

Lamivudine-Induced Recurrent Drug Eruption in HIV: A Curious Case of Its Treatment

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Case report

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Abstract

Background: Drug eruption may occur when HIV patients receive antiviral treatment. However, Lamivudine-induced repeated drug eruption has rarely been reported among the antiretrovirals.

Case presentation: We report a rare case of repeated drug eruption caused by Lamivudine. The treatment history of this patient was interesting. Patients developed repeated drug eruption regardless of treatment TDF+3TC+EFV or TDF+3TC+LPV/r. The viral load of the patient in 2016 and 2017 was 58 copies/ml and < 50 copies/ml respectively by TDF+LPV/r with no drug eruption, but antiviral failure was found in 2018. This patient was successfully treated with TDF+LPV/r+DTG in 2019 and 2020.

Conclusions: Through repeated drug eruption of the patient, we found that the allergenic drug is Lamivudine. The viral load of the patient can be effectively controlled by TDF+LPV/r+DTG.

Background

Lamivudine (3TC) is a nucleoside reverse transcriptase inhibitor (NRTIs) that is widely used for the treatment of HIV-1 infection in combination with other antiretrovirals. It is a highly effective agent that can be dosed once or twice daily due to its long intracellular half-life. It also has one of the best tolerability and long-term safety profiles among all antiretroviral agents and continues to be preferred as part of initial or subsequent combination therapy in HIV-infected patients [1]. In China, there are six free drugs for HIV patients and they are zidovudine (AZT), Tenofovir (TDF), efavirenz (EFV), Lopinavir and Ritonavir (LPV/r), Nevirapine (NVP) and 3TC. 3TC is an integral drug of all free regimens in the Chinese guideline [2–3].

Among the antiretrovirals, adverse drug reactions are most commonly associated with NVP and EFV, and rarely, other anti-retroviral drugs such as AZT and 3TC. Cutaneous drug reactions are more common (10–15%) in people infected with HIV and may vary from mild itching to life-threatening adverse reactions like Stevens-Johnson syndrome [3]. However, the drug allergy to 3TC is rare. Here we report a case of recurrent hypersensitivity reaction in the form of skin rash due to 3TC when initiated on HAART and its treatment.

Case Presentation

ART was initiated with AZT + 3TC + EFV in a 68-year-old HIV positive, asymptomatic female with CD4 count of 536 cells/ μ L in August 2015. Edematous erythematous rashes appeared on her body and limbs and gradually worsened three weeks after initiation of ART. The patient was initially given ebastine or compound glycyrrhizin capsules orally, and the rashes were not relieved. Then she was given dexamethasone 10mg intravenously, combined with the above medication, during hospitalization. The rashes gradually subsided and the dexamethasone gradually decreased to the withdrawal. It is worth noting that patients required to stop ART because of rash and severe fatigue, nausea and poor appetite.

The patient's first drug eruption was considered to be caused by EFV and it was a pity that the drug eruption was not pictured. TDF + 3TC + LPV/r were re-initiated because the fear for nausea and other similar symptoms caused by AZT in March 2016. The patient reappeared rashes after second dose of ART (Fig. 1). The rashes were slightly less than the last time. The anti-allergy treatment similar to the last time was given, and the rash basically subsided after 10 days. The patient developed drug eruption twice in both ART treatments, and both were given 3TC, so we considered that the patient's drug eruption may be caused by 3TC. The patient started the two-drug regimen (2DR: LPV/r + TDF). The patient has not had a rash again.

The viral load of the patient in 2016 and 2017 was 58 copies/ml and < 50 copies/ml respectively. However, the viral load increased to 5800 copies/ml and 14000 copies/ml in July and October 2018, respectively. Then we conducted a drug resistance test on the patient in November 2018 and found she was sensitive to both TDF, 3TC and LPV/r. (Table 1). We tried to give patients TDF + 3TC + LPV/r treatment again because of increased viral load, but after 2 hours of medication, rash and itching occurred again. The patient stopped oral 3TC and anti-allergy treatment for one week, and the rash basically healed. Then, the patient started to be treated with TDF + LPV/r + DTG in January 2019. The patient had no rash again. The viral load was TND (Target Not Detected, patients with sustained undetectable viremia) in June 2019 and 2020. (Patient's viral load in Fig. 2)

Table 1
The result of drug resistance test involving NRTIs, NNRTIs and PIs

Type	Drugs	Drug resistance test
NRTIs	ABC	S
	AZT	S
	FTC	S
	3TC	S
	TDF	S
NNRTIs	EFV	S
	ETR	S
	NVP	S
	RVP	S
PIs	LPV/r	S
	ATV/r	S
	DRV/r	S
INSTIs	No Detected	
nucleoside reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitor (NNRTI); integrase strand transfer inhibitor (INSTI), protease inhibitor (PI); abacavir (ABC); lamivudine (3TC); emtricitabine (FTC); tenofovir disoproxilfumarate (TDF); azidothymidine (AZT); efavirenz (EFV); Nevirapine (NVP); Etravirine (ETR); Rilpivirine (RPV); Lopinavir and Ritonavir (LPV/r); Atazanavir (ATV); Darunavir (DRV); S (sensitivity)		

Discussion And Conclusions

It is routine to consider the non-nucleoside reverse transcriptase inhibitor (NNRTI) component as the culprit agent when the patients are initiated simultaneously with AZT, 3TC, and EFV and cutaneous reaction appears. NNRTIs are never re-introduced and alternate agents like protease inhibitors (PIs) are started (LPV/r etc.). However, the next common drug group suspected are the NRTIs. AZT and 3TC have been reported to be associated with skin rash very rarely. An extensive literature search revealed only a few case reports of drug allergy to 3TC alone. Therefore, we changed the regimen to TDF + 3TC + LPV/r, but the patient reappeared with rashes. The patient stopped taking oral 3TC and no longer had rashes.

The incidence of drug allergy to 3TC is very low. out of the total 9923 patients receiving lamivudine-containing regimen in Kerala, true sensitivity was established in only one patient (incidence of 1/10,000) [4]. Sachdeva RK et al found the frequency of HIV-infected individuals with 3TC-induced hypersensitivity reaction in their center was only 0.7% [5]. This case is the first case of 3TC allergy in our

center (incidence of 1/2000). The hypersensitivity reaction was of grade 1 to 2. The hypersensitivity reaction of our case was grade 2. However, 3TC may cause severe skin rash. There was female preponderance [5]. Modak D et al reported a case series of severe skin rashes in four HIV-infected patients, probably due to lamivudine., three of which were female [6].

Three-drug combinations have been the gold standard since the mid-1990s, and remain preferred in consensus guidelines today. However, there is much interest in exploring ART regimens that reduce drug exposure, which may attenuate some to the challenges described, including the use of 2DR. The HAART regimens without 3TC could lead to early virological failure, and regimens with 3TC are considered to be superior to those without it [7]. The PI-based 2DR and the DTG based 2DR achieved good results [8]. In theory, LPV/r and TDF should be effective for ART. Although drug susceptibility tests confirmed that both LPV/r and TDF were sensitive, the patient experienced an increase in viral load 2 years after 2DR. The patient was given oral 3TC again, and developed rashes again. The conclusion that her drug eruptions were caused by 3TC was again confirmed. We have to add the DTG to the regimen despite the limited financial capacity of the patient. So far, patients have not experienced virological failure. DTG and enhanced PIs are the recommended core agents for the 2DR due to their efficacy, safety, and high resistance barrier [9]. This patient is an elderly woman and TDF may increase her risk of osteoporosis and renal failure. The 2DR (LPV/r + DTG) may be the only alternative for the patient in the long time.

Since 3TC has been an effective, safe, and widely used antiretroviral drug, clinicians must be aware of its adverse reactions to 3TC, which may require treatment discontinuation so that swift treatment can be given in such patients. 2DR will increasingly form part of the choice we are able to offer people with HIV but we must consider some of the limitations to ensure these regimens are used in the most clinically appropriate manner. DTG-based regimen for suppressed switch has high efficacy and no emergent resistance at failure.

Abbreviations

NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; INSTIs: integrase strand transfer inhibitors; PIs: protease inhibitors; ABC: abacavir (ABC); 3TC: lamivudine; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; AZT: azidothymidine; EFV: efavirenz; NVP: Nevirapine; ETR: Etravirine; RPV: Rilpivirine (RPV); LPV/r: Lopinavir and Ritonavir (LPV/r); ATV: Atazanavir; DRV: Darunavir (DRV); S: sensitivity; two-drug regimens: (2DR).

Declarations

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Authors' contributions

GY Xu, H Wang, HB Li, JE Sui, J Zhao, SS Ma, and P Chen carried out clinical practice. H Wang draft the manuscript and made some modification to this thesis. All authors read and approved the final manuscript.

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Availability of data and materials

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Kumar PN, Patel P. Lamivudine for the treatment of HIV. *Expert Opin Drug Metab Toxicol*. 2010;6(1):105-14.
2. 2018 Chinese AIDS Guidelines. *Chinese Journal of AIDS & STD*. 2018. 24(12):1266-1282.
3. Chinese Center for Disease Control and Prevention Sexually Transmitted Diseases and AIDS Prevention and Control Center. *National Free AIDS Antiviral Drugs Treatment Handbook [M]*. 4th edition. Beijing: People's Medical Publishing House, 2016.
4. SacAmrutha PC, Rakesh TP, Kidangazhiyathmana A et al. The enigma of lamivudine rash: Experience on re-challenge from an antiretroviral treatment center in South India. *Indian J Dermatol Venereol Leprol*. 2017. 83(4):502-504.
5. Sachdeva RK, Sharma A, De D, et al. Lamivudine-Induced Skin Rash Remains an Underdiagnosed Entity in HIV: A Case Series from a Single Center. *J Int Assoc Provid AIDS Care*. 2016. 15(2):153-8.
6. Modak D, Guha SK. Severe skin rash with lamivudine in HIV infected patients: Some unusual case reports. *Indian J Pharmacol* 2013; 45:298-300.

7. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS*. 2005;19(11):1183–1188.
8. Waters L, Church H. Two drugs regimens for HIV. *Curr Opin Infect Dis*. 2020;33(1):28-33.
9. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

Figures



Figure 1

Edematous erythematous rashes appeared on her body (grade 1 and 2)

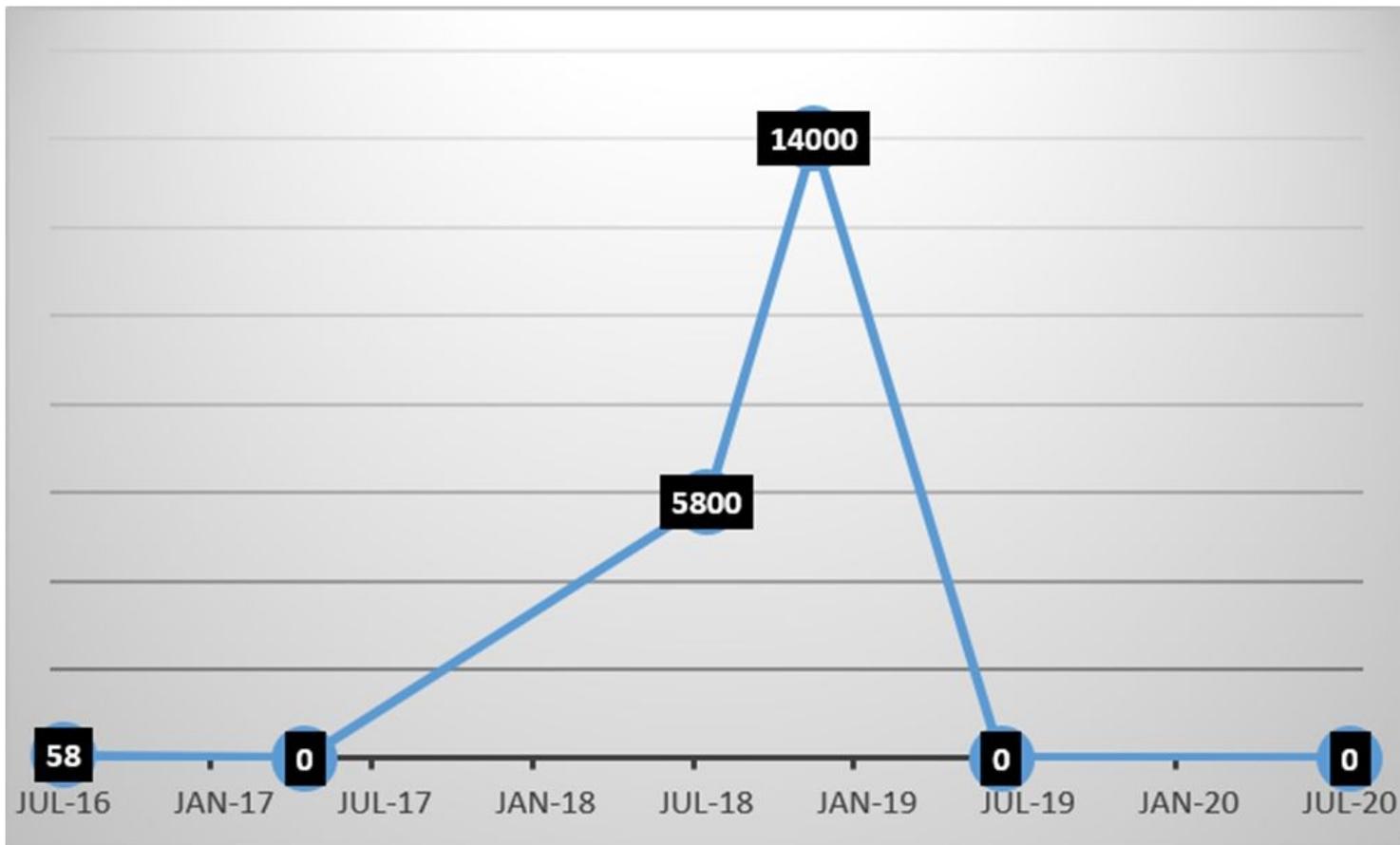


Figure 2

Viral loads of the patient were shown from 2016 to 2020.