High levels of adherence do not prevent accumulation of HIV drug resistance mutations

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Objectives: To assess the relationship between development of antiretroviral drug resistance and adherence by measured treatment duration, virologic suppression, and the rate of accumulating new drug resistance mutations at different levels of adherence.

Methods: Adherence was measured with unannounced pill counts performed at the participant's usual place of residence in a prospective cohort of HIV-positive urban poor individuals. Two genotypic resistance tests separated by 6 months (G1 and G2) were obtained in individuals on a stable regimen and with detectable viremia (> 50 copies/ml). The primary resistance outcome was the number of new HIV antiretroviral drug resistance mutations occurring over the 6 months between G1 and G2.

Results: High levels of adherence were closely associated with greater time on treatment ($P < 0.0001$) and viral suppression ($P < 0.0001$) in 148 individuals. In a subset of 57 patients with a plasma viral load > 50 copies/ml on stable therapy, the accumulation of new drug resistance mutations was positively associated with the duration of prior treatment ($P = 0.03$) and pill count adherence ($P = 0.002$). Assuming fully suppressed individuals (< 50 copies/ml) do not develop resistance, it was estimated that 23% of all drug resistance occurs in the top quintile of adherence (92–100%), and over 50% of all drug resistance mutations occur in the top two quintiles of adherence (79–100%).

Conclusion: Increasing rates of viral suppression at high levels of adherence is balanced by increasing rates of drug resistance among viremic patients. Exceptionally high levels of adherence will not prevent population levels of drug resistance.

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Introduction

Recent studies have suggested a high level of antiretroviral drug resistance among both recently and chronically HIV-infected patients [1–3]. Non-adherence to therapy is closely associated with incomplete viral suppression [4–6] and disease progression [7–9] and is thought to be a risk factor for the development of drug resistance [10–13]. Studies with objective measures of adherence indicate that average adherence is 70% [4–6,14–17].

The relationship between adherence to HIV combination antiretroviral therapy (HAART) and drug resistance, however, has not yet been clearly defined. Support for the stance that non-adherence promotes drug resistance is based on observations with protease inhibitor (PI) monotherapy and on studies with incompletely characterized adherence measures to combination therapy based on non-nucleoside reverse transcriptase inhibitor drugs (NNRTI) [18,19]. More recent cross-sectional data suggest that resistance actually occurs at moderate to high levels of adherence [4,20–22]. These cross-sectional studies are limited by the assumption that adherence over the measured period is temporally related to the observed drug-resistant mutations.

The present study examines whether HIV antiretroviral adherence is prospectively and temporally related to the development of new drug resistance mutations. Adherence and drug resistance was investigated in a prospective cohort of HIV-positive urban poor individuals with objective measurements of adherence to antiretroviral therapy. Among those with incomplete viral suppression, it was assumed that the development of drug resistance was a function of treatment duration and the rate of accumulation of resistance mutations. It was also assumed that those with viral suppression to < 50 copies/ml did not develop drug resistance. Based on these assumptions, the study examined (i) the relationship between adherence and the duration of therapy, (ii) the relationship between adherence and rates of viral suppression to < 50 copies/ml and (iii) the rate of accumulation of new drug resistance mutations in the HIV-1 protease and reverse transcriptase gene with incomplete viral suppression (viral load > 50 copies/ml) while on therapy.

Adherence has been assessed in various ways. Unannounced pill counts at the participant's usual place of residence [23] has a close association with concurrent viral load [4], electronic pill cap adherence assessment [23], and progression to AIDS [7]. Unlike electronic pill cap assessment, however, unannounced pill count does not interfere with the use of 'Mediset' pillbox organizers and does not require multiple devices to measure adherence to all antiretroviral medications. Furthermore, it has the advantage over clinic-based pill count because it results in a more complete count of pills in the participant's possession; the unannounced nature of the visit makes it more difficult for participants to empty their pill bottles (or 'pill dump') prior to the assessment.

Methods

Study design and subject recruitment

Participants were identified from the Research on Access to Care in the Homeless (REACH) cohort, a systematic sample of HIV-positive adults recruited from San Francisco homeless shelters, free meal programs and low-income single-room-occupancy hotels [24, 25]. The REACH cohort recruited 330 HIV-positive subjects between July 1996 and April 2000. The University of California San Francisco Committee on Human Subjects Research approved all procedures.

Adherence monitoring component

Beginning in January 1998, all participants taking three or more antiretroviral medications were invited to participate in adherence monitoring. Every 3 to 6 weeks over a 12-month period, on an unannounced day as previously described [23], pill counts were conducted on all antiretroviral medications at the subject's usual place of residence [4].

Treatment duration over 12 months

Treatment duration over 12 months was assessed with a structured questionnaire administered monthly and confirmed with pill count visits.

Specimen collection

Phlebotomy was conducted monthly. Plasma was processed and stored at $-40^{\circ}C$ within 6 h of collection. HIV viral loads levels were determined monthly, and specimens for genotyping were selected as described below. CD4 cell count was determined at the baseline adherence-monitoring visit.

Eligibility for genotyping

The genotyping strategy was designed to identify the rate of accumulation of new drug resistance mutations over a fixed interval in patients on stable therapy with detectable viremia. Two specimens (G1, G2) separated by a 6-month interval were selected for genotyping the individuals who had (i) at least 1 month of stable combination antiretroviral therapy prior to G1, (ii) no change in antiretroviral regimen between G1 and G2, (iii) a viral load of > 50 copies/ml at G1 and G2, and (iv) a minimum of 3 months of adherence monitoring between the two specimens. These criteria were defined in order to determine the rate of acquiring new drug resistance mutations on stable therapy in

those with detectable viremia and well-characterized adherence between genotype tests.

Viral load and genotyping

HIV-1 viral load was measured using the HIV-1 Amplicor Monitor Version 1.0 ultrasensitive assay (Roche Molecular Systems, Alameda, California, USA). Genotypic HIV drug resistance was determined from plasma-associated HIV RNA using the TruGene HIV-1 Resistance Kit according to the manufacturer's recommendations (Visible Genetics, Toronto, Canada) with the following modification. Plasma samples were thawed, and 500 μl was centrifuged at 22 000 × *g* for 1 h at 4°C. HIV RNA was extracted using a commercial RNA extraction kit from the resulting 140 μl viral pellet (Qiagen, Valencia, California, USA).

The entire HIV-1 protease gene and codons 38–235 of the reverse transcriptase gene were interrogated and analyzed using Gene Objects software (Visible Genetics). Known primary and secondary antiretroviral mutations in both genes, as well as polymorphic changes compared with an HIV-1 subtype B consensus sequence, were recorded for each patient's baseline plasma sample. Primary and secondary mutations for drug resistance were defined according to the IAS-USA consensus statement [26], and the number of total drug resistance mutations was used as the primary outcome [27].

Statistical analysis

Adherence categories were defined by quintiles among all people receiving adherence monitoring. Differences in mean treatment duration during the 12-month adherence-monitoring period for each adherence quintile was tested by analysis of variance. The relationship between the accumulation of new drug resistance mutations between G1 and G2 was examined with univariate and multivariate Poisson regression using percentage adherence as a continuous measure. Total drug resistance mutations, PI mutations (primary and secondary), nucleoside analog reverse transcriptase inhibitor (NRTI) resistance mutations, NNRTI resistance mutations and mutation at codon 184 were examined as separate outcomes for subsets of people on selected regimens. The analysis controlled for viral load, CD4 cell count, time on therapy, prior mono or dual NRTI exposure, and number of drug resistance mutations at G1 to assess the independent relationship between adherence and accumulation of drug resistance in a multivariate model. All analyses were conducted with SAS (SAS Institute, Cary, North Carolina, USA).

Estimation of proportion of drug resistance by adherence strata

To estimate the population burden of new drug resistance mutations by adherence quintile over a standard calendar year of observation, the measurements of viral suppression, treatment duration, and rates of new drug resistance mutations were combined. Measured rates of viral suppression was used to determine the proportion of people with viral suppression (< 50 copies/ml). The number of months that a participant received antiretroviral therapy during the 12 months of observation was used to estimate treatment duration over a calendar year. The measured proportion of individuals with viral suppression was multiplied by the rate of accumulation drug resistance mutations and treatment duration in order to estimate total number of new drug resistance mutations in each adherence quintile over 12 months. This assumed that individuals with complete viral suppression (viral load < 50 copies/ml) do not develop drug resistance mutations [28,29].

Results

Participant characteristics

Of the 330 people followed in the cohort, 182 (54%) received at least 1 month of a three drug combination antiretroviral therapy, and 148 (81%) consented to unannounced adherence monitoring at their usual place of residence. The study sample primarily comprised people of color (56.8%), with a high proportion of injection drug users (37.2%). Most individuals were on PI-based therapy (53.4%), and many had a history of mono or dual NRTI exposure prior to the initial PI-based regimen (48.0%) (Table 1).

Participants were selected for longitudinal genotype analyses if they had two specimens with a viral load > 50 copies/ml over 6 months, no change in therapy, more than 30 days of stable therapy before the first genotype test and at least 90 days of adherence monitoring between the two genotype tests. Of the 148 people who received adherence monitoring, 42 (28%) were excluded from genotyping because their viral load was < 50 copies/ml at either G1 or G2; 25 (17%) were excluded because they discontinued therapy; six (4%) were excluded because they changed therapy between G1 and G2; 13 (9%) were excluded because of insufficient adherence data (less than 90 days covered by pill counts), and one person was excluded owing to an error in specimen handling. Of the remaining 61 eligible individuals, genotypes were obtained in 95% (116/122) of all specimens. Genotyping was obtained for both G1 and G2 in 57 (93%) individuals. Patient and regimens characteristics of the genotype subsample and adherence-monitoring sample were similar (Table 1).

Adherence and viral suppression

Median adherence in the 148 individuals over the 12-month observation period was 64.7%, and it was closely associated with mean viral load ($r = -0.54$; $P < 0.0001$); a mean viral load of < 50 copies/ml viral

Table 1. Patient and treatment characteristics.

Characteristic	Total adherence group[a]	Genotype subgroup[b]
No.	148	57
Mean age [years (SD)]	42.7 (8.8)	43.2 (7.0)
Male [% (SD)]	126 (85.1)	46 (80.7)
Non-Caucasian [% (SD)]	84 (56.8)	24 (59.6)
IDU ever [% (SD)]	55 (37.2)	24 (42.1)
Mean CD4 cell count [$\times 10^6$ cells/l (SD)	336 (223)	345 (238)
Treatment		
PI based	79 (53.4)	39 (68.4)
NNRTI based	52 (35.1)	13 (22.8)
PI–NNRTI	12 (8.1)	5 (8.8)
NRTI only[c]	5 (3.4)	0 (0.0)
Naive	15 (10.1)	4 (7.0)
Mono or dual nucleoside exposure	71 (48.0)	28 (49.1)
Mean pill count adherence (SD)	64.7 (26.6)	63.5 (24.1)

IDU, injection drug user; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor. [a]All participants receiving unannounced pill count adherence monitoring. [b]Participants selected by two genotype resistance tests 6 months apart (G1, G2) based on the following criteria: >1 month stable therapy prior to G1, viral load >50 copies/ml at G1 and G1, no change in therapy between G1 and G2, at least 3 months of adherence monitoring between G1 and G2. [c]Taking three NRTI, no Pi or NNRTI.

load was found for 37 (25%). Mean adherence in those with <50 copies/ml was 82%, compared with 58% in those with >50 copies/ml ($P<0.0001$). Mean adherence between G1 and G2 in the subset receiving genotyping was 63.5%. Other characteristics of this group are given in Table 1.

Treatment duration

The number of months of treatment across the 12 months of adherence monitoring was closely associated with adherence level. Individuals in the 0–41, 42–57, 58–78, 79–91, and 92–100% adherence quintiles received a mean of 6.4, 9.8, 10.1, 11.0, and 11.1 months of HAART, respectively ($P<0.0001$).

Prevalence of drug resistance mutations at baseline

Participants had an average of 3.2 drug resistance mutations at G1. For individual antiretroviral medication classes there were 1.0 mean primary PI mutations, 1.1 mean secondary PI mutations (n = 44), 1.0 mean NRTI mutation (n = 57), 0.77 mean NNRTI mutations (n = 18), and 0.3 mean M184V mutations (n = 43) per individual. In a multivariate Poisson regression, the number of total drug resistance mutations at G1 was positively associated with months of therapy prior to G1 ($P=0.02$) and prior mono or dual NRTI exposure ($P=0.006$).

Incidence of drug resistance mutations over 6 months

Participants who remained viremic on a stable regimen developed a mean of 0.93 new primary or secondary drug resistance mutations between G1 and G2 (0.15 per month). Of the 57 people with genotype data for G1 and G2, 22 (39%) individuals gained at least one net new mutation; 30 (52%) had no net change in drug resistance mutations, and five (9%) had a net loss of drug resistance mutations between G1 and G2.

The number of new drug resistance mutations over 6 months was significantly and positively associated with level of adherence between G1 and G2 ($P=0.004$). The number of resistance mutations was also positively associated with the number of antiretroviral treatment months (mean, 16) prior to G1 ($P=0.005$). The number of new drug resistance mutations was not associated with viral load, number of drug resistance mutations at baseline or prior NRTI exposure. Pill-count adherence remained positively associated with the number of new drug resistance mutations ($P=0.0002$) in a multivariate model including prior months of HAART, baseline CD4 cell count, baseline viral load, baseline number of drug resistance mutations, and prior mono or dual NRTI exposure (Table 2).

For specific antiretroviral drug classes, adherence was associated with accumulation of new PI drug mutations ($P<0.0001$), new primary PI drug mutations ($P<0.0001$) and new secondary PI mutations ($P=0.03$) in the 44 people receiving a PI. Adherence was not significantly associated with new NRTI resistance mutations (n = 57), new NNRTI mutations (n = 18), or M184V mutations (n = 43) in patients receiving these drugs (Table 2; Fig.1).

Estimation of proportions of drug resistance mutations by adherence strata in the treated population

In each adherence stratum, the proportion of drug resistance mutations expected over 12 months was estimated by combining the subgroup with detectable

Table 2. Predictors of new drug resistance mutations by antiretroviral class.

		Univariate		Multivariate		Best multivariate	
Outcome	Predictors[a]	Poisson coefficient	*P* value	Poisson coefficient	*P* value	Poisson coefficient	*P* value
All DRM	Adherence	1.65	0.003	2.01	0.0023	1.36	0.0197
	Log viral load at G1	0.001	0.994	0.0846	0.614	ns	
	CD4 cell count at G1	−0.0007	0.29	−0.0012	0.126	ns	
	No. mutations at G1	0.058	0.22	−0.0707	0.196	ns	
	Months of prior HAART	0.035	0.002	0.0304	0.0292	0.0303	0.0126
	Prior mono or dual ARV	0.39	0.189	0.401	0.235	ns	
Primary PI	Adherence	3.33	0.0037	3.05	0.036	2.79	0.0165
	Log viral load at G1	−0.208	0.444	−0.116	0.719	ns	
	CD4 cell count at G1	−0.0006	0.639	−0.0022	0.303	ns	
	No. mutations at G1	0.0174	0.016	0.0192	0.833	ns	
	Months of prior HAART	0.0671	0.0017	0.0561	0.035	0.0605	0.0075
	Prior mono or dual ARV	0.085	0.157	0.551	0.434	ns	
Secondary PI	Adherence	2.34	0.0434	3.09	0.02	2.34	0.0434
	Log viral load at G1	−0.059	0.83	0.036	0.9	ns	
	CD4 cell count at G1	−0.01	0.612	−0.0018	0.26	ns	
	No. mutations at G1	−0.0087	0.93	−0.0878	0.97	ns	
	Months of prior HAART	0.007	0.74	−0.001	0.97	ns	
	Prior mono or dual ARV	−0.122	0.8	0.2205	0.73	ns	
NAM	Adherence	1.73	0.229	3.63	0.06	ns	
	Log viral load at G1	0.519	0.217	1.07	0.0573	ns	
	CD4 cell count at G1	−0.0013	0.482	−0.0005	0.806	ns	
	No. mutations at G1	0.08	0.496	−0.231	0.094	ns	
	Months of prior HAART	0.075	0.011	0.095	0.024	0.075	0.011
	Prior mono or dual ARV	1.41	0.121	1.55	0.14	ns	
NNRTI	Adherence	−0.835	0.517	−0.966	0.515	ns	
	Log viral load at G1	−0.0121	0.973	0.03	0.943	ns	
	CD4 cell count at G1	0.0006	0.703	0.0011	0.51	ns	
	No. mutations at G1	−0.07	0.619	−0.153	0.381	ns	
	Months of prior HAART	0.0193	0.503	0.0325	0.31	ns	
	Prior mono or dual ARV	0.714	0.345	0.867	0.277	ns	
M184V	Adherence	0.64	0.69	1.759	0.38	ns	
	Log viral load at G1	0.12	0.79	−0.0345	0.94	ns	
	CD4 cell count at G1	−0.003	0.22	−0.005	0.17	ns	
	No. mutations at G1	−0.17	0.42	−0.1856	0.43	ns	
	Months of prior HAART	−0.012	0.73	−0.002	0.97	ns	
	Prior mono or dual ARV	−0.539	0.51	−0.2065	0.83	ns	

ns, no significant predictors; All DRM, all new drug resistance mutations; Primary PI, all new primary protease inhibitor drug resistance mutations; Secondary PI, all new secondary protease inhibitor drug resistance mutations; NAM, all new nucleoside reverse transcriptase inhibitor resistance mutations; NNRTI, all new non-nucleoside resistance reverse transcriptase inhibitor mutations; M184V, all new mutations at codon M184V consistent with lamivudine resistance; G1, genotype resistance test 1; G2, genotypic resistance test 2.

[a]Predictors. Adherence, mean pill count adherence between G1 and G2; mutations, number of drug resistance mutations; months of prior HAART, number of months of three or more drug combination antiretroviral therapy prior to G1; prior mono or dual ARV, presence or absence of single or dual nucleoside exposure prior to three or more drug combination antiretroviral therapy.

viremia (measured rate of new drug resistance mutations) and the subgroup with undetectable viremia (new drug resistance mutation rate assumed to be zero) in their observed proportions. It was estimated that, during 12 months of observation at the population level, 23% of all drug resistance mutations would occur in the 92–100% adherence stratum, compared with 30%, 15%, 20%, and 12% in the 79–91%, 58–78%, 42–57%, and 0–41% strata, respectively (Table 3).

Discussion

Our observations suggest that 23% of drug resistance mutations occur in individuals in the top quintile of adherence (92–100%), and over 50% of all drug resistance occurs in the 40% most adherent patients (79–100%). There are several components to this conclusion. First, the rate of accumulating drug resistance mutations increased with increasing adherence among patients with incomplete viral suppression. Second, individuals with high levels of adherence sustained therapy over a longer period than people with low levels of adherence. Prolonged therapy in the absence of complete viral suppression is more likely to create high-level drug resistance to multiple classes than brief periods of therapy. Third, the proportion of people with sustained viral loads < 50 copies/ml increased with improving adherence. We estimate that these

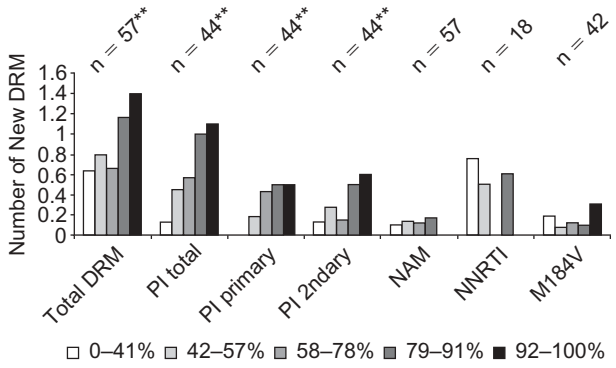

Fig. 1. Observed rates of new drug resistance mutations over 6 months in viremic patients (geometric mean > 50 copies/ml) by adherence quintile. DRM, drug resistance mutations; PI total, all protease inhibitor mutations; PI primary, primary protease inhibitor mutations; PI 2ndary, secondary protease inhibitor mutations; NAM, nucleoside analog reverse transcriptase mutations; NNRTI, non-nucleoside analog reverse transcriptase mutations; M184V, mutations associated with lamivudine. $^{**}P < 0001$ and $^{*}P < 0.01$ by Poisson regression.

phenomena combine such that the combined effect of prolonged treatment duration and more rapid accumulation of drug resistance mutations in viremic patients balances higher rates of viral suppression in highly adherent patients. The net effect at the population level is that a high proportion of drug resistance mutations are in patients with high levels of adherence.

This relationship between adherence and drug resistance was strongest for PI mutations. We did not detect a relationship between adherence and the development of NRTI mutations. This is in contrast to both our earlier report of more common NRTI resistance mutations in highly adherent patients [4] and similar findings by Kuritzkes *et al.* [22]. This discrepancy is likely to result from the fact that half of the participants in our prospective study had pre-existing NRTI resistance mutations at baseline in the setting of prior mono or dual NRTI exposure, and that the rate of subsequent NRTI mutation accumulation may be slower in variants that have already developed high-level drug resistance. Fifty-four percent of baseline NRTI resistance mutations occurred in the highest adherent quintile (data not shown) and theses individuals may be saturated with NRTI mutations at G1 [22].

We also did not see a relationship between adherence and new drug resistance mutations for NNRTI (n = 18) or the M184V mutation associated with lamivudine resistance (n = 42). We cannot exclude a relationship because of the small number of patients; however, different antiretroviral medications and codon mutations likely have different adherence–resistance relationships. Rapid development of resistance has been observed after single-dose nevirapine therapy [30] and short-course lamivudine therapy given for the prevention of mother-to-child HIV transmission [31], suggesting that resistance to these medications may occur rapidly and at low levels of adherence. These mutations are readily selected during therapy because they have potent effects on drug susceptibility compared with their effects on replicative capacity. In contrast, protease mutations are typically insufficient to abrogate PI activity when they occur as single mutations [32], and multiple mutations are associated with substantial costs to replicative capacity [33]. Our data suggest that high levels of adherence may be necessary to create sufficient drug pressure to select and maintain PI drug-resistant virus.

Our finding is consistent with several cross-sectional studies. In a previous study, our group found that HIV-1 PI drug resistance mutations were present only in individuals with 65–100% adherence, and drug resistance mutations in the reverse transcriptase gene

Table 3. Estimated numbers and proportions of new drug resistance mutations generated in the treated population over a 1-year period by adherence quintile.

Adherence quintile	Observed No. DRM/month in viremic individuals	Observed time receiving ARV (months)	Observed proportion with viremia[a]	Estimated No. new DRM/person[b]	Estimated proportion DRM[c]
0–41	0.11	6.4	0.90	0.63	0.12
42–57	0.13	9.8	0.74	0.94	0.20
58–78	0.11	10.1	0.66	0.73	0.15
79–91	0.19	11.0	0.68	1.42	0.30
92–100	0.23	11.1	0.43	1.10	0.23

DRM, drug resistance mutations; ARV, antiretroviral therapy.
[a]Viremia, mean HIV viral load > 50 copies/ml.
[b]Mean number of total DRM developing over 12 months estimated from observed rates of DRM in viremic individuals, observed treatment duration over 12 months, and observed rates of detectable viremia in the treated population (see Methods for derivation of estimate).
[c]Proportion of all DRM occurring in each quintile in the treated populations (see Methods for derivation of estimate).

were also more common in patients with higher levels of adherence [4]. In separate reports, Walsh *et al.* [20] and Howard *et al.* [34] demonstrated that the number of drug resistance mutations was associated with increasing adherence as measured with electronic medication monitors. Kuritzkes *et al.* [22] found that highly adherent patients were more likely to have baseline drug resistance. Finally, Gallego *et al.* [21] found that resistance was limited to individuals reporting $\geq 90\%$ adherence on an indinavir-based regimen. However, these cross-sectional analyses remain limited by the possibility that resistance occurred prior to adherence assessment. Our prospective analysis over a defined interval overcomes this limitation. Collectively, these findings suggest that the greatest risk for resistance is in patients with high levels of adherence and incomplete viral suppression, and this relationship is strongest for PI-based therapy.

There are several limitations to our findings. First, we measured rates of drug resistance mutations over 6 months in a selected subset of individuals on stable therapy in order to avoid changes in mutational pattern caused by starting, stopping, or changing therapy. It is possible that people who change therapy may change because of resistance. However, relatively few people (4%) changed therapy in the group we studied. Second, we assumed that individuals with a viral plasma load < 50 copies/ml did not develop drug resistance based on observations that resistance is uncommon in these individuals [28,29]. If resistance mutations do develop in such individuals, the proportion of all drug resistance at high levels of adherence would be greater than our estimates. Finally, few patients were antiretroviral drug naive and few patients received ritonavir-boosted PI therapy. Our results may not be generalizable to such patients.

These findings have important implications for the practice of using expected adherence as a criterion to determine candidacy for treatment. Based on the expectation that low levels of adherence will lead to drug resistance, current guidelines indicate that the likelihood of patient adherence should be considered in the decision to initiate antiretroviral therapy [35]. If, as we suggest, resistance does not occur more frequently in patients with low levels of adherence, trial therapy in patients who are expected not to adhere gives some patients the opportunity to prove the clinician's expectation of non-adherence mistaken and derive clinical benefit that would be otherwise withheld. Our results suggest that the resistance costs of this approach may be relatively low, especially with respect to protease resistance.

While our findings indicate that resistance is most likely to occur in individuals with high levels of adherence and detectable viremia, these findings do not suggest that low levels of adherence should be advocated in the effort to avoid drug resistance. High levels of adherence predict delayed progression to both AIDS and death [7–9]. Our findings combined with these studies suggest that levels of adherence too low to generate drug resistance are also too low to delay AIDS progression or death. Conversely, high levels of adherence, even with drug-resistant virus, will likely provide more clinical benefit than either low levels of adherence or no treatment [33,36,37]. Consequently, the goal remains for patients and providers to strive for exceptional levels of adherence both to delay progression to AIDS and death and to achieve reliable and durable viral suppression in order to limit the development of drug resistance as much as possible.

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