

Adverse Cutaneous Reactions to Antimicrobials in Patients with Human Immunodeficiency Virus Infection

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Adverse reactions to medication are significant contributors to morbidity and mortality in patients with human immunodeficiency virus (HIV) infection. Cutaneous events not only constitute a significant portion of these reactions, they may also herald developing systemic reactions such as hemato-, nephro-, and hepatotoxicity. The identification of cutaneous adverse reactions and drug culprits and the proper management of reactions are of paramount importance for these patients. This review focuses specifically on adverse cutaneous reactions to antimicrobials that are commonly used in the management of patients with HIV infection.

THE MYRIAD PROBLEMS resulting from the human immunodeficiency virus (HIV) pandemic, now approaching the 25-year mark, cannot be overstated. The World Health Organization currently lists the number of individuals infected worldwide at 39.4 million. In sub-Saharan Africa, 7.5% of the adult population is HIV positive, and percentages of HIV-infected persons in specific countries reach as high as 40%. Areas such as India and Eastern Europe have rapidly exploding HIV epidemics. In the United States, approximately 40,000 individuals are newly infected each year.¹

Patients with HIV infection or acquired immunodeficiency syndrome (AIDS) frequently experience adverse drug reactions. This is explained partly by the large numbers of different medications often required for these chronically ill patients. But HIV-infected individuals are also at significantly increased risk for an adverse reaction to any given medication. This phenomenon has long been recognized but is still a topic of ongoing speculation and research. Various theories have been proposed, including immune system dysregulation, glutathione deficiency, slow acetylator phenotype, the effect of chronic viral infection, and the possible role of coexistent infections such as infections with Epstein-Barr virus (EBV), *Cytomegalovirus* (CMV), and human herpesvirus 6 (HHV-6).

Up to 80% of HIV-infected patients experience adverse drug reactions at some point during therapy.^{2,3}

For example, 40 to 60% of patients taking nevirapine experience a drug-related rash; the incidence of Stevens-Johnson syndrome (SJS) caused by this drug has been estimated to be 0.3 to 1.0%. AIDS patients receiving trimethoprim-sulfamethoxazole (TMP-SMZ), currently first-line prophylaxis against *Pneumocystis carinii* pneumonia and therefore a ubiquitous part of treatment regimens, have a 50-fold increased risk of SJS and toxic epidermal necrolysis (TEN) as compared to uninfected recipients in the general population.⁴ Many other antimicrobials pose similarly increased relative risks in AIDS patients.

The problem of cutaneous drug reactions in HIV-infected patients has been recognized almost since the beginning of this pandemic.⁵ As such, numerous reviews have been written on the subject, covering different subsets of drugs,³ specific reactions (including SJS and TEN),⁴ and rare idiosyncratic responses to highly active antiretroviral therapy (HAART).^{6,7} This review focuses on cutaneous adverse reactions to antimicrobials to which HIV-infected patients are typically exposed and emphasizes newer drugs and recent case reports and studies.

Methods

Information from case reports and clinical trials was obtained via searches of Medline and AIDSline for specific drug names and the keywords "adverse effects," "cutaneous," "skin," "hypersensitivity," "drug eruption," "rash," "Stevens-Johnson syndrome," and "toxic epidermal necrolysis." Subsequent searches of printed journals were also performed.

In certain cases when published studies did not report statistical analyses, we performed these analyses with SAS

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(Statistical Analysis System, SAS Institute Inc., Cary, NC) and identified them as “calculated” in the text. Fisher exact tests were used to examine differences in rates of cutaneous reactions between HIV-positive patients and HIV-negative patients. A significance level of .05 was used in all of the analyses.

Cutaneous Drug Reactions

Adverse events are often graded by severity when described in reports of clinical trials and in other articles. Table 1 lists standard definitions of severity grading for adverse reactions.⁸

Significant difficulty exists in systematically classifying the spectrum of adverse cutaneous drug reactions, which include drug-induced exanthema, urticaria, angioedema, anaphylaxis, hypersensitivity vasculitis, erythroderma, erythema multiforme, hypersensitivity syndrome, acute generalized exanthematous pustulosis (AGEP), SJS, TEN, and SJS-TEN overlap. Collectively, these reactions have at times been referred to as drug eruptions, allergic drug reactions, or drug hypersensitivities. Currently, it appears that these broad terms may be inappropriate for grouping a diverse set of disorders; the exact causes of many of these

phenomena have yet to be conclusively identified. Brief descriptions and some unifying characteristics of these conditions are listed below and in Tables 2 and 3.

Approximately 75% of the events classically referred to as “drug rash” may be described as drug-induced exanthema, typically morbilliform and maculopapular rashes. These eruptions almost always appear within 2 weeks of the initiation of the offending drug and are believed to be the result of type IV delayed hypersensitivity with a cell-mediated immune response.⁹ For this reason, these rashes often respond to corticosteroid therapy.¹⁰ Urticaria, angioedema, and anaphylaxis are all type I hypersensitivity reactions with cutaneous manifestations. They are understood to be immunoglobulin E (IgE) and mast-cell or kinin-pathway mediated, and they typically occur very early (hours to days) after drug exposure. Prior sensitization to the offending drug is common.¹¹

Hypersensitivity vasculitis typically manifests as palpable purpura with or without a maculopapular rash. This vasculitis is believed to be mediated by reactive drug

Table 1. Common Terminology Criteria for Adverse Events

Grade	Description
0	No adverse event (absent) or within normal limits
1	Mild adverse event (minor; no specific medical intervention; asymptomatic laboratory findings only; radiographic findings only; marginal clinical relevance)
2	Moderate adverse event (minimal intervention; local intervention; noninvasive intervention [packing, cautery])
3	Severe and undesirable adverse event (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiologic procedure; therapeutic endoscopy or operation)
4	Life-threatening or disabling adverse event (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiologic procedure, therapeutic endoscopy, or operation)
5	Death related to adverse event

Table 2. Adverse Drug Reactions Observed in HIV-Infected Patients

Reaction	Drug Implicated	References
Anaphylactoid	Zidovudine	17
	Abacavir	29
	Indinavir	67
	Flucytosine	121
	Rifampin	3, 152
	TMP-SMX	161
	Ciprofloxacin	152, 172
HSS or DRESS	Cloxacillin	169
	Abacavir	22
	Zalcitabine	39
	Nevirapine	53
	Efavirenz	31
Leukocytoclastic vasculitis	Indinavir	65
	TMP-SMX	160
	Zidovudine	18
	Indinavir	70
	Acyclovir	94
Erythroderma	Abacavir	30
	Indinavir	68
Ofuji papuloerythroderma	Didanosine	37
Porphyria	Indinavir	69
	Nelfinavir	82
Eosinophilic folliculitis	Foscarnet	100

DRESS = drug rash with eosinophilia and systemic symptoms; HIV = human immunodeficiency virus; HSS = hypersensitivity syndrome; TMP-SMX = trimethoprim-sulfamethoxazole.

Table 3. Antimicrobial Agents Implicated in Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis in HIV-Infected Patients

<i>Drug Class</i>	<i>Suspected Drug</i>	<i>Reports or Frequency</i>	<i>References</i>
Antiretrovirals	Zidovudine	1 case	20
	Abacavir	1 case	31
	Didanosine	1 case	35
	Nevirapine	0.3% of > 2,800 patients	49
	Efavirenz	0.14%*	58
	Indinavir	1 case	66
	Amprenavir	Sporadic reports	5
	Fosamprenavir	1 case	80
Other antivirals	Acyclovir	1 case	95
Antifungals	Fluconazole	Several cases	116
Anti-TB drugs	Rifampin	Numerous cases	3, 151
	Pyrazinamide	1 case	153
	Thiacetazone	Numerous cases	136, 141
Antibiotics	TMP-SMX	0.1% of 5,102 HIV+ patients	162
	Dapsone	Several cases	167
	Vancomycin	1 case	169
	Clindamycin	Several cases	162
	Sulfadoxine-pyrimethamine	1.8% of 227 HIV+ patients	163
	Flucloxacillin	1 case	163
	Sulfadiazine	1 case	165
	Sulfadiazine-pyrimethamine	3 cases	166
	Dicloxacillin	1 case	170
	Erythromycin	1 case	170
	Ciprofloxacin	Several cases	171, 172
	Nitrofurantoin	1 case	168

Adapted from Zangerle R. Cutaneous drug reactions in HIV-infected patients. *Dermatol Ther* 1999;12:115-30

HIV+ = positive for human immunodeficiency virus; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole.

*Total number of patients was not reported.

metabolites, which act as haptens to stimulate an immune response.^{12,13} SJS and TEN are severe mucocutaneous disorders that may manifest with diffuse blistering, epidermal detachment, and significant systemic symptoms. By convention, SJS involves epidermal detachment of less than 10% of the total body surface area (BSA) whereas TEN involves more than 30% of total BSA, and cases that affect between 10 and 30% of the total BSA are classified as SJS-TEN overlap. Mortality for TEN is high. Both disorders are believed to be immunologic in nature, as evidenced by frequent recurrence on rechallenge, but the exact mechanism is unknown.¹¹

Adverse Cutaneous Reactions to Specific Drugs

Nucleoside Analogue Reverse Transcriptase Inhibitors

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) were the first medications introduced for treatment of HIV infection and are still mainstay drugs in HAART. Current recommendations include the use of two NRTIs in combination with a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor. The NRTI group includes zidovudine, zalcitabine, abacavir, didanosine, lamivudine, stavudine, tenofovir, and emtricitabine, a newly introduced drug that has been available since 2003.

Zidovudine

Zidovudine (AZT) was the first drug found to be active against HIV, but it had a long history before the HIV pandemic. AZT was first synthesized in 1964 and was found to have antiviral activity in 1974. Within 3 years of the identification of HIV as the virus causing AIDS, AZT was approved for therapy.¹⁴ The drug is metabolized in vivo to a triphosphate form that binds preferentially to HIV-1 reverse transcriptase and prevents virus chain elongation during replication. AZT has several recognized side effects, including nausea, headache, macrocytic anemia, and granulocytopenia.^{14,15} Cutaneous adverse events are relatively uncommon. Fischl and colleagues estimated the incidence of severe rash secondary to AZT use to be 1%.¹⁶ Wassef and Keiser reported on a patient with anaphylaxis that presented 1 hour after his second dose of AZT with confusion, high fever, diffuse erythema, and swelling that was worse on the lips, hands, and feet.¹⁷ Eight other cases of hypersensitivity to this drug have been documented, including three cases of leukocytoclastic vasculitis^{18,19} and one case each of urticaria and lichenoid dermatitis. The only case of TEN due to AZT was described in 1996; this patient died after a prolonged course that included gingival bleeding, epidermal detachment of more than 75% of total BSA, and *Staphylococcus aureus* sepsis.²⁰

Abacavir

Abacavir is a guanosine analogue that acts on HIV-1 reverse transcriptase to terminate chain elongation during viral deoxyribonucleic acid (DNA) synthesis.²¹ Abacavir has the clearest connection to adverse cutaneous events of any drug

in this class. Both a typical drug rash and a distinct hypersensitivity syndrome (involving rash and fever, with or without gastrointestinal and respiratory symptoms) are well described in regard to abacavir.²² Initial clinical trials demonstrated rash in 10% of recipients and hypersensitivity reactions in 2 to 3%. Rates of hypersensitivity syndrome (HSS) have been repeatedly confirmed as 3 to 4% in small trials.^{23–25} However, a 2001 retrospective study of pooled data from over 200,000 patients found 1,803 cases (0.9%) of hypersensitivity reactions to abacavir. Interestingly, rash was not uniformly part of these reactions and occurred in only 66% of these patients. Nineteen deaths were considered likely to be secondary to hypersensitivity; six of these occurred after rechallenge.²² Rechallenge with abacavir is strictly contraindicated, as all patients experiencing an initial event appear to have a more severe subsequent reaction, which may include death.²⁶ In a retrospective study of 191 patients, the risk of HSS was found to be increased in patients who either had a history of allergic reaction to nevirapine (odds ratio [OR], 8.1; 95% confidence interval [CI], 1.6–40.5; $p = .02$) or were naïve to antiretroviral therapy (OR, 5.8; 95% CI, 1.2–28.5; $p = .04$).²⁷ In another study, with 5,332 patients, black ethnicity was found to be protective against HSS (OR, 0.59; 95% CI, 0.38–0.91).²⁵ The use of steroids has not been shown to prevent HSS on rechallenge.²⁸ Sporadic reports of other reactions to abacavir described three deaths from anaphylaxis,²⁹ diffuse erythroderma and mucositis,³⁰ and one case of SJS.³¹

Emtricitabine

Emtricitabine is an oxathiolane-cytosine derivative with activity against both HIV and hepatitis B virus.³² It is the newest drug in the NRTI class, and case reports of severe cutaneous events have not yet appeared in the literature. Clinical trials mention “rash events” (including maculopapular rash, pruritus, pustular rash, and urticaria) in 30% of patients³³ and purpura of grade 3 severity in 1% of patients.³⁴

Didanosine

A case of SJS associated with didanosine has been reported.³⁵ Didanosine has also been implicated in leukocytoclastic vasculitis³⁶ and Ofuji papuloerythroderma.³⁷ Large-scale clinical trials have reported morbilliform and maculopapular rashes in approximately 3% of didanosine recipients. Another phase I/II trial reported severe rash and stomatitis in 9 (14.8%) of 61 patients.³⁸

Zalcitabine, Tenofovir, Stavudine, and Lamivudine

Two HSS cases similar to those associated with abacavir have been reported in regard to zalcitabine.³⁹ Initial clinical trials documented mucocutaneous eruptions in 70% of patients (14 of 20) who received high dosages of this drug (0.03–0.25 mg/kg every 4–8 hours).⁴⁰ Current therapeutic dosage recommendations are lower (0.75 mg orally every 8 hours),¹⁵ but severe rash and stomatitis are still documented side effects (2% and 4% incidence, respectively).¹⁶

A case of lichenoid eruption with eosinophilia was reported recently in regard to tenofovir. The patient had coexistent HIV and hepatitis B virus infections and a history of rash reaction to cotrimoxazole. Soon after starting tenofovir, he developed a pruritic erythematous lichenoid rash on the arms and scalp; this resolved after discontinuation of the drug and after therapy with an antihistamine and a topical steroid.⁴¹ Phase III studies found rashes in 7% of patients taking tenofovir. Drug rashes from stavudine appear to be common and were reported in 99 (35%) of 285 patients in a 2004 study,³³ but severe adverse cutaneous events have not been reported for this drug or for lamivudine despite their widespread use.⁵ One case of allergic contact dermatitis induced by lamivudine has been reported; this patient developed a pruritic eruption on the palm and forearm 2 to 3 days after holding a lamivudine capsule in her hand for more than 30 minutes during a conversation. Histopathologic analysis indicated an intraepidermal vesicular dermatitis, and subsequent patch testing yielded a positive reaction to a crushed lamivudine tablet.⁴²

Non-nucleoside Analogue Reverse Transcriptase Inhibitors

Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) were introduced in 1996 for the treatment of HIV infection and continue to be part of first-line therapy.⁴³ Unfortunately, the three drugs in this class—delaviridine, efavirenz, and nevirapine—all have significant side effect profiles. NNRTIs have more documented cutaneous side effects than any of the other antiretroviral drugs,⁴⁴ and many of these effects are significant, often requiring the discontinuation of the offending drug.

Nevirapine

Nevirapine inhibits HIV reverse transcriptase by binding to a hydrophobic pocket in the enzyme-DNA complex;

this mechanism is common to all three drugs in this class.⁴⁵ Nevirapine, an otherwise well-tolerated drug, has a wide spectrum of significant cutaneous effects. Hypersensitivity reactions are estimated to be two times more common with nevirapine than with any other antiretroviral medication.⁴⁶ Generalized rash in the first 6 weeks of nevirapine therapy has been observed in 16 to 22% of patients,⁴³ and severe (grade 3 or 4) cutaneous adverse drug reactions are seen in approximately 8% of these patients.⁴⁷ In its first 3 years on the market (1995 to 1998), 19 cases of SJS secondary to nevirapine use were reported to the Food and Drug Administration (FDA),⁴⁸ and many more case reports have followed in subsequent years. Overall SJS and TEN incidence due to nevirapine is estimated to be 0.3%⁴⁹; some authors suggest the rate may actually be as high as 1% of HIV-infected patients taking the drug. Four cases of nevirapine-associated drug rash with eosinophilia and systemic symptoms (DRESS) have also been described.^{50–53} DRESS is considered a severe form of HSS and may include diffuse maculopapular rash, fever, multivisceral involvement, eosinophilia, and abnormalities on liver function tests.⁵⁰ A similar case characterized as fulminant hepatic failure with diffuse maculopapular rash and fever has also been reported; this patient had coexistent HIV and hepatitis C infection and presented to the hospital with fever, right upper-quadrant pain, and a diffuse spreading maculopapular rash 1 month after commencing nevirapine. The authors attributed this reaction to nevirapine because the patient had serum eosinophilia of 18% on admission and because all symptoms dramatically improved after the discontinuation of nevirapine and the initiation of steroid therapy.⁵⁴

Delavirdine

Delavirdine frequently causes mild morbilliform eruptions but does not appear to cause the severe reactions seen with nevirapine use. Transient mild rash in 44% of recipients was observed in phase I/II clinical trials. This reaction was uniformly an erythematous maculopapular rash of mild to moderate severity, and 90% of affected patients were able to continue therapy despite skin symptoms.⁵⁵ A retrospective study published in 2000 compared the incidence of rash in 33 patients taking either nevirapine or delavirdine; the frequencies of rash reaction were not significantly different (40% for delavirdine vs 36% for nevirapine). In this study, approximately 20% of observed nevirapine rashes were classified as severe whereas all delavirdine-related rashes were considered mild to moderate.⁵⁶

Efavirenz

Efavirenz has been implicated in both SJS^{57,58} and HSS⁵⁹; it carries an estimated SJS rate of 0.14%.⁵⁸ However, general adverse cutaneous side effects appear to be less common with efavirenz than with nevirapine or delavirdine. Cutaneous lesions of grade 2 or higher severity appeared in only 3.2% of 250 study patients who were receiving efavirenz,⁶⁰ and a pediatric study found mild diffuse cutaneous eruptions in 5 (15%) of 33 children who were taking the drug.⁶¹

Protease Inhibitors

Protease inhibitors (PIs) prevent the maturation of HIV virions by inhibiting the cleavage of gag and gag-pol viral protein precursors.⁶² PIs are part of both first- and second-line current therapy recommendations for HAART.¹⁵ Perhaps the most well-known of PI side effects is the lipodystrophy syndrome, which causes fat-pad wasting and cushingoid-type fat redistribution and is a significant cosmetic problem for patients who take these drugs.⁶ Cutaneous side effects are well described for many PIs. The rate of rash in patients who take a PI has been recently estimated as 5%, based on data from a randomized multicenter trial of 1,251 patients taking either ritonavir or indinavir.⁶³ The PI class includes amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, and two new drugs introduced in 2003 (atazanavir and fosamprenavir).

Indinavir

Indinavir has been implicated in a wide range of early cutaneous adverse events. Its rate of rash was estimated to be 4.5 to 5.0% in two studies,^{63,64} and a hypersensitivity reaction similar to that observed with abacavir use has been documented in up to 4.5% of patients.⁶⁵ There are sporadic case reports of various cutaneous effects of the drug, including SJS,⁶⁶ anaphylactoid reaction,⁶⁷ erythroderma,⁶⁸ acute porphyria,⁶⁹ leukocytoclastic vasculitis,⁷⁰ and generalized urticarial rash.⁷¹ The patient with porphyria was a 42-year-old man with a vague prior history of the disease who was taking indinavir as part of postexposure prophylaxis for HIV-1 infection. Two days after beginning therapy, he developed a generalized pruritic rash with vesicles on the hands and feet, and his liver function test results and fecal porphyrins were consistent with porphyria cutanea tarda. The rash and

pruritus improved progressively during the 2 weeks following the discontinuation of indinavir.⁶⁹

Ritonavir

Initial trials found cutaneous adverse events in up to 20% of patients who were taking ritonavir,⁷² but clinical experience with approximately 800 patients has shown this rate to be between 5% and 12%.^{63,65} In a small study, Gathe and colleagues found that 8% of 649 patients who were taking a ritonavir-fosamprenavir combination had to discontinue the drugs because of suspected hypersensitivity reactions.⁷³ An interesting case report noted two cases of very early generalized maculopapular eruptions (both on the second day of therapy) caused by ritonavir.⁷⁴ The time course was most consistent with a type I hypersensitivity reaction, but no urticaria was observed, and the patients had no previous exposure to this drug.

Amprenavir

In clinical trials of amprenavir, approximately 3% of patients (11 of 358) experienced grade 3 or 4 rashes that necessitated the discontinuation of the drug.⁷⁵ Investigators in another clinical trial observed rash in 3 (6%) of 53 treated patients.⁷⁶ Sporadic cases of SJS have been reported for amprenavir as well.⁵

Atazanavir and Fosamprenavir

Information on cutaneous reactions to the newest protease inhibitors, atazanavir and fosamprenavir, is currently limited to clinical trial reports. Sax and Kumar reported increased rates of early rash from both of these drugs relative to the other PIs (8% for fosamprenavir and 9% for atazanavir).⁷⁷ Pooled data from clinical trials involving approximately 2,700 patients treated with atazanavir indicated rash of any severity in 12 to 22% of patients.⁷⁸ As previously mentioned, 8% of 649 patients who were taking a ritonavir-fosamprenavir combination in a clinical trial had to discontinue the drugs because of suspected hypersensitivity reactions.⁷³ Severe rash reactions (grades 3 and 4) have been observed from the use of fosamprenavir alone (7% of 112 patients)⁷⁹; manufacturer data also reported one case of SJS among 700 patients in phase III clinical trials.⁸⁰

Other Protease Inhibitors

Reports of cutaneous reactions to other PIs are relatively rare. A study of nelfinavir use in 42 HIV-positive children

found generalized maculopapular rash in 10 patients (23.8%). This rash was generally mild and was managed with prednisone and antihistamines while treatment was continued; no patients required the discontinuation of therapy.⁸¹ A recent report also implicated nelfinavir as the precipitating factor in a case of porphyria cutanea tarda; the patient developed small white plaques, vesicles, and bullae on sun-exposed areas 3 days after commencing HAART. Urinary uroporphyrin levels were increased (2,083 µg per day). Skin lesions dramatically improved in the days following the discontinuation of nelfinavir.⁸² Two cases of fixed drug eruption have been attributed to saquinavir.⁸³

Fusion Inhibitors: Enfuvirtide

Enfuvirtide is one of the newest medications available for treatment of HIV infection. It was introduced in 2003 and is currently the only FDA-approved member of the fusion inhibitor class, a group of drugs that prevent entry of the virus into CD4 cells by inhibiting the gp41 transmembrane glycoprotein and preventing structural changes required for membrane fusion.⁸⁴ Enfuvirtide is not currently part of first-line therapy recommendations for HAART but has shown significant progress in combating HIV infections in clinical trials. The drug is a synthetic peptide and as such must be administered parenterally.⁸⁵ The vast majority of adverse cutaneous events associated with it relate to its subcutaneous administration route. Initial clinical trials demonstrated injection site reactions in up to 98% of enfuvirtide recipients. Ball and Kinchelov characterized these reactions as localized hypersensitivities with various histologic similarities to granuloma annulare and erythema nodosum.⁸⁴ Frequent injection site reactions were further documented in 14 children in 2004.⁸⁵ Severe generalized rash secondary to enfuvirtide administration has been documented in a case report,⁸⁶ and five cases (less than 1% of patients) of systemic hypersensitivity reaction, including rash, were noted in clinical trials.⁸⁷

Other Antiviral Agents

Opportunistic viral infections such as herpes simplex, zoster, and CMV retinitis are common in AIDS patients. As such, other antiviral drugs are used extensively among this patient population. First-line and alternative medications in this group include acyclovir, valacyclovir, famciclovir, ganciclovir, valganciclovir, foscarnet, didanosine, and zalcitabine. As a class, these drugs are extremely safe and well tolerated; the incidence of adverse effects of any kind is low.

Acyclovir

Acyclovir was one of the first antiviral drugs developed; it continues to be the first-line treatment for herpes simplex in immunocompromised patients.¹⁵ Initial clinical trials suggested that a hypersensitivity-type reaction could occur in up to 1% of patients,⁸⁸ but long-term clinical experience with this drug has shown it to be remarkably low in complications.⁸⁹ In the 1980s, cases of generalized maculopapular “drug rash” were uncommon enough to merit case reports,⁹⁰ and allergic contact dermatitis from topical application has rarely been reported.^{91,92} Mild rash occurred in 2 (4%) of 52 patients in a study of non-HIV-infected immunocompromised patients who were receiving intravenous (IV) acyclovir for zoster,⁹³ and a case of leukocytoclastic vasculitis with IV administration has also been observed.⁹⁴ One case of SJS secondary to acyclovir use in an AIDS patient was described in 1995; the authors reported this as the first case of SJS or TEN in any patient taking the drug.⁹⁵

Foscarnet

Foscarnet is approved for the treatment of CMV retinitis and is associated with several adverse cutaneous effects. This drug is perhaps best known to cause genital ulcerations, thought to occur as a direct toxic effect of high concentrations of drug in urine causing erosive changes to genital mucosal surfaces.^{96,97} This phenomenon is well described in the literature, but other cutaneous reactions are rare. Two separate cases of generalized rash secondary to foscarnet use in AIDS patients were reported in 1990.^{98,99} Since then, this drug has also been implicated in TEN in a bone marrow transplant recipient.⁹⁷

Roos and Albrecht described eosinophilic folliculitis in an AIDS patient.¹⁰⁰ An end-stage AIDS patient who started foscarnet for mucocutaneous Kaposi sarcoma developed a pruritic urticarial maculopapular rash on the trunk, arms, and legs on the second day of treatment with the drug; this rash initially cleared several hours after drug administration but re-appeared during the patient’s next infusion and persisted despite discontinuation of foscarnet. The result of a histopathologic study was consistent with eosinophilic folliculitis. The patient required 2 months of ultraviolet B therapy before this condition cleared.¹⁰⁰

Interferon- α and Ribavirin

Coexistent hepatitis, with either hepatitis B virus or hepatitis C virus, is a common phenomenon in HIV-infected individuals. Interferon- α and ribavirin in combination are

first-line treatment for hepatitis C virus (HCV) infection; up to 20% of patients experience adverse cutaneous events secondary to interferon- α treatment.¹⁰¹ The spectrum of these adverse events is wide. Case reports have described eczematous eruptions, including severe generalized nummular eczema,¹⁰² lichen planus and lichenoid-type eruptions,¹⁰³ multiple fixed drug eruption,¹⁰⁴ and cutaneous sarcoidosis,¹⁰⁵ in HCV-infected patients who were receiving combinations of interferon- α and ribavirin. Manjon-Haces and colleagues reported that of 210 HCV-infected patients who were receiving interferon- α -2b plus ribavirin, 27 patients experienced cutaneous side effects. The most common of these events were eczema ($n = 16$, 7.6% of study patients) and prurigo ($n = 4$, 1.9% of study patients). Lichenoid eruption, seborrheic dermatitis, and maculopapular exanthema were also reported.¹⁰⁶

Reports of adverse cutaneous reactions to interferon or ribavirin in HIV-infected patients are infrequent. Bessis and colleagues reported the first observation of cutaneous necrosis at sites of pegylated interferon- α injection in a 50-year-old HIV-infected male after 9 months of weekly subcutaneous injections.¹⁰⁷ A multicenter clinical trial of ribavirin for treatment of HIV infection itself enrolled 215 HIV-positive individuals; 145 patients received ribavirin, and 70 patients received placebo. No significant adverse cutaneous events were reported in either the treatment or control groups.¹⁰⁸

Additional Antiviral Agents

Reports of serious adverse cutaneous events with other antiviral drugs are rare. A patient who was taking ganciclovir experienced a generalized rash and splinter hemorrhages,¹⁰⁹ and 2 (4.9%) of 41 AIDS patients who took this drug in a clinical trial experienced generalized rash.¹¹⁰ The overall rate of rash secondary to ganciclovir was estimated at 6% among 314 immunocompromised patients (167 of whom were HIV positive).¹¹¹ Valacyclovir has been identified as the culprit in a case of rapid-onset contact dermatitis; the patient developed contact sensitization from topical acyclovir and subsequently had a pruritic exanthem on the face, trunk, and extremities after a single oral dose of valacyclovir. Patch-test results were positive for 1% concentrations of both acyclovir and valacyclovir.¹¹² Clinical trials of valganciclovir estimated the incidence of dermatitis at 13 to 20% in HIV-infected patients,¹¹³ and 25% of AIDS patients using topical cidofovir gel experienced application site reactions that included burning, pain, and pruritus.¹¹⁴ A literature search revealed no reports of adverse cutaneous events from famciclovir and fomivirsen.

Antifungal Agents

Fungal infections are also common in AIDS patients; these infections include cryptococcal meningitis, fungal pneumonia (such as coccidioidomycosis and *Histoplasma pneumoniae*), and skin and mucosal *Candida* infections.

Antifungal drugs as a class have very few adverse cutaneous effects although Roujeau and colleagues observed 5 cases of SJS or TEN attributable to fluconazole ($n = 3$), ketoconazole ($n = 1$), and miconazole ($n = 1$) in a group of 245 patients identified to have either SJS or TEN (HIV status of the patients was not reported).¹¹⁵ The authors calculated the crude relative risk of SJS and TEN from imidazole use to be 24 (95% CI, 5.5–104). There are two other case reports of patients (including one HIV patient) with SJS secondary to fluconazole use⁵⁷ and one report of TEN in an AIDS patient.¹¹⁶ Rare reports of angioedema exist, and one study found rash in approximately 4% of 232 patients with severe fungal infections who were taking fluconazole (65% of the study patients had AIDS).¹¹⁶ However, a recent large study of over 34,000 patients who were taking the drug found no incidence of any significant cutaneous events. Itraconazole use was studied in more than 16,000 patients and was also found to entail no increased risk of significant skin side effects.¹¹⁷ However, DeBeule and colleagues observed pruritus and rash in 1.6% of patients who were on long-term itraconazole,¹¹⁸ and there is a report of mild diffuse maculopapular rash in an AIDS patient who was on long-term therapy with this drug.¹¹⁹ Itraconazole was the culprit in a case report of AGEP as well; the patient had a history of hepatitis B, but HIV status was not reported.¹²⁰ One case report also identified flucytosine as the cause of anaphylaxis with significant cutaneous symptoms in an AIDS patient.¹²¹

To our knowledge, voriconazole, caspofungin, and amphotericin B, despite their significant systemic side effect profiles, have not been associated with any significant cutaneous side effects.

Antiparasitic Agents

Antiparasitic drugs include medications for treating both helminthic and protozoal infections and may be required in treating AIDS patients for illnesses such as malaria, giardiasis, and amebiasis. Many drugs in this class have been associated with significant side effect profiles in the general population. Reports have identified cases of SJS secondary to the use of albendazole,¹²² atovaquone-proguanil,¹²³ mebendazole,¹²⁴ mefloquine,¹²⁵ and thiabendazole.¹²⁶ Mefloquine, metronidazole,¹²⁷ and thiabendazole¹²⁸ have been identified as causative agents in cases of TEN. Cases of anaphylaxis with

cutaneous symptoms have been reported for patients who are taking either metronidazole¹²⁹ or flubendazole.¹³⁰ Thirty-five cases of either SJS or TEN were also observed in a Filipino population that was receiving a metronidazole-mebendazole combination as part of a systematic helminth eradication campaign.¹³¹ A Chinese retrospective study of 25,693 patients who were receiving praziquantel for schistosomiasis identified “serious skin rash” in 18 patients (0.07%); one of these patients presented with an exfoliative dermatitis.¹³² A case of generalized vesicular rash involving the oral mucosa was observed in a Sudanese patient who was receiving tinidazole for giardiasis.¹³³

Indications of HIV status in reports of cases of adverse cutaneous events are rare. Fischer and colleagues reported that of 856 Ugandan patients, 43 (5%) of whom were infected with HIV, treatment of onchocerciasis with ivermectin yielded skin rashes in 38% ($n = 16$) of the HIV-infected patients but in only 9% ($n = 73$) of the seronegative patients. It was noted, however, that “the rash seen more often in HIV-positive persons can be treated symptomatically and it disappears after a few days. It is not a reason to exclude HIV-positive persons from ivermectin treatment.”¹³⁴

Antituberculosis Agents

Combined tuberculosis (TB) and HIV infection is a significant world health problem; co-infection exists in approximately one third of HIV-infected patients worldwide.¹³⁵ Most of the drugs in the antituberculosis armamentarium have significant toxicities, and the incidence of adverse cutaneous effects is high, especially in HIV-infected patients. Identifying the one drug responsible for an adverse event in a TB patient is difficult. Three- and four-drug combination therapies are the norm, and the various medications that are in common use (eg, isoniazid, rifampin, pyrazinamide, and ethambutol) all have significant documented adverse effects, cutaneous and otherwise. For this reason, many reports have simply documented the incidence of adverse effects from anti-TB therapy in general.

In a study of 237 Zambian children with pulmonary TB, the incidence of adverse skin reactions from anti-TB therapy was 21% (19 of 88 patients) for HIV-infected patients, as compared to 2% (3 of 149) for seronegative individuals (OR, 11.65; 95% CI, 3.07–34.88). Twelve patients developed SJS during the investigation; all of these children were HIV positive.¹³⁶ A study of adults in San Francisco observed adverse reactions to TB therapy in 18% of 132 HIV-positive patients; the authors noted a reaction rate of 3.7% for HIV-negative patients in a

previous study at the same clinic.¹³⁷ Chaisson and colleagues monitored rates of adverse reactions in 35 HIV-positive patients and 35 HIV-negative individuals who were on anti-TB therapy; they observed a significant risk ($p < .02$) for adverse reactions of any kind in the HIV-positive patients.¹³⁸ We calculated no significant difference for risk of rash (6 of 35 HIV-infected patients vs 1 of 35 non-HIV-infected patients, $p = .106$), but this is likely due to the small sample size. Cutaneous adverse drug reactions were observed by Luo and colleagues in 11% (7) of 65 HIV-infected patients who were on multiple anti-TB medications; these included 2 patients who developed SJS.¹³⁹ Numerous other cases in which HIV-infected patients developed SJS are described in the literature.^{140,141} Kuaban and colleagues noted a significantly higher rate of skin reactions ($p < .001$) among HIV-infected patients in a study of 235 TB patients treated with thiacetazone-free drug regimens.¹⁴² We calculated a relative risk of 29 for HIV seropositivity and risk of adverse skin reaction for this study (calculated 95% CI, 5.1–100.7; $p < .0001$). A case of TEN in an AIDS patient who was on four-drug TB therapy and TMP-SMX was also recently reported; the patient developed flaccid bullae and erosions on more than 90% of his body after 2 months of treatment with isoniazid, rifabutin, pyrazinamide, ethambutol, and cotrimoxazole. Systemic steroid therapy did not halt disease progression, but within 2 weeks of plasma exchange, the patient's condition had improved dramatically.¹⁴³

Isoniazid

Besides the well-known toxic effects on hepatocytes and neuropathy, the cutaneous side effects of isoniazid (INH) are also a recognized phenomenon. Before the onset of the AIDS epidemic, numerous cases of SJS were reported.^{144,145} During the AIDS era, reports of cutaneous reactions to INH have increased significantly. Gordin and colleagues recently observed severe (grade 4 or 5) rashes secondary to INH use in 0.6% of 792 HIV-infected patients.¹⁴⁶ Yee and colleagues calculated a hazard ratio of 2.4 (95% CI, 0.3–19.5) for HIV seropositivity and the risk of rash or fever from INH.¹⁴⁷

Rifampin

Rifampin in particular has raised concern among medical providers because of its increased rate of adverse reactions in HIV-infected patients.^{3,148} In the general population, the rate of urticaria and maculopapular rash secondary to rifampin use has been estimated at 5%,¹⁴⁹ and a case of SJS

was reported prior to the AIDS era.¹⁵⁰ Adverse events, often serious, are much more frequent in HIV-infected individuals; Yee and colleagues estimated the hazard ratio of rifampin for HIV-infected patients to be 8.0 (95% CI, 1.5–43.0).¹⁴⁷ SJS in AIDS patients is well documented. At least one case of TEN has been observed,¹⁵¹ and there are also reports of anaphylactoid immediate hypersensitivity reactions in this population as well.^{3,152}

Pyrazinamide and Ethambutol

Pyrazinamide caused a rash severe enough to necessitate the discontinuation of therapy in 9 (2%) of 405 patients¹⁴⁷; it has induced a documented case of SJS as well.¹⁵³ Gordin and colleagues observed severe (grade 4 or 5) rashes in 1.4% of 791 HIV-infected patients who were taking pyrazinamide and rifampin,¹⁴⁶ and severe skin reactions specific to pyrazinamide were observed by Kuaban and colleagues in four HIV-infected patients.¹⁴² Ethambutol has been implicated in one case of TEN in a patient of unknown HIV status; this patient had been treated with INH, rifampin, and ethambutol and developed biopsy-proven TEN during the fourth week of therapy. Rechallenge with ethambutol triggered fever, erythema, and bullae formation within 2 hours.¹⁵⁴

Thiacetazone

In addition to the anti-TB drugs listed above, thiacetazone, a nonfirst-line TB treatment, merits discussion. Thiacetazone was a ubiquitous anti-TB drug in Africa and was popular owing to its effectiveness and low price; but serious adverse effects, including SJS and other cutaneous manifestations, became increasingly common with anti-TB regimens containing thiacetazone in the late 1980s and early 1990s. The rise of HIV in sub-Saharan Africa likely played a significant role. Chintu and colleagues observed 12 cases of SJS in HIV-positive children who were taking the drug,¹³⁶ and Dukes and colleagues noted that 4 of 5 patients who developed SJS secondary to thiacetazone use were HIV positive.¹⁴¹ These results and numerous other case reports and studies^{155,156} raised concerns about the safety of the drug for HIV-infected patients; in 1992, the World Health Organization issued an advisory against the use of thiacetazone in anti-TB regimens for HIV-positive children.¹³⁶

Antibiotics

Antibiotics, especially sulfonamide derivatives, carry some of the highest rates of adverse events of any drugs. These

Table 4. Adverse Cutaneous Reactions Attributed to Antibiotics in HIV-Positive Patients

<i>Antibiotic</i>	<i>Number of Reactions</i>	<i>Number of HIV+ Patients Exposed</i>	<i>Total Number of Antibiotic Courses</i>	<i>Rate of Reactions per 1,000 Courses</i>
Sulfadiazine or sulfasalazine	4	19	20	200
TMP-SMX	37	172	248	149
TMP, alone or with dapsone	17	88	109	156
Dapsone	25	236	809	31
Aminopenicillins	28	199	300	93
Penicillins	9	161	238	38
Cephalosporins	8	186	294	27
Quinolones	2	64	97	21
Clindamycin or primaquine	3	77	164	18
Tetracyclines	3	139	255	12
Pentamidine	2	102	191	10
Erythromycin	3	278	487	6

Adapted from Coopman SA, Stern RS.¹⁵⁷

HIV+ = positive for human immunodeficiency virus; SMX = sulfamethoxazole; TMP = trimethoprim.

rates are amplified in the setting of HIV infection. Table 4 lists the rates of skin reactions to antibacterials commonly used in HIV-infected patients, as observed in a retrospective study of 684 HIV-positive individuals.¹⁵⁷ Sulfonamide derivatives and dapsone, an agent with high structural similarity to sulfa drugs, are among the most common causes of skin reactions in these patients.

TMP-SMZ has been the most effective therapy and prophylaxis for *Pneumocystis carinii* pneumonia (PCP) and is also used to treat and prevent toxoplasmic encephalitis. Its high rate of adverse reactions in HIV-infected patients has long been recognized, and its effect on these patients has been the subject of many studies. In 1993, Carr and colleagues wrote, "hypersensitivity to cotrimoxazole during prophylaxis of PCP is the most common allergic manifestation of HIV infection." Carr and colleagues observed morbilliform eruptions in 27% ($n = 39$) of 143 patients and reported previous rates of between 29 and 65% for TMP-SMX in the treatment of PCP in HIV-infected patients.⁹ This is much higher than the corresponding rate in non-HIV-infected patients; a previous large-scale study by Jick found a low rate of adverse skin reactions among (non-HIV-infected) hospitalized patients who were on TMP-SMX (38 [3.3%] of 1,121 patients).¹⁵⁸ We compared these studies by Carr and colleagues and Jick and calculated that HIV-positive status confers a relative risk of 8.05 (95% CI, 5.3–12.1; $p < .0001$) for the development of rash secondary to TMP-SMX use. This risk appears to be unique to HIV infection; Kovacs and colleagues found a significantly higher rate of rash ($p = .032$) in HIV-infected patients (10 of 34) compared

to other immunosuppressed patients (0 of 15) who were taking TMP-SMX for PCP.¹⁵⁹ The drug's role in severe skin reactions is also well recognized; it has been implicated in HSS,¹⁶⁰ anaphylactoid reactions,¹⁶¹ and SJS and TEN. The risk of SJS and TEN for those with HIV infection is approximately 0.1% (as studied in 5,102 patients).¹⁶² This is approximately 50 times greater than the risk the drug carries for the general population (26 cases per 1,000,000 patients vs 980 per 1,000,000 HIV-infected patients).⁵ The sulfonamide class in general is associated with a high incidence of SJS; the relative risk for SJS in sulfa-treated patients (as compared to treatment-naïve patients) has been estimated to be 172 (95% CI, 75–396).¹¹⁵ Fansidar (Roche Laboratories; Nutley, NJ) (a combination of pyrimethamine and sulfadoxine) has been implicated in both SJS and TEN in patients with HIV disease. Schmidt-Westhausen and colleagues observed 4 cases of TEN among 227 HIV-infected patients (1.8%) who were taking Fansidar¹⁶³; the incidence of TEN in healthy individuals who are taking the drug for malaria prophylaxis has been estimated at 1 case per 11,000 to 25,000 users.¹⁶⁴ Sulfadiazine alone¹⁶⁵ or in combination with pyrimethamine¹⁶⁶ has caused SJS in AIDS patients; pyrimethamine-sulfadiazine has also caused a reported case of TEN.¹⁶⁶ Other antibacterials implicated in SJS or TEN are listed in Table 3. Dapsone,¹⁶⁷ nitrofurantoin,¹⁶⁸ vancomycin,¹⁶⁹ flucloxacillin,¹⁶³ dicloxacillin, erythromycin,¹⁷⁰ and ciprofloxacin^{171,172} have all caused documented SJS or TEN cases in HIV-infected patients.

Anaphylactoid reactions to ciprofloxacin have also been described in the literature. Four cases of immediate

hypersensitivity reactions in AIDS patients have been reported.^{152,172} The authors found only 22 previous case reports of anaphylaxis from ciprofloxacin in the general population, suggesting an increased rate of type I hypersensitivity for HIV-infected patients taking ciprofloxacin as well. There is also a report of an AIDS patient with anaphylaxis secondary to cloxacillin use.¹⁶⁹

Discussion

Adverse cutaneous drug reactions in HIV-infected patients are a significant problem; rates of such reactions for such persons are approximately 100 times greater than rates for noninfected individuals.¹⁰ HIV-infected patients have up to 1,000 times the risk of the general population for SJS and other severe eruptions.¹⁷³ Multidrug regimens common to most patients not only increase risk through sheer volume but may also promote adverse effects via complex interactions between different drugs. Bonfanti and colleagues observed that two patients with apparent hypersensitivity reaction to ritonavir experienced a regression of symptoms after the discontinuation of long-term prophylaxis with sulfa drugs; the investigators hypothesized that this reaction may have been secondary to cytochrome P-450-dependent drug interactions.⁶⁵

The exact mechanism of increased drug reactions in HIV-infected patients remains unclear. These patients have significant alterations in both immunologic and metabolic pathways, which may contribute to a higher risk for adverse reactions. Several immunologic changes found in the setting of HIV infection appear to put these patients at risk. The direct effect of CD4-cell depletion clearly correlates with increased risk. Battegay and colleagues prospectively collected information on patients treated with amoxicillin-clavulanate in one center and found that HIV-infected patients with rashes secondary to receiving this drug had significantly lower CD4 counts than those without rash reactions (a mean of 75 cells/mm³ in 10 rash patients vs 330 cells/mm³ in 9 patients without rash; $p < .05$).¹⁷⁴ A prospective study of 50 HIV-infected patients found a significant correlation between CD4 counts and the risk of adverse drug reactions. Patients who had adverse drug reactions had mean CD4 levels of 103 cells/mm³ whereas those who did not develop adverse events had a mean of 289 cells/mm³ ($p < .002$).¹⁷⁵ In a study investigating rash in 274 HIV-infected patients who were taking pyrimethamine for toxoplasmosis, the relative risk of rash increased by a factor of 1.13 ($p = .05$) for every decrease of 200 total lymphocytes per cubic millimeter.¹⁷⁶ However, these risks may reach their limits in cases of

severe immunosuppression. Among 143 AIDS patients who were taking cotrimoxazole for PCP, patients with CD4 counts of less than 25 cells/mm³ had a significantly lower risk ($p < .03$) of developing a drug hypersensitivity reaction.⁹

The risk of severe events may be tied to CD4 levels as well; 5 of 7 HIV-infected patients who were identified as having SJS or TEN had CD4 counts of less than 100,¹⁷³ and the mean number of CD4 lymphocytes was 77 (± 83) in 12 HIV-infected patients with TEN identified in a retrospective analysis.¹⁶² This phenomenon may exist for toxic as well as immunologic adverse effects; a study of zalcitabine and AZT therapies in 1,001 patients concluded that the incidence of severe toxic effects such as peripheral neuropathy and anemia was inversely correlated with pretreatment CD4 counts.¹⁶

Increased serum IgE levels may also play a role in cutaneous drug reactions in HIV-infected patients. Although the majority of drug reactions in HIV-infected patients are not immediate type I reactions,¹⁴⁸ IgE and IgE-like substances may play a role in delayed-type hypersensitivities as well.¹⁷⁷ Several studies have shown a correlation between disease progression and increased serum IgE levels in HIV-infected patients in general.^{178,179}

Coexistent viral infections common in HIV-infected patients also appear to be a significant risk factor for the development of adverse cutaneous events. In a study of 283 drug eruptions in 974 HIV-1-positive patients, serologic or culture evidence of acute or reactivated EBV or CMV infection was statistically significantly associated with the risk of drug reactions ($p < .001$).¹⁷⁷ Numerous studies have implicated reactivation of HHV-6 as a risk factor for the development of drug-induced HSS.¹⁸⁰⁻¹⁸² Descamps and colleagues investigated 7 patients (including one with HIV infection) with DRESS secondary to carbamazepine ($n = 5$), ibuprofen ($n = 1$), or sulfasalazine ($n = 1$) use; all patients were seropositive for anti-HHV-6 IgG, and 4 of 7 patients had IgM antibodies as well, suggesting reactivation.¹⁸⁰

These observations appear to be consistent with the "danger hypothesis," a recently proposed theory of immunologic response. The traditional view of the immune system holds that responses are based on the body's ability to differentiate between self- and nonself antigens. The danger hypothesis suggests that the immune system's default pathway is tolerance and that antigens elicit an immune response only when some sort of danger signal cofactor is present. Thus, states of increased circulating cytokines, in such situations as trauma or chronic infection, provide an environment in which

substances such as drug metabolites are more likely to trigger an immune response.^{26,183}

Numerous studies have demonstrated that the body's ability to eliminate reactive drug metabolites is impaired in the setting of HIV infection; this may further increase the risk of adverse drug reaction. Drugs such as sulfonamides may be either acetylated to a nontoxic metabolite or oxidized via the cytochrome P-450 system to form a reactive intermediate. Most drug metabolism is accomplished via acetylation although this depends on genetic factors. Distinct phenotypes of "rapid" and "slow" acetylators exist; rapid acetylators may metabolize up to 75% of drugs with this pathway whereas slow acetylators rely more heavily on the cytochrome P-450 system. Studies have shown slow acetylators to be at increased risk for adverse drug reactions. One study investigated the phenotypes of 21 AIDS patients and noted adverse reactions to dapsone in 46% of slow acetylators (7 of 15 patients) but in only 17% of rapid acetylators (1 of 6 patients).¹⁸⁴ We calculated no statistical difference for this study ($p = .34$), but this could be due to the small sample size.

Glutathione is a "scavenger" antioxidant that participates in redox reactions and works to decrease circulating levels of toxic substances. According to the hapten hypothesis, circulating drug metabolites may bind to proteins large enough to be recognized by immune cells as foreign and subsequently elicit an inappropriate immune response. Glutathione may help prevent this series of events. Glutathione and cysteine, its metabolic precursor, are found in significantly lower levels in lymphocytes and serum samples of HIV-positive individuals.^{184,185}

Management

Management options for patients with adverse cutaneous drug reactions depend on several factors, including the type and severity of reaction involved, the offending drug, and the drug's necessity in the patient's overall medical management. For mild morbilliform rashes, as is often the case with TMP-SMX and other antimicrobial reactions, patients may often be "treated through" the rash and may complete a full course of the drug. For example, more than 90% of 36 patients with drug-induced rash from delavirdine were able to continue therapy.⁵⁵ Another study of 18 patients with adverse reactions to cotrimoxazole found that 67% of patients ($n = 12$) could be successfully treated through the reaction.¹ Concomitant steroid administration may decrease the duration and incidence of rash; this TMP-SMX study and others⁹ found a

protective benefit for corticosteroids in patients with cotrimoxazole-related rash. Prednisone therapy (initially 40 mg orally [PO] every 12 hours) prior to antibiotic (TMP-SMX or dapsone) administration is currently recommended for acutely ill patients (ie, those with an arterial blood oxygen level of less than 70 mm Hg) with PCP.¹⁵

The use of steroids in the management of other drug reactions has had mixed results. Extended (8-week) courses of corticosteroids were successfully used to manage three HIV-infected patients with multiple cutaneous drug reactions; steroids facilitated the introduction of antiretroviral therapy that was not previously tolerated in two of these patients.¹⁸⁶ Prednisone therapy also enabled a patient with multiple hypersensitivity reactions to protease inhibitors to continue saquinavir use without significant complication.¹⁸⁷ However, prednisolone has been found not to be helpful in preventing the hypersensitivity reaction to abacavir,¹⁸⁸ and Roujeau and colleagues demonstrated that corticosteroids pose their own intrinsic risk for SJS, having a multivariate relative risk of 4.4 (95% CI, 1.9–10.0).¹¹⁵

Desensitization protocols may also be appropriate for some drug regimens. Kura developed a desensitization regimen for eight HIV-infected patients who developed SJS while on antituberculosis therapy. A 4-week sequential re-introduction (with escalating doses of ethambutol in the first week, INH in the second week, rifampin in the third week, and pyrazinamide in the fourth week) allowed 7 of 8 patients to resume four-drug therapy without consequence.¹⁵³

As nevirapine is highly effective in both reducing viral load and improving CD4 counts, there has been widespread interest in managing and preventing the adverse cutaneous effects of this drug. Initial trials demonstrated that a 2- to 4-week lead-in period of decreased dosage (200 mg PO every day [qd]) prior to the full dosage (400 mg qd) decreased the incidence of morbilliform rash from 48% to 18% (Cheesman, 1993);¹⁸⁹ a 2-week lead-in dose is now standard practice for nevirapine use. However, Fagot and colleagues concluded that this lead-in period was not helpful for the prevention of SJS or TEN; in 15 patients with SJS or TEN secondary to nevirapine use, the median time from the start of drug therapy to the onset of disease was 12 days.⁵⁷ One trial demonstrated a protective effect for corticosteroids against nevirapine rash,¹⁹⁰ but numerous subsequent studies found no effect or found a paradoxical increase in the rash rate.¹⁹¹ Demoly and colleagues suggested a possible mechanism for this observation when they noted that nevirapine is metabo-

lized by CYP450-3A, which is induced by glucocorticoids.⁴⁶ They hypothesized that steroids may increase nevirapine metabolism and production of reactive metabolites, leading to increased rash. A recent study also found no protective benefit against nevirapine rash for the antihistamine cetirizine; rash occurred in 9.6% (10) of 104 patients who were taking 10 mg of cetirizine daily versus 12.5% (12) of 96 patients in the placebo group (OR, 0.75; 95% CI, 0.31–1.81; $p = .5$).¹⁹²

In 2000, the European Agency for Evaluation of Medicinal Products warned that nevirapine must be permanently discontinued after a serious cutaneous reaction.⁵⁷ The ability to switch from one NNRTI to another after an adverse reaction is an important issue because these drugs are part of preferred HAART regimens and because there are only three from which to choose. There appears to be significant cross-reactivity between nevirapine and delavirdine; 6 (75%) of 8 patients with a history of rash secondary to nevirapine use also developed a rash when they were started on delavirdine.⁵⁶ However, nevirapine and efavirenz have distinctly different chemical structures; starting a patient on efavirenz after a documented rash reaction to nevirapine appears to be relatively safe.^{60,193} Of nine patients who were switched to efavirenz after a nevirapine reaction, none experienced an occurrence of rash.⁴⁴

The management of patients who experience severe cutaneous drug reactions is challenging. Current treatments for SJS and TEN are largely supportive; these include the withdrawal of the offending drug and management similar to that of burn patients. Studies on steroid management are conflictive, and the use of steroids is currently controversial.^{194,195} It has been suggested that steroids may increase the risk of septicemia in TEN cases.¹⁹⁶ Case reports have suggested benefits from immunosuppressive agents such as cyclosporine.^{197,198} Further research is required for definitive recommendations.

Recently, with the proposal of a Fas–Fas ligand interaction model for the apoptosis of epidermal cells in SJS and TEN, intravenous immunoglobulin (IVIG) has been studied as a possible therapy for SJS and TEN cases. To date, no solid evidence exists to advocate the use of IVIG in the management of these patients. A recent study that treated 34 patients who had SJS or TEN (including 12 patients who had HIV/AIDS) with IVIG found no measurable improvement in outcomes.¹⁹⁹ However, based on this same Fas hypothesis, an AIDS patient with TEN (receiving four-drug TB therapy and TMP-SMX) was recently successfully treated with plasma exchange.¹⁴³ Again, further study is warranted.

Conclusion

Adverse cutaneous reactions are a common complication of drug therapy in HIV-infected patients. Rates of both mild typical drug eruptions and severe mucocutaneous and anaphylactoid reactions are significantly increased in this population. Many of the antimicrobials that commonly cause these reactions are crucial to the medical management of HIV-infected patients; thus, identification of offending agents and proper management are of paramount importance.

References

1. AIDS Epidemic Update; Joint UN Programme in HIV/AIDS and WHO. UNAIDS, a joint program of UNICEF, UNDP, UNFPA, UNESCO, WHO and the World Bank. Geneva, Switzerland: UNAIDS. Dec 2004.
2. Lee BL, Safrin S. Interactions and toxicities of drugs used in patients with AIDS. *Clin Infect Dis* 1992;14:773–9.
3. Zangerle R. Cutaneous drug reactions in HIV-infected patients. *Dermatol Ther* 1999;12:115–30.
4. Rotunda A, Hirsch RJ, Scheinfeld N, Weinberg JM. Severe cutaneous reactions associated with the use of human immunodeficiency virus medications. *Acta Derm Venereol* 2003;83:1–9.
5. Roudier C, Caumes E, Rogeaux O, et al. Adverse cutaneous reactions to trimethoprim–sulfamethoxazole in patients with the acquired immunodeficiency and *Pneumocystis carinii* pneumonia. *Arch Dermatol* 1994;130:1383–6.
6. Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. *J Am Acad Dermatol* 2002;46:284–93.
7. Heller HM. Adverse cutaneous drug reactions in patients with human-immunodeficiency virus-1 infection. *Clin Dermatol* 2000; 18(4):485–9.
8. General characteristics of the CTCAE Grading Scale. Available at: https://webapps.ctep.ncl.nih.gov/webobj/ctc/webhelp/Grading_General_Characteristics.htm (accessed August 2, 2005).
9. Stern RS, Shear NH. Cutaneous reactions to drugs and biological modifiers. In: Arndt KA, LeBoit PE, Robinson JK, Wintroub BU, editors. *Cutaneous medicine and surgery*, Vol 1. Philadelphia: W.B. Saunders; 1998. p. 339.
10. Carr A, Swanson C, Penny R, Cooper DA. Clinical and laboratory markers of hypersensitivity to trimethoprim–sulfamethoxazole in patients with *Pneumocystis carinii* pneumonia and AIDS. *J Infect Dis* 1993;167:180–5.
11. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;331:1272–85.
12. Calabrese LH, Duna GF. Drug-induced vasculitis. *Curr Opin Rheumatol* 1996;8(1):34–40.
13. Calabrese LH, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. *Arthritis Rheum* 1990;33(8):1108–13.
14. Hirsch MS. Azidothymidine. *J Infect Dis* 1988;157:427–31.
15. Sande MA, Eliopoulos GM, Moellering Jr RC, Gilbert DN. *The Sanford guide to HIV/AIDS therapy*. 14th ed. Sperryville, VA: Antimicrobial Therapy, Inc. 2005;21.

16. Fischl MA, Stanley K, Collier AC, et al. Combination and monotherapy with zidovudine and zalcitabine in patients with advanced HIV disease. *Ann Intern Med* 1995;122:24–32.
17. Wassef M, Keiser P. Hypersensitivity to zidovudine: report of a case of anaphylaxis and review of the literature. *Clin Infect Dis* 1995;20:1387–9.
18. Carr A, Penny R, Cooper DA. Allergy and desensitization to zidovudine in patients with acquired immunodeficiency syndrome (AIDS). *J Allergy Clin Immunol* 1993;683–5.
19. Torres RA, Lin RY, Lee M, Barr MR. Zidovudine-induced leukocytoclastic vasculitis. *Arch Intern Med* 1992;152:850–1.
20. Murri R, Antinori A, Camilli G, et al. Fatal toxic epidermal necrolysis induced by zidovudine. *Clin Infect Dis* 1996;23:640–1.
21. Ray AS, Yang Z, Shi J. Insights into the molecular mechanism of inhibition and drug resistance for HIV-1 RT with carbovir triphosphate. *Biochemistry* 2002;41:5150–62.
22. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther* 2001;23:1603–14.
23. Saag MS, Sonnerborg A, Torres RA, et al. Antiretroviral effect and safety of abacavir alone and in combination with zidovudine in HIV-infected adults. *AIDS* 1998;12:F203–9.
24. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000;60:447–79.
25. Symonds W, Cutrell A, Edwards M, et al. Risk factor analysis of hypersensitivity reaction to abacavir. *Clin Ther* 2002;24(4):565–73.
26. Vilar FJ, Naisbitt DJ, Park BK, Pirohamed M. Mechanisms of drug hypersensitivity in HIV-infected patients: the role of the immune system. *J HIV Ther* 2003;8:42–7.
27. Chirouze C, Hustache-Mathieu L, Rougeot C, et al. Risk factors for hypersensitivity in the real world [abstract]. *Pathol Biol* 2004;52:529–33.
28. Clay PG, Rathbun RC, Slater LN. Management protocol for abacavir-related hypersensitivity reaction. *Ann Pharmacother* 2000;34:247–9.
29. Escut L, Liotier JY, Albengres E, et al. Abacavir rechallenge has to be avoided in cases of hypersensitivity reaction. *AIDS* 1999;13:1419–20.
30. Walensky RP, Goldberg JH, Daily JP. Anaphylaxis after rechallenge with abacavir. *AIDS* 1999;13:999–1000.
31. Bossi P, Roujeau JC, Bricaire F, Caumes E. Stevens-Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002;35:902.
32. Richman DD. Antiretroviral activity of emtricitabine, a potent nucleoside reverse transcriptase inhibitor. *Antiviral Ther* 2001;6:83–8.
33. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naïve patients. *JAMA* 2004;292:180–90.
34. Gish RG, Trinh H, Leung N, et al. Safety and antiviral activity of emtricitabine (FTC) for the treatment of chronic hepatitis B infection: a two-year study. *J Hepatol* 2005;43:60–6.
35. Parneix-Spake A, Bastuji-Garin S, Levy Y, et al. Didanosine as probable cause of Stevens-Johnson syndrome. *Lancet* 1992;340:857–8.
36. Herranz P, Fernandez-Diaz ML, de Lucas R, et al. Cutaneous vasculitis associated with didanosine. *Lancet* 1994;344:680.
37. Just M, Carrascosa JM, Ribera M, et al. Dideoxyinosine-associated Ofuji papuloerythroderma in an HIV-infected patient. *Dermatol* 1997;195:410–1.
38. Merigan TC, Skowron G, Bozzette SA. Circulating p24 antigen levels and responses to dideoxycytidine in human immunodeficiency virus (HIV) infections. *Ann Intern Med* 1989;110:189–94.
39. Tancrede-Bohin E, Grange F, Bourmerias I, et al. Hypersensitivity syndrome associated with zalcitabine therapy. *Lancet* 1996;347:971.
40. McNeely MC, Yarochan R, Broder S, Lawley TJ. Dermatologic complications associated with administration of 2,3-dideoxycytidine in patients with human immunodeficiency virus infection. *J Am Acad Dermatol* 1989;21:1213–7.
41. Woolley IJ, Veitch AJ, Harangozo CS, et al. Lichenoid drug eruption to tenofovir in an HIV/hepatitis B virus co-infected patient. *AIDS* 2004;18:1857–8.
42. Smith KJ, Buckley R, Skelton H. Lamivudine (3TC)-induced contact dermatitis. *Cutis* 2000;65:227–9.
43. Metry DW, Lahart CJ, Farmer KL, Hebert AA. Stevens-Johnson syndrome caused by the antiretroviral drug nevirapine. *J Am Acad Dermatol* 2001;44:354–7.
44. Mazhude C, Jones S, Murad S. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *AIDS* 2002;16:1566–8.
45. Spence RA, Kati WM, Anderson KS, Johnson KA. Mechanism of inhibition of HIV-1 reverse transcriptase by nonnucleoside inhibitors. *Science* 1995;267:988–93.
46. Demoly P, Messaad D, Fabre J, et al. Nevirapine-induced cutaneous hypersensitivity reactions and successful tolerance induction. *J Allergy Clin Immunol* 1999;104:504–5.
47. Dodi F, Alessandrini A, Camera M, et al. Stevens-Johnson syndrome in HIV patients treated with nevirapine: two case reports. *AIDS* 2002;16:1197–8.
48. Warren KJ, Boxwell DE, Kim NY, Drolet BA. Nevirapine-associated Stevens-Johnson syndrome. *Lancet* 1998;351:567.
49. Barner A, Myers M. Nevirapine and rashes. *Lancet* 1998;351:1133.
50. Bourezane Y, Salard D, Hoen B, et al. DRESS (drug rash with eosinophilia and systemic symptoms) syndrome associated with nevirapine therapy. *Clin Infect Dis* 1998;27:1321–2.
51. Lanzafame M, Rovere P, de Checchi G, et al. Hypersensitivity syndrome (DRESS) and meningoencephalitis associated with nevirapine therapy. *Scand J Infect Dis* 2001;33:475–6.
52. Claudio GA, Martin AF, Perrino SDD, Velasco AA. DRESS syndrome associated with nevirapine therapy. *Arch Intern Med* 2001;161:2501–2.
53. Knudtson E, Para M, Boswell H, Fan-Havard P. Drug rash with eosinophilia and systemic symptoms syndrome and renal toxicity with a nevirapine-containing regimen in a pregnant patient with human immunodeficiency virus. *Obstet Gynecol* 2003;101:1094–7.
54. Leitz Z, Nadeem A, Choudhary A, et al. Nevirapine-induced hepatitis treated with corticosteroids? *AIDS* 1998;12:1115–7.
55. Davey RT, Chait DG, Reed GF, et al. Randomized, controlled phase I/II trial of combination therapy with delavirdine (U-90152S) and conventional nucleosides in human immunodeficiency virus type-1 infected patients. *Antimicrob Agents Chemother* 1996;40:1657–64.
56. Gangar M, Arias G, O'Brien JG, Kemper CA. Frequency of cutaneous reactions on rechallenge with nevirapine and delavirdine. *Ann Pharmacother* 2000;34:839–42.

57. Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *AIDS* 2001;15:1843–8.
58. Colebunders R, Vanwolleghem T, Meurrens P, Moerman F. Efavirenz-associated Stevens-Johnson syndrome. *Infection* 2004;32:306–7.
59. Bossi P, Colin D, Bricaire F, Caumes E. Hypersensitivity syndrome associated with efavirenz therapy. *Clin Infect Dis* 2000;30:227–8.
60. Dona C, Soriano V, Barreiro P, et al. Toxicity associated to efavirenz in HIV-infected persons enrolled in an expanded access program. *Med Clin* 2000;115:337–8.
61. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. *AIDS* 2001;15:241–3.
62. DiPerri G, Del Bravo P, Concia E, et al. HIV protease inhibitors. *N Engl J Med* 1998;339:773–4.
63. Floridia M, Bucciardini R, Fragola V, et al. Risk factors and occurrence of rash in HIV-positive patients not receiving nonnucleoside reverse transcriptase inhibitor: data from a randomized study evaluating use of protease inhibitors in nucleoside-experienced patients with very low CD4 levels. *HIV Med* 2004;5:1–10.
64. Fung HB, Pecini RA, Brown ST, Gropper CA. Indinavir-associated maculopapular eruption. *Pharmacotherapy* 1999;19:1328–30.
65. Bonfanti P, Capetti A, Riva P, et al. Hypersensitivity reactions during antiretroviral regimens with protease inhibitors. *AIDS* 1997;11:1301–2.
66. Teira R, Zubero Z, Munoz J, et al. Stevens-Johnson syndrome caused by indinavir. *Scand J Infect Dis* 1998;30:634–5.
67. Rijinders B, Kooman J. Severe allergic reaction after repeated exposure to indinavir. *Clin Infect Dis* 1998;26:523–4.
68. Rietsema WJ. Fever, erythroderma, abdominal pain, and renal failure following initiation of indinavir therapy. *Clin Infect Dis* 1997;25:1268–9.
69. Fox PA, Boag FC, Hawkins DA, Francis N. Acute porphyria following commencement of indinavir. *AIDS* 1999;13:622–3.
70. Rachline A, Lariven S, Descamps V, et al. Leukocytoclastic vasculitis and indinavir. *Br J Dermatol* 2000;143:1112–3.
71. Woolley I, Tapley N, Korman T. Sequential cutaneous drug reactions to protease inhibitors in the context of occupational post-exposure prophylaxis. *AIDS* 2003;17:1709.
72. Markowitz M, Saag M, Powderly WG, et al. A preliminary study of ritonavir, an inhibitor of HIV-1 protease to treat HIV-1 infection. *N Engl J Med* 1995;333:1534–9.
73. Gathe JC, Ive PB, Wood RC, et al. 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice daily nelfinavir in naïve HIV-1-infected patients. *AIDS* 2004;18:1529–37.
74. Bachmeyer C, Blum L, Cordier F, et al. Early ritonavir-induced maculopapular eruption. *Dermatology* 1997;195:301–2.
75. Pedneault L, Brothers C, Pagano G, et al. Safety profile and tolerability of amprenavir in the treatment of adult and pediatric patients with HIV infection. *Clin Ther* 2000;22:1378–94.
76. Arvieux C, Tribut O. Amprenavir or fosamprenavir plus ritonavir in HIV infection: pharmacology, efficacy and tolerability profile. *Drugs* 2005;65:633–59.
77. Sax P, Kumar P. Tolerability and safety of HIV protease inhibitors in adults. *J Acquir Immune Defic Syndr* 2004;37:1111–23.
78. Busti AJ, Hall RG, Margolis DM. Atazanavir for the treatment of human immunodeficiency virus infection. *Pharmacotherapy* 2004;24:1732–47.
79. Chapman TM, Plosker GL, Perry CM. Fosamprenavir: a review of its use in the management of antiretroviral therapy-naïve patients with HIV infection. *Drugs* 2004;64:2101–24.
80. GlaxoSmithKline. Lexiva (fosamprenavir calcium) tablets: prescribing information (US). Available at: http://us.gsk.com/products/assets/us_lexiva.pdf (accessed August 2, 2005).
81. Fortuny C, Vicente M, Medina M, Gonzalez-Ensenat A. Rash as a side effect of nelfinavir in children. *AIDS* 2000;14:335–6.
82. Roca B, Lapuebla C, Roig B. Porphyria cutanea tarda induced by nelfinavir [abstract]. *Antiviral Ther* 2001;6 Suppl 4:71.
83. Smith K, Yeager J, Skelton H. Fixed drug eruptions to human immunodeficiency virus-1 protease inhibitor. *Cutis* 2000;66:2–32.
84. Ball RA, Kinchelov T. Injection site reactions with the HIV-1 fusion inhibitor enfuvirtide. *J Am Acad Dermatol* 2003;49:826–31.
85. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J* 2004;23:713–8.
86. Shahar E, Moar C, Pollack S. Successful desensitization of enfuvirtide-induced skin hypersensitivity reaction. *AIDS* 2005;19:451–2.
87. Clotet B, Raffi F, Cooper D, et al. Clinical management of treatment-experienced HIV-infected patients with the fusion inhibitor enfuvirtide: consensus recommendations. *AIDS* 2004;18:1137–46.
88. Balfour HH Jr, Bean B, Sachs GW, Mitchell CD. Acyclovir: an effective antiviral. *Minn Med* 1981;64(12):739–43.
89. Arndt KA. Adverse reactions to acyclovir: topical, oral, and intravenous. *J Am Acad Dermatol* 1988;18:188–90.
90. Robinson GE, Weber J, Griffiths C, et al. Cutaneous adverse reactions to acyclovir: case reports. *Genitourin Med* 1985;61:62–3.
91. Goday J, Aguirre A, Ibarra NG, Eizaguirre X. Allergic contact dermatitis from acyclovir. *Contact Dermatitis* 1991;24:380–1.
92. Gola M, Francalanci S, Brusi C, et al. Contact dermatitis to acyclovir. *Contact Dermatitis* 1989;20:394–5.
93. Balfour HH Jr, Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med* 1983;308:1448–53.
94. Armingaud P, Arsac P, Kerdraon R, Esteve E. Localized bullous eruption after intravenous injection of acyclovir: toxic or immunoallergic mechanism? [abstract]. *Ann Dermatol Venerol* 2000;127:496–8.
95. Fazal BA, Turett GS, Justman JE, et al. Stevens-Johnson syndrome induced by treatment with acyclovir. *Clin Infect Dis* 1995;21:1038–9.
96. Saint-Marc T, Fournier F, Touraine JL, Marneff E. Uvula and oesophageal ulcerations with foscarnet. *Lancet* 1992;340:970–1.
97. Wharton JR, Laughlin C, Cockerell CJ. Toxic epidermal necrolysis occurring as a consequence of treatment with foscarnet. *Cutis* 1999;63:333–5.
98. Blanshard C. Generalized cutaneous rash associated with foscarnet usage in AIDS. *J Infect* 1991;23:336–7.
99. Green ST, Nathwani D, Goldberg DJ, et al. Generalized rash associated with foscarnet usage in AIDS. *J Infect* 1990;21:227–8.
100. Roos TC, Albrecht H. Foscarnet-associated eosinophilic folliculitis in a patient with AIDS. *J Am Acad Dermatol* 2001;44:546–7.

101. Poynard T, Yuen MF, Ratzu V, Lai CL. Viral hepatitis C. *Lancet* 2003;362:2095–100.
102. Moore MM, Elpern DJ, Carter DJ. Severe, generalized nummular eczema secondary to interferon alfa-2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Arch Dermatol* 2004;140:215–7.
103. Sookoian S, Neglia V, Castano G, et al. High prevalence of cutaneous reactions to interferon alfa plus ribavirin combination therapy in patients with chronic hepatitis C virus. *Arch Dermatol* 1999;135:1000–1.
104. Sidhu-Malik NK, Kaplan AL. Multiple fixed drug eruption with interferon/ribavirin combination therapy for hepatitis C virus infection. *J Drugs Dermatol* 2003;2:570–3.
105. Hurst EA, Mauro T. Sarcoidosis associated with pegylated interferon alfa and ribavirin treatment for chronic hepatitis C: a case report and review of the literature. *Arch Dermatol* 2005;141:865–8.
106. Manjon-Haces JA, Vazquez-Lopez F, Gomez-Diez S, et al. Adverse cutaneous reactions to interferon alfa-2b plus ribavirin therapy in patients with chronic hepatitis C. *Acta Derm Venereol* 2001;81:223.
107. Bessis D, Charron A, Rouzier-Panis R, et al. Necrotizing cutaneous lesions complicating treatment with pegylated-interferon alfa in an HIV-infected patient. *Eur J Dermatol* 2002;12:99–102.
108. Ribavirin ARC Study Group: Multicenter clinical trial of oral ribavirin in symptomatic HIV-infected patients. *J Acquir Immune Defic Syndr* 1993;6:32–41.
109. Lorenzi S, D'Antuono A, Iorizzo M, Tosti A. Skin rash and splinter hemorrhages from ganciclovir. *J Dermatolog Treat* 2003;14:177–8.
110. Chachoua A, Dieterich D, Krasinski K, et al. 9-(1, 3-dihydroxy-2-propoxymethyl) guanine (ganciclovir) in the treatment of cytomegalovirus gastrointestinal disease with the acquired immunodeficiency syndrome. *Ann Intern Med* 1987;107:133–7.
111. Buhles WC, Mastre BJ, Tinker AJ, et al. Ganciclovir treatment of life- or sight-threatening cytomegalovirus infection: experience in 314 immunocompromised patients. *Rev Infect Dis* 1988;10:S495–506.
112. Lammintausta K, Makela L, Kalimo K. Rapid systemic valaciclovir reaction subsequent to acyclovir contact allergy. *Contact Dermatitis* 2001;45:181.
113. Lalezari J, Lindley J, Walmsley S, et al. A safety study of oral valganciclovir maintenance treatment of cytomegalovirus retinitis. *J Acquir Immune Defic Syndr* 2002;30:392–400.
114. Lalezari J, Schacker T, Feinberg J, et al. A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Infect Dis* 1997;176:892–8.
115. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;333:1600–7.
116. Azon-Masoliver A, Vilaplana J. Fluconazole-induced toxic epidermal necrolysis in a patient with human immunodeficiency virus infection. *Dermatology* 1993;187:268–9.
117. Bradbury BD, Jick SS. Itraconazole and fluconazole and certain rare, serious adverse events. *Pharmacotherapy* 2002;22:697–700.
118. De Beule K, Lubin G, Cauwenbergh G. Safety aspects of itraconazole therapy in vaginal candidosis, dermatomycosis, and onychomycosis. A review. *Curr Ther Res* 1991;49:814–7.
119. Tucker RM, Haq Y, Denning DW, Stevens DA. Adverse events associated with itraconazole in 189 patients on chronic therapy. *J Antimicrob Chemother* 1990;26:561–6.
120. Heymann W, Manders SM. Itraconazole-induced acute generalized exanthemic pustulosis. *J Am Acad Dermatol* 1995;32:130–1.
121. Kotani S, Hirose S, Nijja K, et al. Anaphylaxis to flucytosine in a patient with AIDS. *JAMA* 1988;260:3275–6.
122. Dewerd S, Machet L, Jan-Lamy V, et al. Stevens-Johnson syndrome after albendazole. *Acta Derm Venereol* 1997;77:411.
123. Emberger M, Lechner AM, Zelger B. Stevens-Johnson syndrome associated with malarone antimalarial prophylaxis. *Clin Infect Dis* 2003;37:e5–7.
124. Ajonuma LC, Chika LC. Outbreak of Stevens-Johnson syndrome among Filipino overseas contract workers using mebendazole for helminthiasis prophylaxis. *Trop Doct* 2000;30:57.
125. Smith HR, Croft AM, Black MM. Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports. *Clin Exp Dermatol* 1999;24:249–54.
126. Johnson-Reagan L, Bahna SL. Severe drug rashes in three siblings simultaneously. *Allergy* 2003;58:445–7.
127. Egan CA, Grant WJ, Morris SE, et al. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. *J Am Acad Dermatol* 1999;40:458–61.
128. Robinson HM, Samorodin CS. Thiabendazole-induced toxic epidermal necrolysis. *Arch Dermatol* 1976;112:1757–60.
129. Knowles S, Choudhury T, Shear NH. Metronidazole hypersensitivity. *Ann Pharmacother* 1994;28:325–6.
130. Pedrosa C, Costa H, Oliveira G, et al. Anaphylaxis to povidone in a child. *Pediatr Allergy Immunol* 2005;16:361–2.
131. Chen KT, Twu SJ, Chang HJ, Lin RS. Outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with mebendazole and metronidazole use among Filipino laborers in Taiwan. *Am J Public Health* 2003;93:489–92.
132. Minggang C, Sui F, Xiangjin H, Huimin W. A retrospective survey on side effects of praziquantel among 25,693 cases of schistosomiasis japonica. *Southeast Asian J Trop Med Public Health* 1983;14:495–500.
133. Salih SY, Abdalla RE. Symptomatic giardiasis in Sudanese adults and its treatment with tinidazole. *J Trop Med Hyg* 1977;80:11–3.
134. Fischer P, Kipp W, Kabwa P, Buttner DW. Onchocerciasis and human immunodeficiency virus in western Uganda: prevalences and treatment with ivermectin. *Am J Trop Med Hyg* 1995;53:171–8.
135. World Health Organization: Joint HIV/tuberculosis interventions. Available at: <http://www.who.int/hiv/topics/tb/tuberculosis/en> (accessed July 29, 2005).
136. Chintu C, Luo C, Bhat G, et al. Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-1. *Arch Dis Child* 1993;68:665–8.
137. Small PM, Schecter GF, Goodman PC, et al. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1991;324:289–94.
138. Chaisson RE, Schecter GF, Theuer CP, et al. Tuberculosis in patients with the acquired immunodeficiency syndrome. *Am Rev Respir Dis* 1987;136:570–4.
139. Luo C, Chintu C, Bhat G, et al. Human immunodeficiency virus type-1 infection in Zambian children with tuberculosis: changing

- seroprevalence and evaluation of a thiacetazone-free regimen. *Tuber Lung Dis* 1994;75:110–5.
140. Wirima JJ, Harries AD. Stevens-Johnson syndrome during anti-tuberculosis chemotherapy in HIV-seropositive patients: report on six cases. *East Afr Med J* 1991;68:64–6.
 141. Dukes CS, Sugarman J, Cegielski JP, et al. Severe cutaneous hypersensitivity reactions during the treatment of tuberculosis in patients with HIV infection in Tanzania. *Trop Geogr Med* 1992;44:308–11.
 142. Kuaban C, Bercion R, Koula-Shiro S. Current HIV seroprevalence rate and incidence of adverse skin reactions in adults with pulmonary tuberculosis receiving thiacetazone-free antituberculosis treatment in Yaounde, Cameroon. *Cent Afr J Med* 1998;44:34–7.
 143. Nomura T, Abe R, Fujimoto K, et al. Plasma exchange: a promising treatment for toxic epidermal necrolysis with AIDS. *AIDS* 2004;18:2446–8.
 144. Bomb BS, Purohit SD, Bedi HK. Stevens-Johnson syndrome caused by isoniazid. *Tubercle* 1976;57:229–30.
 145. Ferguson GC, Nunn AJ, Fox W, et al. A second international co-operative investigation into thiacetazone side effects. Rashes on two thiacetazone-containing regimens. *Tubercle* 1971;52:166.
 146. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. *JAMA* 2000;283:1445–50.
 147. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med* 2003;167:1472–7.
 148. Van der Ven AJM, Koopmans PP, Vree TB, Van der Meer JWM. Drug intolerance in HIV disease. *J Antimicrob Chemother* 1994;34:1–5.
 149. Holdiness MR. Adverse cutaneous reactions to antituberculosis drugs. *Int J Dermatol* 1985;24:280–5.
 150. Nyirenda R, Gill GV. Stevens-Johnson syndrome due to rifampicin. *Br Med J* 1977;2:1189.
 151. Prazuck T, Fisch A, Simonnet F, Noat G. Lyell's syndrome associated with rifampicin therapy of tuberculosis in an AIDS patient. *Scand J Infect Dis* 1990;22:629.
 152. Wurtz RM, Abrams D, Becker S, et al. Anaphylactoid drug reactions to ciprofloxacin and rifampicin in HIV-infected patients. *Lancet* 1989;1:955–6.
 153. Kura MM, Hira SK. Reintroducing antituberculosis therapy after Stevens-Johnson syndrome in human immunodeficiency virus-infected patients with tuberculosis: role of desensitization. *Int J Dermatol* 2001;40:481–4.
 154. Pegram PS, Mountz JD, O'Bar PR. Ethambutol-induced toxic epidermal necrolysis. *Arch Intern Med* 1981;141:1677–8.
 155. Nunn P, Kibuga D, Gathua S, et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991;377:627–30.
 156. Hira SK, Wadhawan D, Kamanga J, et al. Cutaneous manifestations of human immunodeficiency virus in Lusaka, Zambia. *J Am Acad Dermatol* 1988;19:451–7.
 157. Coopman SA, Stern RS. Cutaneous drug reactions in human immunodeficiency virus infection. *Arch Dermatol* 1991;127:714–7.
 158. Jick H. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis* 1982;4:426–8.
 159. Kovacs JA, Hiemenz JW, Nacher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med* 1984;100:663–71.
 160. Ong EL, Mandal BK. Multiple drug reactions in a patient with AIDS. *Lancet* 1989;2:976–7.
 161. Johnson MP, Goodwin SD, Shands JW Jr. Trimethoprim-sulfamethoxazole anaphylactoid reactions in patients infected with AIDS: case reports and literature review. *Pharmacotherapy* 1990;10:413–6.
 162. Saiag P, Caumes E, Chosidow O, et al. Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. *J Am Acad Dermatol* 1992;26:567–74.
 163. Schmidt-Westhausen A, Grunewald T, Reichart PA, Pohle HD. Oral manifestations of toxic epidermal necrolysis in patients with AIDS: report of five cases. *Oral Dis* 1998;4:90–4.
 164. Miller KD, Lobel HO, Satriale RF, et al. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986;35:451–8.
 165. Carrion-Carrion C. Fatal Stevens-Johnson syndrome in an AIDS patient treated with sulfadiazine. *Ann Pharmacother* 1999;33:379–80.
 166. Caumes E, Bocquet H, Guernonprez G, et al. Adverse cutaneous reactions to pyrimethamine/sulfadiazine and pyrimethamine/clindamycin in patients with AIDS and toxoplasmic encephalitis. *Clin Infect Dis* 1995;21:656–8.
 167. Pertel P, Hirschtick R. Adverse reactions to dapsone in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1994;18:630–2.
 168. Shilad A, Predanic M, Perni SC, et al. Human immunodeficiency virus, pregnancy, and Stevens-Johnson syndrome. *Obstet Gynecol* 2005;105:1254–6.
 169. Vidal C, Gonzalez Quintela A, Fuente R. Toxic epidermal necrolysis due to vancomycin. *Ann Allergy* 1992;68:345–7.
 170. Porteous DM, Berger TG. Severe cutaneous drug reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in human immunodeficiency virus infection. *Arch Dermatol* 1991;127:740–1.
 171. Livasy CA, Kaplan AM. Ciprofloxacin-induced toxic epidermal necrolysis: a case report. *Dermatology* 1997;195:173–5.
 172. Peters B, Pinching AJ. Fatal anaphylaxis associated with ciprofloxacin in a patient with AIDS related complex. *Br Med J* 1989;298:605.
 173. Rzany B, Hamouda O, Schopf E. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with acquired immune deficiency syndrome in Germany. *Arch Dermatol* 1993;129:1059.
 174. Battegay M, Opravil M, Wuthrich B, Luthy R. Rash with amoxicillin-clavulanate therapy in HIV-infected patients. *Lancet* 1989;2:1100.
 175. Gonzalez-Martin G, Yanez CG, Gonzalez-Contreras L, Labarca J. Adverse drug reactions (ADRs) in patients with HIV infection. A prospective study. *Int J Clin Pharmacol Ther* 1999;37:34–40.
 176. Rousseau F, Pueyo S, Morlat P, et al. Increased risk of toxoplasmic encephalitis in human immunodeficiency virus-infected patients with pyrimethamine-related rash. *Clin Infect Dis* 1997;24:396–402.

177. Smith KJ, Skelton HG, Yeager J, et al. Increased drug reactions in HIV-1-positive patients: a possible explanation based on patterns of immune dysregulation seen in HIV-1 disease. *Clin Exp Dermatol* 1997;22:118–23.
178. Wright DN, Nelson RP, Ledford DK, et al. Serum IgE and human immunodeficiency virus (HIV) infection. *J Allergy Clin Immunol* 1990;85:445–52.
179. Isreal-Bioet D, Labrousse R, Tourani JM, et al. Elevation of IgE in HIV-infected subjects: a marker of poor prognosis. *J Allergy Clin Immunol* 1992;89:68–75.
180. Descamps V, Valance A, Edlinger C, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001;137:301–4.
181. Tohyama M, Yahata Y, Yasukawa M, et al. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch Dermatol* 1998;134:1113–7.
182. Suzuki Y, Inagi R, Aono T, et al. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. *Arch Dermatol* 1998;134:1108–12.
183. Uetrecht JP. New concepts in immunology relevant to idiosyncratic drug reactions: the “danger hypothesis” and innate immune system. *Chem Res Toxicol* 1999;12:387–95.
184. Ruichen G, Thormann W, Lauterberg B. Relationship between high incidence of adverse dapsone reactions and slow acetylate phenotype or low plasma/lymphocyte glutathione level. *Chin Med J* 1996;109:933–6.
185. Rose EW, McCloskey WW. Glutathione in hypersensitivity to trimethoprim/sulfamethoxazole in patients with HIV infection. *Ann Pharmacother* 1998;32:381–3.
186. Dolev J, Reyter I, Maurer T. Treatment of recurring cutaneous drug reactions in patients with human immunodeficiency virus 1 infection. *Arch Dermatol* 2004;140:1051–3.
187. Prins JM, Schellekens PTA, Reiss P. Continued therapy with HIV-1 protease inhibitors, despite previous hypersensitivity reactions, through coadministration of prednisone. *Scand J Infect Dis* 1998;30:612–3.
188. Wit FW, Wood R, Horban A, et al. Prednisolone does not prevent hypersensitivity reactions in antiretroviral drug regimens containing abacavir with or without nevirapine. *AIDS* 2001;15:2423–9.
189. Cheesman SH, Murphy RL, Saag MS, Havlir D. Safety of high-dose nevirapine (NVP) after 200 mg/D lead-in. Presented at the IX International Conference on AIDS/III STD World Conference. Berlin, 1993.
190. Barreiro P, Soriano V, Casas E, et al. Prevention of nevirapine-associated exanthema using slow dose escalation and/or corticosteroids. *AIDS* 2000;14:2153–7.
191. Rey D, Partisani M, Krantz V, et al. Prednisolone does not prevent the occurrence of nevirapine-induced rashes. *AIDS* 1999;13:2307.
192. Launay O, Roudiere L, Boukli N. Assessment of cetirizine, an antihistamine, to prevent cutaneous reactions to nevirapine therapy: results of the Viramune-Zyrted double-blind, placebo-controlled trial. *Clin Infect Dis* 2004;38:e67–72.
193. Soriano V, Dona C, Barreiro P, Gonzalez-Lahoz J. Is there cross-toxicity between nevirapine and efavirenz in subjects developing rash? *AIDS* 2000;14:1672–3.
194. Guibal F, Bastuji-Garin S, Choisdow O, et al. Characteristics of toxic epidermal necrolysis in patients undergoing long-term glucocorticoid therapy. *Arch Dermatol* 1995;131:669–72.
195. van der Meer JB, Schuttelar ML, Toth GG, et al. Successful dexamethasone pulse therapy in a toxic epidermal necrolysis (TEN) patient featuring recurrent TEN to oxazepam. *Clin Exp Dermatol* 2001;26:654–6.
196. Paquet P, Pierard GE, Quatresooz P. Novel treatments for drug-induced toxic epidermal necrolysis (Lyell’s syndrome). *Int Arch Allergy Immunol* 2005;136:205–16.
197. Renfro L, Grant-Kels JM, Darman LA. Drug induced toxic epidermal necrolysis treated with cyclosporine. *Int J Dermatol* 1989;28:441–4.
198. Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000;48:473–8.
199. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2003;139:33–6.