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Adherence and Treatment Response Among HIV-1-Infected Adults Receiving Antiretroviral Therapy in a Rural Government Hospital in Southwestern Uganda

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Background. Large-scale, government-based antiretroviral therapy (ART) programs in rural areas of resource-poor countries remain largely unevaluated. *Methods*. We conducted a retrospective review of all patients receiving ART (n = 399) to assess survival and retention in care and a prospective evaluation of patients on ART for at least 6 months (n = 175). We used 3-day self-report to measure adherence. *Results*. The probability (95% confidence interval [CI]) of surviving and remaining in care was 0.76 (0.72, 0.81) at 1 year. Men and patients with advanced disease were more likely to die or be lost to follow-up. At baseline, 149 (85%) reported 100% adherence. Nonadherence was associated with lack of suppression of viral replication (odds ratio [OR] = 4.5; 95% CI: 1.8, 11.5). Missing a scheduled clinic visit and lack of disclosure of HIV status were associated with nonadherence. *Conclusion*. Viral suppression was high, but counseling to include HIV disclosure to family and keeping scheduled clinic appointments may improve long-term adherence and treatment outcomes.

Keywords: HIV; antiretroviral therapy; adherence; virologic suppression; rural settings; Uganda

Introduction

In most resource-limited settings, large-scale antiretroviral therapy (ART) programs have only recently been introduced and initial reports of their effectiveness indicate that ART improves survival.[1] Most formal evaluations have been of ART programs in large urban hospitals[2] or from donor-funded home-based programs.[3] Antiretroviral therapy adherence has also been reported predominantly among patients in the context of urban[4-6] and research settings.[7] Few studies have evaluated government-based ART programs, serving rural populations where the structural- and patient-level barriers to successful treatment response are unique. Experience from rural programs will provide invaluable information in the scale-up of ART in developing country settings, given the largest majority of the population in these countries is rural.

In this study, we examine treatment outcomes among the first patients enrolled in an ART program at such a facility situated in rural southwestern Uganda. We examined patient adherence to ART,

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the probability of treatment success using clinical and laboratory markers, and survival and retention in care.

Methods

Setting

This study was conducted at Kitagata Hospital, a government-owned district hospital located in the Bushenyi district of rural southwestern Uganda. The hospital started its ART program in December 2004 and receives support from the following 2 sources: (1) Timetable for Regional Expansion of Antiretroviral Therapy (TREAT), the US President's Plan for AIDS Relief (PEPFAR)-funded program of the Joint Clinical Research Centre; and (2) the ART program of the Ugandan Ministry of Health, which is supported by the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Patients are initiated on ART if they are considered to have World Health Organization (WHO) clinical stages 3 or 4 disease and/or total lymphocyte count <1500 cells/mm^3. First-line therapy is a fixed-dose combination of stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP). Clinic is held twice weekly and patients are required to return monthly for HIV care and/or to pick up ART refills; some patients arrange to return every 2 months. Viral load and CD4 count testing were not routinely available at the clinic at the time of this study.

Study Design

In April 2006, we began a cohort study with retrospective and prospective components. We reviewed retrospectively 16 months of records of all patients who received ART since December 2004, the program's inception, and of patients who initiated ART through December 2006. We abstracted information through December 2006 on missed clinic visits, ART, and tuberculosis treatment history, and death, if known.

We conducted a prospective cohort study among adult patients (≥18 years) who received ART for at least 6 months and attended clinic at least once between April and December 2006. At the baseline visit, we collected information on sociodemographics, disclosure of HIV, alcohol use, and ART adherence on each of the previous 3 days. Grams of pure ethanol consumed monthly were calculated from frequency, average quantity, and alcohol content of commonly consumed drinks. Patients were considered nonadherent if they missed at least 1 antiretroviral pill and 100% adherent if they had not.

We measured CD4 count and plasma HIV RNA concentration using the Roche Amplicor v1.5 assay. Patients were classified as having suppressed viral replication if their plasma HIV RNA concentration was <50 copies/mL. Genotypic resistance and HIV-1 subtype was assayed if plasma HIV RNA concentration was ≥1000 copies/mL.

For each clinic visit after baseline, typically monthly, we obtained pill count data performed routinely by the dispenser who would ask patients to bring with them pill bottles and unused medications. When a patient kept their scheduled clinic visit, percentage adherence was calculated as the fraction of doses assumed taken among the total number of doses dispensed since the scheduled clinic visit.[8] When a patient missed a scheduled clinic visit, the denominator was the total number of doses that should have been taken since the last dispensing. For patients whose clinic attendance 6 months after baseline occurred before December 31, 2006, we repeated CD4 count measurements, plasma HIV RNA concentration measurements, and HIV drug resistance testing, if indicated.

Statistical Analysis

To estimate the probability of remaining alive and remaining on ART, we used extended Kaplan-Meier with staggered entries to accommodate patients who started treatment before April 2006 or started elsewhere and then transferred to Kitagata Hospital. Patients still on ART were right censored on December 31, 2006, if they remained at Kitagata Hospital or the date of last observation if they requested transfers to other facilities. Because we could only ascertain mortality passively, we treated death and dropping out of HIV care as both separate and combined events of interest. We assumed patients dropped out of care if they did not return to the clinic for 3 consecutive months.

The Mantel-Haenszel log-rank test was used to compare survival curves and Cox proportional hazards regression to determine the relative hazard (RH) of death and/or dropping of out HIV care according to factors of interest. We used unconditional logistic regression to determine the relative odds of failure to suppress viral replication and of nonadherence to ART at baseline associated with various factors. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

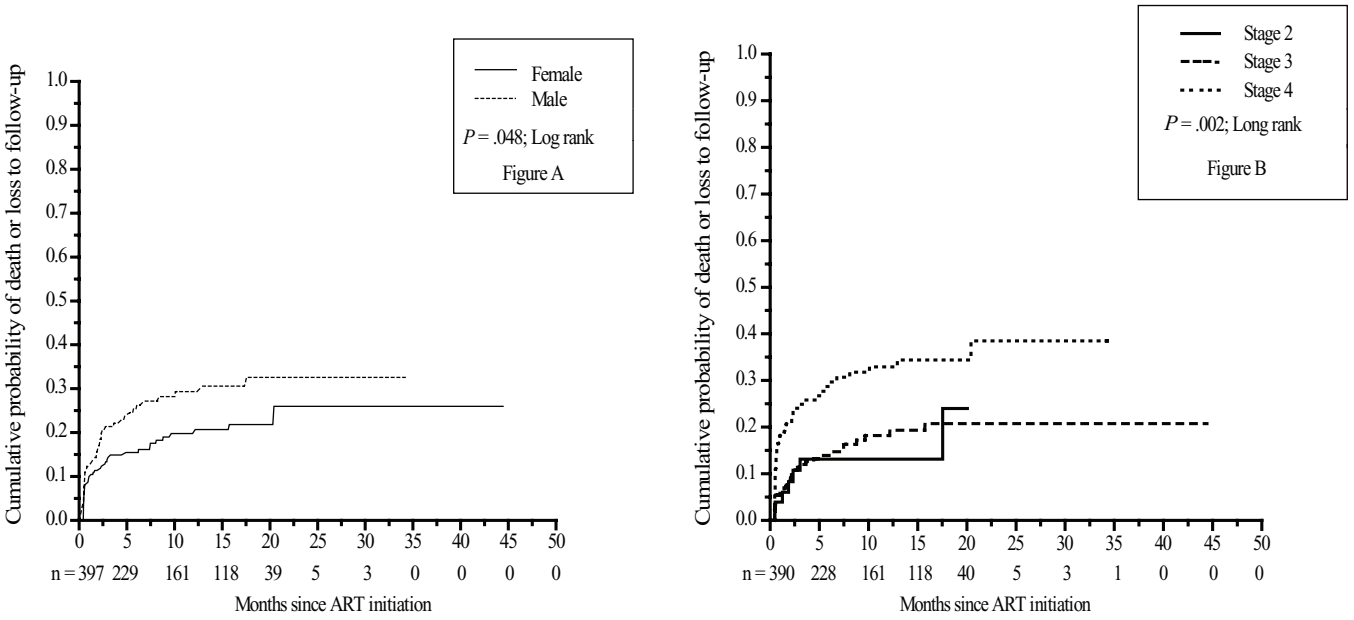

Figure 1. Cumulative probability of death or loss to follow-up since ART initiation according to sex and WHO clinical stage of HIV disease. ART, antiretroviral therapy; WHO, World Health Organization.

Ethical Review

The study received approval from the Institutional Review Boards of The University Hospitals of Cleveland, Mbarara University of Science and Technology, and the Uganda National Council of Science and Technology.

Results

ART Initiation and Follow-up

From December 2004 to December 2006, 399 patients received ART at Kitagata Hospital. Of these, 51 (13%) initiated ART at another health facility and transferred their care to Kitagata Hospital, whereas 25 (6%) had transferred to another facility. Most patients were women (n = 240; 60.2%) and mean (standard deviation; SD) age at ART initiation was 38 (9.3) years. The majority of patients initiated ART in WHO clinical stage 3 (n = 207; 53%) or stage 4 (n = 130; 33%) HIV disease. Through December 2006, 287 (72%) were still in care, 70 (18%) became lost to follow-up, and 17 (4%) were known to have died.

Cumulative probabilities of known death at 1 and 2 years after ART initiation were 0.95 (95% confidence interval [CI]: 0.92, 0.97) and 0.94 (95% CI: 0.91, 0.97), respectively. There was no statistically significant difference in known mortality among men and women (RH = 0.66; 95% CI: 0.25, 1.75). Patients who initiated ART in WHO clinical stage 4 HIV disease were more likely to die compared with those who initiated in WHO clinical stages 3 or 2 (RH = 8.2; 95% CI: 2.32, 29.23).

Cumulative probabilities of either known death or loss to follow-up at 1 and 2 years after ART initiation were 0.76 (95% CI: 0.72, 0.81) and 0.71 (95% CI: 0.64, 0.77), respectively. Men as compared with women were more likely to die or drop out of care (RH = 1.53; 95% CI: 1.002, 2.33; Figure 1A). Patients who initiated ART in WHO clinical stage 4 HIV disease compared with WHO clinical stages 2 or 3 were more likely to die or drop out of HIV care (RH = 2.12; 95% CI: 1.37, 3.28; Figure 1B).

Prospective Cohort Study

Between April and December 2006, 201 of 399 (50.4%) patients met the eligibility criteria for the prospective study. Of these, 175 (87%) were identified in clinic, approached, and consented to participate in the study. None of the patients approached declined participation. Of the 175 evaluated at baseline, 127 (73.4%) returned to the clinic for a 6-month follow-up visit.

Table 1. Regimens Prescribed at Initiation of ART and at the Baseline Study Visit Among HIV-Infected Patients at Kitagata Hospital, Bushenyi District, Uganda

	At the Time of ART Initiation		Baseline Study Visit	
ART Regimen	N	%	N	%
d4T + 3TC + NVP[a]	152	87.9	111	64.2
d4T, 3TC, EFV	7	4.1	25	14.4
AZT, 3TC, NVP	3	1.7	6	3.4
AZT, 3TC, EFV	9	5.2	23	13.3
AZT + 3TC[a], LPV	2	1.1	7	4.1
AZT, 3TC, ABC	0	0.0	1	0.6

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; LPV, lopinavir; NVP, nevirapine.
[a] Is a coformulated combination.

Among the 175 patients recruited, most (n = 147; 84%) initiated ART at Kitagata and received a fixed-dose combination of d4T + 3TC + NVP (Table 1). Only 2 patients had received a protease inhibitor-based regimen as their first regimen and both had transferred to Kitagata after initiating ART elsewhere. At baseline, fewer (n = 111; 64.2%) were still receiving the fixed-dose combination of d4T + 3TC + NVP. The distribution of all ART regimens at the times of treatment initiation and baseline is shown in Table 1. Overall, 7 (4.1%) were on a second-line regimen at baseline. Mean (SD) duration of ART at baseline was 16.6 (5.5) months.

Factors Associated With Failure to Suppress HIV Replication

At baseline, 149 (85%) reported 100% adherence over the past 3 days. In all, 147 (84.0%) and 28 (16.0%) had undetectable and detectable plasma HIV RNA concentrations, respectively (Table 2). Sociodemographic factors were not associated with failure to suppress HIV replication. Mean (SD) age was 39.5 (8.9) and majority (n = 106; 60.7%) of the patients were women. Seventy-four (42.3%) patients were widowed, 75 (42.9%) were married, and 21 (12%) were separated or divorced. Two thirds of the patients had attended primary education or less and about half had monthly incomes of US$6 or less.

Most initiated ART during WHO clinical stage 3 (n = 90; 51.4%) or stage 4 (n = 59; 33.7%). Baseline lower CD4 count was strongly associated with failure to suppress HIV replication: 46%, 23%, and 11% of patients with counts <100, 100 to 200, and >200 cells/mm^3, respectively, had detectable plasma HIV RNA concentration ($P = .004$). Patients with a history of suspected tuberculosis or receipt of tuberculosis treatment were more likely to have detectable plasma HIV RNA concentrations ($P = .028$).

Self-reported ART adherence in the previous 3 days was strongly associated with having detectable plasma HIV RNA concentration at baseline. Nonadherent patients (n = 26; 14.8%) were more likely to have detectable plasma HIV RNA concentration as compared with patients who were 100% adherent ($P < .001$). After adjustment for past or current tuberculosis treatment and CD4 count, nonadherent patients were almost 5 times more likely to fail to suppress HIV replication completely as compared with adherent patients (odds ratio [OR] = 4.9;95% CI:1.9, 13.6; Table 3).

Factors Associated With Nonadherence

Several factors were significantly associated with nonadherence at baseline including missing a scheduled clinic visit (OR = 6.1; 95% CI: 2.4, 15.5), nondisclosure of HIV status to at least 1 family member (OR = 17.5; 95% CI: 3.2, 96.02), and CD4 count of <100 cells/mm^3 (OR = 3.6; 95% CI: 1.1, 12.2). Age, gender, education, and WHO clinical stage of HIV disease at the time of ART initiation were not significantly associated with nonadherence.

The 2 most common reasons cited by patients for nonadherence were "simply forgot" (n = 17; 35%) and "not having the medicines with them at the time they were supposed to be taken" (n = 12 or 25%). The latter occurred when patients were traveling away from home or experienced delays during travel by bus, attending a function such as a wedding, or

Table 2. Baseline Characteristics According to Detectable Plasma HIV RNA Concentration Among Patients Receiving ART for At Least 6 Months, Kitagata Hospital, Bushenyi District, Uganda, April to December 2006

Sociodemographic Characteristic	Plasma HIV RNA Concentration				*P*
	<50 Copies/mL (N = 147; 84%)		≥50 Copies/mL (N = 28; 16%)		
Mean (SD) age	38.7 (9.4)	36.7 (6.7)	.232		
	N	%	N	%	
Gender					
Male	55	80	14	20	.212
Female	92	87	14	13	
Marital status					
Never married	3	75	1	25	.092
Monogamous marriage	52	91	5	9	
Polygamous marriage	16	89	2	11	
Separated or divorced	14	67	7	33	
Widowed	61	82	13	18	
Education attended					
None	19	86	3	14	.580
Primary	80	86	13	14	
Postprimary	48	80	12	20	
Monthly income					
<US$6	74	87	11	13	.433
US$6 to 30	41	84	8	16	
>US$30	32	78	9	22	
Site of ART initiation					
Kitagata hospital	123	84	24	16	1.000
Other health facility	24	86	4	14	
WHO stage of HIV disease at ART initiation					
Stage 2	19	83	4	17	.963
Stage 3	76	84	14	16	
Stage 4	49	83	10	17	
CD4 count					
<100 cells/mm^3	7	54	6	46	.004
100 to 200 cells/mm^3	27	77	8	23	
>200 cells/mm^3	113	89	14	11	
Tuberculosis treatment history					
Completed or currently receiving treatment	20	71	8	29	.028
Suspected disease	3	60	2	40	
No signs of disease	122	87	18	13	
Behavioral characteristic					
ART adherence in previous 3 days					
Missed at least 1 dose	16	61.5	10	38.5	<.001
Did not miss any doses	131	87.9	18	12.1	
Alcohol consumption in the previous month					
None	119	84	22	16	
<200g	21	84	4	16	
>200g	7	78	2	22	.7
Disclosure of HIV status to family member					
Yes	142	84.5	26	15.5	.33
No	5	71.4	2	28.6	

Abbreviations: ART, antiretroviral therapy; WHO, World Health Organization.

going to the market. Some reported having "run out of drugs completely" (n = 9; 19%) and cited their inability to secure money for transportation to the clinic as the reason for not being able to collect their refills. Other reasons for nonadherence included "not having water or porridge to swallow the drugs"

Table 3. Factors Associated With Odds of Detectable Plasma HIV RNA Concentration at Baseline Among Patients Receiving ART for At Least 6 Months, Kitagata Hospital, Bushenyi District, Uganda, April to December 2006

	Unadjusted		Adjusted	
Characteristic	OR	95% CI	OR	95% CI
Missed at least 1 pill in the previous 3 days	4.5	(1.8, 11.5)	4.9	(1.8, 13.6)
ART duration, 1 year or more	0.87	(0.3, 2.3)		-
Missed a scheduled clinic visit	1.8	(0.8, 4.5)		-
Past or current tuberculosis treatment	2.5	(0.97, 6.4)	2.5	(0.91, 6.8)
WHO clinical stage of HIV disease at time of ART initiation				
Stage 3 (vs stage 2)	0.88	(0.3, 2.9)		-
Stage 4 (vs stage 2)	0.97	(0.3, 3.4)		-
CD4 count				
<100 (vs >200 cells/mm^3)	6.9	(2.1, 23.5)	5.1	(1.4, 18.7)
100 to 200 (vs >200 cells/mm^3)	2.4	(0.9, 6.3)	2.9	(1.02, 8.1)
Percentage change in weight since ART start	0.9	(0.3, 2.6)		-
Alcohol in the last 6 months				
<200 g (vs none)	1.0	(0.3, 3.3)		-
>200 g (vs none)	1.6	(0.3, 7.9)		-

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; WHO, World Health Organization.

(n = 3; 6%), "felt too sick to take medicines" (n = 2; 4%), "too much medicine" (n = 1; 2%), and "confused about dosing" (n = 1; 2%).

Rebound in HIV Replication and Pill Count Data

Of the 126 patients who returned for a 6-month follow-up visit before December 31, 2006, 109 (96.5%) had suppression of HIV replication at the baseline evaluation. Of these 109 patients, 100 (91.7%) maintained suppression of HIV replication and 9 (8.3%) experienced rebound in HIV replication.

Mean cumulative adherence derived from available pill count data was calculable for 164 of 175 (92%) patients enrolled in the prospective study. Of them, 68% (111/164) took at least 95% of medication doses prescribed during the 6 months of follow-up. However, there was no association between nonadherence derived from pill count data and rebound in HIV replication ($P = .14$).

Resistance Testing

Of the 28 samples with detectable viral load at baseline assessment, 15 (53.6%) were identified as eligible for resistance testing. Of these, 7 (47%) were successfully sequenced and analyzed; sequencing was unsuccessful for the rest. Of the 7 samples sequenced, 6 carried the M184V mutation, which confers high-level resistance to 3TC and emtricitabine (FTC). Two patients had the T215YF mutation, which confers high-level resistance to zidovudine (ZDV) and d4T. Three patients had the K103N mutation, which confers high-level resistance to all 3 nonnucleoside reverse transcriptase inhibitors (NVP, efavirenz [EFV], and delavirdine [DLV]). The Y181C mutation, which confers high-level resistance to NVP and DLV, was identified in 2 patients. One patient carried the L90M mutation, which confers high-level resistance to protease inhibitor nelfinavir (NFV).

Discussion

Our study demonstrates the effectiveness of a government-based ART program in a Ugandan district hospital serving a predominantly rural population. After a mean duration of 16.6 months on ART, 84% of patients receiving ART for at least 6 months had maintained complete suppression of HIV replication. Self-reported 3-day adherence to ART was a strong predictor of treatment response. Since the inception of the ART program, the cumulative probability of remaining alive was high; however, we observed that 18% had either dropped out of care or died unknowingly, which was substantial.

Our data support the recent evaluations that have shown that treatment success in programmatic ART

in resource-limited settings is comparable with that in individualized approaches in industrialized countries.[9] The proportion of patients achieving suppression of HIV replication is comparable with that in other treatment programs in Africa.[10-12] However, the success at Kitagata Hospital was much higher than that seen in a Senegalese treatment program where only 51.4% of the patients had achieved complete suppression of HIV replication after 12 months of ART[13] and a Ugandan pilot program.[14]

Our findings agree with other studies that have also shown that self-reported adherence is strongly associated with virologic response to ART.[15-20] Although self-reported adherence is known to overestimate actual adherence to ART,[8,21-23] our study demonstrates that a simple measure of adherence can predict plasma HIV RNA concentration.[24-26] In settings where resources to routinely measure plasma HIV RNA concentration are unavailable, standard tools to monitor adherence to ART may be valuable. Such strategies should be brief to enhance their utility at the understaffed, rapidly growing, and overcrowded ART clinics in Africa.

The probability of survival and remaining in HIV care 1 year after ART initiation in our study population was similar to another treatment program in Africa,[12] and also consistent with data from a systematic review on patient retention in ART programs in sub-Saharan Africa.[27] Survival and retention in care in our study population was much higher than that observed from a pilot program at an urban hospital in Kampala, Uganda,[14] and a rural district in Malawi.[28] Survival in our study was likely overestimated. In the absence of standard ascertainment of mortality in Uganda, it is simply unknown whether some of the patients lost to follow-up actually died. In our study, mortality occurred very early after treatment initiation has been observed in many other newly initiated African ART programs[12,14,29]; these early deaths are likely due to the fact that such patients began ART at very advanced stage of HIV disease.

We observed a high rate of loss to follow-up, which has also been reported in other programs in Africa.[6] In a Ugandan pilot ART program, the probability of remaining alive and in HIV care was 63% at 6 months and below 50% at 1 year,[14] and the low rate was predominantly attributed to dropping out of care. Understanding such patients is critical as they may represent individuals who transferred their care to another clinic or individuals who default completely but may later reenter care. Given that men were more likely than women to be lost to follow-up, as was observed in an evaluation of an ART program in Cambodia,[30,31] gender-specific strategies to retain and track patients in HIV care are needed.

Many studies carried out in African ART programs have shown correlation between adherence from pill count and virological suppression.[32-35] The lack of correlation between adherence as estimated by an operationalized pill counting method and rebound in HIV replication may be explained by several reasons. First, the number of events for viral rebound was too few. Second, the pill counts were difficult to accomplish at the pharmacy as some patients hoarded leftover medications at home citing possible future shortages as a reason. In fact, since the time of this study, Kitagata Hospital stopped performing pill counts because of lack of time and convenience to patients. Third, a single summary of adherence over a 1-month time interval may not have accurately represented fluctuations that might have occurred.

Our findings are similar to other studies that showed little to no association between patient demographic characteristics and adherence.[36-38] Predictably, failure to disclose HIV serostatus to at least 1 family member was significantly associated with nonadherence. This finding was also observed in a study of discordant couples in which the HIV-infected partner was receiving ART; that is, patients who disclosed more often to others were more likely to be adherent to ART.[39] Failure to disclose one's HIV status to a partner is associated with stigma, which has been shown to hinder adherence.[4] A study in India found that reminders from family members, an indirect indicator that disclosure had occurred, were associated with better adherence outcomes.[40] Provision of couple HIV counseling and testing and community education encouraging disclosure may improve adherence.

The most common reason cited for nonadherence was that the patient had forgotten. The same reason has been mentioned in other studies.[41,42] However, it is clear from our data that some patients ran out of drugs and were not able to return on time for their refills because of transportation problems. The lack of transportation to the monthly clinic appointments, common in rural areas, poses a barrier to access and maintenance of HIV treatment. Rural ART programs should incorporate strategies to reach patients who have problems accessing transportation.

Mutations conferring antiretroviral resistance were present in all samples that were successfully sequenced. The mutations M184V, K103N, and Y181C were among the most common mutations detected, and, disturbingly, they confer resistance to the drugs in the first-line regimen. Of particular concern, however, is 1 patient who carried high-level resistance to a protease inhibitor but had not yet been exposed to that class of drugs.

Our study has some limitations. There was no measurement of pretreatment CD4 and plasma HIV RNA concentration, as these tests were not routinely available when the ART program began. In addition, our evaluation relied on abstracting of patient medical records, which were often incomplete. Another limitation was our inability to determine whether patients lost to follow-up had died, transferred care, or defaulted from treatment

In a government-based ART program, the proportion of patients who achieved suppression of HIV replication was high, and this was strongly associated with self-reported adherence. Universal access to HIV counseling and testing and early referral into care for timely access to ART should be made to improve the prognosis of patients who initiate treatment with advanced disease. Efforts to scale-up treatment to rural areas, where the majority of people live in developing countries, should continue but must incorporate strategies to achieve and sustain high-level patient adherence to ART and HIV care. Capacity and resources to routinely test plasma HIV RNA concentration are needed urgently to monitor response to ART, identify patients on failing regimens, and make timely regimen changes to prevent the accumulation of mutations and potential spread of drug resistance.

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