

DRUG REACTIONS AND DESENSITIZATION IN AIDS

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Unwanted reactions to drugs are very common in medical practice. Of hospitalized patients, 15% to 30% are reported to experience an adverse drug reaction. However, this is probably an underestimate because mild reactions are not reported and many physicians are not anxious to call attention to problems that occur as a result of medications that they prescribe.

Because patients with AIDS and HIV infection are required to take many drugs to treat and prevent opportunistic infections as well as HIV infection itself, drug reactions would be expected in these patients; however, the incidence of adverse reactions to medications seems to be greatly increased in this population.^{13, 33} In this article some of this evidence and possible causes of the reactions are discussed, and some practical approaches to the management of these problems are provided.

If HIV infection is associated with an increase in the incidence and severity of drug reactions, what group should be used for comparison? Penicillin allergy develops in 0.75% to 8% of administrations.⁸ Anaphylaxis from penicillin therapy occurs in about 0.01% of treatment courses.²⁹ There is no evidence that these rates are increased in HIV patients. Conversely, adverse reactions to sulfonamides occur in 4% to 6% of administrations, but allergic reactions occur in fewer than 3%.³⁹ The incidence of reactions to sulfonamides in HIV patients seems to be much greater than this.

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DEFINITION AND CLASSIFICATION

A World Health Organization 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 pharmacologic effects), *side effects* (undesirable but unavoidable pharmacologic 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 immunologic process is needed for the reaction to be termed allergic. When no such evidence is available, the reactions have been called *pseudoallergic*. Immunologic processes, genetic factors that may influence drug metabolism, and toxic drug metabolites are potential causes of the unexpected reactions.³³

MECHANISMS

Allergic

High-molecular-weight drugs such as insulin and dextran can act as complete antigens, inducing immune responses to cause reactions based on immunologic processes. Lower molecular weight drugs presumably bind to carrier proteins to induce immune reactions. Immunocompetent HIV patients may produce immune responses nearly as well as noninfected persons and have the same reactions. Although there is little direct evidence for any increase in such immune-based drug reactions as urticaria from penicillin sensitivity in HIV-infected persons, two factors make a hypothesis of immunologic hyperreactivity in HIV-associated drug reactions tenable.

First, there is abundant evidence of immunoactivation in HIV infection. B-lymphocyte hyperactivation is associated with a polyclonal increase in serum immunoglobulins, circulating immune complexes, possibly secondary to the many infections that are present, and increased IgE levels. The increase in serum IgE correlates with declining CD4 cell count, increased production of interleukin-4 (IL-4), and decreased production of interferon gamma.⁷¹ The role of this increased IgE in promoting prevalence and severity of atopic diseases is not clear at present. There is little evidence, however, of IgE involvement in most HIV-associated drug reactions. T cells are also activated in HIV infection with increased CD8+DR+ cells and increased production of several cytokines.⁴⁴ Whether this immunoactivation contributes to drug allergy is unknown.

Second, it has been proposed that drug metabolism may be altered in HIV infection, allowing the production of metabolites with increased immunogenicity. Examples of this phenomenon, however, are lacking.

The fact that immunodeficient persons with AIDS often fail to produce normal immune responses to infections and immunizations is

one factor that argues against an allergic basis for many adverse drug reactions in these patients. There is no evidence that immunologic responses to drug antigens are any better than those to bacterial or viral infections, and no evidence that the increased frequency of drug reactions in HIV-infected subjects is due to immunologic causes. On the contrary, most authors have found that the incidence of drug reactions actually increases in persons with advanced HIV infection, and the degree of immune deficiency may play a permissive role. In one report, amoxicillin-clavulanate-induced rashes were seen in 16 of 25 patients with CD4 cell counts less than $200/\text{mm}^3$, compared with only 1 of 9 patients with CD4 cell counts greater than $200/\text{mm}^3$. An inference might be that lack of immune clearance of a (hypothetical) toxic metabolite allows accumulation of such a metabolite, with resulting symptoms.

Toxic Metabolites

It has been proposed that drugs may produce metabolites that cause drug reactions by virtue of their toxicity for cells. As a part of this hypothesis, it is proposed that the cells of affected persons, including those with HIV infection, have increased susceptibility to the cellular toxicity. The nature of such susceptibility could be either acquired or genetic. The disease process itself could contribute to the production of the toxic metabolite.⁵⁷ This hypothesis has been generated by studies with sulfonamides. It has been shown that hepatic microsomal P450 enzymes will convert some sulfamethoxazole (SMX) to a hydroxylamine derivative (SMX-HA). Toxicity of SMX-HA has been demonstrated by its ability to kill peripheral blood lymphocytes (PBL) as assessed by accumulation of dye in vitro. The toxicity of SMX-HA for PBL from patients with previous trimethoprim (TMP)-SMX reactions is slightly greater than that for PBL from nonreactors. SMX-HA toxicity is greater for HIV-infected T-cell lines than HTLV-infected or uninfected cells.¹⁴ These studies have led to the proposal that such cytotoxicity assays be used for diagnostic purposes.³⁶

Doubt has been cast on the toxic metabolite theory by the studies of Koopmans and colleagues, who found that SMX-TMP-allergic subjects also reacted to a different sulfonamide, sulfametrole. Sulfametrole metabolism produces little hydroxylamine, and none is detected in the urine, indicating that the HA metabolite is unlikely to be involved in the adverse reactions to sulfametrole.³⁴

Metabolic Abnormality

Genetic variability in drug catabolism could result in formation of reactive metabolites that act as unwanted antigens or toxic materials. Acetylation of a sulfonamide converts it into a nontoxic metabolite that is excreted by the kidneys; however, hepatic cytochrome P450 can oxidize

sulfonamides to the potentially toxic hydroxylamine derivative (mentioned previously). Some persons acetylate sulfonamides slowly and are designated "slow acetylators." By providing more substrate to the hepatic oxidative pathway for the generation of hydroxylamine metabolites, it has been theorized that slow acetylators deficient in detoxification pathways may be at risk to develop hypersensitivity to sulfonamides.³⁹ Evidence that HIV-infected SMX/TMP reactors are likely to be slow acetylators has been reported.⁹ Conversely, the significance of acetylator phenotype has been questioned by the findings of O'Neill and colleagues, who reported that the slow acetylator phenotype correlated with a decrease in body weight and was unrelated to a history of TMP-SMX reaction.⁵⁴

TYPES OF REACTIONS

Cutaneous

Adverse drug reactions that are increased in frequency in HIV-infected persons often involve the skin. Typically these are pruritic, maculopapular diffuse erythematous rashes beginning 7 to 12 days after a particular therapy is initiated. There are, however, reports of rashes developing much later in treatment courses.⁷ Although several different drugs may initiate the skin rash, they often present in a similar manner and lack the characteristic wheals of urticaria. Systemic signs of fever, malaise, and myalgias are often 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 supporting a diagnosis of Stevens-Johnson syndrome. Agents that commonly cause this type of reaction are listed in Table 1.

Other Drug Reactions

There are no data to support the contention that HIV infection or AIDS has any effect on the frequency, cause, symptomatology, or outcome of anaphylaxis or serum sickness induced by drugs. There is also no evidence of alterations in the incidence or severity of contact dermatitis in HIV infection, although one could postulate that an incompetent immune system would be unable to mount a delayed hypersensitivity response to such agents as poison oak. Drug-induced hematologic and renal dysfunctions 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 confirmed. Pulmonary infiltrative processes and asthma secondary to drug toxicity have been reported in HIV, but no increased incidence of these types of toxicities in HIV-infected patients has been documented.

Table 1. DRUGS PRODUCING FEVER AND RASH IN HIV-INFECTED PERSONS

Agent	Evidence for Increased Incidence in HIV
Trimethoprim-sulfamethoxazole	+ + + +
Clindamycin	+ +
Dapsone	+ +
Trimethoprim	+ +
Pyrimethamine-sulfadoxine	+ +
Aminopenicillins	+ + + +
Clavulanic acid	+ +
Atovaquone	+ + +
Nevirapine	+ + +
Delavirdine	+ +
Thalidomide	+ + + +
Rifampin	+ +
Thiacetazone	+ + + +
Probenecid	+ + +
Pentamidine	+ +

Eosinophilic pneumonia has been reported in a number of HIV patients. Presumed to be immunologic, the exact mechanism underlying this disorder is not known. The reaction presents as fever, chest pain, peripheral and tissue eosinophilia, and lung infiltrates. Causative agents for eosinophilic pneumonia in non-HIV patients include penicillins, sulfonamides, carbamazepine, and nitrofurantoin. Eosinophilia is found in many patients with HIV (discussed elsewhere in this issue). In general, such eosinophilia cannot be ascribed to parasitic infection or atopy but may be related to the presence of dermatologic conditions.⁶⁶

CONCURRENT ILLNESS AND DRUG REACTIONS

An increased incidence of drug allergy in the presence of several non-HIV-related illnesses has been noted. The morbilliform rash occurring in 50% to 80% of patients who receive amoxicillin or ampicillin during an acute infectious mononucleosis episode or the similar rash observed in leukemia patients receiving allopurinol are two common examples. 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 manifestations of drug allergy.

PATIENT-RELATED FACTORS IN DRUG REACTIONS

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, respectively. Women have been reported to have a 35% higher incidence of adverse cutaneous reactions to drugs than men.⁸

Genetic factors may play a role in drug reactions. 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.² Several HLA genes have been linked to allergic reactions to specific drugs, including insulin, sulfonamides, and hydralazine. It has been postulated that these genetic factors may operate through immune response genes, although there is little direct evidence for this. Drug catabolism may exhibit genetic variation as well; the potential role of toxic metabolites and the slow acetylator phenotype have been discussed previously.

DIAGNOSIS

Because HIV-infected patients often require many medications for the treatment of HIV and the prophylaxis of opportunistic infections, it is not always easy to pinpoint which drug is responsible for an adverse reaction. Furthermore, symptoms such as fever may be drug related or infectious. It may be possible to make an educated guess which drug is involved based on the timing of the adverse reaction and the likelihood of a particular agent to cause a reaction. Discontinuation of all possible etiologic agents is often the first and safest recommendation, however.

Because the mechanism of many adverse drug reactions is not understood in HIV-infected patients, specific testing to identify responsible drugs is usually unavailable. There are many reports of apparent successes with skin testing or other immunologic tests, such as antigen-induced lymphocyte proliferation for sulfa drug and other reactions. None of these has been standardized or subjected to rigorous testing as diagnostic instruments. Susceptibility of peripheral blood lymphocytes to *in vitro* cytotoxicity by SMX-HA has been advocated as a diagnostic test for SMX reactions, but this theory needs further validation before a useful test can be produced. If an IgE type reaction has occurred, penicillin skin testing with the major determinants and penicillin G is widely available and can be helpful in determining the safety of reintroducing penicillin. Penicillin skin testing, however, cannot predict the likelihood of a maculopapular eruption or severe cutaneous reaction such as Stevens-Johnson syndrome or toxic epidermal necrolysis after penicillin administration.

A cautious rechallenge with the suspected drug can help to confirm the diagnosis and reintroduce the drug, but severe reactions have been reported with reintroduction of the offending medication.^{32, 42} Therefore, challenges should be done with extreme caution and close monitoring, and the patient should be made aware of all possible complications. Challenges should not be performed if the past adverse reaction was life endangering (e.g., hepatitis or Stevens-Johnson syndrome).

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 to 4 days to a few weeks,¹¹ and oral corticosteroids or antihistamines can be given to help control the symptoms of the adverse reaction.^{58, 65} Interestingly, corticosteroids may decrease the frequency of adverse reactions to drugs when given "prophylactically." In one study, 4 of 21 patients (or 19%) with AIDS-associated *Pneumocystis carinii* pneumonia (PCP) treated with TMP-SMX and prednisone developed rash, compared with 5 of 12 (42%) treated with TMP-SMX alone ($P < 0.05$). The rash that developed in the four patients on corticosteroids was mild, and TMP-SMX did not need to be discontinued.⁷⁰

If there is a compelling need for the offending drug but the previous toxicity was severe, the drug may be reintroduced after an appropriate desensitization protocol is followed. These desensitization methods and protocols are presented here.

For the 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 speed 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. These authors recently had the experience of seeing dramatic improvement in several patients who were given intravenous immunoglobulin for drug reactions.⁶¹ This form of treatment has not yet been validated with a controlled trial but may be considered in some circumstances.

CLINICAL REACTIONS TO SELECTED DRUGS

Sulfonamide Drugs and TMP-SMX

Sulfonamide drugs account for most adverse drug reactions in HIV-infected patients and many serious ones. Assessment of HIV-infected patients with toxic epidermal necrolysis (TEN) suggested that a sulfonamide drug was involved in 12 out of the 14 cases.⁶⁰ In another report, sulfonamides were suspected in one of three cases of TEN and three of five cases of Stevens-Johnson syndrome.⁵⁶ Common adverse reactions to sulfonamide drugs include rash, fever, abnormal liver function test results, hematologic abnormalities, and nephrotoxicity.²⁵

The widespread use of TMP-SMX for prophylaxis and treatment of *Pneumocystis carinii* pneumonia (PCP) makes this the most common drug

allergy problem in HIV. Adverse reactions to TMP-SMX commonly involve a maculopapular eruption with fever 1 to 21 days after the medication is started.^{25, 48, 58} Reports of the frequency of cutaneous reactions vary greatly, from 25% to up to 86%, possibly depending on the assiduity with which symptoms are sought.^{25, 48, 59, 63} At times, the rash may be a result of TMP and not the sulfonamide component. In a study of 31 patients with a history of cutaneous reaction to TMP-SMX, 3 developed rash when challenged with TMP alone.¹¹

When rash is tolerable and mild, TMP-SMX treatment may be continued. In a study of 116 patients given one double-strength tablet of TMP-SMX three times a week for PCP prophylaxis, 29 developed a maculopapular rash, but only 13 of these 29 had to discontinue treatment.⁵⁹ When TMP-SMX was given in high dosage to treat PCP, 12 of 18 or 67%,⁵⁸ 11 of 14 or 79%,⁴⁶ and 16 of 36 or 44%,⁶³ who developed maculopapular rash from the medication were able to continue treatment without problems. In these reports there were no instances of Stevens-Johnson syndrome or exfoliation, and the rash subsided in 2 to 5 days.^{46, 63} Rash and fever were suppressed with acetaminophen and diphenhydramine.⁶³

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. When 26 patients with a previous history of morbilliform rash from TMP-SMX were rechallenged with one double-strength tablet twice a day, 15 (58%), reacted: 7 with rash, 5 with fever, and 5 with both.¹¹ The rashes were not severe and did not progress; however, one patient did become dyspneic with the challenge. The dyspnea resolved in 12 hours, and there was no hemodynamic compromise or wheeze. There have been reports of patients with hypersensitivity to TMP-SMX developing severe rash, hypotension, pulmonary infiltrates, and hepatitis with reintroduction of the drug.³² Therefore extreme caution should be exercised if rechallenge is attempted.

Dapsone

Dapsone is often used for PCP prophylaxis for patients intolerant of TMP-SMX. Dapsone can induce hemolysis in patients who are deficient in red cell glucose 6-phosphate-dehydrogenase, so that normal values of that enzyme should be present before beginning dapsone therapy. Concerns about possible cross-sensitivity with TMP-SMX have been substantially allayed by use of this agent in TMP-SMX sensitive patients. A review of 75 patients who received dapsone because of TMP-SMX intolerance showed a large incidence of anemia (39%) and rash (23%). Only three anemias (4%) and two rashes (3%) were thought to be related to dapsone, however. In 5 of the 75 patients, the intolerance was the same as that seen with TMP-SMX.⁶ Other complications with dapsone include nausea and vomiting, abnormal liver function test results,

and methemoglobinemia. The cutaneous reactions are described as maculopapular pruritic eruptions that develop 5 to 14 days into treatment.^{46, 47} One child developed urticaria and another erythema multiforme with dapsone.⁶⁸ There is a report of a lethal reaction to dapsone, which occurred 2 weeks after the drug was initiated for PCP prophylaxis. The patient developed rash, fever, fulminant hepatitis, and hemolytic anemia.¹⁷

The frequency of cutaneous reactions to dapsone is difficult to determine because dapsone may be given in combination with TMP for both PCP prophylaxis and treatment. When both medications were given, rash occurred in 19% to 40%^{20, 47}; when dapsone alone was used, rash occurred in 10% to 17%.^{20, 68} Rash is often mild, and in one report of 12 patients who developed rash and fever during treatment of PCP with dapsone plus TMP, 9 were able to continue with treatment with rash resolution in 3 to 4 days.⁴⁶

Clindamycin

The frequency of cutaneous reactions to clindamycin in HIV-infected patients ranges from 7% to over 50%.^{15, 21, 40} In studies in which clindamycin was compared with sulfadiazine for treatment of *Toxoplasma* encephalitis, the incidence of rash was higher in the sulfadiazine group.¹⁵ Clindamycin-induced cutaneous reactions often present as maculopapular eruptions with or without fever, and develop 10 to 13 days into treatment, but reactions may occur more than 30 days into a treatment course.^{15, 30} More severe cutaneous reactions, such as toxic epidermal necrolysis, have been reported with clindamycin but are less common than those caused by sulfonamide drugs.⁶⁰ Clindamycin may also cause diarrhea, hepatitis, and hematotoxicity, either alone or in combination. Because adverse reactions to clindamycin often involve only maculopapular eruptions, this drug can also be continued without untoward effects if the rash is mild and resolution of symptoms in 3 to 5 days has been reported.¹⁵

Pentamidine

Pentamidine is used both in the intravenous form for active PCP, and in the aerosolized form for PCP prophylaxis. Adverse reactions to pentamidine include hypoglycemia, hyperglycemia, azotemia, pancreatitis, autonomic neuropathy with postural hypotension, and hepatitis. There are also reports of hypotension and cardiopulmonary arrest with a rapid infusion of intravenous pentamidine.

Rash with intravenous pentamidine has been reported with a frequency of 3% to 18%.^{12, 25, 35, 50, 63} The rash can be morbilliform and resolve spontaneously, but there are reports of patients who have developed urticaria near the site of drug infusion.^{50, 55} In one instance, facial rash,

tongue swelling, and laryngeal edema developed 20 minutes after a fifth intravenous dose of pentamidine for PCP.⁴ Rash can occur rarely with aerosolized pentamidine (AP). In one large study of 176 patients who received AP for PCP prophylaxis, none developed rash.²⁴ There is one case report of a patient who developed urticaria 3 days after receiving AP, however; he was rechallenged with AP and developed urticaria within 1 hour.³⁷ Another patient developed maculopapular rash with AP that recurred with rechallenge.⁷ Pentamidine appears to have histamine releasing properties. In a study of ten normal subjects, all ten had wheal-and-flare responses to subcutaneous pentamidine, with an amelioration of the reactivity after premedication with an antihistamine.¹⁸

Penicillins and Aminopenicillins

There are a few reports in the literature of cutaneous 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.²⁰ The nature of the rash was not described. Ten of twenty-five 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. As noted previously, the incidence increased in those with lower CD4 counts.³ Of note, two of the patients who developed rash were rechallenged without reaction; however, it should be emphasized that penicillins can also cause more severe reactions, such as Stevens-Johnson syndrome.⁵⁶

Zidovudine

Zidovudine (AZT) was the first antiretroviral medication approved for use against HIV. The most common adverse reactions seen with AZT include headache, nausea and vomiting, malaise, and hematologic toxicity. There have been reports of unexplained fever with AZT, which resolves with discontinuation and recurs with reintroduction of the drug.³¹ True hypersensitivity reactions are rare but have been reported. In one case report, a patient developed urticaria 1 hour after starting AZT; blinded rechallenge with the drug resulted in recurrence of both hives and wheeze.⁴⁵ In another report of two patients with AIDS, one developed maculopapular rash, fever, and mild hepatitis 8 days after starting AZT; the rash resolved with discontinuation. That patient was successfully desensitized to AZT over 37 days. The second patient developed a blistering rash 6 weeks after starting AZT, with biopsy showing small-vessel vasculitis. The rash resolved 5 days after discontinuation of the drug.¹⁰

Antimycobacterials

Adverse reactions also occur in HIV-infected persons treated with antimycobacterial drugs for tuberculosis or atypical mycobacteria. Because treatment for these organisms requires multiple medications, it is often difficult to determine which drug causes the adverse effects. Isoniazid can cause hepatotoxicity, peripheral neuropathy, and skin rash; rifampin causes hepatitis and rash; ethambutol causes retrobulbar neuritis; and pyrazinamide may induce hyperuricemia, hepatotoxicity, and arthralgia. One of the more toxic medications appears to be thiacetazone, a drug used in Africa to treat tuberculosis. In one report of 111 HIV-infected persons with tuberculosis in Nairobi, thiacetazone was responsible for cutaneous reaction in 19%, including 3 fatal cases of toxic epidermal necrolysis.⁵² In another study in Uganda, 10 of 90 patients with HIV infection and tuberculosis treated with streptomycin, thiacetazone, and isoniazid developed cutaneous reaction.⁵³ Most had morbilliform rash at an average of 24 days into treatment. There was one case of toxic epidermal necrolysis and two cases of rash with mucosal lesions. In another group of 101 Ugandan HIV patients treated with isoniazid, rifampin, and pyrazinamide, only one had a rash, which was maculopapular and associated with oral lesions.

Rifampin has been reported to cause severe reactions only rarely. HIV-positive patients with previous reaction to rifampin have developed hypotension, fever, and an erythematous rash within minutes of reexposure to the drug.⁷² In a study of 35 patients with HIV infection and tuberculosis, nine (26%) had an adverse reaction requiring change of treatment.¹⁶ Six of these nine had rash; in two, the rash resolved with discontinuation of isoniazid, and in four, the rash resolved with discontinuation of rifampin. In another large review of 125 HIV-infected patients treated for tuberculosis, 23, or 18%, had adverse reactions requiring a change of treatment. Of these, 12% had to discontinue rifampin, 6% pyrazinamide, 4% isoniazid, and 2% ethambutol.⁶⁷

Thalidomide

Thalidomide has been used in patients with HIV. There is now conclusive evidence that thalidomide administration is associated with accelerated healing of oral aphthous ulcers in such patients. In addition, there is speculation that thalidomide may be efficacious in the treatment of AIDS-associated wasting. Unfortunately, the incidence of thalidomide-induced drug reactions appears to be increased in HIV patients. Rashes or fever appeared in 15 of 42 persons given thalidomide, and 11 of the 15 were forced to discontinue treatment. These reactions were not predicted by previous TMP-SMX sensitivity.²⁶

Ciprofloxacin

Ciprofloxacin has induced rash, fever, and hypotension in patients with HIV infection. Experience with this drug suggests that HIV-infected patients exhibit an increased frequency of adverse reactions.²²

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

This group of agents includes nevirapine, now approved for HIV treatment, and delavirdine, currently available on expanded access. Both have the propensity to produce maculopapular rashes in persons with HIV infection. It is not clear whether the incidence is increased in this group because the drugs are used only for therapy of HIV infection. Rash occurs in 20% of those given full doses of the drugs, but the incidence of rash can be halved by starting therapy for the first 2 weeks at a reduced dosage, suggesting a role for the induction of drug metabolizing enzymes to prevent sensitivity.

DESENSITIZATION

Avoidance of unwanted reactions to drugs by desensitization has been successfully applied to many agents. Although the term implies an immunologic mechanism, there is little evidence for that in most situations. The methods of desensitization 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 desensitization, a schedule is prepared that is appropriate for the clinical circumstances. If there is a legitimate possibility of a life-threatening reaction, desensitization probably should not be attempted.

In some situations, rapid desensitization in a few hours may be required. Desensitization over a period of days to weeks may be acceptable if the need is for prophylaxis or more chronic treatment. Desensitization 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 to 1%, of the subject's known tolerance of the agent or by arbitrarily starting with 1 per 100 to 1 per 1000 or even less of a therapeutic concentration. Subsequent doses are then increased by approximate doubling. The frequency and route of administration of doses should reflect a balance between the clinical imperatives and the persistence of the drug in the body. Because the goal is gradual increase in the drug concentration, dosing should be at intervals to allow this to occur. When a therapeutic concentration is reached, the patient should continue to receive the agent.

For those few agents in which IgE-mediated or other immunologic

processes account for the reaction, acute desensitization probably places the subject into antigen excess, thereby preventing the drug antigen from crosslinking antibody or cells to induce hypersensitivity. Over longer periods the desensitization may actually modulate the immune response and prevent hypersensitivity by stimulating blocking or other antibodies that compete with those causing allergy or by downregulating antibodies or immunocompetent cells.

In most instances of drug hypersensitivity, in which immunologic processes are probably not involved, the mechanisms of desensitization are quite speculative. Desensitization may serve simply to demonstrate that the reaction will not recur or was not truly associated with the drug. It may be a means to establish a low, tolerable dose of an agent that causes problems only in higher dosage. It has also been proposed that desensitization may provide the means for agents to induce metabolic enzymes that more effectively metabolize the drugs or their hypothetical toxic metabolites. To date, however, there is no direct evidence for any of these concepts.

Cotrimoxazole (TMP-SMX)

Several desensitization protocols for TMP-SMX have been published. These protocols may be rapid (over hours) or span several days. Desensitization probably should not be performed in patients with history of hepatitis or severe cutaneous reactions (e.g., Stevens-Johnson syndrome). Absar et al published a 10-day desensitization protocol of TMP-SMX for PCP prophylaxis in patients with AIDS.¹ As seen in Table 2, doses were administered and increased daily. Twenty-eight patients with a history of rash with or without fever were enrolled. Four failed

Table 2. PROCEDURE FOR TRIMETHOPRIM/SULFAMETHOXAZOLE (T/S) DESENSITIZATION

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From Absar N, Daneshvar H, Beall G: Desensitization to trimethoprim/sulfamethoxazole in HIV infected patients. J Allergy Clin Immunol 93:1001-1005, 1994; with permission.

in the first 3 weeks; four developed rash later; in two who developed pruritus, TMP-SMX was stopped by their primary care physicians. Six were lost to follow-up. The remainder continued to receive TMP-SMX for prolonged periods.

Nguyen et al developed a faster desensitization protocol, requiring 2 days for completion. The protocol starts with 10 ng of the sulfamethoxazole 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 of 9 months) later. Eight developed adverse reactions early during the desensitization procedure, and ten developed reactions later. None of the failed cases developed severe reactions.⁵¹ Adjunctive prednisone has been used with the 10-day desensitization protocol, but the success rate was not markedly different from that without prednisone, although the study was not controlled.⁵

Sulfadiazine

Sulfadiazine in combination with pyrimethamine is effective treatment for *Toxoplasma* encephalitis. The incidence of rash with sulfadiazine-pyrimethamine ranges from 7% to 34%.^{19, 38} It can occur 7 to 14 days into treatment and presents as a morbilliform rash.²³

Several desensitization protocols for sulfadiazine have been published. de la Hoz Caballer et al studied seven patients (six with toxoplasmosis and one with nocardiosis) with a history of a maculopapular rash to sulfadiazine.²³ One of the seven patients also had a history of angioedema with this drug. All patients except the one with history of angioedema were challenged with sulfadiazine. Two developed a macular rash and one developed both rash and angioedema. These three patients and the patient with the initial history of angioedema to sulfadiazine underwent successful desensitization to sulfadiazine following a 10-day protocol, as outlined in Table 3. Of note, all patients were skin tested to sulfadiazine, but no positive reactions occurred.

In another study, desensitization of 16 patients with a history of toxoplasmosis and hypersensitivity to sulfadiazine was carried out over 5 days.⁶⁹ Ten patients (62%) were successfully desensitized. In another report rapid desensitization over 2 hours and 15 minutes of 11 patients with toxoplasmosis was performed orally.⁴⁹ Some patients were premedicated with corticosteroids and antihistamines. Seven patients out of eleven successfully completed the desensitization protocol, but two later developed fever or rash, and the medication was stopped.

Dapsone

A 42-day desensitization protocol for patients who had maculopapular rash to dapsone has been described earlier. Thirteen of fourteen were successfully desensitized using this regimen.⁴⁷

Table 3. PROCEDURE FOR SULFADIAZINE DESENSITIZATION

Day	Dosage
1	5 mg followed by 10 mg 6 hours later
2	20 mg followed by 40 mg 6 hours later
3	80 mg followed by 160 mg 6 hours later
4	250 mg followed by 500 mg 6 hours later
5	750 mg followed by 750 mg 6 hours later
6	1 gm followed by 1 gm 6 hours later
7	1 gm every 8 hours
8	1 gm every 6 hours
9	1.5 gm every 6 hours
10	2 gm every 6 hours

Thereafter 2 gm of sulfadiazine every 6 hours were continued.

Data from de la Hoz Caballer B, Fernandez-Rivas M, Fraj Lazaro J, et al: Management of sulfadiazine allergy in patients with acquired immunodeficiency syndrome. J Allergy Clin Immunol 88:137-8, 1991.

Clindamycin

There are rare reports of successful desensitization of clindamycin in patients who developed maculopapular rash from this drug. These authors have desensitized one such patient over 10.5 hours orally, using the scheme in Table 4.⁶² Another group has successfully desensitized one patient over 7 days.⁴¹

Pentamidine

A form of desensitization was used for a patient with laryngeal edema to intravenous pentamidine. The patient later required AP and received increasing concentrations of AP beginning with 1:10,000 nebulized and increasing every 15 minutes to eventually tolerate the concen-

Table 4. CLINDAMYCIN ORAL DESENSITIZATION SCHEDULE

Time (hr)	Dose (mg)	Total Dose (mg)
0	0.15	0.15
0.5	0.5	0.65
1.0	1.5	2.15
1.5	5	7.15
2.0	10	17.15
2.5	20	37.15
3.0	50	87.15
3.5	100	187.15
4.0	150	337.15
4.5	300	637.15

Clindamycin 600 mg every 6 hours was begun 6 hours later.

trated material. The patient was continuing to receive the AP without problems at 25 months postdesensitization.⁴

Penicillins and Aminopenicillins

Penicillin skin testing and desensitization are well-established procedures in patients without HIV infection. HIV-infected persons with a history of penicillin allergy and syphilis are a common clinical problem. In some instances, such as neurosyphilis, alternative antibiotics may lack efficacy or CNS penetration, and penicillin may be required. When penicillin skin testing is positive, desensitization with the oral or injection protocols has been successful.⁶⁴ Skin testing is not helpful in predicting non-IgE-mediated maculopapular reactions to penicillins and aminopenicillins. These authors are unaware of any attempts to desensitize such persons.

Antimycobacterial Agents

Desensitization protocols to antituberculosis medications have been used and published.^{28, 43} Although not specifically tested in HIV-infected persons, it appears that these protocols would be equally applicable to this group of patients.

Acyclovir

In a case report, an HIV-infected woman repeatedly developed angioedema with acyclovir administration. A desensitization scheme similar to that used for penicillin was successfully administered, and the patient remained on chronic oral acyclovir.²⁷

CONCLUSION

Drug reactions are a major problem for patients with HIV infection and AIDS. The mechanisms involved in the reactions are often disputed or unknown. Immunologic processes, toxic metabolites and genetic factors have been postulated to be underlying causes of these drug reactions, but full proof is lacking. A common reaction that includes cutaneous rash and fever may be associated with mucosal, hepatic, and hematologic abnormalities. Reactions of this type can be produced 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 judgment, knowledge of alternative treatment options, and an understanding of when to attempt

suppression of the symptoms and when to discontinue the drug. In some instances, desensitization has proven useful.

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