Less Than 95% Adherence to Nonnucleoside Reverse-Transcriptase Inhibitor Therapy Can Lead to Viral Suppression

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(See the editorial commentary by Gulick on pages 942–4.)

For antiretroviral therapy, the 95% adherence “threshold” is based on nucleoside-exposed patients who are receiving partially suppressive, unboosted protease inhibitor regimens. Using unannounced pill counts and electronic medication monitoring, viral suppression is common with a 54%–100% mean adherence level to nonnucleoside reverse-transcriptase-inhibitor regimens. Although perfect adherence is an important goal, viral suppression is possible with moderate adherence to potent regimens.

Adherence to antiretroviral therapy is closely associated with viral suppression [1–3], evolution of drug resistance [4, 5], clinical disease progression [6], and death [7, 8]. On the basis of data reported by Paterson, 95% adherence to therapy is widely cited as the minimum level of adherence necessary to maintain an HIV load suppression of <400 copies/mL in the majority of individuals [1]. This estimate, however, is based on data from treatment-experienced populations receiving an unboosted protease inhibitor (PI) and 2 nucleoside analogues. More potent nonnucleoside reverse-transcriptase inhibitor (NNRTI) regimens lead to greater overall rates of viral suppression than the unboosted PI regimens used in the Paterson study [9]. We previously found that NNRTI regimens are associated with better viral suppression to <50 copies/mL than unboosted PI regimens, but that resistance is more common in NNRTIs in the absence of viral suppression and that these differences are related to virologic fitness [10]. Because minimum goals of 95% adherence are based on a cutoff level of 400 copies/mL [1], an analysis that directly compares viral suppression at 400 copies/mL using objective measures of adherence is needed to assess whether the goal of >95% adherence is still critical for virologic success with more potent therapy.

Methods. Participants were identified from the Research on Access to Care in the Homeless (REACH) cohort, a systematic sample of HIV-positive adults recruited from San Francisco, California, homeless shelters, free meal programs, and low-income, single-room-occupancy hotels. The REACH cohort enrolled 330 HIV-positive participants from July 1996 through April 2000. The objectives, rationale, and sampling methods of this study have been previously described [11]. Written consent was obtained from all participants for adherence monitoring, monthly phlebotomy, and assessment of viral load and CD4 cell count. The University of California, San Francisco Committee on Human Subjects Research approved all study procedures.

Individuals were included in the analysis if they consented to prospective adherence measurements and were receiving stable antiretroviral drug regimens for a minimum of 3 months. A stable regimen was defined as at least 3 antiretroviral drugs with either a single (non–ritonavir-boosted) PI or a single NNRTI and at least 3 monthly adherence measures prior to the viral load determination.

As previously described, individuals who were prescribed ≥3 antiretroviral drugs were recruited into adherence monitoring beginning in January 1998 [12]. Every 3–6 weeks over a period of 12 months, all antiretroviral medications were counted at the participant’s usual place of residence during unannounced visits. Unannounced pill counts do not interfere with the use of pillbox organizers (“medisets”), and because the visits are unscheduled, participants are unlikely to empty bottles prior to assessment (“pill dump”). The calculated number of pills taken was divided by the total number of tablets prescribed for that same period, to determine percent of doses taken. Mean adherence was calculated as the average of the monthly pill count determination over 3 months. Subjects not using medisets also received electronic pill bottle caps (MEMS [Apria]). Electronic bottle cap information was downloaded at monthly visits. Electronic medication monitor adherence was calculated as the number of cap openings divided by the number of prescribed doses of PI or NNRTI.

Phlebotomy was conducted monthly. Plasma was processed and stored at −20°C within 6 h of collection. Plasma HIV RNA levels were determined each month using the HIV-1 Amplicor

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Monitor, version 1.0, ultrasensitive assay (Roche Molecular Systems). The geometric mean viral load was used in the analysis.

Adherence categories were defined by unannounced pill count quartiles. Viral load suppression was defined as <400 copies/mL, to make direct comparisons with prior studies. We compared the proportion of individuals with viral suppression by adherence category on PI and NNRTI regimens with Fischer’s exact test.

**Results.** One hundred ten participants (56 receiving PIs and 54 receiving NNRTIs) were observed for a median of 9.1 months. Participants were largely nonwhite (57%), male (83%), and had a high prevalence of lifetime injection drug use (65%). Participants were also largely nucleoside experienced (47%) and had a median of 14 months of prior antiretroviral therapy. All participants were receiving their first PI or NNRTI. Average adherence to therapy was 70%. PI-treated individuals were receiving nelfinavir (64%), indinavir (27%), saquinavir (7%), or ritonavir (2%). NNRTI-treated individuals were receiving nevirapine (62%) or efavirenz (38%). The most common nucleoside analogue combinations were lamivudine-zidovudine (administered to 46% of the PI group and 33% of the NNRTI group) and lamivudine-stavudine (administered to 39% of the PI group and 35% of the NNRTI group). There were no significant sociodemographic, prior treatment, or adherence differences between PI- and NNRTI-treated individuals. Unannounced pill count data were available for all patients, and electronic medication monitoring data were available for the 65 patients who were not using mediset pillbox organizers.

The viral loads of the majority of NNRTI-treated individuals were suppressed to <400 copies/mL at 54%–100% adherence, whereas the majority of PI-treated individuals’ viral loads were suppressed to <400 copies/mL only at 95%–100% adherence (figure 1A and 1B). Viral suppression was significantly more common for patients receiving NNRTI than for patients receiving PI regimens overall (P = .001) and specifically in the 53%–74% adherence stratum (P = .02).

**Discussion.** Using 2 independent and objective measures of adherence, these data confirm early reports that >95% adherence is necessary to achieve viral suppression of <400 copies/mL on unboosted PI therapy [1–3], but that more-potent NNRTI regimens lead to viral suppression at moderate levels of adherence. These data are consistent with a randomized, controlled trial that indicated greater viral suppression with NNRTI therapy than with early PI therapy [9], and they also confirm the findings of Maggiolo et al. [13], who observed higher rates of viral suppression with NNRTI therapy than with unboosted PI therapy by patient-reported adherence strata. More reliable viral suppression with NNRTI therapy than with unboosted PI regimens at modest levels of adherence may be the result of either an improved potency or the extended half-life of NNRTIs [14, 15].

Although the emphasis that has been placed on near-perfect adherence to antiretroviral therapy has been important in improving HIV treatment outcomes, the average level of adherence to HIV antiretroviral therapy is 70% [16]. Epidemiologic and qualitative studies indicate that the concern about a patient’s ability to achieve 95% adherence is a common reason to withhold therapy [17, 18]. Although it is important to delay treatment to ameliorate modifiable barriers to adherence, failure to treat individuals because they may not achieve 95% adherence inevitably leads to potentially avoidable mortality in marginalized populations [19].

These data have several limitations. They do not address levels of viral suppression with moderate levels of adherence to either ritonavir-boosted PIs or newer PIs, such as atazanavir. More potent PI regimens may also lead to better viral suppression at moderate levels of adherence than early PI regimens.

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**Figure 1.** A, The proportion of patients with an HIV load (VL) <400 copies/mL, as indicated by unannounced pill count adherence. B, The proportion of patients with a VL <400 copies/mL, as indicated by electronic medication monitor. NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.
Because participants were not randomly assigned to PI or NNRTI groups, we cannot exclude selection bias. Patients were largely antiretroviral experienced. NNRTI treatment in antiretroviral-naive patients may lead to even better viral suppression at moderate adherence.

Although viral suppression may be possible with moderate levels of adherence, the probability of viral suppression and, more importantly, reduced disease progression and mortality improves with every increase in adherence level. As such, these data do not alter the goal to achieve the highest level of adherence possible; rather, they provide evidence that patients with moderate levels of adherence may also do well while receiving potent antiretroviral therapy.

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