

Predictors of Incomplete Adherence, Virologic Failure, and Antiviral Drug Resistance among HIV-Infected Adults Receiving Antiretroviral Therapy in Tanzania

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(See the editorial commentary by Flanigan et al. on pages 1499–1501)

Background. Access to antiretroviral therapy is rapidly expanding in sub-Saharan Africa. Identifying the predictors of incomplete adherence, virologic failure, and antiviral drug resistance is essential to achieving long-term success.

Methods. A total of 150 subjects who had received antiretroviral therapy for at least 6 months completed a structured questionnaire and adherence assessment, and plasma human immunodeficiency virus (HIV) RNA levels were measured. Virologic failure was defined as an HIV RNA level >400 copies/mL; for patients with an HIV RNA level >1000 copies/mL, genotypic antiviral drug resistance testing was performed. Predictors were analyzed using bivariable and multivariable logistic regression models.

Results. A total of 23 (16%) of 150 subjects reported incomplete adherence. Sacrificing health care for other necessities (adjusted odds ratio [AOR], 19.8; $P < .01$) and the proportion of months receiving self-funded treatment (AOR, 23.5; $P = .04$) were associated with incomplete adherence. Virologic failure was identified in 48 (32%) of 150 subjects and was associated with incomplete adherence (AOR, 3.6; $P = .03$) and the proportion of months receiving self-funded antiretroviral therapy (AOR, 13.0; $P = .02$). Disclosure of HIV infection status to family members or others was protective against virologic failure (AOR, 0.10; $P = .04$).

Conclusions. Self-funded treatment was associated with incomplete adherence and virologic failure, and disclosure of HIV infection status was protective against virologic failure. Efforts to provide free antiretroviral therapy and to promote social coping may enhance adherence and reduce rates of virologic failure.

Access to antiretroviral drugs for all HIV-infected persons in need is a global health priority; currently, >2 million individuals are receiving antiretroviral therapy (ART), and a rapid scale-up in the number of individuals receiving ART is in progress [1, 2]. ART regimens in resource-limited areas commonly contain the nonnucleoside reverse-transcriptase inhibitor (NNRTI) nevirapine, which is frequently coformulated in a fixed-dose, 3-drug combination with 2 nucleoside reverse-transcriptase inhibitors (NRTIs). Several reports document suppression of plasma HIV RNA levels to below detectable limits, increases in CD4⁺ cell counts, and improved clinical outcomes and survival

with the use of nevirapine-containing ART [3–7]. Adherence to ART, a principal determinant of therapeutic success, is excellent in African countries and may be higher than adherence levels measured in North America [8]. However, the sustained and successful delivery of ART in resource-limited areas involves many challenges, including drug supply, the durability of financial commitments from international donors, the limited financial resources of in-country health ministries, drug-related toxicities, and the need to monitor therapeutic success and recognize treatment failure, including the consequences of antiviral drug resistance [9]. Patients who receive NNRTI-containing regimens are particularly vulnerable to developing drug-resistant infection when virologic failure occurs, which could potentially result in broad resistance to NNRTIs and NRTIs, transmission of drug-resistant viruses, and future compromise of NNRTI- and NRTI-containing regimens among treatment-naïve populations who become infected with drug-resistant virus [10–12]. Therefore, it is essential to identify patients starting ART or who are already receiving ART who are at risk for current or future treatment failure.

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Previous studies in resource-limited areas have identified factors associated with decreased adherence to ART, the development of ART-resistant infection, and survival following ART. In Botswana, a study identified the cost of ART as a barrier to therapy adherence in 47 (44%) of 108 subjects, followed by other factors, including social stigma, migration and travel, and adverse effects [13]. A Ugandan study found that low monthly income and marital status were associated with decreased adherence [14]. A Malawian study assessed adherence, plasma HIV RNA levels, and antiviral drug resistance in a cohort of 1308 persons receiving ART (1279 [98%] of whom were receiving nevirapine-containing regimens) and observed HIV RNA levels <400 copies/mL in 334 (84%) of 397 subjects. Self-reported adherence during the previous 4 days was the best predictor of detectable plasma HIV RNA levels. Of the 397 subjects with HIV RNA levels <400 copies/mL, 52 (13%) had plasma HIV RNA levels >1000 copies/mL. HIV genotyping was performed for 50 (96%) of these 52 subjects. Of these 50 subjects, 42 (84%) were infected with strains with NRTI mutations, and 47 (94%) were infected with strains with non-NRTI mutations [6]. In the ART in Lower Income Countries study, a strong relationship was found between receipt of ART and survival. The greatest survival benefit was realized when ART was administered free of cost to patients in resource-limited areas [15]. A meta-analysis of studies conducted in developing countries reported additional barriers to ART, including fear of disclosure of HIV infection status, concomitant substance abuse, forgetfulness, suspicion of treatment, complicated drug regimens, the large number of pills required, decreased quality of life, work and family responsibilities, falling asleep, and lack of access to medication [16]. To summarize, previous research in Africa has identified associations between poor adherence to therapy and financial constraints, detectable viremia, and antiviral drug-resistant infection, as well as an association between the availability of free ART and survival. However, no study has yet investigated the relationships between sociodemographic characteristics, economic status, adherence to ART, virologic outcome, and antiviral drug-resistant infection in a single cohort. We sought to understand the relationship between these factors and the outcomes of ART adherence, virologic failure, and the development of antiviral drug-resistant infection in a cohort of HIV-infected persons in northern Tanzania.

PATIENTS AND METHODS

Study design and participants. The Antiretroviral Drug Adherence and Resistance (ADAR) study was a cross-sectional cohort study to evaluate predictors of virologic failure among adult (≥ 18 years of age) HIV-infected patients attending the Infectious Diseases Clinic at the Kilimanjaro Christian Medical Centre (Moshi, Tanzania), a referral hospital in northern Tan-

zania. Subjects were required to have been receiving the fixed-dose combination of stavudine, lamivudine, and nevirapine for ≥ 6 months. During the 6-month period before subjects entered the study, payment for ART transitioned from private payment by patients to free medications provided by the Tanzanian Ministry of Health. This transition offered a unique opportunity to study the effect of purchased versus free medications on the outcomes of treatment adherence, virologic failure, and the development of antiviral drug-resistant infection. After informed consent was obtained, subjects were administered standardized questionnaires translated into Kiswahili that assessed demographic, epidemiologic, clinical, and treatment information. Questions addressing potential predictors of incomplete adherence were developed through a literature search for established predictors of incomplete adherence, virologic failure, and the development of antiviral drug-resistant infection from both the developed and developing world. Locally relevant factors were identified through a series of focus group discussions with patients receiving ART. The questionnaires specifically gathered data on factors such as weekly expenditures as a measure of poverty, the frequency of interruptions in ART (defined as a period of >48 without therapy), and disclosure of their HIV infection status to family members or others. We used tools already validated in East Africa, including an asset survey for measuring wealth [17], the Hopkins Symptom Checklist-25 for symptoms of depression and anxiety [18], and an adherence assessment questionnaire [19].

Sample collection and testing. Twenty milliliters of whole blood were collected from each of the 150 subjects. The whole blood samples were centrifuged, and multiple plasma aliquots were frozen at -80°C . After samples for the study were fully accrued, stored plasma samples were shipped to Duke University Medical Center (Durham, NC) for measurement of plasma HIV RNA levels, genotypic antiviral drug resistance testing, and HIV subtyping. Plasma samples were assayed for the presence of HIV RNA using the Roche Amplicor assay, version 1.5 (Roche Molecular Systems), with a lower limit of detection of 100 copies/mL. If plasma HIV RNA levels were >1000 copies/mL, genotypic antiviral drug resistance testing and HIV subtyping were performed on sequences obtained by directly sequencing the PCR products using parallel allele-specific sequencing [20]. Key mutations were identified according to the November 2005 revision of the International AIDS Society-USA Drug Resistance Mutations in HIV document [21]. The pretreatment CD4⁺ cell counts for all subjects were recorded through chart review.

Statistical analyses. Statistical analyses were conducted using Stata software, version 8.2 (StataCorp). Incomplete adherence was defined as self-reported adherence <100%, virologic failure was defined as a plasma HIV RNA level >400 copies/mL, and antiviral drug resistance was defined as ≥ 1 major

NRTI- or NNRTI-resistant mutation. The point prevalences of virologic failure, incomplete adherence, and antiviral drug-resistance mutations were calculated as proportions of subjects sampled. Parametrically continuous variables were compared among subjects with and without virologic failure using the Student's *t* test for means and the sign test for medians. Non-parametric continuous variables were compared among subjects with and without virologic failure using the Wilcoxon rank-sum test. A multivariable logistic regression model was constructed for unmatched study design to determine factors associated with incomplete adherence and virologic failure.

Research ethics. The protocol for this study was approved by the Kilimanjaro Christian Medical Centre Research Ethics Committee, the Tanzania National Institutes for Medical Research National Research Ethics Coordinating Committee, and an Institutional Review Board of Duke University Medical Center.

RESULTS

From June through August 2005, 150 subjects were recruited into the study (table 1). Fifty-six subjects (37%) were male, and the median age was 41 years. The median CD4⁺ cell count at treatment initiation was 114 cells/mm³, and the median duration of ART at study entry was 12 months. The median walking time required to attend clinic visits was 20 min, exclusive of time spent in motor vehicles.

Incomplete adherence. One hundred twenty-six (84%) of the subjects reported not missing any doses of ART from the start of treatment. The remaining 24 subjects (16% of the study population) were defined as having incomplete adherence. Predictors of incomplete adherence on bivariable analysis were sacrificing health care for other necessities (e.g., food, clothing, childrens' school fees, or housing; OR, 20.7; *P* < .01) and walking distance to clinic (OR per 10 min increment, 1.2; *P* =

.05). Disclosure of HIV serostatus to persons other than health care providers (OR, 0.23; *P* = .07) and the proportion of months receiving self-funded treatment (OR, 4.9; *P* = .06) displayed trends toward significant associations, with the disclosure of HIV serostatus exhibiting a trend toward a protective effect (table 2). In multivariable analysis, sacrificing health care for other necessities (adjusted OR [AOR], 19.8; *P* < .01) and the proportion of months receiving self-funded treatment (AOR, 23.5; *P* = .04) were associated with incomplete adherence, and disclosure of HIV infection status again displayed a trend toward a protective effect (AOR, 0.16; *P* = .06) (table 2).

Virologic failure. Forty-eight (32%) of 150 subjects had plasma HIV RNA levels >400 copies/mL and met the definition for virologic failure. In bivariable analysis (table 3), virologic failure was associated with incomplete adherence (OR, 3.8; *P* < .01) and a greater proportion of months receiving self-funded ART (OR, 4.7; *P* = .03), and disclosing HIV status to someone other than the health care provider was protective (OR, 0.17; *P* = .04). In multivariable analysis (table 3), virologic failure remained associated with incomplete adherence (AOR, 3.6; *P* = .03) and the proportion of months receiving self-funded ART (AOR, 13.0; *P* = .02); disclosure of HIV infection status (AOR, 0.10; *P* = .04) and higher weekly household expenditures (AOR, 0.96; *P* = .03) were protective. To better understand the relationship between self-funded ART and virologic failure, further analyses were performed to investigate the role of incomplete adherence. Subjects who paid for ART were more likely than others to be maladherent (*r* = 0.54; *P* < .01).

Antiviral drug-resistance mutations and HIV subtypes. Among the 48 subjects with plasma HIV RNA levels >400 copies/mL, 35 (73%) had plasma HIV RNA levels >1000 copies/mL and had sequencing of their isolates attempted. Of these

Table 1. Demographic and clinical characteristics of 150 patients with HIV infection who received antiretroviral therapy (ART) at Kilimanjaro Christian Medical Centre Infectious Diseases Clinic, Moshi, Tanzania, 2005.

Characteristic	All patients (<i>n</i> = 150)	Adherent to ART (<i>n</i> = 126)	Maladherent to ART (<i>n</i> = 24)
Age, median years (range)	41 (19–69)	41 (19–69)	41 (21–55)
Disclosure of HIV infection status, no. (%) of patients	143 (95)	122 (97)	21 (88)
Weekly ART expenditures per patient, median USD (range)	18.1 (0–104.4)	17.2 (0–104.4)	18.1 (1.7–30.2)
Male sex, no. (%) of patients	56 (37)	47 (37)	9 (38)
Duration of ART, median months (range)	12 (6–27)	12 (6–27)	12 (6–26)
Duration of self-funded treatment, proportion of treatment duration (range)	0.12 (0–0.9)	0.1 (0–0.9)	0.31 (0–0.8)
Depression, no. (%) of patients	31 (21)	24 (19)	7 (29)
CD4 ⁺ cell count at ART initiation, median cells/mm ³ (range)	114 (1–628)	116 (1–515)	94 (9–628)
Walking time to clinic, ^a median min (range)	20 (0–180)	15 (0–90)	25 (5–180)
Sacrifice of health care for other necessities, no. (%) of patients	8 (5)	2 (2)	6 (25)

^a Walking time was assessed in 10-min increments.

Table 2. Bivariable and multivariable logistic regression analyses of risk factors for incomplete adherence to antiretroviral therapy (ART), Kilimanjaro Christian Medical Centre Infectious Diseases Clinic, Moshi, Tanzania, 2005.

Variable	Bivariable analysis		Multivariable analysis	
	OR (95%CI)	P	Adjusted OR (95%CI)	P
Age, years	1.0 (0.95–1.0)	.89	0.99 (0.92–1.1)	.72
Disclosure of HIV infection status	0.23 (0.05–1.1)	.07	0.16 (0.02–1.1)	.06
Weekly expenditures, USD	1.0 (0.97–1.0)	.82	1.0 (0.96–1.0)	.96
Male sex	1.0 (0.41–2.5)	.99	0.69 (0.22–2.2)	.53
Duration of ART, months	1.0 (0.93–1.1)	.92	0.94 (0.84–1.1)	.33
Portion of treatment that was self-funded, months	4.9 (0.92–25.9)	.06	23.5 (1.2–444.4)	.04
Depression	1.8 (0.65–4.7)	.27	2.1 (0.64–6.6)	.22
CD4 ⁺ cell count at ART initiation, median cells/mm ³	1.0 (1.0–1.0)	.92	1.0 (1.0–1.0)	.94
Walking time to clinic, per 10-min increment	1.2 (1.0–1.5)	.05	1.2 (0.94–1.6)	.14
Sacrifice of health care for other necessities	20.7 (3.9–110.3)	<.01	19.8 (3.1–127.8)	<.01

35 subjects, 27 (77%) had successful HIV genotyping. Of these 27 subjects, 10 (37%) were infected with HIV type 1 subtype A, 7 (26%) were infected with HIV type 1 subtype C, and 10 (37%) were infected with HIV type 1 subtype D. Of these 27 subjects, 15 (56%) had isolates with at least 1 major antiviral drug-resistance mutation, and 12 were infected with wild-type virus. The major antiviral drug-resistance mutations found in virus from these 15 subjects are listed in table 4. Two subjects had virus with only 1 major antiviral drug-resistance mutation; in both cases, these were NNRTI-associated mutations (K103N in one and Y181C in the other). Seven subjects had virus with 2 major mutations; all 7 patients had virus with NNRTI-related mutations (K103N in 3, G190A in 3, and Y181C in 1), and all 7 had virus with lamivudine-associated M184V mutations. Six subjects had virus with ≥ 3 major antiviral drug-resistance mutations. In a bivariable analysis, having a CD4⁺ cell count greater than the study population median CD4⁺ cell count at treatment initiation was found to be marginally protective against the presence of a strain with ≥ 1 antiviral drug-resistance mutation (OR, 0.99; $P = .04$). The proportion of months receiving self-funded treatment displayed a trend towards being associated with antiviral drug-resistant infection, whereas disclosure of HIV serostatus to family members or others displayed a trend toward being protective.

DISCUSSION

The ADAR study represents a novel attempt to rigorously assess the link between adherence to therapy, virologic response, and antiviral drug resistance in a resource-limited setting. The results demonstrate outstanding levels of adherence and good virologic success among HIV-infected persons receiving fixed-dose combination ART in northern Tanzania. Conversely, maladherent subjects were more likely to have detectable viremia during treatment. Incomplete adherence and virologic failure were associated with having to pay for medications for a longer

duration, and disclosure of HIV infection status to someone other than a health care provider was protective. These observations carry critical implications for policy makers in resource-limited areas during the remarkable, ongoing scale-up of ART delivery.

The ADAR study used an adaptation of a validated adherence questionnaire for measuring adherence [19]. Numerous studies have demonstrated high levels of adherence among persons receiving ART in resource-limited areas [14, 22–25], including among African cohorts. A recent systematic overview found that 77% of sub-Saharan Africans maintained 100% adherence with ART, compared with 55% of North Americans [8]. Therefore, the ADAR study results regarding adherence in a Tanzanian population are consistent with observations from other cohorts in resource-limited areas.

Other studies have also demonstrated high rates of virologic success among populations in resource-limited countries. Studies from India [26], Malawi [6], and Uganda [27] and the ART in Lower Income Countries study [15] found that 76%–84% of subjects had plasma HIV RNA levels <400 copies/mL, rates which are very similar to those among populations receiving ART in North America and Europe. Accompanying these high rates of virologic suppression have been marked improvements in CD4⁺ cell counts [6, 26] and reductions in HIV-related mortality [26]. These successes have been achieved predominately with nevirapine-based regimens, despite observations that these regimens may be less potent than the efavirenz-based regimens used commonly in less financially constrained countries.

Interruptions in ART with NNRTI-containing regimens may lead to increased rates of virologic failure and antiviral drug resistance [15, 25]. These observations reflect the relatively low genetic barrier to antiviral drug resistance for NNRTIs, as well as the prolonged plasma half-lives of NNRTIs, which lead to functional monotherapy as NRTI concentrations in plasma decrease. In resource-limited areas, treatment interruptions may

Table 3. Bivariable and multivariable logistic regression analyses of risk factors for virologic failure, Kilimanjaro Christian Medical Centre Infectious Diseases Clinic, Moshi, Tanzania, 2005.

Variable	Bivariable analysis		Multivariable analysis	
	OR (95%CI)	P	Adjusted OR (95%CI)	P
Age, years	1.0 (0.97–1.0)	.71	1.0 (0.97–1.1)	.64
Disclosure of HIV infection status	0.17 (0.03–0.92)	.04	0.10 (0.01–0.94)	.04
Weekly expenditures, USD	0.98 (0.95–1.0)	.14	0.96 (0.93–1.0)	.03
Male sex	1.3 (0.65–2.6)	.45	1.1 (0.49–2.6)	.79
Duration of ART, months	1.0 (0.96–1.1)	.49	0.95 (0.87–1.0)	.31
Portion of treatment that was self-funded, months	4.7 (1.2–18.7)	.03	13.0 (1.4–118.2)	.02
Depression	0.84 (0.35–2.0)	.69	0.73 (0.28–1.9)	.53
CD4 ⁺ cell count at ART initiation, median cells/mm ³	1.0 (1.0–1.0)	.68	1.0 (1.0–1.0)	1.0
Walking time to clinic, per 10-min increment	1.2 (0.99–1.4)	.08	1.2 (0.96–1.5)	.10
Sacrifice of health care for other necessities	1.3 (0.30–5.6)	.73	0.47 (0.07–3.1)	.43
Incomplete adherence to therapy	3.8 (1.5–9.3)	<.01	3.6 (1.2–11.0)	.03

be more common because of the relatively high cost of the medications, the difficulty of accessing health care services, and challenges in the distribution and uninterrupted delivery of drug supplies [28].

The role of self-funded treatment in determining the success of ART has been identified by other studies [13, 14]. Presumably, self-funded treatment can result in more frequent treatment interruptions in vulnerable NNRTI-based regimens because of an inability to maintain the burdensome personal financial commitment involved in purchasing ART indefinitely. Within the ART in Lower Income Countries study cohort, access to free care, including ART, was associated with improved survival, which is certainly the most striking indicator of treatment success. The ADAR study results add depth to this understanding by demonstrating that a longer duration of self-funded treatment led to lower rates of 100% adherence and undetectable viremia, as well as a trend toward more antiviral drug-resistance mutations. Similar observations have been made regarding the use of voluntary counseling and testing services in northern Tanzania, where a modest co-payment restricted use and clear cost-effectiveness was identified with removal of financial barriers [29]. Because of the high cost of the failure of first-line ART, access to free ART and related

services in resource-limited areas is very likely to achieve remarkable cost-effectiveness.

In the ADAR study, the protective role of disclosure of HIV infection status to persons other than health care providers was dramatic. This association may be a result of multiple factors, including social stigma, adherence coaching, and social isolation and depression. Strong social stigma regarding HIV infection exists globally and has been investigated for its effect on ART adherence. The effect of “coaching” on adherence has been identified in previous studies, and it may play a positive role. Finally, depression has been identified as a clear factor associated with decreased adherence in multiple studies, but it was not associated with incomplete adherence in the ADAR study. Although a validated tool was used to assess adherence in our study, the limited numbers of subjects with incomplete adherence may have prevented the identification of potential associations [13, 30].

The antiviral drug-resistance mutations found among ADAR subjects with plasma HIV RNA levels >1000 copies/mL fell into patterns of NNRTI mutations alone; NNRTI mutations plus M184V; and NNRTI mutations, M184V, and additional NRTI-associated mutations, including thymidine analogue mutations. These patterns have been previously recognized among persons

Table 4. Summary of genotypic antiviral drug-resistance mutations in isolates obtained from HIV-infected patients at Kilimanjaro Christian Medical Centre Infectious Diseases Clinic, Moshi, Tanzania, 2005.

No. of mutations	No. (%) of isolates (n = 15)	Antiviral drug-resistance mutation(s) (no. of isolates), by type of antiviral drug	
		NRTI	NNRTI
1	2 (13)	None	K103N (1), Y181C (1)
2	7 (47)	M184V (7)	K103N (3), Y181C (1), G190A (3)
≥3	6 (40)	Q151M (1), M184V (4), M184I (1), TAMs:M41L (1), K65R (1), L210W (1), T215Y (1)	K103N (3), V108I (1), Y181C (4), G190A (2)

NOTE. NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

receiving NNRTI-containing regimens, including among persons receiving ART in resource-limited areas [10]. We speculate that the marginal association between antiviral drug-resistance mutations and lower pre-ART CD4⁺ cell counts may be a reflection of higher pre-ART plasma HIV RNA levels, although baseline samples were not available for testing.

The ADAR study does have important limitations. First, the study is cross-sectional, and stronger conclusions would be possible with a longitudinal cohort. Because patients had received ART for ≥ 6 months at the time of evaluation, adherence was measured some time after ART was established. Furthermore, the study did not include those individuals who had defaulted from therapy or switched to second-line therapy prior to the time of inclusion. These 2 factors may have led to an overestimation of adherence. The size of the entire cohort was 150 subjects, but only 23 subjects were maladherent; therefore, the ability of the study to identify factors associated with incomplete adherence was limited. A relatively low proportion of subjects with plasma HIV RNA levels >1000 copies/mL had virus with antiviral drug resistance-mutations (15 of 35 subjects), which may have also diminished the ability of the study to recognize factors associated with antiviral drug resistance. It is notable that, despite these limitations in sample size, significant associations were identified. Finally, baseline samples were not available in this cohort, and their availability would have enhanced our ability to examine the impact of factors such as pre-ART plasma HIV RNA levels, preexisting drug-resistant viruses, and HIV subtypes on virologic failure and antiviral drug-resistance mutations.

In summary, the ADAR study has identified critical factors that are predictive of ART success and failure, and its findings should be incorporated by policy makers into practice. Structural barriers to care, including the time required to reach health care services and, especially, the personal financial burden of funding ART, must be removed. Social coping, including the disclosure of HIV infection status to others who are not health care providers, leads to higher rates of ART adherence and is protective against virologic failure. The availability of enhanced and accessible monitoring services, which promote the early identification of HIV-infected persons and their close monitoring before CD4⁺ cell counts reach extremely low levels, may lead to less antiviral drug resistance. In addition, sentinel programs designed for operational research that can identify detectable viremia in patients who are receiving ART and detect cases of antiviral drug-resistant infection provide valuable feedback to improve service delivery.

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