Clinical Case Reports

CASE REPORT

HIV drug resistance mutations following poor adherence in HIV-infected patient: a case report

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Key Clinical Message

Acquired HIV drug resistance following poor adherence is common. We report a case of HIV-infected patient with poor CD4 gain and self reported poor adherence. Investigations revealed high viral load and resistance to NRTIs and NNRTIs with sensitivity to boosted PIs. HIVDR mutations create treatment challenges in resource limited settings.

Keywords

HIV drug resistance, HIV treatment, resistance mutations, resource-limited setting, Tanzania.

Introduction

The World Health Organization (WHO), together with the Joint United Nations Programmme on AIDS (UNAIDS) and other partners have a stated goal of providing worldwide access to antiretroviral therapy (ART) [1]. Data worldwide show that there is increasing accessibility to HIV treatment. In 2011, approximately 8 million people in low–middle income countries were receiving HIV treatment, compared to only 400,000 in 2003 [2]. In Eastern and Southern Africa, it is estimated that up to 56% of those eligible for HIV treatment had access to therapy while only 10% of patients were treated in 2009. This scale up of HIV treatment in low and middle-income countries has been associated with a significant decline in morbidity and mortality, [3] as well as maternal-to-child transmission. Unfortunately, the expanding access to HIV treatment goes hand in hand with the emergence of HIV drug resistance (HIVDR) with a reported 20% risk of mutations from at least two of the three main drug classes within 6 years [4].

In Tanzania, a nationwide care and treatment program has been established and implemented for HIV-infected individuals since 2004. Despite this fact, these clinics face a number of challenges including limited resources and a low number of available antiretroviral drugs. HIV infection is treated with standardized first and second-line ART regimens and no medications are proposed or available for use as third-line treatment in Care and Treatment Clinics (CTC) [5].

There are a number of mechanisms by which HIVDR occur in treatment-experienced patients. Selection pressures in patients using ART can occur due to sub-optimal dosage, inadequate use of regimens, poor adherence to medication or other pharmacodynamic factors. Genotypic resistance testing (GRT) is, therefore, an important component of treatment and constitutes the standard of care in developed countries. In resource-limited countries, however, GRT is rarely available. In resource-limited settings, the practice is to switch patients who do not respond to therapy based on either clinical findings or immunological criteria from a nonnucleoside reverse

transcriptase inhibitor (NNRTI) to protease inhibitor (PI) based regimens. In most cases, however, treatment failure is detected late and there is significant drug resistance leading to limited efficacy of second-line drugs [6].

There are several reports on acquired HIVDR in Africa, with most cases being associated with poor adherence. This has been shown to limit future treatment options. We report a case of a 54-year-old HIV-infected patient who self reported poor adherence to his ARVs presenting with poor immune recovery and features suggestive of tuberculosis. Investigations revealed a viral load of 89,752 copies/mL and resistance to Abacavir, Didanosine, Zidovudine, Tenofovir, Stavudine, Emtricitabine, Lamivudine, Nevirapine, and Efavirenz with sensitivity to boosted protease inhibitors.

Case Report

A 54-year-old male patient from Mwanza, Tanzania enrolled at Hindu Hospital CTC in 2010 was referred to Bugando Medical Centre CTC in 2012 for management of poor CD4 gain. When he was received at Bugando CTC, his CD4 count was 7 cells/μL and had been taking ARV medication for 2 years.

The patient was started on Atripla in 2010 and a month later was switched to Combivir/Efavirenz because Atripla was out of stock. However, one year later he was switched back to Atripla because of anemia. The chief complains at his current visit were productive cough, pleuritic chest pain, and low-grade evening fevers for 3 weeks prior to admission. The patient also reported a history of significant night sweats and weight loss over the same time period. He had used several over the counter medications without relief. A review of systems was significant for loss of appetite. His past medical history was not significant prior to the diagnosis of HIV. On scrutinizing his medication use, he admitted poor adherence to ART. He divorced his first wife in 1994 and has been remarried to his second wife since 1996. His second wife tested positive for HIV in 2012 and she is also on ART. The patient had history of alcohol abuse, but has abstained since 2003.

The general examination was normal. He had stable vital signs with a blood pressure of 130/90 mmHg, pulse rate of 80 beats/min, respiratory rate of 20 breaths/min and body temperature of 36.7⁰ Celsius. Systemic examination revealed no abnormal findings. Investigations were ordered accordingly and the results were as follows: Sputum for Acid Fast Bacilli (AFB) was negative twice, chest x-ray (CXR) revealed perihilar opacities, CD4 cell count was 78 cells/μl. The viral load performed at a private owned laboratory (Lancet laboratory) was found to be 89,752 copies/mL. Genotypic resistance and drug sensitivity tests were also performed at the Lancet laboratory.

Table 1. Summary of genotypic antiviral drug resistance mutations obtained from HIV-infected patient at Bugando Care and Treatment Clinic.

	NRTIs	NNRTIs	Reverse transcriptase polymorphisms	TAMs
Resistance mutations	E40F	K103N	K20R	M41L
	M41L	P225H	K22R	D67N
	D67N		V35T	T215Y
	L74I		T39A	L210W
	M184V		V60I	
	T215Y		I94L	
	K219E		D121Y	
	L210W		K122E	
			D177E	
			I178M	
			T200K	
			Q207E	
			R211K	
			L228H	
			V245Q	
			D250E	
			A272P	
			K277R	
			L282C	
			L283I	
			T286A	
			A288AT	
			I293V	
			E297	

NRTIs, Nucleoside Reverse Transcriptase Inhibitors; NNRTIs, Non Nucleoside Reverse Transcriptase Inhibitors; TAMs, Thymidine analog Mutations.

Table 2. Summary of sensitivity pattern to antiretrovirals obtained from HIV-infected patient at Bugando Care and Treatment Clinic.

	NRTIs	NNRTIs	PIs
Sensitive	–	Etravirine Rilprivirine	Boosted Atazanavir, boosted Tipranavir, boosted Lopinavir, boosted Indinavir, boosted Saquinavir Darunavir, Fosamprenavir Nelfinavir
Resistant	Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir Zidovudine	Nevirapine Efavirenz	

The pattern of resistance mutations and drug sensitivity are shown in Tables 1 and 2 respectively. The patient was diagnosed with pulmonary tuberculosis, with a possible differential diagnosis of atypical pneumonia, and

antiretroviral treatment failure. Of the medications to which the patient's HIV remained susceptible, only boosted Atazanavir is available in Tanzania. The patient was started on antituberculosis medications and ART was switched from Atripla to Zidovudine, Lamivudine, and boosted Atazanavir. The patient was subsequently seen during follow-up, completed antituberculosis therapy and is currently asymptomatic.

Discussion

In treatment-experienced HIV patients with treatment failure, HIVDR has been found to be very common [7, 8] and is associated with poor adherence [7] and, in some cases, the duration of treatment [8]. Failure to predetermine existence of primary resistance predisposes patients to treatment failure. Without viral load monitoring, treatment failure will often be detected late and risk further accumulation of resistance mutations limiting future treatment options. Our patient was not tested at baseline for primary HIVDR because genotypic resistance testing is not routinely done. Viral load monitoring is not readily available as well and, as a result, treatment failure was diagnosed late. In most cases, treatment failure in resource-limited settings is reached through clinico-immunological criteria. that usually leads to unnecessary switching of drugs or late detection of treatment failure [6, 9].

Nonadherence to ART in adults ranges from 33 to 88%, depending on the definition of adherence used [10]. Evidence shows that high levels of adherence are required for prevention of HIVDR [10]. Fear of disclosure and the resulting stigma, forgetfulness, a lack of understanding of treatment benefits, and complicated regimens have all been found to be barriers to adherence [11]. Adherence can be improved by addressing these barriers through discussions with patients and providing education regarding the treatment benefits to health outcomes [12]. Addressing stigma is a very important intervention in improving adherence levels.

As described in the case report above, our patient has high resistance to all of the NRTIs and NNRTIs available for use in HIV treatment in Tanzania and susceptibility only to the PIs. None of the proposed drugs for third-line use are available in Tanzania [5]. The resistance pattern seen in this patient poses a great challenge in the choice of medication, especially bearing in mind the low availability of different types of antiretroviral drugs. Our patient was kept on Zidovudine, Lamivudine, and boosted Atazanavir, with the only susceptible drug being boosted Atazanavir.

In developed countries, GRT plays an important role in the care of HIV-infected patients. However, in resource-limited settings this cannot be routinely done. Failure to pretest primary HIVDR coupled with the lack of viral load monitoring increases the chances of treatment failure, late detection of treatment failure and accumulation of resistance mutations.

Our case outlines the challenges that care providers encounter in HIV treatment in resource-limited settings, especially in patients failing first-line treatment. Given the limited availability of medications and the inability to detect treatment failure early, it is difficult to switch medications in a timely manner and prevent accumulation of resistance mutations. It also demonstrates the importance of early detection of HIVDR and minimizing acquired resistance by supporting measures to improve adherence to treatment because development of resistance greatly limits treatment options.

Conclusion

The report conclusively outlines how development of HIVDR limits treatment options in resource-limited settings, where there is already limited availability of antiretroviral drug options, and the importance of viral load monitoring for early detection of treatment failure and prevention of accumulation of resistance mutations.

Conflict of Interest

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

Acknowledgments

Consent

Written informed consent for publication of the clinical details was obtained from the patient. The Bugando Medical Centre 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.

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