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Genotypic Resistance at Viral Rebound among Patients Who Received Lopinavir/ritonavir- or Efavirenz-Based First Antiretroviral Therapy in South Africa

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Abstract

NNRTI drug resistance mutations (DRM) are increasingly reported in Africans failing their first antiretroviral regimen. The Phidisa II trial randomized treatment-naïve participants to LPV/r or EFV with d4T+3TC or ZDV+ddI. We report the prevalence of DRM in subjects who achieved HIV RNA < 400 copies/mL at 6-months but subsequently had 2 consecutive HIV RNA >1000 copies/mL. Sixty-eight participants fulfilled the inclusion criteria. NNRTI-DRM were found in 17/36 (47.2%) EFV-recipients, and M184V/I mutation in 14/40 (35.0%) 3TC-recipients. No PI

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mutation was identified in 38 LPV/r-recipients. This is one of the first studies in Africa confirming the paucity of PI-associated DRM despite virologic failure.

Keywords

genotypic resistance; non-nucleoside reverse transcriptase inhibitors; protease inhibitors; HIV; South Africa; antiretroviral naïve

INTRODUCTION

Combination antiretroviral therapy (cART) has been effective in reducing morbidity and mortality of HIV infection in resource-limited countries. In South Africa, cART became available through the national ART roll-out since April 2004¹. Current South African HIV treatment guidelines recommend a non-nucleoside reverse transcriptase inhibitor (NNRTI), combined with two nucleos(t)ide reverse transcriptase inhibitors (NRTI) one of which should be lamivudine (3TC) or emtricitabine, as first-line cART². Although these regimens are highly effective, there are increasing reports of HIV-1 drug resistance compromising treatment. Studies from sub-Saharan Africa have reported drug resistance mutation frequencies of 66% to 91% in those failing first cART. Resistance to 3TC and the NNRTIs were the most commonly identified³⁻⁹.

Ritonavir-boosted protease inhibitor (PI/r)-based regimens are commonly used as first-line cART in developed countries where many additional second-line cART options exist¹⁰, but are seldom available as initial cART regimens in Africa. PI/r have a greater genetic barrier to development of resistance than NNRTI- or NRTI, and presence of PI-associated resistance mutations at virologic failure are uncommon¹¹.

The Phidisa II trial compared the efficacy and safety of efavirenz (EFV) to lopinavir/ritonavir (LPV/r)-based regimens in South Africa.¹² It was designed in 2003 and started enrolment before the national ART roll-out. This study represents one of the largest cohorts initiating PI/r-based first-line cART in Africa, and a unique opportunity to describe genotypic resistance patterns in those failing EFV vs. LPV/r-based cART. We conducted a descriptive substudy to investigate the prevalence and type of genotypic resistance in participants who had viral rebound after viral suppression at 6 months.

METHODS

Phidisa II was a randomized, open-label 2×2 factorial study which enrolled members of the South African National Defence Force (SANDF) and/or their dependents ≥14 years of age, with advanced HIV disease and/or CD4+ cell counts < 200 cells/mm³, who were treatment-naïve or had <7 days of prior therapy. It compared the efficacy and safety of four regimens: (EFV vs. LPV/r) + (stavudine+lamivudine [d4T+3TC] vs. zidovudine+didanosine [ZDV+ddI]). Patients had follow-up visits at months 1, 2, 3, and then every three months. The primary study was approved by the SANDF and the United States National Institute of Allergy and Infectious Diseases (NIAID) Institutional Review Boards. All participants signed written informed consent before enrolment.

This substudy selected participants with confirmed viral rebound (defined as HIV RNA >1,000 copies/mL on two consecutive visits after having documented viral suppression to <400 copies/mL at month 6). Baseline characteristics including age, gender, WHO stage, body mass index (BMI), hemoglobin, CD4 count and HIV RNA level were recorded. All cART regimens and changes were recorded.

Genotypic resistance testing was performed on stored blood samples from the date of second consecutive determination of HIV RNA >1,000 copies/mL, using an in-house genotyping assay previously described¹³. This assay has been successfully validated through regular participation in the Viral Quality Assurance (VQA) program run by the NIH. Briefly, viral RNA was isolated from plasma using the MagNa Pure LC automated system (Roche Diagnostics, Indianapolis, IN, USA) and the region spanning protease (PR, amino acids 1–99) through reverse transcriptase (RT, amino acids 1–440) was amplified by nested PCR using an Expand Long Template kit (Roche Diagnostics, Germany). The PCR products were sequenced using BigDye Terminators v3.1 on an ABI 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). Consensus sequences were aligned and manually edited using the Sequencher v4.5 software (GeneCodes, Ann Arbor, MI). Phylogenetic analysis of nucleic acid sequences was performed using MEGA 4 for internal quality purposes and viral subtype was assigned using the REGA HIV subtyping tool. Drug resistance mutations (DRM) were identified using the 2009 IAS-USA list¹⁴ and confirmed using the Stanford Sequence Resistance Database¹⁵. Prevalence of at least one known HIV-1 RT or PR DRM was reported for samples with successful amplification of the relevant RT or PR region. The participants with and without DRM were compared using the Wilcoxon rank sum test for continuous characteristics and Fisher's exact test for binary characteristics. A p-value of <0.05 was considered statistically significant. Pre-cART samples from participants with DRM at rebound were sequenced to determine the baseline genotype.

RESULTS

Key Findings from the Primary Phidisa II Trial

1,771 participants enrolled into the primary Phidisa II trial. After a median follow-up of 24.7 months, there was no statistically significant difference in the hazard for the primary endpoint of AIDS/death between the EFV and LPV/r groups, and between the d4T+3TC and ZDV+ddI groups. At 36 month of follow-up, there was no difference in the proportion of participants reaching HIV RNA < 400 copies/mL between the EFV and LPV/r groups (66.7% vs. 68.9% respectively, $p=0.588$), but a significantly higher increase in CD4 count (18 cells averaged over all follow-up) in the LPV/r group compared to the EFV group ($P < 0.001$). HIV RNA levels were lower ($P < 0.001$) and CD4 cell counts were greater ($P < 0.01$) over follow-up for d4T+3TC versus ZDV+ddI.¹²

Results of the Current Substudy

Seventy-three of 1,771 Phidisa II participants satisfied the inclusion criteria for this substudy, namely, had confirmed rebound HIV viremia (to > 1,000 copies/mL) after suppression at month 6. Five participants were excluded from this analysis: four were known to have discontinued cART 3–6 months prior to genotype testing, and one had an uncertain treatment history. Amongst the remaining 68 participants, 38 were randomized to LPV/r and 30 to EFV; 36 to d4T+3TC and 32 to ZDV+ddI. The median age =35.9 years (IQR:32.9–38.8), 38.2% were female, median hemoglobin = 12.3g/dl (IQR: 10.6–14.1), median CD4 count = 100 cells/mm³(IQR: 53.5–153), median HIV RNA VL = 5.2 log₁₀ copies/ml (IQR: 4.7–5.6), 44% were WHO Stage 3 or 4, and median BMI =22.7kg/m² (IQR: 20.5–26.7). The median time to confirmed rebound was 17.1 months (15.9 months for patients with RT mutations, and 18.4 months for patients with no RT mutations, $p=0.29$); median CD4 count = 261 cells/mm³ and HIV RNA=3.6 log₁₀ copies/ml at rebound. Eight patients had EFV or LPV/r changes prior to rebound, six due to the need to commence rifampicin-based tuberculosis treatment, necessitating switches from LPV/r to EFV, and two due to adverse effects related to EFV.

Genotypic Drug Resistance

Sixty-eight participants' samples were successfully sequenced in the RT and/or PR region. Of the 68 participants, 23 (33.8%, CI: 22.8–46.3%) had at least one known DRM at rebound. The overall frequencies of DRM are shown in Table 1. The specific DRM, CD4 count and HIV-RNA at baseline and change at rebound, and cART for individual participants with DRM are presented in Figure 1. DRM were not detected from pre-cART samples in any participant who had DRM at failure. HIV subtypes were determined for 65 patients: 61 (93.8%) were subtype C, with two A, 1 of each of C/D, and D.

NRTI-resistance mutations—All patients received ZDV+ddI, d4T+3TC, or ZDV+3TC (after drug substitution for toxicity) as the 2-NRTI backbone. NRTI-resistance mutations were detected in 17 participants. The most common was M184V, found in 14 of 40 (35.0%) 3TC-recipients. Four participants had at least one thymidine-associated mutation (TAM) – two recipients of ZDV+ddI had D67N + K70R, another ZDV+ddI recipient had K70R alone. One participant who received EFV+d4T+3TC had four RT mutations (A62V, K65R, M184V, and K219E) in addition to two NNRTI-associated mutations.

LPV/r-based regimens—No PR resistance mutations were detected in the 38 LPV/r recipients. Six of these individuals also received EFV before rebound. Of the 32 individuals who never received EFV, 6 (18.8%, CI: 7.2–36.4%) had NRTI-associated mutations; five had M184V and one with K70R.

EFV-based regimens—Seventeen of 36 EFV recipients (47.2%) had NNRTI resistance mutations. K103N was the most commonly detected in 9 (25%) participants, V106M in 6 (16.7%), and G190S/A +/- Y188C/L in 6 (16.7%). No Y181C mutation was detected. DRM to both NRTI and NNRTI were found in 11/36 (30.5%) of EFV recipients, with the combination of M184V and K103N being most prevalent. The N348I mutation of the connection domain of RT was detected in two participants; both also had NNRTI mutations. There was no statistical difference in the frequency of NRTI mutations between the group exposed to EFV and those never exposed to EFV ($p=0.4$).

Comparison between participants with and those without RT mutations

There was no statistically significant difference in the following baseline characteristics between the groups with and without RT mutations: age, hemoglobin, CD4 count, HIV RNA, BMI, gender, proportion with WHO Stage 3 or 4 diseases, and the time to viral rebound. Those with RT mutations had a smaller increase in CD4 counts (+139 vs. +155 cells/mm³, $p=0.05$). The HIV RNA levels at rebound were similar between the 2 groups (3.9 vs. 3.6 log₁₀ copies/mL, $p=0.25$).

DISCUSSION

Our study is amongst the largest HIV cohort in South Africa who started PI/r as initial cART to date. Our data confirmed those of other studies that PI-associated DRM is much less common than NNRTI- or NRTI-associated DRM at failure. Compared to other reports from sub-Saharan Africa, a smaller proportion of our participants had DRM at confirmed rebound viremia. This could be due to only a quarter of our population being randomized to a regimen containing both 3TC and an NNRTI, the drugs most frequently associated with DRM at failure¹¹; whereas in other cohorts, 94% to 100% of patients were on these RT inhibitors in their first cART^{5–7}. As seen in other studies, M184V and the NNRTI-associated mutations were most prevalent in our cohort^{5,6}.

Since our participants were enrolled in a randomized control trial, they were evaluated on a relatively frequent follow-up schedule of monthly for the first three months, then every three months thereafter. We performed genotype testing at viral rebound confirmed by the second viremia sample, a time point within three months of the first detection of viremia of > 1,000 copies/mL. As a consequence, patients were viremic on therapy for a relatively short period, which may explain the fewer DRM detected. Greater accumulation of DRM, especially NRTI-associated mutations, occurs the longer one remains on a failing regimen⁵. In a Malawi study where treatment failure was not determined virologically, but clinically or immunologically, 93% of participants with viremia (on stored samples) had NNRTI mutations, 81% had M184V, and 56% harbored at least one TAM along with M184V and NNRTI mutations¹⁶.

Two patients in our study developed the connection domain mutation N348I, identified previously as contributing to substantial increase in AZT resistance, including patients with non-subtype B infection¹⁷. N348I may emerge on NRTI or NNRTI exposure, both of our patients received EFV. The detection of N348I in patients with DRM resistance suggests that sequencing programs that include this portion of RT will be useful in deriving a comprehensive drug resistance evaluation.

The pre-cART samples of those with DRM at failure all had wild-type virus, suggesting that pre-treatment transmitted drug resistance was not a reason for failure. However, as more patients in South Africa receive first-line NNRTI based regimens and failure with NNRTI-resistance increases, transmitted resistance will likely increase, which has already been reported in several African countries^{18,19}.

Reasons for rebound viremia in our cohort are uncertain, but non-adherence most likely plays a key role. Adherence assessments were solely based on participants' adherence reports which have limitations. Measures to improve adherence to cART, like: continuous adherence support, using co-formulations and once-daily dosing of cART, may reduce virologic failure with or without DRM.

Our sub-study has a few limitations. First, we only selected patients who demonstrated viral suppression at six month and then had viral rebound, in order to eliminate those who may have had transmitted HIV drug resistance at baseline. This is not representative of all the patients who either did not respond or fail to achieve viral suppression until a later time point. Secondly, as genotype testing was done on the second rebound samples, we cannot prove that PI-resistance mutations did not emerge at a later time point while the patients were viremic and continued to receive LPV/r. Despite these limitations, our findings are important to note as they confirm data from developed countries showing that PI/r has a greater genetic barrier to resistance than NNRTI-based regimens.

In many settings in sub-Saharan Africa, viral load testing is not available and antiretroviral failure is only recognized by CD4 decline or clinical progression. Based on this study and others, virologic failure with DRM precedes clinical or immunologic failure. Phidisa II utilized a relatively frequent viral RNA determination schedule, permitting early detection of rebound viremia. Development of affordable point of care viral load tests in resource-limited setting is critical to allow for early identification and management of treatment failure.

In conclusion, this study confirms the risk of selection of NNRTI and M184V mutations in patients who received EFV and 3TC in first-line cART. Phidisa II represents the largest cohort of adults who received PI/r as first-line cART in South Africa. In this subgroup analysis, no PI-resistance mutations were detected at failure, demonstrating that a PI/r-containing regimen maybe a potential ART option in Africa. The relatively high cost of PI/r

and lack of co-formulations with other ARV drug classes, however, precludes their use as first-line regimen in this population. The absence of PI DRM noted here suggests, however, that the increased cost may be offset by durable efficacy of these antivirals. More affordable generic PI/r and co-formulations available for initial cART options may reduce development of DRM and transmitted drug resistant HIV in Africa.

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EFV + 3TC-based Regimens								Major NRTI Mutations ³											Major NNRTI Mutations ³													
Subject No.	Pre cART CD4 ¹	Pre cART log ₁₀ HIV RNA ¹	months to failure	CD4 chg ¹ @ failure	log ₁₀ HIV RNA ¹ @ failure	1st cART	ART switch before failure	41L	62V	65R	67N	70R	74V	75I	77L	115F	116Y	151M	184V	210 W	215 Y/F	219 Q/E	101 E/W/P	103N	106 A/M	108I	181 C/L/H	188 C/L/H	190 S/A	230L	N348 I	
1	206	5.34	12	-20	4.78	EFV/i4T/3TC	none																									*
2	74	5.92	12	151	4.4	LPV/i4T/3TC	LPV to EFV																									
3	33	5.99	18	306	3.88	EFV/i4T/3TC	none																									
4	82	5.29	15	186	4.02	EFV/i4T/3TC	None																									
5	140	5.65	9	24	3.42	EFV/i4T/3TC	d4T to ZDV																									
6	189	4.99	18	12	4.3	EFV/ZDV/ddI	d4T to 3TC, EFV to LPV																									
7	10	5.00	15	286	3.24	EFV/i4T/3TC	None																									
8	100	4.73	12	145	3.47	EFV/i4T/3TC	stopped for 2 mgn																									
9	123	5.48	12	139	4.09	EFV/i4T/3TC	None																									
10	61	5.49	9	61	5.35	LPV/i4T/3TC	LPV to EFV, then to LPV																									
EFV or LPV + ZDV/ddI																																
Subject No.	Pre cART CD4 ¹	Pre cART log ₁₀ HIV RNA ¹	Mon to failure	CD4 chg ¹ @ failure	log ₁₀ HIV RNA ¹ @ failure	1st cART	ART switch before failure	41L	62V	65R	67N	70R	74V	75I	77L	115F	116Y	151M	184V	210 W	215 Y/F	219 Q/E	101 E/W/P	103N	106 A/M	108I	181 C/L/H	188 C/L/H	190 S/A	230L	N348 I	
11	132	5.30	12	311	3.91	EFV/ZDV/ddI	None																									
12	181	4.14	9	19	4.22	EFV/ZDV/ddI	None																									
13	149	5.47	12	33	4.26	EFV/ZDV/ddI	None																									
14	60	4.85	9	18	3.25	EFV/ZDV/ddI	None																									*
15	89	5.18	15	21	4.63	LPV/ZDV/ddI	LPV to EFV																									*
16	199	5.95	9	-56	5.87	LPV/ZDV/ddI	LPV to EFV																									
17	318	2.84	21	171	3.55	EFV/ZDV/ddI	None																									
18	94	5.88	21	-445	3.54	LPV/ZDV/ddI	None																									
LPV + d4T/ZDV + 3TC-based regimens																																
Subject No.	Pre cART CD4 ¹	Pre cART log ₁₀ HIV RNA ¹	Mon to failure	CD4 chg ¹ @ failure	log ₁₀ HIV RNA ¹ @ failure	1st cART	ART switch before failure	41L	62V	65R	67N	70R	74V	75I	77L	115F	116Y	151M	184V	210 W	215 Y/F	219 Q/E	101 E/W/P	103N	106 A/M	108I	181 C/L/H	188 C/L/H	190 S/A	230L	N348 I	
19	100	5.63	9	290	4.65	LPV/i4T/3TC	None																									
20	102	4.68	21	193	3.27	LPV/i4T/3TC	None																									
21	93	4.85	9	31	4.93	LPV/i4T/3TC	None																									
22	44	5.43	21	81	3.66	LPV/i4T/3TC	None																									
23	125	4.25	15	231	3.57	LPV/i4T/3TC	None																									*
								Presence of mutation																								

Figure 1. Antiretroviral Therapy, Pre-Treatment CD4 and HIV RNA, Time to Failure, CD4 and HIV RNA at Failure, and Major Genotypic Resistance Mutations for Individual Participants with Detected Mutations at Failure

¹ (cells/mm³)

² (copies/mL)

³ Major reverse transcriptase mutations according to the International AIDS Society-USA Drug Resurgence Mutations in HIV-1, December 2009[14]

3TC = lamivudine, ART = antiretroviral therapy, cART = combination antiretroviral therapy, chg = change, d4T = stavudine, ddI = didanosine, EFV = efavirenz, LPV = lopinavir/ritonavir, mon = months

Table 1
Antiretroviral Drug Exposure and Drug Resistance Mutations Identified at Rebound

Resistance Mutations	No. of subjects with DRM	n (%) who received EFV (total N=36)	n (%) who received 3TC (total N=40)	n (%) who received EFV + 3TC (total N=16)	n (%) who received ZDV/ddI (total N=28)	n (%) who received LPV/r (total N=38)
Major PI mutations	0					0 (0%)
Any major NNRTI mutations	17	17 (47.2%)				
K103N	9	9 (25.0%)				
V106M	6	6 (16.7%)				
Y188C/L +/- G190S/A	6	6 (16.7%)				
Y181C	0	0 (0%)				
Major NRTI mutations						
M184V	14		14 (35.0%)			5 (15.6%)*
K70R +/- D67N	3				3 (10.7%)	1 (3.1%)*
N348I	2			2 (14.1%)		
K103N + M184V	7			7 (43.8%)		
Any NNRTI mutation + M184V	9			9 (56.3%)		

3TC = lamivudine, ddI = didanosine, DRM = drug resistance mutation, EFV = efavirenz, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, ZDV = zidovudine

* 6 patients received both LPV/r and EFV before genotype testing, for calculating the percentage of patients who were on LPV/r and had M184V or K70R +/- D67N mutations, only those who received LPV/r without EFV (n=32) were included.