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Antiretroviral Refill Adherence Correlates with, but Poorly Predicts Retention in HIV Care

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Abstract

If antiretroviral refill adherence could predict non-retention in care, it could be clinically useful. In a retrospective cohort study of HIV-infected adults in Philadelphia between October 2012 and April 2013, retention in care was measured by show v. no-show at an index visit. Three measures of adherence were defined per person: 1) percent of doses taken for two refills nearest index visit, 2) days late for last refill before index visit, and 3) longest gap between any two refills. Of 393 patients, 108 (27.4%) no-showed. Adherence was higher in the show group on all measures with longest gap having the greatest difference: 40 days (IQR, 33–56) in the show v. 47 days (IQR, 38–69) in the no-show group, $p < 0.001$. Yet, no cut-points of adherence adequately predicted show v. no-show. Antiretroviral adherence being associated, but a poor predictor of retention suggests that these two behaviors are related but distinct phenomena.

Keywords

HIV; adherence; antiretroviral therapy; retention in care; monitoring

INTRODUCTION

Human immunodeficiency virus (HIV) infection has been transformed from a uniformly fatal disease to a manageable chronic infection with life expectancy approaching that of HIV-uninfected individuals (1). However, optimal outcomes are limited to those who successfully navigate the HIV care continuum: HIV diagnosis, linkage to care, retention in

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CONFLICTS OF INTEREST

None reported.

care, initiation of and adherence to antiretroviral therapy (ART), and HIV viral suppression (2, 3). Barriers to each step exist to varying degrees in different settings (4–7). Recent data indicate that of the 1.1 million Americans infected with HIV, 82% are aware of their diagnosis, 66% are effectively linked to care, 37% are retained in care, and 33% are prescribed ART (3, 8). Given drop-offs at each step of the continuum, only a relatively low proportion of HIV-infected individuals achieve viral suppression (3). If persistent, this lack of suppression leads to progression of disease, emergence of drug resistant virus, and death in individuals, while contributing to the spread of HIV infection in communities (9–11).

Adherence to ART is the factor most directly related to sustained virologic suppression (12, 13). Retention in regular outpatient care is also associated with virologic suppression, prolonged life, and lower rates of transmission of infection and HIV-related complications (2, 14–16). Retention in care is a quality of care measure by federal agencies, healthcare quality organizations, and the *National HIV/AIDS Strategy for the United States* (17–21). Currently, early prediction of non-retention in HIV care is difficult given the long time period needed for most retention measures (6–12 months) (18). Because of this time lag, the events that drive a patient out of routine care may begin many months before an individual is discovered to be out of care. The longer the period between inciting events and attempts to reengage patients in care, the higher risk they are for complications of HIV (22). Recent work has shown that there is no clear gold standard for measuring retention in care, and that measures including missed visits, operationalized in multiple ways, performed similar to other measures (18, 23). Just a single no-show, as well as failure to meet other retention in care measures, has been demonstrated in multiple studies to increase mortality risk among HIV patients (16, 24).

We hypothesized that pharmacy refill measures of adherence could serve as an early proxy of retention in care. Because refills are commonly obtained monthly, refill non-adherence can be detected on a shorter time horizon than non-retention in care. If non-retention was identified early via refill non-adherence, then refill non-adherence could be used as a trigger for interventions related to both adherence and retention behaviors. In this study, we evaluated whether ART refill adherence differs between patients who do and do not exhibit non-retention behavior and whether refill adherence can serve as an early marker of non-retention in HIV care.

METHODS

Study Design and Population

We retrospectively evaluated HIV-patients who were already successfully linked to care at the Jonathan Lax Treatment Center of Philadelphia FIGHT, an urban, Ryan White funded, HIV primary care clinic in Philadelphia between October 2012 and June 2013. This site was selected because a larger proportion of patients use a single pharmacy for all ART refills. Patients were included in the study if they were 1) 18 years old, 2) prescribed ART during the study period, and 3) had 2 clinic visits at least 4 weeks apart at any point before the refill data window. The third criterion was to ensure enrollment of patients already effectively linked to care since our goal was not focused on using refill data as a measure of linkage to care. Patients were excluded if their ART refills were automatically mailed to

them, since variability in refill adherence is not detectable in this scenario. Potential study subjects were also excluded if their prescription was for >30 day supply since our goal was to test whether short-term refill adherence could be used as a marker of later non-retention. The study was approved by the Jonathan Lax Treatment Center of Philadelphia FIGHT and the University of Pennsylvania Institutional Review Boards.

Measures

The primary outcome was attendance (show or no-show) at an HIV primary care index visit. The index visit was defined as a scheduled HIV primary care appointment with an HIV physician, nurse practitioner, or physician's assistant that occurred between October 2012 and June 2013. Scheduled visits to meet with non-prescribing nursing or laboratory staff were not eligible to be index visits. No-show was defined as a scheduled visit that was missed but not cancelled or rescheduled by the patient prior to the visit. A 150-day period preceding the index visit date was then captured to measure refill adherence, and was chosen to allow sufficient time to examine refill adherence metrics of varying lengths. Refill adherence was calculated for a single antiretroviral ("index drug") *a priori* selected by the following algorithm: 1) protease inhibitor, or if none, 2) non-nucleoside reverse transcriptase inhibitor, and if neither used, 3) an integrase inhibitor. Refill adherence to the index drug was defined using three metrics (Figure 1): 1) percent of doses taken (30 day supply/days between fills)*100% for two fills closest to index visit and 2) number of days late for last refill before index visit, and 3) the maximum number of days between any of the fills in the 150-day period prior to the index visit ("longest gap"). Thus, the complete refill data window began 150 days prior to the index visit.

Sociodemographic and clinical variables were obtained via medical chart abstraction. Age was recorded at time of index visit. Race was categorized as black, white, and other; ethnicity as Hispanic and non-Hispanic. Gender was categorized as male or female. HIV transmission risk factors were grouped into heterosexual transmission, men who had sex with men (MSM), injection drug use (IDU), and other/unknown. Patients who had IDU in combination with another risk factor (e.g. MSM transmission) were classified as IDU. AIDS diagnosis was categorized as ever or never diagnosed. Entry CD4 count and log₁₀ viral load were defined as the CD4 and viral load values nearest to the start of the 150-day window before the index visit. Final CD4 count and log₁₀ viral load were defined as the values nearest to the index visit, either before or after.

Statistical Analysis

We used Wilcoxon rank sum tests and Chi-square tests to compare the show and no-show groups on continuous and dichotomous variables, respectively. We used multivariate logistic regression to control for potential confounders including age, race, gender, AIDS diagnosis, and HIV risk factors in comparing refill adherence measures between the show and no-show groups. Confounding was declared to be present if the point estimate of the association between refill adherence and no show changed by >15% when the potential confounder was included in the models.

To evaluate the discriminative ability of the refill adherence measures for visit attendance, we constructed receiver-operator curves (ROC) across all possible cut-points of the refill adherence measures (25, 26). The corresponding area under the curve (AUC) was calculated for each refill adherence measure. We also assessed sensitivity, specificity, and positive and negative predictive values at cut-points chosen to maximize each test characteristic. We compared the AUC for each of the refill adherence metrics to determine if one had superior accuracy to predict index clinic visit attendance. We plotted the probability by show v. no-show groups at each refill adherence percentage and used Lowess smoothing to give a best approximation of the relation across refill adherence percentages. A plot of proportion of the population represented by the show v. no-show groups at each value of refill adherence metric was constructed separately for days late for last refill before index visit and longest gap.

Analyses were performed using SAS software (version 9.3; SAS Institute). All tests of significance were 2-sided, with $p < 0.05$ used as the threshold of statistical significance.

RESULTS

A total of 393 patients were included. Overall, 272 (69.2%) patients were male, 248 (63.1%) black, and the median age was 48 years (interquartile range [IQR], 41–53 years). Of HIV transmission risk factors, 176 (44.8%) reported MSM, 138 (35.1%) heterosexual transmission, and 77 (19.6%) IDU history. There were 207 (52.7%) patients with an AIDS diagnosis, and 174 (44.3%) patients were on a boosted protease inhibitor regimen. The median entry CD4 cell count was 571.5 cells/mm³ (IQR, 389–813.5 cells/mm³) and the median entry viral load was 2.9 log₁₀ copies/ml (IQR, 2.9–3.9).

Table 1 displays the baseline characteristics compared between the 285 (72.5%) who showed and the 108 (27.5%) who no-showed for the index visit. The only characteristic that was statistically significantly different between groups was black race, with more no shows among black patients than other racial groups ($p = 0.046$).

Table 2 displays the different refill adherence measures and their relation to visit attendance including: percent adherence, number of days late for last refill before index visit, and the longest gap. Overall, the show group had higher refill adherence with 93.8% doses taken (IQR, 75% – >100% doses) v. 80.0% doses taken for the no-show group (IQR, 53.6% – >100%, $p = 0.005$). Fewer than half of the no-show group and fewer than a quarter of the show group were late for refills on the index date. Although the median number of days late for both groups was 0, the distribution of days late was substantially higher for the no-show group (IQR 0–18, range 0–120) than the show group (IQR 0–0, range 0–120), and the difference was statistically significant (Wilcoxon rank sum test $p = 0.003$). There was also a significant difference in median longest gap for patients who showed (40 days; IQR, 33–56) compared to those who no-showed (47 days; IQR, 38–69, $p < 0.001$).

Figure 2 displays the proportion of the population represented by the show and no-show groups by percent adherence (2a), days late for last refill before index visit (2b), and duration of the longest gap between fills (2c). As percent adherence increases, the

probability of being in the show group increases, while the probability of being in the no-show group decreases. As days late for last refill increase, the probability of being in the no-show group increases. Similarly, the probability of being in the no-show group increases as the length of gap between fills increases.

Table 3 displays the test characteristics, based on observed values, for the three different refill adherence measures and their associations with index visit attendance. For percent of doses taken, the AUC was 0.60 (95% CI 0.54–0.67, $p=0.001$). The sensitivity was 55.6% and specificity 69.1%, utilizing the cut point that maximized the sum of sensitivity and specificity. For the measure of days late for last refill before index visit, the AUC was 0.571 (95% CI 0.518–0.624, $p=0.008$), with a sensitivity of 39.8% and specificity of 75.4%, utilizing the same cut point. The AUC for the longest fill gap measure was 0.607 (95% CI 0.548–0.662, $p<0.001$), with a sensitivity of 68.5% and specificity of 53.0%, utilizing the same cut point. None of the differences between the ROC curves for the three measures were statistically significant ($p=0.42$).

No confounding was identified in the multivariable analyses and thus only bivariate analyses are presented.

DISCUSSION

In this retrospective analysis, non-attendance to clinic occurred in slightly more than one quarter of all participants in our cohort. Across all three refill adherence measures, we demonstrated that there are refill adherence differences between the show and no-show groups. These results suggest that ART adherence and clinic visit attendance are related phenomena.

Our results are consistent with prior studies of the association between retention and clinical outcome. Studies by Lucas et al. and Yehia et al. found retention in care to be a strong determinant of virologic suppression (5, 15, 27). Since ART adherence is the main determinant of virologic suppression, it is likely that non-retention operated via its association with refill non-adherence. In a study in the Veterans Health Affairs Medical System, Giordano et al. demonstrated that for every quarter in a year without an HIV clinic visit, Veterans' likelihood of death increased substantially (2). While other behaviors such as substance abuse may have directly caused both non-retention and death, it is also likely that the non-retention was associated with refill non-adherence and subsequent virologic failure to partly explain the deaths. Studies of non-retention in similar settings in the United States have also demonstrated high rates of missed visits and non-retention in care (24, 28).

Despite the association between refill adherence and visit attendance, the differences in magnitude of each refill adherence measure were relatively small, and the discriminant ability of these measures to categorize patients as likely to show or no-show to appointments was poor. The principle challenge of all three refill adherence measures in Figure 2 is that there is no cutoff value where the probability of being in the show or no-show group is so certain that we can accurately declare whether the individual will show or no-show. This makes prediction of a patient's future clinic visit attendance difficult.

One possible explanation may be that two different subgroups are represented in the no-show group. One subset may include patients doing well on medications and thus have little incentive to attend clinic. In a 2013 study by Dombrowski, et al., patients with higher nadir CD4 counts were less likely to be engaged in continuous HIV care (29). Thus, lack of perception of threat to health in those continuing to take their medications may result in no-show. Their perception may in fact be accurate since the impact of no-show on their health is likely to be substantially less than for patients with lower counts. Yet, they do miss other potential benefits from regular clinic attendance such as screening for sexually transmitted infections and ongoing counseling regarding safer sex and other health related behaviors such as substance use. In contrast, a more important group to target for interventions may be patients who both struggle with refill adherence and no-show for clinic visits. Here, the non-attendance may reflect more systemic challenges to maintaining self-care. If this subgroup can be better characterized, refill adherence may be a stronger predictor of no-show in this group and permit early implementation of interventions to prevent non-retention.

It is important to recognize that interventions targeted to the good refill adherence and suboptimal refill adherence subgroups that no-show would by their nature be different. For the good adherers who no-show, clinicians might need to address motivation to still attend clinic visits for ancillary medical care while for the poor adherers who no-show, evidence-based tools such as Managed Problem Solving would be needed in addition to any retention-related intervention (30).

Consistent with previously published works, black individuals in our study sample were more likely to no-show as compared to other races (28, 31). We did not assess health disparities such as socioeconomic status, insurance status, or mistrust of the medical system, nor did we assess barriers faced by individuals with respect to clinic attendance, which may influence this finding. Yet, our finding reinforces the challenges of sustaining virologic suppression in minority racial and ethnic groups. Further investigation into specific barriers for retention in this group is needed.

Our study has several limitations. First, the study population was limited to those using the pharmacy affiliated with the clinical site, which may not represent the full spectrum of patients who receive care there or the general population of individuals for whom refill adherence and clinic visit attendance are important issues. However, this clinic serves a relatively poor and marginalized patient population, which is likely representative of the urban HIV epidemic. Second, we did not capture refill data from outside of the Lax Center affiliated pharmacy system, which could cause participants to be misclassified as having reduced ART adherence if they filled prescriptions intermittently elsewhere. We would expect misclassification of refill adherence to bias the difference in refill adherence between the show and no-show groups toward then null and weaken the predictive ability of adherence to identify no-show. Despite this possibility, we still found large differences in refill adherence between the show and no-show groups. If multiple pharmacy use adversely affected the test characteristics of prediction of no-show, we would still conclude that contacting pharmacies to identify future no-shows is not a useful strategy since it would be too cumbersome to implement in settings with commercial pharmacies. Finally, misclassification of refill adherence behavior is possible since we determined adherence

indirectly (i.e., via pharmacy refill data rather than directly observed). However, the method we are using has already been shown to correlate with a biological measure of treatment success and therefore must to a degree capture the variability between subjects in their adherence behavior (32). Additionally, non-attendance at a clinic visit may not fully represent non-retention in care since patients may have missed visits, but planned to reschedule for a later date. Yet, ‘no-shows’ have been strongly associated with non-retention in other studies (18, 24).

This study has important implications for the HIV care continuum. We provide evidence that ART adherence and clinic visit attendance, a marker of retention in care, are strongly related constructs, but are not superimposable. Thus, next steps for research on interventions to improve HIV outcomes should attempt to clarify the separation between refill adherence and retention in care from a lived-experience perspective. This study serves as proof of concept that early warning indicators might be available, which incorporate tracking of pharmacy data for being late for refills to increase the chance of identifying individuals in need of retention interventions for upcoming visits. However, in order to be practical for implementation, future studies may need to combine pharmacy refill data with other characteristics to predict who will be lost to care and to intervene at the time their barriers are most pressing.

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References

1. Mills EJ, Bakanda C, Birungi J, Chan K, Ford N, Cooper CL, et al. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. *Annals of internal medicine*. 2011; 155(4):209–16. [PubMed: 21768555]
2. Giordano TP, Gifford AL, White AC Jr, Suarez-Almazor ME, Rabeneck L, Hartman C, et al. Retention in care: a challenge to survival with HIV infection. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2007; 44(11):1493–9. [PubMed: 17479948]
3. CDC. HIV in the United States: The Stages of Care. CDC Fact Sheet. 2012
4. Fleishman JA, Yehia BR, Moore RD, Gebo KA, Agwu AL, Network HIVR. Disparities in receipt of antiretroviral therapy among HIV-infected adults (2002–2008). *Medical care*. 2012; 50(5):419–27. [PubMed: 22410406]
5. Yehia BR, French B, Fleishman JA, Metlay JP, Berry SA, Korthuis PT, et al. Retention in care is more strongly associated with viral suppression in HIV-infected patients with lower versus higher CD4 counts. *J Acquir Immune Defic Syndr*. 2014; 65(3):333–9. [PubMed: 24129370]
6. Yehia BR, Fleishman JA, Metlay JP, Moore RD, Gebo KA. Sustained viral suppression in HIV-infected patients receiving antiretroviral therapy. *Jama*. 2012; 308(4):339–42. [PubMed: 22820781]

7. Fleishman JA, Yehia BR, Moore RD, Korthuis PT, Gebo KA, Network HIVR. Establishment, retention, and loss to follow-up in outpatient HIV care. *J Acquir Immune Defic Syndr*. 2012; 60(3): 249–59. [PubMed: 22531758]
8. Yehia BR, Fleishman JA, Metlay JP, Korthuis PT, Agwu AL, Berry SA, et al. Comparing different measures of retention in outpatient HIV care. *Aids*. 2012; 26(9):1131–9. [PubMed: 22382143]
9. Wood E, Hogg RS, Lima VD, Kerr T, Yip B, Marshall BD, et al. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. *JAMA: the journal of the American Medical Association*. 2008; 300(5):550–4. [PubMed: 18677027]
10. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA: the journal of the American Medical Association*. 2001; 286(20):2568–77. [PubMed: 11722271]
11. Nachega JB, Marconi VC, van Zyl GU, Gardner EM, Preiser W, Hong SY, et al. HIV treatment adherence, drug resistance, virologic failure: evolving concepts. *Infectious disorders drug targets*. 2011; 11(2):167–74. [PubMed: 21406048]
12. Gross R, Bilker WB, Friedman HM, Strom BL. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS*. 2001; 15(16):2109–17. [PubMed: 11684930]
13. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of internal medicine*. 2000; 133(1):21–30. [PubMed: 10877736]
14. Berg MB, Safren SA, Mimiaga MJ, Grasso C, Boswell S, Mayer KH. Nonadherence to medical appointments is associated with increased plasma HIV RNA and decreased CD4 cell counts in a community-based HIV primary care clinic. *AIDS Care*. 2005; 17(7):902–7. [PubMed: 16120506]
15. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Annals of internal medicine*. 1999; 131(2):81–7. [PubMed: 10419445]
16. Mugavero MJ, Lin HY, Willig JH, Westfall AO, Ulett KB, Routman JS, et al. Missed visits and mortality among patients establishing initial outpatient HIV treatment. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2009; 48(2):248–56. [PubMed: 19072715]
17. Forum NQ. HIV Medical Visit. NQF# 0403 2010. Mar 1. 2011 Available from: <http://www.qualityforum.org/MeasureDetails.aspx?SubmissionId=580-k=hiv>
18. Mugavero MJ, Davila JA, Nevin CR, Giordano TP. From access to engagement: measuring retention in outpatient HIV clinical care. *AIDS patient care and STDs*. 2010; 24(10):607–13. [PubMed: 20858055]
19. Yehia B, Frank I. Battling AIDS in America: an evaluation of the National HIV/AIDS Strategy. *Am J Public Health*. 2011; 101(9):e4–8.
20. Rebeiro PF, Horberg MA, Gange SJ, Gebo KA, Yehia BR, Brooks JT, et al. Strong agreement of nationally recommended retention measures from the Institute of Medicine and Department of Health and Human Services. *PloS one*. 2014; 9(11):e111772. [PubMed: 25375099]
21. The White House Office of National AIDS Policy. National HIV/AIDS Strategy for the United States. 2010
22. Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. *Tropical medicine & international health: TM & IH*. 2011; 16(10): 1297–313. [PubMed: 21718394]
23. Mugavero MJ, Westfall AO, Zinski A, Davila J, Drainoni ML, Gardner LI, et al. Measuring retention in HIV care: the elusive gold standard. *J Acquir Immune Defic Syndr*. 2012; 61(5):574–80. [PubMed: 23011397]
24. Mugavero MJ, Westfall AO, Cole SR, Geng EH, Crane HM, Kitahata MM, et al. Beyond Core Indicators of Retention in HIV Care: Missed Clinic Visits Are Independently Associated With All-Cause Mortality. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2014; 59(10):1471–9. [PubMed: 25091306]
25. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982; 143(1):29–36. [PubMed: 7063747]

26. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983; 148(3):839–43. [PubMed: 6878708]
27. Yehia BR, Rebeiro P, Althoff KN, Agwu AL, Horberg MA, Samji H, et al. The Impact of Age on Retention in Care and Viral Suppression. *J Acquir Immune Defic Syndr*. 2014
28. Horberg MA, Hurley LB, Silverberg MJ, Klein DB, Quesenberry CP, Mugavero MJ. Missed office visits and risk of mortality among HIV-infected subjects in a large healthcare system in the United States. *AIDS patient care and STDs*. 2013; 27(8):442–9. [PubMed: 23869466]
29. Dombrowski JC, Kitahata MM, Van Rumpae SE, Crane HM, Mugavero MJ, Eron JJ, et al. High levels of antiretroviral use and viral suppression among persons in HIV care in the United States, 2010. *J Acquir Immune Defic Syndr*. 2013; 63(3):299–306. [PubMed: 23572013]
30. Gross R, Bellamy SL, Chapman J, Han X, O'Duor J, Palmer SC, et al. Managed problem solving for antiretroviral therapy adherence: a randomized trial. *JAMA internal medicine*. 2013; 173(4): 300–6. [PubMed: 23358784]
31. Rebeiro P, Althoff KN, Buchacz K, Gill J, Horberg M, Krentz H, et al. Retention among North American HIV-infected persons in clinical care, 2000–2008. *J Acquir Immune Defic Syndr*. 2013; 62(3):356–62. [PubMed: 23242158]
32. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. *Journal of clinical epidemiology*. 2004; 57(10):1107–10. [PubMed: 15528063]

Figure 1.

Adherence metrics: 1) percent of doses taken ($30 \text{ day supply} / \text{days between fills}$)*100% for two fills closest to index visit and 2) number of days late for last refill before index visit, and 3) the maximum number of days in between any of the fills in the 150-day period prior to the index visit (“longest gap”).

Figure 2.

- a. Probability of show v. no-show at each adherence percentage, using Lowess smoothing approximation. Adherence was calculated by percent of doses taken (30 day supply/days between fills)*100% for two fills closest to index visit. Some subjects filled more than once within 30 days, resulting in adherence >100%. Upper limit cutoff of 120% was set. Circles represent observed adherence values for individuals who no-showed. Triangles represent observed adherence value for individuals who showed. As percent adherence increases, the probability of being in the show group increases and no-show decreases.
- b. Proportion of total sample, by show and no-show groups, for number of days late for last refill before index visit. As the number of days late for a patient's last refill increases, the probability that a patient no-shows to index clinic visit increases.
- c. Proportion of total sample, by show and no-show groups, for maximum number of days between any of the fills in 150-day period prior to the index visit ("longest gap"). As the longest gap between fills increases, the probability that a patient no-shows to index clinic visit increases.

Table 1

Baseline demographics compared between show and no-show groups

Characteristic		Overall (n=393)	Show (n=285)	No-Show (n=108)	p-value
Age	Median (IQR)	48.0 (41.0–53.0)	49.0 (42.0–53.0)	47.0 (38.0–52.0)	0.061
Gender	Male	272 (69.2%)	202 (70.9%)	70 (64.8%)	0.245
	Female	121 (30.8%)	83 (29.1%)	38 (35.2%)	
Race	Black	248 (63.1%)	171 (60.0%)	77 (71.3%)	0.046
	White	128 (32.6%)	103 (36.1%)	25 (23.1%)	
	Other	17 (4.3%)	11 (3.9%)	6 (5.6%)	
Ethnicity	Hispanic or Latino	32 (8.2%)	24 (8.4%)	8 (7.4%)	>0.5
	Not Hispanic or Latino	358 (91.8%)	258 (90.5%)	100 (92.6%)	
	Not available	3 (%)	3 (1.1%)		
HIV Risk Factor	Heterosexual	138 (35.1%)	101 (35.4%)	37 (34.3%)	0.199
	MSM	176 (44.8%)	133 (46.7%)	43 (39.8%)	
	IDU History	77 (19.6%)	49 (17.2%)	28 (25.9%)	
	Other/unknown	2 (0.5%)	2 (0.7%)		
AIDS Diagnosis	Diagnosed (ever)	207 (52.7%)	145 (50.9%)	62 (57.4%)	0.370
	Not Diagnosed (ever)	184 (46.8%)	139 (48.8%)	45 (41.7%)	
	Not available	2 (0.5%)	1 (0.4%)	1 (0.9%)	
Index Drug	Efavirenz/tenofovir/emtricitabine fixed dose combination	92 (23.4%)	65 (22.8%)	27 (25.0%)	>0.5
	Raltegravir	57 (14.5%)	46 (16.1%)	11 (10.2%)	
	Ritonavir	174 (44.3%)	121 (42.5%)	53 (49.1%)	
	Etravirine/tenofovir/emtricitabine fixed dose combination	27 (6.9%)	20 (7.0%)	7 (6.5%)	
	Other	43 (10.9%)	33 (11.6%)	10 (9.3%)	
Entry CD4 Count	Median (IQR)	571.5 (389.0–813.5)	585.0 (405.0–835.0)	563.0 (354.0–712.0)	0.423
Final CD4 Count	Median (IQR)	590.0 (403.0–791.0)	608.5 (408.0–821.0)	569.0 (354.0–724.0)	0.143
Log ₁₀ Entry Viral Load	Median (IQR)	2.9 (2.9–3.9)	2.9 (2.9–3.7)	2.9 (2.9–5.0)	0.058
Log ₁₀ Final Viral Load	Median (IQR)	2.9 (2.9–3.4)	2.9 (2.9–3.0)	2.9 (2.9–3.9)	0.143

Abbreviations: IQR, interquartile range; MSM, men who have sex with men; IDU, intravenous drug use.

Table 2

Adherence measures compared between show and no-show groups

Characteristic	Overall (n=393)	Show (n=285)	No-Show (n=108)	p-value ^d
Refill Adherence Over Last Interval Prior to Index Visit	93.8 (66.7–107.1)	93.8 (75.0–107.1)	80.0 (53.6–107.1)	0.005
Days Late for Last Refill Before Index Visit (days)	0 (0.0–4.0)	0 (0.0–0.0)	0 (0.0–18.0)	0.003
Maximum Fill Gap (days)	41.0 (34.0–60.0)	40.0 (33.0–56.0)	47.0 (37.5–69.0)	<0.001

Abbreviations: IQR, interquartile range.

^aWilcoxon rank sum test used to calculate p-values.

Table 3

Test characteristics for adherence measures to identify patients who will not attend their upcoming clinic visit.

Adherence Variable	Selection Criterion for Cut on Adherence Point Variable	Sensitivity %	Specificity %	PPV %	NPV %
Refill Adherence Over Last Interval Prior to Index Visit	Cut point yielding ~90% sensitivity	93.5	12.3	28.8	83.3
	Cut point maximizing sensitivity & specificity	55.6	69.1	40.5	80.4
	Cut point yielding ~90% specificity	10.2	90.2	28.2	72.6
Days Late for Last Refill Before Index Visit	Cut point yielding ~90% sensitivity	100	0	27.5	–
	Cut point maximizing sensitivity & specificity	39.8	75.4	38.1	76.8
	Cut point yielding ~90% specificity	10.2	90.2	28.2	72.6
Maximum Fill Gap	Cut point yielding ~90% sensitivity	92.3	21.4	30.9	88.4
	Cut point maximizing sensitivity & specificity	68.5	53	35.6	81.6
	Cut point yielding ~90% specificity	9.3	90.2	26.3	72.4

Abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value.