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A Case Report of Multiclass HIV Drug-Resistance After an Inappropriate Switch of ARVs with Persistent Unsuppressed Viral Load

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Abstract

HIV drug resistance is an emerging public health concern; appropriate ART combinations and safe drug switches are prerequisites for achieving virologic suppression. In the early 2000, in Sub-Saharan Africa, accent was mostly on prevention and the scale up of Antiretroviral therapy has just initiated. We report a 46-year-old female who was initiated on ART in 2005 in the private sector, had multiple regimens changes for unclear reasons. Over 7 years (2005-2012), she deteriorated and presented with an AIDS defining condition. A genotyping resistance test (GRT) revealed multiple HIV class resistance and was switched to a third-line ART and improved on treatment. This case report shows that the absence of formal ART guidelines in early 2000, long term exposure to ART and failure to timely switch led to treatment failure and development of multiclass drug resistance mutations identified by the HIV-1 GRT and guided the third-line ART regimen with a successful outcome.

Keywords

ART, HIV, national ART guidelines, delayed switch, multiclass resistance

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Background

The era of antiretroviral therapy (ART) has brought hope to millions of people, and there are 21.7 million people on ART globally.[1] With the guidance of the World Health Organization (WHO), the Ministry of Health and Social Services of Namibia (MoHSS) has developed and implemented ART guidelines for patients living with HIV to ensure standardization and ART optimization in both private and public sectors. However, in the early 2000, HIV prevention strategies were prioritized; antiretroviral drugs were scarce in Africa, the guidelines were still to be developed and implemented.[2] Any reduction of antiretrovirals (ARVs) efficacy should impact negatively the control HIV disease.[3] Here, we discuss a case of a patient who was started on ART regimens before the era of formalized ART and who developed multiple drug resistance to ARV medicines.

Patient Presentation

We report on a 46-year-old woman who tested HIV positive in 2005 and was initiated onto IDV/r and EFV in October of the same year. in the private sector. In October 2007, her ARV regimen was changed to AZT/3TC/LPV/r for reasons not clearly elucidated. Furthermore, in June 2009, it was again switched to TDF/3TC/EFV. She deteriorated on this regimen. In September 2012, due to inability to meet medical expenses in private sector, she self-transferred to the government clinic ART managed by medical doctors. Her CD4 counts were at 282 cells/mm^3, VL of 220 126 copies/mL of blood and she was diagnosed with pulmonary

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tuberculosis (PTB), for which she was treated and cured. On the 24 of January 2013, her VL was at 374 783 copies/mL of blood with a CD4 count of 413 cells/mm^3, and seven months later, on the 10 of September 2013, the VL was still high at 5129 copies/mL of blood despite consistent adherence to her ARVs. In April 2014, her CD4 counts dropped to 307 cells/mm^3, and she was switched to the second line ART, TDF/AZT/3TC/LPV/r and six months later, for the first time, she suppressed her VL to < 20 copies/mL of blood. However, despite her excellent adherence to ART, assessed through pill count and clinic follow-ups, she presented with ranges of VLs > 3 logs for two consecutive years: 117899 copies/mL (April 2016), 1695 copies/mL (July 2016), 1364 copies/mL (October 2016). In March 2017, she presented with a low-level viraemia of 192 copies/mL followed by high VLs of 2916 copies/mL in February 2018 and 17 135 in May 2018 and was referred to be seen by an HIV clinical mentor. At the time of referral, on 31 May 2018, her hepatitis B Surface antigen was non-reactive, and her creatinine clearance was at 90 ml/minutes/1.73 m^2, her CD4 counts were 441 cells/mm^3, the clinical examen was unremarkable and an HIV-1 Genotyping Resistance Test (GRT) was ordered. The GRT results confirmed the presence of mutations and provided drug susceptibility results (Table 1) as per the Stanford HIV drug resistance database[4]

The choice of the ART regimen was guided by the drug activity estimated by the Stanford HIV drug resistance database. AZT was susceptible with a total[1] drug activity, DTG was never used in this patient and was estimated to be fully active,[1] DRV/r had a low-level resistance and was estimated at 0.75 activity. 3TC was kept in the regimen to benefit from the crippling effect of the M184V mutation on viral multiplication. The drug activity of the third-line regimen was estimated at 2.75. In July 2018, the patient was started on the third-line ART, namely DTG/AZT/DRV/r/3TC. She has suppressed her VL at six months, and 24 months later, she is still suppressed (VL < 20 copies/mL and her latest CD4 improved to 502 cells/mm^3 (January 2019) (Figure 1).

Discussion

The WHO early warning indicators to combat HIV drug resistance recommends three ARVs from at least two classes as a prerequisite to viral load suppression (VLS).[5] PI combined with two NRTIs in patients initiating ART is standard in certain regions like Germany.[6] However, this patient started ART in Namibia before the scale up of ART in Sub-Saharan Africa. She has commenced ART with dual therapy, including a PI and an NNRTI. It was two years later, in 2007, that she was transitioned to a triple therapy regimen with two NRTIs and one PI (AZT 3TC LPV/r) and self-transferred to the public sector in 2012, while she was on TDF 3TC EFV. The reuse of EFV, a drug with low genetic barrier[7] after a PI led to monotherapy with the emergence of K65R mutation. Unfortunately, the treatment outcome of this patient has not been monitored before her transfer to the public sector. She was exposed to PI based-ART regimens for four years from 2005 to 2009 with an accumulation of mutations explaining the presence of major PI mutations and subsequent treatment failure[8] despite documented good adherence to ART in the public sector. We think that the change from a PI-based regimen (AZT 3TC LPV/r) to an NNRTI based regimen (TDF 3TC EFV) was an error from the health practitioner. Wellesley *et al*[9] reported that errors in prescribing happen even for ART-experienced patients seen by general practitioners. These findings correlate with the study done by Ekama *et al*[10] in 2013 in Nigeria, where most

Table 1. Findings of the Genotyping Resistance Testing Results; Mutations Detected in the Reverse Transcriptase and Protease Associated with Resistance.

Drug class and detected mutations	Drugs	Penalty Scores	Drug susceptibility
NRTIs: A62V, K65R, M184V **RT polymorphs**: V35I, T39E, S68G, T69I, D121H,	ABC	65	High Level Resistance
K122E, I135K, K173T, Q174K, D177E, V179I, T200A, Q207D, R211K, F214L,	AZT	−20	Susceptible
K219H, Q242R, V245Q, A272P, T286A, E291D, V292I, I293V, Q334N, G335D,	3TC	95	High Level Resistance
A355T, R356T, R356K, M357R, G359T	FTC	95	High Level Resistance
	TDF	55	Intermediate Resistance
NNRTIs: K101E, Y188L, G190A, N348I	EFV	120	High Level Resistance
	NVP	165	High Level Resistance
	RPV	120	High Level Resistance
	ETR	45	Intermediate Resistance
PI majors: M46I, I54V, L76V, V82C **PI accessories**: Q58E **Other PIs mutations**:	ATV/r	60	High Level Resistance
L10LV, T12S, I15V, L19I, K20R, E35D, M36I, R41K, K55R, R57K, I62V, L63P, L89M,	LPV/r	100	High Level Resistance
I93L	DRV/r	20	Low level Resistance

The NNRTIs mutations were K101E, Y188L, G190A, N348I and they confer high-level resistance to most NNRTIs; NVP/EFV/RPV and reduced susceptibility to ETR. The NRTIs mutations detected were A62V, K65R, M184V. The K65R mutation reduces TDF and ABC antiviral activity but increases AZT antiviral activity. Besides, 3TC/FTC select the M184V mutation and reduces 3TC and FTC antiviral activity but increases susceptibility to AZT resulting in a −20-penalty score. The major PI mutation selected were M46I, I54V, L76V, V82 explaining high level resistance to ATV/r, LPV/r and reduced susceptibility to DRV/r. Thus, the drug activity of the latest ART regimen (TDF AZT 3TC LPV/r) had only one drug activity with AZT.

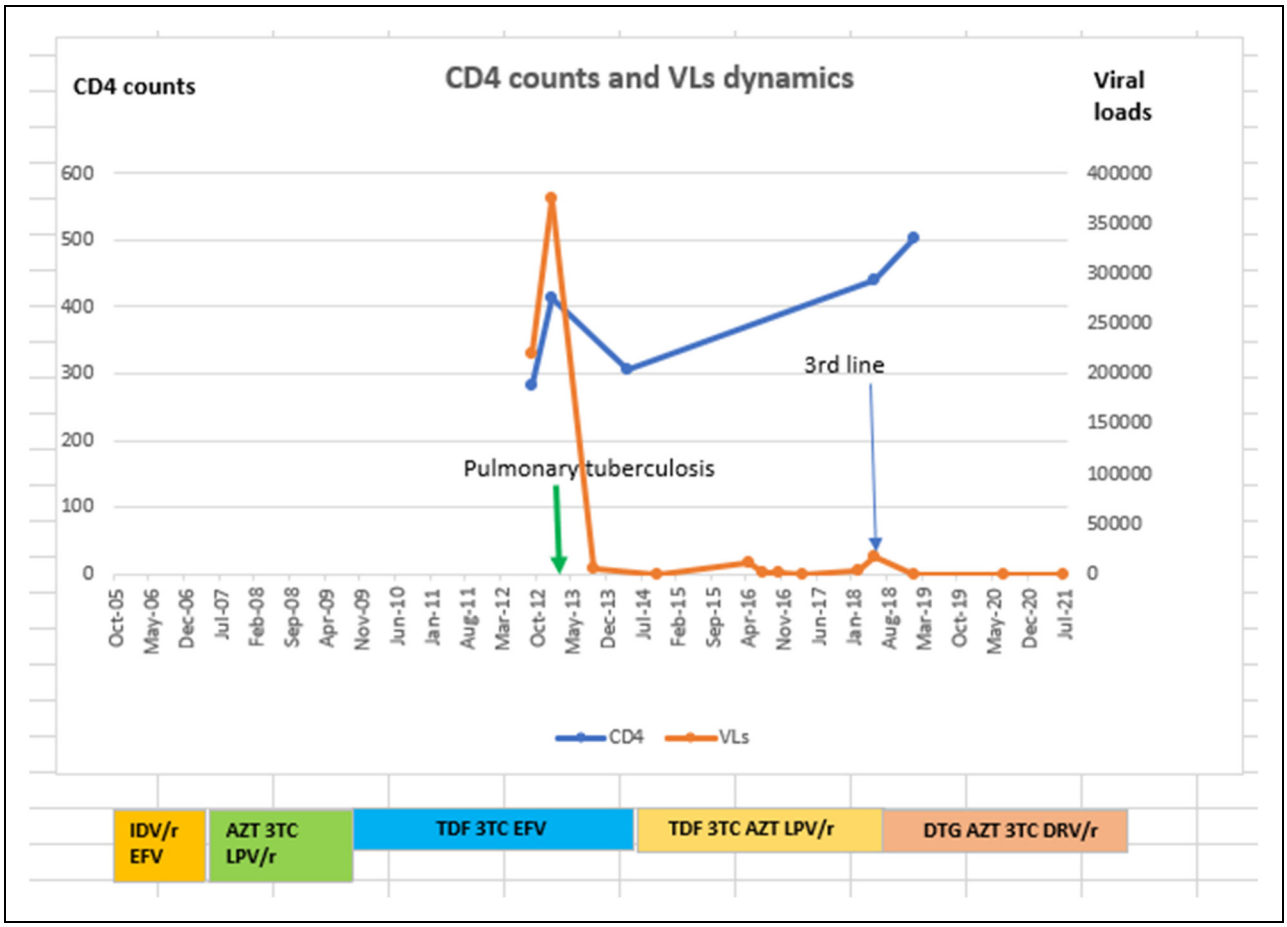

Figure 1. Evolvement of CD4 counts (cells/mm^3) and VL (copies/mL of blood) results.

medication errors from medical doctors were omission errors due probably to polypharmacy in HIV infected individuals.

The GRT was helpful in understanding at a molecular level the reasons behind the virologic failure. The GRT results demonstrate that only AZT had total drug activity due to K65R and M184V mutations, which re sensitizes AZT and reduces its resistance by > 50-fold.[11]

This case report shows that the absence of formal ART guidelines in early 2000, long term exposure and failure to timely switch led to treatment failure and development of multi-class mutations identified by the GRT and guided the third line ART regimen with a successful outcome.

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Authors contributions

M A M Kakubu & PM Katoto contributed to the study conception & design, organized, and revised the manuscript before submission to the journal.
M. Kalonji contributed to patient management and data collection.
All authors proofread the final manuscript and approved the final version of the manuscript.

Ethical Considerations

Patient consent was obtained together with approval from the Ethical Research Committee of the Ministry of Health of Namibia on the 22 November 2019, reference number 17/3/3/**MAK.**

Declaration of Conflicting Interests

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