Virological Outcome of Patients With HIV Drug Resistance Attending an Urban Outpatient Clinic in Uganda: A Need for Structured Adherence Counseling and Third-Line Treatment Options

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Background: HIV drug resistance and suboptimal adherence are the main reasons for treatment failure among HIV-infected individuals. As genotypic resistance testing is not routinely available in resource-limited settings such as Uganda, data on transmitted and acquired resistance are sparse.

Methods: This observational follow-up study assessed the virological outcomes of patients diagnosed with virological failure or transmitted HIV drug resistance in 2015 at the adults' outpatient clinic of the Infectious Diseases Institute in Kampala, Uganda. Initially, 2430 patients on antiretroviral therapy (ART) underwent virological monitoring, of which 190 had virological failure and were subsequently eligible for this follow-up study. Nine patients diagnosed with transmitted drug resistance were eligible. In patients with a viral load > 1000 copies/mL, genotypic resistance testing was performed.

Results: Of 190 eligible patients, 30 (15.8%) had either died or were lost to follow-up. A total of 148 (77.9%) were included, of which 98 had had a change of ART regimen, and 50 had received adherence counseling only. The majority was now on second-line ART (N = 130, 87.8%). The median age was 39 years (interquartile range: 32–46), and 109 (73.6%) were women. Virological failure was diagnosed in 29 (19.6%) patients, of which 24 (82.8%) were on second-line ART. Relevant drug resistance was found in 25 (86.2%) cases, of which 12 (41.3%) carried dual and 7 (24.1%) triple drug resistance.

Conclusion: Two years after initial virological failure, most patients followed up by this study had a successful virological outcome. However, a significant proportion either continued to fail or died or was lost to follow-up.

Key Words: HIV drug resistance, second-line treatment failure, resource-limited setting, adherence, follow-up

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INTRODUCTION

In 2016, more than half of all HIV-infected patients (over 25 million people) lived in sub-Saharan Africa, with an average antiretroviral therapy (ART) coverage of 54%.[1] With the large scale-up of access to ART due to the *test-and-treat* strategy, the number of patients affected by HIV drug resistance is increasing, as recently reported by the World Health Organization (WHO).[2]

According to the Ugandan Population HIV Impact Assessment (UPHIA), 1.2 million Ugandans were living with HIV in 2016 (prevalence 6.2% among adults), and ART coverage was 60%.[3] In the same year, the test-and-treat approach was implemented across the country, and key stakeholders aim to meet the UNAIDS target of 90-90-90 by the end of 2020.[4,5]

Rates of virological suppression on first-line ART have previously been described to be around 85% in Uganda.[6] Inappropriate switching strategies in patients failing first-line regimens have been described in several studies and proofed a consequent higher probability of early failure on second-line therapy.[7,8] So far, the prevalence of acquired HIV drug resistance mutations to second-line ART remains low; however, a mathematical model predicted an increase with 4–6 million patients in need of second-line ART by 2030 in sub-Saharan Africa if routine viral load monitoring was made available.[9–11] As HIV drug resistance testing is still not routinely available in low-income countries including Uganda, detailed information on type and frequency of resistance-associated mutations is sparse, especially for patients on

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second-line treatment. Moreover, at the time of this study, patients on second-line protease inhibitor-based treatment diagnosed with HIV drug resistance had limited treatment options.

In Uganda, previous studies on the prevalence of transmitted HIV drug resistance reported 4% in rural and 7% in urban areas.[12,13] Currently, the WHO reports a much higher prevalence of 18.1% of transmitted resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs).[2]

In this study, we report the 2-year follow-up data on the virological outcomes, as well as HIV drug resistance outcomes of patients previously identified with either virological failure on treatment or transmitted drug resistance in 2015 in an urban Ugandan cohort.[14]

METHODS

Study Design and Setting

We conducted an observational, cross-sectional follow-up study on the virological outcomes of adult patients diagnosed with virological failure or transmitted HIV drug resistance in 2015. This study was conducted in 2017 at the adults' HIV outpatient clinic of the Infectious Diseases Institute (IDI), College of Health Sciences, Makerere University in Kampala, Uganda. The IDI is a center of excellence for HIV treatment and care.[15] Over 8000 HIV-infected patients currently attend the clinic, of which the majority is on ART. In general, patients are seen by a doctor every 3 months. Virological monitoring of patients on ART was introduced recently. Switch options for patients diagnosed with virological failure are discussed at a multidisciplinary switch meeting.[16] Routine resistance testing is currently not available.

Participants and Study Size

In 2015, a first viral load was done in 2430 patients on ART for more than 6 months, of which 190 patients had virological failure defined as a viral load >1000 copies/mL.[14] These 190 patients were eligible for inclusion into this follow-up study. Furthermore, 9 patients diagnosed with transmitted HIV drug resistance in 2015 were eligible for inclusion.

Data Collection

Sociodemographic information and medical history was collected for each study participant. Data were extracted from the IDI electronic medical record (Integrated Clinic Enterprise Application, ICEA) or clinic files.[17] On inclusion, all patients underwent virological testing. HIV-1 RNA viral load was determined using COBAS Ampliprep/COBAS Taqman (Roche diagnostics, South Africa) at the Makerere University-Johns Hopkins University (MUJHU) CORE laboratory certified by the American Pathologists. Additional venous plasma was stored at −80°C and used for retrospective genotypic HIV drug resistance testing at the Ugandan Virus Research Institute/Medical Research Council (UVRI/MRC) in case of persistent virological failure defined as a viral load >1000 copies/mL. The UVRI/MRC is a WHO-accredited laboratory for HIV-1 genotyping and HIV drug resistance testing, which is performed using polymerase chain reaction, gel electrophoresis and purification (QIAquick PCR purification kit; QIAGEN, Germantown, MD), sequencing (Big dye terminator v3.1 cycle sequencing kit; Applied Biosystems Waltham, MA), genetic analysis (ABI 3500 and ABI 3130 machines; Applied Biosystems), base-called sequences (Sequencer v5.3 and sequence alignments, BioEdit v7.2.5 and SeaView v4.0), quality assurance (Calibrated Population Resistance tool, Stanford and the Los Alamos National database for the HIV Sequence Quality Analysis), and assigning of drug resistance mutations (submission of sequences to Stanford HIVdb Program).

Statistical Methods

We determined the proportion of patients on ART with a viral load >1000 copies/mL in 2015. Characteristics were compared using the Pearson χ^2 test or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The following characteristics were considered in the analysis: gender, age, nadir CD4 cell count, WHO stage, year of HIV diagnosis, ART regimen, duration of ART, missed pills, previous side effects, ART switch defined as any switch of drugs including single-drug substitution, and intensified adherence counseling since the start of the study in 2015. The proportions and patterns of detected HIV drug resistance at year 2 were described. Frequencies of most prevalent HIV drug resistance mutations were calculated. For patients with 2 available resistance testing results (2015 and 2017), we investigated for newly detected mutations. Furthermore, for patients with persistent virological failure, we described drug susceptibility to available ART options in Uganda using Stanford HIV drug resistance database program.[20] We evaluated the drug resistance testing results from 2015 and assessed the actions undertaken by the medical personnel, such as treatment switch or adherence counseling. Data management and analysis was performed using STATA version 14.2 (College Station, TX).

The virological outcome of participants previously identified with transmitted drug resistance was described separately. For study participants with newly initiated ART, drug susceptibility was retrospectively assessed comparing Stanford HIV drug resistance database program with first resistance results.[18]

Ethics

This study was reviewed and approved by the Institutional Review Committee of The AIDS Support Organization (IRC TASO, Reference Number: TASOREC/05/17-UG-REC-009) and Uganda National Council for Science and Technology (UNCST, Reference Number: HS33ES). All participants gave written informed consent before study inclusion.

RESULTS

A total of 199 patients were eligible for study inclusion, 190 with previous virological failure, and 9 with previously detected transmitted drug resistance mutations.

Follow-up of Patients With Virological Failure in 2015

Of the 190 patients with virological failure in 2015, 148 were included in this follow-up study and received repeat viral load testing, as well as HIV drug resistance testing in case of persistent failure, as shown in Figure 1 (flow chart). The remaining 42 patients were not included for the following reasons: missing identification numbers (n = 2), death (n = 12), loss to follow-up (n = 18), and declined to participate (10).

Among the 148 patients included in this follow-up evaluation, the median age was 39 years [interquartile range (IQR): 32–46], and 109 (73.6%) participants were women. Most patients had WHO disease stage III (44, 29.9%) or IV (51, 34.7%), and had been on ART for a median time of 6 years (IQR: 4–8 years). In 2015, 115 had been on first-line ART (77.7%) and 33 (22.3%) on second-line ART. At the follow-up evaluation 2 years later, 98 (66.2%) patients had been switched to second-line ART amounting to 18 (12.2%) patients on first-line ART and 130 (87.6%) patients on second-line ART. The median time on second-line ART in 86 patients was 3.82 months (IQR 1–5); for 12 patients, switch data were not recorded. Twenty-eight (23.5%) patients with initial virological failure now attained a viral load <1000 copies/mL on ART without a change in regimen.

During the follow-up evaluation, 29 (19.6%) patients had a viral load >1000 copies/mL with a median viral load of 28,387 (IQR: 8433–75,364) copies/mL. Table 1 compares characteristics of patients with and without virological failure. A significantly higher proportion with virological failure was seen in patients who were on second-line ART in 2015 (14/33 versus 15/115, *P* value: <0.01). Furthermore, patients with virological failure had received a higher number of counseling sessions, and a smaller proportion was switched. Of all patients with virological failure, 24 (82.8%) were on second-line ART. Among these, 16 (55.2%) patients were switched between 2015 and 2017, defined as any change in ART regimen including single-drug substitution, and 10 from first- to second-line ART. Among these patients, the median time on a PI-based regimen was 4.5 months (IQR 2.5–11.25), and switch dates were not available for 2 patients. Furthermore, Table 1 shows the distribution of NNRTI- and PI-based regimens among our study population in 2015 and 2017. In addition, the proportion of patients on a regimen containing tenofovir rose from 44% (857/1932) among patients on first-line ART in 2015, to 71% (101/148) in 2017, taking into account first- and second-line regimens.

For 25 patients, resistance testing results from 2015 were also available. Regarding actions undertaken for these patients, we found that 2 patients were not switched despite available drug resistance testing and treatment options, whereas 9 with available drug resistance testing were not switched because of limited drug options. Furthermore, 12 patients initially identified with HIV drug resistance and scored as susceptible to their treatment respecting their resistance mutations had a persistent viral load >1000 copies/mL.

HIV subtyping and resistance testing was performed in all patients with a viral load >1000 copies/mL (n = 29). Subtypes A (48%) and D (48%) were most common.

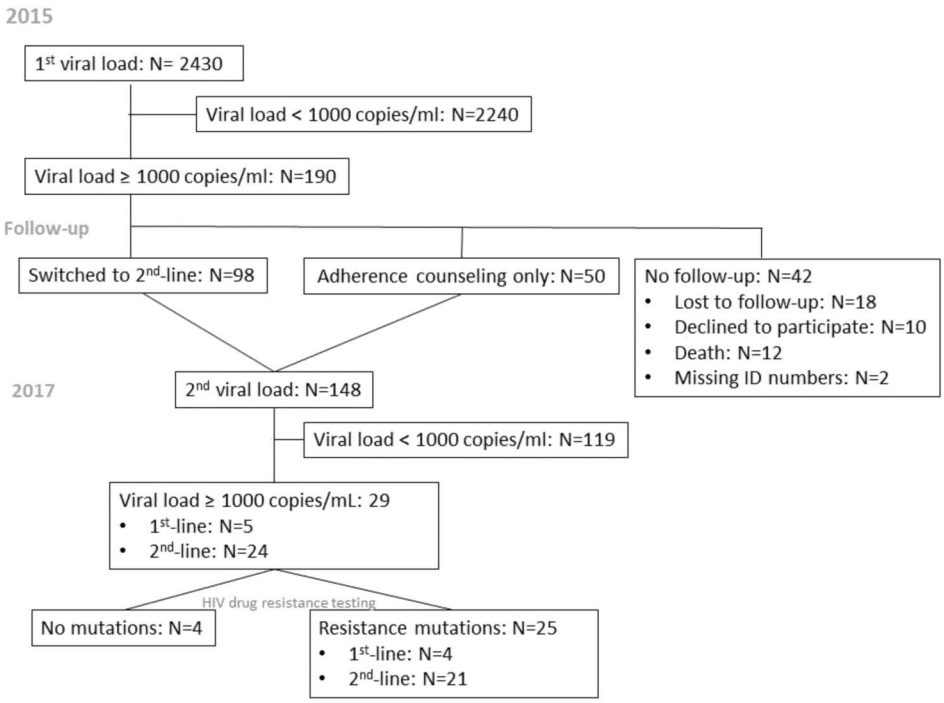

FIGURE 1. Enrollment flow chart.

TABLE 1. Comparing Characteristics of Patients With and Without Virological Failure

Factors	Patients With VF in 2015, N = 148, (%)	Virological Outcomes After 2 yrs		
		Patients Without VF in 2017, N = 119, (%)	Patients With VF in 2017, N = 29, (%)	*P**
Female gender, N (%)	109 (73.6)	90 (75.6)	19 (65.5)	0.27
Age in years, median (IQR)	39 (32–46)	39 (32–45)	42 (34–48)	0.22
Regimen in 2015, N (%)				
EFV- or NVP-based ART	115 (77.7)	100 (84.0)	15 (51.7)	<0.01
AZT/r- or LPV/r-based ART	33 (22.3)	19 (16.0)	14 (48.3)	
Regimen in 2017, N (%)				
EFV- or NVP-based ART	18 (12.2)	13 (10.9)	5 (17.2)	0.35
AZT/r- or LPV/r-based ART	130 (87.8)	106 (89.1)	24 (82.8)	
ART switch, N (%)	107 (72.3)	91 (76.5)	16 (55.2)	0.02
WHO disease stage†, N (%)				
1	10 (6.8)	7 (5.9)	3 (10.3)	0.03
2	42 (28.6)	37 (31.3)	5 (17.3)	
3	44 (29.9)	39 (33.1)	5 (17.2)	
4	51 (34.7)	35 (29.7)	16 (55.2)	
Months since ART initiation†, median (IQR)	72 (49–107)	73 (50–105)	65 (49–115)	0.80
CD4 cell count nadir (cells/μL), median (IQR)	102 (31–182)	108 (37–184)	43 (10–172)	0.17
Number of counseling sessions received, median (IQR)	2 (1–3)	2 (1–3)	3 (2–4)	<0.01
Missed a pill within past 4 weeks, median (IQR)	27 (18.4)	19 (16.1)	8 (27.6)	0.15
Reported side effects, N (%)	18 (12.2)	11 (9.3)	7 (24.1)	0.03

VF, virological failure defined as viral load >1000 copies/mL.
*Pearson χ^2 *P* value or Fisher's exact *P* values.
†Missing values for: months since ART initiation [1], WHO stage [1].

Relevant drug resistance mutations were found in 25 (86.2%) patients, of which 21 patients were on second-line ART. Twelve patients (41.3%) carried dual drug resistance mutations, and 7 (24.1%) were resistant to the 3 drug classes currently available in Uganda, which include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). As shown in Figure 2, most common resistance mutations were M184V (18, 72%), K103N (16, 64%), and thymidine analogue mutations (TAM) (10, 40%). Among patients with ≥1 relevant drug resistance mutation, HIV-1 susceptibility was reduced in 15 (60%) for zidovudine, in 19 (76%) for lamivudine, in 14 (56%) for tenofovir, in 22 (88%) for efavirenz and nevirapine, and in 9 (36%) for atazanavir and lopinavir. Resistance mutations to PIs were only seen in patients on second-line ART.

New resistance mutations were seen in 23 patients comparing repeated HIV drug resistance testing from 2015 to 2017. The following mutations were most likely to be accumulated: A98G, TAMs, E44D, and M184V, as illustrated in Figure 3.

Follow-up of Patients With Transmitted HIV Drug Resistance Mutations

Nine patients with transmitted drug resistance were eligible for inclusion, of which 8 were enrolled. One patient was lost to follow-up. Table 2 summarizes their outcomes. Six patients were initiated on ART with tenofovir, lamivudine, and efavirenz. Of these, one was switched to second-line ART with lopinavir/ritonavir 6 months after initiation due to treatment failure. Two patients were still ART naive. Five of 6 patients were started on an ART regimen to which HIV drug resistance was initially detected for at least one substance. Nevertheless, 4 were virologically suppressed at a median of 18 (IQR: 17–19) months after initiation of ART. A new viral load >1000 copies/mL at year 2 was found in one patient out of 6 on ART with a viral load of 48,583 copies/mL. This patient was also the only one who reported having missed pills.

DISCUSSION

Of the 190 patients identified with virological failure in 2015, 148 were included in this follow-up study, most of which were found to have a successful virological outcome after 2 years. In these cases, the successful outcome was achieved by switching these patients to second-line ART according to national guidelines. A smaller proportion of patients with initial virological failure were now suppressed on ART without a change in regimen. These patients likely benefitted from intensive adherence counseling.

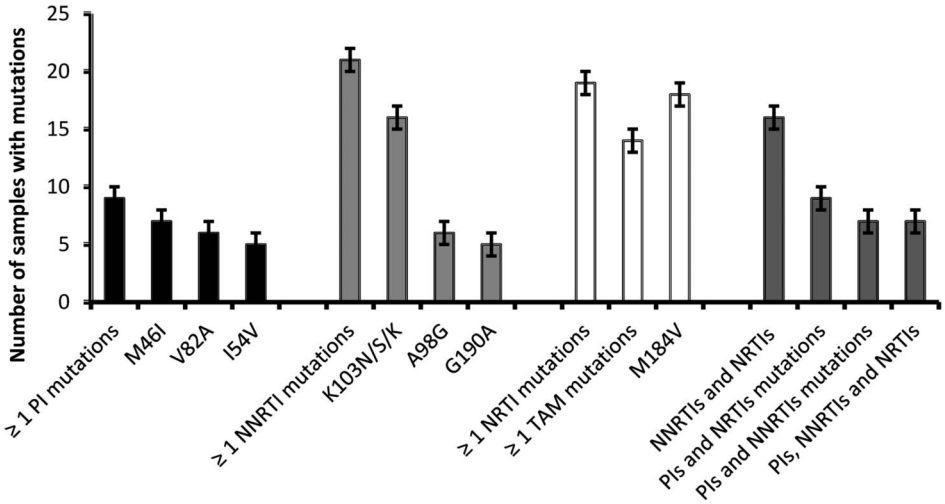

FIGURE 2. Type and frequency of most prevalent HIV drug resistance mutations (n = 25). NNRTI, non-nucleoside/nucleotide reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

A total of 30 (15.8%) patients with virological failure in 2015 had either died or were lost to follow-up. Furthermore, a concerning number of patients with a viral load >1000 copies/mL were identified by this study. Most of these patients were already on second-line ART. Furthermore, we found a high prevalence (86.2%) of HIV drug resistance mutations among individuals with virological failure, primarily M184V, TAMs, and K103N. This finding is largely in line with other studies from the region. However, our result on the prevalence of TAMs differs from other studies in which TAMs were found less frequently.[19,20] Among the 23 study participants with accumulation of HIV drug resistance mutations, TAMs were also most frequently observed in the 2-year follow-up. This observation is likely driven by delayed switching of a failing regimen. As TAMs might impair second-line treatment, it is important to prevent their accumulation and transmission. In our study, we found a small group of patients with resistance to tenofovir (K65R/N or K70E/G/Q), unlike the TenoRes study that reported a high prevalence of tenofovir resistance in sub-Saharan Africa reaching over 50% of patients with virological failure on a tenofovir-based regimen.[21]

The high proportion of patients failing second-line treatment is concerning and, regardless of the cause, puts this group at high risk of morbidity and mortality.[22] We found a need for third-line ART (confirmed by resistance testing) in almost half of the patients failing on second-line ART. This finding is in agreement with other studies showing 36% of patients failing on second-line ART at 3 years in resource-limited settings, mainly due to suboptimal adherence rather than drug resistance.[10,23,24] This suggests that reasons for suboptimal adherence during first-line treatment may not have been effectively addressed before switching to second-line treatment. Considering that 14/24 patients with virological failure on second-line ART in 2017 were switched to second-line ART more than 24 months ago, patients were on a PI-based regimen with unsuppressed viral load for a prolonged time. Interestingly, 19 specimens showed newly acquired NNRTI resistance mutations in 2017, although only 5 were on a NNRTI-based regimen at

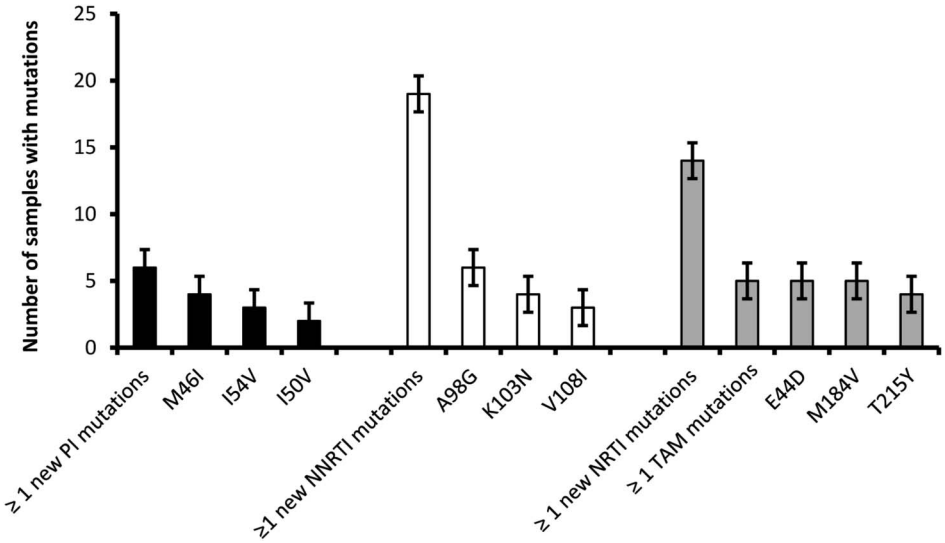

FIGURE 3. Type and frequency of most prevalent newly accumulated mutations comparing results from resistance testing in 2015 with results from this study (n = 23). NNRTI, nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

TABLE 2. Outcome of Patients With Transmitted Drug Resistance Mutations in 2015 (n = 9)

	Type of HIV Drug Resistance Mutations (2015)	Current ART Regimen	VL in Copies/mL	Type of HIV Drug Resistance Mutations (2017)
1	Y181C	TDF-3TC-EFV	<20	Not applicable
2	K101E, Y181C, G190S, K65R, and M184V	AZT-3TC-LPV/r	<20	Not applicable
3	K101E	TDF-3TC-EFV	<20	Not applicable
4	G190A and T215S	TDF-3TC-EFV	<20	Not applicable
5	K101E	TDF-3TC-EFV	<20	Not applicable
6	M41L	Naive	29,579	None
7	K103N	Naive	4864	None
8	M230L and T215I	TDF-3TC-EFV	48,583	M184V, T215F, K103N, V108I, F227L, and M230L
9	LTFU	LTFU	LTFU	LTFU

3TC, lamivudine; AZT, zidovudine; EFV, efavirenz; HIVDR, HIV drug resistance; LFTU, lost to follow-up; LPV/r, lopinavir/ritonavir; TDF, tenofovir; VL, viral load.

the time. We assume ongoing adherence problems in these patients.

Furthermore, patients with multiclass drug resistance mutations undermine that the idea of *treatment as prevention* as transmission of such virus strands poses a tremendous public health risk.[25] The reason for continued virological failure and therefore the accumulation of drug resistance mutations over the course of time must be evaluated in detail in these patients.

The extraordinary setting of this longitudinal follow-up study allowed us to compare 2 subsequent resistance testing results, which are not generally available in resource-limited settings, and to describe its impact on the standard of care in our clinic. We identified 2 patients who should have had a switch of ART regimen according to their initial resistance testing result. Furthermore, 5 patients were initiated on an ART regimen with previously detected reduced susceptibility.

Our findings show the need to strengthen procedures on managing patients with virological failure and HIV drug resistance. After this study, the IDI clinic staff planned and implemented a specialized clinic for patients with a viral load >75 copies/mL constituted by a trained team of physicians, nurses, and counselors. Selected patients are now referred to this specialized team, which can see patients more frequently and guide each patient according to their personal needs. This promising patient management concept could reduce rates of patients with virological failure through a very personalized approach to care. In addition, making HIV drug resistance testing available in a setting with professional staff in problematic cases could greatly advance ART decision-making.[26]

Our study has some limitations. Our findings lack generalizability, as data were collected at one site only. We were further unable to contact 18 patients and subsequently declared them as lost to follow-up. This is of concern, as these patients were at high risk of developing HIV-associated complications. Furthermore, we were unable to investigate risk factors for continued virological failure due to small numbers of participants.

In conclusion, ART options as recommended by WHO treatment guidelines combined with adherence counseling are successful in achieving suppression in the majority of HIV-infected patients with treatment failure. Nevertheless, we found a concerning group of patients with persistent treatment failure on second-line ART who require special attention. We recommend close follow-up and intensified adherence counseling for patients with persistent treatment failure. And finally, for those with extensive resistance patterns, affordable third-line drug options need to be made accessible.

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