CHAPTER 6: DRUG ERUPTIONS

Introduction: Drug eruptions are more common in HIV-infected individuals, up to 100-fold by some estimates - Mild and transient to life threatening, skin deep or multisystem. The reason for the increased incidence of drug eruptions in HIV-infected individuals may be as a result of the use of multiple medications including treatment for opportunistic infections and antiretroviral therapy; genetic predisposition; and HIV-associated immune dysregulation, which lowers the threshold of T cell activation coupled with persistent stimulation of CD8 T cells.

Classification

Two types of reactions to medications and they are either predictable (type A) and unpredictable (type B).

Type A includes lipodystrophy and pigmentation. Type B reactions include morbilliform eruptions, Steven Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, erythroderma, vasculitis and fixed drug eruptions, lichenoid reactions.

Further reading

1. Luther J, Glesby MJ. Dermatologic adverse effects of antiretroviral therapy: recognition and management. Am J Clin Dermatol. 2007; 8(4):221-33.
2. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. J Am Acad Dermatol. 2010 ;63(4):549-61; doi: 10.1016/j.jaad.2010.01.061.
3. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. No nucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010; 63(4):563-9.
4. Sharma A, Vora R, Modi M et al. Adverse effects of antiretroviral treatment. Indian J Dermatol Venereol Leprol 2008; 74:234-7.

Table 5: Cutaneous reactions due to antiretroviral agents including both types A and B reactions

Antiretroviral drug	**Cutaneous reaction**
Nucleoside reverse transcriptase inhibitor (NRTI)	
Zidovudine	Mucocutaneous and nail hyperpigmentation, rarely: Hypertrichosis, vasculitis, paronychia
Stavudine	Lipodystrophy
Didanosine	Vasculitis, SJS, alopecia
Abacavir	Hypersensitivity reaction -Maculopapular eruption, urticaria, erythema multiforme
Lamivudine	Paronychia, allergic contact dermatitis
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	
Nevirapine	DRESS, SJS
Efavirenz	Skin eruption (usually mild)
Etravirine	Maculopapular eruption (mild to moderate)
Protease inhibitors (PI)	
General	Lipodystrophy, hypersensitivity reaction
Indinavir	Paronychia, porphyria, SJS, alopecia, gynaecomastia
Nelfinavir	Maculopapular eruption, urticaria
Atazanavir	Maculopapular eruption, asymptomatic jaundice and sclera icterus
Darunavir	Maculopapular eruption
Integrase inhibitor	
Raltigravir	Diaphoresis

Type A reactions

Antiretroviral Lipodystrophy

Lipodystrophy syndrome (includes lipoatrophy and lipohypertrophy) is one of the long-term toxicities of stavudine (d4T) which was one of the back bones of first line antiretroviral therapy. Protease inhibitors (PIs) are also implicated in causing this syndrome.

Lipoatrophy is characterized by loss of subcutaneous tissue from facial pads, extremities, and buttocks. Apart from abnormal fat redistribution in stavudine toxicity, metabolic abnormalities including hyperlipidaemia may also be associated. Studies have reported a prevalence of between 18% and 33%. Stavudine is thought to cause lipoatrophy by inducing adipocyte apoptosis.

As a result of lipodystrophy and other toxicity effects of stavudine, national treatment programmes have dropped d4T and moved to zidovudine or abacavir based regimens. Replacing stavudine with abacavir or zidovudine resulted in improvement in established stavudine-induced lipoatrophy in HIV-infected subjects.

Further reading

1. Amaya RA, Kozinetz CA, McMeans A et al. Lipodystrophy syndrome Antiretroviral in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2002; 21:405-10.
2. Vigano` A, Thorne C, Brambilla P et al. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS. 2004; 18:1443 - 51.
3. Sanchez Torres AM, Munoz Muniz R, Madero R et al. Prevalence of fat redistribution and metabolic disorders in human immunodeficiency virus-infected children. Eur J Pediatr. 2005; 164:271 - 6.
4. McComsey GA, Ward DJ, Hessenthaler SM et al. Improvement in Lipoatrophy Associated with Highly Active Antiretroviral Therapy in HIV-infected Patients Switched from Stavudine to Abacavir or Zidovudine: The Results of the TARHEEL Study. Clin Infect Dis 2004; 38:263-270.
5. Ene L, Goetghebuer T, Hainaut M et al. Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study. Eur J Pediatr. 2007; 166:13-21.
6. Piloya T, Bakeera-Kitaka S, Kekitiinwa A et al. Lipodystrophy among HIV-infected children and adolescents on highly active antiretroviral therapy in Uganda: a cross sectional study. J Int AIDS Soc. 2012; 15(2):17427. doi: 10.7448/IAS.15.2.17427.

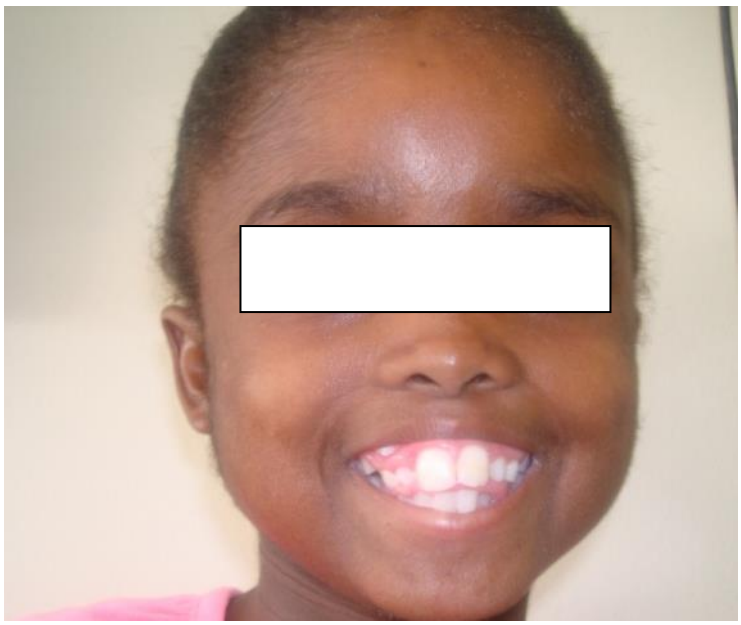

Figure 84 Nine year old girl who had been on stavudine based regimen from the first year of life. Stavudine was substituted with abacavir 6 months prior on account of lipoatrophy.

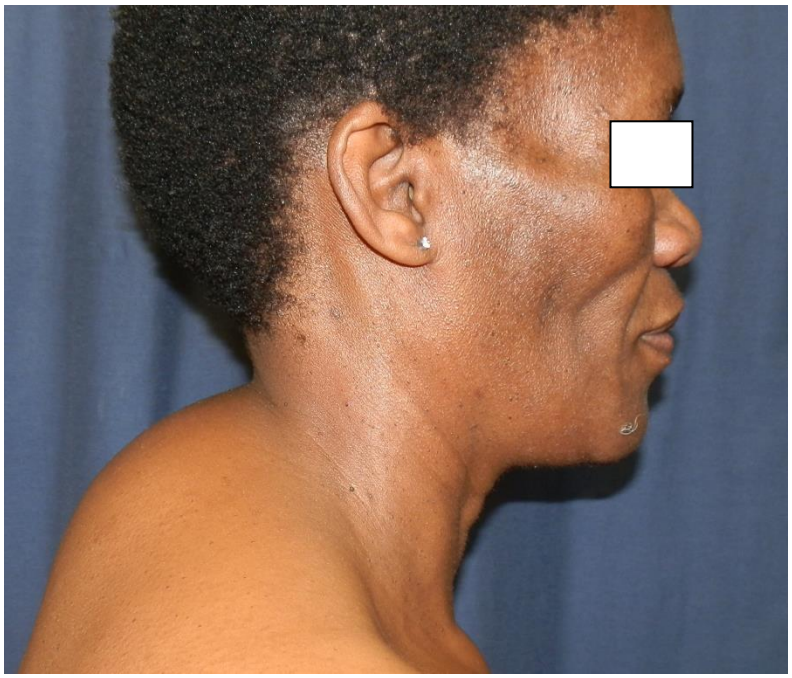

Figure 85: An adult with stavudine-associated lipodystrophy. Note the temporal wasting loss of buccal fat pad and the enlarged dorsocervical fat pad.

Type B reactions

Morbilliform drug eruptions

Definition and clinical presentation: Morbilliform (measles-like) drug eruption or maculopapular exanthems usually manifest 7–14 days after drug exposure. The lesions can progress and become confluent resulting in erythroderma. There are no associated systemic features. The rash is transient and treatment should not be interrupted. However, morbilliform rash can be the initial presentation of more serious reactions such as DRESS.

Aetiology: There is a very wide spectrum of drugs that cause morbilliform eruptions.

Epidemiology: This accounts for 95% of all cutaneous drug reactions.

Treatment: Usually not necessary, but topical steroids may speed up resolution.

Further reading

1. Bigby M. Rates of cutaneous reactions to drugs. Arch. Dermatol. 2001;137 (6): 765–770.

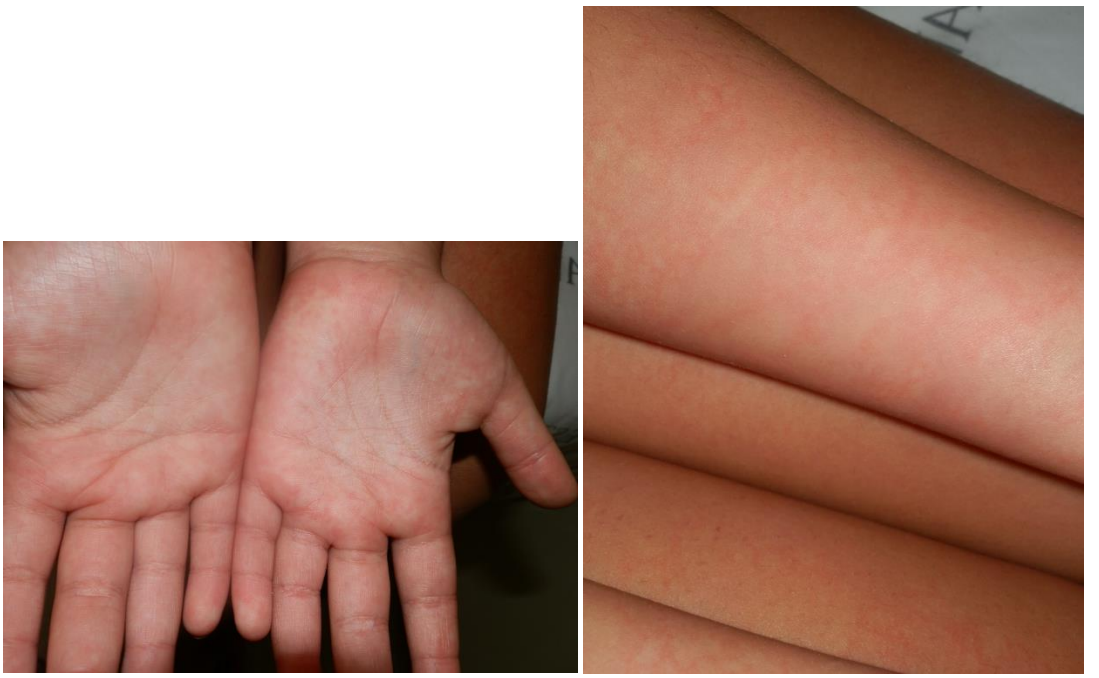

Figure 86: Transient morbilliform drug eruption on a young girl.

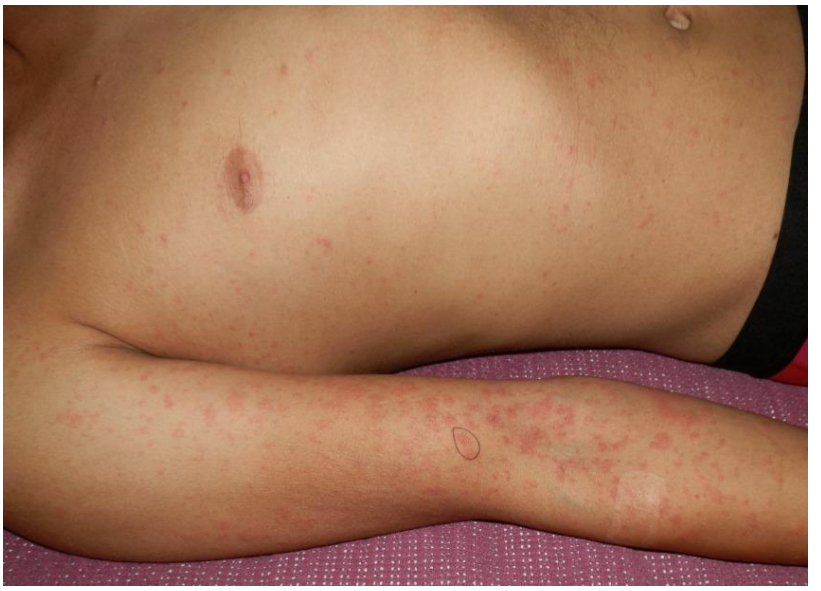

Figure 87: Morbilliform rash (measles-like) in an adolescent with a drug reaction.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Definition and presentation: Also known as drug hypersensitivity syndrome is a drug reaction characterized by a long latency period (> 3 weeks), a rash, fever, oedema, lymphadenopathy, leukocyte abnormalities (leucocytosis, eosinophilia and/or atypical lymphocytosis) and hepatitis. The eruption is usually urticaria-like or maculopapular, but may present as vesicles, pustules or purpura.

Aetiology: A large number of drugs are associated with DRESS; however, in HIV-infected persons anti-tuberculosis drugs, co-trimoxazole and nevirapine are often implicated.

Epidemiology: **The incidence in HIV-infected people is much higher**

Treatment: Immediate withdrawal of the offending drug improves outcomes but treatment is mainly supportive. Topical steroids are helpful but in severe cases systemic steroids are used.

Complications: DRESS has mortality of up to 10%. Complications include liver failure, renal failure, myocarditis, pneumonitis and pancreatitis.

Further reading

1. Cacoub P, Musette P, Descamps V et al. The DRESS syndrome: a literature review. Am J Med. 2011; 124(7):588-97.
2. Noguera-Morel L, Hernández-Martín Á, Torrelo A. Cutaneous drug reactions in the paediatric population. Pediatr Clin North Am. 2014; 61(2):403-26.
3. Cacoub P, Musette P, Descamps V et al. The DRESS syndrome: a literature review. Am J Med. 2011;124(7):588-97.
4. Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin. Exp. Dermatol. 36(1), 6–11 (2011).

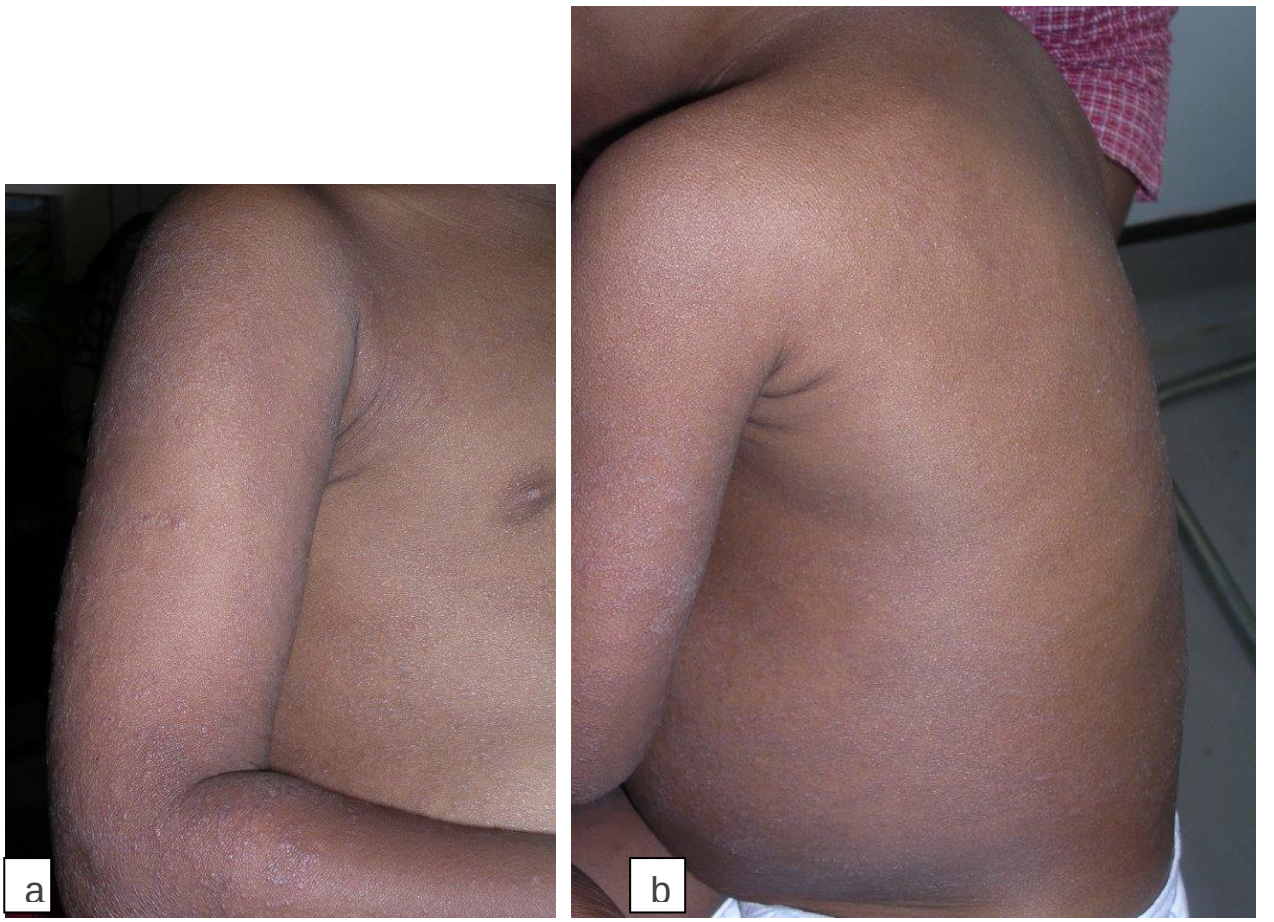

Figure 88a and b: DRESS

Abacavir Hypersensitivity

Abacavir (ABC) is a nucleoside analogue reverse transcriptase inhibitor. Approximately 3-5% of individuals who receive abacavir develop an immune-mediated hypersensitivity reaction (HSR) which occurs within the first six weeks of therapy. The HSR is rare but life threatening and is associated with individuals who carry the *57:01 variant in the human leukocyte antigen B (HLA-B) gene.

Diagnosis: The most common symptoms are fever, skin rash, gastrointestinal disorders and respiratory symptoms. A reduction in the incidence of abacavir hypersensitivity and unwarranted interruptions of therapy have been demonstrated with prospective screening for HLA-B*57:01 allele.

Considering the lower risk for abacavir hypersensitivity reaction and cost implications, implementation of genetic testing in this regard, in African settings in routine clinical practice may not be feasible. The importance of clinical monitoring of patients on abacavir cannot be overemphasized.

Treatment: Clinical management of suspected hypersensitivity reaction is discontinuation of abacavir and supportive care with analgesics, antihistamines, adequate fluids and appropriate laboratory monitoring for systemic organ involvement. Rechallenge with abacavir is contraindicated due to the risk of precipitating a life-threatening reaction.

Further reading

1. Borrás-Blasco J, Navarro-Ruiz A, Borrás C et al. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J. Antimicrob. Chemother. 2008; 62 (5): 879-888.
2. Calmy A, Hirschel B, Cooper DA et al. Clinical update: adverse effects of antiretroviral therapy. Lancet; 370 (2007): 12–14.
3. Rauch A, Nolan D, Martin A et al. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. Clin Infect Dis 2006; 43: 99–102.
4. Martin MA, Kroetz DL. Abacavir Pharmacogenetics - From Initial Reports to Standard of Care. Pharmacotherapy 2013; 33(7): 765-75
5. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008; 358:568-79.
6. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. J Am Acad Dermatol. 2010; 63(4):549-61; doi: 10.1016/j.jaad.2010.01.061.

Nevirapine Hypersensitivity

Nevirapine (NVP) induced rash or toxicity occur in estimated 7-15% of patients receiving the drug. NVP rash can vary from a mild morbilliform rash to Stevens-Johnson syndrome. The rash typically develops within six weeks of initiating therapy. The introduction of NVP at a low dose with escalation over a 2-week period is recommended.

Patients with higher CD4 cell counts, including patients using NVP as post-exposure prophylaxis, are reported to have a higher risk of systemic hypersensitivity reaction, and therefore NVP is not recommended as part of post-exposure prophylaxis regimens.

A patient on NVP who develops a rash should be assessed for hepatotoxicity. If a morbilliform exanthem occurs in the setting of a fever, hepatitis, or other systemic symptoms, NVP must be discontinued immediately.

Further reading

1. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. Non-nucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010; 63(4):563-9.
2. Namayanja GK, Nankya JM, Byamugisha JK. Stevens - Johnson syndrome due to nevirapine. Afr Health Sci. 2005;5 (4):338-40.
3. Kiertiburanakul S, Sungkanuparph S, Charoenyingwattana A et al. Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. Curr HIV Res 2008;65–9.

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN represent a spectrum of rare but potentially fatal mucocutaneous diseases characterized by widespread epidermal necrosis and mucosal involvement. SJS and TEN are considered to be part of a spectrum of severe cutaneous adverse reactions with increasing severity and extent of skin detachment, ranging from SJS (less than 10% body surface area skin detachment, 1-5% mortality) to TEN (greater than 30% skin detachment, 25-35% mortality).

In HIV-infected patients, the most common antiretroviral drug implicated to cause SJS/TEN is nevirapine and less commonly protease inhibitors. Co-trimoxazole and antituberculosis drugs are also implicated. Re-exposure to the drug results in recurrence.

Diagnosis: The reaction develops around 7-14 days after initiation of the drug. The rash is preceded by a prodrome with constitutional symptoms of high fever, malaise, myalgia and arthralgia. This is often misdiagnosed as an upper respiratory infection and treated with drugs that are later incorrectly blamed as offenders. Mucocutaneous lesions develop abruptly as macules that progress to papules, vesicles, bullae or confluent erythema.

Although minor presentations may occur, significant involvement of oral, nasal, eye (acute conjunctivitis, eyelid oedema, and crusting to conjunctival membrane or pseudomembrane, corneal erosions, conjunctival fornix foreshortening, and corneal ulcers), vaginal, urethral, gastrointestinal, and lower respiratory tract mucous membranes may develop in the course of the illness.

Treatment: Treatment should involve a multi-disciplinary team in a high-level health facility. Identification and withdrawal of the suspected offending agent is important. Supportive care involves analgesia and maintenance of adequate fluid and electrolyte balance. Frequent ophthalmological assessment and antiseptic/antibiotic eye drops 2-hourly are advocated. Barrier nursing and infection control prevention measures are important.

The use of prophylactic broad-spectrum systemic antibiotics, intravenous immunoglobulin (IVIG) and steroids is controversial. Topical cleansing/antibacterial agents could include 0.5% silver nitrate solution on gauze or 10% chlorhexidine gluconate washes or saline washes or polymixin/bacitracin or 2% mupirocin.

For wound care, silver sulfadiazine needs to be avoided. Removal of necrotic epidermis is discouraged, as intact epidermis prevents bacterial inoculation onto the underlying viable dermis. Paraffin gauze or hydrogel dressings may be beneficial. Biological dressings may be required (xenografts, allografts, skin substitutes).

Complications: Acute complications are similar to those of extensive burns. The high morbidity and mortality associated with the condition occurs mainly from infection. Long-term sequelae of SJS/TEN include; recurrence, dyspigmentation, oesophogeal and genital tract stenosis, eye problems, genital fibrosis. Multidisciplinary care during the acute stage is necessary to prevent these complications.

Further reading

1. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. Non-nucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010; 63(4):563-9.
2. Tartarone A, Lerose R. Stevens-Johnson syndrome and toxic epidermal necrolysis: what do we know? Ther Drug Monit. 2010; 32(6):669-72. doi: 10.1097/FTD.0b013e3181f2f24f.
3. Mason AR, Cortes GY, Pollack RB. Nevirapine-Induced Stevens–Johnson Syndrome in a Pediatric Patient. Pediatr Dermatol. 2008; 25(1):128-9. doi: 10.1111/j.1525-1470.2007.00605.x.
4. Chung WH, Hung SI, Hong HS et al, Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004; 428(6982):486.
5. Wei CY, Ko TM, Shen CY et al. A recent update of pharmacogenomics in drug-induced severe skin reactions. Drug Metab Pharmacokinet. 2012;27 (1):132-41.
6. Peters PJ, Polle N, Zeh C et al. Nevirapine-associated hepatotoxicity and rash among HIV-infected pregnant women in Kenya. J Int Assoc Physicians AIDS Care (Chic). 2012;11(2):142-9.

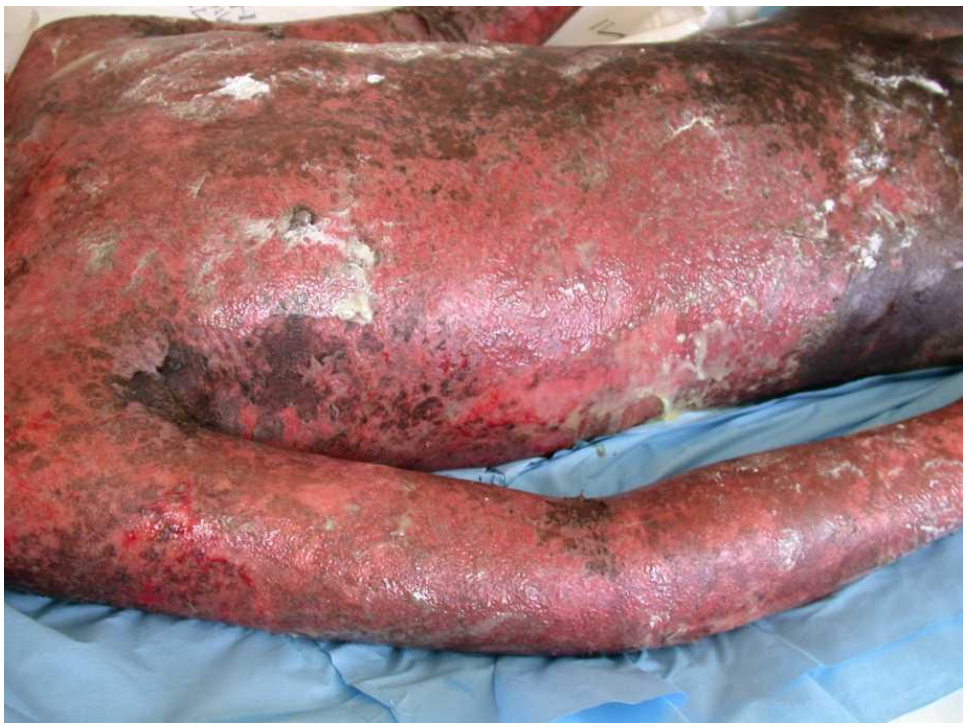

Figure 89: Extensive epidermal necrosis with areas of stripping in a case of TEN

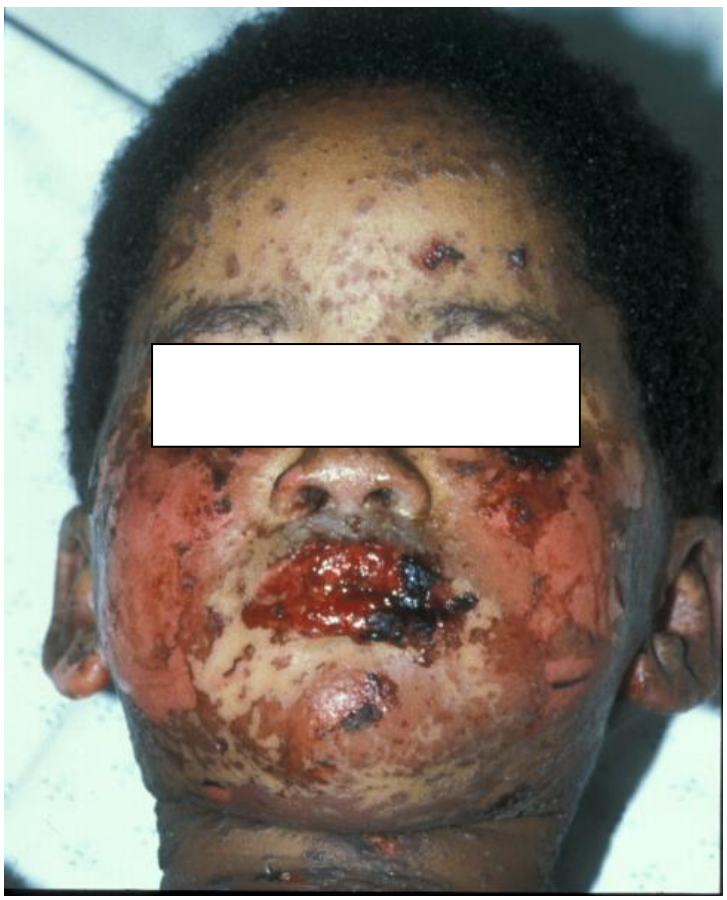

Figure 90: Epidermal necrosis with stripping and haemorrhagic cheilitis in a child with toxic epidermal necrosis.

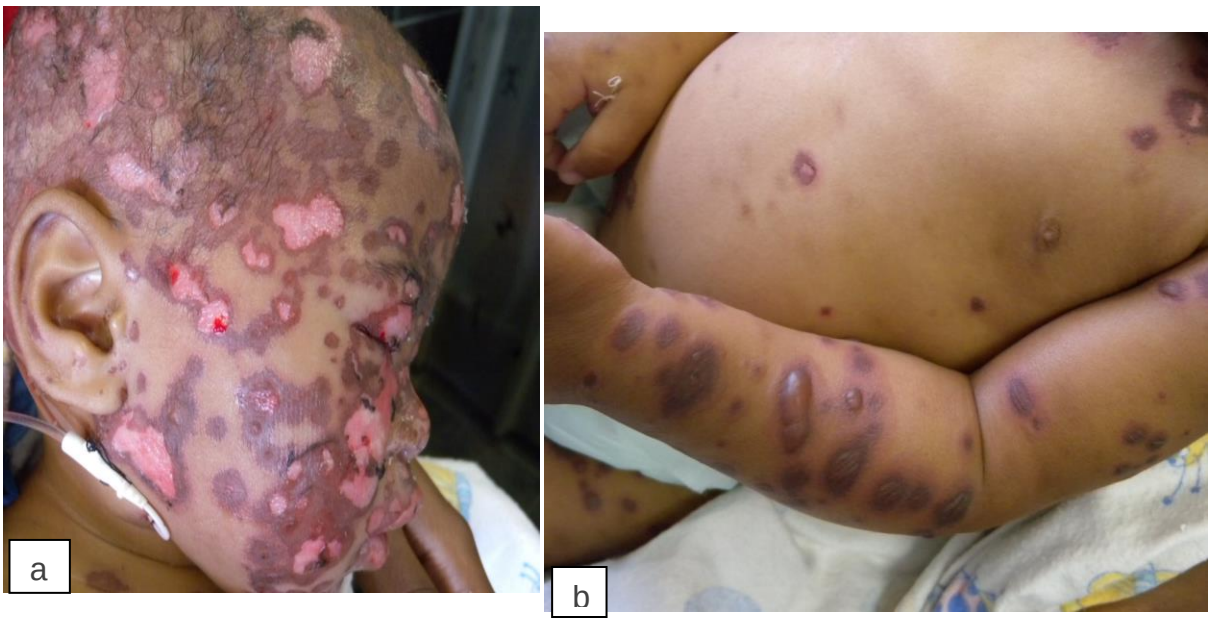

Figure 91a and b: Focal areas of epidermal necrosis with stripping in a case of SJS.

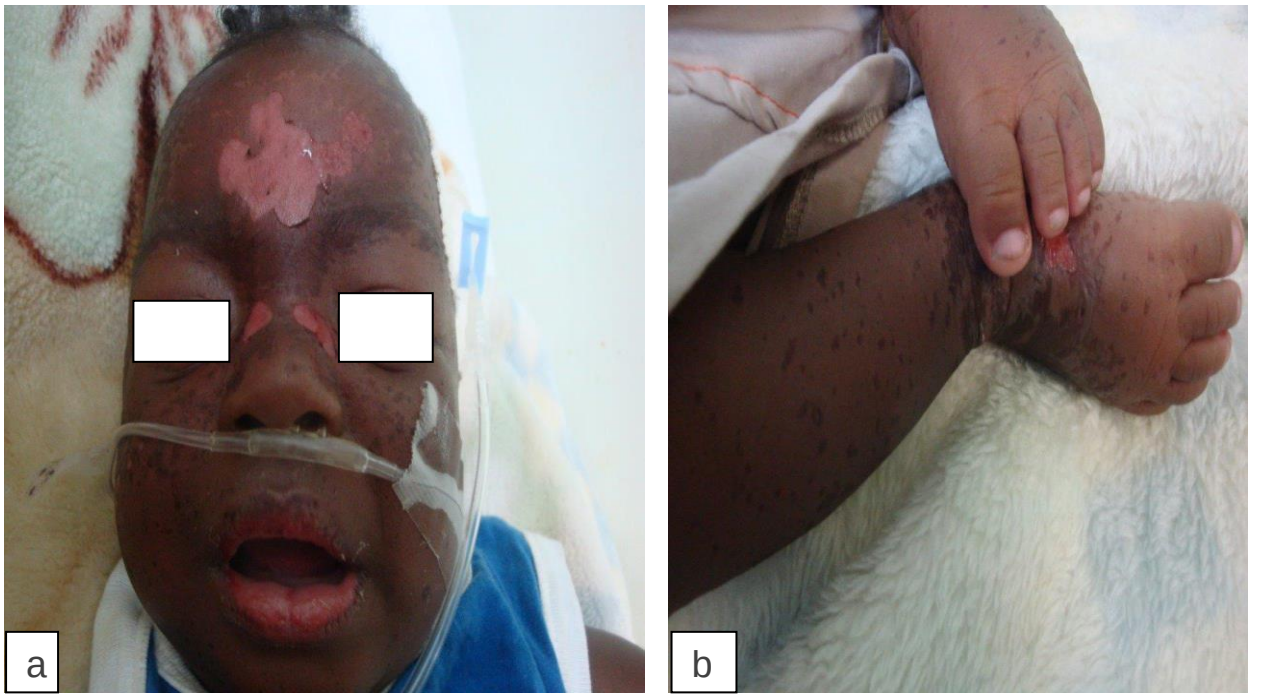

Figure 92a and b: SJS- Focal areas of epidermal necrosis with stripping.

Fixed Drug Eruptions

A fixed drug eruption characteristically recurs in the same site or sites each time the drug is administered. With each exposure, the number of involved sites may increase. Usually, just one drug is involved, although independent lesions from more than one drug have been described.

Cross-sensitivity to related drugs may occur, such as between tetracycline-type drugs, and between anticonvulsants. Fixed drug eruptions may occur with protease inhibitors. There may be a refractory period after the occurrence of a fixed eruption. Acute lesions usually develop 30 min to 8 hours after drug administration as sharply marginated, round or oval itchy plaques of erythema and oedema becoming dusky violaceous or brown, and sometimes vesicular or bullous.

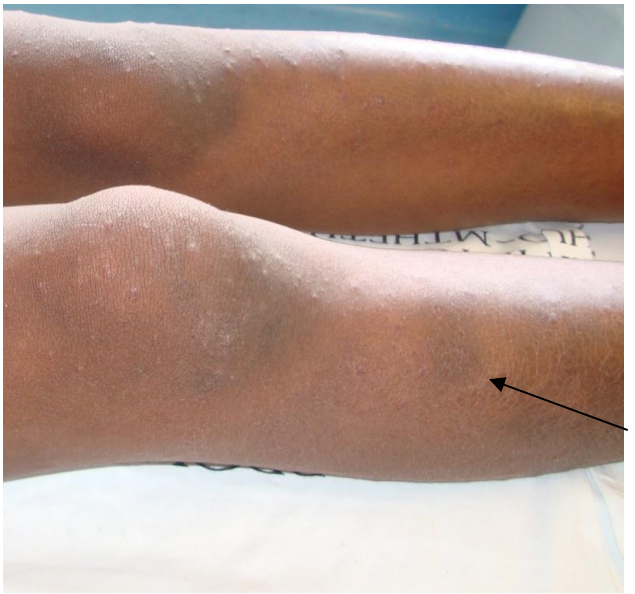

Figure 93: Mild fixed drug eruption/hyperpigmentation following cotrimoxazole prophylaxis therapy.

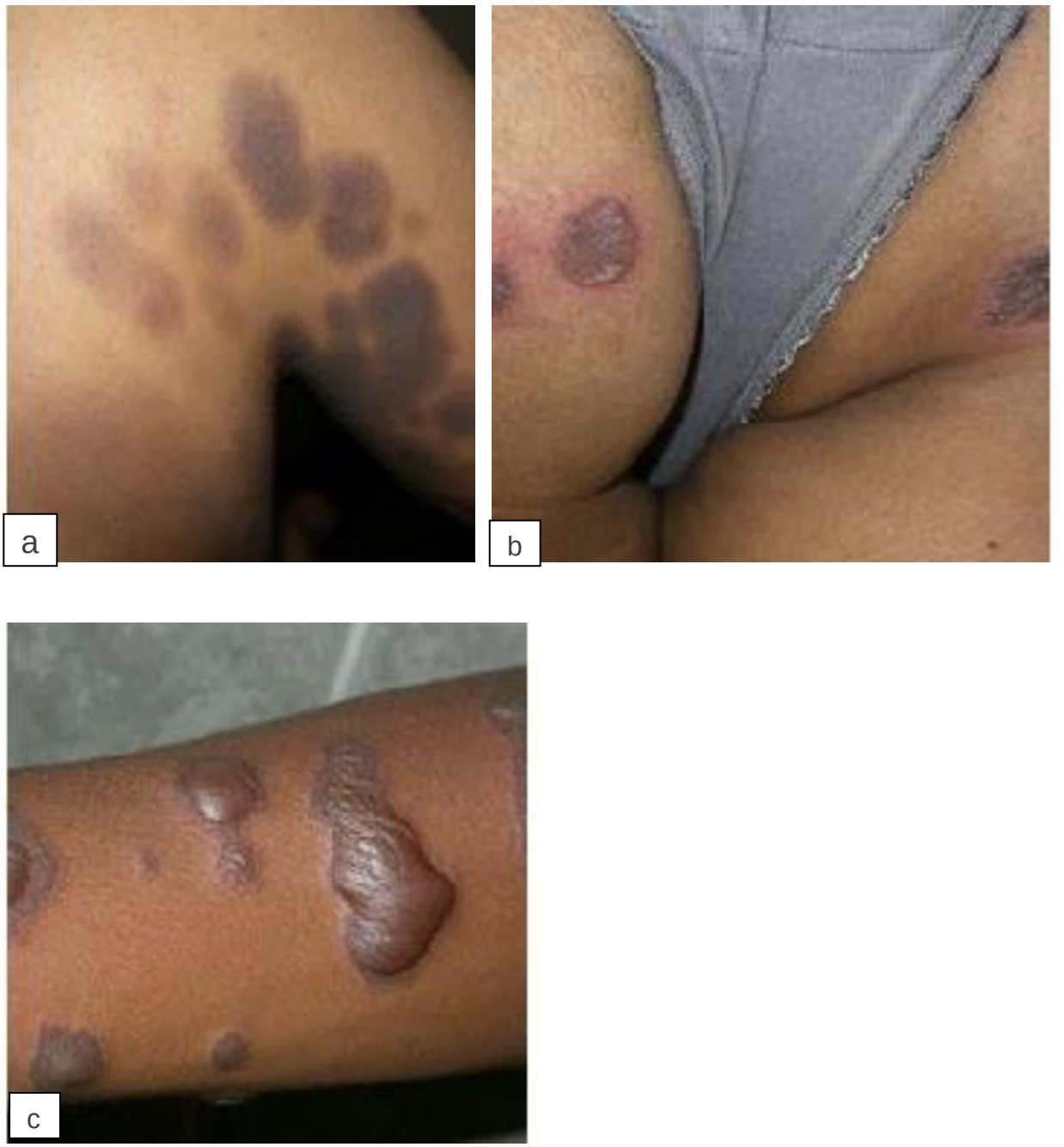

Figure 94a and b: Fixed drug eruption. a. Early lesions with rim of erythema and small blister. b. Bullous fixed drug eruption. c. Classic round pigmented macules of resolved fixed drug eruption.