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Perspective

A Paradigm Shift to Prevent HIV Drug Resistance

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Standard care for HIV antiretroviral treatment in resource-rich regions of the world includes HIV RNA monitoring every three to four months for viral rebound (i.e., an increase in HIV RNA to detectable levels following suppression). Viral rebound confirmed by two HIV RNA determinations prompts adherence counseling, and a change in regimen based on prior antiretroviral treatment and antiretroviral resistance testing. Because of the prohibitive cost of viral RNA monitoring, standard care for resource-limited regions of the world includes clinical monitoring, together with CD4 monitoring if it is available. A new WHO (World Health Organization) Stage IV opportunistic infection, a 50% decline from peak CD4 level, failure to increase CD4 levels to 50–100 cells/mm^3 after one year, or a fall in CD4 cell count to pretreatment levels after one year prompts a change to second-line therapy if available [1].

The major limitation of CD4 and clinical monitoring alone is that clinical deterioration and CD4 decline often occur well after virologic failure and the accumulation of resistance mutations that may compromise the efficacy of limited second-line treatment options [16]. Conversely, CD4 and clinical decline can occur in the absence of virologic failure, which can prompt a premature switch to second-line therapy. This limitation has prompted a search for low-cost approaches to HIV RNA monitoring, including new surrogates of HIV RNA [2]. This search, however, has yet to yield a reliable, inexpensive, and scalable approach for resource-limited regions of the world.

The Perspective section is for experts to discuss the clinical practice or public health implications of a published article that is freely available online.

Linked Research Article

This Perspective discusses the following new study published in *PLoS Medicine*:

Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, et al. (2008) Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. PLoS Med 5(5): e109. doi:10.1371/journal.pmed.0050109

Analyzing pharmacy and laboratory records from 1,982 patients beginning HIV therapy in southern Africa, Gregory Bisson and colleagues find medication adherence superior to CD4 count changes in identifying treatment failure.

Adherence Monitoring to Detect Viral Rebound in Resource-Limited Settings

In a study published in this issue of *PLoS Medicine*, Gregory Bisson and colleagues compared the ability of CD4 counts and adherence to medication to predict virologic failure [3]. They conducted an observational cohort study involving 1,982 patients in nine countries in southern Africa, who were being treated with a non-nucleoside reverse transcriptase inhibitor–based antiretroviral regimen. Adherence was assessed using pharmacy claim data. Virologic failure was defined as an HIV RNA level of more than 1,000 copies/ml at an initial assessment either six or 12 months after starting combination antiretroviral therapy and after a previous undetectable viral load (less than 400 copies/ml).

Pharmacy claim adherence data outperformed CD4 count change in predicting viral suppression and were as good as CD4 count change at predicting viral rebound subsequent to viral suppression. Bisson and colleagues conclude that systematic adherence monitoring should be considered as an alternative to CD4 cell monitoring to identify patients at high risk for incomplete viral suppression.

Proactive Prevention rather than Reactive Response to Viral Rebound

Real-time adherence monitoring offers an important strategic advantage to traditional approaches in both resource-rich and resource-limited regions of the world. While most patients achieve initial viral suppression with current antiretroviral regimens, eventual viral rebound is common as adherence declines over time [4–6]. Modest declines or even complete lapses in adherence are rarely detected in advance of viral rebound. Rather, viral rebound is usually detected during routine laboratory monitoring after lapses in adherence. Regimens prescribed in response to viral rebound are often more complex than the initial regimen and can lead to a continuous loop of less effective, poorly tolerated therapies that may require even higher levels of adherence to sustain viral suppression [7]. Bisson and colleagues' new study supports Robert Gross and

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colleagues' earlier proof-of-concept data, which suggested that that a more effective approach might be to focus on continuous adherence monitoring with a goal of intervening before HIV RNA rebounds and resistance mutations accumulate [8].

Improving Precision in Adherence Monitoring

While Bisson and colleagues suggest that a switch from biologic to behavioral monitoring may be the preferred monitoring strategy in resource-limited settings, it is unclear if pharmacy refill measures will be sufficiently precise and/or time sensitive to proactively predict, and therefore prevent, viral rebound. Pharmacy refill adherence measures have been closely associated with viral suppression, drug resistance, and death in several studies [9–11]. The drug possession ratio, calculated by the number of doses dispensed divided by the number of doses prescribed in the interval between dispensing dates, has a scale of 0 to 1 (or 0% to 100%), where 1 (or 100%) represents the maximum level of adherence possible for a given patient. Because actual adherence is less than or at most equal to the drug possession ratio, pharmacy refill adherence information will not detect all patients with viral rebound. In addition, since medications are prescribed every month (sometimes less frequently), and viral rebound can occur in a matter of weeks, monthly pharmacy dispensing data may also not be sufficiently time sensitive to preemptively predict viral rebound. Finally, pharmacy refill measures cannot differentiate patterns of adherence, such as treatment interruption, which may be more risky for non-nucleoside reverse transcriptase inhibitor resistance than a longer run of occasional missed doses [12,13].

There are several strategies that may move us closer to more accurate adherence monitoring. Electronic medication pill box organizers have been introduced, with encouraging results [14]. Cell phones, widely available in resource-limited settings, are being tested to promote health behaviors in many regions of the world [15]. Cell phone adherence monitoring systems, however, often require a patient to respond to a reminder message to confirm they took their dose. Systems that require a patient-initiated response to detect the health behavior in question (i.e., taking a dose), may suffer from patient habituation to the reminder, and will fail in patients who are nonadherent to the measurement strategy, which may be the same patients who miss their medication. Electronic pill container devices, and more recently wireless devices, overcome some of these difficulties. While such systems are currently prohibitively expensive in resource-limited settings, current user fees are comparable to viral load monitoring, and wide-scale implementation could reduce costs several-fold.

Antiretroviral treatment has transformed HIV from a terminal to a chronic disease in many regions of the world. Despite this important advance, relatively little progress has been made in monitoring missed doses, which are the proximal event to viral rebound and drug resistance. The report by Bisson and colleagues provokes a potential paradigm shift away from reactively responding to proactively preventing antiretroviral drug resistance. ■

Note Added in Proof

Reference 16 is cited out of order because it was added while the article was in proof.

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