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Antiretroviral Failure Despite High Levels of Adherence: Discordant Adherence–Response Relationship in Botswana

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Abstract

Background—Although adherence to antiretroviral therapy may be higher in sub-Saharan Africa, knowledge regarding the magnitude of adherence needed to maintain virological suppression in this setting is limited.

Methods—A case–control study among HIV-infected individuals initiating highly active antiretroviral therapy (HAART) in Gaborone, Botswana, was performed. Cases were randomly selected from subjects on HAART ≥6 months with plasma HIV-1 RNA levels (viral loads) >1000 copies/mL. Controls were randomly selected from subjects on HAART ≥6 months with all viral loads <400 copies/mL. HAART adherence was determined using pharmacy refill records.

Results—In total, 302 individuals were included; 57 cases were compared with 245 controls with respect to adherence levels on nonnucleoside reverse transcriptase inhibitor–based HAART. Median adherence levels, as measured using pharmacy refill patterns, were consistently high but differed among cases and controls (91%, interquartile range 83%–97% for cases vs 97%, interquartile range 91%–100% for controls, $P < 0.001$, rank-sum test). Adherence <95% was independently associated with virological failure (odds ratio 4.19, 95% confidence interval 2.2 to 8.3).

Conclusions—Very high rates of adherence were present in this setting, yet virological failure occurred nonetheless. Future work should explore other factors that might explain treatment failure in the setting of high levels of adherence.

Keywords

HIV-1; HAART; Africa; case-control study; virologic response; adherence

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INTRODUCTION

Adherence to highly active antiretroviral therapy (HAART) is important in achieving and maintaining maximal suppression of HIV replication,[1–3] immunologic response,[4,5] and survival.[6] Although a dose–response relationship between adherence and virological suppression exists, some patients with high levels of adherence to nonnucleoside reverse transcriptase inhibitor (NNRTI)–based HAART experience virological failure, whereas others with suboptimal adherence do not.[3,7] A recent study from South Africa documented relatively high virological suppression rates (80%–89%) among individuals initiating NNRTI-based HAART.[3] This finding was interpreted as indicating that NNRTI-based HAART may be more forgiving of suboptimal adherence when compared with unboosted protease inhibitors, which has been suggested by observational studies[7,8] and a randomized clinical trial[9] and which could potentially be explained by the longer half-life or greater potency of NNRTI-based regimens.[9,10] Yet in the same study, nearly 25% of patients with adherence levels of 100% experienced virological failure.[3]

The possibility that many patients globally are experiencing virological failure despite high levels of adherence to NNRTI-based HAART is cause for concern given their frequent use as initial therapy in global antiretroviral (ARV) scale-up efforts.[11–13] We therefore conducted a study in Botswana's National ARV Therapy Program specifically examining the relation between adherence and viral suppression in treatment-naive patients initiating NNRTI-based HAART.

METHODS

Study Design

This was a case–control study among treatment-naive, HIV-1–infected adults older than 18 years initiating therapy with 2 nucleoside reverse transcriptase inhibitors plus an NNRTI at the Infectious Disease Care Clinic (IDCC), a major ARV clinic in Botswana's National ARV Therapy Program. Treatment naive was defined as no record of previous ARV therapy at HAART initiation. Because Botswana National Guidelines use NNRTI-based HAARTas first-line ARV therapy, only patients initiating NNRTI-based HAART were included. All patients had to be on ARV therapy for at least 6 months. Cases were defined as patients with at least 1 HIV-1 RNA level (viral load) >1000 copies/mL at any point after at least 6 months after therapy initiation, and controls were defined as patients for whom all viral loads performed after 6 months were <400 copies/mL. Because of the unclear significance of low-level viremia,[14] subjects with detectable viral loads < 1000 copies/mL after 6 months were excluded.

Study Setting

The IDCC is located in Botswana's capital, Gaborone. All patients treated at the IDCC were enrolled in Botswana's National ARV Therapy Program, which provides free HAART to individuals with CD4 counts <200 cells/mm^3 or qualifying opportunistic infections. First-line HAART at the IDCC was fixed-dose combination of zidovudine and lamivudine plus either nevirapine for women of childbearing potential or efavirenz for men and women not

of childbearing potential, although substitutions were allowed. Patients received viral loads pretherapy (Amplicor HIV-1 Monitor Assay; Roche Molecular Systems, Branchburg, NJ) and CD4 count testing (EPICS; Beckman Coulter, Fullerton, CA), which were repeated approximately every 3–6 months after HAART initiation.

HAART was dispensed on-site, and patients brought a paper medication card to each clinic visit. Medications were refilled monthly, and the pharmacist recorded the drug names and doses, the visit, the number of pills remaining since the last medication visit, and the number of pills dispensed on the patient's card.

Data Collection

Patients who scheduled clinic visits during the study were prospectively screened for eligibility. As eligible patients were identified, they were asked for consent to participate in the study; those who agreed gave verbal and written informed consent in Botswana's native language, Setswana. Once consented, all available medical records, including paper clinic charts, Botswana's electronic laboratory and pharmacy database, and medication cards, were reviewed.

Adherence was expressed as a continuous variable[15] and calculated as the number of days of medication taken divided by the number of days to obtain a 90-day supply of HAART, expressed as a percent, as described.[16] The number of days to obtain a 90-day supply was calculated as the number of days between the last fill and 3 previous fills. The number of days of medication taken was calculated as the sum of the number of days prescribed minus the sum of the number of days of medication left in the bottle at the time of each refill.

Statistical Analysis

Univariate testing used the χ^2 or Fisher exact test (for categorical variables), the Student *t* test (for normally distributed continuous variables), or Wilcoxon rank-sum test or Kruskal–Wallace test (for continuous variables not normally distributed). The measure of association was an odds ratio and a 95% confidence interval. Risk factors identified in univariate analysis were entered in a multivariable logistic regression model. Factors whose inclusion changed the unadjusted relationship by more than 15% were retained in an adjusted model.[17] We assessed for effect modification of the adherence–suppression relationship by baseline CD4 count, baseline viral load, and history of tuberculosis separately. This was assessed by the inclusion of interaction terms in the multivariable logistic regression models. *P* values <0.05 for the interaction term were considered formal evidence of effect modification.

We targeted a sample size of 310 subjects in a 4:1 ratio of controls per case to have 80% power with an alpha of 0.05 to detect a 10% difference in adherence between cases and controls based on an expected SD of adherence of 0.25.

RESULTS

A total of 302 qualifying adults were consented to participate in the study between July 25 and September 26, 2005. Less than 10% of the patients approached refused to enroll in the

study. Of the 302 who consented, 57 (21%) were cases of virological failure and 247 (79%) were controls with all viral loads documented as undetectable. The mean age was 38 (range 18–76) years, 73 (24%) patients had a history of tuberculosis, the median CD4 count was 110 cells/mm^3 (interquartile range 55–155), and the median viral load was 5.5 $\log_{10}$ copies/mL (interquartile range 5–5.9) at the time of HAART initiation. Two hundred sixty-seven (88%) patients had initiated zidovudine, lamivudine, and an NNRTI; 32 (11%) initiated stavudine, lamivudine, and an NNRTI; and 3 (1%) had initiated didanosine, stavudine, and an NNRTI. One hundred forty (46%) patients had initiated efavirenz and 162 (54%) had initiated nevirapine.

The median adherence level for the group was high (97%, IQR 0.90–1). Despite high adherence levels, patients with virological failure had lower adherence levels than patients without virological failure (median 97%, IQR 91%–100% vs 91%, IQR 83%–97%; rank-sum $P < 0.001$). This association was unchanged when categorizing adherence levels at ≥95% or as above or below the median adherence value for the group. Although sample size was limited, we found no evidence that adherence mattered more or less within groups defined as having a pretreatment viral load >100,000 copies/mL, a CD4 count <100 or <50 cells/mm^3, or tuberculosis. Time on HAART at consent was approximately 1.5 years (median 568 days, IQR 436–794) and was approximately 4 months longer in cases than in controls ($P < 0.001$), but inclusion of this difference or any other factors listed in Table 1 in a multivariable analysis did not change the association between adherence and virological failure. There was also a statistically significant relationship between increasing risk of virological failure as adherence levels decreased (Table 1). Virological suppression despite only moderate levels of adherence was also observed: 52 of 77 (68%) patients with adherence <90% and 23 of 35 (66%) patients with adherence <80% did not experience virological failure.

DISCUSSION

This study confirms a strong relationship between adherence, when measured by pharmacy refill data, and virological response among HIV-1–infected individuals initiating NNRTI-based HAART in sub-Saharan Africa. Importantly, this study indicates that virological failure may occur despite high levels of adherence to HAART in this setting, as the median level of adherence among patients with virological failure was more than 90%.

We have previously documented very high (ie, >90%) rates of achieving an initial undetectable viral load among adults who survive long enough to have a follow-up viral load measured in the IDCC in Botswana.[18] Furthermore, Mills et al[19] documented high rates of adherence to HAART across multiple sites in sub-Saharan Africa. However, because relatively small differences in adherence separate those with and without virological failure, this study underscores the need for ongoing attendance to adherence after HAART initiation. Our data also suggest that pharmacy refill information can be used to identify patients who are late for pharmacy refills and are therefore at high risk for virological failure. Programmatic tracking of pharmacy refill information could be useful in relaying patient adherence information to support staff to direct adherence interventions and should be examined via operations research.

Research into understanding the causes of the discordance between high adherence and lack of suppression that we and others[3] have observed may yield important insights into factors associated with virological outcomes. For example, polymorphisms in the cytochrome P450 enzyme CYP2B6, which seems more commonly in Africans,[20] may result in slower drug metabolism and greater drug exposure in certain individuals,[21] who may therefore achieve virological suppression despite lower adherence levels. Conversely, mechanisms explaining why patients with high levels of adherence are failing, such as malabsorption and drug–drug interactions, should also be explored.

Several potential limitations of this study exist. Selection bias may have resulted from a relatively brief enrollment period during which patients need to present to clinic. Median rates of adherence among all individuals in a population who experience virological failure (eg, including those who do not return for care and therefore cannot be enrolled in clinic-based studies such as this) may be lower. However, adherence assessments are primarily relevant to those who remain in care and therefore are able to have their adherence measured. Thus, we do not believe selection bias to be a major limitation of the study. It is also possible that our pharmacy refill method overestimated subjects' adherence. However, because ARV therapy is free in Botswana, it is unlikely that many patients were sharing pills and thereby appearing more adherent.

High adherence levels in resource-limited settings have given major hope to global ARV therapy scale-up efforts. Still, because HIV therapy must be lifelong, our data indicate the importance of maintaining very high levels of adherence over time and suggest the critical role of monitoring and improving adherence in scale-up efforts to ensure the durable success of these efforts.

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TABLE 1

Risk Factors for Virological Failure Among Adults Initiating HAART at the IDCC, Gaborone, Botswana

	n (%)		
Characteristic	**Cases (n = 65)***	**Controls (n = 247)**	**OR (95% CI)†**
Female	42 (65)	179 (72)	0.69 (0.39 to 1.24)
Age ≤35 yr	23 (35)	103 (42)	0.77 (0.43 to 1.35)
Baseline CD4 count ≤100 cells/mm^3	34 (52)	111 (45)	1.34 (0.78 to 2.32)
Baseline HIV RNA level ≥100,000 copies/mL	51 (78)	193 (78)	1.02 (0.52 to 1.98)
Hemoglobin ≤10 gm/dL	19 (29)	89 (36)	0.73 (0.40 to 1.33)
Weight ≤55 kg	26 (40)	120 (49)	0.71 (0.40 to 1.22)
Tuberculosis	18 (28)	58 (23)	1.24 (0.67 to 2.31)
Adherence category (%)			
≥95	21 (32)	159 (64)	Reference‡
90 to <95	16 (25)	36 (15)	3.37 (1.57 to 7.23)
80 to <90	15 (23)	29 (12)	3.92 (1.76 to 8.69)
<80	13 (20)	23 (9)	4.23 (1.83 to 9.98)

*Defined as presence of a viral load >1000 copies/mL at any time after at least 6 months of ARV therapy.

†No confounding variables were identified in multivariable analyses.

‡*P* value for χ^2 test for trend <0.001.

CI, confidence interval; OR, odds ratio.