

Drug hypersensitivity in HIV

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Purpose of review

Drug hypersensitivity has been reported to occur 100 times more commonly in those living with HIV. In the first decade of HIV treatment, this mainly involved drugs used to treat HIV-related infections but now primarily includes drugs used to treat HIV. This review focuses on the current knowledge of the epidemiology, pathophysiology and clinical features of drug hypersensitivity reactions of drugs used in the management of the HIV-infected patient.

Recent findings

Our understanding of the immunogenetics and host predisposition to drug hypersensitivity has been advanced considerably by the antiretroviral drugs abacavir and nevirapine. The association of abacavir hypersensitivity reaction with *HLA-B*5701* has been particularly important and provides a basis for genetic screening in the clinic setting.

Summary

The increased predisposition of drug hypersensitivity disease in HIV will continue to provide a fertile ground for study of the diverse and complex processes that drive its pathophysiology. Our knowledge of drug hypersensitivity will also increase as the expanding armamentarium of antiretroviral therapy is applied to more diverse populations in the developing world. The potential for widespread implementation of *HLA-B*5701* screening for abacavir hypersensitivity will set an important precedent for bringing individualized medicine to the clinic and the use of genetic testing to improve drug safety.

Keywords

antiretroviral therapy, drug hypersensitivity, HIV, major histocompatibility complex, pharmacogenetics

Introduction

From the inception of HIV disease it became clear that the immune dysregulation associated with HIV has some important clinical consequences, including a higher incidence of cutaneous disease as well as drug-associated hypersensitivity reactions [1]. Initially this was illustrated with drugs used to treat infections and other complications associated with HIV such as dapsone, sulfamethoxazole and antituberculous therapy. With the evolution of more potent combination antiretroviral regimens as well as an increasing number of new antiretroviral agents, many of the complications associated with HIV have become much less common and in the developed world at least, hypersensitivity reactions are now more commonly associated with antiretroviral treatment (ART) itself [2]. One such example, the abacavir hypersensitivity reaction (ABC HSR), has both advanced our understanding of the immunogenetic basis for drug hypersensitivity reactions as well as created a basis for preventive screening. Expansion of the diversity of drugs and treatment populations over the subsequent decade will be further enlightening as to the multitude of immune, metabolic, genetic, viral and acquired factors that play into the complex pathophysiology of drug hypersensitivity in HIV. Following the indication to initiate treatment of antiretroviral drugs, current HIV treatment guidelines dictate the initiation and continuation of combination antiretroviral therapy which typically consists of three or more drugs in combination [3*]. The expanding armamentarium of antiretroviral drugs currently approved by the US Food and Drug Administration is shown in Table 1.

Overview of the pathophysiology of drug hypersensitivity in HIV

It has been well established that HIV-infected individuals show an increased frequency of common cutaneous diseases (psoriasis, atopic dermatitis and seborrheic dermatitis), drug rashes and, in general, hypersensitivity reactions, compared with the HIV-negative population [1]. Drug hypersensitivity reactions or rashes have been described to occur 100 times more commonly in HIV-infected patients [1]. Hypersensitivity reactions in the setting of HIV are clinically similar to those in the non-HIV patients, being generally characterized by a combination of fever, rash and internal organ involvement within 6 weeks of drug initiation. The exposure to any given drug is necessary but not sufficient, meaning that several patient-specific factors are likely to be important such as concurrent viral or opportunistic infections,

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Abbreviations

ABC HSR	abacavir hypersensitivity reaction
MHC	major histocompatibility complex
NNRTI	nonnucleoside reverse transcriptase inhibitor
TMP-SMX	trimethoprim sulfamethoxazole

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Table 1 US Food and Drug Administration approved antiretroviral agents currently in use

Nucleoside/nucleotide reverse transcriptase inhibitors	Nonnucleoside reverse transcriptase inhibitors	Protease inhibitors	Entry inhibitors	CCR5 inhibitors	Integrase inhibitors
Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir	Delavirdine Efavirenz Nevirapine	Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir/ritonavir Nelfinavir Ritonavir Saquinavir Tipranavir	Enfuvirtide (T-20)	Maraviroc	Raltegravir ^a
Fixed dose combinations					
Once daily Atripla (emtricitabine + tenofovir + efavirenz) Kivexa (Epzicom) (abacavir + lamivudine) Truvada (emtricitabine + tenofovir)			Twice daily Combivir (lamivudine + zidovudine) Trizivir (abacavir + lamivudine + zidovudine)		

^aExpected approval summer 2007.

immune dysregulation and increased susceptibility of HIV-infected individuals to oxidative stress. Hence, the pathophysiology of drug hypersensitivity in HIV is most likely multifactorial and related to a number of metabolic, immunologic, host and viral factors. In addition to the potential for contribution to the development of drug hypersensitivity in HIV, concurrent illnesses such as immune restoration syndromes and viral illnesses may themselves present with fever, rash and multisystem disease and hence may confound the diagnosis of drug hypersensitivity reactions.

Hypersensitivity associated with drugs used to treat HIV-associated infections

Trimethoprim sulfamethoxazole (TMP-SMX) has been the mainstay for the treatment and prophylaxis of *Pneumocystis jirovecii* (formally *carinii*) pneumonia. Drug hypersensitivity associated with TMP-SMX is estimated to occur in approximately 5% of HIV-negative patients compared with up to 60% or higher of HIV patients who have been reported to experience TMP-SMX hypersensitivity reactions at some time during treatment [4–7]. Furthermore, rare and life-threatening hypersensitivity reactions related to TMP-SMX and occurring in less than one in 10 000 of the general population have been reported in up to 4% of HIV-infected individuals [8]. Multiple theories exist to explain the high rate of TMP-SMX hypersensitivity in HIV-infected individuals, including a number of acquired and host factors such as slow acetylation, oxidative stress and depletion of thiols and cysteine [9–13]. Cellular studies have supported the role of reactive sulfamethoxazole metabolites, such as the reactive hydroxylamine metabolite generated by cytochrome p450 2C9 oxidation of the arylamine at the N4 position [14–16]. In-vitro evidence suggests that HIV-infected cells may be more susceptible to the direct cell injury and death provoked by reactive sulfamethoxazole metabolites and that this necrotic cell death may

provide a 'danger signal' to sensitized T cells leading to the cascade of immune response and cytokine release manifesting as drug hypersensitivity [15,16]. Glutathione deficiency in HIV disease has been proposed as another predisposing mechanism to TMP-SMX and other drug hypersensitivities by resulting in increased reactive and toxic metabolites [12]. Active HIV disease may contribute since HIV replication is stimulated by the HIV protein Tat. Tat expression is associated with increased oxidative stress and decreased glutathione biosynthesis and cellular concentrations. This is supported by a study demonstrating increased toxicity of sulfamethoxazole hydroxylamine in lymphocytes transfected with the HIV Tat gene [17]. In the case of TMP-SMX, glutathione likely protects cells from toxic metabolites by deterring oxidation of the reactive hydroxylamine to a more toxic nitroso metabolite. Despite this, the use of N-acetylcysteine to increase intracellular glutathione in an attempt to prevent or mitigate TMP-SMX hypersensitivity in HIV-infected individuals showed no such effect in two randomized controlled trials [18,19]. Slow acetylator phenotype has been associated with greater exposure to reactive and toxic metabolites but has not been predictive of TMP-SMX hypersensitivity in HIV-infected patients in all studies [20]. Recent research supports that more complex interactions between metabolic and immunoregulatory factors are likely to be important in the pathogenesis of sulfamethoxazole hypersensitivity [21].

Lack of clinical reproducibility of symptoms in HIV patients who have previously received a diagnosis of TMP-SMX hypersensitivity supports the proposition that a number of host and acquired factors are likely both necessary and important in its development. Reintroduction of TMP-SMX in patients who have previously experienced mild to moderate reactions (without internal organ involvement or severe skin involvement) has been

successful, with literature supporting that desensitization or dose escalation has better long-term success with fewer adverse events than direct rechallenge [22,23*].

Little information is available on cross-reactivity between TMP-SMX and other sulfa antimicrobials. Dapsone, a sulfone antimicrobial used in the treatment and prophylaxis of *Pneumocystis jirovecii* pneumonia (PJP), has also been commonly associated with drug hypersensitivity and rash in HIV and there is some evidence to support a 22% cross-reactivity rate in patients previously experiencing TMP-SMX hypersensitivity, although the pathophysiology is not well understood [24]. Other drugs, in particular isoniazid, rifampin and pyrazinamide, used in the first line treatment of *Mycobacterium tuberculosis*, have been associated with significantly higher rates of drug hypersensitivity in those with HIV infection versus HIV-negative patients [25]. In one study, thiacetazone, which has been used as a cheaper follow-on treatment for *M. tuberculosis* in the developing world, was associated with an almost 20-fold increase in severe cutaneous reactions in HIV-infected patients compared with HIV-negative individuals [26].

Hypersensitivity associated with antiretroviral drugs

Although there have been case reports of nearly all antiretroviral drugs and drug hypersensitivity, the antiretroviral drugs most commonly associated with such syndromes include abacavir, a nucleoside analogue, the nonnucleoside reverse transcriptase inhibitors (NNRTIs; nevirapine, efavirenz, delavirdine, TMC-125, TMC-278), fosamprenavir, an HIV protease inhibitor and enfuvirtide (T-20), an HIV fusion inhibitor.

Abacavir

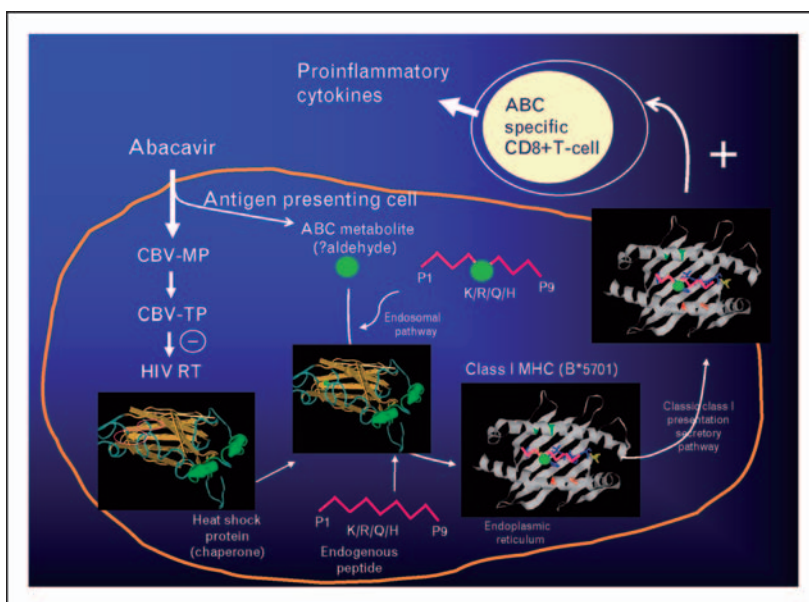
Abacavir is a guanosine, nucleoside reverse transcriptase inhibitor which has been approved for the combination treatment of HIV for almost 9 years. The short-term safety profile of abacavir was established in the premarketing phase of the drug when it became apparent that abacavir was associated with a hypersensitivity reaction characterized by fever, rash and combinations of other constitutional, headache and gastrointestinal symptoms occurring within 6 weeks of drug initiation [27]. It was also established early on that the reaction increased in severity and rapidity of onset on reexposure, making rechallenge a contraindication and suggesting an immunologic basis of the hypersensitivity reaction [28]. Early studies that documented a Caucasian predisposition for ABC HSR as well as a case report documenting familial occurrence were also strong early clues for a genetic basis for this syndrome [29]. Meta-analyses of clinical trials have suggested that ABC HSR occurs in approximately 5% of those who initiate the drug. Two early studies independently established an association between ABC

HSR and the major histocompatibility complex (MHC) class I allele *HLA-B*5701*, which is one of the strongest associations ever described between a genetic marker and disease [30,31]. Cellular and ex-vivo studies showing strong tumour necrosis factor- α (TNF- α), interferon- γ (IFN- γ) responses and CD8+ proliferation after ex-vivo exposure to abacavir also support the premise that ABC HSR is a class I MHC disease mediated by *HLA-B*5701* restricted CD8+ lymphocytes [32,33]. Candidate genetic factors specific for the 57.1 ancestral MHC haplotype have been examined and have narrowed the region of susceptibility to that which includes *HLA-B*5701* and a nonsynonymous variant with heat shock protein 70 [33]. A proposed pathogenetic model for ABC HSR is shown in Fig. 1.

Abacavir metabolism may also be important in the development of ABC HSR, most likely related to the oxidation of abacavir to an aldehyde intermediate and carboxylic acid metabolite both mediated by class I alcohol dehydrogenase (ADH) and supported by the ability to block ex-vivo responses with the class I ADH inhibitor, 4-methylpyrazole [34,35]. Differences that have occurred between clinical studies with regards to the incidence, sensitivity and predictive value of *HLA-B*5701* and associated genes have largely reflected differences in study population, study design as well as misclassification from difficulties in the diagnosis or phenotyping of ABC HSR [36]. Abacavir patch testing, using various concentrations of abacavir applied to the skin in a petrolatum vehicle, has been successfully used to correctly identify true immunogenetically mediated ABC HSR and 100% of patch test positive patients identified worldwide to date have been *HLA-B*5701* positive [33,37,38*]. The difficulties in correctly phenotyping patients with ABC HSR are best evidenced in blinded clinical trials in which rates of hypersensitivity in patients in the nonabacavir-containing arm have ranged from 2 to 7% [39–41]. Abacavir patch testing has emerged as an important research tool to increase diagnostic precision and is also being used in this context in two complementary clinical trials whose results will be presented in July 2007: Predict-1, a randomized controlled trial testing the utility of *HLA-B*5701* screening for ABC HSR, and SHAPE, a retrospective case–control study to examine the sensitivity of *HLA-B*5701* for ABC HSR in both white and black patients. Current observational studies using open screening for *HLA-B*5701* have supported that genetic screening will significantly reduce both true immunogenetically mediated hypersensitivity as well as false positive clinical diagnosis [42*,43**,44,45*]. The expense and longer turnaround time associated with high-resolution HLA typing will likely limit its widespread application, however, more cost-effective methods for identifying the *HLA-B*5701* allele, including molecular typing methods such as sequence specific amplification

Figure 1 Proposed pathogenic model of abacavir (ABC) hypersensitivity

Abacavir hypersensitivity appears to be exquisitely *HLA-B*5701* restricted both clinically and experimentally. Abacavir is metabolized by cytosolic alcohol dehydrogenase to produce a reactive metabolite that haptenates an endogenous peptide which undergoes classical class I processing. This culminates in presentation of the peptide–HLA complex on the surface of an antigen presenting cell to the T-cell receptor of an abacavir-specific CD8+ T cell, triggering the release of inflammatory cytokines. MHC, major histocompatibility complex. Adapted with permission from Martin *et al.* [32].



(SSP) and a serological approach by flow cytometry methods using a B57 monoclonal antibody are currently being explored as part of larger quality assurance programs [46,47].

Hypersensitivity associated with nonnucleoside reverse transcriptase inhibitors

All NNRTIs, either approved or in the premarketing stage, have been associated with rash and less commonly hypersensitivity reactions marked by combinations of fever, rash and internal organ involvement or severe skin involvement such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The epidemiology and immunopathogenesis of these latter more severe reactions have been most commonly associated and completely studied with the NNRTI nevirapine. Although skin rash has occurred in over 35% of patients started on nevirapine, the typical strategy of dose escalation due to autoinduction of the drug's metabolism of 200 mg daily for 2 weeks followed by 200 mg twice daily thereafter has resulted in 9–32% of patients experiencing rash in clinical studies, with overall 16% of rash attributable to nevirapine [48]. More severe reactions associated with fever and hepatitis have occurred in approximately 5% of those initiating nevirapine [49,50]. Severe skin involvement such as SJS/TEN occurs in approximately 0.3% of those initiating the drug [50]. Most hypersensitivity reactions occur within 10 days to 6 weeks of treatment initiation and it is recommended that the dose not be increased until resolution of the rash if it occurs during the 200 mg once daily

introduction period. Rash-associated hepatitis occurs about three-fold more commonly in women and severe rash seven-fold more common in women [51]. Severe hypersensitivity events have also been more commonly documented in non-HIV-infected individuals receiving postexposure prophylaxis as well as hepatotoxicity in HIV-infected individuals with higher CD4+ counts (women > 250/ μ l and men > 400/ μ l) and hence treatment with nevirapine is not recommended in these settings [49,52]. An animal model has supported a strong immunological and a CD4+ dependent basis for nevirapine hypersensitivity and has been successful in reproducing skin but not liver pathology in Brown Norway rats [53]. Ex-vivo and clinical studies have also supported an immunogenetic and CD4+ dependent basis for nevirapine hypersensitivity, with data from the Western Australian cohort supporting an association between rash-associated hepatitis and the MHC HLA class II allele *HLA-DRB1*0101* among patients with CD4+ cells greater than 25% (odds ratio 17.7, $P = 0.0006$) [54,55]. Class I MHC alleles may confer a different pathophysiology, with HLA-Cw8 and HLA-B14 reported in association with nevirapine hypersensitivity in Sardinian HIV patients and HLA-Cw8 from a recent Japanese report [56,57]. SJS occurring in both a Ugandan HIV-infected mother and her 8-year-old son additionally raise the question that severe cutaneous disease associated with nevirapine may have a genetic basis [58].

Efavirenz, an NNRTI commonly used in clinical practice, has frequently been associated with rash in 10–27% of patients starting the drug, but rarely associated with a

true hypersensitivity reaction comprising fever or internal organ involvement [59]. Patients who develop isolated rash in the absence of fever or internal organ involvement can often be treated symptomatically with antihistamines or topical steroids and usually successfully maintained on the drug. Although structurally different from nevirapine, the issue of the question of clinical cross-reactivity between nevirapine and efavirenz often arises and there are limited data to address this issue [60–62]. A recent retrospective cohort study [63•] conducted in Thailand looked at patients with CD4+ cells less than 200/ μ l who had been diagnosed with nevirapine skin rash and subsequently received efavirenz over a 1.5-year period. Despite the fact that more than a third of patients included in the study had experienced rash with constitutional symptoms with nevirapine and that there was a trend toward more rash events with efavirenz in patients who had experienced severe reactions with nevirapine, 91.8% of 122 patients receiving efavirenz were tolerant without rash and 8.2% developed efavirenz-associated rash that required discontinuation. Data for other NNRTIs are more limited, although a new drug under study, TMC-278, appears to be associated with a lower frequency of rash and hypersensitivity compared with efavirenz [64].

Other antiretrovirals associated with hypersensitivity reactions

Fosamprenavir, an HIV protease inhibitor, is a prodrug of amprenavir which was its predecessor. Fosamprenavir has been associated with skin rash of varying severity in 19% of patients in clinical studies, however, less than 1% of these were deemed severe or required discontinuation [65]. Fosamprenavir shares a sulfonylarylamine structure with sulfamethoxazole and darunavir (TMC-114), another HIV protease inhibitor [66]. There is currently limited information as to the clinical cross reactivity between TMP-SMX and fosamprenavir, and indeed this would be difficult to measure since even for TMP-SMX itself drug hypersensitivity may not be reproducible in the same patient over time [66]. In the case of darunavir, although the drug is associated with rash in 7% of patients, severe rash occurs in less than 1% [67]. Furthermore, although there is limited information on clinical cross reactivity, patients with 'sulfa' or 'sulfonamide antimicrobial' hypersensitivity were not excluded from darunavir clinical trials.

Enfuvirtide, is a 36-amino-acid synthetic peptide, administered by subcutaneous injection that inhibits the fusion of HIV-1 with CD4+ cells and is generally reserved for treatment in antiretroviral experienced patients [68]. The most common adverse event associated with this drug is a local reaction at the injection site [69]. True hypersensitivity reactions involving combinations of fever, rash, systemic features and hepatitis

have occurred in less than 1% of patients started on the drug [70–72]. Reports have generally been of delayed hypersensitivity reactions occurring more than 1 week after drug initiation [70–72] aside from a case presenting with fever, chills, nausea, myalgias and shortness of breath occurring 50 min after injection of the first dose, raising the possibility of an alternate mechanism [73]. Desensitization has been used with some success to reinstate the drug in patients who have experienced this syndrome [71–73]. Based on these clinical features the pathogenesis of the syndrome is likely, at least in part, to be immunologically mediated, but the mechanism has not been delineated.

Conclusion

Drug hypersensitivity reactions are common in those living with HIV and their pathophysiology is complex and multifactorial. In the developed world, there has been a shift such that these are most commonly associated with ART, although hypersensitivity associated with TMP-SMX and antituberculous treatment in the developing world are still of major concern. The association of *HLA-B*57:01* and ABC HSR has advanced our understanding of the immunopathogenesis of drug hypersensitivity and promises to be the first example for which widespread genetic screening in HIV clinic populations could be used to prevent drug ABC HSR, establishing a role for personalized medicine to improve drug safety.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 361).

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