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Outcomes of a Remote, Decentralized Health Center-Based HIV/AIDS Antiretroviral Program in Zambia, 2003 to 2007

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A cross-sectional study of patients living with HIV/AIDS treated during 2003 to 2007 in decentralized, rural health centers in Zambia was performed to measure virological outcomes after 12 months of antiretroviral therapy and identify factors associated with virological failure. Data from 228 patients who started antiretroviral therapy >12 months prior were analyzed. In all, 93% received stavudine + lamivudine + nevirapine regimens, and median antiretroviral therapy duration was 23.5 months (interquartile range 20-28). Of the 205 patients tested for viral load, 177 (86%) had viral load <1000 copies/mL. Probability of developing virological failure (viral load >1000 copies/mL) was 8.9% at 24 months and 19.6% at 32 months. Predictors for virological failure were <100% adherence, body mass index <18.5 kg/m^2, and women <40 years old. Of those with virological failure who underwent 3 to 6 months of intensive adherence counseling, 45% obtained virological success. In a remote, resource-limited setting in decentralized health centers, virological and immunological assessments of patients on antiretroviral therapy >12 months showed that positive health outcomes are achievable.

Keywords: antiretroviral therapy; HIV; rural health centers; sub-Saharan Africa; viral load

Introduction

Located in northern Zambia, Nchelenge district of Luapula Province is a remote, rural, and relatively poor area with an estimated population of 136 000 people. About 60% of the population live under the poverty line, with high levels of unemployment, illiteracy, maternal mortality (830/100 000 live births),[1] and gender inequality. The health care sector in Nchelenge is underdeveloped, and HIV prevalence is high at an estimated rate of 15.2% (adults 15-49 years old).[1] In 2001, an HIV/AIDS care program was started in Nchelenge district as part of a collaborative partnership between Médecins Sans Frontières (MSF) and the Zambian Ministry of Health (MOH) with the aim of reducing the high level of related morbidity and mortality.

The MSF program started in 6 catchment areas with home-based care (HBC) and information, education, and communication (IEC) activities. It expanded in 2002 to 2003 to include HIV testing and care in the rural health centers of 6 villages, including prevention of mother-to-child transmission (PMTCT) and antiretroviral therapy (ART). The program was extended to 2 additional rural health centers in 2005. By July 2007, more than 1300 HIV-positive patients had been started on ART.

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To evaluate the effectiveness of this program, clinical, immunological, and treatment outcomes on ART were routinely monitored. Although immunological (eg, CD4 count) and clinical indicators (eg, weight gain), incidence of opportunistic infections (OIs), and mortality are surrogate measures of ART effectiveness, it is most accurately predicted by measuring rates of viral suppression. However, this is not routinely available in resource-limited settings (RLS).

In a recent meta-analysis virological outcomes from ART programs in Africa have been variable, ranging from 37% to 84% of patients with undetectable viral load (VL) after 12 months.[2] For MSF programs, undetectable VL rates (<400 copies/mL) after 12 months have ranged from 75% to 90%.[3-5] However, most of these data come from programs in large urban centers with better access to resources. In this study, we aimed to assess the effectiveness of ART in a rural, remote, health center-based HIV program, by determining the virological outcomes of patients with at least 12 months of ART experience in Nchelenge, and to identify factors associated with poor virological control.

Methods

Study Population

All patients ≥18 years of age who started ART before August 31, 2005, and remained on ART in the program were eligible for the study. Medical background and follow-up information were collected routinely at each consultation on standardized forms and entered into monitoring software (FUCHIA; Epicentre, Paris, France).

All patients received free comprehensive HIV care, including ART, through the rural health centers. World Health Organization (WHO) prequalified generic antiretroviral (ARV) drugs, mainly as fixed-dose combination (FDC), were provided. Medical doctors, clinical officers, and nurses of both MSF and MOH provided the clinical care.

Eligibility criteria for ART were all patients in WHO clinical stage 4, clinical stage 3 with CD4 <350 cells/mm^3, or clinical stages 1 and 2 with CD4 <200 cell/mm^3. All who met the criteria, showed commitment to the program, and were assessed as likely to reliably take ART were offered treatment. In addition, prophylaxis (cotrimoxazole) and treatment of OIs, nutritional support, and psychosocial support were provided. Patients underwent intensive adherence counseling by nurse counselors prior to and after commencing ART. Peer support groups facilitated by adherence counselors were established at all health centers to provide psychosocial and socioeconomic support.

Virological Testing and Analysis

In September-October 2006 and February-March 2007, a cross-sectional survey of serum VL was conducted for all eligible patients on treatment. Blood samples were collected upon presentation to the clinic for routine HIV care.

For virological examination, separate plasma samples were collected (5 mL in EDTA tube) after centrifugation. Handling time was never >3 hours between collection and processing. After processing, the samples were stored at −20°C for no longer than 1 week. All samples were referred frozen to the Centre for Infectious Diseases Research Zambia laboratory in Lusaka where VL measurements were performed using the Roche Amplicor system. CD4 counts were performed using a fluorescence-activated cell sorting (FACS) count machine.

Virological failure (VF) was defined as a VL >1000 copies/mL, and virological success (VS) as VL ≤1000 copies/mL. Immunological failure was defined as a CD4 count less than or equal to baseline after 6 months of ART, a >50% decrease from CD4 peak on therapy, or failure to increase CD4 by >25 cells/mm^3 over the first year of ART (in the absence of a transient concomitant infection).

All analyses were performed using the Epi-Info statistics program and STATA 9.1 software (Stata Corp, College Station, Tex). Probabilities of developing VF over time were determined using the Kaplan-Meier method.

Ethical Considerations

The Research Ethics Committee of the University of Zambia, Lusaka, approved the research protocol in August 2006 (Ref: 007-08-06, No: FWA 00000338). The MSF Ethics Review Board also approved the protocol in June 2006. Patients were free to accept or refuse participation in the study and signed a consent form before inclusion. All patients were informed about their VL result at their next consultation, and those with VF received appropriate predefined clinical follow-up.

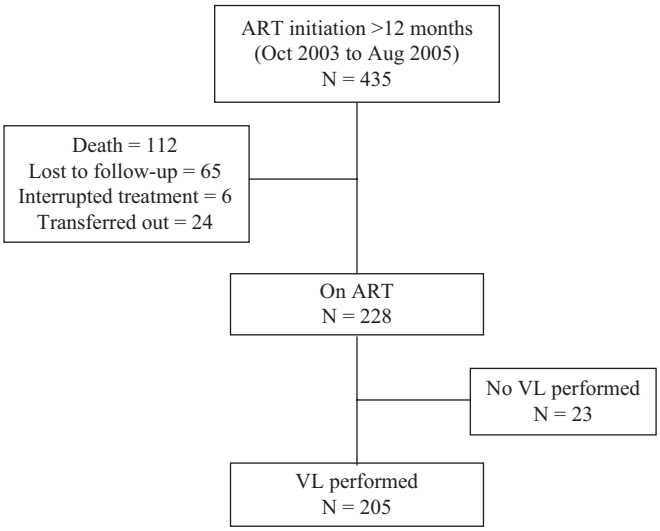

Figure 1. Flowchart of patients included in virological assessment. ART, antiretroviral therapy; VL, viral load.

Results

Baseline Characteristics

Total patient cohort. Among all patients on ART at August 31, 2006, 435 adults had started treatment more than 12 months previously (Figure 1). Of these, 262 (60%) were female, 47% had a body mass index (BMI) <18.5 kg/m^2, and the majority had advanced stages of immunosuppression: 43% in WHO clinical stage 3 and 43% in stage 4, and median baseline CD4 count of 163 cells/mm^3 (interquartile range [IQR] 88-229; n = 143). Median age at ART initiation was 36.4 years (IQR 29.6-42.6). Antiretroviral therapy regimens included stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP) for 380 patients (88%) and d4T + 3TC + efavirenz (EFV) for 45 (10%). Nine (2%) were ART-experienced at their first ARV prescription in the program, and none were on second-line therapy.

By the time of the study, after a median duration on ART of 1.71 years (IQR 0.46-2.24), 112 (26%) patients had died, 65 (15%) were lost to follow-up (LFU), 6 (1%) had interrupted treatment, and 24 (6%) were transferred out. The 12-month mortality rate was 18%, with 82% of these deaths occurring within the first 6 months of treatment. Six-month mortality rates decreased from 18% in 2004 to 7% in 2006. The 12-month LFU rate was 12%, with 62% of these patients lost within 6 months of commencing treatment. The remaining 228 (52%) patients alive and on ART were included in the study.

Cohort of patients remaining on ART. Baseline characteristics of the 228 patients remaining on ART are shown in Table 1. As with the total cohort population, the majority of patients still on ART were in advanced stages of immunosuppression at baseline (89% WHO clinical stage 3 or 4; median CD4 count 163 cells/mm^3). Median duration of ART was 23.5 months with most patients (213; 93%) on d4T + 3TC + NVP at the time of study.

None of the 228 patients refused VL testing, but 23 (10%) did not have VL performed because the collecting team was not present at the time of the patient's visit. However, this group of patients was reported to be 100% adherent to ART. No significant differences were observed in the characteristics of those who had their VL measured compared with those who did not (Table 1).

Virological Outcomes

Of the 205 VL samples analyzed, 177 (86%) met the criteria for VS (Table 2). The probability of developing VF was 8.9% at 24 months, and 19.6% at 32 months (Figure 2). Baseline characteristics for those with VS and VF are shown in Table 3, with significant differences between the groups for median CD4 counts ($P = .03$) and median BMI ($P = .03$). Two patients died just after VL was taken; both had VL >200 000 copies/mL and were known to be adhering poorly to treatment. Two patients had confirmed malaria just before VL was taken (VL of 8270 and 6440 copies/mL, respectively).

Immunological Outcomes

CD4 counts were obtained on the same day as the VL sample for all but 1 patient (204/205; 99.5%). Median CD4 count at the time of study was 455 cells/mm^3: this was significantly greater for the VS group (488 cells/mm^3; IQR 349-586) than the VF group (263 cells/mm^3; IQR 197-400; $P < .001$). Overall median CD4 gain at the time of the study was 294 cells/mm^3, with a median gain of 301 cells/mm^3 for those with VS, compared with 162 cells/mm^3 for those with VF ($P < .01$).

Less than 1% and 9% of patients had a CD4 count persisting <50 and <200 cells/mm^3, respectively.

Table 1. Characteristics of Patients Remaining on ART, With or Without VL

Characteristic	VL Performed (n = 205)	VL Not Performed (n = 23)	Total (n = 228)[a]	*P* Value
Sex	M = 86, F = 119	M = 7, F = 16	M = 93, F = 135	.29
Median age, years (IQR[b])	38 (34-46)	36 (33-45)	38 (34-45)	.58
WHO clinical stage at ART baseline	I = 9, II = 14, III = 124, IV = 58	I = 1, II = 1, III = 15, IV = 6	I = 10, II = 15, III = 139, IV = 64	.96
Median CD4 count, cells/mm^3, at ART baseline (IQR)	161 (103-217)	174 (96-317)	163 (103-232)	.26
ART regimen[c]	d4T/3TC/NVP = 191; AZT/3TC/EFV = 2; AZT/3TC/NFV = 1; d4T/3TC/EFV = 7; d4T/3TC/NFV = 4	d4T/3TC/NVP = 22; d4T/3TC/EFV = 1	d4T/3TC/NVP = 213; AZT/3TC/EFV = 3; AZT/3TC/NFV = 1; d4T/3TC/EFV = 7; d4T/3TC/NFV = 4	.93
Median ART duration, months (IQR)	24 (20-28)	23 (22-26)	23.5 (20-28)	.60
Median BMI, kg/m^2, at ART baseline (IQR)	19.0 (17.6-21.0)	20.0 (17.6-21.8)	19.1 (17.6-21.6)	.28

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; d4T, stavudine; EFV, efavirenz; F, female; M, male; NFV, nelfinavir; NVP, nevirapine; VL, viral load; WHO, World Health Organization.
[a] Not all characteristics have the same number of patients.
[b] IQR, interquartile range (25%-75%).
[c] ART regimen at date of viral load test.

Table 2. Viral Load Measurements of Patients on ART >12 Months

Viral Load (Copies/mL)	N	%	95% CI
≤1000	177	86.4	81-91
>1000 to <10 000	9	4.4	2-8
≥10 000 to <30 000	3	1.4	0-4
≥30 000	16	7.8	5-12
Total	205	100	

Abbreviation: CI, confidence interval.

Patients with VS were 5 times less likely to have a CD4 count <200 cells/mm^3 compared with those with VF (odds ratio [OR] 0.20, 95% CI 0.06-0.65).

Eight patients showed evidence of immunological failure during the study. Immunological failure was 24 times more likely in those with VF (6 patients) compared with those with VS (2 patients; OR 23.7, 95% CI 4.0-182.7).

Anthropometric Outcomes

At >12 months on ART, median BMI was 20.8 kg/m^2 (IQR 18.8-22.5; n = 129). Patients with VS had a significantly higher median BMI (21.1 kg/m^2; IQR 19.6-23.0) than patients with VF (19.8 kg/m^2; IQR 18.7-21.6; $P = .02$).

Predictors of VF

Most of the baseline characteristics (duration of treatment, ART regimen, WHO clinical stage, clinic site, distance living from the clinic, occupation) were not associated with VF (Table 3). Tuberculosis (TB) was specifically examined, but no association was found.

Multivariate logistic regression analysis showed that adherence <100% ($P = .02$) and BMI <18.5 kg/m^2 at baseline ($P = .01$) were positive predictors of VF (Table 4). An interaction between age and sex was observed in predicting those who were more at risk of VF (Table 4). Women >40 years of age were the least likely (OR 0.49), whereas women <40 years were most likely to have VF (OR 2.62). However, men >40 years were more likely to have VF as opposed to men <40 years (OR 2.1).

Follow-up of Patients With VF

Eleven of the 14 patients with VF in September 2006 were followed up after their VL result was obtained (1 could not be traced, and 2 had died). After 3 to 6 months of close monitoring and intensive adherence counseling, 5 (45%) of the 11 patients achieved VS, and overall 7 (63%) had a decrease in VL levels. Four patients (27%) had an increase in VL and were

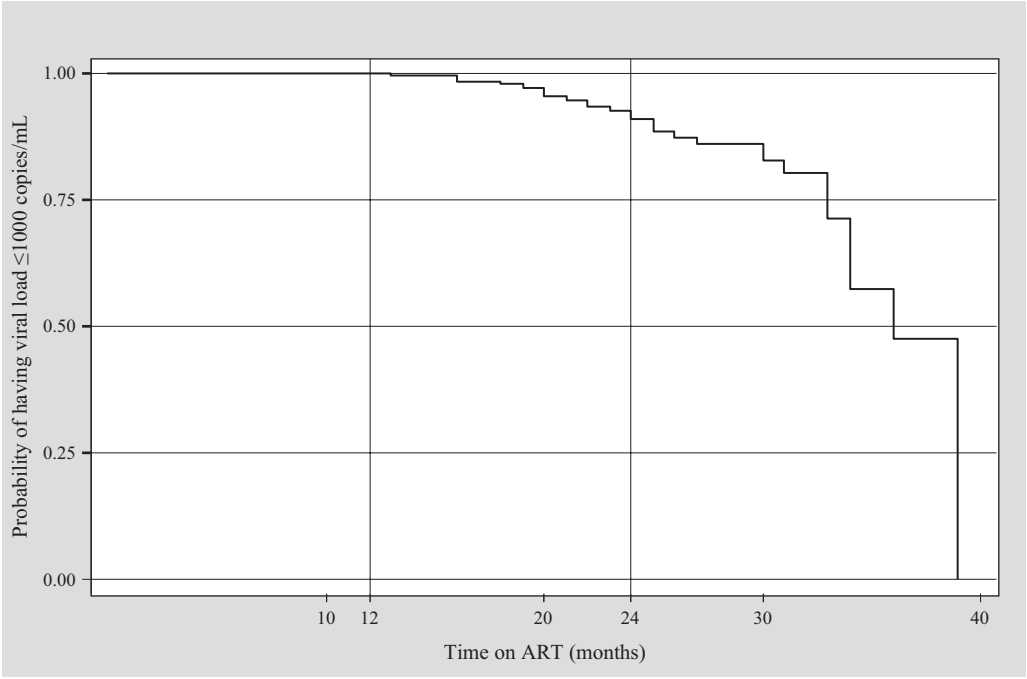

Figure 2. Probability of virological success by time on ART. ART, antiretroviral therapy.

found to have had problems affecting adherence to treatment.

Discussion

Our study of patients with HIV/AIDS cared for through rural health centers in Nchelenge, Zambia, demonstrated positive outcomes for those alive and taking ART for more than 12 months. An estimated 86% of these patients had VS, and immunological gains were robust, with only 9% remaining at risk of life-threatening OIs or disease (CD4 <200 cells/mm^3).

These results compare favorably with other MSF HIV/AIDS programs and were similar to or better than other studies in RLS.[5-8] Although ART has been shown to be successfully provided in these settings, with adherence to treatment equivalent or better than that in more developed settings,[4] most of these data come from large urban centers in RLS. In this study, we show that similar outcomes can be achieved in a remote, rural region of southern Africa, with treatment and care provided through decentralized primary health care centers.

Several factors likely contributed to these results. First, access to health care was increased by decentralizing care to rural health centers closer to patients' homes, and by providing all HIV/AIDS treatment free of charge. Second, the effectiveness of the ART regimens were aided by the use of WHO prequalified generic FDC ARV drugs that ensured the quality of the drugs and adherence-friendly low pill burdens. Third, emphasis was placed on patient education, literacy, and empowerment with respect to the provision of ART, and peer support was available through the formation of support groups. Fourth, people were supplied with supplementary food, which provided nutritional and socioeconomic support. Finally, MSF provided resources, training, and logistical support to the MOH, initially via a parallel service, to ensure quality care and an uninterrupted ARV drug supply.

Of note, although positive immunological outcomes were achieved even in those with VF (median CD4 gain at time of study: 148 cells/mm^3), these results were not as robust as those with VS. In addition, VF patients were 5 times more likely to remain at risk of life-threatening OIs or disease (CD4 count <200 cells/mm^3). These findings demonstrate that people with virologically failing regimens do obtain benefit from treatment (compared with no treatment), but nevertheless improved results can be obtained if full virological suppression is achieved.

Table 3. Baseline Characteristics of Patients With VL Performed

Characteristic	Virological Success (n = 177)[a]	Virological Failure (n = 28)	Total (n = 205)[b]	*P* Value
Sex	M = 74, F = 103	M = 12, F = 16	M = 86, F = 119	.92
Median age, years (IQR[c])	39 (35-46)	37 (30-42)	38 (34-46)	.21
WHO clinical stage at ART baseline	I = 9, II = 12, III = 105, IV = 51	II = 2, III = 19, IV = 7	I = 9, II = 14, III = 124, IV = 58	.61
Median CD4 count, cells/mm^3, at ART baseline (IQR)	164 (112-232)	115 (75-169)	161 (103-217)	.03
ART-experienced	5	0	5	1.0
ART regimen[d]	d4T/3TC/NVP = 165; AZT/3TC/EFV = 2; AZT/3TC/NFV = 1; d4T/3TC/EFV = 7; d4T/3TC/NFV = 2	d4T/3TC/NVP = 26; d4T/3TC/NFV = 2	d4T/3TC/NVP = 191; AZT/3TC/EFV = 2; AZT/3TC/NFV = 1; d4T/3TC/EFV = 7; d4T/3TC/NFV = 4	.19
Median ART duration, months (IQR)	23 (20-28)	25 (20-27)	24 (20-28)	.45
Median BMI, kg/m^2, at ART baseline (IQR)	19.0 (18.0-22.0)	18.0 (16.6-19.2)	19.0 (17.6-21.0)	.03
Distance from clinic, km	<1 = 32; 1-5 = 108; 6-10 = 20; >10 = 17	<1 = 4; 1-5 = 21; 6-10 = 1; >10 = 2	<1 = 36; 1-5 = 129; 6-10 = 21; >10 = 19	.47
Marital status	Single = 28; married = 92; divorced = 38; widowed = 19	Single = 6; married = 16; divorced = 4; widowed = 2	Single = 34; married = 108; divorced = 42; widowed = 21	.68
TB treatment starting ART	16	3	19	.35
TB treatment during ART	7	2	9	
TB treatment at time of VL	9	0	9	

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; d4T, stavudine; EFZ, efavirenz; NFV, nelfinavir; NVP, nevirapine; TB, tuberculosis; WHO, World Health Organization.

[a] Samples with very low levels of HIV, for this study <400 copies/mL, were classified as having "undetectable" viral load.

[b] Not all characteristics have the same number of patients.

[c] IQR, interquartile range (25%-75%).

[d] ART regimen at date of viral load test.

Table 4. Predictors of Virological Failure

Variable/Category	Odds Ratio	95% CI	*P* Value
Men <40 years of age (reference group)	1		
Men >40 years	2.1	0.46-9.21	.34
Women <40 years	2.62	0.66-10.4	.17
Women >40 years	0.49	0.07-3.3	.46
Adherence <100% (reference: 100% adherence)	4.1	1.21-13.7	.02
Baseline BMI <18.5 kg/m^2 (reference: ≥18.5 kg/m^2)	3.2	1.26-7.93	.01

Abbreviations: BMI, body mass index; CI, confidence interval.

These results only represent those patients who remained alive and in the program; significant numbers of patients died (18% at 12 months) or were LFU (12% after 12 months). Thus, a selection bias may have been present in our study as virological suppression rates are likely to be lower in those who died or were LFU. In fact, early mortality rates on ART were high, especially in 2004 when ART activities started (18% at 6 months). Nevertheless, high mortality rates during the first year of ART have been reported from several other RLS countries.[7,9,10] Most deaths (82%) occurred within the first 6 months of treatment, likely related to late initiation of ART when the patient was severely immunosuppressed. In addition, high rates of malnutrition and TB coinfection likely played roles, and immune reconstitution or adverse events from ART may have contributed. However, as cause of death was not

prospectively collected, we could not assess these correlations. Over time, mortality rates decreased (from 18% in 2004 to 7% in 2006 after 6 months of ART), which likely resulted from earlier diagnosis and treatment of HIV and OIs (especially TB) and increasing experience in managing HIV by health staff.

As expected, adherence of <100% was the strongest predictor of VF (OR 4.1), reaffirming the need for excellent adherence to achieve optimal treatment outcomes. This poses a formidable challenge for patients in RLS, especially if faced with stigma and barriers to accessing treatment, and underlines the need for intensive adherence strategies to be implemented in those identified having suboptimal adherence.

Our results also showed that patients with a baseline BMI <18.5 kg/m^2 were more likely to develop VF after 12 months on ART. Although the reasons for this result are not clear, coexistent conditions leading to ARV drug malabsorption may be contributing factors. Nevertheless, this finding may thus help identify patients at increased risk of failure who should be more closely monitored while on ART.

Gender and age were also found to be predictors of VF. The majority of women with VF were <40 years old and were at higher risk (OR = 2.6) than men <40 years, whereas older women were less likely to have VF than men <40 years (OR = 0.49). Although we do not have definitive data to support this, it is postulated that younger women are less likely to disclose their HIV status and are more likely to face abandonment, stigma, and discrimination, negatively affecting treatment adherence. In contrast, older women may have better adherence because their position in the community is often stronger, allowing them an increased ability to make their own decisions and care for themselves.[11] However, we found men >40 years had increased rates of VF (OR = 2.1) compared with men <40 years of age. It is possible that older men have weaker support systems than younger men, contributing to reduced ART adherence. However, some evidence suggests that older age is a risk factor for increased rates of VF,[12] so older men may simply respond less well to ART.

Some patients will fail treatment on first-line ART over time, and second-line ART will be needed.[13] Although no patients in our study required second-line therapy, and numbers requiring second-line across all MSF programs are relatively small (6% of patients switched to second-line after 48 months),[14] this has been influenced by the lack of routine virological monitoring in RLS. It is known that patients with VL >10 000 copies/mL are at increased risk of clinical and immunological failure if they continue their current regimen.[15] Thus, for the 9% of our cohort with VL >10 000 copies/mL, consideration should be given to switching to second-line therapy on the basis of VF alone (assuming intensive counseling and adherence support were properly provided). However, this is limited by the many obstacles to second-line ART in RLS, including high costs, limited availability of newer, more potent drugs (including heat-stable formulations of boosted protease inhibitors), and adherence challenges from the lack of fixed-dose regimens not requiring food restrictions. Such obstacles need to be urgently addressed.

Important to note is that in nearly one half of the patients studied, VF resolved after 3 to 6 months of intensive adherence counseling. Thus, initial failure was likely due to adherence rather than significant antiviral resistance. This must be comprehensively addressed, because if adherence is suboptimal, virologically failing patients will respond no better to second-line ART and will be at risk of prematurely exhausting all their effective ARV drug options through the development of resistance to second-line therapies.

Viral load measurement is an important monitoring tool as evidence from RLS suggests that clinical and immunological failure has poor sensitivity and specificity for detecting VF.[16] Thus, reliance on clinical information can result in delayed detection of treatment failure, which can lead not only to an increased risk of clinical disease progression but also a risk of ARV resistance due to ongoing ARV drug exposure in the presence of high levels of viral replication. In the presence of limited second-line options, such resistance mutations (eg, thymidine analogue mutations [TAMs]) may jeopardize the effectiveness of second-line ART regimens.[17] Therefore, adapted, affordable, and reliable means of measuring VL in RLS are needed for detecting early treatment failure.

Our study has a number of limitations. First, 23 patients had no VL measurement performed. As the majority of these people were traders who traveled out of the area on a regular basis, these patients may have had more difficulty adhering to treatment. However, against this postulation is the fact that all these patients had visited the clinics during the time of the VL study, were all reported to be 100% adherent to ART, and showed no indication of illness or other specific problems.

Second, this cohort study was cross-sectional, with time on ART varying between patients. We were therefore unable to determine exact rates of VF at any specific time points, and this lack of information needs to be considered when making comparisons with other studies where VL is prospectively measured at defined time points (eg, 24 months).

Based on our study findings in Nchelenge, Zambia, we conclude that HIV/AIDS treatment and care delivered free of charge through decentralized and remote rural health centers can result in positive outcomes when patients are on ART for more than 12 months. In addition, BMI and adherence rates <100% can be useful as predictors for VF.

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References

1. *UNAIDS/WHO Epidemiological Fact Sheets on HIV and AIDS, 2008 Update*. Zambia. UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance; July 2008; Geneva, Switzerland.
2. Akileswaran C, Lurie MN, Flanigan TP, Mayer KH. Lessons learned from use of highly active antiretroviral therapy in Africa. *Clin Infect Dis*. 2005;41:376-385.
3. Bedelu M, Ford N, Hilderbrand K, Reuter H. Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. *J Infect Dis*. 2007;196(suppl 3):S464-S468.
4. Ferradini L, Jeannin A, Pinoges L, et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. *Lancet*. 2006;367: 1335-1342.
5. Calmy A, Pinoges L, Cirera A, et al. Increased access to ART in resource-poor settings in Médecins Sans Frontières programmes: outcomes of adults at 18 months of treatment. Presented at: XV International AIDS Conference; 2004; Bangkok, Thailand. [abstract THPEB7179].
6. Ahoua L, Guenther G, Olaro C, et al. Evaluation of antiretroviral therapy for HIV+ adults and children in the Arua HIV/AIDS care program, Uganda, January 2007. Final report, Epicentre and MSF.
7. Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration and ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. 2006;367:817-824.
8. Ivers LC, Kendrick D, Doucette K. Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. *Clin Infect Dis*. 2005;41:217-224.
9. Etard J, Ndiaye I, Thierry-Mieg M, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort. *AIDS*. 2006;20:1181-1189.
10. Zachariah R, Fitzgerald M, Massaquoi M, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. *AIDS*. 2006;20:2355-2360.
11. Bates I, Fenton C, Gruber J, et al. Vulnerability to malaria, tuberculosis, and HIV/AIDS infection and disease. Part 1: determinants operating at individual and household level. *Lancet Infect Dis*. 2004;4:267-277.
12. Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. *AIDS*. 2004;18:2029-2038.
13. Alcorn K. First-line treatment choices proving challenging for African ART programmes. *Aidsmap*. June 27, 2007.
14. Pujades-Rodríguez M, O'Brien D, Humblet P, Calmy A. Second-line antiretroviral therapy in resource-limited settings: the experience of Médecins Sans Frontières. *AIDS*. 2008;22:1305-1312.
15. Murri R, Lepri AC, Cicconi P, et al, ICoNA Study Group. Is moderate HIV viremia associated with a higher risk of clinical progression in HIV-infected people treated with highly active antiretroviral therapy: evidence from the Italian cohort of antiretroviral-naive patients study. *J Acquir Immune Defic Syndr*. 2006;41:23-30.
16. Chaiwarith R, Wachirakaphan C, Kotarathititum W, Praparatanaphan J, Sirisanthana T, Supparatpinyo K. Sensitivity and specificity of using CD4+ measurement and clinical evaluation to determine antiretroviral treatment failure in Thailand. *Int J Infect Dis*. 2007;11: 413-416.
17. Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Chantratital W. Reply to Vogenthaler. *Clin Infect Dis*. 2007;44:1387-1388 [letter].