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Directly Administered Antiretroviral Therapy for HIV-Infected Drug Users Does Not Have an Impact on Antiretroviral Resistance:

Results From a Randomized Controlled Trial

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Abstract

Background—Directly administered antiretroviral therapy (DAART) is an effective intervention that improves clinical outcomes among HIV-infected drug users. Its effects on antiretroviral drug resistance, however, are unknown.

Methods—We conducted a community-based, prospective, randomized controlled trial of DAART compared with self-administered therapy (SAT). We performed a modified intention-to-treat analysis among 115 subjects who provided serum samples for HIV genotypic resistance testing at baseline and at follow-up. The main outcomes measures included total genotypic sensitivity score, future drug options, number of new drug resistance mutations (DRMs), and number of new major International AIDS Society (IAS) mutations.

Results—The adjusted probability of developing at least 1 new DRM did not differ between the 2 arms (SAT: 0.41 per person-year [PPY], DAART: 0.49 PPY; adjusted relative risk [RR] = 1.04; $P = 0.90$), nor did the number of new mutations (SAT: 0.76 PPY, DAART: 0.83 PPY; adjusted RR = 0.99; $P = 0.99$) or the probability of developing new major IAS new drug mutations (SAT: 0.30 PPY, DAART: 0.33 PPY; adjusted RR = 1.12; $P = 0.78$). On measures of GSS and FDO, the 2 arms also did not differ.

Conclusion—In this trial, DAART provided on-treatment virologic benefit for HIV-infected drug users without affecting the rate of development of antiretroviral medication resistance.

Keywords

adherence; HIV/AIDS; directly administered antiretroviral therapy; directly observed therapy; HIV genotypic resistance substance use disorders

HIV-infected drug users are at particular risk of poor clinical outcomes and antiretroviral medication resistance.^{1–4} Decreased access to,⁵ prescribing of,^{6–8} and inconsistent adherence

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or nonadherence to antiretroviral medications^{1,9,10} are central components of this increased risk. Because of the high prevalence of risk behaviors in this population, drug resistance mutations (DRMs) that are acquired by active drug users as a result of inconsistent adherence may be readily transmitted.³ It is thus critical to develop interventions aimed at improving access and adherence to antiretroviral medications among this population. Directly administered antiretroviral therapy (DAART) is emerging as an important strategy for improving outcomes among HIV-infected patients at risk for poor adherence.¹¹⁻¹⁸ Although DAART shows promise in improving clinical outcomes, there are no empiric data on the impact that DAART may have on the development of antiretroviral resistance.

There are limited data on the extent to which different adherence interventions may influence the risk of resistance. Inconsistent adherence and episodes of HIV suppression and viremia can lead to the development of new DRMs.¹⁹ Additionally, because of the complex shapes of modeled adherence-resistance curves, improved adherence may paradoxically lead to greater resistance.^{20,21} In one cohort, for example, 50% of all DRMs occurred among patients adhering to >80% of their doses.²² In another cohort, development of virologic rebound with a DRM was increased among those with self-reported adherence of 70% to 90%, with similar rates found in groups with >90% and <70% adherence.²³ These rates also vary with antiretroviral regimen; lamivudine, for example, exhibits maximum DRM rates at 85% to 90% adherence, whereas maximum DRMs for nelfinavir occur at 75% to 80% and at 80% to 85% for lopinavir/ritonavir.²⁴ Given the low adherence rates typically found among active drug users, DAART could potentially increase resistance rates if it were to increase adherence to these intermediately high levels but were not able to achieve full adherence.

Markov simulation models have suggested that DAART, although likely to produce improvements in morbidity and mortality rates among poorly adherent patients, would not have an impact on antiretroviral drug resistance. The authors of these models themselves admit to the uncertainties inherent in their data, however, because the models are based on scarce observational data.²⁵ Clearly, data from prospective randomized controlled trials (RCTs) are necessary.

In other analyses, we have demonstrated the short-term (6 months) benefits of DAART on virologic and immunologic outcomes in an RCT among 141 HIV-infected drug users.^{18,26} Here, we extend this analysis to determine the impact of DAART on the development of resistance.

METHODS

Study Setting and Design

The study design and DAART intervention have been described previously.^{18,26,27} Briefly, a RCT of 6 months of DAART versus self-administered therapy (SAT) was conducted among 141 drug users. Entry criteria included (1) being HIV-seropositive, (2) being eligible for and/or being prescribed highly active antiretroviral therapy (HAART), (3) living within the city of New Haven, (4) reported using heroin and/or cocaine in the previous 6 months, and (5) receiving no more than a twice-daily regimen. The study was approved by the Yale University Institutional Review Board, had a Certificate of Confidentiality, and is registered (NCT00367172; available at: www.clinicaltrials.gov).

After providing informed consent, eligible subjects were randomized at a ratio of 2:1 to DAART or SAT stratified on the following criteria: (1) antiretroviral experience, (2) problematic alcohol use, (3) baseline HIV-1 RNA level dichotomized as $\leq$ or >1000 HIV-1 copies/mL, and (4) baseline CD4⁺ T-lymphocyte count dichotomized as $\leq$ or >500 cells/ μ L.

The 2:1 design was undertaken because of the anticipated increase in refusals to participate in the DAART arm.

HIV-1 RNA level (Amplicor 1.5; Roche Diagnostic Systems, Branchburg, NJ) and CD4 lymphocyte count (FACScan; Becton-Dickinson, San Jose, CA) were collected at randomization and at 1, 3, 6, 9, and 12 months subsequent to randomization. Genotype resistance samples were processed by Quest Diagnostics. After amplification by reverse transcription polymerase chain reaction of the entire protease (to codon 99) and reverse transcriptase genes (to codon 400), sequencing was performed on an Applied Biosystems 3700 capillary sequencer, and assembly of sequenced data was done by AutoAssembler (Applied Biosystems, Foster City, CA) or Sequencher (Genecodes Corporation, Ann Arbor, MI) software. Amplification was attempted on all samples at baseline and at 6 and 12 months, regardless of viral load. Resistance results were sent to providers so that they could use the data in the clinical care of the study subjects.

Mutations listed by Quest Diagnostics were used in the analysis; the Stanford HIV Drug Resistance Database version 4.2.2 (available at: <http://hivdb.stanford.edu/>; accessed December 12, 2006) was then used for interpretation. Samples with ≤ 1000 HIV-1 copies/mL that failed to amplify were imputed to have no new resistance.²⁴ Samples with >1000 copies/mL that failed to amplify or were otherwise unavailable were considered to be missing values. Subjects with at least 1 sample at the end of 6 months were included, with the first amplifiable sample used in the analysis. Subjects with no available samples subsequent to the end of the intervention were excluded.

The 3-day AIDS Clinical Trials Group (ACTG) recall²⁸ and the visual analog scale (VAS)^{29,30} were used to assess adherence at baseline and after 6 months. Because the data were highly skewed, subjects were dichotomized into high ($\geq 80\%$) and low ($<80\%$) adherence levels. This was done based on the distribution of adherence scores in the data, recognizing that clinical benefit has been associated with adherence levels ranging from $>70\%$ to 95% .³¹⁻³³

Among the SAT subjects, antiretroviral regimen changes during the intervention period were determined by clinical chart review; among the DAART subjects, daily observed doses were recorded by the DAART specialist. These were supplemented by self-report during the quarterly interviews. The Spearman rank correlation coefficient between self-report and the chart reviews/DAART records ranged between 0.68 and 0.75.

The primary outcome of the original trial was virologic success, defined as an HIV RNA level reduction $\geq 1.0 \log_{10}$ or an HIV-1 RNA level <400 copies/mL at the end of the 6-month intervention.³⁴

Outcomes Measures

Because of cost and availability, genotypic resistance testing is the most commonly employed method for determining resistance profiles. When using database-derived algorithms, genotypic resistance is strongly correlated with phenotypic resistance and clinical outcomes.^{35,36} There currently is no single comprehensive approach to analyzing DRMs. Analysis is complicated by the fact that different drug mutations have differing degrees of clinical significance, absolutely and because of the effects that a mutation may have on another. As such, count data of the number of DRMs may not provide the most direct correlation with patient-level outcomes. Conversely, DRMs provide the most straightforward analysis and do not rely on algorithms that heavily alter the raw data. Finally, because several mutations are merely polymorphisms that do not have an impact on drug resistance, we analyzed the data

considering only major DRMs as defined by the International AIDS Society (IAS).³⁷ We therefore performed the following 4 main analyses:

1. Total genotypic sensitivity score (GSS), based on the 17 drugs currently in the Stanford HIV Drug Resistance Database version 4.2.2. This represents an average of the individual GSS for each of the 17 drugs.
2. Future drug options (FDO). This gives a measure of the number of classes and total number of antiretroviral medications to provide a summary of the future antiretroviral medications options available to a patient. We used FDO1 from Jiang et al.³⁸ In this analysis, values of $GSS_{drug} > 15$ were considered to be resistant.³⁹
3. Number of new DRMs (count data). Any DRM conferring resistance to at least 1 antiretroviral medication was counted. A similar analysis was performed counting only major IAS mutations.
4. Presence or absence of any new DRMs (binomial data). This was also performed for major IAS mutations.

The GSS and FDO presented here were constructed assuming that archiving of drug resistance detected at baseline occurred. To test the robustness of these results, we also assessed whether differences emerged when archiving of drug resistance was not assumed. For the GSS, we also constructed an alternative GSS measure that averaged the GSS for each of the drugs in a subject's current regimen. Finally, we analyzed the data restricted only to those samples taken at the immediate postintervention phlebotomy session ($n = 105$) and restricted only to the 6-month postintervention samples ($n = 103$).

Statistical Analysis

A modified intention-to-treat analysis was performed, consisting only of those subjects who were randomized to a treatment arm, accepted the intervention, and had a baseline and at least 1 subsequent genotypic measurement. All statistical analyses were implemented in SAS version 9.1.3 (SAS Institute, Cary, NC). The functional (parametric) forms of all multivariate relationships were first explored through local linear regression using Proc LOESS. These functional forms were then used in the final models on which inferences were made. For all analyses, $P < 0.05$ was considered to be statistically significant.

The major assumptions of the analyses pursued here are as follows: (1) new DRMs do not occur at HIV-1 RNA levels < 50 copies/mL; (2) when the laboratory sample is unamplifiable and the number of HIV-1 RNA copies/mL is < 1000 , no new DRMs have occurred; (3) resistance develops at a constant rate throughout the study period; and (4) previous resistance persists (archived) even when there are no detectable mutations or the participant is not viremic. For assumptions 1 and 2, there is evidence that new DRMs do, in fact, occur even when current laboratory assays are unable to amplify the HIV genotype. These DRMs occur at a lower rate, however, and the total number of new DRMs is more driven by the periods of persistent viremia.⁴⁰ For large enough sample populations, assumption 3 is reasonable. Indeed, nearly all analyses of resistance data assume a constant rate, because most parametric models depend on this.²² Most data suggest that assumption 4 is true, which is supported by the persistence of DRMs even among patients with fully suppressed viral loads and who had been off of the DRM-associated drug for > 1 year.⁴¹⁻⁴³

For the GSS and FDO, preliminary analyses indicated that rank-based or polytomous regression performed no better than dichotomized outcomes. Although they do not offer the richness of more complex measures, dichotomized outcomes provide intuitive interpretations. Total GSS was dichotomized at < 0.8 or ≥ 0.8 , with the latter meaning the genotype is at least 80% susceptible to the 17 antiretroviral medications measured. FDO was dichotomized at < 3

or ≥ 3 , with the latter meaning that the genotype is susceptible to at least 1 drug in all 3 antiretroviral medications classes measured. Multivariate relative risk (RR) regression was used to fit binomial resistance outcomes using a log-binomial model. This is similar to traditional logistic regression, except that the latter is more appropriate when there are varying follow-up times and when the event is common.^{44,45} For assessing the validity of the model, the Pearson standardized residuals and a LOESS-smoothed curve of them was plotted against the predicted values to assess for deviation from the expected mean value of 0.

For analyses of the number of new DRMs, we pursued 4 potential models: Poisson, negative binomial, zero-inflated Poisson, and 0-inflated negative binomial. We used the natural logarithm of the time, because baseline measurement is an offset. Likelihood and residual diagnostics revealed the negative binomial to model the data most effectively. Thus, we modeled count data through negative binomial log-linear regression, adjusting for time to sample to compute a rate of new DRMs.

For the analysis of the subset of participants with amplifiable virus at baseline, the model was not adjusted. This was because the heterogeneity of viral loads and number of mutations were less important in this smaller subset than they were in the general participant pool, which also included patients without a genotype at baseline.

RESULTS

Subject disposition and primary outcomes have been described previously¹⁸ and are briefly summarized here. Of the 141 subjects meeting entry criteria, 88 were randomized to DAART and 53 to SAT, and 74 (84%) of 88 of those randomized to DAART participated in the intervention (received at least 1 dose of HIV medication observed). Of the 74 subjects who initiated DAART, 51 (69%) completed the full 6-month intervention. At the end of 6 months, a significantly greater proportion of the DAART group achieved the primary outcome (70.5% vs. 54.7; $P = 0.02$). Additionally, DAART subjects demonstrated a significantly greater mean reduction in HIV-1 RNA level (-1.16 vs. -0.29 $\log_{10}$; $P = 0.03$) and mean increase in CD4 lymphocyte count ($+58.8$ vs. -24.0 cells/ μL ; $P = 0.002$).

Of the original 127 subjects who were randomized and agreed to their intervention assignment, 115 (91%) had a baseline genotype and at least 1 paired sample subsequent to the 6-month intervention. Baseline characteristics of the study population have been previously described in detail.^{18,27} Characteristics of the 115 subjects constituting this analysis are shown in Table 1. The DAART and SAT populations differed nonsignificantly with respect to median baseline CD4 count (261 vs. 384 cells/ μL ; $P = 0.16$) and median $\log_{10}$ HIV-1 RNA (3.9 vs. 2.8; $P = 0.05$). Although they did not reach statistical significance, these differences were likely attributable to differential refusal to accept DAART after randomization by healthier subjects.

Of the 230 total samples provided by the study subjects, 121 (53%) were successfully amplified and provided information on new DRMs. Among those 112 samples with HIV-1 RNA levels ≤ 400 copies/mL, 14 (13%) were amplified; among those 20 samples with HIV-1 RNA levels >400 and ≤ 1000 copies/mL, 12 (60%) were amplified; among those 98 samples with HIV-1 RNA levels >1000 copies/mL, 95 (97%) were amplified.

The median time to sample measurement after baseline was 193 (interquartile range [IQR]: 188 to 210) days; this did not vary between the 2 groups (Wilcoxon $P = 0.16$). Summaries of the susceptibility of the subject's genotype to his or her antiretroviral regimen at baseline and during the intervention are shown in Table 2. At baseline, the number of antiretroviral medications that were susceptible to the subject's virus differed between the subjects, with SAT subjects being more likely to have effective regimens ($P = 0.04$). During the course of the study, however, only 10 (22%) of SAT subjects compared with 38 (54%) of DAART subjects

switched regimens. This resulted in the finding that the susceptibility of the regimens of the 2 arms did not significantly differ subsequent to changing medications.

Primary Outcomes

The prevalence of major IAS DRMs and the drug resistance measures before and after intervention are shown in Table 3 and Figure 1. The participant population had a high burden of resistance at baseline, with 22 (19%) of 115 subjects having <80% susceptibility based on the GSS, 26 (23%) having lost at least 1 antiretroviral medications class, 61 (53%) showing at least 1 DRM, and 50 (35%) showing at least 1 IAS major DRM. These baseline resistance profiles did not, however, differ by study arm (see Table 1).

The primary outcomes comparing the development of resistance among SAT and DAART subjects are shown in Table 4. The rate of new DRMs did not differ between the 2 groups (SAT: 0.76 per person-year [PPY], DAART: 0.83 PPY; adjusted $P = 0.99$), nor did the rate of development of at least 1 new mutation (SAT: 0.41 PPY, DAART: 0.49 PPY; adjusted $P = 0.90$) or the rate of development of at least 2 new DRMs (SAT: 0.30 PPY, DAART: 0.23 PPY; adjusted $P = 0.45$). The finding of no difference was seen before and after adjusting for baseline virologic suppression <400 copies and resistance. These results also did not change when analyzing the subset of participants with amplifiable samples at baseline. In particular, among the 23 (51%) SAT and 48 (69%) DAART participants with amplifiable virus at baseline, the rate of new DRMs did not differ between the 2 groups (SAT: 0.63 PPY, DAART: 0.77 PPY; $P = 0.67$), nor did the rate of development of at least 1 new mutation (SAT: 0.35 PPY, DAART: 0.55 PPY; $P = 0.29$) or the rate of development of at least 2 new DRMs (SAT: 0.21 PPY, DAART: 0.22 PPY; $P = 0.93$).

None of the other resistance measures, adjusted for baseline HIV-1 viral level and DRMs, differed between the 2 arms (Fig. 1; see Table 4). Similar results were seen when the analysis was restricted only to those samples taken at the immediate postintervention phlebotomy ($n = 105$); an analysis restricted to those samples taken at the 6-month postintervention phlebotomy ($n = 103$) also produced the same result.

In multivariate models, the ACTG recall predicted GSS (RR = 3.0, 95% confidence interval: 1.4 to 7.4; $P = 0.02$) and the FDO (RR = 2.1, 95% confidence interval: 1.1 to 4.3; $P = 0.04$). That is, subjects reporting high adherence after intervention were 3.0 times more likely than those with low adherence to achieve a GSS ≥ 0.8 and were 2.1 times more likely to maintain susceptibility to 3 antiretroviral classes. The ACTG 3-day recall did not significantly predict the number or any of the new DRMs; the VAS did not significantly predict any of the resistance outcomes. The use of a protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) during the intervention did not predict rates of new DRMs or any of the other resistance measures.

DISCUSSION

The DAART program is a comprehensive intervention that includes daily observation of medications by a trained outreach worker who provides social support and linkage to medical and social services. There have been some concerns that in poorly adherent populations, DAART may increase adherence sufficiently to improve virologic and clinical outcomes but may concomitantly lead to increased antiretroviral resistance rates. This would occur by moving patients to an intermediate level of adherence at which resistance rates are maximized.

The results of this RCT, however, indicate that DAART can provide short-term virologic benefit while not increasing the rate of antiretroviral medication resistance among HIV-infected drug users. Although the lack of a statistically significant effect does not mean that a

real effect does not exist, this study provides assurance that DAART is possible without leading to higher levels of resistance. In keeping with results from mathematic models,²² however, it does not seem to help prevent the development of resistance.

The patient population of drug users in this study was heavily antiretroviral experienced, as evidenced by high rates of baseline resistance (see Table 1; see Fig. 1). Hence, even among highly antiretroviral medication-resistant and poorly adherent patients, DAART can improve virologic outcomes while not leading to the development of excess new resistance. Nevertheless, it is clear that DAART did not work completely for all subjects, and some subjects were unable to maintain virologic suppression and avoid drug resistance. Although this study was not designed to detect this, it is possible that certain subsets of patients on DAART have poorer resistance outcomes than they would have had on SAT. This highlights the need for DAART programs to maintain persistence in working with their clients to remain adherent and to identify clients who are not achieving desired adherence goals despite the intensive intervention.

There are several important limitations of this study that make a null finding tentative. Primary among these is that the trial was small, with analysis available for 115 subjects. Furthermore, the patient population was heterogeneous, with high variance of viral load ranges, resistance profiles, and antiretroviral regimens. Although multivariate adjustments were made to account for the known differences between the 2 groups, it is possible that several unknown variables confounded the analysis. For example, given that some of these patients were using illicit drugs, the acquisition of new resistance strains by means of needle sharing may have occurred, and we were unable to control for this possibility. Such superinfections, however, do not seem to occur as commonly as resistance developing from poor adherence.

Another factor contributing to the lack of a detected difference is confounding by different treatment regimens. It is clear that the 2 arms received significantly different antiretroviral regimens during the course of the study (see Table 2). Although in multivariate analyses, including covariates for antiretroviral regimen, the lack of a relationship persisted. It is therefore possible that certain antiretroviral regimens are differentially affected by the DAART intervention. Additionally, adherence-resistance relations differ by regimen, with the largest differences being between NNRTI and PI regimens.³² These issues would have to be evaluated in a larger trial that included a more systematic sampling of antiretroviral regimens.

Cumulative historical resistance data before the start of the study were not available. In this heavily antiretroviral-experienced and poorly adherent patient population, it is likely that archived mutations were present that were not detected because of failure to amplify or because a patient had recently switched regimens.⁴⁶ Thus, we were unable to adjust for baseline differences in DRMs that were archived, particularly among those participants who had nonamplifiable virus at baseline. This problem, however, was largely unavoidable, given restraints in time and financial resources, and the design that we used is the standard analytic approach in current investigations. In fact, recent evidence suggests that conventional assays may underestimate the prevalence of resistance by as much as 2-fold.^{47,48} As such, this is a design limitation confronted by most analyses. The RCT design likely controlled for potential differences between the 2 groups; therefore, the lack of these data did not bias our inferences. Future studies should attempt to measure resistance patterns several months before the introduction of the intervention so as to avoid this problem. They should also use newer assays that can more sensitively detect resistant virus at lower viral loads.

Even if these data were available, current genotypic methods of determining resistance challenge our ability to make inferences about the effects of the intervention. Bangsberg and colleagues⁴⁹ have argued, for example, that the relationship between adherence and resistance

to PIs is driven by the proportion of individuals who have complete suppression at each level of adherence. This is confounded, however, by the fact that resistance cannot be detected at undetectable levels. Existing data strongly suggest that the assumption of no new resistance mutations during virologic suppression is not true, although the rate is certainly decreased. This limitation is unavoidable, given current technology.

A final limitation of the study was the heterogeneity of subjects' subsequent antiretroviral regimens. Although the clinicians treating the DAART and SAT subjects were provided the resistance profiles obtained at the outset of the trial, DAART subjects tended to switch their regimens more frequently than SAT subjects. This is likely because the outreach workers detected problems in adherence and side effects more rapidly, although these data were not prospectively collected. DAART thus may improve the likelihood of better clinical management, resulting in decreased development of resistance. This RCT shows the potential benefits of the entire program; future studies should be required to parse out which specific aspects of the program are most important in conferring benefits (or harms) and affecting drug resistance.

Despite these limitations, to our knowledge, this is the largest RCT of DAART for active HIV-infected drug users with longitudinal resistance data. Although a null result does not mean that a difference does not exist, we have shown, through multiple and robust analytic approaches, that DAART likely does not lead to a clinically meaningful increase in antiretroviral resistance. Our results provide further support for DAART as a strategy to improve antiretroviral adherence among drug users who are poorly adherent. We emphasize that this study does not provide support for DAART as a coercive strategy⁵⁰ or for general patient populations that are not at risk for, or have not demonstrated, poor adherence.³⁴ Additionally, it is unclear which specific aspects of DAART are important; in post hoc multivariate analyses we have found utilization of medical and case management services to be important influences on outcomes among the DAART group.²⁷ Indeed, others have found that adherence and clinical outcomes can be greatly improved with case management services alone.⁵¹ Future prospective studies are needed to evaluate these possible impacts on adherence and determine whether further improvements to the DAART program could actually lead to decreases in antiretroviral resistance.

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FIGURE 1. Resistance measures at baseline and after intervention among SAT (n = 45) and DAART (n = 70) subjects.

TABLE 1

Baseline Characteristics of the Study Population (n = 115)

Characteristic	SAT Arm (n = 45) Value	DAART Arm (n = 70) Value	P
Age, median y (IQR)	44.9 (40.9 to 49.7)	42.5 (36.9 to 48.5)	0.05
Gender			
Female	13 (29%)	22 (31%)	0.77
Male	32 (71%)	48 (69%)	
Baseline HAART regimen			
PI only	14 (31%)	33 (47%)	0.07
NNRTI only	15 (33%)	13 (19%)	
PI plus NNRTI	6 (13%)	4 (6%)	
Triple nucleoside	3 (7%)	12 (17%)	
Off antiretroviral medications	7 (16%)	8 (11%)	
HIV-1 viral load			
≤400 copies/mL	22 (49%)	22 (31%)	0.08
>400 copies/mL	23 (51%)	48 (69%)	
Median log ₁₀ (IQR)	2.8 (1.7 to 4.4)	3.9 (2.2 to 5.1)	0.05
CD4 ⁺ T lymphocytes			
>350 cells/mL	25 (56%)	29 (41%)	0.18
≤350 cells/mL	20 (44%)	41 (59%)	
Median CD4 count, cells/mL (IQR)	384 (285 to 516)	261 (100 to 522)	0.01
Major and minor baseline DRMs			
Amplifiable genotype	23 (51%)	48 (69%)	0.08
No DRMs	24 (53%)	30 (43%)	0.55
1 to 2 DRMs	11 (24%)	22 (31%)	
>2 DRMs	10 (22%)	18 (26%)	
Major IAS baseline DRMs			
No IAS major DRMs	30 (67%)	45 (64%)	0.64
1 to 2 IAS major DRMs	9 (20%)	11 (16%)	
>2 IAS major DRMs	6 (13%)	14 (20%)	
FDOs			
<3 susceptible ARV classes	9 (20%)	17 (24%)	0.65
3 susceptible ARV classes	36 (80%)	53 (76%)	
Total GSS			
<0.8 total GSS	8 (18%)	14 (20%)	0.81
≤0.8 total GSS	37 (82%)	56 (80%)	

All values are in the form of number (%) unless otherwise specified. Reported *P* values are from the Fisher exact test for categorical variables and from the Wilcoxon rank sum test for quantitative variables.

ARV indicates antiretroviral medication.

TABLE 2**Antiretroviral Regimen Change and Susceptibility**

Characteristic	SAT Arm (n = 45) Value	DAART Arm (n = 70) Value	P
Change of regimens			
Any change of regimen	10 (22.2%)	38 (54.3%)	0.001
Addition of PI	3 (6.7%)	18 (25.7%)	0.01
Addition of NNRTI	3 (6.7%)	12 (17.1%)	0.16
No. ARVs susceptible, baseline			
≤1	11 (24.4%)	28 (40.0%)	0.04
2	5 (11.1%)	14 (20.0%)	
≥3	29 (64.4%)	28 (40.0%)	
No. ARVs susceptible, after change			
≤1	8 (17.8%)	17 (24.3%)	0.29
2	7 (15.6%)	17 (24.3%)	
≥3	30 (66.7%)	36 (51.4%)	

P values computed using exact tests.

ARV indicates antiretroviral medication.

TABLE 3

Prevalence of Major DRMs at Baseline and After Intervention

DRM	DRMs Detected at Baseline		New DRMs Detected After Intervention	
	SAT Arm (n = 45) Number (%)	DAART Arm (n = 70) Number (%)	SAT Arm (n = 45) Number (%)	DAART Arm (n = 70) Number (%)
NRTI				
M41L	3 (6.7%)	6 (8.7%)	0 (0.0%)	1 (1.4%)
E44D	1 (2.2%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
K65R	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
D67N	2 (4.4%)	4 (5.8%)	1 (2.2%)	0 (0.0%)
T69D	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
K70E/G/R	1 (2.2%)	5 (7.2%)	0 (0.0%)	0 (0.0%)
L74I/V	1 (2.2%)	4 (5.8%)	0 (0.0%)	0 (0.0%)
Y115F	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
F116Y	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
V118I	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Q151M	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
M184I/V	6 (13.3%)	14 (20.3%)	3 (6.7%)	6 (8.7%)
L210W	3 (6.7%)	4 (5.8%)	0 (0.0%)	0 (0.0%)
T215C/D/F/I	1 (2.2%)	3 (4.3%)	0 (0.0%)	0 (0.0%)
T215Y	4 (8.9%)	6 (8.7%)	0 (0.0%)	0 (0.0%)
K219E/Q	1 (2.2%)	4 (5.8%)	0 (0.0%)	0 (0.0%)
G333E	1 (2.2%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Any NRTI DRM	9 (20.0%)	18 (25.7%)	4 (8.9%)	7 (10.0%)
Total NRTI DRMs	25 (0.56 PP)	56 (0.80 PP)	4 (0.15 PPY)	8 (0.20 PPY)
PI				
L10F/I/V	3 (6.7%)	11 (15.9%)	2 (4.4%)	3 (4.3%)
K20M/R/T	3 (6.7%)	3 (4.3%)	1 (2.2%)	1 (1.4%)
L24V	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
D30N	1 (2.2%)	1 (1.4%)	1 (2.2%)	0 (0.0%)
V32I	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
L33F/V	0 (0.0%)	2 (2.9%)	1 (2.2%)	1 (1.4%)
M36I	6 (13.3%)	10 (14.5%)	1 (2.2%)	3 (4.3%)
M46I/L	1 (2.2%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
I47V	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
F53L	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
I54L/V	2 (4.4%)	5 (7.2%)	0 (0.0%)	1 (1.4%)
L63P	14 (31.1%)	22 (31.9%)	6 (13.3%)	2 (2.9%)
A71T/V	3 (6.7%)	9 (13.0%)	0 (0.0%)	0 (0.0%)
G73S	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
V77A/I/V	7 (15.6%)	8 (11.6%)	3 (6.7%)	4 (5.8%)
V82A/F/T	2 (4.4%)	4 (5.8%)	1 (2.2%)	1 (1.4%)
I84V	1 (2.2%)	3 (4.3%)	0 (0.0%)	0 (0.0%)
N88D/S	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

DRM	DRMs Detected at Baseline		New DRMs Detected After Intervention	
	SAT Arm (n = 45) Number (%)	DAART Arm (n = 70) Number (%)	SAT Arm (n = 45) Number (%)	DAART Arm (n = 70) Number (%)
L90M/L	1 (2.2%)	6 (8.7%)	0 (0.0%)	1 (1.4%)
Any PI DRM	20 (44.4%)	39 (55.7%)	10 (22.2%)	13 (18.6%)
Total PI DRMs	47 (1.04 PP)	88 (1.26 PP)	16 (0.60 PPY)	18 (0.45 PPY)
NNRTI				
A98G	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
L100I	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
K101E	0 (0.0%)	2 (2.9%)	0 (0.0%)	2 (2.9%)
K103N	6 (13.3%)	12 (17.4%)	0 (0.0%)	0 (0.0%)
K103R	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
V106A/M	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
V108I	0 (0.0%)	3 (4.3%)	0 (0.0%)	0 (0.0%)
V179D/E	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)
Y181C/I	0 (0.0%)	5 (7.2%)	0 (0.0%)	0 (0.0%)
G190A/Q/S	3 (6.7%)	3 (4.3%)	0 (0.0%)	2 (2.9%)
P225H	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
P236L	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Y318F	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Any NNRTI DRM	9 (20.0%)	17 (24.3%)	0 (0.0%)	3 (4.3%)
Total NNRTI DRMs	11 (0.24 PP)	30 (0.43 PP)	0 (0.00 PPY)	5 (0.13 PPY)

Major IAS mutations are in bold.

PP indicates per person; PPY, per person-year.

TABLE 4**Comparison of Rates of DRMs After Intervention**

Outcomes Measure	SAT Arm (n = 45) Rate* (95% CI)	DAART Arm (n = 70) Rate (95% CI)	RR[†] (95% CI)	P
Any new DRM [‡]	0.41 (0.25 to 0.68)	0.49 (0.33 to 0.71)	1.04 (0.56 to 1.95)	0.90
>1 new DRM [‡]	0.30 (0.16 to 0.56)	0.23 (0.12 to 0.43)	0.71 (0.29 to 1.73)	0.45
No. new DRMs [§]	0.76 (0.41 to 1.41)	0.83 (0.51 to 1.36)	0.99 (0.21 to 1.78)	0.99
<3 FDOI [‡]	0.34 (0.19 to 0.6)	0.51 (0.35 to 0.75)	1.45 (0.77 to 2.74)	0.25
<0.8 Total GSS [‡]	0.34 (0.19 to 0.6)	0.41 (0.27 to 0.63)	1.22 (0.6 to 2.47)	0.59
Any new major IAS DRM	0.30 (0.16 to 0.55)	0.33 (0.2 to 0.54)	1.12 (0.51 to 2.45)	0.78
No. new major IAS DRMs	0.37 (0.18 to 0.76)	0.44 (0.25 to 0.75)	1.17 (0.13 to 2.2)	0.74

All rates are in units of per person-year (PP Y).

* This is the modeled unadjusted rate.

[†] This is the modeled RR, adjusted for baseline viral load and resistance.

[‡] Modeled with log-binomial regression. Rates interpreted as probability of exhibiting the binomial outcome PPY.

[§] Modeled with negative binomial log-linear regression. Rates interpreted as number of outcomes exhibiting PPY.