

HIV and drug allergy

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Drug-related rashes have been estimated to be 100 times more common in HIV-positive patients than in the general population. The reasons for this are not clear, but are likely to be multifactorial, and include changes in drug metabolism, oxidative stress, cytokine profiles and immune hyperactivation. HIV itself may also serve as a danger signal, leading to the development of an immune response rather than tolerance. Drugs that are implicated in causing hypersensitivity have changed since the advent of highly active antiretroviral therapy. This is largely as a result of a decrease in the use of antimicrobials such as co-trimoxazole, and the introduction of new drugs of different classes, including abacavir, non-nucleoside reverse transcriptase inhibitors such as nevirapine, and protease inhibitors such as amprenavir. Laboratory evidence supporting a role of the immune system in the mechanism of co-trimoxazole hypersensitivity is available. However, this is not the case for the newer antiretrovirals; hypersensitivity to these agents is presumed to be immune-mediated based only on the symptomatology. It is essential that research be carried out into the mechanisms of hypersensitivity reactions associated with these important new classes of drugs so that their benefit–risk ratio can be improved, and lessons learned for future drug development. *Curr Opin Allergy Clin Immunol* 1:311–316. © 2001 Lippincott Williams & Wilkins.

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Abbreviations

HAART	highly active antiretroviral therapy
MHC	major histocompatibility complex
NNRTI	non-nucleoside reverse transcriptase inhibitor
SMX	sulphamethoxazole

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Introduction

There have been remarkable advances in the treatment of HIV over the past 5 years. This has essentially resulted in HIV becoming a chronic disease; with the use of highly active antiretroviral therapy (HAART) there has been a marked reduction in mortality, and through maintenance of immune function, there has also been a reduction in the frequency of opportunistic infections [1]. However, the introduction of new drugs that have improved disease-related morbidity and mortality has not been accompanied by an improvement in the adverse reaction profile for this patient group. Indeed, a wide variety of adverse effects have been reported over the past few years. Although there has been a great deal of focus on the metabolic lipodystrophy syndrome that is associated with HAART [2], drug allergy in HIV-positive individuals remains a major problem. The present review focuses on allergic reactions that have been reported with the drugs used to treat both HIV and its associated opportunistic infections (Table 1).

Epidemiology and drugs implicated

A study in 1993 [3] showed that the frequency of drug hypersensitivity in HIV-positive patients ranges from 3 to 20%. It has been estimated [4] that drug-related rashes are 100 times more frequent in HIV-positive patients than in the general population. Clinically, most patients present with erythematous rashes, which in approximately 0.5% of cases are blistering in nature. The rashes may be accompanied by fever, and in some cases by internal organ involvement. The effect of rechallenge varies with the drug; for example, rechallenge is strictly contraindicated with abacavir [5], for which deaths have been reported on re-exposure, whereas it is deliberately attempted as a desensitization procedure in patients with a history of trimethoprim–sulphamethoxazole (co-trimoxazole) allergy [6]. Although these reactions are termed allergic, it is important to note that this is largely based on the typical symptomatology; with the exception of co-trimoxazole (discussed below), few studies have been done to determine whether the reactions are truly immune mediated.

The drugs implicated in causing the reactions have changed over the past 5 years. In the 1980s, the commonest drugs responsible for allergy were the antimicrobials used to treat or protect against opportunistic infections. Co-trimoxazole, used for *Pneumocystis carinii* pneumonia, received the greatest attention [7]. However, a significant incidence of hypersensitivity was

Table 1. Drugs used in HIV disease that are associated with allergic reactions

Drug type	Drugs
Antimicrobials	Aminopenicillins
	Co-trimoxazole
	Dapsone
	Primaquine
	Clindamycin
	Thioacetazone
	Rifampicin
	Isoniazid
	Abacavir (NRTI)
	Amprenavir (PI)
Anti-HIV drugs	Delavirdine (NNRTI)
	Efavirenz (NNRTI)
	Nevirapine (NNRTI)

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

observed with other antimicrobials, including aminopenicillins, isoniazid, rifampicin, thioacetazone, clindamycin, primaquine and dapsone, as well as the other sulphonamides. With the advent of HAART, there is no longer the same need for prophylactic therapy, and thus problems associated with the antimicrobials have decreased, but not disappeared. However, these have largely been replaced by reactions to the new anti-retroviral agents, detailed below.

Abacavir

Abacavir, a nucleoside reverse transcriptase inhibitor, has been associated with life-threatening hypersensitivity reactions in 3–5% of patients [8•]. The adverse effect occurs after a mean of 11 days (range 3–56 days), and is characterized by (in rank order of frequency) fever, rash, gastrointestinal, mouth/throat, respiratory and musculoskeletal symptoms, as well as malaise, lymphadenopathy, parasthesiae and fatigue. This reaction should be distinguished from rash (without systemic manifestations), which can occur in 15% of patients. The mechanistic relationship between rash and severe hypersensitivity reactions is unknown. In cases of proven or suspected hypersensitivity, abacavir should be discontinued, and rechallenge (which can be rapidly fatal) should not be attempted [5,8•,9]. The mechanism of abacavir hypersensitivity, and specifically the nature of the immune response, has not been defined.

Non-nucleoside reverse transcriptase inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) include delavirdine, efavirenz and nevirapine. All NNRTIs are associated with rashes, which are presumed to be hypersensitivity phenomena. All grades of rash have been observed at a rate 10% greater than that in control individuals with efavirenz, and 15–17% greater with nevirapine and delavirdine

[10•]. Although the rash frequencies with nevirapine and delavirdine are similar, cutaneous eruptions appear to be more severe in patients on nevirapine [11•]. Thus, Stevens–Johnson syndrome occurs in 0.3% of patients on nevirapine [12,13], and rarely with the other NNRTIs.

The issue of cross-sensitivity between the NNRTIs has not been resolved [14]. One study that compared nevirapine with delavirdine [11•] suggested a cross-sensitivity rate of 70%; however, whether this was true cross-reactivity or merely coincidental is unclear. Certainly, occurrence of rash, hepatic abnormalities or flu-like symptoms with nevirapine did not prevent the use of efavirenz [15].

Of the NNRTIs, nevirapine has been most widely investigated with respect to the occurrence of hypersensitivity reactions. Slow introduction of nevirapine reduces the risk of rash [16•]. The effect of steroids in preventing rash remains controversial with contradictory reports [16•,17]. The risks of severe rashes and discontinuation of nevirapine therapy in women are 7-fold and 3.5-fold higher, respectively, than in men [18]. Nevirapine is also associated with raised transaminases in 7% of patients, with 1% developing hepatitis [10•]. In some cases, the hepatic abnormalities are due to concomitant infection with hepatitis viruses, but undoubtedly in some of the patients the hepatitis is a manifestation of the hypersensitivity reaction. Worrisomely, there have recently been reports of severe hepatotoxicity and rash in individuals given nevirapine as part of postexposure prophylaxis [19]. Evaluation by the US Food and Drug Administration of reports received by MedWatch over the past 3 years has revealed that there were 22 cases of serious adverse events associated with postexposure prophylaxis, including 12 reports of hepatotoxicity, 14 of skin reactions and one of rhabdomyolysis, occurring a median of 21 and 9 days after start of therapy for the hepatic and skin reactions, respectively [20•]. The use of nevirapine for postexposure prophylaxis is therefore no longer recommended.

Protease inhibitors

Adverse reactions, such as skin rashes and abnormal liver function tests, that are presumed to be manifestations of hypersensitivity have been reported with all protease inhibitors. Rash, however, appears to be more common with amprenavir than with the other protease inhibitors [21••]. It has been reported in up to 28% of patients; 4% have grade 3 or 4 rashes, 3% discontinue treatment and 1% can develop Stevens–Johnson syndrome. A sulfa moiety in amprenavir has been implicated in the higher incidence of rashes; however, there is no laboratory evidence to support this.

Mechanisms of hypersensitivity to co-trimoxazole

Co-trimoxazole is used in the treatment and prophylaxis of *Pneumocystis carinii* pneumonia. The use of co-trimoxazole has decreased over the past few years since the advent of HAART, and consequent immune reconstitution [22,23]. Nevertheless, it is still associated with hypersensitivity reactions, and represents a good paradigm by which to investigate the mechanisms of hypersensitivity in HIV-positive patients.

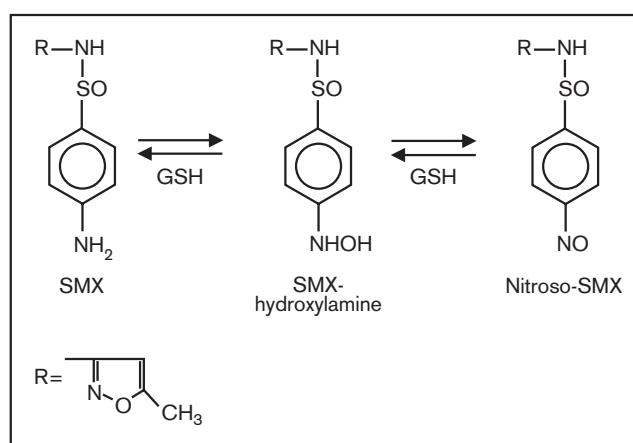
Co-trimoxazole is associated with hypersensitivity in 1–3% of HIV-negative patients [24]. In HIV-positive patients the frequency is much higher, occurring in 30% of patients at prophylactic doses and in 50% of patients at doses used for treatment [7]. Sulphamethoxazole (SMX), rather than trimethoprim, is responsible in most cases. The mechanism by which SMX causes hypersensitivity is not clear. There are two complementary hypotheses, both of which can be supported by experimental evidence.

The first hypothesis is that the parent drug itself may be responsible through a pathway that is major histocompatibility complex (MHC)-restricted, but processing- and metabolism-independent [25,26•]. This requires labile, reversible binding of SMX to the MHCs on antigen-presenting cells. The presence of T-cell clones that proliferate only in response to SMX, and the rapid downregulation in expression of the T-cell receptor on stimulation are consistent with this mechanism.

The second hypothesis is that immune response occurs through the traditional hapten pathway, in which bioactivation and haptenation are critical in initiating the immune response [27,28•]. SMX undergoes biotransformation by CYP2C9 to the protoxin hydroxylamine metabolite, which is then auto-oxidized to the ultimate toxin–nitroso-SMX (Fig. 1) [29]. In support of the role of nitroso-SMX in the pathogenesis of hypersensitivity, the following findings have been reported:

- (1) the hydroxylamine metabolite can be detected in the urine of HIV-positive patients [30];
- (2) keratinocytes, which are site of attack in cutaneous eruptions, can bioactivate SMX to the hydroxylamine [31•]. This is consistent with recent findings [32•] that keratinocytes express multiple P450 isoforms and drug transporters;
- (3) nitroso-SMX can bind covalently to thiol residues in proteins and on surfaces of lymphocytes [33] and keratinocytes [31•]; and
- (4) finally, CD8⁺ dermal T cells proliferate more vigorously in response to microsome-generated SMX metabolites when compared with the parent compound alone [34].

Figure 1. Metabolism and bioactivation of sulphamethoxazole to its hydroxylamine and nitroso metabolites



The reactions are reversible in the presence of thiols such as glutathione (GSH). SMX, sulphamethoxazole.

It is of course possible that both mechanisms may be important in the overall pathogenesis. For example, the hapten-dependent pathway may be more important for primary immune stimulation (sensitization), whereas the metabolism-independent pathway may be all that is necessary for secondary stimulation and elicitation of tissue damage.

It is also known that nitroso-SMX is directly toxic to cells [33]. However, in HIV-negative patients, cells from hypersensitive patients are more sensitive to the nitroso metabolite than are control cells, suggesting a deficiency in cellular defence [35]. A similar finding was also reported in HIV-positive patients [36], although this was not replicated in a more recent study [37]. The nature of individual susceptibility to the cellular toxicity of SMX metabolites therefore remains undefined. Glutathione and other thiols have received some attention in this respect. Glutathione can reduce the cytotoxicity of the nitroso metabolite [33], and can also reduce the lymphocyte proliferative response of T-cell clones that are reactive to nitroso-SMX [38]. Biochemically, glutathione can act as a reducing agent, converting the nitroso metabolite to the hydroxylamine and the parent drug [39]. Interestingly, cysteine reacts more rapidly with the nitroso metabolite than does glutathione [33], suggesting that, in certain bodily compartments (it is mainly an extracellular thiol), it may be more important than glutathione in detoxification of nitroso-SMX. The importance of thiols in detoxification of the toxic metabolites of SMX lies in the fact that HIV infection exerts a degree of oxidative stress, and leads to alteration in ratios of reduced to oxidized thiols [40]. A recent study [41•] showed that HIV-positive patients not only have decreased plasma cysteine levels, but also a

decreased capacity to reduce nitroso-SMX back to its parent compound, providing evidence for reduced detoxification as one factor in determining susceptibility to SMX hypersensitivity in HIV-positive patients.

Another set of factors that may determine individual predisposition are the known polymorphisms in drug metabolizing enzymes. In HIV-negative patients, a deficiency of N-acetylation (at both phenotypic and genotypic levels) has been reported to be a risk factor [42–44]. In contrast, N-acetylase genotype does not predict individual susceptibility in HIV-positive patients [45•]. Furthermore, polymorphisms in *CYP2C9*, and the glutathione transferase genes (*GSTM1*, *GSTT1*, *GSTP1*) were also not associated with co-trimoxazole hypersensitivity [45•]. This suggests that, in HIV disease, irrespective of genetic polymorphisms in metabolism that will lead to variability in the formation of the toxic metabolites, the immune system is so dysregulated that only small amounts of antigen may be required to initiate an immune reaction. To this end, genetic determinants of the immune response may be more influential than those that control metabolism.

The role of HIV in predisposing to drug allergies

Infection with the Epstein–Barr virus, and more recently human herpesvirus-6, has been shown [46•,47•,48•] to increase the risk for allergic drug reactions. This also appears to be true for HIV; for co-trimoxazole, the rate of allergic reactions is at least 10 times higher than that in non-HIV patients [49•]. Although the NNRTIs and protease inhibitors are not used in non-HIV patients, the high frequency of hypersensitivity in HIV patients may also be a manifestation of the interaction between the virus and drug (metabolite). Thus, the increased risk of adverse reactions in this patient group appears to occur irrespective of chemical or pharmacological class.

There are many reasons why HIV predisposes to allergic drug reactions [48•], including the following:

- (1) chronic drug therapy;
- (2) multiple drug therapy with unforeseen interactions;
- (3) use of novel drugs, often with unknown biological effects;
- (4) accelerated licensing;
- (5) use of high drug doses;
- (6) perturbation of drug metabolism;
- (7) increased oxidative stress; and
- (8) immune hyperactivation.

Although a disease that is characterized by immunodeficiency, HIV is also associated with chronic immune hyperactivation [50]. Various cytokines, including interferon- γ , are elevated in the sera of HIV-positive patients [51]. Interferon- γ can in turn increase the expression of

various proinflammatory cytokines, which contributes to the oxidative stress seen in HIV disease [52]. Such an enhancement of the proinflammatory state may be an important factor in the alteration in metabolism that has been observed in HIV patients [53]. This may lead to alterations in the balance between bioactivation and bioinactivation of drugs used in HIV. Another effect of interferon- γ over-expression is the upregulation of MHC class II and costimulatory molecules on antigen-presenting cells and other cells, including keratinocytes, which overall will lead to enhancement of antigen presentation [46•,54].

The increased expression of costimulatory molecules on cell surfaces, which serves as a secondary signal, is also in keeping with the danger hypothesis [55•]. According to the danger model, the immune system responds not to non-self, but rather to dangerous entities, with the ultimate aim of the immune response being the need to detect and protect against danger. In the context of HIV disease, the increased expression of proinflammatory cytokines, as noted above, may be one source of the danger signal. However, a direct interaction between viral infection and the drug (metabolite) may also serve to provide alternative danger signals. For example, with SMX, it has been shown [56] that HIV-infected cells may be more sensitive to the cytotoxic effects of nitroso-SMX. Necrosis of cells may further increase proinflammatory cytokine expression, and in addition release other factors, the nature of which has not been clearly defined, which may act to increase 'danger'. Theoretically, therefore, nullification of these danger signals may be a method that could be used to reduce the frequency of drug hypersensitivity in HIV disease.

Conclusion

Hypersensitivity reactions to a variety of drugs are common in HIV-positive patients. Although co-trimoxazole was the main cause before the widespread use of HAART, the most common culprits now are the antiretroviral drugs themselves. Evidence that these reactions are immune mediated is largely based on the typical symptomatology, apart from co-trimoxazole, for which there is accumulating evidence of the role of T cells in the pathogenesis of skin rashes and the other manifestations of the hypersensitivity reaction. There is a need for further research to define the mechanisms of antigen processing and antigen presentation in the pathogenesis of the hypersensitivity reactions. To this end, co-trimoxazole represents a very good paradigm, because the tools necessary to investigate its disposition, metabolism, and how these are related to the final clinical manifestation of hypersensitivity are available. It is essential that research is now also carried out into the mechanisms by which antiretrovirals cause hypersensitivity. This is important not only for currently available

drugs, but also for the drugs that are now in development. To this end, it is important to identify how the virus interacts with the way in which the drugs are handled in the body, and how this predisposes to hypersensitivity, as this will provide evidence-based avenues for prevention.

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