

Title: Pharmacy Refill Adherence Compared with CD4 Count Changes for Monitoring HIV-Infected Adults on Antiretroviral Therapy

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Background World Health Organization (WHO) guidelines for monitoring HIV-infected individuals on combination antiretroviral therapy (cART) in resource-limited settings recommend using CD4 count changes to monitor treatment effectiveness, but in practice falling CD4 counts are a consequence, rather than a cause, of virologic failure. Adherence lapses precede virologic failure and, unlike CD4 counts, data on adherence are immediately available to all clinics dispensing cART. However, the accuracy of adherence assessments in predicting virologic failure and the relative accuracy of adherence levels compared to CD4 count changes have not been determined.

Methodology and Findings We conducted an observational cohort study among 1,982 of 4,984 (40%) HIV-infected adults initiating non-nucleoside reverse transcriptase inhibitor-based cART in the Aid for AIDS Disease Management Program, which serves 9 countries in Southern Africa. Pharmacy refill adherence was calculated as the number of months of cART claims submitted divided by the number of complete months between cART initiation and the last refill prior to the endpoint of interest, expressed as a percentage. The main outcome measure was virologic failure defined as a viral load >1,000 copies/mL (1) at an initial assessment either 6 or 12 months after cART initiation and (2) after a previous undetectable (i.e., < 400 copies/mL) viral load (breakthrough viremia). Adherence levels outperformed CD4 count changes in the first year after cART initiation [area under the receiver operating characteristic (ROC) curves (AUC) were 0.79 and 0.68 (difference = 0.11; 95%

CI 0.06-0.16; $\chi^2=20.1$) respectively at 6 months and 0.85 and 0.75 (difference = 0.10; 95% CI 0.05-0.14; $\chi^2=20.2$) respectively at 12 months; $P < 0.001$ for both comparisons]. When used to detect breakthrough viremia, adherence and CD4 counts were equally accurate [AUCs of 0.68 vs. 0.67, respectively (difference = 0.01; 95% CI -0.06-0.07); $\chi^2=0.1$, $P > 0.5$]. In addition, adherence levels assessed 3 months prior to viral loads had equal discriminatory ability for virologic failure as did CD4 count changes calculated from cART initiation to the time of the viral loads, and combinations of CD4 count and adherence data appeared useful in identifying patients at very low risk of virologic failure.

Conclusions Pharmacy refill adherence assessments are as accurate as CD4 counts for identification of virologic failure on cART and may be used to identify patients at high and low risk of virologic failure, potentially before this event occurs. Approaches to cART scale-up in resource-limited settings should include an adherence-based monitoring approach.

INTRODUCTION

As the number of patients on combination antiretroviral therapy (cART) grows worldwide, developing simple, affordable ways of monitoring patients after treatment initiation has become a major public health priority. Since the central paradigm of antiretroviral therapy is suppression of viral replication, and since costs of second line cART are higher than first-line regimens[1], monitoring efforts should, to whatever extent possible, focus on preserving the virologic effectiveness of first-line combinations. Failure to identify patients on partially suppressive regimens may result in selection of viral resistance mutations, which have been associated with more rapid disease progression and death[2-4].

In the developed world, the standard of care for monitoring virologic response involves measuring plasma HIV-1 RNA levels (viral loads)[5]. These assays are often unavailable in the developing world due to financial and technical constraints[6]. Since CD4⁺ T-cell (CD4) counts are comparatively inexpensive, World Health Organization (WHO) guidelines for scaling up antiretroviral therapy in resource-limited settings advocate use of CD4 count criteria to identify patients on failing cART regimens[7]. Thus, CD4 counts are considered an essential tool for monitoring patients on cART[8], and there is a widespread movement to incorporate cheaper, less technologically demanding CD4 count assays into clinical care in the developing world[9].

Quantifying and monitoring adherence levels to cART is one potentially useful and low-cost method of monitoring patients at high risk for virologic failure in resource-limited settings[10]. Adherence is strongly associated with virologic

response in a dose-dependent manner[11-16]. Furthermore, among patients on first-line therapy, lapses in adherence usually precede immunologic declines and, unlike CD4 counts, adherence data are available to all clinics that dispense cART, may be simple to compile[10], and directly measure the variable on which providers can intervene. Thus adherence assessments focus on the cause rather than the consequence of virologic failure and may potentially enable guided interventions capable of preventing virologic failure from occurring. Therefore although CD4 count monitoring in patients on cART is deeply ingrained in HIV care[5,7], if adherence assessments are as accurate as CD4 count changes for identification of patients with virologic failure sites currently performing or planning CD4 count measurements for this purpose could instead choose to monitor adherence, thereby preserving scarce resources for triaged virologic monitoring[17,18] or other treatment-related activities.

Despite this potential, the diagnostic accuracy of various adherence levels for predicting virologic failure has not been determined, and current WHO guidelines for monitoring cART in resource-limited settings only include non-specific recommendations for assessing adherence without providing specifics as to what levels of adherence should trigger interventions[7]. To address this, we compared the diagnostic accuracy of CD4 cell count changes and adherence measurements for virologic failure on cART.

METHODS

Study Design

This observational cohort study evaluated the relative abilities of pharmacy refill adherence and CD4 counts to predict or identify viral loads indicative of treatment failure. Two primary outcomes were used: lack of virologic response (defined as a viral load >1000 copies/mL) either 6 or 12 months after cART initiation and a follow-up test done after achievement of an undetectable (i.e., < 400 copies/mL) viral load (i.e., to detect breakthrough viremia). Lack of response within the first year was chosen as an outcome given the clinical relevance of initial response to cART on subsequent disease outcomes[19] and breakthrough viremia was chosen as an outcome since several studies have reported that a majority of patients initiating cART achieve viral loads < 400 copies/mL within the first year [19-22]. For all analyses, the available CD4 count and adherence data were analyzed up to the time the provider was assessing the likelihood of virologic failure. Sensitivity was defined as the proportion of patients with virologic failure who met certain CD4 count change or adherence level criteria and specificity was defined as the proportion of patients without virologic failure who did not. Positive (negative) predictive value was defined as the probability that a patient meeting (not meeting) conditions for a CD4-guided treatment change had (did not have) a virologic failure at that time. Breakthrough viremia was defined as occurrence of virologic failure at any time > 30 days after a prior undetectable viral load.

Study Setting

We examined medical records from HIV-1-infected adults enrolled in Aid for AIDS, a private healthcare management program available to subscribers of medical insurance funds in 9 countries in southern Africa. Patient demographic and clinical data and pharmacy drug information have been recorded by Aid for AIDS since June 1998 and have been described previously[12,20]. In brief, if HIV-infected patients consent, baseline demographic and clinical data are recorded in the electronic Aid for AIDS database at the time of patient enrollment. After enrollment, individuals with CD4 counts <350 cells/mm³ or with an AIDS-defining condition are eligible to initiate cART. Patients submitting pharmacy claims are reimbursed by their medical insurance fund for the cost of drugs. All claims are processed through the coordinating center at the Aid for AIDS Cape Town office. Claims include the drug names and date of the prescription refill, and drugs are dispensed in uniform increments of 30 days of an entire cART regimen each time a prescription is refilled. Differential delays between countries or sites within countries with respect to returning prescriptions for processing are rare.

Study Participants

Patients who met the following general criteria were eligible: (1) age ≥ 18 years; (2) pre-treatment plasma viral load level of >2000 copies/mL; (3) initiated non-nucleoside reverse transcriptase inhibitor (NNRTI)-based cART, a criterion chosen given its relevance to resource-limited settings[23,24] and defined as an NNRTI plus 2 nucleoside reverse transcriptase inhibitors ; and (4) had a CD4

count and viral load within 90 days prior to or on the day of therapy initiation. In addition, for the evaluation of treatment response at 6 and 12 months patients needed: (1) a follow-up CD4 count within 3-9 or 9-15 months after initiating cART, respectively, and (2) a follow-up viral load within 45 days of the corresponding follow-up CD4 count. The analysis of breakthrough viremia was limited to patients meeting general criteria who also had (1) at least one undetectable viral load obtained after cART initiation, (2) a subsequent follow-up viral load obtained at least 30 days after the first undetectable viral load, and (3) a CD4 count obtained within at least 45 days of this follow-up viral load. Patients could be included in one or more analyses.

Data Collection

Decisions to monitor patients in Aid for AIDS are left up to the patients' physicians, and patient specimens are sent to a variety of clinical laboratories, although physicians are instructed to use the same laboratory for each patient.

WHO-advocated criteria of a CD4 count drop to pretreatment levels or below, a CD4 count drop to 50% or less of maximum on-therapy levels, and a CD4 count persistently below 100 cells/mm³ as well as alternative CD4 count criteria were examined[7]. The analysis of a CD4 count decrease to 50% of maximum on-therapy levels was limited to the analysis of breakthrough viremia, since this criterion implies that previous monitoring has been done. The last viral load and corresponding CD4 count available in the database were chosen as the endpoint values for patients who did not break through.

Pharmacy claims adherence data in this dataset have been validated for virologic response and for survival [12,20]. Adherence was calculated as the number of months with cART claims submitted divided by the number of complete months from cART commencement to the date of the relevant study endpoint and the result multiplied by 100, as described[12,16]. Since patients fill entire cART regimens with each refill, we tracked the entire regimen rather than using an “index drug” approach.

Statistical Analysis

The overall goal of the analysis was to examine and compare the predictive ability of CD4 counts and adherence data for virologic response rather than to explore etiologic associations with these outcomes. However, in order to first understand risk factors for virologic failure in the patient population, we performed unadjusted and adjusted analyses for this outcome. Differences in baseline characteristics were assessed with two-sample t tests or with Wilcoxon rank sum tests (continuous variables), depending on the distribution of the data, and chi square tests were used to compare categorical variables. A relative risk for the primary exposures (e.g., CD4 count criteria and adherence level) with a 95% confidence interval (CI) was determined and then evaluated in multivariable logistic regression analysis [which produced odds ratios (OR)] to assess possible confounding. Confounding was considered present if the unadjusted odds ratio changed by 15% or more after adjustment. However, in order to evaluate if the inclusion of possible confounders not meeting this criterion in the analysis affected the study’s findings, we also evaluated the results after forcing variables

plausibly associated with virologic failure in the multivariable model[25]. **For uniformity, all presented ORs are adjusted values.**

Overall diagnostic accuracy of adherence and CD4 count changes were expressed using receiver operating characteristic (ROC) curves and 95% CIs. Larger areas under the ROC curve (AUC) indicate greater overall ability to **discriminate** between patients with and without virologic failure. **For tests with binary outcomes (e.g., presence or absence of virologic failure), the area under the ROC curve is equal to the c (for concordance) statistic[26]. For binary endpoints, c statistics are the proportion of all pairs of patients, 1 with and 1 without the outcome, in which the patient with the event had a greater predicted probability of the outcome[27]. For example, a coin toss would have a c statistic of 0.5, whereas a test with perfect discrimination would have a c statistic of 1.0[28]. C statistics were compared using chi-square (χ^2) tests** in Stata version 9.0 (Intercooled) (STATA Corp., College Station, Texas). P values for the primary comparison of AUCs at 6 and 12 months at for breakthrough viremia were not adjusted for multiple comparisons. Furthermore, we used bootstrap resampling to evaluate the robustness of our findings by resampling with replacement observations from the original dataset 999 times, which produced 95% CIs for the mean difference in AUCs[29]. The sensitivity of our findings to the definition of virologic failure was analyzed using a level of $\geq 10,000$ copies/mL as the outcome in secondary analyses. In addition, AUCs for ROC curves derived from rules created using specific criteria are presented in order to enable rapid evaluation of overall diagnostic accuracy of

each criterion with respect to others, and to permit comparison of these ROC areas with a reference test of a CD4 count decrease to pretreatment levels or below. Since this involved multiple comparisons, these P values were corrected for multiple comparisons using Sidak's method. Test characteristics of each specific criterion were determined using logistic regression.

Sub-analyses

The discriminative ability of an adherence assessment performed approximately 3 months prior to the date of viral load measurement with the discriminative ability of a CD4 count change calculated at the time the viral load was performed (e.g., 3 months later) for 6 and 12 months were also determined in a sub-analysis of virologic failure in the first year. This was done comparing AUCs as in the primary analysis. A schematic of this approach is given in Figure 1. We also examined if use of days, rather than months, to calculate adherence altered the discriminatory ability of adherence assessments in these shorter intervals.

In addition, combinations of CD4 count and adherence data were assessed to determine whether combined approaches could be created that resulted in positive or negative predictive value that were sufficiently high (e.g., 95%) that providers could avoid viral load testing altogether. The proportion of patients with or without virologic failure who met a specific criterion was also determined in order to evaluate how applicable the criterion would be in clinical practice. These results were analyzed by computing the exact binomial 95% CIs

for these test characteristics and proportions and comparing these to characteristics of adherence or CD4 count changes alone.

Regulatory Approvals

This study was approved by the University of Cape Town Research Ethics Committee, by the Aid for AIDS Clinical Advisory Committee and Board, Cape Town, South Africa, by the Johns Hopkins Bloomberg School of Public Health's Committee on Human Research and by the University of Pennsylvania Institutional Review Board. Data were analyzed anonymously, and a waiver of informed consent was obtained for the study.

RESULTS

There were 5,723 adults who initiated cART and had registration information included in the Aid for AIDS database used in this study. Of these, 739 patients (13%) initiated non-NNRTI-based regimens and were therefore excluded. Of the remaining 4,984, 1,982 (40%) initiating NNRTI-based cART between December 20, 2000 and February 28, 2003 had sufficient paired CD4 count and viral load data both at baseline and at follow-up to be included in at least one of the analyses below. The pre-treatment median (IQR) CD4 counts were slightly lower among those who did not have sufficient follow-up data [165 (75-241) vs. 144 (61-223) cells/mm³], and the median (IQR) viral loads were similar [5.12 (4.6-5.6) vs. vs. 5.16 (4.7-5.6) log₁₀ copies/mL]. All patients meeting inclusion criteria described above were analyzed. 890 of 1,982 patients (45%)

initiated zidovudine, lamivudine, and efavirenz; 538 (27%) initiated zidovudine, lamivudine, and nevirapine; 206 (10%) patients initiated didanosine, stavudine, and an NNRTI; the remaining 348 patients (18%) initiated other three-drug, NNRTI-based regimens.

Detecting Virologic Failure at 6 and 12 months

The analyses of response at 6 and 12 months included 958 and 872 individual patients, respectively; 293 patients who met inclusion criteria for both endpoints were included in both analyses. 235 of 958 (25%) patients at 6 months and 229 of 872 (26%) patients at 12 months had virologic failure according to our definition (Table 1). Factors associated with virologic failure are shown in Table 1. The median (IQR) number of days between cART initiation and follow-up CD4 count was 201 (158-241) at 6 months and 353 (296-399) at 12 months, and more than 95% of follow-up CD4 counts and viral loads were done on the same day. CD4 cell count increases were significantly smaller for those experiencing virologic failure [median (IQR) increase in cells/mm³ of 70 (6-145) vs. 142 (72-251) at 6 months (**z=8.4**; P<0.001, **rank sum test**) and 51 (-5-153) vs. 184 (95-316) at 12 months (**z=11.4**; P<0.001, **rank sum test**)]. Adherence levels and CD4 count changes according to virologic response at 6 and 12 months are shown in Figures 2-5.

Adherence values had greater overall accuracy for virologic failure at 6 and 12 months compared to CD4 count changes [AUCs (95% CIs) of 0.79 (0.76-0.83) vs. 0.68 (0.64-0.72) at 6 months and 0.85 (0.82-0.88) vs. 0.75 (0.72-0.79) at 12 months; **$\chi^2=20.1$ and 20.2 , respectively, P <0.001 for both comparisons]**

(Figure 6 A and B). The bootstrapped 95% CIs for the differences between adherence and CD4 count AUCs were 0.11 (0.06-0.16) at 6 months and 0.10 (0.05-0.14) at 12 months. The adherence level that would result in the fewest unnecessary treatment changes if used at either time point (i.e., <50%) had greater overall ability to identify patients with virologic failure than the CD4 count change level with the highest specificity at 6 months (i.e., a CD4 count drop to pretreatment levels or below; $\chi^2=6.6$, $P=0.01$ comparing AUCs) and at 12 months (i.e., CD4 cell counts <100 cells/mm³ at baseline and follow-up; $\chi^2=8.0$, $P<0.001$). The superiority of adherence persisted if virologic failure was defined as a viral load >10,000 copies/mL [6-month AUC of 0.80 (0.75-0.84) vs. 0.71 (0.66-0.76); $\chi^2=7.6$, $P=0.005$; 12-month AUC of 0.87 (0.84-0.90) vs. 0.78 (0.75-0.82); $\chi^2=14.6$, $P<0.001$]. **Test characteristics for CD4 count changes and adherence levels when used as tests for virologic failure in the first year of cART are shown in Tables 2 and 3, respectively.**

Detecting Breakthrough Viremia After Initial Virologic Suppression

1,101 patients met inclusion criteria for the analysis of breakthrough viremia. 151 (14%) patients had breakthrough viremia after an initial undetectable viral load (Table 4). The median (IQR) duration of follow-up for these patients was 648 days (533-721), or approximately 1.75 years.

Only 9 of 1,101 patients (1%) had CD4 cell count values that were persistently below 100 cells/mm³, and this criteria was therefore not evaluated further. 54 (5%) and 42 (4%) of patients experienced a CD4 cell count drop to

pretreatment levels or below or to levels 50% or less than the maximum on treatment value, respectively. Both criteria were strongly associated with breakthrough viremia, as was adherence (Table 4).

There was no significant difference between adherence values and CD4 count changes from maximum on-treatment values to follow-up with respect to identification of patients with breakthrough viremia [AUCs, 0.68 (0.64-0.73) for CD4 counts vs. 0.67 (0.62-0.72); $\chi^2=0.1$, $P>0.5$]. The bootstrapped 95% CI for the difference between adherence and CD4 count AUCs was 0.01 (-0.06-0.07). The CD4 count criterion with the largest AUC was not significantly different than the adherence criteria with the largest AUC [a CD4 count drop of 20% or more from maximum on-treatment values vs. an adherence level of <90% ($\chi^2=0.0$, $P>0.5$)] (Table 5). Similar to above, altering the definition of virologic failure did not significantly change the results [AUC of 0.65 (0.58-0.72) vs. 0.70 (0.65-0.76); $\chi^2=1.6$, $P=0.21$].

Ability of Early Adherence Assessments to Identify Patients with Virologic Failure

The area under the ROC curve for pharmacy refill adherence measured during the initial 3 months after cART initiation for virologic failure at 6 months was 0.72 (0.68-0.75), which was smaller than that resulting from the adherence assessment at 6 months ($\chi^2=31.8$, P value <0.01), but similar (0.72 for adherence vs. 0.68 for CD4 count change; $\chi^2=2.0$, $P=0.15$) to that resulting from evaluation of the change in the CD4 count over the first 6 months of cART. The

area under the ROC curve for pharmacy refill adherence measured during the first 3 months after the 6-month assessment for virologic failure at 12 months was 0.76 (0.73-0.80). Similar to above, although the early assessment was statistically significantly less able to discriminate between those with and without virologic failure at 12 months when compared to the 12-month assessment ($\chi^2=46.0$, P value <0.001), the area under the ROC curve was similar [0.76 for adherence vs 0.75 for CD4 counts; $\chi^2=0.39$, P>0.5] to that resulting from evaluation of the change in the CD4 count over the first 12 months of cART. Use of days did not significantly alter the results (data not shown).

Adherence and CD4 Counts Combined

Positive predictive values and the proportions of patients with virologic failure meeting each combined criterion are shown in Table 6. At 6 months, combined criteria did not significantly increase positive predictive values above that resulting from adherence alone. For example, although a CD4 count decrease from pretreatment values and adherence <50% at 6 months increased the point estimate for positive predictive value compared to the adherence level with the highest positive predictive value at 6 months (<50%, positive predictive value = 87% (77%-93%)), Table 3), the confidence intervals overlapped and the sensitivity for virologic failure decreased [from 28%, (22%-34%) to 12% (8%-17%)]. Similar results were seen at 12 months (Table 6). For example, an adherence level with the highest positive predictive value at 6 months (<50%, Table 3) at 12 months resulted in a positive predictive value of 88% (79%-93%),

which was increased by addition of a CD4 count decrease but the confidence intervals overlapped and the sensitivity for virologic failure significantly decreased [from 37% (30%-43%) to 18% (14%-24%)].

Negative predictive values and the proportions of patients without virologic failure meeting each combined criterion are shown in Table 7. Use of an adherence threshold alone of 100% at both 6 and 12 months resulted in negative predictive values of 91% (88%-93%) and 94% (91%-97%), respectively. Furthermore, 66% (61%-70%) and 42% (38%-46%) of all patients without virologic failure met this criterion at the 6- and 12-month visits, respectively. Two criteria, adherence $\geq 70\%$ or $\geq 80\%$ and a CD4 count increase of at least 50 cells/mm³ at 6 months maintained the point estimate for negative predictive value above 90% while increasing the proportion of patients meeting that criterion at 6 months (Table 7). At 12 months, several criteria that maintained negative predictive values at or above 94% while significantly increasing the proportion of patients meeting that criterion were identified (bold values in the “12 Months” column in Table 7).

DISCUSSION

These results demonstrate that adherence levels, as estimated by pharmacy claims data, are at least as accurate as CD4 count changes for detection of virologic failure among patients receiving cART. This finding was consistent when evaluating patients at two time points during the first year and

after initial virologic suppression and was not dependent on the level of viremia used to define virologic failure. Because monitoring CD4 counts is ingrained in HIV care, and because cART scale-up guidelines for resource-limited settings suggest use of CD4 count monitoring after cART initiation[7], these findings are relevant to ongoing antiretroviral treatment efforts in resource-limited settings.

A clinical implication of these results is that systematic monitoring of pharmacy refill adherence should be considered as an alternative to CD4 count monitoring for identification of patients with a high probability of virologic failure. As shown, the ROC curve analyses indicate that given a fixed level of sensitivity, specificity resulting from monitoring adherence will tend to be higher than that seen with WHO-advocated CD4 count changes in the first year and similar thereafter. This translates into fewer patients with unnecessary regimen changes and fewer virologic failures missed. For example, if an adherence level of <50% was used in place of a CD4 count decrease to pretreatment levels or below to identify virologic failure at 12 months, the proportion of unnecessary regimen changes would decrease (from 6% to 2%) and the proportion of virologic failures identified would increase (from 28% to 37%). Furthermore, the fact that the ROC areas for adherence measured months prior to a viral load were relatively consistent with adherence assessments and CD4 count changes performed later indicate that adherence monitoring may be a useful approach for early identification of patients at high risk of future virologic failure. This result is intuitive given the causal pathway wherein poor adherence leads to virologic failure which leads in turn to immunologic declines[30]. Importantly, however,

poor adherence does not invariably result in virologic failure[12-14]. Therefore although detection of a CD4 count decline would be unlikely to lead to a treatment change in the first year of cART, detection of adherence lapses early may enable targeted adherence interventions capable of preventing virologic failure[31,32] and prolonging time on less expensive first-line cART. This contrasts with CD4 count monitoring, which inherently identifies virologic failure after this event has already occurred.

How should these data be used clinically? For clinics that do not have CD4 counts or viral load monitoring capabilities, pharmacy-based adherence monitoring should be adopted in order to identify patients in need of adherence interventions. Alternatively, adherence monitoring could be used to pursue focused virologic or genotypic testing in settings where these assays are available to some but not all or after cheaper assays become more widely available. The high negative predictive values resulting from adherence monitoring indicate that adherence data can be used to identify a relatively large group of patients who have a probability of virologic failure that is 10% or less. Moreover, if combined with a simple CD4 count threshold (e.g., adherence <90% and no CD4 count decrease at 12 months), this probability could be reduced to 5% while also avoiding virologic monitoring in approximately two-thirds of patients with suppressed viral loads at 12 months in this study. Finally, clinics able to perform viral loads in all patients routinely could use adherence monitoring to guide when these tests are done. For example, patients with perfect adherence and a CD4 count increase of more than 100 cells/mm³ at 6

months could have their viral load preserved for 12 months, or patients with adherence <90% at 3 months could have a viral load performed at 6 months (e.g., after an early adherence intervention). Although pharmacy refill adherence monitoring appears useful in these types of approaches, ultimately monitoring strategies must consider the resources available to the setting and should be informed by formal cost-effectiveness studies.

Our inclusion criteria were strict, yet comparison of patients included and excluded did not indicate clinically meaningful differences in the baseline CD4 counts or viral loads. Moreover, the estimates of the accuracy of CD4 count changes for virologic failure documented in this study concur with results presented from two other settings[17,33]. We do not therefore feel that significant bias resulted from patient exclusions. However, although the NNRTI-based cART regimens used and the immunologic responses were similar to several other cohorts[17,21-23], this study was performed in a private care setting and so the potential generalizability of the results should also be considered. For example, the adherence calculation was based on claims, and patients receiving cART at free clinics do not generally submit pharmacy claims. However, dates of actual refills were used to calculate intervals between dispensations. As such, an adherence calculation such as that performed here should be feasible in large public clinics where medications are often free. Furthermore, pharmacy claims data may overestimate true adherence because patients may not take all claimed medications. However, the goal of this study was to determine if pharmacy refill data, as observed in clinical practice, could be used as a test for virologic failure,

and to compare this approach with CD4 count levels, which also suffer from measurement error and biological variability. In addition, alternative measures of adherence, including subjective measures which were not available to us[34,35], should be examined, as should accuracy of this approach in patients on non-NNRTI-based cART. Finally, the area under the ROC curve for adherence was lower in the analysis of breakthrough viremia compared to the areas for assessments done in the first year of HAART. One possible explanation of this finding is that selection of resistance mutations, caused by subtle lapses in adherence not captured by pharmacy claims data, caused a decrease in the diagnostic accuracy of adherence over time. Patterns of adherence may influence the risk of virologic failure differently when patients initiate therapy compared to when their viral loads are suppressed below quantifiable levels. Since nearly 25% of all drug resistance occurs in patients with high levels of adherence[36], it would have been interesting to understand the relationship between virologic failure, resistance, and diagnostic accuracy of adherence in this setting, but genotyping data were unavailable.

Although CD4 counts inform when to start antiretroviral therapy and when to stop prophylaxis for opportunistic infections, these data indicate that guidelines for monitoring patients in resource-limited settings, such as those produced by the WHO[7], should consider an adherence-based monitoring approach.

Furthermore, future research should examine this approach in other settings with variable testing capabilities and should identify and address possible barriers to operationalizing systematic monitoring of adherence. For example, a requirement

of adherence monitoring is ready access to drug refill information as well as conversion of these data into an adherence metric at the time a patient is seen. Provision of adherence data to patients at the point of care, however, could be either simple or more complex. In Botswana, for example, patients present to providers with a paper pharmacy card on which dates of cART dispensation (and pill counts) are noted. Providers conceptually can calculate adherence directly using these cards. A more complex approach for clinics with computers would be to link pharmacy and patient care records electronically, so that a program would automatically supply the pharmacy refill adherence. The ability of adherence to identify patients at high risk of virologic failure early and to provide data on the behavior on which providers often wish to intervene should be considered a reason for clinics organize these data in a way that can be used in simple algorithmic approaches to patient care.

Conflict of Interest Statement

All authors declare that they do not have conflicts of interest to disclose.

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Table 1. Characteristics of patients with and without virologic failure at 6 and 12 months				
	6 months after cART (n=958)		12 months after cART (n=872)	
Characteristic	Virologic Failure (n=235)	Adjusted Odds Ratio (95% CI)[†]	Virologic Failure (n=229)	Adjusted Odds Ratio (95% CI)
Sex				
Female	142 of 621 (23%)	Reference	130 of 548 (24%)	Reference
Male	93 of 337 (28%)	1.37 (1.02-1.87)	99 of 324 (37%)	1.47 (1.07-2.01)[‡]
Age				
< 35 years	112 of 399 (28%)	Reference	115 of 389 (30%)	Reference
> 35 years	123 of 559 (22%)	0.70 (0.52-0.95)	114 of 483 (24%)	0.72 (0.53-0.98)
Treatment naïve				
Yes	198 of 849 (23%)	Reference	167 of 717 (23%)	Reference
No	37 of 109 (34%)	1.81 (1.17-2.82)	62 of 155 (40%)	1.30 (1.01-1.61)
Baseline CD4 count				
≤ 100 cells/mm ³	85 of 338 (25%)	Reference	71 of 259 (27%)	Reference
> 100 cells/mm ³	150 of 620 (24%)	0.96 (0.69-1.32)	158 of 613 (26%)	1.07 (0.76-1.52)
Baseline HIV-1 RNA level				
≤ 100,000 copies/mL	89 of 427 (21%)	Reference	93 of 373 (25%)	Reference
> 100,000 copies/mL	146 of 531 (28%)	1.45 (1.07-1.99)	136 of 499 (27%)	1.13 (0.80-1.60)
Adherence level				
> 90%	45 of 481 (9%)	Reference	36 of 475 (8%)	Reference
≤ 90%	190 of 477 (40%)	6.48 (4.51-9.28)	193 of 397 (49%)	11.84 (7.94-17.64)
CD4 count drop to pretreatment levels or below				
No	181 of 854 (21%)	Reference	162 of 768 (21%)	Reference
Yes	54 of 104 (52%)	4.12 (2.70-6.31)	67 of 104 (64%)	7.25 (4.63-11.38)
Baseline and follow-up CD4 count < 100 cells/mm³				
No	191 of 869 (22%)	Reference	193 of 820 (24%)	Reference
Yes	44 of 89 (49%)	5.30 (3.28-8.54)	36 of 52 (69%)	7.58 (4.35-13.23)
[‡] Defined as a viral load > 1,000 copies/mL [†] All odds ratios are adjusted for confounding. CI = Confidence interval				

Table 2. Test characteristics for CD4 cell count changes for identifying patients with virologic failure after initiating cART when assessed at 6 or 12 months.								
Cut-point for CD4 cell count change	Area under the ROC curve (95% CI)	P value*	Sensitivity	Specificity	Positive predictive value	Negative predictive value	% of virologic failures missed	% with regimen changes despite suppressed viral loads
At 6 months (n=958)								
Decrease to pretreatment levels or below	0.58 (0.55-0.61)	Reference	23%	93%	52%	79%	77%	7%
All CD4 counts < 100 [†]	0.56 (0.54-0.59)	P>0.5	23%	93%	52%	79%	77%	7%
<25 [‡]	0.61 (0.58-0.65)	P=0.005	34%	89%	51%	81%	66%	11%
<50	0.62 (0.58-0.65)	P=0.023	41%	82%	43%	81%	59%	18%
<100	0.63 (0.59-0.66)	P=0.029	62%	64%	36%	84%	38%	36%
At 12 months (n=872)								
Decrease to pretreatment levels or below	0.62 (0.59-0.65)	Reference	29%	94%	64%	79%	71%	6%
All CD4 counts < 100	0.57 (0.54-0.59)	P=0.03	20%	96%	64%	77%	80%	4%
<25 [‡]	0.66 (0.62-0.69)	P=0.001	40%	91%	62%	81%	60%	9%
<50	0.68 (0.64-0.71)	P<0.001	49%	87%	57%	83%	51%	13%
<100	0.68 (0.64-0.72)	P=0.002	62%	73%	46%	73%	38%	27%
<p>* P values are adjusted for multiple comparisons, and are for comparisons of the AUCs at each CD4 cell count change cut-point to the reference of a CD4 cell count drop to pretreatment levels or below.</p> <p>[†] cells/mm³</p> <p>[‡] Increases of <25, 50 or 100 cells/mm³ had greater overall accuracy than the two WHO-recommended criteria at 6 and 12 months, but were not significantly different from each other (all P values >0.4 for pair-wise comparisons of AUCs).</p>								

Table 3. Test characteristics for adherence levels for identifying patients with virologic failure after initiating cART when assessed at 6 or 12 months.								
Adherence level	Area under the ROC curve (95% CI)	P value*	Sensitivity	Specificity	Positive predictive value	Negative predictive value	% of virologic failures missed	% with regimen changes despite suppressed viral loads
At 6 months (n=958)								
<50%	0.63 (0.60-0.66)	Reference	28%	99%	87%	81%	72%	1%
<60%	0.68 (0.64-0.71)	P=0.01	39%	96%	75%	83%	61%	4%
<70%	0.70 (0.66-0.73)	P<0.001	51%	88%	59%	85%	49%	12%
<80% [†]	0.74 (0.71-0.78)	P<0.001	63%	86%	59%	88%	37%	14%
<90%	0.71 (0.67-0.74)	P<0.001	81%	60%	40%	91%	19%	40%
<100%	0.71 (0.67-0.74)	P<0.001	81%	60%	40%	91%	19%	40%
At 12 months (n=872)								
<50%	0.67 (0.64-0.71)	Reference	37%	98%	88%	81%	63%	2%
<60%	0.68 (0.64-0.71)	P>0.5	41%	94%	72%	82%	59%	6%
<70%	0.70 (0.67-0.73)	P>0.5	48%	91%	66%	83%	52%	9%
<80% [†]	0.70 (0.67-0.74)	P>0.5	55%	86%	58%	84%	45%	14%
<90%	0.76 (0.73-0.79)	P<0.001	84%	68%	49%	92%	16%	32%
<100%	0.67 (0.65-0.70)	P>0.5	93%	42%	36%	94%	7%	58%
<p>* P values are adjusted for multiple comparisons, and are for comparisons of the AUCs at each CD4 cell count change cut-point to the reference of a CD4 cell count drop to pretreatment levels or below. CI = confidence interval [†]Adherence <80% and <90% outperformed all other adherence values at 6 and 12 months, respectively (P<0.05 for all pair-wise comparisons).</p>								

Table 4. Characteristics of patients with and without breakthrough viremia after initial virologic suppression on NNRTI-based cART (N=1,101).		
	Virologic Failure (n=151)	Adjusted Odds Ratio (95% CI)[†]
Characteristic		
Sex		
Female	106 of 728 (15%)	Reference
Male	45 of 373 (12%)	0.77 (0.53-1.12)
Age		
≤ 35 years	67 of 456 (15%)	Reference
> 35 years	84 of 645 (13%)	0.84 (0.60-1.20)
Treatment naive		
Yes	128 of 979 (13%)	Reference
No	23 of 122 (19%)	1.54 (0.94-2.51)
Baseline CD4 count		
≤ 100 cells/mm ³	53 of 357 (15%)	Reference
> 100 cells/mm ³	98 of 744 (13%)	1.26 (0.87-1.83)
Baseline HIV-1 RNA level		
≤ 100,000 copies/mL	68 of 516 (13%)	Reference
> 100,000 copies/mL	83 of 585 (14%)	1.08 (0.76-1.54)
Adherence level		
> 90%	55 of 669 (8%)	Reference
≤ 90%	96 of 432 (22%)	3.24 (2.26-4.65)
CD4 count drop to pretreatment levels or below		
No	128 of 1047 (12%)	Reference
Yes	23 of 54 (43%)	5.87 (3.27-10.51)
Follow-up CD4 < 50% maximum therapy level		
No	129 of 1062 (12%)	Reference
Yes	22 of 39 (56%)	9.03 (4.62-17.63)
* Defined as a viral load > 1,000 copies/mL after initial virologic suppression.		
† All odds ratios are adjusted for confounding.		
CI = confidence interval		

Table 5. Test characteristics for CD4 cell count changes and adherence levels for identifying patients with breakthrough virologic failure after initial response to cART. (N=1,101)								
Criteria to define virologic failure	Area under the ROC curve (95% CI)	P value*	Sensitivity	Specificity	Positive predictive value	Negative predictive value	% of virologic failures missed	% with regimen changes despite suppressed viral loads
Decrease to pretreatment levels or below	0.56 (0.53-0.59)	Reference	15%	97%	43%	88%	85%	3%
Decrease to 50% of maximum on treatment value	0.56 (0.53-0.59)	P>0.5	15%	98%	52%	88%	85%	2%
Decrease to 40% of maximum on treatment value	0.59 (0.56-0.63)	P=0.40	23%	96%	47%	89%	77%	4%
Decrease to 30% of maximum on treatment value [†]	0.62 (0.58-0.66)	P=0.020	32%	91%	38%	90%	68%	9%
Decrease to 20% of maximum on treatment value	0.64 (0.60-0.68)	P<0.001	44%	85%	31%	90%	56%	15%
Adherence <50% [‡]	0.57 (0.54-0.60)	P>0.5	17%	97%	49%	88%	83%	3%
Adherence <60%	0.60 (0.57-0.64)	P=0.43	25%	96%	48%	89%	75%	4%
Adherence <70%	0.63 (0.59-0.67)	P=0.04	34%	92%	40%	90%	66%	8%
Adherence <80%	0.63 (0.59-0.67)	P=0.09	42%	84%	29%	90%	58%	16%
Adherence <90%	0.64 (0.60-0.68)	P=0.02	64%	64%	22%	92%	36%	36%
Adherence <100%	0.59 (0.55-0.63)	P>0.5	72%	46%	18%	92%	28%	54%
<p>* P values are adjusted for multiple comparisons, and are for comparisons of the AUCs at each CD4 cell count or adherence cut-point to the reference of a CD4 cell count drop to pretreatment levels or below.</p> <p>[†]CD4 cell count decreases of >20% and >30% were significantly more accurate than other CD4 cell count criteria (P<0.006 for all AUC comparisons), but were not different from each other (P>0.1).</p> <p>[‡] All adherence values except a level of <60% were more accurate than either WHO-advocated CD4 count criteria.</p>								

Table 6. Positive Predictive Values of CD4 Count and Adherence Data Combined for Virologic Failure at 6 and 12 Months				
	6 Months (N=958)		12 Months (N=872)	
	Positive Predictive Value (95% CI)	% with virologic failure meeting criterion (95% CI)	Positive Predictive Value (95% CI)	% with virologic failure meeting criterion (95% CI)
Adherence <50% AND				
CD4 count decrease*	93% (78%-99%)	12% (8%-17%)	95% (85%-99%)	18% (14%-24%)
CD4 increase <25	89% (77%-96%)	18% (13%-23%)	93% (83%-98%)	23% (18%-29%)
CD4 increase <50	86% (75%-94%)	22% (17%-28%)	91% (82%-97%)	28% (22%-34%)
CD4 increase <100	84% (74%-90%)	32% (26%-39%)	90% (82%-96%)	32% (27%-39%)
Adherence <60% AND				
CD4 count decrease	88% (64%-99%)	6% (4%-10%)	96% (86%-100%)	21% (16%-27%)
CD4 increase <25	89% (77%-96%)	18% (13%-23%)	94% (85%-98%)	27% (21%-33%)
CD4 increase <50	86% (75%-94%)	22% (17%-28%)	91% (83%-96%)	32% (26%-39%)
CD4 increase <100	84% (74%-90%)	32% (26%-39%)	88% (80%-94%)	38% (32%-45%)
Adherence <70% AND				
CD4 count decrease	89% (76%-96%)	17% (13%-23%)	95% (86%-99%)	24% (19%-31%)
CD4 increase <25	83% (72%-91%)	25% (19%-31%)	93% (84%-97%)	32% (26%-39%)
CD4 increase <50	78% (67%-86%)	29% (24%-36%)	90% (82%-95%)	38% (32%-45%)
CD4 increase <100	74% (65%-81%)	43% (36%-49%)	85% (78%-91%)	46% (40%-53%)
Adherence <80% AND				
CD4 count decrease	89% (76%-96%)	17% (13%-23%)	88% (78%-95%)	27% (21%-33%)
CD4 increase <25	83% (72%-91%)	25% (19%-31%)	87% (79%-93%)	36% (30%-43%)
CD4 increase <50	78% (67%-86%)	29% (24%-36%)	84% (76%-90%)	43% (37%-50%)
CD4 increase <100	74% (65%-81%)	43% (36%-49%)	80% (73%-86%)	52% (46%-59%)
Adherence <90% AND				
CD4 count decrease	66% (53%-77%)	20% (15%-25%)	83% (72%-90%)	27% (21%-33%)
CD4 increase <25	64% (55%-73%)	29% (24%-36%)	82% (74%-89%)	37% (30%-43%)
CD4 increase <50	61% (52%-69%)	36% (30%-42%)	78% (70%-85%)	45% (38%-51%)
CD4 increase <100	53% (47%-60%)	52% (46%-59%)	73% (65%-79%)	57% (50%-63%)
Adherence <100% AND				
CD4 count decrease	66% (53%-77%)	20% (15%-25%)	74% (64%-83%)	28% (22%-34%)
CD4 increase <25	64% (55%-73%)	29% (24%-36%)	75% (66%-82%)	38% (32%-45%)
CD4 increase <50	61% (52%-69%)	36% (30%-42%)	69% (61%-76%)	47% (40%-53%)
CD4 increase <100	53% (47%-60%)	52% (46%-59%)	59% (52%-65%)	60% (53%-66%)

CI = confidence interval; *cells/mm³

Table 7. Negative Predictive Values of CD4 Count and Adherence Data Combined for Virologic Failure at 6 and 12 Months				
	6 Months (N=958)		12 Months (N=872)	
	Negative Predictive Value (95% CI)	% with suppressed viral loads meeting criterion (95% CI)	Negative Predictive Value (95% CI)	% with suppressed viral loads meeting criterion (95% CI)
Adherence =100% AND				
CD4 increase >100*	93% (89%-95%)	39% (35%-43%)	95% (91%-98%)	30% (27%-34%)
CD4 increase >50	92% (89%-94%)	50% (46%-54%)	95% (92%-98%)	36% (33%-40%)
CD4 increase >25	92% (89%-94%)	55% (51%-59%)	95% (92%-98%)	38% (34%-42%)
No CD4 decrease	92% (89%-94%)	57% (53%-60%)	95% (92%-98%)	40% (36%-43%)
Adherence >90% AND				
CD4 increase >100	93% (89%-95%)	39% (35%-43%)	93% (90%-96%)	49% (45%-53%)
CD4 increase >50	92% (89%-94%)	50% (46%-54%)	94% (91%-96%)	59% (55%-63%)
CD4 increase >25	92% (89%-94%)	55% (51%-59%)	93% (91%-96%)	62% (58%-66%)
No CD4 decrease	92% (89%-94%)	57% (53%-60%)	95% (92%-98%)	65% (61%-68%)
Adherence >80% AND				
CD4 increase >100	90% (87%-93%)	54% (51%-58%)	92% (89%-94%)	59% (55%-63%)
CD4 increase >50	90% (87%-92%)	71% (67%-74%)	94% (89%-94%)	70% (67%-74%)
CD4 increase >25	89% (87%-92%)	77% (74%-80%)	91% (88%-93%)	74% (70%-77%)
No CD4 decrease	88% (86%-91%)	80% (76%-82%)	91% (88%-93%)	76% (73%-79%)
Adherence >70% AND				
CD4 increase >100	90% (87%-93%)	54% (51%-58%)	91% (88%-93%)	64% (60%-67%)
CD4 increase >50	90% (87%-92%)	71% (67%-74%)	90% (87%-92%)	76% (72%-79%)
CD4 increase >25	89% (87%-92%)	77% (74%-80%)	89% (87%-92%)	80% (76%-83%)
No CD4 decrease	88% (86%-91%)	80% (76%-82%)	89% (86%-91%)	82% (79%-85%)
Adherence >60% AND				
CD4 increase >100	89% (85%-91%)	60% (57%-64%)	90% (87%-93%)	68% (64%-71%)
CD4 increase >50	88% (85%-90%)	78% (75%-81%)	89% (86%-92%)	80% (77%-83%)
CD4 increase >25	87% (85%-90%)	85% (82%-87%)	88% (86%-91%)	84% (81%-87%)
No CD4 decrease	86% (84%-89%)	88% (85%-90%)	87% (84%-90%)	87% (84%-90%)
Adherence >50% AND				
CD4 increase >100	87% (84%-90%)	63% (59%-66%)	88% (85%-91%)	72% (69%-76%)
CD4 increase >50	85% (82%-87%)	81% (78%-84%)	86% (83%-88%)	86% (83%-88%)
CD4 increase >25	85% (82%-87%)	88% (86%-91%)	85% (82%-88%)	90% (87%-92%)
No CD4 decrease	81% (78%-83%)	92% (90%-94%)	84% (81%-87%)	93% (90%-95%)

CI = confidence interval; *cells/mm³

Figure 1. Schematic illustrating intervals during which pharmacy refill data were assessed as early markers of subsequent virologic failure. Adherence in the first 3 months of cART was compared with the CD4 count change from cART initiation to the time of the 6-month viral load. Adherence in the first 3 months after the 6-month viral load was compared with the CD4 count change measured from baseline to the time of the 12-month viral load.

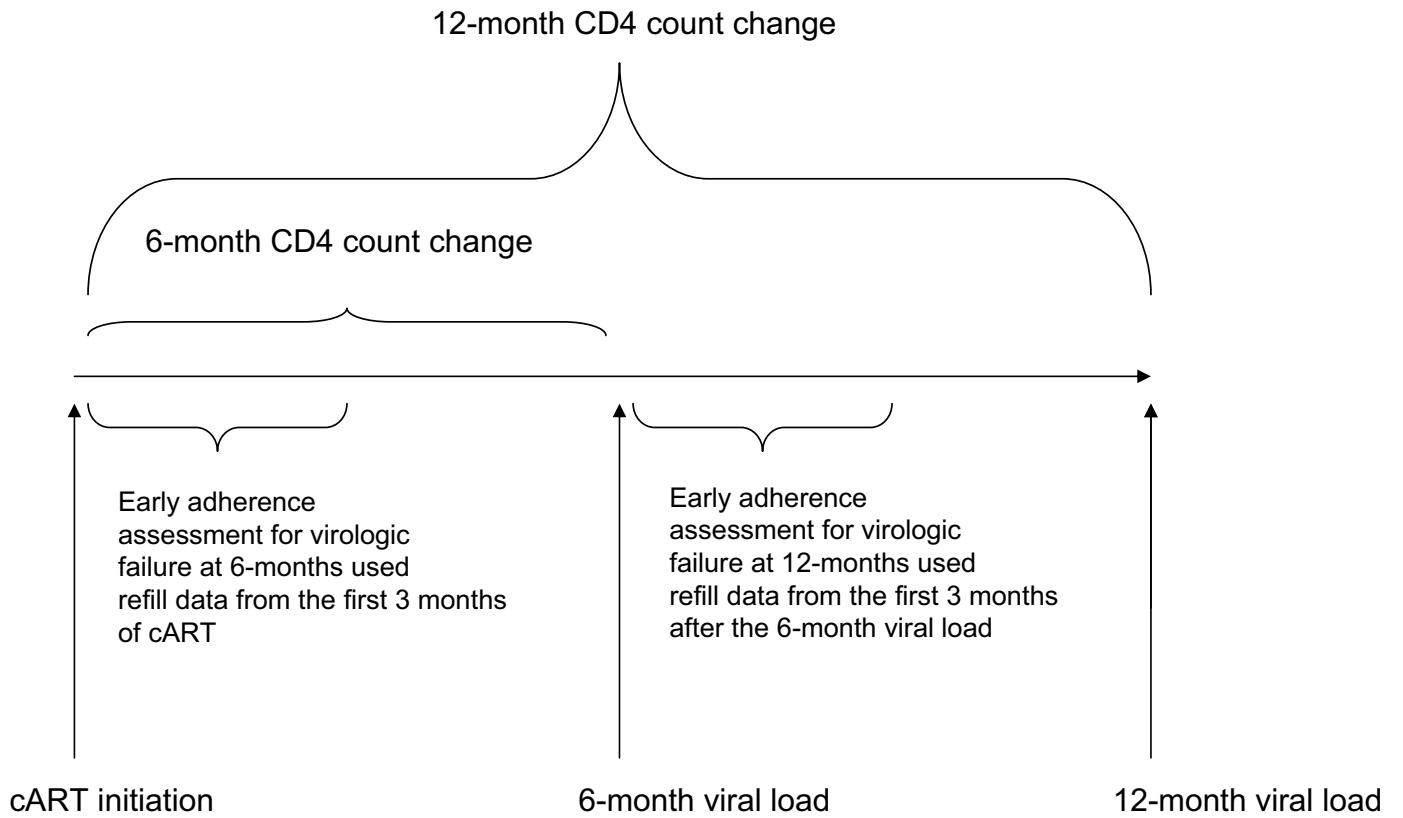
Figure 2. Plot of pharmacy refill adherence levels at 6 months after starting cART for patients with and without virologic failure.

Figure 3. Plot of CD4 count change (cells/mL) at 6 months after starting cART for patients with and without virologic failure.

Figure 4. Plot of pharmacy refill adherence levels at 12 months after starting cART for patients with and without virologic failure.

Figure 5. Plot of CD4 count change (cells/mL) at 12 months after starting cART for patients with and without virologic failure.

Figure 6. ROC curves for CD4 count change and adherence levels when used to identify patients with virologic failure when assessed 6 (**A**) and 12 (**B**) months after starting cART. The ROC areas were significantly larger for adherence values compared to CD4 cell count changes at both time points (P values <0.001).



Graphs by virologic failure at 6 months

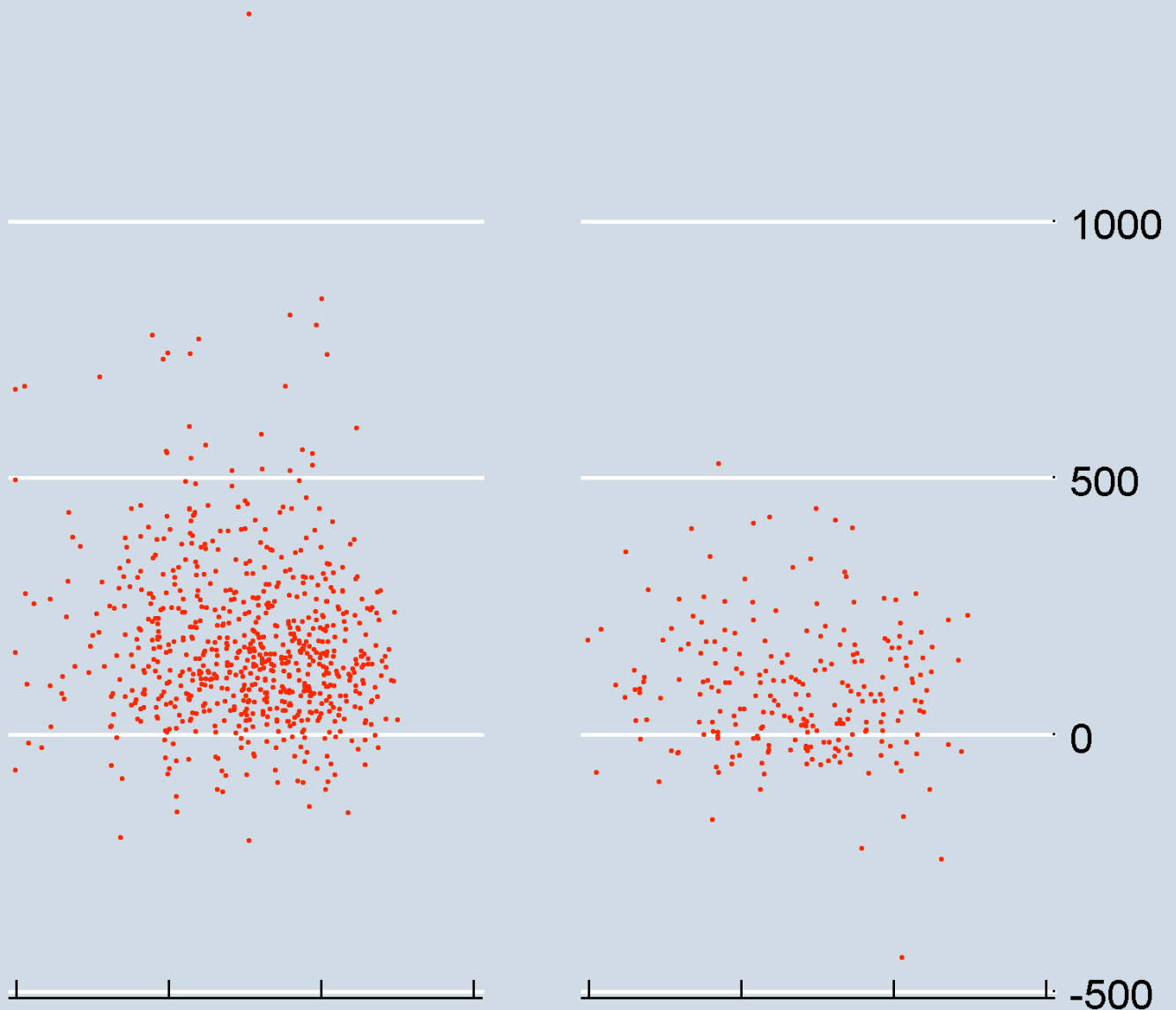


Graphs by virologic failure at 6 months

No virologic failure

Virologic failure

CD4 count change (cells/mL)



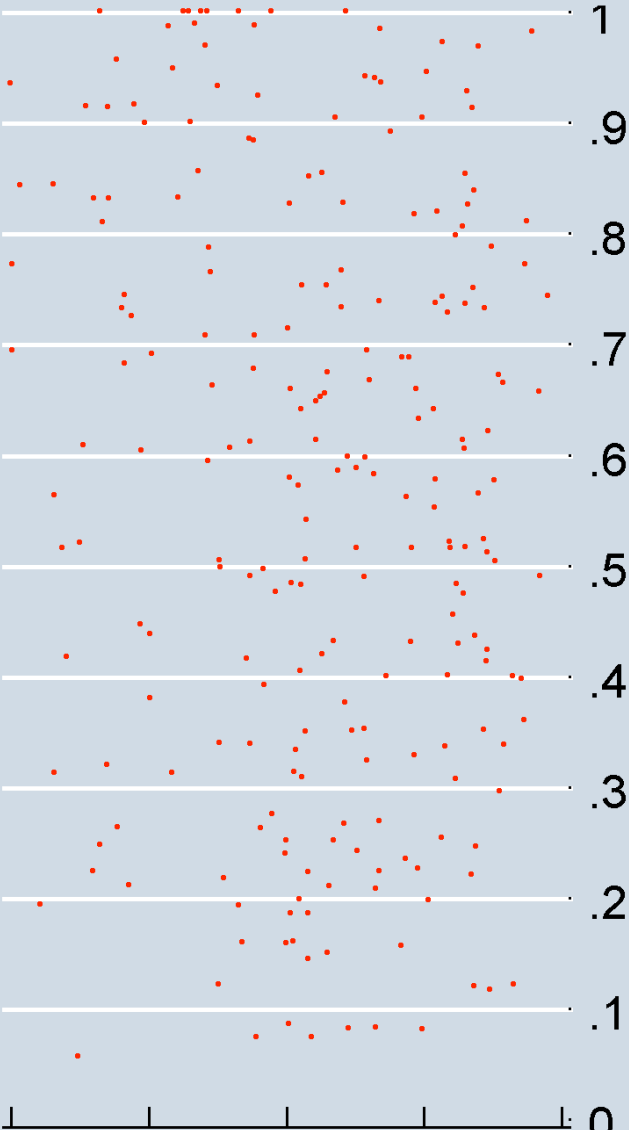
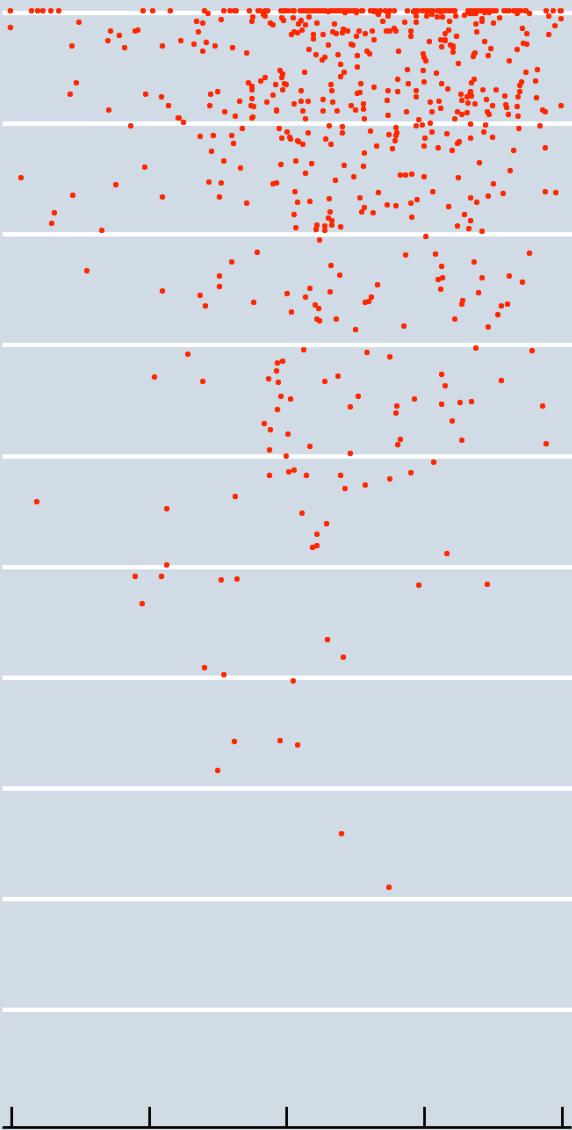
Patient ID number

Graphs by virologic failure at 12 months

No virologic failure

Virologic failure

Pharmacy refill adherence



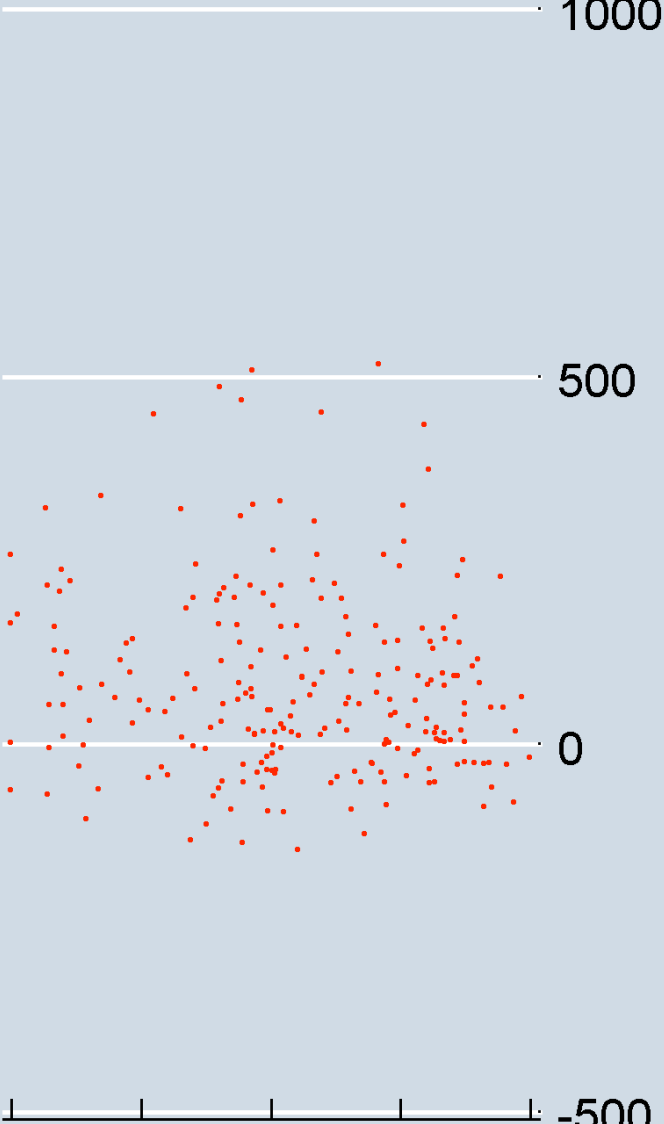
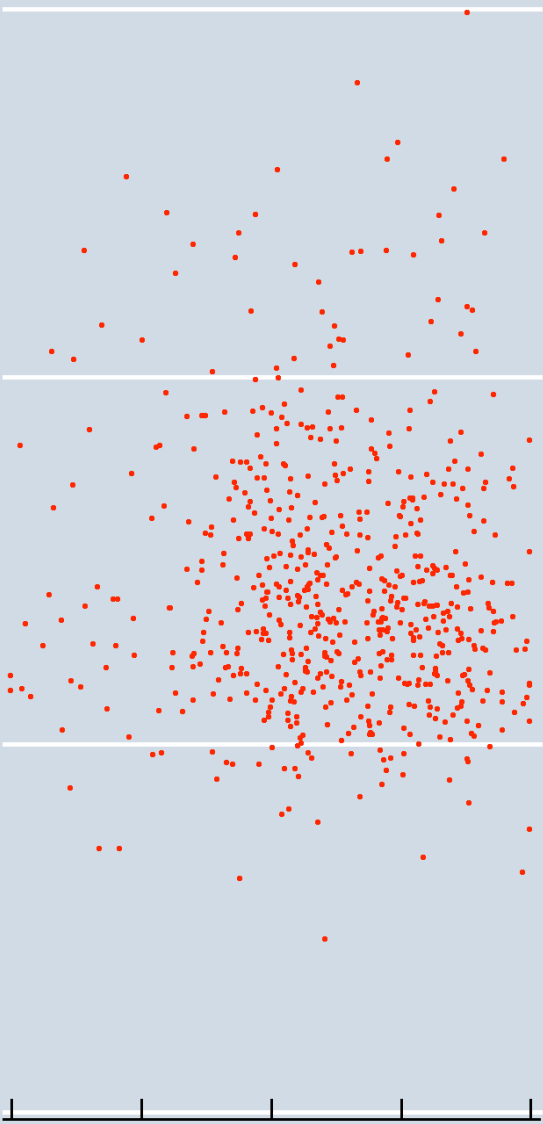
Patient ID number

Graphs by virologic failure at 12 months

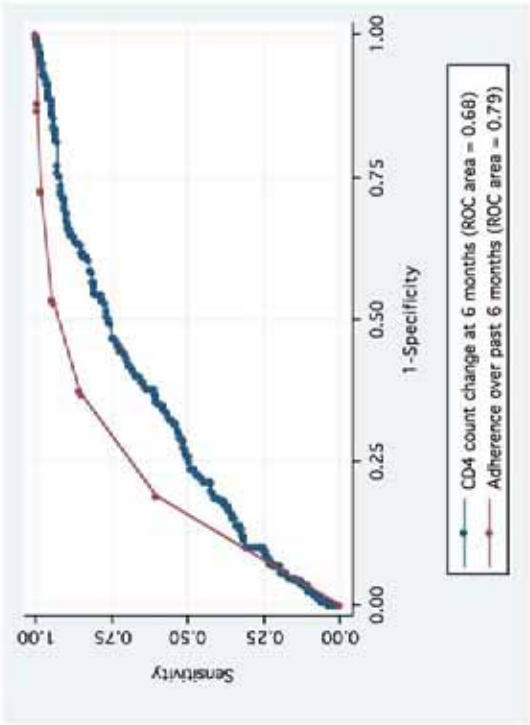
No virologic failure

Virologic failure

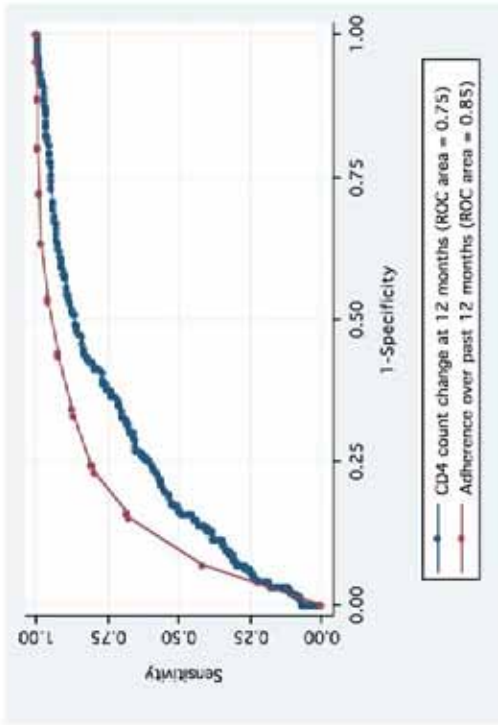
CD4 count change (cells/mL)



Patient ID number



A



B