

## DRUG REACTIONS AND THE SKIN IN HIV/AIDS

C N Dlova, MB ChB, FCDerm (SA)

A Mosam, MB ChB, FCDerm (SA), MMed

Department of Dermatology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban

Drug reactions are common in HIV-positive individuals, approximately 100 times as common as in the general population, and they increase with increasing immunodeficiency.<sup>1</sup> Factors associated with drug reactions in HIV disease are polypharmacy to deal with opportunistic infections, the nature of drugs prescribed for AIDS-related illnesses, slow acetylator status, relative glutathione deficiency, CD4 count < 200 cells/ $\mu$ l and > 25 cells/ $\mu$ l,<sup>2</sup> latent cytomegalovirus and Epstein-Barr virus infections<sup>3</sup> and high CD8+ cell counts (> 460 cells/ $\mu$ l).

The majority of reactions involve the following agents:

- trimethoprim-sulfamethoxazole
- other sulfonamide drugs, and
- various penicillins.

These drugs account for 75% of all adverse drug reactions. Trimethoprim-sulfamethoxazole adverse reactions are the commonest, the prevalence increasing from approximately 2 - 8% in the general population to 43% in HIV-positive individuals and to approximately 69% in patients with AIDS.<sup>4-6</sup> One reason suggested for the striking incidence of reactions to trimethoprim-sulfamethoxazole is the systemic glutathione deficiency in individuals with HIV/AIDS, which increases the likelihood of accumulation of toxic intermediates such as the hydroxylamine derivatives in the circulation, hence inciting adverse drug reactions.<sup>7</sup> Other agents implicated are antituberculosis drugs, antiretrovirals, non-steroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants.

### DIAGNOSIS OF ADVERSE CUTANEOUS DRUG REACTIONS (ACDRs)

A thorough knowledge of the presentation, identification and management of ACDRs is important, since they are a significant cause of morbidity and mortality. They most commonly present as a morbilliform eruption 7 - 14 days after the initiation of therapy, which resolves after withdrawing the offending agent. The rash may present as an itchy, symmetrical, fine, erythematous, maculopapular eruption on the trunk, sparing the face and worse in the intertriginous areas (Fig. 1). Other features are fever, headache, myalgia, arthralgia, granulocytopenia, thrombocytopenia and raised liver enzymes. Histological examination of the skin reveals a superficial perivascular infiltrate of lymphocytes and histiocytes, with vacuolar interface changes and spongiosis.<sup>3</sup> The morbilliform eruption occurs in 95% of cutaneous adverse drug reactions,<sup>8</sup> with other types listed below.

### TYPES OF ACDR

- Morbilliform: erythematous maculopapular rash, measles-like (Fig. 1).
- Erythema multiforme: erythematous iris-shaped papules

and vesicobullous lesions on extremities and mucosal surfaces (Fig. 2).

- Urticaria/angioedema: erythematous itchy wheals sometimes with lip and tongue swelling.
- Fixed drug eruption: dusky round macules with blistering which heal with hyperpigmentation (Fig. 3).
- Lichenoid eruption: itchy, violaceous eruption similar to lichen planus, healing with dusky grey pigmentation.
- Vasculitis: palpable purpura accentuated on extremities.
- Stevens-Johnson syndrome (SJS): erythema multiforme lesions involving two or more mucosal surfaces; may occur with skin exfoliation less than 10% of the total body surface area (Fig. 4, a, b, c).
- Toxic epidermal necrolysis (TEN): a syndrome which begins with erythema and tenderness of the skin and progresses to stripping of the skin of more than 30% body surface area (Fig. 5, a, b, c).

### LIFE-THREATENING ACDR

It is vital to look for the following signs of life-threatening ACDR:

- Confluent erythema, palpable purpura, blisters, skin necrosis and mucosal erosions.

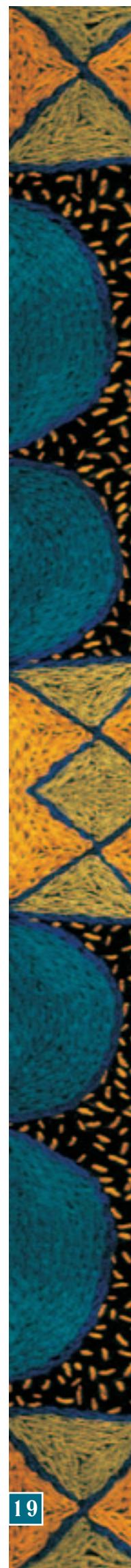




Fig. 1. Morbilliform rash.



Fig. 3. Fixed drug eruption.



Fig. 2. Erythema multiforme: urticarial plaques with targetoid centres.

- Urticaria, tongue swelling, dyspnoea, wheezing, hypotension.
- Fever (temperature over 40°C), enlarged lymph nodes, arthralgia/arthritis, eosinophilia (> 1 000/ $\mu$ l), lymphocytosis with atypical cells, and abnormal liver function test (LFT) results, i.e. > 5 times the upper limit of normal (ULN).

#### ACDRs TO CO-TRIMOXAZOLE

This is the commonest ACDR in HIV infection. The prevalence in the general population is 2.6 - 8%, increasing 10-fold in HIV infection. It rises from 43% in HIV infection to 69% in AIDS.<sup>4-6</sup> At least 50 - 60% of patients will experience a morbilliform

reaction with associated fever 1 - 2 weeks after initiating therapy. If the reaction is non-life-threatening, therapy can be continued with symptomatic treatment using systemic antihistamines and topical corticosteroids for the rash. It is important to carry out regular assessment and patient education for danger signs. If the rash persists, the dose of co-trimoxazole should be reduced. If this is still ineffective, corticosteroids (0.5 mg/kg) should be prescribed up to a maximum of 21 days.

Re-challenge is safe in patients with non-life-threatening hypersensitivity.<sup>9</sup> Desensitisation of patients with documented, non-life-threatening ACDR has been shown to effectively induce tolerance in 63% of cases.<sup>10</sup> Patients requiring re-challenge and desensitisation should be referred to a tertiary centre.

#### ACDRs TO ANTITUBERCULOSIS THERAPY

Historically, severe cutaneous hypersensitivity has been an extremely rare complication of antituberculosis chemotherapy in TB patients in Africa. However, there has been an increase in cutaneous reactions in HIV-infected patients on tuberculosis (TB) therapy, reported to occur in 23% of patients in one series.<sup>11</sup> Reactions are usually morbilliform and may be severe, and are commonest against thiacetazone, followed by streptomycin, para-aminosalicylic acid (PAS) and isoniazid (INH). However, reactions to antituberculosis therapy are common in HIV-infected patients even when using thiacetazone-free regimens.

If reactions are minor and self-limiting, symptomatic therapy may be all that is required. If persistent, stop all treatment and identify the drug(s) responsible, and try to resume therapy as soon as possible.



Fig. 4 (a). Stevens-Johnson syndrome: conjunctival erosions.



Fig. 5 (a). Toxic epidermal necrolysis: generalised stripping of the skin.



Fig. 4 (b). Stevens-Johnson syndrome: oral erosions.



Fig. 5 (b). Toxic epidermal necrolysis: stripping of skin of sole.



Fig. 4 (c). Stevens-Johnson syndrome: penile erosions.



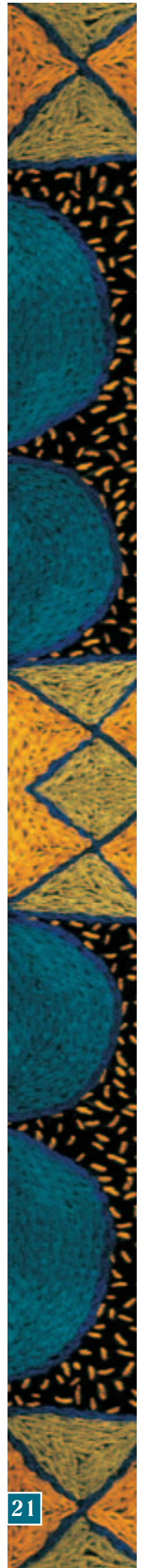
Fig. 5 (c). Toxic epidermal necrolysis: stripping of palmar skin.

To re-challenge, after the reaction subsides daily challenge doses should be administered. Aim to start with those drugs least likely to be implicated (Table I), and if there is no reaction to challenge doses, continue with full doses.

#### ACDRs AND HAART

ACDRs are common with antiretroviral (ARV) drugs, especially with the non-nucleoside reverse transcriptase

inhibitors (NNRTIs), but can occur with all ARVs. Most reactions are morbilliform and non-life-threatening, and the majority will resolve despite continuation. They are commonest with the NNRTIs, nevirapine (NVP) and efavirenz (EFZ) and usually occur within the first 4 - 6 weeks. They most commonly present with a morbilliform eruption or urticaria and occur in 9 - 32% of patients on NVP. The major risk factors for NVP rash are female gender, HLA DRB1\*0101, and high CD4 count (> 250 in females and > 400 in males). However, in the



**TABLE I. ANTI-TUBERCULOSIS DRUG RECHALLENGE REGIMEN\***

Drug	Day 1	Day 2	Severe reaction (1/10 dose)
INH	50 mg	300 mg	5 mg
RIF	75 mg	300 mg	7.5 mg
PZA	250 mg	1.0 g	25 mg
ETH	100 mg	500 mg	10 mg
STREP	125 mg	500 mg	12.5 mg
PAS	1.0 g	5.0 g	0.1 g

INH = isoniazid; RIF = rifampicin; PZA = pyrazinamide; ETH = ethambutol; STREP = streptomycin; PAS = para-aminosalicylic acid.

\* Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1981; **23**: 56-74.

absence of blisters, erythroderma, mucosal involvement and hepatitis, therapy can be continued and the reaction treated symptomatically with antihistamines and corticosteroids. Approximately 6 - 7% of patients will require discontinuation. Signs indicating that treatment should be stopped are:

- mucosal involvement, blistering and exfoliation
- clinically significant hepatic dysfunction, temperature of 39°C or higher and intolerable pruritus.

SJS (Fig. 4, a, b, c) and TEN (Fig. 5, a, b, c) occur in approximately 1% of treated patients and require prompt recognition and permanent discontinuation of the drug. In these patients reintroduction is contraindicated. Close monitoring of patients on NVP is therefore essential in the first 8 weeks after initiation of therapy. Patients who develop a rash should always be assessed for hepatotoxicity.

### HYPERSENSITIVITY SYNDROME

This is a life-threatening reaction that occurs in the first 42 days of ART. It presents with a diffuse maculopapular eruption, fever, eosinophilia, atypical lymphocytosis, multivisceral involvement and abnormal LFT results (AST and ALT > 5 X ULN) and occurs most commonly with NVP (2%), EFZ, abacavir (ABC), amprenavir and indinavir. The mortality rate is 10% with NVP, death usually being due to liver failure. If hypersensitivity is suspected, discontinue without re-challenge.

### RECURRING DRUG REACTIONS

Persistent non-life-threatening drug reactions or recurrent reactions can seriously impede effective management of HIV and opportunistic infections. These reactions occur during the first 8 weeks of therapy, coinciding with the increase in CD4+ cell count, and are a manifestation of immune reconstitution. The use of a protracted course of steroids (0.5 mg/kg for the

first 8 weeks of therapy) in patients who develop recurrent and potentially severe cutaneous eruptions and have a past history of ACDRs allows suppression of reactions while initiating and continuing crucial medications.<sup>12</sup>

### CONCLUSION

ARV therapy has significantly reduced overall mortality from HIV. In patients on highly active antiretroviral therapy (HAART) cutaneous manifestations of HIV have been reduced by 40%<sup>13</sup> and dermatological consultations by 63%,<sup>13</sup> and the resultant burden of disease from inflammatory, infective disorders and malignant disease has also been reduced, enabling patients to enjoy a better quality of life. The incidence of cutaneous drug reactions has increased from 8% to 20%,<sup>13</sup> the most severe reactions being SJS, TEN and hypersensitivity syndrome. These severe life-threatening adverse cutaneous reactions occur most commonly with the NNRTIs, NVP and EFZ; the NRTI ABC, and the protease inhibitors (PIs) indinavir and amprenavir. Most reactions (86%) occur within 4 weeks of therapy and require prompt recognition and treatment discontinuation without re-challenge, and appropriate drug substitution.

### REFERENCES

1. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000; **356**: 1423.
2. Battegay M, Opravil M, Wuthrich B, Luthy R. Rash with amoxicillin-clavulanate therapy in HIV-infected patients. *Lancet* 1989; **2**: 1100.
3. Coopman SA, Stern RS. Cutaneous drug reactions in human immunodeficiency virus infection. *Arch Dermatol* 1991; **127**: 714-717.
4. Jick J. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis* 1982; **4**: 426-428.
5. De Raeve L, Song M, Van Maldergem L. Adverse cutaneous drug reactions in AIDS. *Br J Dermatol* 1991; **127**: 714-717.
6. Mitsuyasu R, Groopman J, Volberding P. Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308**: 1535-1536.
7. Van der Ven AJAM, Koopmans PP, Vree TB, Van der Meer JWM. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431-433.
8. Johnson RA. Cutaneous manifestations of human immunodeficiency virus disease. In: Friedberg IM, Eisen AZ, Wolf K, et al., eds. *Fitzpatrick's Textbook of Dermatology*. 5th ed. McGraw-Hill, 1999: 2138-2150.
9. Carr A, Penny R, Cooper DA. Efficacy and safety of rechallenge with low-dose trimethoprim-sulfamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; **7**: 65-71.
10. Belchi-Hernandez J, Espinosa-Parra FJ. Management of adverse reactions to prophylactic trimethoprim-sulfamethoxazole in patients with human immunodeficiency virus infection. *Ann Allergy Asthma Immunology* 1996; **76**: 355-358.
11. Kuaban C, Bercion R, Koulla-Shiro S. HIV seroprevalence rate and incidence of adverse skin reactions in adults with pulmonary tuberculosis receiving thiacetazone free anti-tuberculosis treatment in Yaounde, Cameroon. *East Afr Med J* 1997; **74**: 474-477.
12. Dolev J, Reyter I, Maurer T. Treatment of recurring cutaneous drug reactions in patients with human immunodeficiency virus 1 infection. *Arch Dermatol* 2004; **140**: 1051-1053.
13. Calista D, Morri M, Stagno A, Boschini A. Changing morbidity of cutaneous diseases in patients with HIV after the introduction of highly active antiretroviral therapy including a protease inhibitor. *Am J Clin Dermatol* 2002; **3**(1): 59-62.