Response to Antiretroviral Therapy in HIV-Infected Patients Attending a Public, Urban Clinic in Kampala, Uganda

Lisa A. Spacek,[1] Hasan M. Shihab,[4] Moses R. Kamya,[5] Doris Mwesigire,[4] Allan Ronald,[4,6] Harriet Mayanja,[5] Richard D. Moore,[1] Michael Bates,[3] and Thomas C. Quinn[1,2]

[1]Johns Hopkins Medical Institutions, Baltimore, and [2]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; [3]Monogram Biosciences, South San Francisco, California; [4]Academic Alliance for AIDS Care and Prevention and [5]Makerere University, Kampala, Uganda; and [6]University of Manitoba, Winnipeg, Canada

(See the editorial commentary by Carpenter on pages 260–1)

Background. Access to antiretroviral therapy and human immunodeficiency virus (HIV) care is increasing in resource-limited settings. We evaluated clinical, behavioral, and demographic risk factors associated with virologic suppression in a public, urban clinic in Kampala, Uganda.

Methods. We conducted a cross-sectional, observational study of 137 HIV-infected patients who were receiving antiretroviral therapy at the infectious diseases clinic at Mulago Hospital (Kampala). We measured the prevalence of viral suppression, evaluated risk factors associated with virologic failure, and documented phenotypic resistance patterns and genotypic mutations.

Results. A total of 91 (66%) of 137 participants had an undetectable viral load (<400 copies/mL) after a median duration of 38 weeks (interquartile range, 24–62 weeks) of antiretroviral therapy. Median CD4 cell count was 163 cells/mm^3 (interquartile range, 95–260 cells/mm^3). The majority of the patients (91%) were treated with nonnucleoside reverse-transcriptase inhibitor–based 3-drug regimens. In multivariate analysis, treatment with the first antiretroviral regimen was associated with viral suppression (odds ratio, 2.6; 95% confidence interval, 1.1–6.1). In contrast, a history of unplanned treatment interruption was associated with virologic treatment failure (odds ratio, 0.2; 95% confidence interval, 0.1–0.6). Of 124 participants treated with nonnucleoside reverse-transcriptase inhibitors, 27 (22%) were documented to have experienced virologic treatment failure. The most common mutation detected was K103N (found in 14 of 27 patients with virologic treatment failure).

Conclusions. Although many HIV-infected people treated in Kampala, Uganda, have advanced HIV disease, the majority of patients who received antiretroviral therapy experienced viral suppression and clinical benefit. Because of the frequent use of nonnucleoside reverse-transcriptase inhibitor–based therapy, the majority of resistance was against this drug class. In resource-limited settings, initiation of therapy with a potent, durable regimen, accompanied by stable drug supplies, will optimize the likelihood of viral suppression.

Recent studies have shown dramatic improvements in the survival of HIV-infected patients treated with antiretroviral therapy (ART) in Senegal [1], Nigeria [2], South Africa [3], and Uganda [4, 5]. As ART is rolled out in resource-limited settings, a primary concern is that the benefit of therapy should be optimized. Emerging resistance to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) has been documented in the United States [6] and Europe [7]. It has also been associated with single-dose nevirapine for prevention of vertical transmission of HIV in Uganda [8] and Thailand [9]. Resistance to NNRTIs poses a serious threat to the sustained success of ART where inexpensive nevirapine-based combination pills are commonly used.

Evaluation of small cohorts in Côte d'Ivoire [10], Zimbabwe [11], and Uganda [12] has demonstrated drug resistance. Richard et al. [13] found a high prevalence of resistance (52%) in 50 members of a Ugandan cross-sectional cohort. However, few studies have determined risk factors for virologic failure in persons

Received 17 February 2005; accepted 16 September 2005; electronically published 12 December 2005.

Reprints or correspondence: Dr. Lisa A. Spacek, Johns Hopkins School of Medicine, 1830 East Monument St., Rm. 456, Baltimore, MD 21287 (lspacek@jhmi.edu).

Clinical Infectious Diseases 2006; 42:252–9

1058-4838/2006/4202-0015$15.00

receiving HAART and undergoing resistance testing during routine visits to clinics in resource-limited settings [4, 14].

This study examines clinical, behavioral, and demographic factors associated with virologic suppression in a cross-sectional, observational cohort of HIV-infected patients in Kampala, Uganda. In addition, it assesses response to ART outside of clinical trials and documents drug resistance in patients with HIV-1 non-B subtypes.

Unlike previous studies of drug resistance conducted in resource-limited settings, the majority of participants (74%) were treatment naive, and all participants received HAART. Furthermore, this study reflects the success of ART during an interim period when the price of NNRTI-based treatment was reduced from US$500 per month to approximately US$30 per month.

METHODS

Study site. At the time of the study, August–December 2003, more than 3500 patients were receiving care at the infectious diseases clinic at Mulago Hospital (Kampala), run by the Academic Alliance for AIDS Care and Prevention in conjunction with Mulago Hospital. Mulago Hospital is the Ugandan national referral hospital in Kampala, the capital city. The infectious diseases clinic provides free HIV care, including counseling, prophylaxis and treatment of opportunistic infections, and laboratory measurement of complete blood cell count and CD4 lymphocyte count. Clinic physicians prescribe ART on the basis of World Health Organization (WHO) clinical stage and CD4 lymphocyte count.

Patients enrolled in this study purchased their own antiretroviral medications. Our study included ~95% of all patients attending the clinic who were receiving treatment during this 5-month period. Since the time at which the study was completed, governmental and nongovernmental organizations have initiated programs to provide ART at no cost. There are currently 12,000 registered patients at the infectious diseases clinic, and ~3000 of these patients are receiving ART.

Study design and subject recruitment. A total of 137 consecutive patients who were identified during routine visits to the infectious diseases clinic and treated with ART without interruption for at least 12 weeks were enrolled in a cross-sectional observational study. Each patient participated in a clinical evaluation, structured interview, and laboratory assessment. All participants provided written informed consent. The Makerere Institutional Review Board, the Uganda National Committee of Science and Technology, and the Johns Hopkins Institutional Review Board approved this study.

Clinical evaluation. A study physician conducted a clinical evaluation, including WHO clinical staging prior to ART, WHO performance scale status after ART, and Karnofsky performance scale status after ART. Medical history data included diagnosis, prophylaxis, and treatment for opportunistic infections. Pharmacy and medical records provided an up-to-date antiretroviral history. The evaluation also included a review of symptoms and a physical examination.

Structured interview. Trained research staff questioned participants about their health status before and after initiation of ART, their health beliefs related to ART, and their adherence to treatment. Questions were modified from the Adult AIDS Clinical Trials Group Adherence Instruments [15]. Questions regarding socioeconomic issues included the amount spent to purchase ART and the amount earned per month. Participants were asked whether they spent less on essential items or accepted money from family or friends to purchase medications.

Laboratory assessment. Laboratory measurements included a complete blood cell count, CD4 lymphocyte count, aspartate transaminase level, and quantitative measurement of HIV load with use of Amplicor Monitor standard assay, version 1.5 (Roche Molecular Systems), with a detection limit of 400 copies/mL. Drug-resistance testing, including genotype and phenotype testing, was conducted for 46 samples from patients with a viral load >400 copies/mL (Phenosense GT; Monogram Biosciences). Results were obtained for 36 samples. Drug-resistance testing was not successful in the remaining 10 samples because of low viral copy number (7 samples), reduced viral fitness (2), and the presence of an internal restriction site (1).

Statistical analysis. χ^2 and Fisher's exact tests were used to compare categorical data, and Student's t test was used to compare continuous variables. P values of $<.05$ were considered to be statistically significant. Logistic regression models assessed variables associated with undetectable viral load (<400 copies/mL). Models were examined for interaction. Analyses were conducted using the SAS statistical software package, version 8.02 (SAS Institute).

RESULTS

Clinical data. Of 137 participants, 54% were women. The mean age ($\pm$SD) of the patients was 38.8 $\pm$ 8.0 years. Prior to receipt of ART, no participants were classified as having WHO clinical stage 1 HIV disease, 6% of the patients had stage 2 disease, 28% had stage 3 disease, and 66% had stage 4 disease. Participants reported a median duration of ART of 37.7 weeks (interquartile range [IQR], 23.6–62.1 weeks). Current ART was a 3-drug regimen containing nevirapine for 77% of the participants, a 3-drug regimen containing efavirenz for 14%, and a 3- or 4-drug regimen containing protease inhibitors for 8%. One percent of the patients were treated with a triple-nucleoside combination. The majority of patients (101 patients) were treated with a combination pill containing nevirapine, lamivudine, and either stavudine or zidovudine. Only 4 participants had experienced treatment with both NNRTIs and protease inhibitors. Two of the 74 women had taken perinatal nevira-

pine, 1 of whom had virus with the K103N mutation. The other woman had a viral load of 557 copies/mL, which did not allow for successful genotype testing.

Medical history. Fifty-seven participants (42%) reported a history of tuberculosis treatment. Eight participants were receiving medications for tuberculosis treatment. Prophylaxis against opportunistic infections included fluconazole (36% of patients), trimethoprim-sulfamethoxazole (70%), and dapsone (8%). Of 86 patients with a CD4 lymphocyte count <200 cells/mm^3, 75 (87%) were treated with either trimethoprim-sulfamethoxazole or dapsone. Of 49 patients with a history of cryptococcal meningitis, 46 (94%) were treated with fluconazole.

Treatment outcomes. A total of 91 (66%) of 137 participants had undetectable viral loads (<400 copies/mL). Among patients with detectable viral loads, the mean (±SD) viral load at the study visit was 4.1 ± 1.0 $\log_{10}$ copies/mL. Median CD4 lymphocyte count was 163 cells/mm^3 (IQR, 95–260 cells/mm^3). The median CD4 lymphocyte count was lower for men (138 cells/mm^3; IQR, 81–217 cells/mm^3) than for women (mean CD4 lymphocyte count, 182 cells/mm^3; IQR, 102–273 cells/mm^3; $P = .03$). Median total lymphocyte count was 1900 cells/mm^3 (IQR, 1300–2200 cells/mm^3) for men and 1800 cells/mm^3 (IQR, 1500–2300 cells/mm^3) for women. Mean hemoglobin level (±SD) was 14.2 ± 1.5 g/dL for men and 12.6 ± 1.4 g/dL for women.

CD4 lymphocyte count and HIV load prior to study visit were extracted from medical records. The mean number of weeks (±SD) between the previous measurement of CD4 lymphocyte count and the study visit was 18.7 ± 12.7 weeks. For participants who were not receiving ART at the time of prior CD4 lymphocyte measurement (40 patients), median CD4 lymphocyte count recorded prior to this study visit was 55 cells/mm^3 (IQR, 11–147 cells/mm^3). Participants treated with ART at the time of prior CD4 lymphocyte measurement (97 patients) had a median CD4 lymphocyte count of 145 cells/mm^3 (IQR, 72–237 cells/mm^3). Prior CD4 cell count was significantly different for treatment-naive versus treatment-experienced participants ($P < .001$). HIV load prior to study visit was available for only 23 participants. Mean viral load (±SD) was 4.4 ± 1.4 $\log_{10}$ copies/mL. In 8 treatment-naive participants with viral load measured prior to treatment initiation, mean viral load (±SD) was 5.5 ± 0.4 $\log_{10}$ copies/mL, compared with 3.2 ± 1.4 $\log_{10}$ copies/mL for 15 treatment-experienced participants ($P = .007$).

Characteristics associated with undetectable viral load. Characteristics of patients with detectable viral load were compared with those of patients with undetectable viral load (table 1). In bivariate analysis, treatment-naive participants, compared with treatment-experienced participants, were more likely to have an undetectable viral load (OR, 3.3; 95% CI, 1.5–7.3). Duration of ART of <1 year was also associated with undetectable viral load (OR, 2.2; 95% CI, 1.1–4.7). For patients initiating therapy at the infectious diseases clinic, the OR for undetectable viral load was 1.7 (95% CI, 0.8–3.6). This finding was attributable to the large number of treatment-naive patients beginning ART at the infectious diseases clinic.

History of unplanned ART interruption for a period of >4 days (OR, 0.2; 95%CI, 0.1–0.5) was associated with virologic failure. Median duration of ART interruption was 30 days (IQR, 14–59 days). Exposure to substandard ART, including dual nucleoside reverse-transcriptase inhibitor (NRTI) regimens, was also associated with virologic failure (OR, 0.2; 95% CI, 0.1–1.0). CD4 cell count before and at study visit, change in CD4 cell count over time, and total lymphocyte count at any time were not associated with viral load suppression. Notably, median CD4 cell counts at any time for patients with viral suppression or treatment failure were all <200 cells/mm^3.

In the multivariate model, 2 characteristics remained significantly associated with treatment outcomes. Treatment-naive patients had a greater likelihood of viral suppression than did treatment-experienced patients (OR, 2.6; 95% CI, 1.1–6.1), and a history of unplanned treatment interruption was associated with virologic treatment failure (OR, 0.2; 95% CI, 0.1–0.6).

Health outcomes. Prior to initiation of ART, 93% of patients reported that they were unable to hold a job, work at home, or go to school, and 69% stayed in bed >1 week per month. After ⩾12 weeks of ART, 85% of patients reported a health status of "good," "very good," or "excellent." A total of 96% of patients reported better performance at home or work, 99% reported feeling stronger, and 93% reported increased energy. None of the participants reported feeling weaker while receiving ART.

After ART, 77% of patients were asymptomatic according to the WHO performance scale, 20% were symptomatic, and 3% were bedridden. Self-reported health status was a median of 70 (IQR, 60–80) on a scale of 0–100. Median Karnofsky score was 90 (IQR, 90–100) on a scale of 10–100. WHO performance scale, self-reported health status, and Karnofsky score were uniformly high for patients with virologic failure and suppression; an association with viral suppression was not detected.

Adherence. A total of 89% of participants reported not having missed any doses in the preceding 4 days, and 82% reported not having missed any doses in the preceding 2 weeks. Of those who reported having missed pills, the most frequent reasons reported were "did not have money to buy pills" (21% of patients) and "ran out of pills" (19%). Other reasons reported for missing pills included "away from home" (9% of patients), "forgot to take pills" (3%), "pills not available" (3%), and "afraid of side effects" (2%). When asked if they missed pills because they "felt sad, depressed, or hopeless," no participants agreed.

A history of treatment interruption >4 days in duration was

Table 1. Demographic and clinical characteristics associated with viral load suppression for 137 patients receiving antiretroviral therapy (ART) at a public, urban clinic in Kampala, Uganda.

Characteristic	All patients (n = 137)	Patients with detectable viral load (n = 46)	Patients with undetectable viral load (n = 91)	Bivariate analysis, OR (95% CI)	P
Age, mean years ± SD	39 ± 8	40 ± 10	38 ± 7	…	.15[a]
CD4 count, median cells/mm^3	163.0	169.0	153.5	…	.30[b]
Sex					
Male	63 (46)	20 (43)	43 (47)	1.2 (0.6–2.4)	.68
Female	74 (54)	26 (57)	48 (53)	Referent	
ART naive					
Yes	102 (74)	27 (59)	75 (82)	3.3 (1.5–7.3)	.003
No	35 (26)	19 (41)	16 (18)	Referent	
Duration of ART					
<52 weeks	91 (66)	25 (54)	66 (73)	2.2 (1.1–4.7)	.04
⩾52 weeks	46 (34)	21 (46)	25 (27)	Referent	
ART initiated at infectious diseases clinic					
Yes	66 (48)	18 (39)	48 (53)	1.7 (0.8–3.6)	.13
No	71 (52)	28 (61)	43 (47)	Referent	
Karnofsky score					
>80	115 (84)	42 (91)	73 (80)	0.4 (0.1–1.2)	.10
⩽80	22 (16)	4 (9)	18 (20)	Referent	
History of ART interruption					
Yes	32 (23)	20 (43)	12 (13)	0.2 (0.1–0.5)	<.0001
No	105 (77)	26 (57)	79 (87)	Referent	
History of substandard ART[c]					
Yes	9 (7)	6 (13)	3 (3)	0.2 (0.1–1.0)	.06[d]
No	128 (93)	40 (87)	88 (97)	Referent	
Total monthly household income					
>US$120	89 (65)	32 (70)	57 (63)	0.7 (0.3–1.6)	.42
⩽US$120	48 (35)	14 (30)	34 (37)	Referent	
Social support					
Yes	40 (29)	15 (33)	25 (27)	0.8 (0.4–1.7)	.53
No	97 (71)	31 (67)	66 (73)	Referent	
Education					
Technical or university	66 (48)	23 (50)	43 (47)	0.9 (0.4–1.8)	.76
Primary or secondary	71 (52)	23 (50)	48 (53)	Referent	

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] By Student's t test.

[b] By the Kruskal-Wallis test.

[c] Substandard ART included regimens limited to dual nucleoside reverse-transcriptase inhibitors or dual nucleoside reverse-transcriptase inhibitors and hydroxyurea.

[d] By Fischer's exact test.

documented by medication histories for 32 participants. This was strongly associated with virologic failure (OR, 0.2; 95% CI, 0.1–0.5). Treatment interruption was due to financial difficulties (63% of cases), toxicity or illness (31%), medication not available for purchase (3%), or unknown reasons (3%). Self-reported nonadherence was not associated with virologic failure. There were similar proportions of patients reporting adherence in the suppressed (89%) and unsuppressed (89%) groups.

A total of 100% of participants agreed that "taking all of the drugs in combination or as directed is important to fight the HIV virus," and 91% understood that missing doses encouraged viral resistance. To buy antiretroviral medication, 58% spent less money on food, and 66% spent less money on clothes. A total of 91% received money from family or friends to purchase medications. Eleven percent reported that, despite having money to purchase ART, medications were not available.

Socioeconomic status. Reported monthly income was less than US$30 for 31% of the patients, US$30 to US$120 for 30%, and more than US$120 for 39%. The median monthly income

Table 2. Results of genotyping for resistance to nonnucleoside reverse-transcriptase inhibitors among patients receiving antiretroviral therapy at a public, urban clinic in Kampala, Uganda.

Patient	HIV-1 subtype	Treatment		Reverse-transcriptase mutation(s)
		Current	Previous	
78	A	NVP, 3TC, d4T	NR	M184V, K219E, K103N, V108I
75	A	NVP, 3TC, d4T	NR	G190A
4	A	NVP, 3TC, d4T	NR	Y181C
131	A	NVP, 3TC, d4T	NR	M184V, Y188H, G190A
66	A	NVP, 3TC, d4T	NVP, 3TC, d4T	D67G, M184V, V108I, Y181C, G190A
61	A	NVP, AZT, 3TC	EFV, 3TC, d4T	M184V, K103N, M230L
132	A	NVP, 3TC, d4T	AZT, 3TC, d4T	M184V, Y188L
16	A	NVP, 3TC, d4T	ddI, d4T AZT, 3TC	A62V, K65R, V75I, F77L, Y115F, F116Y, V118I, Q151M, K103N, V106A
102	A	NVP, 3TC, d4T	NR	V106A
19	A	NVP, 3TC, d4T	EFV, ddI, d4T	K65R, Y188L, G190A
101	A	NVP, 3TC, d4T	NR	M184V, K101E, G190A
20	D	LPV/r, AZT, 3TC	NVP, AZT, 3TC EFV, ddI, d4T	M41L, D67N, L210W, T215Y, L100I, K103N, G190A
70	D	EFV, 3TC, d4T	NR	M184V, K101E, K103N, V108I, P225H
137	D	NVP, 3TC, d4T	NR	M184I/V, G190A
80	D	NVP, 3TC, d4T	NR	M184V, K101E, G190A
35	D	NVP, 3TC, d4T	EFV, ddI, d4T, IDV, AZT, 3TC, LPV/r	M184V, K103N, M230L
133	D	NVP, 3TC, d4T	NR	D67G, M184V, K103N, G190A
81	D	NVP, 3TC, d4T	NR	M184I, Y181C
124	D	NVP, 3TC, d4T	NR	M184V, K103N, P225H
121	D	NVP, 3TC, d4T	EFV, ddI, d4T	M184V, K103N, V108I
49	D	NVP, 3TC, d4T	NVP, AZT, 3TC	M184V, K103N
112	A/D	NVP, 3TC, d4T	NR	M184V, K103N
127	A/D	EFV, AZT, 3TC	NR	M184V, K103N, M230L
42	A/D	NVP, 3TC, d4T	NR	M184V, Y181C
89	AE	NVP, 3TC, d4T	ddI, d4T, 3TC	M184V, K103N, Y181C

NOTE. AZT, zidovudine; d4T, stavudine; ddI, didanosine; EFV, efavirenz; IDV, indinavir; LPV/r, lopinavir/ritonavir; NR, none reported; NVP, nevirapine; 3TC, lamivudine.

in Uganda is approximately US$30. Eighty-six participants spent at least US$32 per month to purchase the generic combination pill of nevirapine, lamivudine, and stavudine. Seventeen patients spent from US$32 to US$60 per month, and 32 spent more than US$60 per month on ART. Two participants received drugs from family or friends overseas. We found that the household income level of US$120 per month did not predict viral suppression and that the majority of participants (91%) supplemented household income with money from family and friends to purchase drugs.

Clinical events. The most frequently reported clinical events included pain, numbness, or tingling in the hands or feet (55% of patients) and skin rash with dryness or pruritis (51%). The relationship between peripheral neuropathy and stavudine exposure was not significant, nor was the relationship between rash and exposure to NNRTIs. Rash was reported for 49% of the 125 patients treated with NNRTI-containing regimens. Mean aspartate transaminase level ($\pm$ SD) for 84 participants was 35.4 $\pm$ 27.6 U/L, with a range of 13–189 U/L. Four patients had aspartate transaminase values >70 U/L.

Drug-resistance data. Of the 46 participants with detectable viral loads, 36 had complete genotypic and phenotypic drug-resistance results (tables 2–4). HIV-1 subtypes were A (44% of patients with complete results), D (42%), A/D (8%), and A/E (6%). Twenty-six (72%) of 36 genotypes revealed resistance to the NNRTI class, and the most common mutation was K103N (14 patients). Resistance to NRTIs was predominantly due to the M184V/I mutation (23 patients). Six samples did not reveal genotypic resistance to drugs in the current regimen. Twenty-five participants who were found to be infected with virus that was resistant to NNRTIs now receive second-line protease inhibitor–based ART from the Ugandan Ministry of Health.

DISCUSSION

Our findings suggest that, despite advanced HIV disease, patients treated in a public, urban, infectious diseases clinic in Kampala experienced viral suppression and clinical benefit. The majority of participants (66%) attained viral suppression while

Table 3. Results of genotyping and phenotyping for detection of resistance to protease inhibitors (PIs) and nucleoside reverse-transcriptase inhibitors (NRTIs) among patients receiving antiretroviral therapy at a public, urban clinic in Kampala, Uganda.

Resistance type, patient	HIV-1 subtype	Treatment		Mutations		Phenotype resistance[a]
		Current	Previous	Reverse-transcriptase	PI	
PI resistance						
71	A	LPV/r, AZT, 3TC	IDV, AZT, 3TC	M41L, D67N, V118I, M184V, L210W, T215Y	L10I/V, K20I, M36I, M46I/L, I54V, A71V, V82T	NRTI, IDV, LPV/r, NFV, RTV
108	A	NVP, 3TC, d4T	NVP, AZT, 3TC, ddI, d4T, EFV, IDV, RTV, LPV/r	M41L, M184V, T215F K103N	K20I, L33F, M36I/T, M46I, I84V	3TC, AZT, NNRTI, PI
51	D	IDV/r, ddI, d4T	3TC, d4T	M41L, E44D, D67N, V118I, L210W, T215Y	L10I, K20R, L24I, M36I, M46L, I54V, V82A	NRTI, ATV, IDV, LPV/r, NFV, RTV
NRTI resistance						
55	AE	AZT, 3TC, ABC	EFV, AZT, 3TC	M41L, D67N, M184V, L210W, T215Y, A98G	L10I, M36I	NRTI, NVP
18	D	AZT, 3TC, ABC	AZT, 3TC, ABC, EFV, d4T, 3TC	D67G, K70R, M184V, T215F/I/N/Y, K219Q	L33I, M36I, M46I, L90M	NRTI, IDV

NOTE. ABC, abacavir; ATV, atazanavir; AZT, zidovudine; d4T, stavudine; ddI, didanosine; EFV, efavirenz; IDV, indinavir; IDV/r, indinavir/ritonavir; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NVP, nevirapine; 3TC, lamivudine.

[a] Phenotype resistance is listed according to drug class or specific drugs.

paying for their own drug supply without the additional support of clinical trial infrastructure. The prevalence of viral suppression in our study is greater than the prevalence of viral suppression seen in industrialized countries when HAART was first introduced and evaluated outside of clinical trials [16–18].

Other studies conducted in resource-limited settings [19–21] show that treatment interruption caused by unreliable drug supply is a significant challenge. Our results demonstrate that unplanned treatment interruptions were associated with virologic failure. Of 32 patients who experienced interruption of ART, 20 cited financial constraints as the cause of the lapse in treatment. ART interruption is particularly problematic for patients treated with NNRTI-based regimens. Because of the long half-life of NNRTIs and the comparatively short half-life of NRTIs, patients who experience interruption of NNRTI-based combination therapy are exposed to monotherapy with NNRTIs. In addition, because of the low genetic barrier to resistance, the development of a single mutation, such as the K103N mutation, results in drug resistance.

Twenty-seven (22%) of 124 participants treated with NNRTI-based therapy developed NNRTI resistance. NNRTIs were the current regimen for 91% of participants, because of the availability and inexpensive price of the NNRTI-based combination pills. Because of the frequent use of NNRTI-based therapy, the majority of resistance was against this drug class. Protease inhibitor resistance was limited to 3 participants. Two participants showed extensive resistance against protease inhibitors and NRTIs that required salvage therapy. This type of resistance is of greatest concern, because future options are limited. The longevity of NNRTI treatment may be compromised, because there are few NRTI combinations to serve as a backbone for therapy.

Although adherence to therapy is necessary for viral suppression, our data did not show a significant association be-

Table 4. Genotype and phenotype results among patients receiving antiretroviral therapy at a public, urban clinic in Kampala, Uganda, without documented genotypic resistance to current regimen.

Patient	HIV-1 subtype	Treatment		Mutations		Phenotype resistance
		Current	Previous	Reverse-transcriptase	PI	
122	A	NVP, AZT, 3TC	NVP, d4T, 3TC	None	L10V, K20R, M36I	None
97	A	EFV, AZT, 3TC	NR	None	M36I	None
114	A	NVP, 3TC, d4T	EFV, d4T, 3TC, NVP, 3TC, d4T	None	M361, L63P	Low level
6	D	LPV/r, ddI, d4T	NFV, d4T, ddI, EFV, AZT, 3TC	None	M36I	None
37	D	NVP, 3TC, d4T	NVP, ddI, d4T	None	M36I	None
120	D	NVP, 3TC, d4T	AZT, 3TC	None	None	None

NOTE. AZT, zidovudine; d4T, stavudine; ddI, didanosine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NR, none reported, NVP, nevirapine; 3TC, lamivudine.

tween self-reported adherence and viral suppression. However, because our assessment of adherence was limited to self-report of missed doses and did not include clinic-based pill counts, our results may reflect reporting bias and overestimation of adherence in the unsuppressed group. In this population, drug resistance limited the effect of adherence. Genotype and phenotype testing found evidence of drug resistance in 31 of 36 participants with virologic failure (drug-resistance testing was not successful for 10 participants).

Although we assessed health status after initiation of ART, our conclusions regarding adherence are limited, because we did not evaluate mental health, which may well be a significant variable in this population. However, when asked if they missed pills because they "felt depressed, sad, or hopeless," no participants agreed. The reasons for missing doses were most often related to financial constraints. Recent studies conducted in South Africa, Uganda, and Senegal demonstrate higher medication adherence than that reported in industrialized countries [22–24]. These studies show that the majority of nonadherence is due to treatment interruption as a result of inadequate supply and financial constraints rather than as a result of individual poor adherence.

We found that participants receiving ART reported an improved sense of well-being and the ability to perform activities of daily living. WHO performance scale, health status, and Karnofsky scores were high for all participants, regardless of virologic status. This finding emphasizes that virologic failure occurs in conjunction with clinical well-being. Furthermore, patients with virologic failure may have virus that becomes drug resistant prior to the development of illness. However, our findings are limited by the cross-sectional study design, and we cannot discern the time when virologic failure occurred. Despite the additional cost, viral load measurement may benefit patients at risk for virologic failure. Finally, prospective studies that develop low-cost methods to identify virologic failure by combining clinical health status, adherence, and laboratory assessment are urgently needed.

Although the combined cost of medications and laboratory-based monitoring may require resources that are not yet available in developing countries, the consequences of continuing to provide a failing regimen must be considered. Over time, the clinical benefit will wane if drug resistance increases. In our study, we saw that relatively few participants had been treated with both the NNRTI and protease inhibitor classes. The sequential use of these 2 different classes remains an effective option. Unfortunately, protease inhibitor–based regimens are more expensive and are therefore considered second-line therapy and may be difficult to obtain.

Our findings demonstrate that patients who begin ART when HIV disease is far advanced and CD4 lymphocyte count is extremely low experience a clinical benefit that improves their ability to perform activities of daily living. Treatment-naive participants were more likely to attain viral suppression than were treatment-experienced participants. As suggested by our results, the overwhelming challenge is to prevent unplanned treatment interruptions.

Acknowledgments

Financial support. Bill and Melinda Gates Foundation, HIV Prevention Interventions in the Context of Antiretroviral Therapy; National Institutes of Health K23 Award (AI060384-01); Doris Duke Charitable Foundation President's Planning Fund Grant (20020336); Johns Hopkins University Center for AIDS Research Grant (P30 AI42855); and the Bristol-Myers Squibb Virology, HIV Fellows Research Program. Monogram Biosciences provided drug-resistance testing, including genotype and phenotype testing (Phenosense GT; Monogram Biosciences).

Potential conflicts of interest. M.B. serves as Vice President of Clinical Research for Monogram Biosciences. All other authors: no conflicts.

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