

A case of undisclosed prior exposure to antiretroviral therapy (ART) and early virologic failure that improved on a pre-emptive third-line ART regimen

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Abstract

Introduction The test and treat strategy recommends starting ART on the same day of diagnosis; yet, in Namibia neither baseline viral load (VL) nor genotypic resistance testing (GRT) are recommended prior to ART initiation. However, some clients return to care having defaulted ART and undergo HIV testing as "new" clients without disclosing their previous exposure, which predisposes them to primary virologic failure.

Case report A 53-year-old man tested HIV positive in 2019 without disclosing his prior exposure to ART from 2010-2015 and who stopped medication from 2015-2019 due to religious advice. He was thus initiated of first-line ART on the same day of his new diagnosis with a nadir CD4 count of 102 cells/mm³. He had a negative cryptococcal serum antigen, a normal creatinine clearance but with hepatitis B coinfection. He presented later with a primary virologic failure (VL >1000 copies/mL) and severe immunosuppression. The in-depth discussion revealed previous exposure to ART. He consequently benefited from a presumptive third-line ART that suppressed his VL while a GRT was being processed which later confirmed ART resistance.

Conclusions In poor resource settings where GRT is not performed regularly, undisclosed exposure to ART might lead to subtherapeutic treatment and primary virologic failure. In such patients where primary virologic failure is suspected despite good adherence, presumptive third-line ART can be considered in severely immunocompromised patients while waiting for GRT.

Keywords Undisclosed ART, early virologic failure, genotyping resistance test.

Introduction

A successful outcome of antiretroviral therapy (ART) depends on the drug potency and activity¹ as well as on patient adherence.² In 2010, the World Health Organization (WHO) recommended tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and efavirenz (EFV) as the first line for adult patients, yet, the transmitted HIV drug resistance with non-nucleoside reverse transcriptase (NNRTI) had translated into an increased number of patients

failing ART after initiating with a NNRTI-based regimen.³ Also, in low and middle-income countries (LMICs), baseline genotyping is not routinely done and is only estimated at 0.1% in Africa.¹ In Namibia, no genotyping resistance testing (GRT) at ART initiation is recommended and the fifth edition of ART guidelines recommended same-day ART initiation as part of the test-and-treat strategy and TDF+3TC+EFV as the preferred first-line for newly HIV-diagnosed adult patients.⁴ The same guidelines

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recommended viral load (VL) monitoring to assess treatment outcome at six months and twelve months after ART initiation then every 12 months for virally suppressed patients.

It is reported in some regions that close to 40% of patients failed to disclose their HIV status to health care workers due to stigma, denial, and poor understanding of HIV infection, and consequently presented themselves to care for HIV retesting.⁵ Similarly, religious beliefs with treatment interruption are barriers to ART adherence.⁶ Prior exposure to ART in patients who restart ART coupled with non-adherence was found to be associated with pre-treatment drug resistance and virologic failure.² In many African countries, there is insufficient use of the electronic system in the HIV testing services (HTS), representing a gap and a missed opportunity to identify patients who had previously tested HIV positive.⁵

The latest Namibian ART guidelines only recommend GRT for patients failing second-line ART and eligible for the third-line ART and exceptionally for patients failing the first-line ART.⁷ Nevertheless, early identification of patients presenting with high VL after ART initiation should alert the clinicians and guide management. Thus, we present the case of a patient who presented to care at a public outpatient ART clinic in Windhoek, Namibia, with undisclosed prior exposure to ART; he was initiated on the first-line ART but had persistent high VL >1000 copies/mL of blood at six, nine, and twelve months after ART initiation with a declining immune system.

Case report

A 53-year-old man presented to care at an outpatient ART clinic on the 08th of March 2019 for an HIV test. He tested HIV positive and was initiated on TDF 3TC EFV, cotrimoxazole and isoniazid for opportunistic infections and tuberculosis prevention, respectively. He was classified as WHO stage 1; the weight was 67 kg with a body mass index (BMI) of 27 kg/m². He was on anti-hypertensive medicine (hydrochlorothiazide-amiloride 2.5/5 mg and perindopril 4 mg daily). His CD4 count was 102 cells/mm³, the hepatitis B screening panel

revealed a chronic hepatitis (hepatitis B surface Ag and the anti-hepatitis B core were positive with negative IgM anti-hepatitis B core) with alanine transaminase of 24 units/L, normal creatinine clearance of 67 mL/min and hemoglobin of 13 g/dL. He was reviewed at the clinic at two weeks, and one month after ART initiation. He had good adherence to ART based on pill counts and did not report side effects to ART. Six months later, on the 15th of September 2019, his VL was checked according to the national guidelines and was found to be high at 52,011 (log 4.71) with an unremarkable clinical examination. He went through enhanced adherence counselling with a multidisciplinary team, and his VL remained persistently high at nine months with a VL of 24,536 (log 4.38) and 12 months with a VL of 21,048 (log 4.32) despite self-reported good adherence to ART and evidenced by pill counts. At this latest clinic visit, after in-depth discussion, the patient revealed a previous exposure to ART for five years, from 2010 to 2015 in a private health clinic both in Namibia and South Africa. He could not remember the name of the medications and efforts to obtain previous clinical information were unsuccessful. He also revealed that between 2015 and 2019, he was off medication due to religious beliefs. The CD4 counts had dramatically dropped to 35 cells/mm³ from baseline, the cryptococcal serum antigenemia remained negative, the total cholesterol, LDL and triglycerides were 4, 2.86 and 1.37 mmol/L, respectively, and he had a 15% drop in his weight from baseline (57 kg); the tuberculosis screening was negative. Thus, a GRT test was requested, and a presumptive third-line ART was initiated with TDF+3TC+dolutegravir (DTG) and darunavir/ritonavir (DRV/r). Four weeks later, his VL had significantly reduced and was estimated at 34 copies/mL of blood. The GRT obtained six weeks later demonstrated the HIV drug associated mutations and drug susceptibility after analyses with the Stanford HIV drug resistance database⁸ (Table 1).

The GRT results demonstrated non-polymorphic mutations on the reverse transcriptase enzyme, the K103N and L100I that reduce the susceptibility to EFV and NVP, the

Table 1. Findings of the genotyping resistance testing

Drug class and detected mutations	Drugs	Penalty Scores	Drug susceptibility
NRTI: K65R, M184V, Y115F	AZT	-25	Susceptible
	TDF	60	High level resistance
	Abacavir (ABC)	120	High level resistance
	Emtricitabine (FTC)/3TC	90	High level resistance
NNRTI: L100I, K103N	EFV/nevirapine (NVP)	120	High level resistance
	Etravirine (ETR)	30	Intermediate resistance
	Rilpivirine (RPV)	60	High level resistance
PI: none	Atazanavir/ritonavir (ATV/r),	0	Susceptible
	Lopinavir/ritonavir (LPV/r),	0	
	DRV/r	0	

L100I, K103N are NNRTIs mutations, and they confer high-level resistance to most NNRTIs; NVP/EFV/RPV, and reduced susceptibility to ETR. The major NRTIs mutations detected were the K65R and M184V. The K65R is a signature mutation for TDF with reduced antiviral activity to TDF, ABC, and increased AZT antiviral activity. Besides, the M184V mutation is selected by 3TC/FTC and reduces 3TC and FTC antiviral activity but increases susceptibility to AZT, explaining the penalty score of -25. No mutation selected by PI was detected, explaining their total drug activity. The drug activity of the ART regimen (TDF 3TC EFV) that the patient was previously on before the pre-emptive 3rd line regimen was equal to 0.

K65R a signature mutation to TDF that reduces its drug activity and sensitizes AZT, and the M184V mutation that affects the drug activity of 3TC and also sensitizes AZT.

On receipt of the GRT results, the patient was clinically stable and had no signs and symptoms of either immune reconstitution inflammatory syndrome or TB. The ART regimen was changed to TDF+3TC+DTG (fixed-dose combination) plus ATV/r. This new regimen was estimated at two full drug activities i.e., DTG+ATV/r, and continued with a daily dose of cotrimoxazole 960 mg. The VL at 12 weeks was undetectable, the patient was clinically stable, and the weight had improved to 62 kg.

Discussion

We describe a patient with undisclosed exposure to ART, initiated on treatment as an ART naïve-patient, with early virologic failure and who later benefited from a pre-emptive third-line ART regimen. The lack of a unique national electronic system linking all ART sites within the public sector and between the private and the public sectors in LMICs,⁹ was a significant gap in identifying that the patient had prior ART exposure. Jacob et al.⁵ reported known HIV

positive patients that present to care for retest without disclosing their status with the main reasons being stigma, low literacy and poor understanding of HIV infection. The patient reported in this paper stopped his treatment due to religious beliefs after being convinced by a preacher that he no longer had HIV. It was through enhanced adherence counselling with a multidisciplinary team that the patient disclosed his previous exposure to ART without additional information on the drugs. Günthard et al.¹⁰ noted NNRTI pre-treatment drug resistance in Namibia to be 13.8% between 2015-2016, with a risk of early virologic failure being reported by Kang et al.¹¹ Also, the same authors reported that a prolonged period on a failing ART regimen predisposes to an accumulation of mutations.

The patient reported in this paper presented with primary virologic failure with three consecutive high VL >1000 copies/mL of blood, severe immunosuppression with a CD4 <50 cells/mm³, on a failing regimen for 12 months with the risk of accumulating HIV drug-associated mutations. As a result, the GRT results demonstrated multiple non-polymorphic mutations and the patient's drug regimen activity was equal to 0, explaining the high VL and the

CD4 count decline in the presence of presumed good adherence. There are reports that established that an empirical switch to the third-line ART resulted in poor treatment outcomes.¹² However, our patient benefited from a presumptive third-line ART regimen because he had severe immunosuppression necessitating an urgent ART switch before GRT results. The patient was initiated on TDF+ 3TC+ dolutegravir (DTG) and darunavir/ritonavir (DRV/r). The drug selection was guided firstly by the clinical judgment, the knowledge of possible HIV mutations, the drug cross-resistance, the genetic drug barrier, the patient's age, the comorbidities, and the availability of the drugs. TDF has an antiviral activity on hepatitis B virus and it was kept in the regimen to avoid the risk of hepatitis B flares that may occur when stopping TDF.

We presumed that due to probable prolonged treatment failure, the patient had NRTIs archived thymidine analogues mutations (TAMs) to AZT or D4T, NNRTIs mutations due to possible exposure to NVP or EFV, as part of the first-line ART regimen and also possible mutations to LPV/r used in the second line as recommended by the national guidelines. Therefore, we considered the high genetic barrier of DRV/r in case of prior exposure to protease inhibitors (PI), and DTG, a new drug in our setting, was added since the patient was unlikely to have been exposed to it. Consideration of 3TC was to benefit from the crippling effect of the M184V mutation commonly seen in patients failing ART and TDF to address the hepatitis B coinfection. Besides, we considered the negative impact of possible archived TAMs type 1 on TDF antiviral activity² contained in the first-line ART that the patient initiated when he returned to care in 2019 (TDF+3TC+EFV). The pre-emptive third-line ART regimen selection led to good treatment outcome at four weeks follow-up, and the GRT results were only received six weeks after initiating the third-line line ART.

Conclusions

In a setting where baseline GRT is not recommended, early virologic failure in patients initiating on NNRTI-containing ART-regimen with persistent viremia in the presence of good

adherence should raise suspicion of possible transmitted HIV drug resistance infection or previous exposure to ART. Clinicians should aggressively investigate the early virologic failure, which can be due to pre-treatment drug resistance or previous treatment failure, and avoid an accumulation of HIV drug-associated mutations. When a delay is expected in receiving GRT results, consider starting a presumptive third line in severely immunocompromised patients. Besides, the HTS should implement ways to identify patients that could have previously been exposed to ART using either their identifying document card or the electronic system.

Consent: Written informed consent was obtained from the patient for publication of this case report. We also received approval from the Ethical Research Committee of the Ministry of Health of Namibia on 23 February 2021, reference number 17/3/3/MAK.

Authors' contributions statement: MAMK, PDMCK, TB, and ESL contributed to the study conception and design; TB and ESL collected the data; MAMK prepared the manuscript, MAMK, PDMCK, TB, and ESL revised the manuscript and appraised several drafts before approving the final version submitted for publication. All authors read and approved the final version of the manuscript.

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