Impact of Medication Adherence on Virologic Failure in A5202: A Randomized, Partially Blinded, Phase 3B Study

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In AIDS Clinical Trials Group A5202, participants who reported missing their medication within the past month or not providing adherence reports at both 8 and 24 weeks had 5 times the hazard of virological failure compared to more adherent participants. Adherence interventions should focus on such patients.

Keywords. HIV; missing medication; self-report; adherence; virologic failure.

Adherence to antiretroviral therapy (ART) is critical for sustained human immunodeficiency virus (HIV) suppression, but there is no gold standard for assessing adherence [1]. While some data suggest that self-report measures are reliable, a recent abstract concluded that self-report using 3-day pill counts is unreliable for monitoring adherence [2, 3]. We assessed whether a single question—"When was the last time you missed any of your medications?"—was useful in predicting virologic failure (VF).

METHODS

Data Source

We used data from AIDS Clinical Trials Group (ACTG) A5202, which randomized ART-naive, HIV-infected participants to receive placebo-controlled abacavir–lamivudine or tenofovir disoproxil fumarate–emtricitabine with open-label efavirenz or atazanavir/ritonavir [4–6]. All participants provided informed consent, were aged ≥18 years, HIV type 1 infected, and had 7 days or less of ART prior to enrollment. Exclusion criteria included significant drug or alcohol abuse thought likely to impact adherence. A total of 1857 participants were randomized and followed for a median (interquartile range) of 138 (106, 169) weeks.

Adherence Data

Participants underwent adherence training on entry and completed the ACTG self-report adherence form at study weeks 8 and 24 and every 24 weeks thereafter [7]. Site staff entered the collected data.

Ninety-seven percent (1798/1857) of participants completed at least 1 adherence self-report during the entire study. We had adherence information from 94% (10 355) of the 10 977 forms expected and an additional 948 reports, for a total of 11 303 self-reports available for analysis.

Definition of Adherence

We used the question "When was the last time you missed any of your medications?" for our assessment of adherence. There were 6 potential responses (number responses): never skip medications (6459), more than 3 months ago (1265), 1–3 months ago (1179), 2–4 weeks ago (864), 1–2 weeks ago (649), and within the past week (887). Previous A5202 reports separated adherence based only on the final category [4, 5]. We categorized responses as adherent (if reported never or missed doses at least 1 month ago; 79% [8903/11 303] of all self-reports) or not adherent (if reported missed doses 2–4 weeks ago, 1–2 weeks ago, or within the past week). We considered participants who did not provide a self-report form to be not adherent for that report.

Outcomes

Virological failure was defined as confirmed HIV-1 RNA level ≥1000 copies/mL at or after 16 weeks and before 24 weeks or ≥200 copies/mL at or after 24 weeks. Time to the first of 2 viral load measurements showing VF was defined as the time point for VF.

Analysis

We analyzed 2 groups (Supplementary Figure 1). The analysis of short-term VF through week 24 was based on self-reported adherence at the week 8 visit. For the analysis of VF after 24 weeks, we used the following 3 categories: adherent (reported
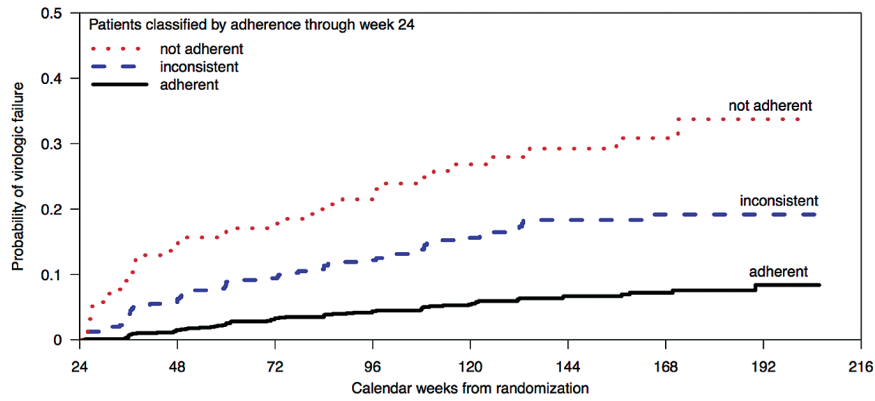
Figure 1. Virologic failure by early adherence behavior through week 24. The probability of virologic failure (VF) in participants based on the first 24 weeks of self-reported adherence is shown. Each participant was categorized into 1 of 3 groups at week 24 and remained in that group over time. There were 1085 participants who were adherent (reported not missing medication within the previous month on both reports), 159 who were not adherent (90 who were not adherent on 2 self-reports, reporting missing medication within the previous month on both reports; 55 who were not adherent on 1 self-report, reported missing medication within the previous month on 1 report and missing the other report; and 14 with no self-report data through week 24), and 405 with inconsistent responses (290 with 2 inconsistent self-reports, reported missing medication within the previous month on 1 report but not on the other; and 115 with only 1 adherent report, reported not missing medication within the previous on 1 month but missing the other report). Participants with VF before 24 weeks (N = 95) or discontinued from study follow-up before the week 24 visit (N = 113) were excluded.

never or missing their last dose more than 1 month ago on both the week 8 and week 24 reports), not adherent (reported missing their last dose within the past month on the available week 8 and week 24 reports or missing both reports), or inconsistent (reported adherence on either the week 8 or week 24 report and either not adherent on the other report or missing the other report). Analysis was limited to those who could have VF after week 24 by excluding participants who had VF or discontinued study follow-up by week 24.

Baseline characteristics (age, gender, race or ethnicity, viral load, CD4 count, hepatitis B or hepatitis C, history of AIDS) between groups were compared using a Wilcoxon rank sum test or Fisher exact test. Proportions with VF were Kaplan-Meier estimates. Hazard ratios (HRs) were calculated using Cox proportional hazards model.

RESULTS

At the week 8 visit, 406 participants (23% of the total study sample) were classified as not adherent based on self-report. There were 46 VF in this group through week 24 for a short-term VF rate of 12% (95% confidence interval (CI), 8%–15%) compared to 4% (49/1388; 95% CI, 2%–5%; $P < .001$) in the adherent participants. Of the 95 VF cases through week 24, 48% were classified not adherent.

Eighty-nine percent of participants (1649/1857) continued on study after the week 24 visit. Study participants were excluded from this analysis if, on or before the week 24 visit, they had VF (N = 95; 46% of all those excluded) or were discontinued from study follow-up (N = 113). Excluded participants were significantly younger, less likely to be white, more likely to have hepatitis B or C, had lower CD4 counts, and higher reported history of AIDS than the continuing participants at

baseline (all $P < .05$, other baseline covariates not statistically significant; data not shown).

Among these 1649 participants, nearly two-thirds (N = 1085; 66%) reported not missing any medication in the preceding month on both reports, while 159 (10%) were considered not adherent by our definition. Adherent participants were significantly more likely to be white (42% vs 34%, $P = .02$) and older (median age 39 vs 35 years, $P < .001$) compared to those not adherent (other baseline covariates not statistically significant). VF occurred in 127 (8%; 95% CI, 6%–10%) participants through week 96 and 174 had VF at any time after week 24 (Figure 1). Adjusting for age and race/ethnicity, participants who were not adherent had a higher hazard of VF after week 24 compared to participants who were consistently adherent (HR = 5.2; 95% CI, 3.5–7.8; $P < .001$). We found similar results in the unadjusted analysis (HR = 5.5; 95% CI, 3.7–8.1; $P < .001$). Among those defined as not adherent at week 24, 23% (95% CI, 15%–30%) had VF by 96 weeks compared to 4% (95% CI, 3%–6%) of those defined as adherent.

There were 290 (18%) individuals with inconsistent adherence reports and 115 (7%) with only a single week 8 or week 24 report of not missing medication in the past month; these 405 participants (25%) were grouped together as inconsistent. Inconsistent participants had an intermediate VF rate (HR = 2.8 compared to the adherent group; 95% CI, 2.0–4.0; $P < .001$ adjusted for age and race/ethnicity, with similar unadjusted HR, 2.9; 95% CI, 2.0–4.1; 12% VF at 96 weeks, 95% CI, 8%–16%). Supplementary Figure 2 shows VF over time for each specific pattern of inconsistent adherence. Combining nonadherent and inconsistent adherence reports together, the sensitivity and specificity of our criterion for predicting VF after week 24 were 61% and 69%. Supplementary Table 1 provides sensitivity

and specificity of alternative definitions of adherence for this question. Defining not adherent strictly as missing a dose at any time, sensitivity was 72% and specificity was 57%. A loose definition of nonadherence as missed medications within the past week provides sensitivity of 43% and specificity of 83%.

Among 1857 study participants, 631 did not meet the criteria for adherence at either the week 8 or week 24 visits; they accounted for 152 (57%) of all 269 VF throughout the entire study.

DISCUSSION

We found in a large clinical trial that participants who reported missing medication within the past month or failing to provide information shortly after starting ART can identify a subgroup of individuals at increased risk of VF. This single question may provide a simple method to target adherence interventions after starting ART to those at risk of VF.

Physicians routinely ask patients whether they are taking their ART medication. Typical questions include "How many doses of medication have you missed in the prior 4 days?" and "Have you missed any medication since your last visit?" Both may be subject to social desirability bias as they imply that missing medication is bad and might inhibit individuals from truthfully answering "yes." In contrast, asking "When was the last time you missed any of your medications?" implies that missing medication is common, which potentially should elicit more truthful answers [8].

Our study had several limitations. First, data were collected by participant self-report. Whether patients would answer similarly in face-to-face encounters in a care setting is unclear. Although fewer individuals might be willing to admit nonadherence in person, reports of missing medication recently are likely to be reliable, but the self-report cannot be validated against other adherence measures. Second, although the increased risk of VF is clear in the study population, the criterion we used identified only 57% of those having VF during the study, so a substantial fraction of patients with subsequent VF would not be identified by this approach. Identifying nonadherence whenever a patient reports missing medication in the past month might increase the proportion of the VF population identified. We also did not do a formal statistical test to determine whether an alternative definition of adherence using the same question would perform better than the specific criterion we used to define adherence. Our criterion gave similar sensitivity and specificity with higher specificity, while defining adherence as not missing pills within the past 3 months gave better sensitivity but lower positive predictive value. Third, this analysis is post hoc and results should

be interpreted cautiously. Finally, these results may not generalize to other ART types, including integrase inhibitors.

In summary, we found that a single adherence question can help identify patients most at risk of VF. As adherence interventions have been proven effective, those who acknowledge missing medication within the previous month would be a worthwhile group on whom to focus such strategies [9].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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