Approach to Hypersensitivity Syndromes Associated with Antiretroviral Agents

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ADVERSE DRUG REACTIONS (ADRS) REPresent a major health problem. They are ranked as the fourth most common cause of death after heart disease, cancer, and stroke and claim more than 100,000 lives in the United States each year. This is of particular concern in the setting of HIV, in which potent—and often toxic—antiretroviral therapy remains the best option for the vast majority of people living with the virus.

Like the pathogenesis and etiology of HIV, the mechanisms by which ADRs occur are complex and not entirely understood. One cluster of side effects in particular, hypersensitivity syndromes, is, perhaps, one of the most perplexing and unique of them all. Rightly, these reactions have become a common fear among clinicians, despite their occurrence in only a small percentage of HIV-positive patients receiving antiretroviral therapy.

To help make sense of these hypersensitivity syndromes in the context of HIV/AIDS treatment, Dr. Elizabeth Phillips provided a detailed review of what is known about this particular ADR and offered guidance for its recognition and management.

The Nomenclature of Hypersensitivity

DR. PHILLIPS POINTED OUT THAT THERE ARE two types of ADRs: Type A, which are predictable, and Type B, which are unpredictable. Type A ADRs account for 70% to 80% of all adverse reactions. These are the side effects—nausea, for example—that would be expected to occur in most patients who take a drug or combination of drugs at high doses. In this sense, Dr. Phillips explains, "type A are predictable extensions of pharmacologic effect. They are

drug- and dose-dependent; they are not as dependent on host factors."

Type B ADRs account for 20% to 30% of all adverse reactions. They are bizarre, idiosyncratic, pseudoallergic reactions that are typically dose-independent and host-dependent. Unlike type A ADRs, idiosyncratic reactions are almost totally unpredictable and account for 20% to 30% of all ADRs. "Type B reactions are not as dependent on dose or the pharmacologic action of the drug," Dr. Phillips said. "A number of genetic and acquired factors are likely important in the development of these reactions."

Drug-induced hypersensitivity syndromes are bizarre, idiosyncratic, and clearly host-dependent. They are rare events usually captured only in case reports. For example, anticonvulsant and sulfonamide hypersensitivity syndromes occur in only one of 5,000 or 10,000 people treated with these drugs in the general population. Confusing matters is the incidence of hypersensitivity reactions in HIV-positive patients; sulfonamide hypersensitivity is approximately 100 times more common in this population of patients.

Data regarding hypersensitivity reactions are limited in controlled clinical trials. For example, sample sizes are often too small to pick up unusual ADRs. Hypersensitivity reactions are also more likely to occur in specific populations often excluded from clinical trials, including children, the elderly, premenopausal women, and patients with comorbid conditions.

A number of drug classes have been associated with the hypersensitivity syndromes. These are: anticonvulsants, including phenytoin, phenobarbital, carbamazepine, lamotrigine; antibiotics, including various sulfa-based drugs, nitrofurantoin, minocycline, metronidazole; non-steroidal anti-inflammatory drugs; al-

lopurinol; diuretics; lipid-lowering agents; and, of course, antiretrovirals.

Clinical Features

THE CLINICAL FEATURES OF HYPERSENSITIVITY syndromes typically occur within the first two months of therapy, but not usually until the second week of treatment. Fever is a common initial symptom, as is rash, both usually occurring in more than 90% of patients with drug-induced hypersensitivity. Lymphadenopathy is another common feature associated with drug-induced hypersensitivity. Other internal organs may also be involved, including the liver, kidneys, or lungs.

As explained by Dr. Phillips, hypersensitivity syndromes can be mixed bags of tricks. "Very often we'll see a constellation of cutaneous and extracutaneous involvement," she said. "In some cases, we might see a mild rash and severe internal-organ involvement. Some may present with severe rash and minimal or no internal-organ involvement. There are also some patients who may present with fever alone."

Rash, one of the most common features of hypersensitivity syndromes, varies from mild to severe. The most common rash tends to be mild and exanthematous in nature. Less common, but definitely more troublesome, are urticarial plaques, pustular eruptions, and severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome and toxic epidermal necrolysis.

With respect to extracutaneous involvement, Dr. Phillips listed various hematologic manifestations, including atypical lymphocytosis, leukopenia, pancytopenia; impaired liver function, ranging from mild LFT increases to fulminant hepatitis necrosis; muscle and heart damage, including

pericarditis and cardiac arrest; colitis; thyroid problems, perhaps manifesting first as hyperthyroidism followed by hypothyroidism; and breathing complications, including cough, pharyngitis, dyspnea, and acute respiratory distress syndrome (ARDS). "Upper respiratory symptoms such as coryza are not part of hypersensitivity syndrome," Dr. Phillips added. "The symptoms to look out for are really quite specific."

Table 1: Antiretroviral Drugs: Rash and Hypersensitivity

Drug	Rash (%)	Severe Rash(%)	Onset (Days)	Tx D/C (%)	Clinical Features	Rechallenge
Nevirapine	17	6-8	14–21	7	Fever, mucosal membrane rash, SCAR (0.3%), hepatitis (1%)	Only during 400 mg/day phase if mild-to-moderate rash.
Delavirdine	18	4	7–14	4	Headache	Unknown
Efavirenz	10	0.7	11–14	2	CNS symptoms	Unknown
Abacavir	3	—	9–11	3	Fever, nausea, malaise, GI, respiratory	Avoid
Amprenavir	20	3	10	3	Fever (7%)	Unknown; anecdotal reports:possible

Source: Elizabeth Phillips, MD, FRCPC. Based on data pooled from various published clinical trials.

Pathogenesis of Hypersensitivity Syndromes

HOW DO HYPERSENSITIVITY REACTIONS occur? A search of the literature reveals three potential theories. The first theory suggests that a given drug or its metabolite could directly modify the activation of immune complexes. The second theory holds that a drug or its metabolite could alter the function of some cells involved in control of the immune system (i.e., CD4+ or CD8+ cells). Dr. Phillips is partial to the third theory suggesting that idiosyncratic hypersensitivity can be etiologically tied to the production of reactive/toxic metabolites that act as haptens and bind to cellular macromolecules. Often, the drug itself is not immunogenic because it lacks the ability to conjugate with proteins in a stable covalent linkage. In the event of insufficient detoxification of these bound reactive metabolites, cellular necrosis or death can occur. This in turn could precipitate a cascade of secondary host immunologic responses leading to cytokine release and more extensive cell death.

A prime example of this theory can be found in sulfamethoxazole, a drug metabolized by the enzyme N-acetyltransferase and the cytochrome P450 isoenzyme system. During oxidation, a hydroxylamine derivative is produced that can undergo further oxidation to form nitroso metabolites. Both the hydroxylamine and nitroso metabolites of sulfonamides have been reported to be toxic in various *in vitro* systems (Rieder, 1988).

"We still don't know why some people go down the non-reactive metabolic pathway while others go down the reactive/toxic pathway," offered Dr. Phillips. "There could be underlying genetic factors that predispose someone to reactive metabolite production, along with a number of other host and acquired factors."

While not specifically addressed by Dr. Phillips, some of the potential host factors related to sulfamethoxazole hypersensitivity have been explored. For example, the rate of reactive hydroxylamine metabolite formation is determined by the acetylator status of the individual. According to an April 1999 report in *Pharmacy Practice*, patients who are slow acetylators may see high levels of sulfamethoxazole metabolized via a reactive metabolite pathway. For example, in 21 healthy individuals with prior idiosyncratic reactions to sulfonamides, 19 (90%) were found to be slow acetylators (Rieder 1991).

The issues for those living with HIV are clearly much more complex. Some studies have suggested that HIV-infected patients with a history of TMP-SMX idiosyncratic reactions are more likely to express the slow-acetylator phenotype. In one study by Dr. Andrew Carr and his colleagues in Sydney, 15/16 (94%) patients with a previous hypersensitivity to TMP-SMX—defined as cutaneous morbilliform eruption, fever and hepatic or renal dysfunction—expressed the slow-acetylator phenotype, compared with only 5/12
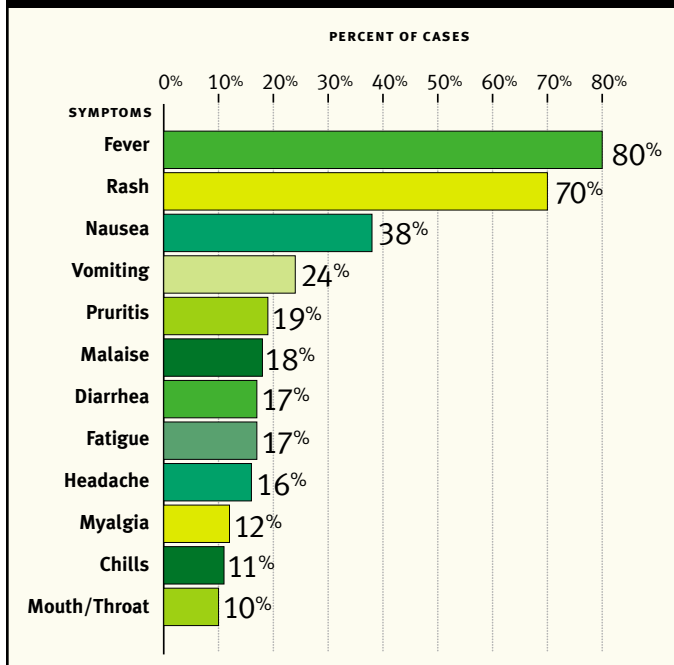
(42%) without prior hypersensitivity reactions (Carr, 1994).

Hypersensitivity in HIV-Positive Patients

THERE IS A HIGHER INCIDENCE OF ADRS, including both minor and severe cutaneous ADRs (e.g., SCAR), in HIV-positive patients. Dr. Phillips was careful to point out that during the first year of HAART, ADRs—not virologic or immunologic failure—are the most common reason for treatment discontinuation or required switches (d'Arminio Monforte, 2000).

As hinted above, TMP-SMX-associated ADRs are, perhaps, the most widely known of all drug-induced hypersensitivity syndromes in HIV-positive patients. In clinical trials using TMP-SMX as a treatment for AIDS-related *Pneumocystis carinii* pneumonia (PCP), between 24% and 57% of patients had to discontinue the agent because of ADRs (Klein, 1992; Medina, 1990). What's more, a retrospective study comparing patients with HIV-related immune suppression with other immunosuppressed patients with PCP found that the prevalence of ADRs associated with TMP-SMX treatment was 65% and 12%, respectively (Kovacs, 1984). With respect to primary and secondary prophylaxis using TMP-SMX, ADRs have been reported in 31% and 52% of HIV-positive patients, respectively (Wormser, 1991).

Figure 1. Signs and Symptoms of Abacavir Hypersensitivity (n=636)

PERCENT OF CASES

SYMPTOMS	
Fever	80%
Rash	70%
Nausea	38%
Vomiting	24%
Pruritis	19%
Malaise	18%
Diarrhea	17%
Fatigue	17%
Headache	16%
Myalgia	12%
Chills	11%
Mouth/Throat	10%

Source: Elizabeth Phillips, MD, FRCPC. Based on data pooled from various published clinical trials.

"What's interesting upon looking at TMP-SMX hypersensitivity is the success of desensitization protocols," Dr. Phillips said. "We normally don't expect that idiosyncratic ADRs, such as sulfa-associated hypersensitivity, would depend on the dose of the drug being used, especially upon rechallenging. Yet our ability to successfully rechallenge HIV-positive patients with TMP-SMX has helped us understand that there may, in fact, be dose-related mechanisms at work."

Hypersensitivity associated with antiretroviral agents is a particularly thorny issue. For starters, HIV-positive patients rarely initiate therapy with just one drug and may end up taking two or more drugs with overlapping toxicities. Consequently, rechallenging a patient using a single drug is not an option due to the rapid development of resistance.

Of the 15 antiretroviral drugs now available, five have been more commonly associated with rash and the more complex hypersensitivity syndromes. All three of the non-nucleoside reverse transcriptase inhibitors—nevirapine (Viramune), delavirdine (Rescriptor), and efavirenz (Sustiva)—have been indicted, along with the protease inhibitor amprenavir (Agenerase) and the nucleoside reverse transcriptase inhibitor abacavir (Ziagen). A breakdown of the hypersensitivity reactions associated with each of these drugs is provided in Table 1.

Abacavir Hypersensitivity Syndrome

ABACAVIR HYPERSENSITIVITY syndrome occurs in 3% to 5% of patients during the first five to six weeks of therapy, with a median onset of 11 days. "The times to onset of symptoms vary," Dr. Phillips pointed out. "Some patients in clinical trials developed systemic problems in as little as three days after taking their first dose. In turn, we can't rely on the typical time-to-onset rule associated with other hypersensitivity-prone drugs when following our patients receiving abacavir."

Symptoms worsen progressively with continued dosing and, again, unlike the high incidence rate of rash seen using other drugs, rash is absent in approximately 30% of patients who are hypersensitive to abacavir. "When the rash is present," added Dr. Phillips, "it is usually mild and often goes unnoticed by the patient."

SCARs, including Stevens-Johnson syndrome, are rarely associated with abacavir-containing regimens and are seen when the drug is combined with a non-nucleoside reverse transcriptase inhibitor.

Hypotension occurs in about one of four patients with abacavir hypersensitivity who are rechallenged with the drug after initially discontinuing therapy. Deaths have also been reported with rechallenge. Dr.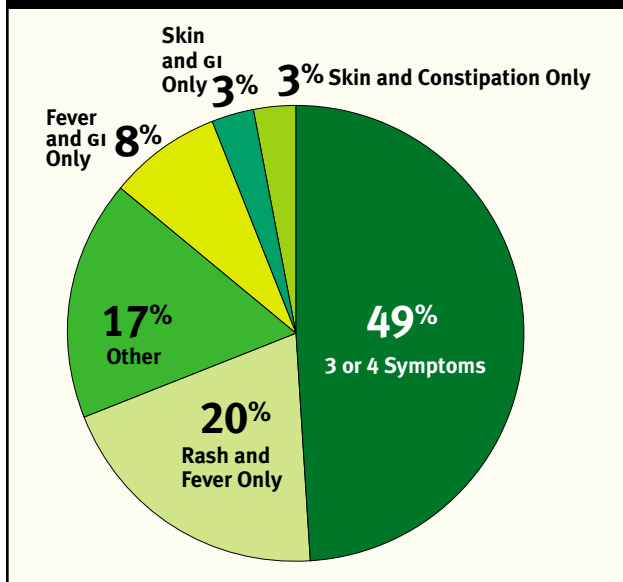 Phillips noted that a similar syndrome is seen in patients treated with the immune-suppressant azathioprine (Imuran); fever, mild rash, and GI symptoms can occur in some patients, with more than 30 cited cases of severe reactions upon rechallenging (Knowles et al).

The most common signs and symptoms (>10%) of hypersensitivity syndromes associated with abacavir use are provided in Figure 1. Figure 2 reflects a number of the combinations of reported symptoms associated with abacavir hypersensitivity. With respect to the clinical presentations seen in patients receiving abacavir for the first time or on subsequent rechallenge, data involving 112 patients with hypersensitivity are reported in Figure 3.

A number of laboratory abnormalities can occur in patients with abacavir hypersensitivity. Such abnormalities may indicate systemic organ involvement and include lymphopenia and thrombocytopenia; elevated transaminase levels; increases in serum creatinine; elevated creatine phosphokinase; and, on chest X-ray, diffuse bilateral infiltrates.

Dr. Phillips was clear in stating that the key to diagnosing hypersensitivity reaction to abacavir is a careful history. All patients should be aware of the possible symptoms and report them immediately. To avoid worsening of symptoms, abacavir therapy should be stopped if hypersensitivity reaction is suspected. However, abacavir may be

Figure 2. Combination of Reported Symptoms Presenting as Abacavir Hypersensitivity (n=789)

- Skin and GI Only 3%
- Skin and Constipation Only 3%
- Fever and GI Only 8%
- 49% 3 or 4 Symptoms
- 17% Other
- 20% Rash and Fever Only

Source: Elizabeth Phillips, MD, FRCPC. Based on data pooled from various published clinical trials.

Figure 3. Abacavir Hypersensitivity: Clinical Presentations Initially and on Rechallenge (n=112)

PERCENT OF CASES

SYMPTOMS	Initial	Rechallenge
Fever	59%	71%
Rash	51%	64%
GI	42%	45%
Lethargy	41%	45%
Respiratory	16%	21%
Headache	9%	10%
Hypotension	5%	24%
Abnormal Renal Function	5%	12%
Tachycardia	1%	11%

Source: Elizabeth Phillips, MD, FRCPC. Based on data pooled from various published clinical trials.
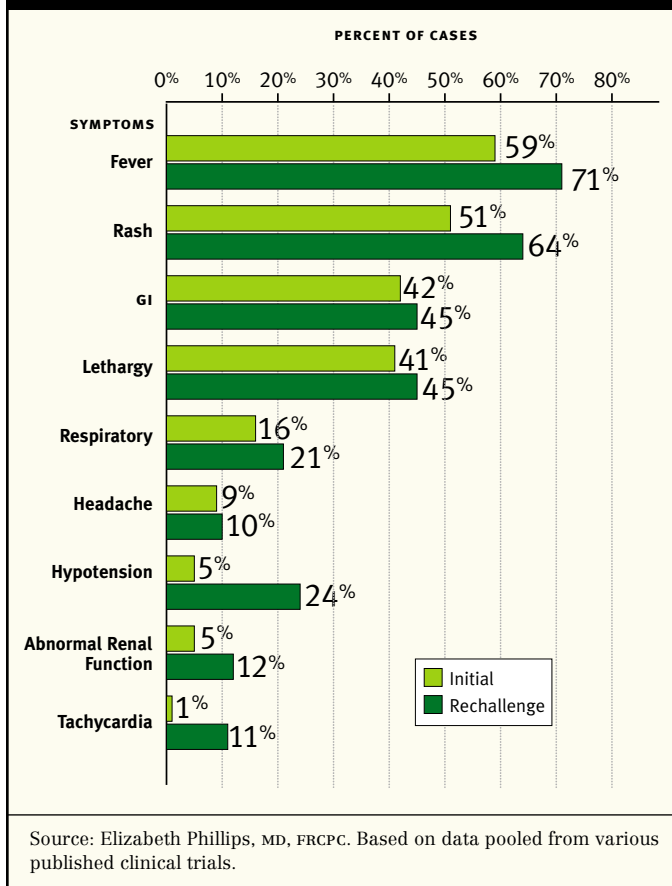
continued if the only symptom is rash, with the proviso that it be discontinued immediately if other symptoms develop.

If therapy is stopped due to hypersensitivity, it should not be restarted. In view of a lack of safety information on desensitization to abacavir, compounded by the risk of inducing viral resistance, such a procedure is not encouraged outside of a study setting.

When to Treat? When to Stop?

IN DISCUSSING POTENTIAL TREATMENT STRATEGIES for patients with drug-induced hypersensitivity, Dr. Phillips remained cautious through her lecture. Conditions such as a nonpruritic skin rash in the absence of fever may not require any treatment. Antihistamines (e.g., hydroxyzine, diphenhydramine, fexofenadine, or cetirizine) are useful to control the itch but do not generally affect the duration of the skin rash. Topical corticosteroids are also quite useful for symptom control. Systemic corticosteroids will quiet down a reaction, but the reaction will often recur upon tapering the dose. "It's important to keep in mind that intervening with additional drugs may not be a long-term solution," warned Dr. Phillips. "Most clinicians are aware of the fact that symptoms may very well return upon stopping systemic corticosteroids therapy. Besides, the last thing many of us want to do is to keep our HIV-positive patients on chronic systemic corticosteroids therapy, so it's important to think this option through." [*Editor's note: Data from a clinical trial of nevirapine suggest that prednisone may exacerbate hypersensitivity-related rash. See the nevirapine news capsule on page 3 for more information.*]

When should an offending antiretroviral agent be discontinued? Dr. Phillips explained that, "while we've had a great deal of success treating NNRTI rash using topical corticosteroids, we often have to discontinue therapy in patients with more severe rash and extracutaneous symptoms of hypersensitivity. This is also true when it comes to our patients receiving abacavir who develop progressive systemic symptoms. Again, abacavir hypersensitivity generally evolves over time, like many of the antiretroviral drugs associated with hypersensitivity reactions. Abacavir is a good drug, just so long as we're monitoring patients carefully and educating patients about its potential ADRs and what they should do if they occur, we'll be one step ahead of the game." *prn*

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