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A Heavily Treated HIV-1 Infected Patient with Multiclass Drug Resistance: A Case Report and Review of Management Challenges in Settings with a Limited Formulary

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Abstract

There is a trend of increasing burden of pre-treatment and acquired HIV drug resistance in sub Saharan Africa (SSA). The HIV drug resistance (HIVDR) is mainly due to non-nucleoside reverse transcriptase inhibitors (NNRTI) resistance, followed by Lamivudine associated Resistance associated mutations (RAMs). Use of thymidine analogue nucleoside reverse transcriptase (NRTIs) inhibitors account for development of Thymidine Associated Mutations (TAMs) as acquired drug resistance. Late diagnosis of anti-retroviral (ART) failure, use of ARVs with low genetic barrier to resistance and potential for cross-resistance between regimens are important drivers of HIV drug resistance in sub Saharan Africa (SSA) settings. Here we report a case with profound immune deficiency, high viral load and genotypic testing revealed resistance to nucleoside, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. The key message is prolonged antiretroviral therapy failure poses a significant risk for developing acquired HIV drug resistance. Additionally, blind switching of ARVs without virologic monitoring is a major concern for HIV programs in resource-limited settings where treatment options are limited.

Keywords: HIV drug resistance; Heavily treated HIV1-Infection; Multiclass drug resistance; Drug resistant associated mutations

Abbreviations: HIVDR: HIV drug resistance; TAMs: Thiamidine Associated mutations; RAMS: Resistance associated mutations; DTG: Dolutegravir; NNRTIs: Non nucleoside Reverse transcriptase inhibitors; NRTIs: Nucleoside reverse transcriptase; PIs: Protease inhibitors respectively

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Introduction

Antiretroviral treatment (ART) is the most effective intervention in managing HIV infection and transmission. In 2004 Tanzania national AIDS Control program started scaling up ART program from referral, regional and district hospitals to primary health care facilities whereby only 96 care and treatment centers (CTC) were available [1] and by 2010 more than 1100 CTCs were providing ART [2]. The successful ART scale up has been associated with significant reduction of HIV related morbidity and mortality [1]. The United Nations has committed to the goal of ending the AIDS pandemic as a public health threat by 2030, ensuring that by 2020, 90% of people with HIV know their HIV status, 90% of those infected are receiving ART, and 90% of those on ART have sustained viral suppression [3,4]. To ensure that people living with HIV (PLHIV) achieve sustained viral suppression, we must maximize HIV care including early ART initiation and successfully maintaining PLHIV on effective ART for life, restrict the emergence of HIV drug resistance and transmission of drug resistance mutations to other individuals [5]. Despite the successful access to ART, there are reports showing increasing burden of virologic failure [6], emerging HIV drug resistance [7] which poses a significant barrier to achieve desired ART outcomes as a lifelong therapy [3,5]. During ART, acquired HIV drug resistance occurs when there is persistence viral replication under selective pressure of ARVs which in due course lead to the selection of HIV mutations associated with drug resistance [8].

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The accumulation of mutations will compromise ART outcomes limiting further options incase cross resistance has occurred [8,9]. Therefore, prolonged exposure of HIV-infected individual to failing ART poses higher risk of accumulating mutations [10] and eventually drug resistance [9]. In Tanzania the access to virologic monitoring became available in 2014 to zonal referral hospitals; there was limited access to viral load testing to all PLHIV on ART. Lack of virologic testing may have contributed to some delays in switching first line ART failures to second line ART. Our case report is of an adult HIV-1 infected individual presenting with features of pulmonary tuberculosis and esophageal candidiasis while on second line ART. The serial laboratory work up revealed serial high viral loads, profound immune deficiency and high level resistance to Non-Nucleoside Reverse Transcriptase Inhibitors, Nucleoside Reverse Transcriptase Inhibitors and partial resistance to Protease Inhibitors.

Case Report

A 46-year-old woman presented at our national hospital with a three weeks history of productive cough, painful swallowing and profound weight loss. Physical examination revealed a wasted, febrile woman with oral candidiasis and features of HIV lipodystrophy. Laboratory investigations confirmed the diagnosis of smear positive pulmonary tuberculosis and Esophago-gastroduodenoscopy showed extensive Oesophageal candidiasis. Her CD4 cell count was 14 cells/mm^3 and HIV viral load was 145,900copies/ml. At the time the diagnosis of smear positive pulmonary tuberculosis, oral and Oesophageal candidiasis, HIV lipodystrophy and virological failure were established. She had been on a number of combination antiretroviral treatment (cART) regimens for 10 years since 2007 **(Table 1)** before she reported at our hospital. In 2007 she presented at the referring regional hospital with advanced HIV disease, with WHO clinical criteria stage 4 and with a CD4 cell count of 8cells/ml. She was initiated on first line ART which comprised of Stavudine (D4T), Lamivudine (3TC) and Nevirapine (NVP) in a single pill (Triomune). She developed Stavudine induced lipodystrophy in 2010, this prompted her clinicians to stop Stavudine and substitute it with Zidovudine (AZT) while maintaining the rest of the regimen (AZT/3TC/NVP). In 2015 there was a change in National HIV management guidelines, which recommended the use of Tenofovir (TDF) based first line cART regimens. Her combined ART regimen was then changed to Tenofovir (TDF)/ Lamivudine (3TC)/ Efavirenz (EFV). Within a short while, her CD4 cell count dropped to 14 cells/ml from 180 cells/ml. She was diagnosed as having immunological failure based on CD4 criteria and she was switched to TDF/3TC/LPV/r. The patient adherence was assessed to be > 90% before switch to second line and thereafter continued with enhanced adherence counselling (EAC).

Boosted lopinavir being the only drug added to the TDF/3TC backbone. Her condition deteriorated and she was referred to National hospital in 2016. In the same year when she presented to our hospital, she had virological, immunological and clinical cART failure. Determination of genotypic drug resistance revealed multiple Thymidine Analogue Mutation (TAMS) identified as D67N, M41L, L210W and T215Y with NNRTIs resistance associated mutations (RAMS) identified as Y181C and Y188L. However, there was a low to intermediate level resistance to boosted Lopinavir **(Table 2).** It is clear from the resistance associated mutations (RAMS) pattern; this patient had no effective ARVs options left among the NRTIs, NNRTIs except for partially effective boosted lopinavir. Due to lack of new ARVs, the patient was maintained on a failing TDF/3TC/LPV/r regimen. When dolutegravir (DTG) became available in March 2019, the regimen was changed to TDF/3TC/DTG, in essence DTG was added to the existing TDF/3TC backbone. This case highlights the challenges of using Thiamidine analogue nucleoside reverse transcriptase inhibitors backbones with low genetic barrier to resistance NNRTIs. Such regimens lead to development of TAMS which limit NRTIs options in second line cART regimens used in resource limited settings. It also underscores the challenge of blind switching without genotypic HIV drug resistance testing a typical practice in limited resource countries. Finally it points out the risk of sequential monotherapy in settings with limited ARV formularies and absence of genotypic drug resistance testing.

Discussion

To ensure that PLHIV achieve sustained viral suppression, clinicians must successfully maintain PLHIV on effective ART for life, limiting the development of HIV drug resistance and transmission of drug resistance mutations. When the universal ART programme started in Tanzania in 2004, initial cART regimens comprised of Stavudine or Zidovudine with Lamivudine as NRTI backbones combined

Table 1 ARV regimen, CD4 and Viral load profiles over time.

Month and Year	ARV regimen	CD4 cells/mm^3	HIV viral load (copies/ml)	Reason for ARV regimen
2007	D4T/3TC/NVP	8	Not done	Preferred first line
2010- 2014	AZT/3TC/NVP	Not done	Not done	Lipodystrophy
2015	TDF/3TC/EFV	188	Not done	guideline change to TDF preferred first line regimen
December 2015	TDF/FTC/LPV/r	14	242,400	Immunologic & virologic failure
2016-2017	TDF/FTC/ATV/r	18	145,990	Immunologic & virologic failure with progressive lipodystrophy
March 2019	TDF/3TC/DTG	11	346,800	Immunologic & virologic failure with >90% self-reported adherence, given DTG based regimen as salvage therapy
July 2019	TDF/3TC/DTG	104	3,718	Salvage therapy
September 2019 to date	TDF/3TC/DTG	184	14,420	Salvage therapy

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Table 2 Genotypic drug resistance testing results of 2017 and mutation interpretation from Stanford University HIV Drug Resistance Database.

ARV class and drugs	Level of drug resistance	Drug resistance mutations	Mutations interpretation
NNRTs			
NVP	High	Y188C	Reduces EFV susceptibility by 2-fold, associated with a reduced response to an EFV- based regimen in NNRTI-experienced patients
EFV	High	Y181C	Selected by NVP and EFV, confers high-level resistance
ETV RPV	High High	L100I	In combination with K103N, reduces susceptibility to ETR by 5-10 fold and > 10 fold RPV
NRTIs			
ABC	high	D67N	When present with TAMs, reduces susceptibility of ABC and TDF
3TC FTC	High	M184V	Increase susceptibility to AZT, reduces viral fitness
AZT	High	T215Y, L210W, M41L	These occur in combination and confers intermediate to high-level resistance to AZT and d4T; reduces ABC and TDF susceptibility
TDF	High	K65R	Reduced viral replication capacity and fitness
PIs			
ATV	High Intermediate	I50L L24I	Selected by ATV, confers high-level resistance to ATV and increases susceptibility to other PIs reduces susceptibility to LPV and ATV
LPV	Intermediate	L76V	Conferring high-level resistance to LPV
DRV	Low	K20T	Reduces susceptibility to each of the PIs except DRV

with Nevirapine or Efavirenz (NNRTI). The first-generation NNRTIs Efavirenz and Nevirapine were the most used drugs which are prone to selecting drug resistance mutations because of their low genetic barrier to resistance, when one mutation occurs it results to complete loss of drug effectiveness [11-13]. Monitoring of cART was until recently done using CD4 and Clinical criteria which are late markers to detect ART failure and associated with risk of accumulation of resistance associated mutations long after virological failure develops [14]. The immunologic monitoring is a not only poor indicator of ART failure but also create delays to switch to an effective regimen posing a significant risk for development of drug resistance limiting future ARV treatment options [15].

When this patient's stavudine/lamivudine/nevirapine regimen failed, the patient had four Thymidine associated mutations (TAMS) with boosted Lopinavir as the only effective ARV remaining in the second line cART regimen. Thiamidine analogue NRTIs backbones with low genetic barrier to resistance lead to development of TAMs [16]. The prevalence of TAMs has been reported to range from 19-42% and T215Y/F mutation carrying the highest prevalence [17]. The mutation T215Y/F causes intermediate to high-level resistance to AZT and D4T. Generally the accumulation of TAMs causes a progressive reduction in drug susceptibility for most NRTIs [18]. Therefore, delayed detection of virologic failure and blind switching without genotypic resistance testing renders a patient to accumulation of mutations especially TAMs. In our case, most likely switching from AZT/3TC/NVP to TDF/3TC/EFV was unseemly because TAMs would render the entire regimen ineffective. Further, the selection of K103N and Y181C mutations cause loss of activity to all currently available NNRTIs [19].

Notably substituting stavudine (D4T) with zidovudine (AZT) because of HIV lipodystrophy was unsuitable because AZT a thymidine analogue NRTI like Stavudine causes HIV lipodystrophy albeit to a lesser extent. Additionally, Zidovudine (ZDV) and stavudine (D4T) select for the same set of thymidine analogue resistance mutations (TAMs) [20]. The combined presence of M41L and T215Y mutations confers substantial AZT resistance and has been reported to be a HIV significant predictor of increased risk of HIV disease progression [20]. Our patient was found to have high level resistance to TDF, in particular K65R mutation which has been reported that its presence is associated with a reduced virologic response to tenofovir [21].

Poor adherence to ART results in suboptimal viral suppression that increase the potential for ART failure and emergence for drug resistance [22]. However, this patient adherence (self-reported) was documented to be > 90% at all visits since the first detection of virologic failure in 2015. In the course of HIV care, replacing TDF/3TC/EFV with TDF/3TC/DTG was sequential monotherapy with DTG as the only effective antiretroviral. In 2019, most of the African countries were reported to have pretreatment NNRTI resistance that was more than 10% and therefore recommended to implement the non NNRTI first line ART regimen [13]. Transition from non NNRTI based first line ART to Dolutegravir (DTG) based regimen was launched however; this may be posing new challenges in relation to HIV drug resistance [23] as the NRTI backbone is still in use. Although we can be confident that dolutegravir-based first-line triple therapy will lead to favorable virological outcomes in sub Saharan Africa, the reported benefits of DTG in both ART naïve and ART experienced PLHIV are expected only if there is a combination with a functional NRTI backbone. To enhance the durability of this patient regimen it needed the removal of TDF and addition of boosted Atazanavir (currently we do not have Darunavir) with maintenance of Emtricitabine or

Lamivudine with MI84V to reduce viral fitness. In Tanzania there is limited access to genotypic drug resistance testing but there are on-going processes to establish a standard of care for second line ART failure before they switch to third line ART.

Conclusion

Prolonged exposure of HIV-infected individual to failing ART poses higher risk for viral replication, accumulation of resistant mutations and eventually drug resistance. This case has demonstrated a delayed detection of virologic failure and blind switching without genotypic resistance testing that renders a patient to accumulation of mutations especially TAMs.

Conflict of Interest

The authors confirm that there is no conflict of interest to declare.

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Authors' contributions

JR conceptualized the case report, prepared the manuscript, conducted ART monitoring and patient follow up. JR wrote the manuscript in consultation with SEK. In addition, SEK supervised the interpretation of the patient drug resistance data and patient management. All authors approved the final version of the manuscript.

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Ethics Approval and Consent

Written informed consent for publication of the clinical details was obtained from the patient. The Muhimbili National Hospital ethics review board provided the approval to publish this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Data Availability Statement

Raw data were generated at Muhimbili National Hospital. Derived data supporting the findings of this study are available from the corresponding author JR on request.

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