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(Article begins on next page)
Impact of Medication Adherence on Virologic Failure in A5202: A Randomized, Partially Blinded, Phase 3B Study

Robert A. Parker,1,4,5 Dustin J. Rabideau,1 Paul E. Sax,4 Camlin Tierney,1 Eric S. Dean,7 Ann C. Collier,7 Elena Losina,7 William J. Graviss,3 Kenneth A. Freedberg8,10,13

1Biostatistics Center, and 2Medical Practice Evaluation Center, Massachusetts General Hospital; 3Harvard Medical School; 4Harvard University Center for AIDS Research; 5Division of Infectious Diseases, Brigham and Women’s Hospital; and 6Center for Biostatistics in AIDS Research in the Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; 7Division of HIV Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, and 8David Geffen School of Medicine at UCLA, Los Angeles, California; 9Division of Allergy and Infectious Diseases, University of Washington, Seattle; and 10Department of Orthopedic Surgery, Brigham and Women’s Hospital; 11Department of Biostatistics, Boston University School of Public Health; 12Divisions of General Internal Medicine and Infectious Diseases, Massachusetts General Hospital; and 13Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts

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.

METHODS

Data Source
We used data from AIDS Clinical Trials Group (ACTG) A5202, which randomized ART-naïve, 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% (10355) of the 10977 forms expected and an additional 948 reports, for a total of 11303 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% [8903/11303] 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

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Correspondence: R. A. Parker, ScD Massachusetts General Hospital, 50 Staniford Street, 5th Floor Boston, MA 02114 (rparkera@mgh.harvard.edu).

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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 both 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.

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.

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; data not shown).

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 fewer individuals than those 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.

**Notes**

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**References**


