particularly those in carbohydrate metabolism, can occur very quickly, with some PIs (notably, indinavir) and NNRTIs showing much more activity in the insulin receptor compared with NRTIs.

Other changes, such as fat wasting, the most troubling complication of therapy for many patients, and visceral fat accumulation, take much longer to develop. By the time these side effects appear, switching strategies are definitely recommended. However, whether these strategies will result in dramatic improvement is a question that inspires little optimism, at least given the clinical experience and clinical trial data to date.

**Changing a “Successful” Regimen**

Whether to change, intensify, or continue antiretroviral therapy depends much on the patient's specific situation—ie, adequate viral suppression but poor tolerability or serious toxicity, inadequate viral suppression but good tolerability, viral rebound after initial suppression, etc. However, each situation has multiple causes that must be evaluated before making a decision regarding therapy. Moreover, it is difficult to define all possible disease- and therapy-related pathways a patient may have followed in the past.

In this article, the term “successful” is used pharmacologically, although it is also a function of the potency of the antiretroviral regimen and its ability to suppress HIV-1, as well as the patient’s ability to take the regimen that is being used and tolerate its side effects.

There are many situations in which changing from a potent antiretroviral regimen that is fully suppressing virus is warranted. Among them are early complications, such as hypersensitivity reactions. Some of these early complications may be indicators of more permanent side effects that the patient will not be able to tolerate. In contrast, other early side effects may be severe at first but resolve over time.

![Figure 1. Metabolic and Morphologic Changes in Patients Taking HAART](image-url)

NRTI = nucleoside reverse transcriptase inhibitors; d4T = stavudine; ZDV = zidovudine; PI = protease inhibitor.
Other manifestations of poor tolerance of an otherwise successful antiretroviral regimen are adverse effects, some of which may occur early, and a flare in a comorbid condition that reflects direct drug effect versus immune recovery. Hepatic toxicity, an example of flare, may require discontinuation of antiretroviral therapy in extreme cases, but it may also resolve over time. Yet another indication of poor tolerability is regimen inconvenience, which seems trivial in comparison to hypersensitivity and toxicity but may be just as serious as adverse effects if patients forget to take their pills or cannot incorporate the treatment regimen into their daily lives.

If a patient cannot tolerate an otherwise successful regimen because of a drug reaction, toxicity, or inconvenience, the drug responsible for the problem should be identified and replaced with another drug that is at least as potent and either belongs to a different antiretroviral drug class and has a different adverse-effect profile or is more convenient to use. In the case of comorbid disease flares or immune response reactions, the regimen should be continued if possible, despite the occurrence of side effects, because these effects often resolve over time.

Although morphologic changes associated with HAART, such as fat wasting, are troublesome to many patients, the development of dyslipidemia is also a matter of concern. Three switch studies that have measured lipid changes in patients who developed dyslipidemia on HAART are CAN 30017,1 TRIZAL,2 and LIPNEFA.3 In each of these studies, a switch from a PI-based or NNRTI-based regimen to an abacavir-based triple-NRTI regimen maintained virologic suppression up to 48 weeks in patients with sustained undetectable viral loads for 6 to 24 months.

In CAN 30017, which involved 211 patients, there was a decrease in total cholesterol and triglycerides, improved adherence and quality of life, and easier dosing.1 In TRIZAL, which involved 209 patients and a switch from NNRTI-based or PI-based HAART to a combination tablet of abacavir/lamivudine/zidovudine, there was a decrease in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.2 In LIPNEFA, which involved a switch from a PI to nevirapine, efavirenz, or abacavir in 460 patients, there was a decrease in LDL cholesterol.3

Other reports over the past several years of switching to or within the NRTI family, switching to an abacavir-based regimen, and switching away from a PI to an NRTI or NNRTI have shown rather consistently that these strategies seem to be beneficial in controlling dyslipidemia. Whether these strategies will have any beneficial effects on morphologic changes, the most pressing concern for many patients, remains unclear. The recently approved PI atazanavir, which does not cause dyslipidemia, may also prove to be an attractive switch option.

Problems associated with switching drugs in an otherwise successful regimen include, but are certainly not limited to, difficulties in maintaining or improving potency, the possibility that changing one drug in a coformulation may decrease convenience, the possible need for total discontinuation of therapy at least temporarily (as is the case with comorbid conditions, especially hepatitis), and the inability to predict whether the new drug will be better tolerated or result in recovery from toxicity, especially in cases of lipatrophy.

Whether to wait until lipatrophy and other changes in body habitus are obvious before switching therapy is a provocative question. If a regimen or drug has a statistically higher chance of producing lipatrophy, should it be switched preemptively before that side effect occurs? Relying on past or future clinical trial results is of little help in this instance because side effects seen in clinical trials are unpredictable.

Figure 2. Assessment of Incomplete Viral Suppression

![Diagram of assessment process]

- Incomplete suppression of viremia
  - Is the patient adherent?
  - Has a new drug caused drug-drug interactions?
  - Is the drug well absorbed?

Make decision rapidly if goal is full suppression

- May decide to continue despite persisting viremia, risk is resistance selection
- Check for baseline resistance
- Assess and support full adherence or drug interactions
- Decide if drug should be stopped
- Redesign regimen
Side effects such as lipoatrophy also take a long time to develop and often occur against the backdrop of a complex history of antiretroviral therapy. Therefore, standardizing a protocol would be nearly impossible. Until there is more information on genetic or laboratory markers for some of these toxicities that would allow more accurate prediction of a given patient’s risk, questions will remain regarding delays and preemptive switching.

**Intensifying Therapy Because of Incomplete Viral Suppression**

**Video Commentator:** The goal of our current approach to starting therapy is to drive the viral replication rate to such a low level that it cannot be measured in the peripheral blood. With current regimens, we can be successful about 80% of the time in patients who have not been treated previously. We know that when this happens, the effect is durable and patients do well for a long time. However—and patients ask this often—what do you do when this doesn’t happen? What are the therapeutic options when the viral replication rate doesn’t decline to undetectable levels and is allowed to molder along in a few thousand copies? Should I change the regimen or should I continue with the regimen I am using? What tests should I order to help me decide what regimens I should move to?

An incomplete response to the initial regimen—the regimen is reasonably well tolerated but the viral load never reaches undetectable levels—requires patience if the patient has been on the regimen for less than 6 months and a careful evaluation of several factors that may be responsible for the poor virologic response. These factors are outlined schematically in the decision tree shown in Figure 2 and also apply to rebound viremia.

Depending on the patient’s baseline viral load, it may take an antiretroviral regimen 6 months to suppress viral replication completely. Therefore, if a patient with a detectable level of virus who recently started therapy is otherwise doing well—the CD4 cell count is rising, the viral load is decreasing rapidly, and the regimen appears to be well tolerated—it is advisable to wait longer for a complete response. However, a previously undetectable viral load that starts to increase during the course of therapy is a cause for great concern.

The first factor to assess in cases of incomplete viral suppression is adherence to therapy. Lack of adherence is the most common reason for a potent regimen not to work. The regimen may work very well if taken as directed. Other factors to assess are drug interactions, which may be blunting the action of one or more drugs in the regimen, absorption problems, and resistance selection. If drug interactions or absorption problems are present, they should be corrected if possible. If resistance selection is noted, it may identify which drug in the regimen should be removed.

When the response to an initial regimen is incomplete, it should be altered or changed completely to increase potency. If the regimen is well tolerated and seems to be providing nearly adequate viral suppression, it should be intensified by the addition of another drug to increase net potency so that the second regimen is more potent than the first. However, it is important to recognize that the price to pay for increased potency may be increased toxicity or decreased convenience. Thus, a regimen that is more potent in terms of its virologic activity may not necessarily be more effective overall.

**REFERENCES**