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Abstract

We evaluated adult Nigerian patients with antiretroviral switch to second-line treatment with ritonavir-boosted protease inhibitor (PI/r)-based regimens due to virologic failure (confirmed HIV-1 RNA viral load [VL] >1000 copies/mL) during first-line antiretroviral therapy. Proportion of patients with VL >400 copies/mL and characteristics associated with nonsuppression during second-line treatment are described. Approximately 15% of patients (34 of 225) had VL >400 copies/mL at 1-year after treatment switch to PI/r-based regimens. In adjusted analyses, VL $\geq$5 $\log_{10}$ copies/mL at treatment switch (odds ratio [OR] 2.90 [confidence interval (CI) 1.21-6.93]); duration of first-line treatment after virologic failure >180 days (OR 2.56 [CI 1.0-6.54]); and PI/r regimen adherence <90% (OR 3.27 [CI 1.39-7.68]) were associated with VL >400 copies/mL at 1 year of second-line treatment. We therefore recommend that the maximum permissible time between suspicion of virologic failure and completion of antiretroviral treatment switch should not exceed 6 months when patients develop first-line antiretroviral failure in resource-limited settings.

Keywords

antiretroviral, virologic failure, treatment switch, first-line, ART

Introduction

As HIV treatment programs in resource-limited countries mature, a growing number of patients are failing first-line antiretroviral therapy (ART).[1–3] Detection of ART failure may be delayed due to suboptimal access to HIV-1 RNA plasma viral load (VL) testing for routine follow-up of treatment in these settings.[4,5] Continuation of virologically nonsuppresive highly active antiretroviral therapy (HAART) is associated with increased risk of morbidity as well as accumulation of antiretroviral resistance mutations.[6–9] A need exists for locally generated data to inform prompt treatment switch when patients fail first-line ART within underresourced programs.[6] The HAART was introduced into Nigeria in 2002, and ART scale-up has been ongoing for nearly a decade. Nigeria, with a HIV seroprevalence of 4.1% in 2010, has the second largest number (estimated at 3.1 million) of people living with HIV/AIDS (PLWHA) in sub-Saharan Africa, of which approximately 360 000 patients are on HAART.[10] Currently, VL testing is not routinely available within ART programs in Nigeria. Therefore, analyses of virologic outcomes of ART are few,[11] and patients failing first-line ART are typically detected by using clinical and immunological criteria.[12] In the AIDS Prevention Initiative in Nigeria (APIN) PLUS program, VL testing is used for routine monitoring of ART, and patients who develop virologic failure during first-line ART (with a nonnucleoside reverse transcriptase inhibitor-based regimen) are switched to a ritonavir-boosted protease inhibitor (PI/r)-based regimen for second-line treatment. We analyzed a cohort of such patients for proportion with detectable VL at 6 months and 1 year following initiation of PI/r-based treatment as well as characteristics associated with virologic nonsuppression at these time points.

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Methods

This study was conducted at the HIV clinic of the University College Hospital (UCH), Ibadan. The clinic is an integrated facility providing care, treatment, and support to over 10 000 PLWHA in Nigeria. Since 2004, UCH HIV clinic has received support from the Nigerian Government and the US President's Emergency Plan for AIDS Relief (PEPFAR) through the APIN PLUS program. This study was approved by the joint Ethics Committee of the University of Ibadan and UCH, and by the Northwestern University Institutional Review Board.

We performed an on-treatment analysis of 225 HIV-infected adults (at least 18 years old) enrolled in UCH HIV clinic who met the following inclusion criteria: (1) initiation of first-line combination ART (an NNRTI plus 2 nucleoside reverse transcriptase inhibitors NRTIs) between January 2006 and December 2008; (2) diagnosis of virologic failure (defined as 2 consecutive VL >1000 copies/mL after 6 months of first-line ART; (3) treatment switch to a PI/r-based regimen without drug resistance testing; (4) treatment with a second-line regimen (PI/r plus 2 NRTIs and 1 nucleotide reverse transcriptase inhibitor) for at least 1 year. The ART eligibility was determined according to the Nigerian National Adult ART Guidelines[12] (now revised) which recommended ART for PLWHA with CD4 counts $\leq$200 cells/mm^3, and for PLWHA with CD4 counts between 200 and 350 cells/mm^3 in the presence of World Health Organization stage 3 or 4 disease. We excluded patients who had switched to PI/r regimen due to other reasons besides virologic nonsuppression. We obtained de-identified data from UCH HIV clinic electronic database which contained the following information collected at the time of initial and follow-up clinical visits: (1) demographics; (2) CD4 counts; (3) VL; and (4) antiretroviral drugs dispensing records. All patients had VL and CD4 count estimations done once every 6 months as part of routine treatment monitoring. These tests were performed at the UCH HIV Reference Laboratory using Cobas Amplicor HIV-1 Monitor assay, version 1.5 (Roche Diagnostic systems, Inc., Branchburg, New Jersey) for VL testing, and flow cytometry (Partec GmbH, Munster, Germany) for CD4 count estimations. We defined detectable VL as >400 copies/mL based on the threshold of the assay used. The primary outcome measure was proportion of patients with a detectable VL at 1 year following initiation of PI/r regimen. Second-line regimen adherence was determined according to pharmacy-based antiretroviral dispensing records, which defined drug adherence as percentage of actual versus expected pharmacy refills of PI/r regimen over the first year of second-line treatment. The duration of first-line treatment after virologic failure was defined as the time interval (in days) between the first VL >1000 copies/mL and treatment switch to PI/r-based ART. We analyzed virologic suppression at 6 months and 1 year of PI/r-based treatment in relation to the following characteristics: sex, age, switch VL, switch CD4 count, nadir CD4 count, duration of first-line treatment after virologic failure, and PI/r adherence. We dichotomized covariates as follows: (1) age $\leq$35 years, (2) switch VL <5 $\log_{10}$ copies/mL, (3) switch CD4 count $\leq$200 cells/mm^3, (4) nadir CD4 count $\leq$100 cells/mm^3, (5) duration of first-line treatment after virologic failure $\leq$180 days, and (6) PI/r adherence <90%. We performed bivariate comparisons of categorical and continuous variables using Fisher exact and Wilcoxon rank sum tests, respectively, and utilized logistic regression to estimate multivariate odds ratios (ORs, with 95% confidence intervals) associated with detectable VL at 6 months and 1 year of PI/r-based therapy. Continuous variables are presented as median and interquartile range (IQR), and categorical variables as percentages. A P value <.05 was considered statistically significant.

Table 1. Virologic and Immunologic Characteristics of Study Patients.

Patient Characteristic	Median (IQR)
Pre-ART VL, $\log_{10}$ copies/mL	5.4 (4.8, 5.8)
Switch VL, $\log_{10}$ copies/mL	4.6 (3.9, 5.2)
Nadir CD4 count, cells/mm^3	63 (29, 132)
Switch CD4 count, cells/mm^3	139 (58, 235)
CD4 count at 6 months of PI/r follow-up, cells/mm^3	264 (178, 400)
CD4 count at 1 year of PI/r follow-up, cells/mm^3	312 (214, 453)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; PI/r, ritonavir-boosted protease inhibitor; VI, viral load.

Results

Out of 225 patients, 212 (94.2%) had complete data on all study variables. All patients (100%) had VL results at 6 months and 1 year of PI/r-based ART. Sixty-five percent (146 of 225) were women; median age was 34 years (IQR 29, 40). Seventy-three percent (164 of 225) and 27% (61 of 225) of patients received nevirapine (NVP)-based and efavirenz (EFV)-based first-line regimens, respectively. The median duration of first-line ART was 16.0 months (IQR 12, 23). The virologic and immunologic characteristics of study patients are depicted in Table 1. The proportion of patients with switch VL <5 $\log_{10}$ copies/mL was 64.4% (145 of 225). Patients with duration of first-line treatment after virologic failure $\leq$180 days made up 38.2% (86 of 225). The median duration of first-line treatment after virologic failure was 258 days (IQR 112, 379). Ninety-nine percent of patients received ritonavir-boosted lopinavir-based regimens. Concerning PI/r regimen adherence, 77.3% (174 of 225) had $\geq$90% adherence performance. At 6 months and 1 year of second-line treatment, 21.3% (48 of 225) and 15.1% (34 of 225) of patients, respectively had VL >400 copies/mL. In unadjusted analysis, patient characteristics significantly ($P <$ .05) associated with VL >400 copies/mL at 6 months and 1 year of second-line ART were switch VL $\geq$5 $\log_{10}$ copies/mL; duration of first-line treatment after virologic failure >180 days; and PI/r adherence <90%. As shown in Table 2, patients who had VL >400 copies/mL at 1 year of PI/r-based treatment (N = 34) were significantly more likely to have had a switch VL $\geq$5 $\log_{10}$ copies/mL (16 of 34); to have experienced duration of first-line treatment after virologic failure >180 days (27 of 34), and to have recorded PI/r adherence <90%

Table 2. Comparison of Virologic Outcomes at 1 Year of PI/r-Based Antiretroviral Therapy for 225 Included Patients.

Patient Characteristic	VL ≤400 Copies/mL at 1 Year of Treatment Number of Patients (%) N = 191	VL >400 Copies/mL at 1 Year of Treatment Number of Patients (%) N = 34	*P* Value
Sex			.25
Male	70 (36.6%)	9 (26.5%)	
Female	121 (63.4%)	25 (73.5%)	
Age			.91
≤35 years	103 (53.9%)	18 (52.9%)	
>35 years	88 (46.1%)	16 (47.1%)	
Switch viral load			.01
<5 log_{10} copies/mL	130 (68.06%)	15 (44.12%)	
≥5 log_{10} copies/mL	51 (26.70%)	16 (47.06%)	
Missing	10 (5.24%)	3 (8.82%)	
Duration of first-line ART after virologic failure			.02
≤180 days	79 (41.4%)	7 (20.6%)	
>180 days	112 (58.6%)	27 (79.4%)	
PI/r regimen adherence			.001
<90%	36 (18.8%)	15 (44.1%)	
≥90%	155 (81.2%)	19 (55.9%)	
Switch CD4 count			.74
≤200 cells/mm^3	119 (62.30%)	19 (55.88%)	
>200 cells/mm^3	66 (34.56%)	12 (35.29%)	
Missing	6 (3.14%)	3 (8.83%)	
Nadir CD4 count			.72
≤100 cells/mm^3	122 (63.87%)	23 (67.6%)	
>100 cells/mm^3	67 (35.08%)	11 (32.4%)	
Missing	2 (1.05%)	0 (0%)	

Abbreviations: ART, antiretroviral therapy; PI/r, ritonavir-boosted protease inhibitor; VI, viral load.

Table 3. Logistic Regression Results for Undetectable Viral Load at 6 Months and 1 Year of PI/r-Based Antiretroviral Therapy for 225 Included Patients.

Patient Characteristic	VL ≤400 Copies/mL at 6 Months of Treatment OR	95% CI	VL ≤400 Copies/mL at 1 Year of Treatment OR	95% CI
Sex				
Male	1.87	0.80-4.37	1.56	0.60-4.04
Age				
≤35 years	0.52	0.24-1.13	0.77	0.33-1.83
Switch viral load				
<5 log_{10} copies/mL	2.40	1.09-5.27	2.90	1.21-6.93
Duration of first-line ART after virologic failure				
≤180 days	2.23	1.0-4.97	2.56	1.0-6.54
PI/r regimen adherence				
≥90%	3.56	1.6-7.7	3.27	1.39-7.68
Switch CD4 count				
>200 cells/mm^3	0.81	0.35-1.85	0.78	0.30-2.0
Nadir CD4 count				
>100 cells/mm^3	0.67	0.31-1.51	1.07	0.41-2.74

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; PI/r, ritonavir-boosted protease inhibitor; VI, viral load.

(19 of 34) when compared with patients who achieved virologic suppression (N = 191). Multivariate analyses (see Table 3) adjusting for sex, age, switch VL, duration of first-line treatment after virologic failure, PI/r adherence switch, CD4 count, and nadir CD4 count showed the following factors to be independently associated with VL>400 copies/mL at 6 months and 1 year of PI/r-based ART: switch VL ≥5 log_{10} (OR 2.40 [CI 1.09-5.27]), and (OR 2.90 [CI 1.21-6.93]), respectively; duration of first-line treatment after virologic failure >180 days (OR 2.23 [CI 1.0-4.97]), and (OR 2.56 [CI 1.0-6.54]), respectively; and PI/r adherence <90% (OR 3.56 [CI 1.6-7.7]), and (OR 3.27 [CI 1.39-7.68]), respectively.

Discussion

Our study describes virologic outcomes among 225 patients on PI/r-based second-line treatment for at least 1 year in a Nigerian ART program. The proportion of patients (191 of 225) with undetectable VL at 1 year of follow-up in our cohort is comparable to an MSF study[13] which reported 81.2% (513 of 632) virologic suppression rate after 12 months of follow-up of African and Asian patients on second-line ART. A smaller sized Cambodian study[14] reported that 92.3% (60 of 65) of second-line ART patients achieved undetectable VL by 24 months of follow-up. Our protocol-specified definition of virologic failure (>1000 copies/mL) is similar to that utilized in the Cambodian study by Ferradini et al.[14] The key finding of our study is that patients with a high switch VL (≥5 log_{10} copies/mL) and prolonged time (>180 days) on a failing first-line regimen are twice as likely to be virologically nonsuppressed within the first year of second-line ART when compared to patients who had a lower level of switch VL and a shorter treatment exposure to a failing first-line regimen. Comparable with our median switch VL of 4.6 log_{10} copies/mL, Ferradini and colleagues[14] reported a median VL of 4.7 log_{10} copies/mL at switch to second-line ART in their cohort. Multiple factors contribute to VL setpoint during treatment failure, including the extent of drug resistance mutations, and viral fitness. In Nigeria, genotypic resistance testing is not routinely available for management of ART patients and was not performed in this study. Ferradini et al[14] reported that (at ART switch) HIV drug resistance analysis in the reverse transcriptase gene showed that 100% (41 of 41) of those tested (41 of 70) had resistance mutations conferring viral resistance to both lamivudine/emtricitabine (3TC/FTC) and NVP/EFV, and 60.9% had resistance to these agents in addition to stavudine/zidovudine (d4T/ZDV), suggesting that failure to achieve virologic suppression was due to drug resistance. A Togolese study[15] of 188 patients on NNRTI-based first-line ART found that only 24.5% (46 of 188) had drug resistance mutations, of which 100% (46 of 46)

were resistant to NNRTIs, and 54.3% (25 of 46) harbored the M184V mutation conferring resistance to 3TC/FTC. Our study finding that prolonged exposure to a failing first-line regimen is associated with virologic nonsuppression on second-line ART supports previous reports[16] that accumulation of resistance mutations to first-line drugs plays a role. In our cohort, the median duration of first-line treatment after virologic failure extended well over 180 days. This observation merits closer scrutiny and suggests clinician ambivalence to suspicion and confirmation of virologic failure. Occasions of prolonged turnaround time for VL test may contribute to this observation, with the implication that treatment switch processes are delayed for as long as it takes clinicians to receive VL test results. Economic considerations may also inform switch-delaying behavior by patients, and physician wariness of unnecessary ART switches.[17] Current public health-oriented ART switch guidelines[18] recommend first-line to second-line treatment switch when confirmed VL exceeds 5000 copies/mL after at least 6 months of HAART in a person whose drug adherence is determined to be sufficient. Our study protocol exceeded these standards. The limitations of this study include being an on-treatment analysis with a small sample size, and without the benefit of HIV drug resistance analysis at any point during ART. Furthermore, due to the low proportion of patients with switch VL <4 $\log_{10}$ copies/mL in this study, a switch VL threshold below 5 $\log_{10}$ copies/mL was not accommodated in our analysis. Nonetheless, our findings suggest that as VL testing becomes increasingly available for ART monitoring in low-and middle-income countries, a need will emerge to proactively manage patients at risk of first-line ART failure by putting in place measures that are sensitive to the time-consuming aspects of the treatment switch process.

We conclude that the success of second-line ART is threatened when the processes for confirmation of virologic failure and completion of ART switch exceed 6 months. We therefore suggest that clinical guidelines for ART switch that are based on a patient's level of viremia as well as a maximum permissible time of 6 months on a failing first-line regimen may improve collective insight for prompt response to suspicion and confirmation of virologic failure during first-line ART in resource-constrained programs.

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