

HIV and drug allergy

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The availability of potent antiretroviral drugs and their use in three or more combination regimens—highly active antiretroviral therapy (HAART)—has led to a dramatic decline in the morbidity and mortality associated with HIV infection [1]. Currently, 20 individual antiretroviral drugs and two additional coformulated products categorized in four classes are approved by the US Food and Drug Administration (FDA). These drugs are listed in Table 1. Several others are in various stages of basic and clinical development. Although the benefits of these drugs are undeniable, they have been linked to several short- and long-term adverse events, including drug reactions and hypersensitivity [2,3].

Drug hypersensitivity became an important concern with the use of co-trimoxazole (TMP-SMX) for pneumocystis pneumonia (PCP) in the early days of the HIV epidemic. A small but significant percentage of patients who were administered TMP-SMX were noted to experience constitutional symptoms, fevers, and cutaneous reactions at a greater frequency than previously reported in immunocompetent hosts [4]. A study in the early 1990s showed that the frequency of drug allergy or hypersensitivity in patients infected with HIV ranged from 3% to 20% [5]. Another study documented that drug-related rashes were 100 times more common in HIV-infected patients than controls [6]. Since then, similar observations have been made with regard to various antiretroviral agents and other medications in HIV-infected populations. These adverse drug reactions range from simple limited cutaneous rashes to more complicated systemic symptoms and even death. Such reactions may require the discontinuation of the responsible drug and replacement by a potentially less potent or desirable antiretroviral agent. Although these reactions are termed allergic based on symptomatology, with the exception of TMP-SMX, few studies have documented an immune-mediated response linked to these drugs [7].

This article provides an overview of the allergic/hypersensitivity reactions that have been reported for antiretroviral drugs that are currently licensed, including

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Table 1

Current FDA-approved antiretroviral drugs

NRTI/NtRTI	NNRTI	Protease inhibitor	Fusion inhibitor
Zidovudine (ZDV)	Nevirapine (NVP)	Saquinavir (SQV)	Enfuvirtide (T-20)
Didanosine (ddI)	Delavirdine (DLV)	Indinavir (IDV)	
Zalcitabine (ddC)	Efavirenz (EFV)	Ritonavir RTV)	
Stavudine (d4T)		Nelfinavir (NFV)	
Lamivudine (3TC)		Amprenavir (APV)	
Abacavir (ABC)		Lopinavir/r (LPV/r)	
Tenofovir (TDF)		Atazanavir (ATV)	
Emtricitabine (FTC)		Fosamprenavir	
Combivir (COM)			
Trizivir (TZV)			

Abbreviations: NRTI, nucleoside analogue reverse transcriptase inhibitor; NtRTI, nucleotide analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

what is known about their pathogenesis and the implications for the management of HIV infection. Because of its common and prevalent use in HIV infection and the significant drug reactions that have been attributed to it, TMP-SMX is also included in the discussion. Although limited information is available regarding the management of various adverse drug reactions, the authors attempt to provide a concise review of strategies that have documented success.

Pathogenesis

Drug hypersensitivity occurs in a relatively small number of patients but is often associated with significant morbidity and mortality. Cutaneous eruptions are the most common manifestation, but significant systemic findings, including fever and internal organ involvement, can occur [8]. The pathogenesis of hypersensitivity or drug reactions is not well defined. Nonetheless, a few theories have been proposed. These explanations include the hapten hypothesis and the danger hypothesis. According to the hapten hypothesis, reactive drug products covalently bind to tissue macromolecules to produce antigens that set off a host response. The danger hypothesis contends that oxidative cell damage from reactive drug metabolites sets off a cytokine-mediated cascade that promotes an immune response to eliminate these modified “dangerous” cells [8].

Individuals infected with HIV show an increased frequency of drug eruptions when compared with the normal population. This increased occurrence of drug eruptions in patients with active viral illnesses such as HIV has been attributed to dysregulation of the immune system and particular vulnerability to oxidative stress [9]. Exposure of a causative agent (drug) is a necessary component but is not sufficient on its own to cause the hypersensitivity reaction; it also depends on a susceptible individual. What causes a particular individual to be more or less susceptible to these adverse effects is unknown at present but is likely to be

multifactorial, including various immunologic factors, genetics, and concurrent medication use.

Clinical presentation

Drug hypersensitivity typically presents as an erythematous maculopapular or morbilliform rash. Typically, the rash is pruritic, confluent, and most prominent on the body and arms. Constitutional symptoms, such as fever, myalgias, arthralgias, and rigors, are also common and often precede the rash or occur without the rash. The rash can present at anytime between 1 to 8 weeks after exposure to the offending agent. Cutaneous manifestations appearing after 8 weeks of presentation are highly unlikely to be drug hypersensitivity. Patients with prior hypersensitivity or exposure can experience reactions within the first few hours of the dose. Stevens-Johnson syndrome or toxic epidermal necrolysis is rare and develops in 0.5% of patients. Other less common but reported manifestations of the HIV-associated drug hypersensitivity syndrome include anicteric hepatitis, hypotension, acute interstitial nephritis, and acute interstitial pneumonitis [2,3,10].

The diagnosis of hypersensitivity is based on clinical criteria. Unfortunately, there are no particular laboratory data to help confirm or refute the diagnosis. The single most important clinical criterion is the time of onset of symptoms after initiation of therapy. Furthermore, knowledge of the different antiretroviral reactions may help in elucidating whether the diagnosis truly exists. Other causes of similar rashes and constitutional symptoms, such as infection, malignancy, and immune reconstitution, should be ruled out if the diagnosis is in question. No demographic, metabolic, or immunologic factors have been found to predict accurately which patients will experience the more severe reactions. Unfortunately, this fact has led to a largely trial-and-error type approach based primarily on the efficacy of medications.

Nucleoside/nucleotide reverse transcriptase inhibitors

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTIs) block reverse transcriptase activity by competing with the natural substrates and incorporating into viral DNA to act as chain terminators in the synthesis of proviral DNA. Among the agents in this class, the drug responsible for the largest proportion of hypersensitivity reactions is abacavir. Abacavir has been associated with life-threatening hypersensitivity reactions in approximately 3% to 5% of patients [11]. A total of 1015 cases among 26,769 patients enrolled in phase II and III clinical trials have been described [12].

The reaction usually begins within days to 6 weeks of drug exposure, with a mean of 11 days. Multiorgan symptoms including fever, rash, gastrointestinal, pharyngeal, musculoskeletal, and respiratory symptoms, and hypotension char-

acterize the abacavir hypersensitivity reaction. Fever is an important feature of the syndrome. Other common complaints include a rash (maculopapular or morbilliform), gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea), and malaise or fatigue. Less common complaints include pharyngeal symptoms (cough, sore throat, dyspnea), musculoskeletal symptoms (myalgias, arthralgias, edema), headache, paresthesias, or hypotension. Hypotension is present in approximately 5% of reactions. The rash is rarely severe and often appears 1 to 3 days after the fever and gastrointestinal symptoms. Complicating matters is the fact that approximately 15% of patients can have a rash without the systemic manifestations [11] and are distinct from patients with the hypersensitivity syndrome described previously.

Laboratory data abnormalities may include elevated transaminase and creatinine phosphokinase. Symptoms typically escalate with each successive dose of abacavir. Discontinuation of the medication results in complete resolution of the symptoms over a course of 2 to 3 days, although resolution of the rash may take longer. Similarly, laboratory abnormalities correct within a few days after stopping the medication. In cases of suspected hypersensitivity reactions, abacavir should be discontinued rapidly. Furthermore, rechallenge with abacavir or an abacavir-containing medication (eg, Trizivir) is strongly contraindicated, because it can lead to worsening of the systemic illness and even death [13]. Patients known to be nonadherent to medication regimens should always be questioned in detail about whether they have had potential symptoms of abacavir hypersensitivity in the past that may have gone unrecognized before restarting the medication. Severe anaphylactic shock after rechallenge with abacavir without preceding hypersensitivity has been reported. Recent genetic research in this area has been geared toward uncovering genetic polymorphisms that may predispose an individual to the hypersensitivity syndrome. An association between HLA-B5701, HLA-DR7, and HLA-DQ3 and the abacavir hypersensitivity syndrome has been reported [14].

The remainder of the NRTI/NtRTIs have not been associated with a hypersensitivity syndrome, although minor rashes have been reported. In general, there are no cross-hypersensitivity reactions among NRTI/NtRTIs.

Nonnucleoside reverse transcriptase inhibitors

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) bind directly and noncompetitively to the enzyme reverse transcriptase. Although individual drugs differ chemically from each other, they all bind to the same site distinct from the substrate-binding site. They block DNA polymerase activity by causing conformational change and disrupting the catalytic site of the enzyme. Unlike nucleoside analogues, NNRTIs do not require phosphorylation to become active and are not incorporated into viral DNA. NNRTIs include delavirdine, nevirapine, and efavirenz. Each of these NNRTIs is associated with the development of cutaneous eruptions presumed to be hypersensitivity reactions. Although the

frequency of rashes associated with all three drugs is similar, patients receiving nevirapine seem to exhibit the most severe eruptions [15]. Stevens-Johnson syndrome is exceedingly rare with all of the NNRTIs, including nevirapine (0.3% of patients) [16].

The incidence of cross-hypersensitivity reactions between NNRTIs is unknown. Most experienced clinicians would not use another NNRTI in a patient who has experienced a severe reaction with an NNRTI. Initiating an NNRTI in a patient with a history of a reaction with another NNRTI should be performed with caution and close follow-up even if the reaction was mild. Delavirdine is well tolerated; between 18% to 36% of patients experience a maculopapular rash. In a phase I/II study of delavirdine monotherapy, approximately 36% of patients had a rash compared with none of the nucleoside-treated subjects [17]. The rash usually occurs a median of 10 days after the initiation of therapy and is rare after the first month of treatment. It is erythematous, maculopapular, pruritic, and most likely to be found on the upper body and proximal arms and less likely on the neck, face, trunk, and limbs [18]. Interestingly, the rash will often dissipate even after continuation of the drug. It may also be more common in patients with higher delavirdine trough levels [17]. A severe rash requiring complete discontinuation of the drug occurs in approximately 5% to 10% of patients [18].

Of all the NNRTIs, most of the investigational work in regards to hypersensitivity reactions has been carried out on nevirapine. In one combination therapy trial with nevirapine, the incidence of rash in the nevirapine group was close to 35% compared with 19% in controls [19]. The rash is usually maculopapular and often pruritic in nature and occurs within the first 6 weeks of initiation. It is generally mild and self-limited. Stevens-Johnson syndrome has been documented in 9 of 2861 (0.3%) nevirapine-treated patients in various clinical trials [20]. The occurrence of a severe rash is approximately sevenfold higher in women than in men [21]. In contrast to the findings for delavirdine, plasma concentrations have not been correlated with the occurrence of rash. Some studies have indicated that a combination of slow-dose nevirapine escalation with steroids may reduce rash frequency by 60% [22]. The current recommendation for dose escalation is 200 mg once daily for 2 weeks, followed by 200 mg twice daily thereafter. In contrast, other studies suggest that corticosteroids do not help in reducing the occurrence of hypersensitivity reactions in patients taking abacavir or nevirapine [23]. Nevirapine has also been implicated in elevated transaminase levels in 7% of patients [24]. In certain patients, the elevated transaminases are secondary to co-infection with hepatitis viruses; however, in patients without evidence of co-infection, the elevations most likely represent manifestations of the hypersensitivity reaction.

Management of the nevirapine hypersensitivity reaction depends on the severity of clinical symptoms. For mild-to-moderate rashes, nevirapine can be continued without interruption. If the rash occurs during the introduction period (200 mg once daily), the dose should not be escalated until the rash resolves. If nevirapine has been discontinued for greater than 7 days, it should be resumed at 200 mg once daily and escalated after 2 weeks without complication. Any rash

accompanied with constitutional findings, such as fevers ($>39.0^{\circ}\text{C}$), myalgias/artralgias, malaise, oral ulcers, or severe transaminase elevations (greater than five times normal), requires immediate discontinuation of the drug and no further re-introduction. Additionally, severe rashes with desquamation, angioedema, or Stevens-Johnson syndrome/toxic epidermal necrolysis require immediate discontinuation and no re-introduction [20].

The frequency of rash associated with efavirenz is approximately 27% in adults and 45% in children. Systemic signs and symptoms, including fevers, rigors, myalgias, arthralgias, and transaminase elevations, occur in a pattern similar to that seen with nevirapine. Rashes in patients taking efavirenz are maculopapular in nature and usually occur in the second week of therapy (median, 11 days). If the rash is not severe (ie, no signs of desquamation, blistering, mucosal involvement, or fever), treatment with efavirenz can be continued, and the rash will usually resolve within 4 weeks [25]. A pulmonary hypersensitivity reaction with concomitant transaminase elevations induced by efavirenz has been documented, and re-exposure in these patients is contraindicated [10].

Protease inhibitors

Protease inhibitors exert their antiviral effect by inhibiting the HIV-1 protease enzyme, which is responsible for cleavage of the large viral *gag* and *gag-pol* polypeptide chains into smaller functional proteins, allowing maturation of the HIV virion. Inhibition of the protease enzyme results in the release of structurally disorganized and noninfectious viral particles. All protease inhibitors have been documented to cause cutaneous reactions and transaminase elevation abnormalities consistent with the drug hypersensitivity syndrome. In general, there is no allergic cross-reactivity between protease inhibitors. The main protease inhibitor implicated in the hypersensitivity syndrome is amprenavir. A possible explanation for the reaction is the fact that amprenavir is a sulfonamide. The potential for cross-reactivity between other sulfonamides and amprenavir is unknown. The overall rate of cutaneous adverse events was approximately 18% in one multicenter phase II study established to investigate the safety, tolerability, and pharmacodynamics of amprenavir (PROAB2002) [26]. Approximately 4% of patients exhibited grade 3 or 4 rashes, 3% required discontinuation of treatment, and 1% experienced Stevens-Johnson syndrome. The rash usually occurs at a mean of 10 days from initiation of the drug and may be accompanied by fever (7%) or transaminase elevation. Unfortunately, there are no data available regarding rechallenge after development of the hypersensitivity syndrome secondary to amprenavir.

Fosamprenavir, a prodrug of amprenavir, has recently been approved by the FDA for the treatment of HIV infection. Fosamprenavir is rapidly converted to amprenavir by cellular phosphatases in the gut epithelium as it is absorbed. In a clinical study of fosamprenavir used as the sole protease inhibitor, rash occurred in 2 of 10 patients (20%) with a history of sulfonamide allergy compared with

42 of 126 patients (33%) with no history of sulfonamide allergy [27]. In two clinical studies of fosamprenavir plus low-dose ritonavir, rash occurred in 8 of 50 patients (16%) with a history of sulfonamide allergy compared with 50 of 412 patients (12%) with no history of sulfonamide allergy. [28,29].

The allergic reactions that have been reported with the other protease inhibitors are usually minor allergic cutaneous reactions that rarely lead to discontinuation of the medications.

Fusion inhibitors

With the increasing prevalence of HIV resistance to current antiretroviral therapies, there has been a movement to define other targets for drug action outside of the reverse transcriptase and protease enzymes. Fusion inhibitors represent a new class of medication with the main goal of preventing viral entry into host cells. Enfuvirtide is the first FDA-approved drug in this class. Preliminary data from two recent phase III international multicenter trials with enfuvirtide suggest significant antiretroviral and immunologic benefit through 24 weeks in patients with multidrug-resistant HIV-1 infection [30,31]. Unfortunately, this medication requires administration by subcutaneous injection and has been associated with local cutaneous reactions. The injection-site reactions occurred in 97.6% of patients treated with enfuvirtide. In most patients, these reactions were initially noted in the first week of treatment. The most common signs and symptoms of the injection-site reactions were the development of induration (94.4%), erythema (90.8%), and nodules and cysts (70.3%). Mild tenderness was documented in 38.1% of patients, with another 51.7% indicating moderate pain but without limitation of usual activity. Despite the high prevalence of these reactions, discontinuation of the drug was required in 3% of patients only.

Two patients (0.3%) in these preliminary studies also had hypersensitivity reactions thought to be secondary to enfuvirtide, which recurred on rechallenge. One patient experienced a rash, fever, and vomiting; a second patient had membranoproliferative glomerulonephritis and, with rechallenge, experienced significant respiratory distress [31]. Further investigational work is needed in this area to quantify the exact nature of the enfuvirtide hypersensitivity syndrome and to determine whether it shares similarities with other reactions to antiretroviral agents. Currently, if a patient should show signs of hypersensitivity, it is recommended that enfuvirtide be discontinued without rechallenge.

Co-trimoxazole

Co-trimoxazole (TMP-SMX) is a medication that has significant benefit in the HIV-infected population. It is used for prophylaxis and treatment of PCP. TMP-SMX also has important historical significance in the area of drug allergy. Owing primarily to the fact that it was used in normal patients and HIV-infected

individuals, it provided a direct comparison of hypersensitivity rates in these two distinct populations. TMP-SMX is associated with hypersensitivity reactions in 3% to 5% of HIV-negative patients [32]. The prevalence of TMP-SMX–associated adverse reactions is significantly higher in the HIV-positive population [10,33–35]. According to one report, all HIV-infected patients treated with TMP-SMX experienced adverse effects; rash occurred in 33% [33]. Additionally, only half of the patients who started therapy with TMP-SMX were able to complete a 21-day course because of the high incidence and severity of adverse effects.

The sulfonamide (SMX) component of co-trimoxazole seems to be responsible in most cases. The multiorgan toxicity of sulfonamides is thought to result from the way sulfonamides are metabolized in certain patients, most likely the inability of the body to detoxify reactive metabolites. Scavengers, such as glutathione, normally detoxify the metabolites; however, some individuals, such as HIV-infected patients, have low concentrations of glutathione, and the metabolites accumulate, producing toxicity [10].

The presentation of TMX-SMX hypersensitivity is similar to reactions to anti-retroviral agents, including fevers, a maculopapular or morbilliform skin rash that is often pruritic, and other signs of systemic manifestations, such as transaminase elevations. Although exceedingly rare, fatalities have occurred secondary to Stevens-Johnson syndrome or fulminant hepatic failure. Any signs of hypersensitivity should result in complete discontinuation of the medication. Despite their high prevalence, there are relatively few data on the optimal management of TMP-SMX–related adverse events [36]. Many authorities recommend continuing therapy if the adverse reaction is non–life threatening, such as a mild rash or abnormalities in liver function. Others recommend reintroduction of the drug at a lower and gradually increasing dose. A meta-analysis of 35 randomized trials involving 6538 patients suggested that the rate of adverse events was reduced by 43%, without loss of efficacy, when TMP-SMX was given as one double-strength tablet three times weekly instead of daily [37]. Similarly, another report indicated that gradual initiation of TMP-SMX might reduce the incidence of treatment-limiting adverse effects within the first 12 weeks when compared with commencing immediately with the full dose (960 mg) [38]. Various investigators have also attempted to desensitize patients to TMP/SMX following the development of hypersensitivity reactions. The reported success rate of desensitization regimens varies considerably according to the protocol adopted [39–41]. The presence of mucositis, exfoliation, or anaphylaxis is a contraindication to desensitization. As many as 40% of patients with adverse reactions to TMP-SMX may also be intolerant of dapsone, another sulfa drug used for the prophylaxis and treatment of PCP and toxoplasmosis in HIV-infected patients [42].

Summary

Patients infected with HIV experience drug-related adverse events at a higher rate than the general population. Noted first with TMP-SMX and now even with

the newest fusion inhibitors, drug allergies/hypersensitivity reactions continue to pose a challenge for the optimal management of HIV infection. Distinguishing between drug hypersensitivity reactions and manifestations of HIV-related opportunistic infections and conditions is exceedingly difficult. Nonetheless, this distinction is critical. It is crucial for clinicians to recognize the presentations of these particular syndromes and to realize when medications can be continued or need to be terminated. As new antiretroviral agents become available, the issue of drug-related adverse events, including allergic and hypersensitivity reactions, and their management may become even more complex. Further investigative work in this area is required to elucidate the mechanisms of allergy/hypersensitivity in individuals infected with HIV so that successful management strategies for these conditions can be offered, preventing the loss of potent and viable antiretroviral agents from the therapeutic armamentarium.

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