title

Perfect adherence in taking antiretroviral drugs – role of the doctors

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summary

Adherence to antiretroviral medications is essential to therapeutic success. The health care professional represents an essential element of care that should be evaluated and optimized in order to maximize adherence and therefore success in HIV clinical care.

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The introduction of highly active antiretroviral therapy (HAART) in 1996 has radically modified the management and care of HIV positive patients (1, 2), and soon adherence to HAART has been shown to play a crucial role in determining virological response. Common types of non-adherence with medication include not filling prescriptions, taking an incorrect dose (too little or to much), taking a dose at the incorrect time, missing doses of one or more drugs from a regimen, stopping all treatment and taking treatment prescribed for others (3). Several factors are related to non-adherence, especially patient-related factors such as depression, abuse, but also regimen complexity, patient's lack of trust in the treatment, their attitudes about medication-taking and disease, and poor patient-physician relations.

How important is adherence to success of antiretroviral therapy?

Paterson et al. (4) observed adherence of patients taking protease inhibitor (nelfinavir) who neither used a medication organizer nor received their medication in an observed setting, such as jail or nursing house. Adherence was significantly associated with successful virologic outcome and increase in CD4 lymphocyte count. Virologic failure was documented in 22% of patients with adherence of 95% or greater, 61% of those with 80,0% to 94,9% adherence, and 80% of those with less than 80% adherence. While treatment with unboosted protease inhibitors (PI) requires near perfect adherence for virologic suppression, the introduction of more potent non-nucleoside reverse transcriptase inhibitors (NNRTI) and ritonavir boosted PI therapy has lead to reliable virologic suppression at moderate levels of adherence for most, but not all patients (5). Maggiolo et al. (6) followed up a large cohort of patients who were receiving a steady (duration > 6 months) and effective (viral load achieved, < 50 HIV RNA copies/ml) HAART. The main conclusion that could by drawn from the study were that patients who were receiving NNRTI reported greater adherence that did those who were receiving protease inhibitors (PI). But the risk of virologic failure associated with suboptimal adherence was greater for patients who were receiving PI-based regimens than for patients who were receiving NNRTI-based regimens. For NNRTI adherence window is 2 – 70% (7). Moderate levels of adherence (range: 23,5% – 53,5%) can lead to virologic suppression in most patients taking lopinavir/ritonavir-based HAART (8).

The main mechanism involved in the association between adherence and virologic failure is development of drug resistance, which is the product of 2 necessary conditions: subtherapeutic drug levels and persistence of viral replication. For some regimens, drug resistance may be more likely to develop in patients with better adherence, for the other regimens, the opposite may be true (5). Current understanding of the relationships between adherence and viral resistance suggest that the risk of the development of resistance varies by class of antiretroviral drugs and that there is no single cutoff below which the risk of resistance clearly outweighs the potential drug benefit (9). Patterns of adherence may be more critical than overall level of adherence. Patient reported treatment discontinuation of more than 48h is an independent risk factor for non-nucleoside reverse transcriptase inhibitor resistance, even controlling for average adherence over time (10).

When perfect adherence is most important?

For antiretroviral-naive individuals, simulated and observed results both suggests that the likelihood of accumulating new mutations will increase sharply with even small departures from perfect adherence, with a rise to 1.9 times higher for individuals with 90% adherence and to 2.4 times higher for individuals with 80% adherence. Indeed, the maximum likelihoods of accumulating mutations occur at some of the most commonly observed adherence rates – 60-80%(11). This implies that many antiretroviral-naïve individuals may benefit substantially from adherence interventions not only because of the short-term benefit that accrues from greater viral load suppression, but also because a long-term benefit would accrue due to preservation of future drug options. Carrieri et al. (12) showed the need for strict initial adherence (up to 4 months) to maintain prolonged viral suppression. In the first 4 months of HAART, the patients who were moderately adherent did not significantly differ from non-adherent patients in terms of prolonged viral suppression at months 36. If viral replication is not drastically reduced early in treatment, the remaining replication may favor the later emergence of resistant strains.

Miller et al. (13) suggested that patients' knowledge of antiretroviral therapy was often suboptimal at regimen initiation but improved over time. Poor knowledge 8 weeks after regimen initiation was associated with lower adherence. Patients' knowledge of their HIV condition and its treatment, which influences adherence to antiretroviral therapy, can be improved through educational programs and should be initiated early in therapy (14).

Whether doctors can exactly estimate adherence of their patients

Physicians estimate their patients' adherence to medications, and base decisions about treatment on these estimates. In HIV, misjudgment of patients adherence can have adverse consequences, including withholding of therapy, unnecessary changes in therapy, or unnecessary laboratory testing. A review of literature demonstrates that physicians' are often inaccurate in estimating patient adherence with HAART. Gilbert et al. (15) evaluated the adherence estimates made by 10 primary physicians of patients taking digoxin. Adherence was also assessed through pill count and measurement of serum digoxin levels. The sensivity of clinical judgment for detecting nonadherence was 10%. Similar results were found for patients with whom physicians had relationship >5 years. According to Paterson et al. (4) physicians predicted adherence incorrectly for 41% of patients, and clinic nurses predicted it incorrectly for 30% patients. In a study by Haubrich et al. (16), in 173 patients for whom adherence was assessed by self-report, there were discordance between patients' and physicians' assessments in 45% of cases. Hugen et al. (17) compared multiple methods of assessing medication adherence. They found that the correlation of the physician's estimate with Medication Event Monitoring System (MEMS) was lower that other methods, including self report, therapeutic drug monitoring (TDM), and estimation by a clinical nurse specialist. In comparison of adherence