M.J. Sousa[1], S. Cadinha[1], M. Mota[2], T. Teixeira[2], D. Malheiro[1], J.P. Moreira Silva[1]

Hypersensitivity to antiretroviral drugs

[1]Immunoallergology, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal
[2]Infectious Diseases, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal

Keywords
hypersensitivity; antiretroviral drugs; patch tests; emtricitabine; tenofovir; nevirapine

Corresponding author
Maria João C.S. Sousa
Serviço de Imunoalergologia
Rua Conceição Fernandes 4434-502
Vila Nova de Gaia, Portugal
E-mail: mariaj.sousa@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.42

Abbreviations
NW, North-West; NE, North-East; C, Centre; S, South; Is, Islands subset.

Summary
Background. *Antiretroviral treatment improved the prognosis of patients with Human Immunodeficiency Virus (HIV) infection. Antiretroviral drugs may be responsible for hypersensitivity reactions varying in severity, clinical manifestations and frequency. Individuals infected with HIV show an increased frequency of drug eruptions when compared with general population. Reports of delayed allergic reactions to antiretroviral drugs in patients with HIV have been described, but diagnostic methods are scarce.* ***Case report.*** *We report the case of a 47-year-old woman, with diagnosis of HIV infection since 2009, who developed a delayed mucocutaneous reaction after treatment with antiretroviral drugs. Hypersensitivity reaction (HR) to emtricitabine and tenofovir was considered probable based on positive patch tests (PT), which were negative in 7 controls. Delayed HR to nevirapine was confirmed by drug provocation test.* ***Discussion.*** *The diagnosis of HR to antiretroviral drugs in patients with HIV infection remains a diagnostic challenge, partly due to unknown mechanism and to the absence of validated diagnostic tools. Patch testing may represent a useful method for confirming hypersensitivity to antiretroviral drugs, however the use of PT is not widespread, so the predictive value of testing has not been ascertained. Further investigation in this area is required to elucidate the mechanisms in HIV-infected patients, so that successful management strategies can be offered, preventing loss of potent and viable antiretroviral agents.*

Introduction

The availability of potent antiretroviral drugs - highly active antiretroviral therapy (HAART) - has led to a dramatic decline in the morbidity and mortality associated with HIV infection (1). Since the introduction of HAART in the late 1990s, hypersensitivity to antiretroviral agents has increased (2). The increased frequency of drug reactions in patients with active viral illness has been attributed to dysregulation of the immune system and particular vulnerability to oxidative stress (3). Evidence that these reactions are immune mediated is largely based on typical symptomatology, and few studies have been done to determine the pathogenic mechanisms (4). The pathophysiology of drug hypersensitivity in HIV is most likely multifactorial and related to a number of metabolic, immunologic, host and viral factors (5). Concurrent illnesses such as immune reconstitution syndromes and viral illnesses may themselves present with fever, rash and multisystem disease, and hence may confound the diagnosis of drug hypersensitivity reactions (HR) (5).

There are currently six groups of antiretrovirals agents, comprising nucleoside reverse transcriptase inhibitors (NRTIs), non nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion inhibitors, CCR5 inhibitors and integrase inhibitors (6).

The diagnosis and management of drug hypersensitivity in HIV-infected patients is particularly difficult because of the multiple medication regimens that are used to treat patients (2). Skin reactions are the most common manifestation (6)

and drug-related rashes have been estimated to be 100 times more common in HIV-positive patients than in general population (7,8) and up to 1000 times greater when entities like Stevens-Johnson syndrome or toxic epidermal necrosis (SJS/TEN) are assessed (9). The diagnosis is based on clinical criteria (10) and diagnostic work-up includes a detailed clinical history, physical examination, symptom resolution on withdrawal, and reintroduction of the suspected drugs and exclusion of other causes.

Usually the onset of an allergic reaction is delayed, between 1-6 weeks after commencing the drug (6).

The authors present a case of HR to nevirapine confirmed by drug provocation test (DPT) and probable HR to emtricitabine and tenofovir based on positive patch tests (PT).

Case report

We report the case of a 47-year-old Caucasian woman with diagnosis of HIV infection since 2009, that started HAART with tenofovir, emtricitabine and nevirapine in 2011. The genetic screening for HLA B5701 was negative, pretreatment $CD4^+$ T-cell count was 345 cells/mm^3 and HIV-1 RNA level was 463 copies/mL.

On the second day of treatment, she developed pruritic exanthema and palpebral edema that improved two weeks after the infectiologist discontinued HAART and prescribed anti-histamines (AH) and oral corticosteroids (CS). Laboratory tests (complete blood count and biochemistry with liver and renal function tests) performed at the time of reaction were normal.

One month later, treatment with tenofovir and emtricitabine was restarted in association with darunavir/ritonavir. The patient reported a reproducible reaction on the second day of treatment which improved after discontinuation of therapy and treatment with AH and CS, with symptoms resolution in 8 days.

Two months later, the patient restarted darunavir/ritonavir in association with abacavir and lamivudine. On the second day she developed palpebral edema and discontinued the treatment once again. She was then referred to our Drug Allergy Clinic for suspected HR to antiretroviral drugs.

PT were performed with ritonavir 1% and 10% in petrolatum and with 1%, 10% and 30% in petrolatum with the other suspected drugs. Results were recorded using a standardized scoring system (11).

As summarized in **table I**, PT were considered strong positive for emtricitabine (1%, 10% and 30%) and tenofovir (10% and 30%), doubtful (erythema only) for lamivudine (10 and 30%) and negative to the other suspected drugs.

PT with emtricitabine, tenofovir and lamivudine (1%, 10% and 30%) were negative in 7 controls (**table II**).

DPT with darunavir (800 mg), ritonavir (100 mg) and abacavir (600 mg) were followed by home treatment with no adverse reactions. DPT with nevirapine up to 400 mg was positive, with development of pruritic exanthema in the upper limbs one hour after the conclusion of the oral challenge and palpebral edema 24 hours after.

DPT with raltegravir (800 mg) as alternative drug was negative.

She currently maintains treatment with darunavir/ritonavir, raltegravir and abacavir uneventfully.

Table I *- Results of patch testing.*

Patient							
patch tests	**ABC**	**FTC**	**TDF**	**3TC**	**NVP**	**TV**	**TMC114**
48 h							
1%	-	++	-	-	-	-	-
10%	-	++	++	?	-	-	-
30%	-	++	++	?	-	np	-
negative control	-	-	-	-	-	-	-

Standard patch test scores (adapted from Brockow K., et al. Allergy 2002; 57:45-51).	
?	doubtful (faint erythema only)
+	weak positive (erythema, infiltration, possibly papules)
++	strong positive (erythema, infiltration, papules, vesicles)
+++	extreme positive (bullous, ulcerative)
-	negative

ABC, abacavir; FTC, emtricitabine; TDF, tenofovir; 3TC, lamivudine; NVP, nevirapine; TV, ritonavir; TMC114, darunavir; np, not performed.

Discussion

Although nearly all antiretroviral drugs have been reported to cause HR, the most commonly associated with such syndromes include abacavir, nevirapine, efavirenz, etravirina, rilpivirina, fosamprenavir and enfuvirtide (5).

The diagnosis of drug hypersensitivity in HIV-infected patients is a challenging task. It is only based on clinical criteria, and complicated by the fact that many patients take multiple drugs and develop diseases such as opportunistic infections and immune restoration disease that can make determination of causality difficult (6).

HLA-B*5701 has great utility as a screening test, with 100% negative predictive value generalizable across different ethnicities to identify patients at risk to develop abacavir hypersensitivity (12,13). The complexity of HLA associations across different phenotypes and ethnicities with other drugs like nevirapine is such that currently HLA testing has limited utility as a screening strategy to prevent nevirapine hypersensitivity syndromes before nevirapine prescription (14). MHC HLA class II allele HLA-DRB1*0101 has been associated with nevirapine hypersensitivity (15).

Drug-related rashes occur at a much higher frequency in HIV-positive patients than in the general population (2). Cutaneous eruptions are the most common manifestation, but significant systemic findings, including fever and internal organ involvement can occur (10). The most common cutaneous drug reaction in HIV-infected patients are maculopapular exanthemas, often accompanied by pruritus without fever (15). These eruptions usually appear between 2 and 10 weeks after primary exposure to antiretroviral therapy and within 1 to 2 days of rechallenge (14).

Cutaneous problems and hepatoxicity are the main side effects induced by NNRTIs (14). All NNRTIs have been associated with rash and less commonly with HR marked by combinations of fever, rash and internal organ involvement or severe skin involvement such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (5).

The most common drug-related adverse event secondary to nevirapine is nonurticarial eruption (2). Female sex, ethnicity (Hispanic, Chinese and African), individuals with higher $CD4^+$ T-cell count (> 250 cells/mm^3 for women and > 400 cells/mm^3 for men), and uncontrolled HIV viremia in early studies seemed to be at higher risk for nevirapine-related rash (2,16).

Hypersensitivity to tenofovir has been rarely reported, as described by Borras-Blasco, et al. (17); another case of hypersensitivity to emtricitabine/tenofovir was reported with similar clinical symptoms to abacavir HR (18).

All HR in our patient were mild cutaneous reactions on the second day of HAART: first with combination of emtricitabine, tenofovir and nevirapine; then with the combination of emtricitabine, tenofovir, darunavir/ritonavir; and last with the combination of darunavir/ritonavir, lamivudine and abacavir.

Our patient had at least three risk factors that may facilitate nevirapine-related rash: higher pretreatment $CD4^+$ T-cell count, lower HIV-1 RNA level, and female sex.

PT is the most studied cutaneous testing approach in delayed drug HR (11). In the case of HR to antiretroviral drugs the true diagnostic sensitivity is unknown, except for abacavir. Guidelines have recommended concentrations of 1-10% of the pure drug and 30% of the commercialized form (19). Based on this, PT were prepared 1% and 10% in petrolatum of ritonavir, and with 1%, 10% and 30% in petrolatum with the other suspected drugs (emtricitabine, tenofovir, nevirapine, darunavir, lamivudine and abacavir).

Table II *- Results of patch testing in controls.*

	Controls					Patch tests									
	sex	**age (years)**	**atopy**	**HIV**	**exposure to ART**	**1%**	**FTC 10%**	**30%**	**1%**	**TDF 10%**	**30%**	**1%**	**3TC 10%**	**30%**	**NC**
1	f	45	NP	+	3TC	-	-	-	-	-	-	-	-	-	-
2	m	49	NP	+	FTC, TDF	-	-	-	-	-	-	-	-	-	-
3	m	52	NP	+	FTC, TDF	-	-	-	-	-	-	-	-	-	-
4	f	46	A	+	3TC	-	-	-	-	-	-	-	-	-	-
5	f	63	NA	-	-	-	-	-	-	-	-	-	-	-	-
6	m	34	A	-	-	-	-	-	-	-	-	-	-	-	-
7	f	61	A	-	-	-	-	-	-	-	-	-	-	-	-

f, female; m, male; HIV, human immunodeficiency virus; ART, antiretroviral treatment; FTC, emtricitabine; TDF, tenofovir; 3TC, lamivudine; NC, negative control; NP, not performed; NA, non atopic; A, atopic.

HR to emtricitabine and tenofovir was considered probable based on positive PT in the patient and negative PT in 7 controls (**table II**).

Delayed HR to nevirapine was confirmed by DPT. It was possible to exclude HR to darunavir, ritonavir and abacavir based on DPT.

Although anti-retroviral drugs may share a structure, such as a shared sulfa antimicrobial group in the case of darunavir and fosamprenavir, or shared mechanism of action and propensity to develop skin rash, as for the HIV NNRTIs, clinical and immunologic cross-reactivity between antiviral drugs is uncommon in clinical practice (14).

Since lamivudine is chemically similar to emtricitabine (20), the doubtful result of PT with lamivudine could be explained by a possible cross-reactivity between both drugs, although new sensitization to lamivudine can not be excluded.

This is an interesting case, because HR to antiretroviral drugs in HIV-infected patients are increasing, and management of these patients represents a diagnostic and therapeutic challenge. In addition, HAART affects the prognosis of patients with HIV infection.

PT may represent a useful method for confirming hypersensitivity to antiretroviral drugs. PT performed with emtricitabine and tenofovir in 7 controls (**table II**) were negative, suggesting that the concentrations used were not irritative. However, the use of PT is not widespread, so the predictive value of testing has not been ascertained.

Further investigation in this area is required to elucidate the mechanisms in HIV-infected patients, so that successful management strategies can be offered, preventing loss of potent and viable antiretroviral agents.

Informed consent

The authors have obtained the informed consent of the patients mentioned in the article.

References

1. Palella F, Delaney K, Moorman A, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection: HIV Outpatient Study Investigators. N Engl J Med 1998; 338:853-860.
2. Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. J Allergy Clin Immunol 2008; 121:826-832.e825.
3. Skulachev V. Possible role of reactive oxygen species in antiviral defense. Biochemistry 1998; 63:1438-1440.
4. Marcos Bravo MC, Ocampo Hermida A, Moreno Rodilla E. Hypersensitivity reactions to antiretroviral agents in HIV-infected patients. Med Clin (Barc) 2007; 128(2):61-69.
5. Phillips E, Mallal S. Drug hypersensitivity in HIV. Curr Opin Allergy Clin Immunol 2007; 7:324-330.
6. Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. British Journal of Clinical Pharmacology 2011; 71(5):659-671.
7. Roujeau J, Stern R. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994; 331:1272-1285.
8. 8. Pirmohamed M, Park BK. HIV and drug allergy. Curr Opin Allergy Clin Immunol 2001; 1(4):311-316.
9. Rotunda A, Hirsch R, Scheinfeld N, Weinberg J. Severe cutaneous reactions associated with the use of human immunodeficiency virus medications. Acta Derm Venereol 2003; 83:1-9.
10. Temesgen Z, Beri G. HIV and drug allergy. Immunol Allergy Clin N Am 2004; 24:521-531.
11. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002; 57(1):45-51.
12. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008; 358(6):568-579.
13. Schackman BR, Scott CA, Walensky RP, et al. The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. AIDS 2008; 22(15):2015-2033.
14. Milpied-Homsi B, Moran EM, Phillips EJ. Antiviral drug allergy. Immunol Allergy Clin N Am 2014; 34:645-662.
15. Martin AM, Nolan D, James I, et al. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1*0101 and abrogated by low CD4 T-cell counts. AIDS 2005; 19(1):97-99.
16. De Maat MM, ter Heine R, Mulder JW, et al. Incidence and risk factors for nevirapine-associated rash. Eur J Clin Pharmacol 2003; 59(5-6):457-462.
17. Borras-Blasco J, Navarro-Ruiz A, Borras C, et al. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J Antimicrob Chemother 2008; 62(5):879-888.
18. De Perio MA, Gomez FJ, Frame PT, Fichtenbaum. AIDS 2007; 21(16):2252-2253.
19. Shear NH, Milpied B, Bruynzeel DP, Phillips EJ. A review of drug patch testing and implications for HIV clinicians. AIDS 2008:999-1007
20. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. Clin Infect Dis 2006; 42:126-131.