

Diagnosis and management of HIV drug hypersensitivity

Carla M. Davis, MD, and William T. Shearer, MD, PhD *Houston, Tex*

Drug hypersensitivity reactions are an important cause of morbidity in HIV-infected patients who take complex medication regimens. Correct diagnosis and management of these reactions are essential in the clinical care of HIV disease. Trimethoprim-sulfamethoxazole, abacavir, nevirapine, atazanavir, and enfuvirtide can all cause hypersensitivity rashes. In this review, we discuss the evidence for immunologic mechanisms of hypersensitivity reactions to HIV medications, the clinical characteristics of these reactions, and guidelines that currently exist for their identification and management. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Human immunodeficiency virus, drug hypersensitivity, trimethoprim-sulfamethoxazole, antiretroviral agents, protease inhibitor, fusion inhibitor, integrase inhibitor

The diagnosis and management of drug hypersensitivity HIV-infected patients is particularly difficult because of the multiple medication regimens that are used to treat patients. Hypersensitivity reactions have been described with many antiretroviral agents (Table I) and antibiotics used to treat opportunistic infections. Drug-related rashes occur at a much higher frequency in HIV-positive patients than the general population. The reasons proposed are multifactorial, including immune hyperactivation, changes in drug metabolism, patient cytokine profiles, oxidative stress, and genetic predisposition.¹ It is well known that IgE levels increase when HIV disease progresses,² and there is an extraordinary incidence of skin rashes (as many as 50% of patients) with HIV medications. Since the introduction of highly active antiretroviral therapy in the late 1990s, hypersensitivity to antiretroviral agents has increased.

The chemical factors and drug administration factors that can predispose patients to drug hypersensitivity include a large molecular mass, specific immunologic structural moieties, reactive metabolites, parenteral or topical administration, a longer

Abbreviations used

PI: Protease inhibitor
SJS: Stevens-Johnson syndrome
TEN: Toxic epidermal necrolysis
TMP-SMX: Trimethoprim-sulfamethoxazole

duration of exposure, and frequent, repetitive courses of therapy.^{3,4} Patient predictors of drug reactions include genetic polymorphisms of metabolic enzyme pathways that prolong drug clearance. EBV-infected, atopic children or young adults are at highest risk.³

HYPERSENSITIVITY TO TRIMETHOPRIM-SULFAMETHOXAZOLE

Since the discovery of HIV in 1983, cutaneous drug reactions have been noted to occur with increased frequency in patients with AIDS. With the development of immunosuppression and *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX), hypersensitivity became well described. Between 44% and 83% of HIV-infected individuals experience some form of adverse reactions associated with TMP-SMX, whereas these events occur in less than 10% in the general population.⁴ These adverse events include rash, fever, neutropenia, thrombocytopenia, nephritis, and transaminase elevation.⁵ In the treatment of *Pneumocystis jiroveci* pneumonia in patients with AIDS compared with other immunodeficient states, the incidence of adverse reactions to TMP-SMX was 65% in the patients with AIDS versus 12% in other immunodeficient states.⁶ Only 13% of patients with hypersensitivity reactions with intravenous TMP-SMX experienced reactions to oral TMP-SMX requiring discontinuation of the medication.⁷ The range of sulfonamide-induced cutaneous drug reactions includes urticaria, macular exanthemas, eczematous and fixed drug eruptions, erythema multiforme, and severe and life-threatening manifestations such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Many of these cutaneous drug reactions are observed 7 days after drug initiation, suggesting idiosyncratic, delayed hypersensitivity reactions.⁸ Risk factors include higher CD4⁺ T-cell count >20 × 10⁶ cells/L,⁹ CD4:CD8 ratio <0.10, treatment for less than 14 days,¹⁰ and possibly a slow acetylation phenotype.¹¹ Male sex, higher CD4⁺ T-cell percentage, a history of syphilis, and a higher total protein are also associated with cutaneous reactions to TMP-SMX.¹² The treatment of patients with corticosteroids within the first 24 hours of TMP-SMX treatment decreases the incidence of hypersensitivity.¹³

HIV has also been found to be a risk factor for rash with antimicrobials used to treat tuberculosis such as isoniazid, pyrazinamide, and rifampin.¹⁴ Five cases of TEN and 3 cases of

From the Department of Pediatrics, Baylor College of Medicine.

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Reprint requests: Carla M. Davis, MD, Division of Allergy and Immunology, Department of Pediatrics, Baylor College of Medicine, 6621 Fannin St, MC FC 330.01, Houston, TX 77030-2399. E-mail: cmdavis@texaschildrenshospital.org.

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TABLE I. Approved medications to treat HIV infection

Drug name	Brand name	Molecular weight	Elimination pathway	Half-life (h)
Nucleoside reverse transcriptase inhibitors				
Zidovudine (ZDV)	Retrovir	267	Hepatic	0.5-3
Didanosine (DDI)	Videx	236	Renal	1.5
Abacavir (ABC)	Ziagen	671	Hepatic (alcohol dehydrogenase and glucuronyl transferase)	1.5
Lamivudine (3TC)	Epivir	229	Renal	5-7
Tenofovir (TDF)	Viread	636	Renal	17
Emtricitabine (FTC)	Emtriva	247	Renal	10
Stavudine (D4T)	Zerit	224	40% renal 60% by endogenous pathways	1.6
Nonnucleoside reverse transcriptase inhibitors				
Zalcitabine (DDC)	Hivid	211	Renal	2
Nevirapine (NVP)	Viramune	266	Hepatic (cytochrome P450)	45
Efavirenz (EFV)	Sustiva	316	Hepatic (cytochrome P450)	52-76
Delavirdine (DLV)	Rescriptor	553	Hepatic	2-11
Protease inhibitors				
Nelfinavir (NFV)	Viracept	664	Hepatic	3.5-5
Amprenavir (APV)	Agenerase	506	Hepatic	7-10.5
Fosamprenavir (FPV)	Lexiva	633	Hepatic	7.7
Indinavir (IDV)	Crixivan	712	Hepatic	1.8
Saquinavir (SQV)	Invirase	767	Hepatic	7
Lopinavir (LPV)	Kaletra	629	Hepatic	5-6
Atazanavir (ATV)	Reyataz	705	Hepatic	7
Tipranavir (TPV)	Aptivus	603	Hepatic	4.8-6
Ritonavir (RTV)	Norvir	721	Hepatic	3-5
Darunavir (TMC114)	Prezista	594	Hepatic	15 (with ritonavir)
Fusion inhibitor				
Enfuvirtide (T-20)	Fuseon	4492	Unknown, thought to be through amino acid catabolism	3.8
Integrase inhibitor				
Raltegravir (MK-0518)	Isentress	444	Hepatic (glucuronosyl transferase) and renal	7-12

SJS were reported in patients with AIDS after the initiation or restart of rifampin-isoniazid combination therapy.¹⁵

Pathogenesis

The exact pathogenesis of TMP-SMX hypersensitivity is not completely understood. There is likely involvement of 1 or more metabolic, toxic, and immunologic factors. In normal hosts, 45% to 70% of sulfamethoxazole is acetylated by N-acetyltransferase to N-acetylsulfamethoxazole, and only a small fraction of sulfamethoxazole undergoes oxidation by cytochrome P450 to sulfamethoxazole hydroxylamine. Sulfamethoxazole hydroxylamine is a reactive metabolite and may spontaneously form nitro-sulfamethoxazole. The nitroso metabolite may covalently link to host proteins, causing direct cellular toxicity, which leads to immune responses. It has been suggested that when glutathione levels are low and there is a deficiency in the ability to detoxify reactive metabolites, patients are at higher risk for hypersensitivity. Lymphocytes from immunocompetent patients with a history of TMP-SMX hypersensitivity display higher sulfamethoxazole cytotoxicity than those of control subjects.^{8,16}

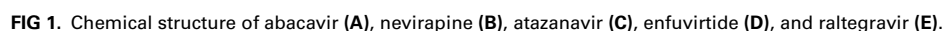
Desensitization

Several desensitization protocols have been developed for use in both adults and children with TMP-SMX hypersensitivity. Drug desensitization is defined as the conversion of a state of drug hypersensitivity to a nonreactive state by the cautious introduction of increasing amounts of antigen at regular time intervals over a relatively short period (4-6 hours). Graded challenges

involve increasing the amount of antigen over a longer period (from 48 hours to 14 days). These are in contrast to rechallenge, in which the entire dose of an agent is given at 1 time to the patient. The success percentages of desensitization with cotrimoxazole reported in the literature are generally higher for desensitization or graded challenges than for rechallenge. Desensitization and graded challenge success percentages vary from 80% to 100%. It is likely that the drug-induced reactions in patients with AIDS are non-IgE-mediated, and it is not known why or how the desensitization or challenge protocols work in these patients. Many of the desensitization protocols used with TMP-SMX are more similar to cautious graded challenge protocols rather than true desensitization protocols. Desensitization is preferable to rechallenge in patients with HIV with allergy to sulfonamides given the fact that desensitization is less dangerous and there are few data in the literature regarding rechallenge.¹⁷

HYPERSENSITIVITY TO ANTIRETROVIRAL AGENTS

Current Food and Drug Administration–approved antiretroviral medications are classified in 3 categories: reverse transcriptase inhibitors, protease inhibitors (PIs), and fusion inhibitors (Table I). A fourth class of antiretroviral agents, the integrase inhibitors, is just now entering clinical trials. HIV replicates by binding to the CD4⁺ receptor and a chemokine receptor and fusing to the host cell. The fusion inhibitor enfuvirtide blocks this step. After this initial step, reverse transcriptase converts single-stranded HIV RNA to double-stranded HIV DNA. The nucleoside and nonnucleoside reverse transcriptase inhibitors prevent this action.



treated patients (Fig 1, A).^{18,19} Its appearance is unrelated to dose, and its onset is generally within 9 to 11 days after the initiation of therapy.²⁰ Symptoms can include fever, rash, malaise, fatigue, tachypnea, pharyngitis, cough, wheezing, nausea, vomiting, and diarrhea. Cutaneous reactions, maculopapular or urticarial, only occur in 66% of abacavir-treated patients.¹⁹ Rhabdomyolysis has been described as a case report.²⁰ In 90% of the cases, hypersensitivity reactions occur within the first 6 weeks after initiation of the drug and, after an initial reaction, rechallenge with abacavir results in the reappearance of symptoms within hours of re-exposure. Hypotension occurs in 25% of the rechallenge reactions. Among patients who have received abacavir in clinical trials, the mortality rate is 0.03%. Given the severity of reactions on rechallenge, hypersensitivity to abacavir is an absolute contraindication to subsequent treatment with any formulation that includes it.²¹⁻²³

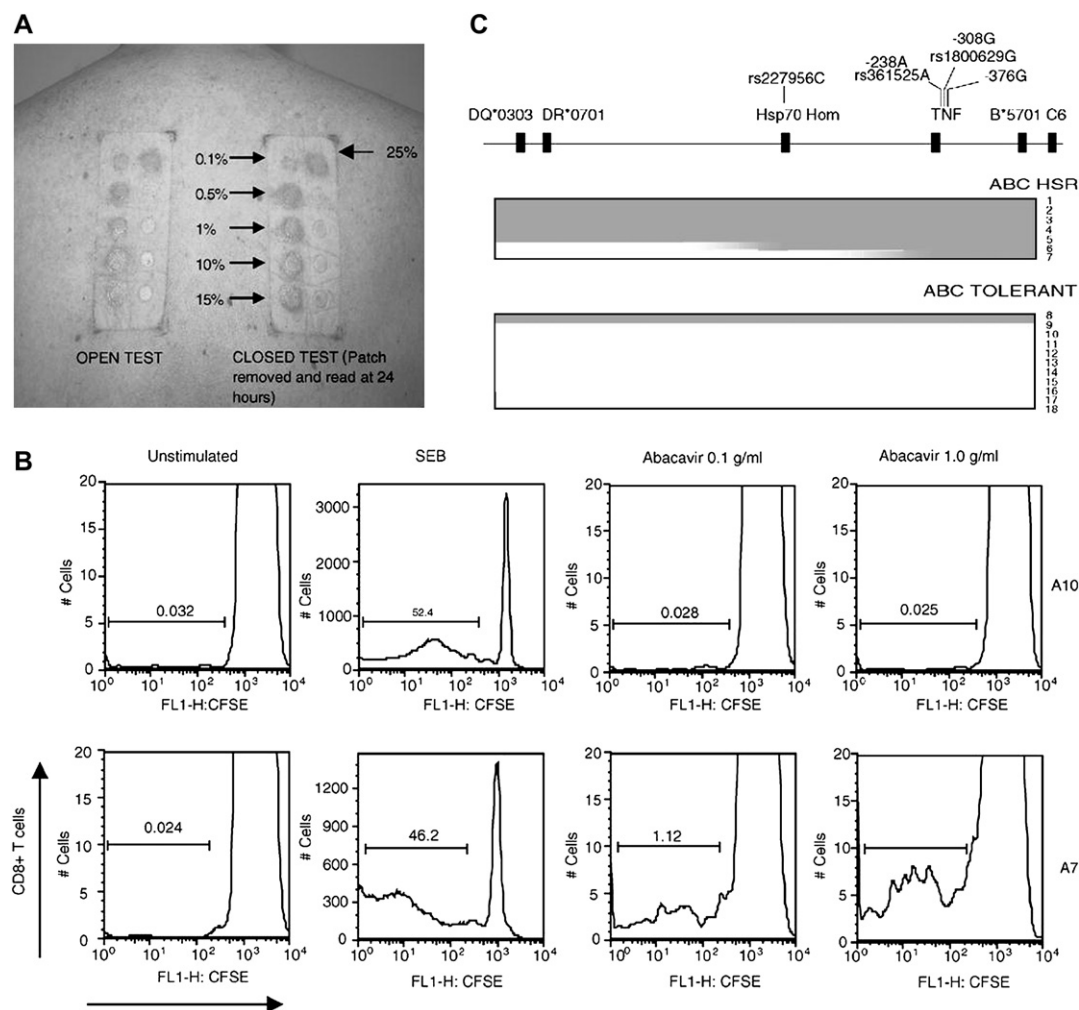


FIG 2. **A**, Representative positive patch test in an abacavir (ABC)-sensitive patient. **B**, Peripheral blood CD8 proliferation by CFSE assay in the patch test-positive patient and an ABC-tolerant control patient. **C**, Increased frequency of MHC alleles of the 57.1 haplotype and heat-shock protein 70 haplotypic variant among ABC patch test-positive patients versus ABC-tolerant controls. CFSE, Carboxyfluorescein diacetate succinimidyl ester; HSR, hypersensitivity reaction syndrome; SEB, staphylococcal enterotoxin B; FL, fluorescence. Reprinted with permission from Phillips EJ, Wong GA, Kaul R, Shahabi K, Nolan DA, Knowles SR, et al. Clinical and immunogenetic correlates of abacavir hypersensitivity. *AIDS* 2005;19:979-87.

Prophylactic prednisolone at 40 mg once daily was given to patients who were begun on a regimen of abacavir, zidovudine, and lamivudine in 1 randomized, open-label study. The patients were randomized to a prednisolone or no prednisolone regimen. There was no prevention of hypersensitivity reactions in patients who received prednisolone (17% incidence in the prednisolone treated group vs 10% in the nonprednisolone group) and no difference in the type of rashes between the 2 groups.²⁴ This is surprising because patch testing was positive in a separate group of patients who developed syndromes compatible with abacavir hypersensitivity (Fig 2, A). All HIV control patients were negative to patch testing.²⁵ The immunohistochemistry on the acute skin rash biopsies and patch biopsies were identical.²⁶

CD8⁺ T-cell proliferation has been demonstrated to carboxy fluorescein diacetate succinimidyl ester in peripheral blood of patients with positive patch tests to abacavir (Fig 2, B). These same patients had an increased frequency of MHC alleles of the 57.1

ancestral haplotype and heat-shock protein 70 haplotypic variant (Fig 2, C).²⁷ Also, a multivariate analysis has determined clinical risk factors associated with abacavir hypersensitivity include white race and a higher CD8⁺ T-cell count at initiation of abacavir (>850 vs ≤850 cells/mm³).²⁸ There is relative protection against hypersensitivity associated with African racial origin, male sex, and more advanced HIV.²⁹ Genetic susceptibility conferred by the HLA allele HLA B*5701 has emerged as a dominant risk factor for abacavir hypersensitivity with a positive predictive value of greater than 70% and a negative predictive value of 95% to 98%.^{30,31} These findings are consistent with a direct role for MHC specific alleles in the pathogenesis of abacavir hypersensitivity. Abacavir metabolites could conceivably undergo haptentation to endogenous proteins, thus becoming immunogenic.³⁰

A recent prospective genetic screening study involving 260 abacavir-naïve patients stratified patients on the basis of their HLA-B*5701 status into low-risk and high-risk groups. High-risk groups

did not receive abacavir therapy. This Western Australian HIV cohort had a dramatic decrease in incidence of abacavir hypersensitivity from 8% to 2% after the implementation of genetic screening methods. The 2% incidence of reactions was secondary to patients who were inadvertently exposed to abacavir because of a lack of review of HLA results before the abacavir prescription.³¹ Genetic screening for abacavir hypersensitivity would likely be cost-effective in a predominantly white population, but much less cost-effective in Asian or African populations for whom the prevalence of the HLA-B*5701 allele is less than 1%.³²

Nonnucleoside reverse transcriptase inhibitor: Nevirapine

Nevirapine has been associated with drug reactions of varying severity (Fig 1, B). The most common drug-related adverse event secondary to nevirapine is nonurticarial eruption. It occurs most frequently within the first 6 weeks of therapy and, per the manufacturer, 13% of patients receiving nevirapine develop mild rashes.³³ They are usually maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face, and extremities.³³ Pollard et al³⁴ reported rashes of any severity occurring in 19.8% and SJS in 0.3% of 906 adult patients reviewed from prospective, controlled, and uncontrolled multi-dose, clinical adult and pediatric trials conducted in the United States and abroad. Effective guidelines have been developed for the management of nevirapine-associated rash and, when implemented, approximately half of patients with mild or moderate rash can continue nevirapine therapy under close supervision.³⁵ Risk factors for the development of rash associated with nevirapine include higher pretreatment CD4⁺ T count (>250 cells/mm³ for women and >400 cells/mm³ for men), lower HIV-1 RNA level, Chinese ethnicity, and female sex.^{36,37} Therefore, a black box warning recommends intensive monitoring during the first 18 weeks of therapy, especially in women with CD4⁺ T counts greater than 250 cells/mm³.³³ Prednisone 40 mg once daily for 14 days with a lead in dosage of 200 mg once daily followed by an increase to 200 mg twice daily after 2 weeks did not decrease the occurrence of nevirapine-associated rash in a 24-week prospective, randomized, open-label study.³⁸ A multicentered, randomized, double-blind, placebo-controlled clinical trial with prednisone (30 mg/d × 2 weeks) and lead-in dosing also failed to prevent nevirapine-associated rash.³⁹ Cetirizine has not been effective in reducing the incidence of the rash.⁴⁰

Severe life-threatening cutaneous rashes also occur with nevirapine therapy at a rate of 0.5% to 1%³⁹ with more than 40 cases in the literature.⁴¹ Patients with AIDS have as much as a 1000-fold higher risk of developing severe cutaneous reactions such as SJS⁴² and TEN compared with the general population. SJS and TEN have a high mortality rate of about 5% and 30%, respectively, in non-HIV populations.⁴³ Patients with AIDS and TEN do not appear to exhibit a significantly worse outcome.⁴⁴ Cases have been reported to respond to treatment with IVIG and, in 1 reported case, intravenous immunoglobulin plus N-acetylcysteine was associated with rapid recovery.^{45,46}

Hepatotoxicity associated with nevirapine has been described in at least 2 distinct patterns: an early form of liver enzyme elevation that occurs less than 6 weeks after the initiation of therapy and is associated with cutaneous hypersensitivity and/or eosinophilia, and a delayed variant that is usually devoid of extrahepatic findings and manifests after more than 2 to 3 months

of exposure. Most of the liver-related fatalities associated with nevirapine have manifested as the early variant. Liver biopsy results in the early variant of nevirapine hepatotoxicity have supported an immune mechanism as evidenced by intrahepatic eosinophilic infiltrates.⁴⁷ An immune mechanism is further supported by a recent report of T cells obtained from a nevirapine-hypersensitive patient that were found to proliferate in the presence of nevirapine with a stimulation index of greater than 2 compared with an absence of proliferation in HIV-positive nevirapine-treated asymptomatic controls.⁴⁸ A CD4⁺ T-cell-dependent immune response to nevirapine specific antigens has been postulated because a predisposition to nevirapine hypersensitivity is associated with HLA-DRB1*0101.⁴⁹

Treatment of nevirapine hypersensitivity consists of surveillance of liver transaminase for elevations, especially in patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection and alcoholic liver disease. HIV-negative individuals are also at risk for reactions to nevirapine when it is used for postexposure prophylaxis,⁵⁰ because 2 cases of fulminant hepatitis, 1 requiring liver transplantation, have been described in healthy individuals treated for occupational exposure.⁵¹ Antiretroviral therapy should be discontinued in association with significant elevations in serum hepatic transaminase measurements, hyperlactatemia, symptoms of acute hepatitis, or features of drug hypersensitivity. Caution should be taken in discontinuation of antiretrovirals in HBV-coinfected patients. Aggressive supportive care is indicated, and rechallenge with nevirapine is contraindicated.⁵⁰

Protease inhibitor: Atazanavir

Rash has been reported in 6% of patients taking atazanavir, a new azapeptide protease inhibitor (Fig 1, C). Only 4 descriptive cases of rash in patients taking atazanavir have been reported in the literature. A 35-year-old HIV-positive man who began atazanavir 12 days before the episode developed generalized, blanching, nonpruritic, maculopapular erythema with no fever. The rash subsided 2 days after discontinuation, and lopinavir-ritonavir was tolerated.⁵² The other 3 cases developed in patients taking atazanavir, but causality was not determined. All 3 patients developed rash after approximately 10 days but, in 2 of the cases, the medication was continued and there was resolution of the rash. The latter case had associated jaundice, elevated liver enzymes, and hyperbilirubinemia to 20 mg/dL associated with the reaction. In the final case, atazanavir, lopinavir, and lamivudine were begun, and an antihistamine-unresponsive rash developed. The medications were discontinued and the rash resolved. It was never determined which antiretroviral medication was causative.⁵³

Fusion inhibitor: Enfuvirtide

Hypersensitivity reactions to enfuvirtide have been associated with this medication, but they are reported to occur in less than 1% of patients (Fig 1, D).⁵⁴ In contrast, injection site reactions with enfuvirtide occur in a majority of cases (98%), and the inflammatory infiltrate surrounding the site is consistent with a localized hypersensitivity reaction because of the presence of eosinophils, histiocytes, rare lymphocytes, and plasma cells. In some biopsies of these reactions, multinucleated giant cells have also been noted. Symptoms include erythema, mild induration, and nodules at the site.⁵⁵

A 42-year-old man noted chest tightness, tachycardia, fever (temperature, 38.3°C), chills, diffuse myalgias, shortness of

breath, and nausea 50 minutes after taking the first dose of enfuvirtide. All of the symptoms resolved spontaneously in 6 hours. He was treated with subcutaneous enfuvirtide with the first dose of 0.00625 mg increasing at 1-hour intervals to 90 mg. He had no further symptoms 12 weeks after this desensitization.⁵⁴

Neither enfuvirtide clinical trials nor postmarketing analysis has documented any immediate hypersensitivity reactions such as the one this patient experienced. Of 2 hypersensitivity reactions attributed to enfuvirtide in clinical trials of multidrug-resistant patients, the occurrence of the rash was days to weeks after drug initiation.⁵⁶ A desensitization protocol was developed for isolated generalized severe rash. Beginning doses of 0.0009 mg were doubled to 90 mg at 30-minute intervals, followed by a full dose challenge.⁵⁷ Recommendations for patients with systemic hypersensitivity to enfuvirtide include discontinuation of the medication.⁵⁸

Integrase inhibitor: Raltegravir

Raltegravir (MK-0518) is an HIV-1 integrase strand transfer inhibitor that has been shown to be active against multidrug-resistant HIV-1 and both chemokine C-C motif receptor CCR5 trophic and chemokine C-X-C motif receptor CXCR4 trophic HIV-1 *in vitro* (Fig 1, E). A phase II dose-ranging study to assess the safety and efficacy of raltegravir compared with placebo in treatment-experienced patients with multidrug-resistant HIV-1 revealed that raltegravir at all doses had a safety profile similar to placebo and no dose-related toxicities.⁵⁹ All injection site reactions were related to enfuvirtide. Pruritus occurred in 4% to 9% of patients, but no rashes or hypersensitivity reactions were reported.⁵⁹

MANAGEMENT OF HIV DRUG HYPERSENSITIVITY

Appropriate management of HIV drug hypersensitivity involves recognition of the risk factors for drug reaction, knowledge of the metabolism and half-life of antiretroviral agents, and an ability to estimate the probability that a particular antiretroviral is causative. An adverse drug reaction probability scale has been shown to increase the ability of caregivers to determine whether the adverse event was related to drug therapy by classifying reactions as definite, probable, possible, or doubtful.⁶⁰ Antihistamine, steroid, epinephrine therapy, and withdrawal of the agent may all be necessary to control symptoms. Absolute avoidance is necessary in abacavir hypersensitivity reactions, nevirapine hepatotoxicity, and SJS/TEN. Desensitization protocols exist for hypersensitivity reactions to TMP-SMX, and this is preferable to rechallenge.¹⁷ Enfuvirtide desensitization protocols have been developed for use with generalized rash, but it is not appropriate in patients with systemic symptoms.^{57,58} The management of these reactions will become even more challenging as different antiretroviral agents are formulated in 1 pill for the ease of patient administration.

Conclusion

Treatment of drug hypersensitivity in patients with HIV requires a clinical awareness of the myriad of manifestations of disease. The complex medication regimens of HIV-infected patients make the determination of a causal agent a challenging task. Knowledge of the potential immunologic mechanisms of hypersensitivity and the metabolism of each drug will be useful in

the clinician's ability to determine the most appropriate treatment for each patient. The very high incidence of immune-related hypersensitivity reactions, some of them overtly mediated by IgE, is proof positive that HIV infections create a hyperallergic state that lends itself to an extraordinary incidence of allergy to HIV medications. In the future, large-scale pharmacologic, immunologic, and genetic studies should contribute to a better understanding of this important clinical problem.

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ZIDOVUDINE

The first antiretroviral used for treatment of HIV was zidovudine. Although toxicities of zidovudine such as myelosuppression, headache, nausea, insomnia, and myopathy have been reported frequently, hypersensitivity reactions have been reported in only 9 cases. We describe case reports associated with these reactions.

McKinley et al^{E1} described urticaria and wheezing 2 hours after zidovudine 300 mg was administered to a 32-year-old woman. This responded to diphenhydramine, epinephrine, and nebulized albuterol within 15 minutes. This is a case of zidovudine hypersensitivity with clinical symptoms consistent with a type I hypersensitivity reaction.

Wassef and Keiser^{E2} reported a case of fever, erythematous rash, angioedema, hypotension (58/40 mmHg), mental status changes, and renal and liver abnormalities 1 hour after repeat zidovudine administration in a 41-year-old man. This reaction was treated with fluids, corticosteroids, epinephrine, and inotropic agents and resolved within 24 hours. No skin testing was performed.

Slayter et al^{E3} report a 29-year-old patient with a pruritic maculopapular rash, fever, angioedema, nausea, and vomiting 12 to 24 hours after zidovudine. Intravenous fluids, diphenhydramine, and corticosteroids were used. The reactions were diagnosed as urticaria and anaphylaxis given the pruritic rash and angioedema.

Torres et al^{E4} describe leukocytoclastic vasculitis in 2 cases of HIV treated with zidovudine. There was no visceral involvement in these cases. One of these cases had mild hypocomplementemia, and the other had an elevated C1q binding assay.

Toxic epidermal necrolysis (Lyell syndrome) is a serious adverse drug reaction and is associated with a mortality rate of 21% to 55% in HIV-infected individuals.^{E5} It occurred in a 42-year-old man after retreatment with zidovudine. He was initially treated for ulcerative lesions of the gingivae and was diagnosed with erythema multiforme on biopsy. This was attributed to sulfonamide therapy. He was admitted to the hospital, all medications were discontinued, and he dramatically improved within 14 days on high-dose methylprednisolone. Zidovudine was restarted on discharge, and he experienced a recurrence of symptoms. The patient was readmitted with TEN with characteristic biopsy features with a mononuclear perivascular infiltrate of the superficial derma with bullous epidermal detachment and keratinocytes in eosinophilic necrosis.^{E6}

Fever, a lichenoid drug eruption (small, firm, papular rash), and hepatitis occurred in a 40-year-old HIV-infected man, and lymphocytic small-vessel vasculitis was noted in a 36-year-old man treated with zidovudine. The first case was treated with desensitization and the latter with a drug challenge. The eruptions and clinical symptoms gradually resolved within 6 to 9 weeks while zidovudine therapy continued.^{E7} Only 3 of the 8 cases of zidovudine hypersensitivity had a previously documented drug allergy to TMP-SMX or other antibiotics.

DIDANOSINE

There are fewer reported cases of drug hypersensitivity to didanosine. Only 2 cases are described, both clinically consistent with non-IgE-mediated reactions. Papuloerythroderma, pruritic chronic dermatosis, which can be associated with cutaneous T-cell lymphoma, was diagnosed in a 31-year-old with HIV and chronic hepatitis C who had received didanosine therapy for 1 month. The pruritic rash began symmetrically with erythema

and hyperkeratosis on the palms and soles. It progressed over a period of 5 months to red, flat papules that were granulomatous with a perivascular and periadnexal lymphohistiocytic infiltrate of CD8⁺ T cells, eosinophils, multinucleated giant cells, and Langerhans cells on histologic examination. Mucous membranes were not involved. After 2 months of topical administration of psoralen followed by ultraviolet A light therapy, complete clearing was obtained.^{E8,E9} Cutaneous leukocytoclastic vasculitis was noted after 3 to 4 days of didanosine therapy and consisted of multiple palpable purpuric elements distributed symmetrically over both legs with confluent small plaques over the ankles. The patient had mild anemia and thrombocytopenia. The resolution of the rash occurred with only discontinuation of the drug.^{E10} Maculopapular, mild morbilliform rash, and SJS have also been described with didanosine.^{E11,E12}

LAMIVUDINE

Lamivudine was approved for use in HIV in 1995 and for only 2 years existed in a solo formulation. In 1997, lamivudine was available in multidrug tablet formulations.^{E13} Given that lamivudine has been used in combination with other antiretrovirals since 1997, there are only 2 cases in the literature of drug allergy to lamivudine alone. The first is a case of an anaphylactoid reaction, angioedema, and urticaria 30 minutes after the first dose of lamivudine (150 mg) in a 49-year-old man.^{E14} He subsequently developed hypotension and was treated with intravenous and nebulized epinephrine, hydrocortisone, antihistamines, and IV fluids. A full recovery was observed within the next 24 hours. A case of contact dermatitis was reported in a health care worker taking lamivudine for postexposure prophylaxis after occupational exposure to HIV. She was distracted while holding the lamivudine tablet in her hand. The rash developed in her hand, evolved over 2 to 3 days, and was successfully treated with topical corticosteroids. Patch testing confirmed the diagnosis. The health care worker successfully took lamivudine orally for 2 weeks without reaction.^{E15} This case highlights the importance of route of administration as an important factor in the development of hypersensitivity. Topical application was more likely to cause symptoms than oral administration in this case.

The remainder of the information in the literature regarding lamivudine is in the context of multidrug formulations. A recent evaluation of long-term safety and tolerability of the lamivudine/abacavir combination as components of highly active antiretroviral therapy (HAART) found that 1585 of 2279 (70%) patients experienced at least 1 drug-related adverse event, and of these, 175 patients (8%) experienced a drug hypersensitivity reaction, compared with 10 patients of 325 (3%) in the control group receiving a lamivudine, zidovudine, and efavirenz combination.^{E16}

TENOFOVIR

Tenofovir is generally well tolerated with very uncommon adverse events such as nephrotoxicity with renal tubular dysfunction.^{E17,E18} There is only 1 case report of a cutaneous drug hypersensitivity with a lichenoid drug eruption in a 60-year-old HIV and chronic hepatitis B virus-infected, immunosuppressed man with a history of drug reaction to cotrimoxazole. Skin biopsies within 4 months of beginning tenofovir revealed florid lichenoid reaction with eosinophils. He was treated with discontinuation of all medications, corticosteroids, and oral antihistamines with subsequent resolution.^{E19}

EMTRICITABINE

Emtricitabine is a once-daily nucleoside reverse transcriptase inhibitor that is used in combination with other antiviral agents. It is generally very well tolerated with most adverse events being mild to moderate in severity.^{E20} Patients treated with emtricitabine may experience discoloration of their skin, nails, or tongue, which manifests as a mild increased pigmentation of the skin. Of 814 patients enrolled in phase 3 clinical trials of emtricitabine, 29 (4%) of participants developed the skin discoloration, and higher rates were reported in black patients. There were no severe effects from this discoloration, and it did not result in any treatment discontinuation. The pathogenesis of this skin reaction is unknown.^{E21} A smaller ($n = 294$) randomized study of lamivudine versus emtricitabine with stavudine or zidovudine and a PI or nonnucleoside reverse transcriptase inhibitor revealed a rash event rate of 17% for emtricitabine versus 14% for lamivudine. Eruption events included pruritus, maculopapular eruptions, urticaria, and vesiculobullous or pustular and allergic reactions.^{E22} A second randomized, double-blind trial with either emtricitabine or lamivudine with didanosine and efavirenz ($n = 286$) revealed a rash event rate of 30% and a 3% skin discoloration rate.^{E23} A case of hypersensitivity to emtricitabine/tenofovir was reported with similar clinical symptoms to abacavir (ABC) hypersensitivity reactions.^{E24}

STAVUDINE

Stavudine is very well tolerated, and hypersensitivity reactions have been described only in multidrug therapy clinical trials. Of several trials including stavudine with lamivudine, efavirenz, nevirapine, and abacavir, rashes, hypersensitivity reactions, and SJS have been reported.^{E25-E27} None of these reactions have been attributed by the treating physicians to stavudine. It is not surprising that nevirapine and abacavir are likely responsible for the hypersensitivity reactions noted in patients concomitantly taking stavudine.

ZALCITABINE

A hypersensitivity syndrome has been described in 2 patients who were treated with the combination of zidovudine and zalcitabine. Both patients had CD4⁺ T counts less than 10/ μ L and developed rashes 5 and 12 days after beginning zalcitabine.^{E28} The reaction in the first patient was described as an exfoliative dermatitis with fever, eosinophilia (3100 cells/ μ L), and lymphadenopathy. Skin biopsy revealed a perivascular CD8⁺ T lymphocytic infiltrate. Improvement occurred within a few days of discontinuation of therapy. Rechallenge with zalcitabine reproduced the symptoms within 1 to 2 days. The second patient presented with fever, facial swelling, a diffuse maculopapular rash, and eosinophilia of 8700/ μ L.^{E28} In phase I clinical trials, macular and papular eruptions occurred in 14 of 20 patients treated with a high dose of intravenous zalcitabine, and systemic symptoms occurred in those receiving higher-dose therapy.^{E29,E30} Erythema multiforme has been reported secondary to zalcitabine.^{E31} Stomatitis and mouth ulcers may occur frequently with zalcitabine therapy but tend to resolve with continuing treatment.^{E30}

NELFINAVIR

Primary adverse reactions to nelfinavir are nephrolithiasis, gastrointestinal intolerance, and an inconsequential increase in indirect bilirubin. The incidence of rash with nelfinavir is reported

to be low at <5%. Diarrhea is reported more commonly in nelfinavir-treated patients, although this has not been determined to be associated with immunologic reactivity.^{E32} Hypersensitivity manifested by rash has been reported in detail in some case reports. Most of the rashes have been maculopapular with some vesicular or bullous features,^{E33} but 3 cases have been urticarial,^{E34} indicating a probable type I hypersensitivity mechanism. The onset of the rash ranges from 5 days to 2 weeks. One-day desensitization protocols have been used with dose escalation from 25 μ g or 500 μ g to 750 to 1000 mg, and urticarial rashes have developed during these protocols. One patient is described who received a 3-week graded challenge protocol with an initial dose of 250 mg with escalation in dosing by 250 mg every 3 days until a dose of 750 mg 3 times daily was achieved. No viral resistance was observed in these 4 cases.^{E33,E34}

Cutaneous drug reactions to PIs have occurred in the context of postexposure prophylaxis. In the 1 case reported, an urticarial rash developed to nelfinavir 6 days after initiation of the drug. The patient had a history of urticaria 8 days after initiating indinavir. Cross-reactivity has been suggested in the literature for indinavir and nelfinavir in 2 cases in which a rash developed to both of these agents sequentially.^{E34,E35}

Porphyria cutanea tarda has also been reported as temporally related to nelfinavir use. This rash is characterized by skin photosensitivity with blistering on sun-exposed areas, skin fragility, hyperpigmentation, and hypertrichosis. Biochemically, it is characterized by high levels of porphyrins, principally uroporphyrin, in plasma and urine and is associated with exposure to precipitating agents, all of which cause liver dysfunction.^{E36} nelfinavir is metabolized through the cytochrome P450 enzyme CYP2C19 in the liver, which makes it a likely candidate for causing this type of rash in patients with HIV.^{E37}

EFAVIRENZ

The incidence of efavirenz-induced hypersensitivity ranges between 10% and 34%. The most common manifestation of this reaction is an erythematous, maculopapular rash with or without fever, occurring 1 to 3 weeks after initiation of therapy, and lasting between 13 and 39 days. In the majority of cases, the rash is of mild to moderate severity, with only 2% of patients requiring discontinuation of efavirenz therapy. The skin eruption can be associated with fever and internal organ involvement. If no systemic manifestations occur, continuation of therapy is indicated with symptomatic control with antihistamines.^{E38} The incidence of this rash in efavirenz-treated patients ranges from 6% to 8.5%. More than 90% of HIV-infected patients with CD4 counts <200 cells/mm³ who had preceding efavirenz-associated rash can tolerate efavirenz well.^{E39,E40}

A similar phenomenon is seen with efavirenz-associated hepatotoxicity, with most of those patients asymptomatic on subsequent efavirenz therapy.^{E41} Although the histories of reported cases of efavirenz-induced rash are not suggestive of IgE-mediated disease, a 14-day desensitization protocol was performed in a 37-year-old man with a generalized pruritic rash 8 days after initiation of efavirenz. The symptoms resolved with discontinuation of all antiretrovirals. On rechallenge within 24 hours, a red, itchy rash involving his face and chest occurred. During desensitization day 12, he again developed a rash, but diphenhydramine and topical corticosteroid creams were used, and the protocol was extended 4 days. The patient was able to tolerate

efavirenz with no symptoms after the desensitization.^{E38} Photosensitive drug eruption diagnosed by patch test with light exposure has also been reported with efavirenz.^{E42} Hepatotoxicity in association with efavirenz has been reported in 8% of patients,^{E41} and at least 1 case of fulminant hepatic failure has been reported with efavirenz.^{E43}

DELAVIDINE

Skin rash is the most frequently reported adverse effect of delavirdine, and in a trial of monotherapy with delavirdine in 120 patients, rash developed in 36% of subjects who received delavirdine. The rash was self-limited, and the median time to the onset of the rash was 10 days. When the National Institute of Allergy and Infectious Diseases Division of AIDS Table for Grading Adult Adverse Experiences was used to grade toxicity from grade 1 to 4, 77% of patients had grade 2 or less.^{E44} Only 1 subject developed fever with the rash. The concentration of delavirdine achieved at 1 week was a significant predictor of rash.

Rash occurs in 18% to 50% of patients receiving delavirdine-containing combination therapy in clinical trials.^{E45-E47} Although a high proportion of patients developed a rash, it was typically mild to moderate in intensity, did not result in discontinuation or adjustment of treatment in most patients, and resolved quickly. The occurrence of SJS was rare (1 case in 1000 patients).^{E47} There was a trend toward higher frequency of rash in Latino patients in 1 small trial of 80 patients.^{E48} One small case report describes a 30-year-old patient with an erythematous maculopapular rash within 3 days of beginning delavirdine. With rechallenge 1 week after initial discontinuation, within 1 hour pruritus began, and within 2 hours erythematous rash with wheezing developed. No drop in blood pressure occurred. The reaction was unresponsive to promethazine or hydrocortisone but was responsive to epinephrine.^{E49} Gastrointestinal side-effects such as nausea, diarrhea, and hyperbilirubinemia have also been reported with delavirdine.^{E45,E50}

AMPRENAVIR OR FOSAMPRENAVIR

Maculopapular rashes are reported in clinical trials with amprenavir or the phosphate ester prodrug of amprenavir, fosamprenavir, in as many as 3% of patients. These reports are confounded by the use combination regimens including abacavir.^{E51,E52} There are no reports describing development of a rash associated with amprenavir or fosamprenavir, proven through reintroduction of other concomitantly taken medications.

INDINAVIR

Hypersensitivity reactions to indinavir are rarely reported. Ten years ago, a possible case of indinavir associated rash occurred in a 24-week open-label, phase I-II study evaluating the agent's safety,^{E53} but more recently, other cases have been described. An observational study in Italy observed 84 patients who had not responded to previous therapies with 2 nucleoside reverse transcriptase inhibitors or were naive: 34 (40.5%) developed diffuse cutaneous dryness and pruritus and 48 patients (57.1%) experienced other cutaneous effects such as cheilitis, asteototic dermatitis, scalp defluvium, and alopecia with indinavir therapy.^{E54} A review of hypersensitivity reactions in 132 subjects on indinavir, 6 (4.5%) developed symptoms. Five were cases of maculopapular rash, and 1 was urticarial. The reactions appeared after about

25 days and disappeared after discontinuation.^{E55} Hypersensitivity to ritonavir was noted in 12.5% of the patients with reactions to indinavir-ritonavir combination therapy. The risk factors of sex (women greater than men) and previous non-HAART therapy were noted in a randomized multicenter trial of 1251 nucleoside-experienced patients with CD4⁺ T-cell counts <50 cells/ μ L who started treatment with PIs (ritonavir or indinavir). Sixty-six (5.3%) patients developed rash in that cohort.^{E56}

Acute generalized exanthematous pustulosis, a well known entity typically characterized by an acute onset, a temperature higher than 38°C, and a cutaneous eruption with widespread exfoliative dermatitis after pustular and maculopapular eruption, was described in a 31-year-old HIV-seronegative man who took prophylactic combination therapy with indinavir, zidovudine, and lamivudine. The rash occurred on day 3 and improved with methylprednisolone 80 mg/d with a relapse 2 days after stopping therapy. The man had concurrent enterovirus infection in his throat, which may have been a contributing factor to the development of rash. Acute generalized exanthematous pustulosis is consistent with a type IV hypersensitivity reaction and is diagnosed by cutaneous patch testing, but this was not performed in this case.^{E57}

Two other case reports describe more immediate reactions to indinavir. A diffuse rash, hypotension, fever, diarrhea, elevated liver function tests, and neutropenia to 200 cells/mm³ were observed after initiation and reintroduction of indinavir in a patient with AIDS. The reaction occurred after 5 to 8 hours of exposure. With IV fluids, antihistamine, and corticosteroids, the rash resolved in 12 hours, and the elevated liver function tests responded within 36 to 72 hours.^{E58} Another case of maculopapular eruption 2 to 3 hours after rechallenge with indinavir has been reported.^{E59}

SAQUINAVIR

There are only 3 case reports of possible hypersensitivity reactions to saquinavir. A 50-year-old woman developed fever and a swollen knee 10 days after starting ritonavir. She then experienced fever and a skin rash after 7 days of a HAART regimen including indinavir. The rash was a red-bluish erythematous purpuric rash. Then, 8 days after beginning saquinavir, she developed a vasculitic rash with neutrophil infiltration and many eosinophils in the superficial dermis on biopsy. Immunofluorescence showed IgA deposition suggesting an antibody-mediated hypersensitivity reaction. Prednisone at 40 mg once daily controlled the symptoms and was decreased to 20 mg daily without recurrence of symptoms.^{E60} The recurrence of the rash in 1 case in which the patient was on the 3 PIs suggests a mechanism of cross-reactivity between these agents in this probable antibody-mediated reaction. Fixed drug eruptions have been reported in 2 patients with HIV while saquinavir therapy was given. These responded to topical steroids, and the medication was continued.^{E61}

LOPINAVIR

Acute generalized exanthematous pustulosis was reported in a health care worker receiving postexposure prophylaxis with zidovudine, lopinavir, and lopinavir-ritonavir. Pustular rash and fever began 24 hours after the first dose of antiretroviral combination prophylaxis and resolved 48 hours after discontinuation of lopinavir-ritonavir.^{E62}

TIPRANAVIR-RITONAVIR

Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported by the manufacturer for tipranavir. Ritonavir is an antiretroviral agent that is used principally to boost the blood levels of other antiretroviral agents by competitive use of the same P450 enzyme clearance system in tissues (eg, hepatic cytochrome CYP3A). Females administered ethinyl estradiol followed by tipranavir-ritonavir had 33% incidence of rash. No additional data exist in the medical literature regarding drug allergy to tipranavir.^{E63}

DARUNAVIR

Darunavir (TMC114) is a PI that contains a sulfonamide moiety. Despite this, <1% of patients have experienced skin disorders with therapy.^{E64} With further use clinically, more information will be available. Although the sulfonamide moiety is a theoretical concern, at this time, allergy to sulfonamides is not a contraindication to darunavir therapy.

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