

DRUG-INDUCED ADVERSE REACTIONS IN HIV AND AIDS

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INTRODUCTION

Adverse reactions to drugs are frequently encountered in patients with HIV and AIDS, particularly those on prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP).¹ Adverse events to drugs are more common in HIV-infected adults than children.

Whether these frequent reactions are due to increased propensity or increased use of certain drugs in this disease is unclear. In the general population, penicillin allergy develops in 0.75-8% of administrations³ and anaphylaxis from penicillin therapy occurs in about 0.01% of treatment courses.⁴ There is no evidence that these rates are increased in HIV patients. However, the incidence of reactions to sulphonamides in HIV patients seems to be much higher. Since being introduced in the 1930s, the sulphonamides have caused many adverse reactions after co-trimoxazole (trimethoprim-sulfamethoxazole (TMP-SMX)) exposure. Before the HIV epidemic, less than 4% of adults experienced adverse reactions after TMP-SMX exposure. In contrast, approximately 60% of adults with HIV infection may react adversely with most reactions consisting of mild drug eruptions.⁵

This article focuses on possible causes and types of adverse reactions to drugs in HIV and AIDS and some practical approaches to the management of these problems.

DEFINITION AND CLASSIFICATION OF DRUG REACTIONS

A World Health Organization (WHO) definition that an adverse drug reaction is 'any noxious and unintended reaction to a drug' is used in this article. Predictable problems such as *overdose* (toxic pharmacological effects), *side-effects* (undesirable but unavoidable pharmacological effects) and *interactions* (consequences of administering more than one drug that may alter the efficacy or toxicity of another drug) are not discussed. Unexpected reactions have been called *idiosyncratic* or *allergic*. Ordinarily, some evidence for involvement of an immunological mechanism process is needed for the reaction to be termed allergic. When no such evidence is available, the reactions have been called *non-allergic*. Immunological processes, genetic factors that may influence drug metabolism, and toxic drug metabolites are potential causes of the unexpected reactions.²

MECHANISMS

The exact pathogenesis of drug-induced adverse reactions in HIV and AIDS is unknown. Several mechanisms have been proposed, both immunological (allergic or non-allergic) and non-immunological. Common features of TMP-SMX hypersensitivity such as erythematous or maculopapular eruptions, leucopenia and fever suggest an IgG-, IgM- or cell-mediated reaction. Evidence supporting the role of IgE in the pathogenesis exists, i.e. skin-prick and intradermal test responses to sulphonamide determinants have been documented in patients who have had adverse events. Non-immune mechanisms may also contribute to TMP-SMX reactivity. Additional factors that may predispose HIV-infected individuals to TMP-SMX reactions include the slow acetylator phenotype, high TMP-SMX dosages, severe immunosuppression and polypharmacy.

CONCURRENT ILLNESS AND DRUG REACTIONS

An increased incidence of drug hypersensitivity in the presence of several non-HIV-related illnesses has been noted. The *morbilliform rash* occurring in 50-80% of patients who received amoxicillin or ampicillin during an *acute infectious mononucleosis* episode is a common example. The high incidence of ampicillin-induced rash in Epstein-Barr virus (EBV) infection may be due to viral stimulation of the immune system, although this has not been proven. HIV-infected patients have many *concurrent viral infections*, for example, hepatitis B, cytomegalovirus (CMV), herpes simplex (HSV), and EBV. These viruses or HIV itself may alter the immune system and render these patients more susceptible to the development of drug allergy.

PATIENT-RELATED FACTORS IN DRUG REACTIONS

Age and gender may play a role in drug reactions generally. Most drug reactions occur in young and middle-aged adults. In infants and the elderly, drug allergy is less common, probably owing to immaturity or involution of the immune system. Women have been reported to have a 35% higher incidence of adverse cutaneous reactions to drugs than men.³

Genetic factors may also be important. A child born to a family in which one parent has a drug allergy has a 15-fold relative risk of drug allergy compared with a child whose parents do not have drug allergy. Several HLA genes have been linked to allergic reactions to specific drugs, including insulin, sulphonamides, and hydralazine. It has been postulated that these genetic factors may operate through immune response genes, although there is little direct evidence to support this theory.

TYPES OF REACTIONS

Adverse drug reactions in HIV-infected persons most commonly involve the skin (cutaneous). Typically these are *pruritic, maculopapular diffuse erythematous rashes* beginning 7-12 days after a particular therapy is initiated. There are, however, reports of rashes

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developing much later in treatment courses. *Systemic signs* including fever, malaise, and myalgias may also be present. *Mucosal involvement*, particularly of the conjunctivae and mouth, is frequently observed, and *hepatitis* may also occur. These rashes sometimes have the bullous characteristics and mucosal ulcerations of *Stevens-Johnson syndrome*. Agents that commonly cause this type of reaction are listed in Table I.

Table I. Drugs producing fever and rash in HIV-infected persons

Agent	Evidence for increased incidence in HIV
Trimethoprim-sulfamethoxazole	++++
Clindamycin	++
Dapsone	++
Trimethoprim	++
Aminopenicillins	++++
Clavulanic acid	++
Nevirapine	+++
Rifampicin	++

Other manifestations include anaphylaxis, serum sickness, contact dermatitis, haematological reactions, renal and liver toxicity and respiratory manifestations (asthma, eosinophilic pneumonia). HIV and AIDS do not appear to affect the frequency, symptomatology, or outcome of *anaphylaxis* or *serum sickness* induced by drugs. There is also no evidence of any effect on the incidence or severity of *contact dermatitis*. Drug-induced *haematological and renal dysfunction* may be more of a problem in advanced HIV infection or AIDS because of previous bone marrow and kidney damage, but an increased incidence of these disorders in HIV-infected patients has not been reported.



Fig. 1. Reaction to sulphonamide drug in a patient with toxic epidermal necrolysis.

(Photograph courtesy of Department of Dermatology, Groote Schuur Hospital).

CLINICAL REACTIONS TO SELECTED DRUGS

Sulphonamide drugs and TMP-SMX

Sulphonamides account for the majority of adverse drug reactions in HIV-infected patients. Common manifestations include *rash*, *fever*, *abnormal liver function tests*, *haematological abnormalities*, and *nephrotoxicity*.¹⁷ Adverse reactions to TMP-SMX commonly present as a *maculopapular eruption with fever* 1-21 days after the medication is started.⁶⁻⁸ Reports of the frequency of cutaneous reactions vary from 25% to as high as 86%.^{6,7,9,10} In HIV-infected patients with toxic epidermal necrolysis (TEN) (Fig. 1) a sulphonamide drug was involved in 12 out of 14 cases.¹¹ In another report, sulphonamides were suspected in 1 of 3 cases of TEN and 3 of 5 cases of Stevens-Johnson syndrome.¹² In certain cases, the rash may be caused by TMP and not the sulphonamide component.

Dapsone

Dapsone is occasionally used as an alternative agent for PCP prophylaxis for patients intolerant of TMP-SMX. Dapsone can induce haemolysis in patients who are deficient in red cell glucose 6-phosphate-dehydrogenase – so ideally values of this enzyme should be checked before beginning dapsone therapy. Other complications with dapsone include nausea and vomiting, abnormal liver function test results, and methaemoglobinaemia. The cutaneous reactions are described as maculopapular pruritic eruptions that develop 5-14 days into treatment.¹⁴⁻¹⁶ Urticaria and erythema multiforme have also been reported with dapsone.¹⁷ There is a report of a fatal reaction to dapsone, which occurred 2 weeks after the drug was initiated for PCP prophylaxis.¹⁸

Penicillins

There are a few reports in the literature of adverse reactions to penicillins and aminopenicillins in HIV-infected patients. In one report, rash occurred in 4% of 239 courses of penicillin, and 10% of 300 courses of aminopenicillin.¹⁹ Ten of 25 patients with HIV given amoxicillin-clavulanate for various infections developed macular rash and pruritus between 3 and 21 days after the initiation of treatment. One of the 25 developed urticaria but not anaphylaxis. The incidence is higher in those with very low CD4 counts. Of note, two of the patients who developed rash were rechallenged without reaction. Penicillins can also cause more severe reactions, such as Stevens-Johnson syndrome.

Clindamycin

The frequency of cutaneous reactions to clindamycin in HIV-infected patients ranges from 7% to over 50%.^{20,21} Clindamycin-induced reactions often present as maculopapular eruptions with or without fever, and develop 10-13 days into treatment, but reactions may occur more than 30 days later.^{22,23} More severe cutaneous reactions, such as toxic epidermal necrolysis, have also been reported with clindamycin but are less common than those caused by sulphonamide drugs.⁶ Clindamycin may also cause diarrhoea, hepatitis, and haematotoxicity.

Antimycobacterials

Adverse reactions to antimycobacterial agents have been reported in HIV-infected persons treated for tuberculosis or atypical mycobacteria. *Isoniazid* is known to cause hepatotoxicity, peripheral neuropathy, and skin rash; *rifampicin* causes hepatitis and rash;

ethambutol can cause retrobulbar neuritis; and *pyrazinamide* may induce hyperuricaemia, hepatotoxicity, and arthralgia. Hepatotoxicity is more likely to occur in patients who are also on antiretroviral agents.

Rifampicin has been reported to cause severe reactions only rarely. HIV-positive patients with previous reaction to rifampicin have developed hypotension, fever, and an erythematous rash within minutes of re-exposure to the drug.²⁴ In a series of 35 patients with HIV infection and tuberculosis, 9 (26%) had an adverse reaction requiring change of treatment.²⁵ Six of these 9 had rash; in 2, the rash resolved

Antiretroviral agents (ARVs)

Antiretrovirals are an important breakthrough in the treatment of HIV and AIDS. There are four major classes of ARVs in clinical practice (Table II). Side-effects from ARVs may be classwide or individualistic. The severity of adverse reactions also varies greatly, from mild to life-threatening.

Category I NRTI – thymidine base	Stavudine (d4T) Zidovudine (AZT)
Category II NRTI – other	Didanosine (ddl) Lamivudine (3TC) Abacavir (ABC)
Category III NNRTI	Nevirapine (NVP) Efavirenz (EFV)
Category IV PI	Ritonavir (RTV) Nelfinavir (NFV) Lopinavir/ritonavir (LPV/RTV) Saquinavir (SQV) soft gel Indinavir (IDV)
NRTI – nucleoside reverse transcriptase inhibitor; NNRTI – non-nucleoside reverse transcriptase inhibitor; PI – protease inhibitor.	

Classwide side-effects for nucleoside reverse transcriptase inhibitors (NRTIs) include hepatotoxicity, lactic acidosis, peripheral neuropathy and lipoatrophy. Individual NRTIs may cause other types of adverse reactions as well, e.g. haematological toxicity, unexplained fever,²⁶ urticaria, maculopapular rash²⁷ and small-vessel vasculitis from zidovudine (AZT).²⁸ Abacavir can cause skin rashes and severe allergic reactions (5% cases). Classwide side-effects to non-nucleoside reverse transcriptase inhibitors (NNRTI) include urticaria, maculopapular rash and hepatotoxicity (more likely to occur in patients co-treated with anti-TB drugs and ARVs or those who have underlying liver disease (e.g. acute viral hepatitis)). *Nevirapine* has the propensity to produce maculopapular rashes in persons with HIV infection. The rash occurs in 20% of those given full doses of the drugs, but its incidence can be halved by starting therapy at a reduced dosage for the first 2 weeks, suggesting a role for the induction of drug-metabolising enzymes to prevent an adverse reaction.

Protease inhibitor (PI) side-effects are mainly metabolic, including hyperglycaemia, lipoaccumulation, dyslipidaemia and gastrointestinal intolerance.

DIAGNOSIS

It is not always easy to identify which drug is responsible for an adverse reaction because HIV-infected patients are often on many medications. Furthermore, symptoms such as fever may be drug-related or due to infection. At best, it may be possible to make an edu-

cated guess which drug is involved based on the timing of the adverse reaction and the likelihood of a particular agent to cause a reaction.

Laboratory tests

Currently available laboratory tests are generally of limited value for evaluating drug reactions in HIV and AIDS, especially as immunological mechanisms may not be involved in many instances. *Skin testing* and other immunological tests, such as *antigen-induced lymphocyte proliferation* for sulpha drug and other reactions may be helpful in some cases. However, none of these has been standardised or subjected to rigorous testing as diagnostic instruments. Susceptibility of peripheral blood lymphocytes to *in vitro* cytotoxicity of SMX-HA has been advocated as a diagnostic test for SMX reactions, but this technique needs further validation. If an IgE-type reaction has occurred to penicillin, skin testing with the major determinants and penicillin G is widely available and may be helpful in confirming the diagnosis. A relatively new test, the CAST 2000 ELISA (*in vitro* provocation test), is available in South Africa for investigating adverse reactions (allergic and non-allergic) to a variety of substances including antibiotics, food additives, occupational allergens, anti-inflammatory drugs and anaesthetic agents. CAST assays are available for several antibiotics (listed in Table III). The test involves isolation and stimulation of basophils and determining leukotriene release using an ELISA assay. It is still undergoing evaluation for diagnosis of drug allergy.

Pen G	Sulphamethoxazole
Pen V	Trimethoprim
Benzylpenicilloyl	Tetracycline
Ampicillin	Ciprofloxacin
Cephalosporin C	Cefuroxime
Cefamandole	Cefazolin

Challenge testing

The gold standard for diagnosis of drug hypersensitivity is challenge testing. For patients with a history of rash from TMP-SMX, confirmation of the hypersensitivity or determination of the safety of reintroducing this drug can be established by *rechallenging* the patient with the medication. However there have been reports of patients with hypersensitivity to TMP-SMX developing severe rash, hypotension, pulmonary infiltrates, and hepatitis with reintroduction of the drug.²⁹ Rechallenge with the suspected drug can help to confirm the diagnosis, as well as enable reintroduction of the drug. However challenges should be done with extreme caution and with close monitoring. Challenges should not be performed if the past adverse reaction was life-threatening (e.g. hepatitis or Stevens-Johnson syndrome). Sulphonamides must be discontinued immediately in situations listed in Table IV.

In the following cases sulphonamides should be discontinued immediately:	
<ul style="list-style-type: none"> • Persistent rash/fever >5 days • Absolute neutrophil count <500/mm³ • Hypotension/dyspnoea • Blistering desquamation/mucous membrane involvement. 	

MANAGEMENT

Once an adverse reaction occurs and a drug is suspected or identified as the cause, several courses of action are available. If an adequate alternative drug is available and effective against the disease being treated, then the *offending drug should be discontinued* and replaced by an unrelated drug. If the offending agent is necessary treatment and the adverse reaction is mild, such as an uncomplicated skin rash, one may continue to treat the patient with the offending drug. Often, the rash may subside within 3-4 days to a few weeks, and oral corticosteroids or antihistamines can be given to help control the symptoms of the adverse reaction.³⁰ Alternatively, if the offending drug is deemed essential, desensitisation (induction of tolerance) to the offending drug should be performed.

Desensitisation/induction of tolerance

Desensitisation (induction of tolerance) has been successfully applied to many agents. The methods of inducing tolerance are all similar but specifics vary. Assuming that there is a need for the drug that cannot be met in any other way and warrants the risks of desensitisation, a schedule is prepared that is appropriate for the clinical circumstances.

In some situations, rapid desensitisation in a few hours may be required. Desensitisation over a period of days to weeks may be acceptable if the need is for prophylaxis or more chronic treatment. Desensitisation via the oral route may be safer than by the parenteral route, but the process is dependent on adequate absorption and may be complicated by vomiting. A beginning dose can be selected as a fraction, possibly 0.1-1%, of the subject's known tolerance of the agent or by arbitrarily starting with 1 per 100 to 1 per 1 000 or even less of a therapeutic concentration. Subsequent doses are then increased by approximate doubling. After the therapeutic concentration (dose) is reached, the patient should continue to receive the agent. Desensitisation to specific agents are discussed below.

• Co-trimoxazole (TMP-SMX)

Several desensitisation protocols for TMP-SMX have been published. These protocols may be rapid (over hours) or span several days. Absar *et al.*³¹ published a *10-day desensitisation protocol of TMP-SMX for PCP prophylaxis* in patients with AIDS. (see Table V). Twenty-eight patients with a history of rash with or without fever were enrolled. Four failed in the first 3 weeks; 4 developed rash later; in 2 who developed pruritus, TMP-SMX was stopped by their primary care doctors. Six were lost to follow-up. The remainder continued to receive TMP-SMX for prolonged periods without any problem.

Nguyen *et al.*³² developed a *more rapid desensitisation protocol*, requiring 2 days for completion. The protocol starts with 10 mg of the sulphamethoxazole component and dosages are increased every 15 minutes to 40 mg, then increased every 2 hours to reach 800 mg of SMX. Of the 45 patients enrolled, 27 completed the protocol and were still tolerating TMP-SMX from 4 to 16 months (mean 9 months) later. Eight developed adverse reactions early during the desensitisation procedure, and 10 developed reactions later. None of the failed cases developed severe reactions.³²

If PCP therapy is urgently required, a 6-hour graded TMP-SMX challenge may be used.³³ Where minor reactions have occurred, cautiously 'treating through' the event will allow patients to tolerate TMP-SMX.^{34,35} When TMP-SMX prophylaxis is needed a more gradual approach may be adopted.

Table V. Procedure for trimethoprim/sulphamethoxazole (SMX-TMP) desensitisation

Day	Dose	SMX-TMP
1	1 ml of 1:20 paediatric suspension of SMX-TMP	0.4 mg/2 mg
2	2 ml of 1:20 paediatric suspension of SMX-TMP	0.8 mg/4 mg
3	4 ml of 1:20 paediatric suspension of SMX-TMP	1.6 mg/8 mg
4	8 ml of 1:20 paediatric suspension of SMX-TMP	3.2 mg/16 mg
5	1 ml of paediatric suspension of SMX-TMP	8 mg/40 mg
6	2 ml of paediatric suspension of SMX-TMP	16 mg/80 mg
7	4 ml of paediatric suspension of SMX-TMP	32 mg/160 mg
8	8 ml if paediatric suspension of SMX-TMP	64 mg/320 mg
9	1 tablet of SMX-TMP	80 mg/400 mg
10	1 table of double-strength (DS) SMX-TMP	160 mg/800 mg

Thereafter 1 tablet of DS SMX-TMP on Monday, Wednesday, and Friday for PCP prophylaxis or two tablets a day for the treatment of isosporiasis

*From Absar et al.*³¹

• Other agents

Desensitisation protocols for dapsone,¹⁶ clindamycin,^{36,37} penicillins³⁸ and anti-mycobacterial agents^{39,40} are also available. Although not specifically tested for HIV-infected persons, it appears that these protocols would be equally applicable to this group of patients.

For severe reactions that persist after drug withdrawal and symptomatic treatment, therapy with *corticosteroids* is often considered. There are many potential risks associated with the use of corticosteroids in HIV. Corticosteroids have been shown to accelerate the spread of Kaposi's sarcoma, promote outbreaks of herpes zoster and simplex, exacerbate some infections, and further impair the immune response to intracellular parasites. Dramatic improvements have been reported with intravenous immunoglobulin (IVIg) in certain cases.⁴¹ This form of treatment has not yet been validated with a controlled trial but may be considered in some circumstances.

CONCLUSION

Drug reactions are a major problem for certain patients with HIV infection and AIDS. In general, there is a lower tendency for adverse events to drugs in HIV-infected children than adults. The exact *mechanisms* involved in the reactions are often unknown. A *common reaction* that includes cutaneous rash and fever may be associated with mucosal, hepatic, and haematological abnormalities. This type of reaction can be caused by many different agents, although the typical and best documented cause of drug reactions in HIV-infected patients is TMP-SMX. *Management* of adverse drug reactions requires sound medical judgement and knowledge of alternative treatment options. In some instances, *desensitisation (induction of tolerance)* has proven useful. Desensitisation should only be undertaken at institutions that have the facilities to manage severe adverse reactions, particularly anaphy-

laxis. Propensity for adverse reactions to sulphonamides may decline with HIV disease/progression (unlike reactions to amoxicillin and TB medications). Finally, certain patients with adverse cutaneous reactions may tolerate the drug after interruption of treatment or lowering of the dose.

Declaration of conflict of interest

The authors have no conflict of interest.

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