Association between Adherence to Antiretroviral Therapy and Human Immunodeficiency Virus Drug Resistance

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Nonadherence to highly active antiretroviral therapy (HAART) is a major cause of human immunodeficiency virus (HIV) drug resistance; however the level of nonadherence associated with the greatest risk of resistance is unknown. Beginning in February 2000, 195 patients at the Johns Hopkins Outpatient Center (Baltimore, MD) who were receiving HAART and who had HIV loads of <500 copies/mL were recruited into a cohort study and observed for 1 year. At each visit, adherence to HAART was assessed and plasma samples were obtained and stored for resistance testing, if indicated. The overall incidence of viral rebound with clinically significant resistance was 14.5 cases per 100 person-years. By multivariate Cox proportional hazards regression, a cumulative adherence of 70%–89%, a CD4 cell nadir of <200 cells/μL, and the missing of a scheduled clinic visit in the past month were independently associated with an increased hazard of viral rebound with clinically significant resistance. Clinicians and patients must set high adherence goals to avoid the development of resistance.

Since it became available in 1996, the use of HAART to treat HIV infection has led to decreases in AIDS-related mortality rates in the developed world and to increases in the number of persons living with HIV infection [1, 2]. For HIV-infected individuals, drug resistance is a major concern, but it is unknown whether resistance is an inevitable consequence of long-term HAART. Nonadherence to therapy is a major cause of drug resistance. As proposed by Friedland and Williams [3], the relationship is thought to be "bell shaped," such that complete adherence and total nonadherence to HAART are associated with low probabilities of resistance, whereas intermediate levels of adherence increase the risk of resistance. Although the level of adherence associated with the highest risk of resistance is unknown, it has been suggested that only marginally suboptimal adherence can lead to resistance [4].

It is common for individuals taking HAART to miss doses [5]. However, few studies have examined the effect of long-term nonadherence to antiretroviral therapy (ART) on the development of drug resistance. To address this, we conducted a cohort study of patients receiving HIV care and HAART at a large urban HIV clinic in Baltimore, Maryland.

METHODS

Study design. In February 2000, a cohort study was initiated at the Moore Clinic, an outpatient HIV clinic of the Johns Hopkins AIDS Service in Baltimore. Approval to conduct the study was obtained from the Investigational Review Board. Participants who dem-

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onstrated viral suppression after initiating HAART were recruited and observed over time. Study visits were scheduled to coincide with clinic appointments to maximize participation. At each visit, ART adherence was assessed, and plasma samples were obtained and stored for genotypic resistance testing, as indicated. Participants were reimbursed $15 per study visit and were observed for 1 year. Medical records were abstracted to obtain data on ART history, virus loads, CD4 cell counts, genotypic resistance, and clinic visit attendance.

Recruitment and follow-up. Patients were recruited from February through December 2000. To improve participation, posters describing the study were displayed in the clinic, and clinicians were briefed on the study before and during the recruitment period. Interested patients were referred to the General Clinical Research Center (GCRC), which is adjacent to the clinic. Study visits were also conducted at the GCRC.

To maximize the chance that resistance that developed during the study was incident rather than prevalent, eligibility required (1) current use of HAART, (2) a virus load of <500 copies/mL, (3) no documentation of major mutations associated with ART, and (4) no previous virologic failure, defined as 2 consecutive virus loads of ⩾500 copies/mL while receiving HAART. Treatment experience before receipt of HAART, discontinuation and reinitiation of HAART for reasons other than virologic failure, and regimen changes did not prohibit participation. In addition to regimens specified by the Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* at the time (28 January 2000) [6], the regimen of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus abacavir was also classified as HAART. Tenofovir disproxil fumarate was categorized as an NRTI for the purpose of this study. Patients had to be ⩾18 years old, had to receive HIV care at the Moore Clinic, and had to provide informed consent.

ART adherence. The ART adherence instrument was modeled after the Adult AIDS Clinical Trials Group questionnaire [7] and supplemented with pictures of specific antiretrovirals [8]. Persons who had difficulty identifying their medications were asked to describe pill colors and shapes before subsequent adherence questions were administered. Information was also obtained on taking ART doses late (defined as ⩾2 h after the scheduled dosing time), adhering to food restrictions, and methods used to improve adherence.

Adherence to a regimen was approximated by the proportion of doses taken in the past 3 days, according to the formula $[P - M]/P$, where P and M represent the number of doses prescribed and missed, respectively. Specifically, $P = 3[p_1 + p_2 + \ldots + p_d]$ and $M = m_1 + m_2 + \ldots + m_d$, where d represents the number of drugs in a regimen, p_d represents the number of times each drug was taken per day, and m_d represents the number of missed doses of each drug in the past 3 days. At each visit v, cumulative 3-day adherence was estimated according to the formula, $[(P_1 + P_2 + \ldots + P_v) - (M_1 + M_2 + \ldots + M_v)] / [P_1 + P_2 + \ldots + P_v]$.

Main study outcome. The main outcome was time from viral suppression to rebound with clinically significant resistance. Viral suppression was defined as the first virus load of <500 copies/mL after the initiation of HAART. On the basis of medical chart data, the time of viral suppression was estimated by extrapolation, assuming a linear decrease in the virus load on the log scale between consecutive measurements bracketing the point when an individual achieved a virus load of <500 copies/mL.

Genotypic resistance testing was performed by Quest Diagnostics (Baltimore, MD), which conducts routine resistance testing for the Moore Clinic, and results were interpreted by an expert. The expert was an experienced HIV clinician and researcher, was blinded to all data except the genotype report, and sometimes supplemented or confirmed his interpretation using the Stanford algorithm [9]. The expert indicated the mutations associated with no, low-, intermediate, or high-level resistance to 16 antiretroviral agents approved by the US Food and Drug Administration. Intermediate and high-level resistance to a drug was deemed clinically significant such that the expert would be less likely to use that drug in a subsequent regimen.

Statistical methods. Baseline demographic characteristics of and ART received by adherent and nonadherent participants were examined. Time from viral suppression to rebound with clinically significant resistance was described by Kaplan-Meier survival methods using staggered entry. A participant entered the analysis on the date of the most recent documentation (relative to enrollment) of a virus load of <500 copies/mL. Failure was defined as the date a participant was shown to have viral rebound with clinically significant resistance. Subjects were censored at the end of the study (1 year after enrollment) or earlier if their clinician discontinued ART, they stopped ART on their own and did not develop clinically significant resistance, did not return for HIV care for 6 months, or died.

To assess the associations between nonadherence and other factors on viral rebound with clinically significant resistance, we used Cox proportional hazards regression with time-dependent covariates. Cumulative adherence and missing a scheduled clinic visit were lagged 1 visit to assure that they preceded the outcome of interest. The relative hazard (RH) and 95% CIs for covariates were estimated. Factors associated with viral rebound with resistance on univariate analysis ($P < .20$) were entered into multivariate models. The likelihood ratio test was used on nested models to determine covariates for the final model.

RESULTS

Recruitment. From February through December 2000, 364 patients were identified as being eligible for the study. A total of 310 patients (85%) completed ⩾1 scheduled appointment with their clinician during the recruitment period. Of these, 199 (64%) were referred to the GCRC by their clinician, and 195 (63%) were recruited into the study, for a total of 1188 visits. Participants contributed a median of 7 visits (interquartile range [IQR], 5–9 visits), and the median time between study visits was 49 days (IQR, 41–77 days).

Baseline demographic characteristics and ART adherence. At baseline, 39 participants (20%) reported missing ⩾1 dose of ART in the previous 3 days (table 1). Adherent and nonadherent participants were similar at baseline with respect to sex, education, employment, whether they had their own residence, whether they lived with others, whether they had dependents, and whether they had health insurance. Although not statistically significant, nonadherent participants tended to be younger, to be African American, and to have a lower income; were less likely to have acquired HIV through homosexual contact; and were less likely to have participated in other HIV research.

At baseline, 79 participants (41%) were receiving protease inhibitor (PI)–based regimens, 78 (40%) were receiving nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based regimens, 20 (10%) were receiving PI- and NNRTI-containing regimens, 10 (5%) were receiving NRTI-only regimens, and 8 (4%) were receiving regimens containing NNRTIs and PIs only. Although the regimens prescribed to nonadherent and adherent individuals contained similar numbers of antiretroviral agents, nonadherent participants had fewer prescriptions and lower pill burdens. Individuals who were nonadherent at baseline were more likely to miss ART doses during follow-up. Eighty-eight subjects (45%) reported missing ART doses at some follow-up visits but complete adherence at others. Cumulative adherence was classified as 100%, 90%–99%, 80%–89%, 70%–79%, 60%–

Table 1. Baseline demographic and antiretroviral therapy (ART) data, by adherence, for 195 participants receiving HIV care at the Moore Clinic (Baltimore, MD) who had a virus load of <500 copies/mL at the time of study enrollment.

Variable	Baseline ART adherence in the past 3 days: Missed ART dose(s) (n = 39)	Baseline ART adherence in the past 3 days: Did not miss any doses (n = 156)	P[a]
Demographic characteristic			
Age at enrollment, median years (IQR)	42.2 (36.2–46.9)	43.1 (37.6–48.2)	.140
African American race	32 (82.1)	112 (71.8)	.192
Annual income of <$10,000	27 (69.2)	87 (55.8)	.127
HIV infection risk factor			
Homosexual contact	6 (15.4)	47 (30.1)	.108[b]
Heterosexual contact	18 (46.2)	49 (31.4)	
Injection drug use	15 (38.5)	58 (37.2)	
Unknown	0 (0)	2 (1.3)	
Previously participated in an HIV research study	14 (35.9)	76 (48.7)	.151
ART data			
Median no. of agents in regimen (IQR)	3 (3–3)	3 (3–4)	.691
Median no. of unique prescriptions[c] in regimen (IQR)	2 (2–3)	3 (2–3)	.045
Median no. of pills per day (IQR)	8 (5–12)	10.5 (7–14)	.092
Took ART dose(s) late	13 (33.3)	48 (30.8)	.757
Followed meal requirements[d]	18 (46.2)	76 (48.7)	.774
Felt uncomfortable taking ART doses around others	12 (30.8)	47 (30.1)	.938
Missed ART dose(s) during follow-up[e]	32 (84.2)	73 (47.7)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] Student's t test was used for normally distributed, continuous data; Kruskal-Wallis test (allowing ties) was used for non–normally distributed, continuous data; and Pearson χ^2 test or Fisher's exact test (cell size less than 5) was used for categorical data.

[b] Significance tests were conducted among individuals with a known HIV risk category only.

[c] Unique no. of pills in a regimen.

[d] Compared with individuals who did not follow meal requirements or who did not have meal requirements.

[e] Among 38 nonadherent subjects and 153 adherent subjects at baseline who completed ⩾1 follow-up visit.

69%, and <60% of doses taken; 717 (60%), 256 (22%), 103 (9%), 63 (5%), 26 (2%), 23 (2%) person-visits were observed for each of these categories, respectively.

Time from viral suppression to resistance. Figure 1 shows Kaplan-Meier estimates for time from viral suppression to rebound with clinically significant resistance. The median time between viral suppression and study enrollment was 1.05 years (IQR, 0.38–2.50 years). Of the 195 participants enrolled, 28 (14%) developed clinically significant resistance during the study, 129 (66%) had complete follow-up and never developed clinically significant resistance, and 38 (19%) had incomplete follow-up. Reasons for censoring included discontinuation of ART by the clinician (14 patients), discontinuation of ART by a patient without resistance at the time of viral rebound (9 patients), loss to follow-up (5 patients), death (6 patients), transfer of care to other sites (3 patients), and incarceration (1 patient). Clinicians discontinued ART for 3 subjects because of toxicity and for 11 patients who were no longer felt to have indications for treatment. Participants contributed 195.09 person-years of follow-up; those censored early contributed a median of 4 visits (IQR, 2–5 visits).

Table 2 shows the findings of Cox univariate analysis of factors associated with viral rebound with clinically significant resistance. Participants who were employed or returned to work during the study were less likely to have viral rebound with resistance, whereas those with lower income were more likely to experience viral rebound with resistance. Individuals who began receiving HAART after their CD4 cell count had decreased to <200 cells/μL were more likely to have viral rebound with resistance than were those who began receiving HAART at an earlier stage.

Cumulative adherence of 70%–89% was strongly associated with an increased hazard of viral rebound with clinically significant resistance (RH, 3.40; 95% CI, 1.61–7.20; $P = .001$), compared with cumulative adherence of ⩾90% and <70%. We did not observe clinically significant resistance among individuals with cumulative adherence of <60%. Among those with cumulative adherence of 100%, 90%–99%, 80%–89%, and <70%, we observed 12, 5, 6, 4, and 1 events among 124.9, 36.8, 16.4, 8.9, and 8.1 person-years of observation, respectively. The incidences of viral rebound with clinically significant resistance were 9.6, 13.6, 36.6, 44.9, and 12.3 cases per 100 person-years, respectively. A plot of unadjusted incidence rates and 95% CIs for each cumulative adherence stratum suggested a "bell-shaped" relationship (figure 2), although we could not rule out other relationships, because few patients reported lower cumulative adherence.

Subjects reported recently taking ART doses late at 351 study visits (30%), but this was not significantly associated with viral rebound with clinically significant resistance. In addition, failure to adhere to food restrictions and higher pill burden were not associated with resistance in our study sample. Individuals who had recently missed a scheduled clinic visit were more likely to have viral rebound with clinically significant resistance ($P = .015$). Participants who had difficulty identifying their ART, which was noted at 86 visits (7%), were more likely to experience viral rebound with resistance ($P = .011$). Subjects who identified methods that helped them remember to take ART doses were somewhat less likely to develop resistance ($P = .120$); however, only 7 participants reported having no such method during the study.

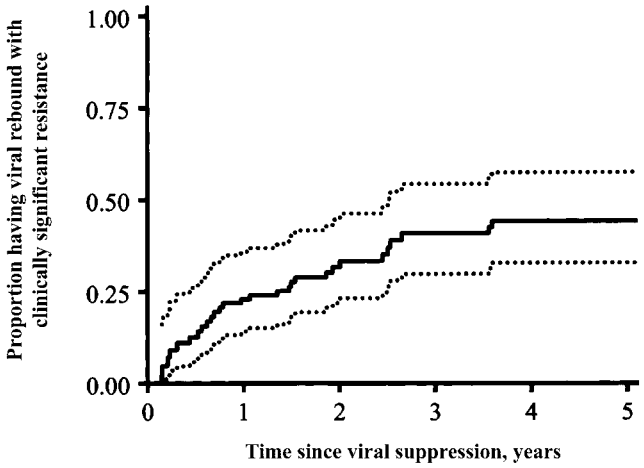

Figure 1. Kaplan-Meier survival estimate and 95% confidence bands for time from viral suppression to rebound with clinically significant resistance for 195 participants receiving HIV care at the Moore Clinic (Baltimore, MD).

By multivariate Cox proportional hazards regression, a cumulative adherence of 70%–89% remained strongly associated with viral rebound with clinically significant resistance, compared with cumulative adherence of ⩾90% and <70%, after adjusting for nadir CD4 cell count and the recent missing of scheduled clinic visits (adjusted RH, 2.91; 95% CI, 1.37–6.20; $P = .005$).

Patterns of genotypic resistance. The most common RT mutations were K103N ($n = 16$) and M184V ($n = 13$). Primary protease mutations found were D30N ($n = 3$) and L90M ($n = 2$). Seven (25%) of 28 patients who developed clinically significant resistance had resistance only to NRTIs, 10 (36%) had isolated NNRTI resistance, 6 (21%) had NRTI and NNRTI resistance, 3 (11%) had NNRTI and PI resistance, and 1 (4%) had resistance to all 3 drug classes. Twenty-seven patients (96%) were infected with virus that had resistance to ⩾1 drug in their HAART regimen.

DISCUSSION

This study indicated that HAART adherence of 70%–89% was strongly associated with viral rebound with clinically significant

Table 2. Factors associated with time from viral suppression to rebound with clinically significant resistance among 195 participants receiving HIV care at the Moore Clinic (Baltimore, MD).

Factor	Unadjusted RH (95% CI)	*P*	Multivariate adjusted RH (95% CI)	*P*
Demographic characteristic				
African American race	2.62 (0.85–8.07)	.092	…	…
Employed[a]	0.36 (0.14–0.95)	.039	…	…
Lives with others	2.58 (0.79–8.40)	.115	…	…
Annual income of <$10,000	2.51 (1.03–6.12)	.042	…	…
Ever received ART from an HIV research study	0.38 (0.09–1.56)	.181	…	…
Clinical characteristic				
Treatment naive	0.50 (0.22–1.14)	.099	…	…
Received ⩾2 unique regimens[b] before HAART	1.94 (0.96–3.93)	.066	…	…
Nadir CD4 cell count of <200 cells/μL before HAART	4.18 (1.28–13.69)	.018	3.66 (1.05–12.75)	.042
Highest $\log_{10}$ virus load of >5.0 before HAART	1.77 (0.78–4.01)	.171	…	…
Cumulative adherence, % doses taken[a]				
100%	1.0 (reference)	…	1.0 (reference)	…
90%–99%	1.35 (0.48–3.78)	.566	1.24 (0.44–3.51)	.690
80%–89%	3.14 (1.23–8.04)	.017	2.71 (1.02–7.19)	.045
70%–79%	5.01 (1.62–15.51)	.005	3.60 (1.15–11.23)	.027
0%–69%[c]	1.26 (0.21–7.62)	.805	0.75 (0.15–3.83)	.732
Other adherence factors				
Previously took ART doses late[a,d]	1.39 (0.67–2.89)	.378	…	…
High pill burden[e]	0.73 (0.34–1.55)	.408	…	…
Missed a scheduled clinic visit in the past 30 days[a]	2.63 (1.21–5.74)	.015	2.40 (1.13–5.09)	.023
Previously unable to identify all pills prescribed during ART adherence assessment	3.05 (1.29–7.23)	.011	…	…

NOTE. ART, antiretroviral therapy; RH, relative hazard.

[a] Lagged 1 visit and modeled as a time-dependent covariate.

[b] Participants had previously received ⩾2 different combinations of ART before the HAART they were prescribed when they were eligible for the study.

[c] No viral rebound with clinically significant resistance observed when cumulative adherence was <60%.

[d] Since baseline.

[e] At least 10 pills per day.

resistance. Our data support the "bell-shaped" model proposed by Friedland and Williams [3] and also demonstrate that self-reported adherence data collected longitudinally correlate well with incident HIV drug resistance. Although patients tend to overestimate their adherence to treatment [10], methods such as provider estimation, pill counts, and use of pharmacy records and electronic devices also have their shortcomings [11]. Self-reported adherence is the most feasible method and can be replicated by clinic staff who routinely assess ART adherence in their patients.

There are several advantages of examining cumulative versus recent adherence as a predictor of resistance. Although virus load correlates well with recent nonadherence [12], drug resistance is a consequence of continual nonadherence, which the cumulative measure approximates. In addition, the cumulative adherence measure becomes more robust over time, and, thus, it is more representative of a subject's overall adherence to HAART. However, this is not the case for individuals who develop resistance early during follow-up and complete fewer study visits. Because it is based on the total number of HAART doses prescribed, the cumulative adherence measure is not affected by regimen changes that might have occurred; however, specific agents missed are not captured.

Twelve participants developed clinically significant resistance despite having a 100% cumulative adherence. Although 3 patients reported nonadherence at the visit when they were found to have clinically significant resistance, this was not captured, because cumulative adherence was lagged. Response bias may have also contributed to this apparent discrepancy if adherence was reported more accurately among respondents who reported missed doses [13]. Misclassification could have occurred if participants who reported perfect adherence were more adherent during the days preceding clinic and study visits but less adherent earlier [14]. Although we could not rule out these biases,

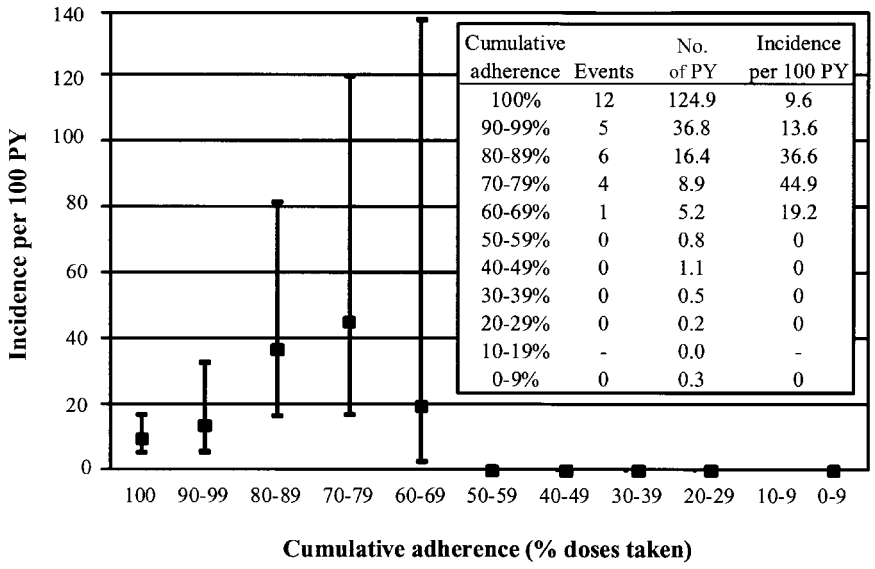

Figure 2. Unadjusted incidence rates and 95% CIs for viral rebound with clinically significant resistance, by cumulative 3-day adherence (percentage of doses taken), among 195 participants receiving HIV care at the Moore Clinic (Baltimore, MD). PY, person-years.

we did observe that participants who developed resistance despite reporting 100% adherence had fewer visits (median, 2.5 visits; IQR, 2–4.5 visits) than did those who developed resistance and reported nonadherence (median, 5 visits; IQR, 3.5–5.5 visits) and those who did not develop resistance (median, 6 visits; IQR, 5–8 visits). These differences, which were statistically significant ($P < .001$, by Kruskal-Wallis test), highlight the limitation of the cumulative adherence measure.

Because recent adherence to ART had greater influence on cumulative adherence earlier rather than later in the study, we lagged cumulative adherence to avoid detection bias, because resistance testing was contingent on the virus load being ⩾1000 copies/mL and virus load was strongly related to recent adherence. Lagging also established temporality between cumulative adherence and viral rebound with clinically significant resistance. In fact, a cumulative adherence of 70%–89% was still predictive of future resistance when lagged by 2 visits (RH, 3.01; 95% CI, 1.24–7.34; $P = .015$).

By creating a plasma repository, we eliminated the interval between identification of viral rebound and return to the clinic for resistance testing. Although the latter approach would be standard practice in routine patient care, it would result in a bias in the epidemiologic study setting if the reasons that patients did not return for testing were the same as those that caused them to have viral rebound and be indicated for resistance testing.

Recently missing a scheduled clinic visit and a nadir CD4 cell count of <200 cells/μL, which have been shown to be associated with virologic failure in this study population [15], were also associated with viral rebound with resistance. Although a lower nadir CD4 cell count may be associated with higher probability of resistance due to increased viral replication during advanced disease, participants with lower nadir CD4 cell counts may have sought HIV care late and may not have been prepared to begin receiving HAART. Limited sample size prevented us from detecting smaller effects of other forms of nonadherence, such as adherence to food restrictions and taking doses late. Given few observations at lower levels of cumulative adherence, we were not able to determine the extent that resistance develops among individuals with a rate of adherence of <60%.

Most providers would halt therapy if patients reported very low adherence. Therefore, in most clinical settings, it may not be possible to study the adherence-resistance relationship at very low levels of adherence. We argue that it would be unethical to observe individuals reporting nonadherence unless it was assured that they understood the consequences and efforts were made to improve adherence. For patients who cannot understand the long-term consequences of nonadherence, clinicians will have to be creative in explaining the importance of preventing resistance. Ultimately, patient adherence depends on acceptance of and belief in HAART and the clinician [16]. Other important factors include psychiatric comorbidity [17] and concurrent alcohol [18] and illicit drug use [19]. In our study, we also collected information on illicit drug use; its effect on the development of resistance will be presented in a separate analysis.

Previous studies found that fewer drug resistance mutations were present among patients with lower adherence rates [4, 12, 20]. Small sample size and absence of long-term follow-up data limited inferences that could be drawn from these investigations. Our longitudinal study design and multiple adherence

assessments allowed us to establish temporality between ART adherence and the development of HIV drug resistance. Because we studied individuals who demonstrated viral suppression and had no prior evidence of resistance or virologic failure, we were able to increase the likelihood that resistance identified during the study was causally associated. Some participants may have had underlying resistance, because 58% were treatment experienced before receiving HAART. However, 27 of 28 participants who developed resistance were infected with virus that was resistant to drugs included in their current regimens. One person was taking zidovudine, lamivudine, and nelfinavir as his initial regimen but had viral rebound with the T69N mutation, which conferred resistance to zalcitabine. Because relapse of injection drug use was the presumed cause of treatment failure, we cannot rule out acquisition of this mutation through needle sharing.

One question that arises is whether the risk of resistance after nonadherence is reversible. If a patient adheres poorly to his or her regimen for 1 month and then adheres completely for the next 11 months, is the risk of resistance similar to that for someone who adheres perfectly for all 12 months? This has important implications for the construction of the cumulative adherence measure such that one might give less or even no weight to earlier compared to recent assessed adherence. If the risk is reversible, then there is hope for clinicians and patients as they work together to explore new ways to improve adherence.

Our data suggest that missing 11%–30% of HAART doses after achieving viral suppression is associated with the greatest risk of viral rebound with clinically significant resistance. These data support Wainberg and Friedland's [21] suggestion that missing 1 dose in 5 leads to ART resistance. Recently missing a scheduled clinic visit also predicted subsequent viral rebound with resistance, indicating the need for clinic staff to assess the underlying reasons for missed appointments and to find ways to improve clinic attendance rates. Our findings emphasize the need to set high adherence goals to achieve a durable response to HAART and to preserve options for future therapy.

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