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Adherence to Nonnucleoside Reverse Transcriptase Inhibitor–Based HIV Therapy and Virologic Outcomes

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Background: Adherence of 95% or more to unboosted protease regimens is required for optimal virologic suppression in HIV-1–infected patients. Whether the same is true for nonnucleoside reverse transcriptase inhibitor (NNRTI)–based therapy is unclear.

Objective: To assess the relationship between adherence to NNRTI–based therapy and viral load in treatment-naive patients.

Design: Observational cohort study.

Setting: Private-sector HIV and AIDS disease management program in South Africa.

Patients: 2821 adults infected with HIV who began NNRTI–based therapy between January 1998 and March 2003 (2764 patients [98%] were enrolled after December 2000).

Measurements: Adherence was assessed by monthly pharmacy claims. The primary end point was sustained viral load suppression (<400 copies/mL) in 100% of recorded viral load measurements throughout follow-up. Secondary end points included time to initial viral load suppression and time to subsequent virologic failure (>400 copies/mL).

Results: The median follow-up period was 2.2 years (interquartile range, 1.7 to 2.7 years). The proportion of patients with sustained viral load suppression ranged from 13% (41 of 325 patients) in patients who filled less than 50% of antiretroviral drug prescriptions to 73% (725 of 997 patients) in those who filled 100% of antiretroviral drug prescriptions. Each 10% increase in pharmacy claim adherence greater than 50% was associated with a mean absolute increase of 0.10 in the proportion of patients with sustained virologic suppression ($P < 0.001$). Predictors for shorter time to virologic failure after initial suppression in multivariable Cox regression included $CD4^+$ T-cell counts of 0.50×10^9 cells/L or less (hazard ratio, 1.60 [95% CI, 1.22 to 2.10] vs. $CD4^+$ T-cell counts $>0.20 \times 10^9$ cells/L), baseline viral load greater than 10^5 copies/mL (hazard ratio, 1.39 [CI, 1.14 to 1.70]), nevirapine-based regimen (hazard ratio, 1.43 [CI, 1.16 to 1.75]), and low pharmacy claim adherence (hazard ratio, 1.58 [CI, 1.48 to 1.69], per 10% decrease in adherence to 50%).

Limitations: Observational study with adherence stratification at study end and lack of standardized timing for outcome measurement.

Conclusion: Virologic outcomes improve in a linear dose–response manner as adherence to NNRTI–based regimens increases beyond 50%.

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Researchers have shown that adherence to highly active antiretroviral therapy (HAART) is a major predictor of viral suppression of HIV replication (1–3), emergence of drug resistance (4–6), disease progression (7), and death (8–10). Nonnucleoside reverse transcriptase inhibitor (NNRTI)–based HAART has emerged as the preferred option for first-line treatment of HIV and AIDS worldwide (11, 12), including the increase of HAART programs in resource-limited settings (13). When patients receive unboosted protease inhibitor–based HAART regimens, nearly perfect adherence (≥95%) is required for sustained virologic suppression (2). Emergence of drug resistance is highest at intermediate levels (70% to 90%) of adherence (5, 14). Data from a prospective study conducted by Maggiolo and colleagues (15) in Italy suggest that, at intermediate levels of adherence, patients who receive NNRTI–based regimens may have higher rates of viral suppression than those who receive unboosted protease inhibitor–based regimens. Similarly, a study of homeless and indigent HIV-infected patients with antiretroviral therapy experience in San Francisco, California, found that, in contrast to patients who received unboosted protease inhibitors, approximately 70% of patients who received NNRTI–based HAART who had intermediate adherence (70% to 90%, as evaluated by pill count or electronic monitor) achieved undetectable viral load (<400 copies/mL) with lower levels of resistance compared with patients who had low adherence (0% to 50%) (16, 17). These studies were limited by small sample sizes and reduced generalizability to other populations. As a result, it remains unclear whether the relationship between adherence and viral suppression in patients receiving NNRTI–based HAART treatment resembles a linear dose–response relationship or whether there is a threshold adherence level below which virologic failure rapidly increases.

Antiretroviral therapy is now being rolled out in resource-limited settings (13). Therefore, characterizing its effectiveness and identifying factors associated with its out-

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Context

It is unclear whether HIV treatment regimens that contain nonnucleoside reverse transcriptase inhibitors (NNRTIs) require the same high level of adherence for optimal viral suppression as regimens that do not contain these agents.

Contribution

This study evaluated adherence and viral suppression among 2821 HIV-1–infected patients who began NNRTI–based therapy between 1998 and 2003. The proportion of patients with sustained viral load suppression was 25% for those who had 50% to 60% adherence, increasing linearly to 73% for those who had 90% to 100% adherence.

Implication

Although maximal adherence to NNRTI–based therapy is optimal, it often leads to sustained viral suppression at moderate levels of adherence.

—The Editors

comes is important. Thus, measurements of medication adherence that are both practical and validated are urgently needed. However, to date, researchers have not established a "gold standard" for measuring HAART adherence, and the various tools currently available, which include patient self-reports, clinician assessments, pill counts, measurements of plasma drug levels, and medication event monitoring systems, are not feasible for wide use outside of focused cohorts or randomized, clinical studies. Pharmacy refill or claim data are relatively simple to collect and have been validated with data on electronic medication monitor adherence (18), viral suppression or viral rebound after suppression (19, 20), drug resistance (6), and death (8–10). Pharmacy records are also reliable and valid indicators of actual patient adherence (21). One way to validate pharmacy data measures is to define their association with outcomes in a real-world setting.

To evaluate the relationship between adherence and viral suppression with NNRTI–based HAART, we measured adherence by using pharmacy claims and assessed virologic responses in HIV-1–infected adults who were enrolled in a large HIV and AIDS disease management program in South Africa.

METHODS

Data Sources

We evaluated records from HIV-1–infected adults enrolled in Aid for AIDS, a private-sector disease management program available to beneficiaries of contracted medical insurance funds (subsidized by employers) in southern Africa. Patient data and pharmacy claims have been recorded by Aid for AIDS since June 1998 and have been described in detail elsewhere (9). In brief, baseline demographic and clinical data are recorded with the patient's permission in the Aid for AIDS database on application to the program. Acceptance is subject to confirmation of HIV-1 infection and proof of eligibility. Once enrolled, patients who have a $CD4^+$ T-cell count less than 0.350×10^9 cells/L on 2 occasions or who have an AIDS-defining condition are eligible for HAART. Patients' medical insurance funds authorize reimbursement of HAART expenditure, which is subject to receipt of a HAART prescription from their physician and review and approval of the prescription by the Aid for AIDS clinical staff in accordance with prespecified clinical guidelines (22). Highly active antiretroviral therapy is dispensed in monthly increments to patients at a pharmacy of the patient's choice or via a confidential mail-order pharmacy. For reimbursement, a claim is submitted to the patient's health insurance fund. Each claim contains information about the dispensation date, specific medication regimen, and quantity supplied. All claims received (>95%) are reimbursed without any patient copayment.

Study Participants

We included all Aid for AIDS participants who met the following criteria: 1) qualified for and claimed at least 1 month of NNRTI–based HAART between January 1998 and March 2003, 2) were 18 years of age or older at HAART initiation, 3) had no indication of previous HAART in their medical records that were provided by the medical practitioner or attending physician, 4) did not have HIV-1 RNA levels less than 400 copies/mL before HAART initiation, and 5) had at least 1 viral load measurement recorded between 30 and 365 days after initiating HAART. For 1 secondary analysis (viral suppression at first measurement within prespecified time strata), we did not apply the last inclusion criterion.

Measurement of Plasma HIV-1 RNA Levels

The frequency and timing of viral load measurements were performed in pathology laboratories at the discretion of the treating physician. Physicians were requested to use the same laboratory for follow-up viral load measurements, but the actual assay used to measure viral load in each laboratory was not recorded.

Operational Definitions, Outcome Measures, and Exploratory Variables

We expressed pharmacy claim adherence as a percentage and calculated it as the number of months with HAART claims submitted divided by the number of complete months from HAART initiation to death, withdrawal from the Aid for AIDS program, or study end (1 September 2004), with the result multiplied by 100. We categorized patients into 7 groups on the basis of calculated pharmacy claim adherence: 1) less than 50%, 2) 50% to 59%, 3) 60% to 69%, 4) 70% to 79%, 5) 80% to 89%, 6) 90% to 99%, and 7) 100%. We defined adherence strata in increments of 10% a priori. We included patients who had less than 50% adherence in a single stratum because of the small sample size. Our primary outcome was the proportion of patients achieving viral suppression, defined as an

HIV-1 RNA level less than 400 copies/mL, at all measurements from 1 month after HAART initiation until the end of follow-up. We also measured the proportion of patients achieving viral suppression at their first viral load measurement in predefined 6-month strata (3 to 9 months, 9 to 15 months, 15 to 21 months, and 21 to 27 months). We investigated age, sex, race, baseline $CD4^+$ T-cell count, specific NNRTI prescribed, date of HAART initiation, and baseline plasma HIV-1 RNA levels in relation to pharmacy claim adherence and viral suppression in univariate and multivariate analyses.

We performed additional analyses for the end points of time to viral suppression (HIV-1 RNA level <400 copies/mL) and time to viral load rebound (HIV-1 RNA level >400 copies/mL) for patients who achieved initial viral suppression. In these analyses, we censored patients who switched to protease inhibitor–based therapy at the time of the therapy change, with the assumption that suppression status at this time was similar to that at their last viral load measurement.

Statistical Analysis

We assessed differences in baseline characteristics with 2-sample Student *t*-tests (continuous variables) and chi-square tests (categorical variables). We calculated the mean absolute increase in the proportion of patients achieving sustained viral suppression, per 10% increase in pharmacy claim adherence, by variance-weighted, least-squares regression (adherence modeled as categorical). To do this, we used sustained viral suppression as a binary-coded, dependent variable among patients with at least 50% adherence. We used Kaplan–Meier plots and log-rank tests to examine survival by strata of medication adherence. We used Cox proportional hazards regression to model the individual and simultaneous effects of baseline variables and medication adherence on time to viral suppression or failure. We used plots of $-\log[-\log(\text{survival})]$ against log(analysis time) and analysis of scaled Schoenfeld residuals to assess the proportionality assumption (data not shown). We included all available variables a priori in multivariate models and stratified them into discrete categories as follows: viral suppression (>400 copies/mL or <400 copies/mL), sex (male or female), race (black or other), HIV-1 RNA level (>5 $\log_{10}$ copies/mL or <5 $\log_{10}$ copies/mL), HAART regimen (efavirenz- or nevirapine-based), and date of HAART initiation (in 4 calendar year strata). All *P* values that we report are exact and 2-tailed; a value less than 0.05 is considered statistically significant. We performed statistical analyses by using Stata, version 8.0 (StataCorp, College Station, Texas).

Regulatory Approvals

This study was approved by the University of Cape Town Research Ethics Committee and by the Aid for AIDS Clinical Advisory Committee and Board, Cape Town, South Africa, and by the Johns Hopkins Bloomberg School of Public Health's Committee on Human Research, Baltimore, Maryland.

Role of the Funding Source

This study was funded by the National Institute of Allergy and Infectious Diseases, National Institutes of Health. The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit this manuscript for publication.

RESULTS

We identified 2821 patients who met all inclusion criteria; of whom, 1822 (64.6%) received efavirenz-based regimens and 999 (35.4%) received nevirapine-based regimens. The mean age at HAART initiation was 37.0 years (SD, 7.8), 1775 patients (62.9%) were women, and 2734 patients (96.9%) were black Africans (**Table 1**). The median follow-up period was 2.2 years (interquartile range, 1.7 to 2.7 years), and the median frequency of viral load measurement was 1.2 measurements per year (interquartile range, 0.7 to 1.7 measurements per year). For viral load measurements less than 400 copies/mL (5513 [75.6%] of 7290 total measurements), 65.9% were recorded as less than 50 copies/mL, 22.1% as less than 400 copies/mL, and 11.9% as between 50 and 400 copies/mL. The median $CD4^+$ T-cell counts at HAART initiation for men and women were 0.130×10^9 cells/L (interquartile range, 0.56 to 0.211×10^9 cells/L) and 0.157×10^9 cells/L (interquartile range, 0.69 to 0.236×10^9 cells/L), respectively ($P = 0.002$). The median HIV-1 RNA levels at HAART initiation for men and women were 5.1 $\log_{10}$ copies/mL (interquartile range, 4.6 to 5.6 $\log_{10}$ copies/mL) and 5.2 $\log_{10}$ copies/mL (interquartile range, 4.7 to 5.6 $\log_{10}$ copies/mL), respectively ($P = 0.184$).

We identified a statistically significant dose–response relationship between viral load suppression and pharmacy claim adherence across all adherence strata. Rates of sustained viral suppression in the 7 adherence strata were 13% (41 of 325 patients), 25% (51 of 202 patients), 39% (78 of 200 patients), 45% (116 of 258 patients), 59% (287 of 489 patients), 69% (241 of 350 patients), and 73% (725 of 997 patients), respectively (**Table 1** and **Figure 1**). Thus, every 10% increase in adherence beyond 50% was associated with a mean absolute increase of 0.10 in the proportion of patients achieving sustained viral suppression. In pairwise comparisons, each stratum of increased adherence had significantly ($P < 0.004$) higher rates of sustained viral suppression than those of the preceding stratum, except for the comparisons of 100% vs. 90% to 99% adherence ($P = 0.168$) and 60% to 69% vs. 70% to 79% adherence ($P = 0.20$). Similarly, pharmacy claim adherence, modeled as a continuous variable among patients with adherence greater than 50%, was significantly associated with the odds of achieving persistent viral suppression ($P < 0.001$). When we examined substrata within the adherence stratum of less than 50% (for example, 40% to

Table 1. **Baseline Characteristics of Study Population according to Achievement of Sustained Virologic Suppression***

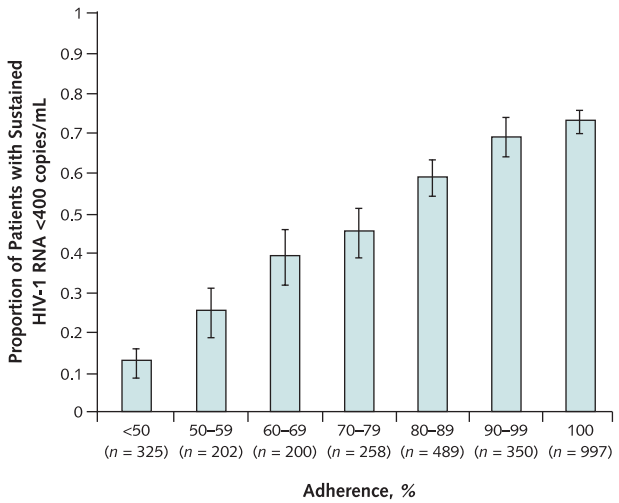
Variable	Patients with Sustained Virologic Suppression (*n* = 1539)†	Patients without Sustained Virologic Suppression (*n* = 1282)	Total Patients (*n* = 2821)	*P* Value‡
Mean age (SD), *y*	37.2 (7.9)	36.7 (7.7)	37.0 (7.8)	0.052
Sex, *n* (%)				0.045
Male	545 (35.4)	501 (39.1)	1046 (37.1)	
Female	994 (64.6)	781 (60.9)	1775 (62.9)	
Race, *n* (%)				0.012
Black	1480 (96.2)	1254 (97.8)	2734 (96.9)	
Other	59 (3.8)	28 (2.2)	87 (3.1)	
Baseline CD4$^+$ T-cell count, *n* (%)				<0.001
≤0.50 × 10^9 cells/L	286 (18.6)	299 (23.3)	585 (20.7)	
0.51–0.20 × 10^9 cells/L	698 (45.3)	602 (47.0)	1300 (46.1)	
>0.20 × 10^9 cells/L	555 (36.1)	381 (29.7)	936 (33.2)	
Baseline viral load, *n* (%)				<0.001
≤10^5 copies/mL	711 (46.2)	445 (34.7)	1156 (41.0)	
>10^5 copies/mL	828 (53.8)	837 (65.3)	1665 (59.0)	
NNRTI therapy, *n* (%)				<0.001
Efavirenz	1056 (68.6)	766 (59.8)	1822 (64.6)	
Nevirapine	483 (31.4)	516 (40.2)	999 (35.4)	
NRTI, *n* (%)				<0.001
3TC + ZDV	1228 (79.8)	962 (75.0)	2190 (77.6)	
3TC + d4T	56 (3.6)	56 (1.9)	80 (2.8)	
d4T + ddI	246 (16.0)	277 (21.6)	523 (18.5)	
ddI + ZDV	9 (0.6)	19 (1.5)	28 (1.0)	
Date of HAART initiation, *n* (%)				<0.001
1998–2000	21 (1.4)	36 (2.8)	57 (2.0)	
2001	503 (32.7)	582 (45.4)	1085 (38.5)	
2002	917 (59.6)	596 (46.5)	1513 (53.6)	
2003	98 (6.4)	68 (5.3)	166 (5.9)	
Pharmacy claim adherence, *n* (%)				<0.001
<50%	41 (2.7)	284 (22.1)	325 (11.5)	
50–59%	51 (3.3)	151 (11.8)	202 (7.2)	
60–69%	78 (5.1)	122 (9.5)	200 (7.1)	
70–79%	116 (7.5)	142 (11.1)	258 (9.2)	
80–89%	287 (18.7)	202 (15.8)	489 (17.3)	
90–99%	241 (15.7)	109 (8.5)	350 (12.4)	
100%	725 (47.1)	272 (21.2)	997 (35.3)	

* 3TC = lamivudine; d4T = stavudine; ddI = didanosine; HAART = highly active antiretroviral therapy; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; ZDV = zidovudine.
† Defined as <400 copies/mL at all measured time points during follow-up.
‡ Based on the chi-square test comparing patients who achieved sustained virologic suppression with those who did not.

49% adherence), we found a similar dose–response pattern, but this finding was limited by small sample size. We found a similar dose–response pattern, with viral suppression rates consistently more than 70%, in patients with pharmacy claim adherence rates of 80% or more when we measured the outcome as viral suppression (<400 copies/mL) at the first viral load measurement within 4 prespecified time strata after HAART initiation rather than viral suppression at all time points throughout follow-up (**Figure 2**).

Statistically significant variables associated with shorter time to viral suppression in multivariate analyses were female sex (hazard ratio, 1.17 [95% CI, 1.06 to 1.28]), baseline viral load of 10^5 copies/mL or less (hazard ratio, 1.28 [CI, 1.18 to 1.40]), use of efavirenz versus nevirapine (hazard ratio, 1.20 [CI, 1.10 to 1.32]), and high pharmacy claim adherence (hazard ratio, 3.79 [CI, 3.13 to 4.58], comparing 100% vs. <50% adherence) (**Table 2**). All higher pharmacy claim adherence groups had statistically significantly shorter time to viral suppression than the group with less than 50% adherence, and patients with 100% pharmacy claim adherence had significantly shorter time to suppression than groups with less than 90% adherence. When we modeled pharmacy claim adherence as a continuous variable, each 10% increase in adherence beyond 50% was associated with a hazard ratio of 1.19 (CI,

Figure 1. **Proportion of patients at each level of pharmacy claim adherence to nonnucleoside reverse transcriptase inhibitor–based highly active antiretroviral therapy with sustained viral suppression less than 400 copies/mL.**



The error bars represent 95% CIs around the estimate of the respective proportions based on a binomial probability distribution and using the sample sizes listed.

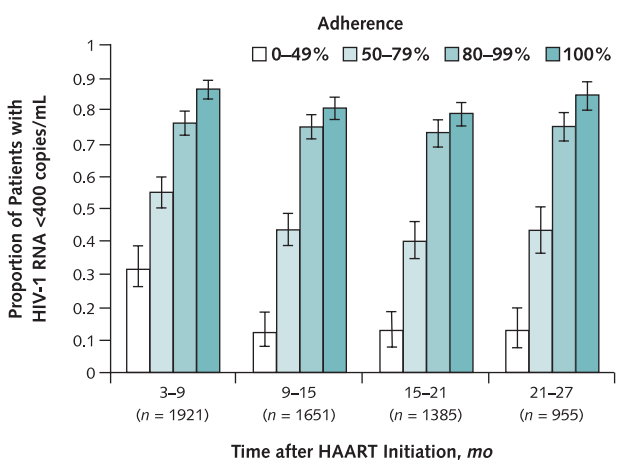
1.15 to 1.23) for time to viral suppression of less than 400 copies/mL. This hazard ratio increased to 1.25 (CI, 1.22 to 1.28) when we restricted adherence to the first 6 months of follow-up among a subset of patients (n = 2436 [86.4%]) with available data.

Statistically significant pretherapy baseline multivariate predictors of shorter time to virologic failure (viral load >400 copies/mL) after previous suppression included low $CD4^+$ T-cell counts (hazard ratio, 1.60 [CI, 1.22 to 2.10] for ≤50 vs. >200 cells/μL), viral load of more than 10^5 copies/mL (hazard ratio, 1.39 [CI, 0.14 to 1.70]), use of nevirapine (hazard ratio, 1.43 [CI, 1.16 to 1.77]), later date of HAART initiation (hazard ratio, 1.43 [CI, 1.16 to 1.77] for patients who started therapy after vs. before 1 January 2002), and low pharmacy claim adherence (hazard ratio, 10.78 [CI, 7.69 to 15.12], for <50% vs. 100% adherence) (**Table 2**). Increased pharmacy claim adherence was associated with longer time to failure in all strata, except in the 90% to 99% adherence stratum versus the 100% adherence stratum, for which we saw no difference in time to failure. Pharmacy claim adherence of 90% or more was associated with a statistically significantly longer time to failure compared with all adherence strata less than 90% (**Figure 3**). When we modeled pharmacy claim adherence as a continuous variable, each 10% decrease in adherence to 50% was associated with a hazard ratio of 1.58 (CI, 1.48 to 1.69) for time to virologic failure (**Table 2**, inverse of final cell). To assess the possibility of bias from differential frequency of viral load measurement, we examined this variable in strata of pharmacy claim adherence and sustained viral suppression (**Appendix Table**, available at www.annals.org). Patients in all groups with sustained viral suppression received fewer viral load measurements ($P < 0.001$ for global association); however, patients in higher pharmacy claim adherence groups had significantly more viral load measurements per year than those in lower adherence groups ($P < 0.001$; nonparametric test for trend). In a multivariate analysis, an increase in frequency of 1 viral load measurement per year was associated with a hazard ratio of 1.06 (CI, 0.998 to 1.13) for faster time to initial viral suppression and a hazard ratio of 1.79 (CI, 1.51 to 2.12) for faster time to subsequent failure. Inclusion of this variable in multivariate analyses had no effect on associations with time to suppression, but it mildly strengthened the association between pharmacy claim adherence and time to failure.

DISCUSSION

Our data suggest that increased adherence to NNRTI–based HAART, as measured by pharmacy claims, is associated with improved virologic outcomes at all levels of adherence greater than 50%. This relationship remains when virologic success is measured as sustained viral suppression throughout follow-up, time to first viral suppression (<400 copies/mL), or time to virologic failure (>400 copies/mL) after initial suppression. For each 10% increase in pharmacy claim adherence beyond 50%, one can expect an additional 10% of persons in an HIV-1–infected population to maintain complete viral suppression over a me-

Figure 2. **Pharmacy claim adherence to nonnucleoside reverse transcriptase inhibitor–based highly active antiretroviral therapy (*HAART*) and viral suppression less than 400 copies/mL within specified time strata after HAART initiation.**



For patients with >1 viral load measurement within each time stratum, only the first qualifying measurement was included in this analysis. The error bars represent 95% CIs around the estimate of the respective proportions based on a binomial probability distribution and using the sample sizes listed.

Table 2. **Adjusted Associations between Patient Characteristics and Time to Viral Load Suppression and Time to Subsequent Virologic Failure***

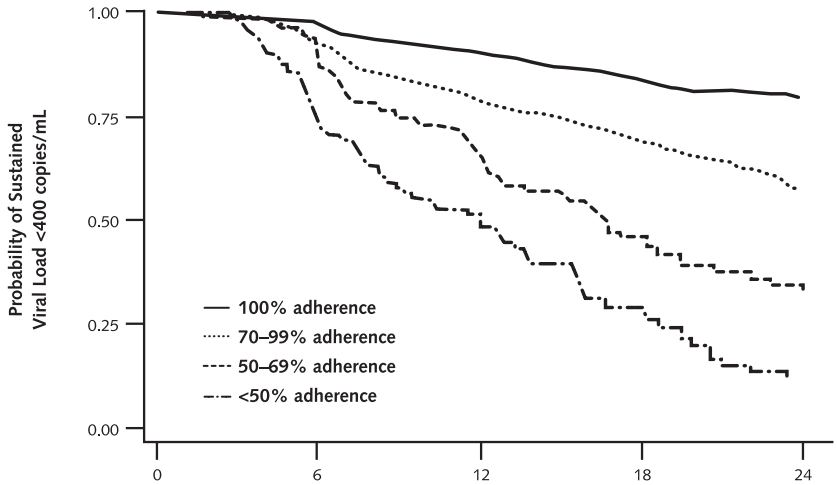
Variable	Predictors of Time to Viral Suppression (n = 2821)		Predictors of Time to Subsequent Virologic Failure (n = 1579)	
	Univariate HR (95% CI)	Multivariate HR (95% CI)†	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age (per 10 y)	1.04 (0.98–1.10)	1.04 (0.98–1.10)	0.86 (0.76–0.98)	0.91 (0.80–1.04)
Sex				
Male	1.00	1.00	1.00	1.00
Female	1.20 (1.10–1.31)	1.17 (1.06–1.28)	1.01 (0.82–1.23)	1.17 (0.95–1.44)
Race				
Black	0.84 (0.66–1.06)	0.90 (0.71–1.15)	1.50 (0.71–3.16)	1.17 (0.55–2.49)
Other	1.00	1.00	1.00	1.00
Baseline CD4$^+$ T-cell count				
$\leq 0.50 \times 10^9$ cells/L	1.00	1.00	1.53 (1.18–1.99)	1.60 (1.22–2.10)
$0.51–0.20 \times 10^9$ cells/L	1.06 (0.94–1.18)	1.03 (0.92–1.15)	1.27 (1.02–1.59)	1.18 (0.94–1.48)
$>0.20 \times 10^9$ cells/L	1.16 (1.03–1.31)	1.07 (0.92–1.18)	1.00	1.00
Baseline viral load				
$\leq 10^5$ copies/mL	1.29 (1.19–1.41)	1.28 (1.18–1.40)	1.00	1.00
$>10^5$ copies/mL	1.00	1.00	1.37 (1.13–1.67)	1.39 (1.14–1.70)
NNRTI				
Efavirenz	1.19 (1.09–1.30)	1.20 (1.10–1.32)	1.00	1.00
Nevirapine	1.00	1.00	1.28 (1.05–1.55)	1.43 (1.16–1.75)
Date of HAART initiation				
1998–2000	0.88 (0.64–1.22)	1.01 (0.73–1.40)	1.73 (1.05–2.85)	1.33 (0.80–2.21)
2001	1.00	1.00	1.00	1.00
2002	1.22 (1.12–1.34)	1.09 (0.99–1.20)	1.03 (0.84–1.27)	1.41 (1.13–1.75)
2003	1.18 (0.98–1.42)	0.81 (0.66–0.99)	1.83 (1.12–3.00)	4.63 (2.69–7.94)
Pharmacy claim adherence‡				
<50%	1.00	1.00	8.27 (6.07–11.27)	10.78 (7.69–15.12)
50–59%	1.65 (1.28–2.12)	1.63 (1.27–2.10)	5.11 (3.56–7.34)	6.59 (4.52–9.63)
60–69%	2.17 (1.71–2.75)	2.16 (1.70–2.75)	4.24 (2.99–5.99)	5.24 (3.64–7.54)
70–79%	2.34 (1.87–2.93)	2.42 (1.93–3.03)	2.81 (1.99–3.96)	3.45 (2.41–4.96)
80–89%	2.90 (2.38–3.54)	2.84 (2.33–3.47)	1.81 (1.34–2.46)	2.20 (1.59–3.03)
90–99%	3.38 (2.75–4.16)	3.45 (2.80–4.24)	0.81 (0.55–1.18)	0.97 (0.65–1.45)
100%	3.78 (3.14–4.55)	3.79 (3.13–4.58)	1.00	1.00
Pharmacy claim adherence (per 10% increase)§	1.19 (1.16–1.23)	1.19 (1.15–1.23)	0.66 (0.62–0.71)	0.63 (0.59–0.68)

* Viral load suppression is defined as <400 copies/mL. HAART = highly active antiretroviral therapy; HR = hazard ratio; NNRTI = nonnucleoside reverse transcriptase inhibitor.
† Adjusted for all other variables in the table.
‡ As measured by pharmacy claims.
§ Restricted to patients with >50% adherence (n = 2496); in multivariate analysis, other variables were adjusted for adherence by strata, not as a continuous variable.

dian of 2.2 years (**Figure 1**); a 19% (CI, 15% to 23%) increase in the hazard of achieving first-time viral suppression; and a 37% (CI, 32% to 41%) decrease in the hazard of virologic failure, given initial viral suppression (**Table 2**). Our study therefore documents a dose–response relationship between NNRTI–based HAART adherence, as measured by pharmacy claims, and viral suppression in HIV-1–infected patients.

Our findings show that NNRTI–based regimens often lead to viral suppression even at moderate levels of adherence. For example, more than one half of patients in our study who had 80% to 89% adherence documented by pharmacy claims achieved 100% viral suppression. These data corroborate previous results from a randomized, controlled trial (23), indicating greater viral suppression with NNRTI therapy than with early protease therapy. They also confirm findings from small studies conducted in Italy (15) and the United States (16, 17) that found higher rates of viral suppression with NNRTI than with unboosted protease inhibitor therapy in patients with the same levels of HAART adherence. However, pharmacy refill and claim adherence is probably an estimate of maximum possible individual adherence and might overestimate the actual adherence because patients may not take all claimed medica-

Figure 3. **Kaplan–Meier plots of patients with sustained HIV-1 RNA less than 400 copies/mL after initial viral suppression according to levels of pharmacy claim adherence.**



Patients at risk, *n*					
100% adherent	917	816	585	345	161
70–99% adherent	411	351	243	144	68
50–69% adherent	162	136	81	44	18
<50% adherent	89	64	37	19	7
Total	1579	1367	946	552	254

tions. Therefore, our measures of adherence are conservatively biased. More reliable viral suppression with NNRTI regimens than with unboosted protease inhibitor regimens at modest levels of adherence may be due to improved potency or extended half-life of NNRTIs (23–26).

In addition, our study found that efavirenz-based regimens led to higher rates of sustained virologic suppression, faster time to viral suppression, and slower time to viral rebound than nevirapine-based regimens after adjustment for adherence and other baseline variables. These latter findings are in agreement with those of a meta-analysis by Bartlett and colleagues (27) that also indicated superior virologic responses to efavirenz versus nevirapine. In that meta-analysis, 47% of patients who received any NNRTI, including efavirenz, versus 38% who received NNRTIs other than efavirenz had HIV-1 RNA levels less than 50 copies/mL at 48 weeks. Also, the authors of a recent observational study from the Antiretroviral Therapy Cohort Collaboration (28) found that patients who started therapy with efavirenz-based regimens were more likely than patients who started therapy with nevirapine-based regimens to have suppressed HIV-1 RNA levels by 6 months. The study also found that the adjusted hazard ratio for all-cause mortality for the nevirapine group was 2.28 (CI, 1.20 to 4.36) during the first 6 months. A major limitation of the analysis was its failure to account for adherence to treatment. In contrast, our data differ from findings from the 2 Non-Nucleoside trial in which Van Leth and colleagues (29) showed that nevirapine- and efavirenz-based HAART had similar efficacy (viral load <50 copies/mL at 24 weeks). The study, however, did not statistically exclude the possibility that virologic outcomes with nevirapine may be inferior to those with efavirenz. Our findings are particularly important for sub-Saharan Africa, where nevirapine is a component of the most commonly used first-line HAART regimen. Our findings may reflect the true superiority of efavirenz-based HAART or, alternatively, may result from underlying unmeasured confounding factors (for example, prescribing patterns, drug toxicity, and drug interaction between nevirapine and rifampin). Further research is needed to elucidate the mechanism of these differences in virologic outcomes between efavirenz- and nevirapine-based HAART.

Our data add to the results of the studies mentioned by clearly demonstrating that increased adherence to NNRTI–based HAART is strongly associated with improved virologic outcomes in a linear dose–response relationship. Furthermore, our time-to-event analyses suggest that moderate levels of adherence (70% to 90%) to NNRTIs often lead to viral suppression and are not associated with maximum rates of resistance, as is the case for protease inhibitor–based HAART (6, 17), and that time to virologic failure after initial suppression begins to increase at any level of NNRTI adherence less than 90%. In this regard, our data suggest that there is no threshold below

which decreased adherence to NNRTI–based HAART is benign.

In a multivariable analysis, we found that pretherapy $CD4^+$ T-cell counts less than 0.50×10^9 cells/L were associated with a greater risk for subsequent virologic failure, independent of other factors. These findings are in agreement with results from other studies (30, 31) but may nevertheless reflect unmeasured confounding factors associated with lower $CD4^+$ T-cell counts and thus with advanced HIV disease. The fact that the relationship between adherence and virologic outcome persisted despite adjustment for $CD4^+$ T-cell count suggests that this relationship is not explained by poor access, adherence among the most ill, or both. A low baseline $CD4^+$ T-cell count may be a marker of virologic or immunologic factors, such as increased quasi-species diversity, which in turn may generate drug-resistant HIV-1 variants or lower HIV-specific host immunity (31, 32).

Our study has several important clinical and public health implications. First, concern exists that the low genetic barrier (1 single-step mutation) of the NNRTIs may result in the rapid selection of resistance in patients with moderate to low levels of adherence (33, 34). For that reason, some clinicians suggest that NNRTIs should be avoided in patients who are expected to have less than 95% adherence. The results of our study and another (16) argue against this. Indeed, our data suggest that NNRTI–based regimens may be an appropriate alternative to protease inhibitor–based regimens in areas in which adherence between 70% to 94% is expected. Nevertheless, individuals and populations who receive NNRTI–based HAART should benefit from increased adherence regardless of existing adherence patterns.

Second, our results suggest that good clinical outcomes can be achieved in routine clinical practice even without perfect adherence. In addition, more than 60% of patients in our cohort maintained pharmacy claim adherence greater than 80% and had corresponding high rates of viral suppression over a median follow-up of 2.2 years. These data corroborate similar findings (35) in other resource-limited settings and argue that concerns of suboptimal adherence among patients in such settings should not delay expansion of access to HAART. Of note, in our study, patients did not receive adherence-support mechanisms. Although delaying treatment to ameliorate modifiable barriers to adherence is important, failure to treat individuals because they may not achieve perfect adherence (36) inevitably leads to disease progression and the potential for increased morbidity and death. Also, failure to initiate therapy may risk substantial immunologic progression, which, as shown in our study, can increase the risk for subsequent virologic failure. The dramatic dose–response pattern between adherence and viral suppression and the reasonable rates of suppression achieved at moderate levels of adherence (**Figure 1**) support the recommendations to treat all eligible HIV-1–infected individuals and to encourage maximum adherence with each patient (37, 38).

Our data confirm that pharmacy data measures are an appropriate population-level method to monitor adherence in resource-limited settings. Our study sample included patients enrolled in a privately managed insurance program. Only 18% of South Africans, and an even lower proportion of persons in other developing countries, have private medical insurance (39). Although our study sample may not generalize to all South Africans, our results argue for further assessment of pharmacy data to evaluate HAART adherence in public-sector programs. For example, the total proportion of person-months in which the drug was dispensed to program participants could be used to assess the overall adequacy of adherence within the program.

Our study has several limitations. First, it provides no evidence that pharmacy claim data reflect the number of pills taken correctly by a patient. Claim data may underestimate adherence if patients acquire their medications from other sources and do not submit the claims. As discussed earlier, however, claims will more likely overestimate actual adherence because patients may not take all of their claimed medications. However, other studies have found that pharmacy records correlate well with other adherence behaviors, such as appointment keeping and medication consumption (21); electronic monitors (18); drug resistance (6); viral load suppression or rebound (19, 20); and survival (8–10). One may reasonably assume that patients would not continue to refill a prescription (or, in this case, to claim medication) without intending to adhere (40). The dose–response relationship between adherence and viral suppression found in our study suggests that pharmacy claims may be appropriately used as a program-level measure of HAART adherence, regardless of whether pharmacy claims directly correlate with consumption.

Second, because adherence data were reported from pharmacies only in aggregate form, we could not measure individual adherence in a time-dependent fashion. As such, patient adherence may be misclassified because adherence at the time of initial virologic suppression or failure might not be the same as that at the end of the study. This concern is greatest for our time-to-event analyses in which patient adherence would ideally be classified in an ongoing fashion rather than at the end of the study. These concerns, however, would be expected to dilute any true dose–response relationship toward the null of no association. Thus the relationship between adherence and virologic response may be even stronger than that seen in our analysis, as suggested by the statistically significant association between adherence and time to suppression when adherence was measured during only the first 6 months of therapy.

Finally, our findings are subject to "reverse causation" because patients who experience poor clinical outcomes due to viral nonsuppression may subsequently stop taking their medication.

In summary, this analysis of data from a South African private-sector program suggests that increased adherence to NNRTI–based HAART regimens, as measured by pharmacy claims, is associated with improved virologic outcome in all strata of adherence greater than 50% in a linear dose–response pattern. More than 60% of patients in this setting maintained pharmacy claim adherence greater than 80% and had corresponding high rates of viral suppression over a median follow-up of 2.2 years. The linear dose–response relationship is true in a resource-limited setting using a very simple measure of adherence and persists regardless of whether virologic outcome is measured as sustained viral suppression, time to suppression, or time to subsequent virologic failure. Nonnucleoside reverse transcriptase inhibitors often lead to viral suppression at moderate adherence levels; however, maximum NNRTI adherence should be encouraged for all patients regardless of existing adherence patterns.

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Appendix Table. **Frequency of Viral Load Measurements per Year***

Adherence	Patients with Sustained Virologic Suppression (n = 1539)	Patients without Sustained Virologic Suppression (n = 1282)	Total Patients (n = 2821)	P Value†
<50% (n = 325)	0.61 (0.40–0.90)	1.02 (0.74–1.49)	0.97 (0.67–1.46)	<0.001
50–59% (n = 202)	0.91 (0.46–1.47)	1.10 (0.76–1.75)	1.08 (0.69–1.68)	0.028
60–69% (n = 200)	0.93 (0.46–1.35)	1.20 (0.89–1.71)	1.11 (0.66–1.56)	<0.001
70–79% (n = 258)	0.85 (0.56–1.22)	1.47 (0.93–2.06)	1.14 (0.70–1.76)	<0.001
80–89% (n = 489)	1.05 (0.67–1.55)	1.39 (1.02–1.90)	1.21 (0.84–1.69)	<0.001
90–99% (n = 350)	1.06 (0.66–1.49)	1.51 (0.95–1.93)	1.19 (0.74–1.68)	<0.001
100% (n = 997)	1.18 (0.66–1.63)	1.32 (1.00–1.91)	1.23 (0.77–1.69)	<0.001
Total	1.08 (0.63–1.55)	1.24 (0.88–1.81)	1.17 (0.74–1.65)	<0.001

* Values are expressed as medians (interquartile ranges).
† Wilcoxon rank-sum test.