

Skin in HIV

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Cutaneous Manifestations of Anti-Retroviral Therapy

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Worldwide, over 40 million people are infected with the Human Immunodeficiency Virus (HIV). Global AIDS-related deaths peaked at 2.3 million in 2005, and decreased to 1.6 million by 2012. The incidence of new infections decreased from 3.3 million in 2002, to 2.3 million in 2012. HIV prevalence is increasing worldwide because people on antiretroviral agents (ART) are living longer.

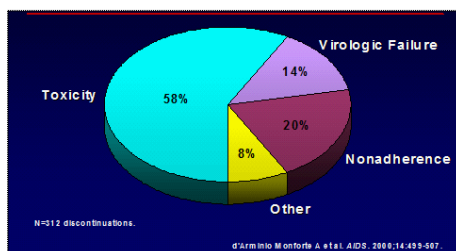
Before the introduction of ART in the mid 1990s, HIV-associated cutaneous disorders were among the most common complications (upto 80%) of the immunodeficiency [1]. Skin conditions such as Kaposi's syndrome, oropharyngeal candidosis or persisting herpes simplex infection were therefore among the AIDS-defining diseases. After the advent of ART, the commonly associated dermatological diseases have decreased and now, cutaneous drug reactions are more associated with the immunodeficiency [1,2].

For successful ART, along with other factors like adherence, cost, it is necessary to know the toxic effect of drugs, which will help in early diagnosis and pro-active management, should an adverse reaction arise. For example, Nevirapine can give rise to Steven-Johnson syndrome, so if the patient is advised to watch for any skin rash, the drug can be stopped in time and the fatal outcome can be prevented.

Antiretroviral drugs fall into eight categories [nucleoside reverse transcriptase inhibitors

(NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), co-receptor inhibitors (CRIs) and integrase inhibitors (INIs). Maturation inhibitors (i.e. bevirimat) represent the most recent advance in the search for effective and selective anti-HIV agents. The High Activity Antiretroviral Therapy (HAART) combines atleast three antiretroviral (ARV) drugs and, for over a decade, has been used to increase their lifespan and quality of life of the HIV-infected patients [3-5].

Within the first year of treatment, adverse drug reactions are the most common reasons for the discontinuation of HAART among HIV-infected patients, rather than treatment failure. Patients infected with HIV are highly susceptible to adverse dermatological reactions to specific medications. Up to 80% of HIV-infected patients experience adverse drug reactions at some point during their therapy, presumably as a result of immune dysregulation, altered drug metabolism and/or polypharmacy [6]. When compared to the general population, HIV infected patients have a higher risk of developing cutaneous reactions. The severity of cutaneous adverse reactions varies greatly, and some may be difficult to manage [4].



What Causes ART ADRs / Toxicities ?

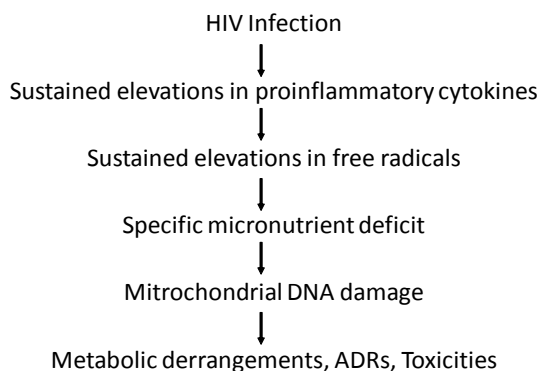


Figure 5.1: Graph showing reasons for discontinuation of ART.

TOXIC REACTIONS, IN GENERAL, CAN BE CLASSIFIED IN VARIOUS WAYS

Augmented or Bizarre

Augmented adverse reaction is explicable in pharmacological terms and is generally dose dependent. Examples include dose- dependent increase in CNS toxicity with Efavirenz.

Bizarre adverse reaction is neither predictable nor dose dependent and occurs only in individual patients. This category includes allergic reactions such as skin rashes or hypersensitivity reactions, like that seen with Abacavir [7].

Acute or Chronic

Acute toxicities:

- *Organ:* Liver, kidney, bone marrow.
- *Cutaneous reactions:* Hypersensitivity, SJ syndrome.

Chronic toxicities:

- *Morphologic complications:* Lipodystrophy, gynaecomastia, dorso-ventral fat pad, cosmetic disfigurement.
- *Metabolic Abnormalities:* Insulin resistance, abnormalities of glucose metabolism, dyslipidemias, lactic acidosis, hepatosteatorosis, osteopenia, osteonecrosis, osteoporosis, increased bleeding in haemophiliacs.

Mild, moderate, severe or fatal (grade I, II, III, IV respectively)

TOXIC REACTIONS, PERTAINING TO SKIN, CAN BE CLASSIFIED AS ALLERGIC AND NON-ALLERGIC, ACCORDING TO INDIVIDUAL DRUGS

Non-Allergic Cutaneous Effects of ART

Lipodystrophy

HIV-associated lipodystrophy is a disorder of body fat distribution characterized by a combination of fat loss (face, arms and legs) (Figure 5.2a,5.2b,5.2c) and fat accumulation (abdomen, chest and neck) (Figure 5.3, 5.4). 20% to 80% of patients develop lipodystrophy [6]. The pathogenesis of lipodystrophy is multifactorial. Causal factors are HIV infection, the antiretroviral drugs and further risk factors such as the duration of antiretroviral therapy, extent of the immunodeficiency and the concentration of triglycerides [7]. The disorder is based on mitochondrial damage to the cells. The NRTIs interfere with DNA polymerase gamma, the enzyme responsible for replication of mitochondrial DNA [7,8]. The most potent effect on lipodystrophy

is exerted by the thymidine analogues, especially stavudine (d4T). Alternatively, a NRTI-free HAART may be attempted. Cosmetic remedies such as liposuction or lipotransplantation can be attempted, but generally have only a temporary effect. The administration of growth hormones can inhibit the proliferation of fat. Endurance training also has beneficial effects on disorders of fat distribution. The injection of poly-L-lactic acid can improve the lipoatrophy. In therapy with protease inhibitors, cholesterol and triglyceride levels can also increase and insulin resistance may develop [9].



Figure 5.2a, 5.2b, 5.2c: Stavudine induced Lipoatrophy.



Figure 5.3: Buffalo hump-Lipodystrophy by stavudine.

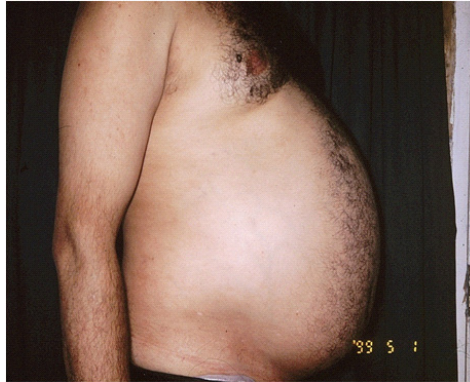


Figure 5.4: Crix belly.

Hyperpigmentation

Hyperpigmentations due to melanin incorporation are occasionally observed during ART, most commonly as longitudinal nail pigmentation (Figure 5.5), and more rarely as mucosal hyperpigmentation (Figure 5.6). The longitudinal discoloration of the nails is diagnosed especially during therapy with azidothymidine (AZT), more rarely with lamivudine (3TC), with an increased incidence and intensity in the dark skin type [10]. The hyperpigmentation may fade after switching medications. Palmar hyperpigmentations develop in 3% of cases treated with the recently approved emtricitabine.



Figure 5.4: Zidovudine AZT induced nail pigmentation.



Figure 5.5: AZT induced mucosal pigmentation.

Retinoid-like effects

During monotherapy with indinavir (IDV) 14% of patients developed xerosis and 8% dry mouth. These adverse drug reactions, however, only rarely cause discontinuation of therapy. Subsequently, an increased incidence of hair loss, paronychia (Figure 6) and ingrown toenails was observed during indinavir-containing combination therapy. These adverse reactions appear to be rare with the other protease inhibitors [11].

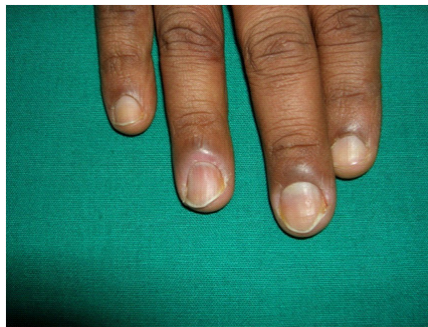


Figure 5.6: Indinavir induced paronychia.

The combination of these adverse drug reactions was previously also observed during retinoid therapy, which is why this type of adverse reaction is also called retinoid-like [7].

Ritonavir is a protease inhibitor which is no longer used in therapeutic dosages because of its numerous side effects. Even in low doses, it inhibits the cytochrome P450 mixed oxygenases, especially the subforms 3A4 and 5. The other PIs are metabolized via these cytochromes. By combining the PIs with low dose ritonavir, the total dose can be reduced (boosted PI) [7]. Since this therapeutic principle was introduced, retinoid-like side effects, being dose-dependent, are observed only very rarely or in a milder form during IDV therapy [7]. On switching to a PI regimen reduced by ritonavir or on a PI-free therapy the cutaneous changes gradually regress.

Ingrown toe nails

Ingrown toe nails (Figure 5.7) or paronychia with pyogenic granuloma-like lesions may be seen with Indinavir, Zidovudine, Lamivudine.



Figure 5.7: Indinavir induced ingrown toe nail.

Injection site reactions

In the registration studies (TORO) for the fusion inhibitor enfuvirtide (T20), which is administered subcutaneously, 98% of the patients complained of erythema, indurations or subcutaneous nodules (76%) at the injection site. 3% of the patients discontinued the therapy for these reasons [12]. These injection site reactions are more severe in patients with HIV-associated lipodystrophy. They are not classified among the allergic reactions because these reactions are induced by cytokines released by high concentrations of the fusion inhibitor. Massaging the injection site and surrounding area may encourage resolution of the symptoms. Needle-free injection therapy involves lower local concentrations and has been used with success in clinical studies [7]. Injection site reactions have also occurred with other immunotherapeutic agents such as etanercept.

Immune reconstitution syndrome (IRIS)

Since the beginning of HAART, progressive flares of diseases associated with the immunodeficiency have been observed. These symptoms are provoked by recovering immune functions and are known as immune reconstitution inflammatory syndrome. They start a few weeks after instituting antiretroviral therapy, after a decrease in HIV-RNA and a rise in the

CD4 cell counts and are most pronounced when the CD4 counts are low at therapy onset [13]. Dermatological manifestations of IRIS - Kaposi's sarcoma, HSV/VZV infections, human papilloma viruses (HPV), mollusca contagiosa, demodicidosis, mycobacterioses (Figure 5.8.a, 5.8.b), sarcoidosis and eosinophilic folliculitis. Kaposi's sarcoma can spread rapidly in IRIS: an anogenital HSV infection can take a severe erosive course. The reactivation of herpes zoster occurs after 2 to 4 months with typical clinical symptoms and in most cases is confined to one dermatome [7]. Occasionally zoster sine herpette may develop. In subclinical atypical mycobacteriosis, reactivation with granulomatous or necrotic cutaneous lesions occurs. Eosinophilic folliculitis may manifest with intolerable pruritus after HAART.

Management of IRIS consists in treating the underlying disease and, where appropriate, providing adjuvant immunosuppressive therapy [7]. In individual cases HAART may have to be interrupted.



Figure 5.8a, 5.8b: IRIS.

ALLERGIC CUTANEOUS EFFECTS

Drug Rashes

The commonest adverse drug reactions are maculopapular exanthems (Figure 5.9) which are observed during treatment with many medications such as antibiotics or diuretics. They occur mainly between the first and third week of treatment onset, are usually most evident on the trunk and are characterized by severe pruritus. When the symptoms are typical and the medical history unambiguous, the diagnosis can be established on clinical criteria [7].

While the introduction of the NRTIs and PIs was not associated with an increase in allergic drug

reactions, rashes were diagnosed in 10% to 20% of patients following approval of the NNRTIs [14]. These patients' medical history is found on enquiry to have an above average incidence of drug exanthems associated with sulfonamide use. Cross-reactions are to be expected in approximately 30% of all cases. The prophylactic administration of steroids and/or antihistamines cannot reduce the rate of exanthems [7,15]. Hyposensitizations are possible with both substances.

It is contentiously debated whether treatment with NNRTI, especially nevirapine, should be interrupted because of potentially severe adverse drug reactions when exanthems occur [16]. In many cases, switching therapy to other medications is not possible because of resistance or side effects. When the therapy is continued the cutaneous manifestations often subside after 3 to 5 days. If therapy continuation is considered, however, immediate discontinuation is essential in the event of urticarial drug reactions, vesiculation, mucosal involvement or systemic signs such as fever, transaminase elevation or general malaise [7]. Even if there is a risk of resistance development, discontinuation is justified if there is a potential for serious health impairment [17]. No therapy is necessary apart from terminating the medication; antihistamines provide relief of pruritus. The administration of NRTI or PI is frequently followed by the development of rash, for example with abacavir (ABC) in 70% of cases with associated symptoms, with fosamprenavir (fAPV) – the prodrug of amprenavir – in 2% to 7% and with atazanavir (ATV) in 6% of cases. Rash is rarely reported in the literature for zalcitabine (ddC), indinavir (IDV), nelfinavir (NFV), saquinavir (SQV) and enfuvirtide (T20).



Figure 5.9: Drug rash.

Serious Adverse Drug Reactions

While therapy may sometimes be continued in the presence of maculopapular exanthem, it must be discontinued in cases of serious adverse drug reactions. These are classified into Stevens-Johnson syndrome (SJS), SJS/TEN transitional form and toxic epidermal necrolysis (TEN) (Figure 5.10). Multiform erythemas develop on the integument which usually does not exhibit the concentric annular form of erythema exudativum multiforme (EEM). Erosions develop on the mucous membranes, at the body orifices with crusty deposits or whitish pseudomembranes.

Involvement of the oral mucosa is typical. In the SJS/TEN transitional form, 10% to 30% of the skin is affected and in TEN more than 30% of the skin. Treatment consists in discontinuing the medication and corresponds to that provided for severe burns. In contrast to SJS, mortality

increases sharply with TEN [7]. The Nikolsky sign is positive: clinically normal skin can be removed easily with light tangential pressure. TEN-related mortalities have been described after administration of nevirapine [18]. These severe cutaneous reactions develop in up to 1% of patients treated with nevirapine, women or patients with high HIV-RNA are more often affected. The long half-life of NNRTIs can create problems. SJS or TEN rarely develops during AZT therapy [7]. Stevens- Johnson syndrome may develop after administration of DDI, IDV and APV [17]. Severe adverse drug reactions to nevirapine therapy also occur in HIV negative patients [19].

The severe adverse drug reactions also include hypersensitivity reaction (HSR). HSR is a multi-organ reaction in genetically predisposed patients. HSR occurs most frequently during abacavir therapy. Symptoms most commonly reported in HIV-infected patients were maculopapular exanthem, followed by fever and nausea or vomiting. For diagnostic purposes it should be noted that the symptoms occur in combination, on average after 11 days. Every third patient with HSR has no cutaneous manifestations. After resumption of the medication the symptoms rapidly worsen again and the patients often become hypotensive. The symptoms improve rapidly after discontinuing abacavir [7,20]. Interruption of therapy does not subsequently increase the HSR rate.

The allele HLA-B5701* occurring in Caucasians is detectable in up to 90% of cases in HSR [21,22]. Epicutaneous testing frequently demonstrates sensitization to abacavir [23].

A hypersensitivity reaction or “drug rash with eosinophilia and systemic symptoms” (DRESS) are relatively rare after starting therapy with nevirapine, efavirenz or T20.

Hyposensitizations were successful with T20. Management of HSR consists in withdrawing the medication: the symptoms then improve rapidly.



Figure 5.10: Toxic Epidermal Necrolysis.

Table 5.2: ART Drugs and their cutaneous adverse reaction.

DRUG		CUTANEOUS REACTIONS
PROTEASE INHIBITORS	Indinavir (IDV)	• Acute porphyria • Drug eruption, SJS • Gynaecomastia • Alopecia, Striae • Paronychia with nailfold pyogenic granuloma-like lesions • Urticaria, pruritus • Leukocytoclastic vasculitis
	Ritonavir (RTV)	• IgA-mediated hypersensitivity reaction • Drug reaction, SJS • Hematoma • Melanoma
	Nelfinavir (NFV)	• Morbilliform eruption • Generalized urticaria
	Saquinavir (SQV)	• Gynecomastia • Xerosis, Eczema • Fixed drug reaction, SJS, Hypersensitivity syndrome (DRESS)
	Lopinavir (LPV) Tipranavir (TPV) Darunavir (TMC114) Amprenavir (APV) Fosamprenavir (FPV) Atazanavir (ATV)	• Lipodystrophy • Hypersensitivity reaction • AGEP • SJS
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)	Zidovudine (ZDV)	• Nail hyperpigmentation, Mucocutaneous hyperpigmentation • Hypertrichosis, Eyelash hypertrichosis • Leukocytoclastic vasculitis • Urticaria, heightened reaction to mosquito bites • Paronychia with lateral nailfold pyogenic granuloma-like lesions • Hypersensitivity syndrome, SJS, TEN
	Lamivudine (3TC)	• Allergic contact dermatitis • Paronychia with lateral nailfold pyogenic granuloma-like lesions
	Stavudine (d4T)	• Rash
	Emtricitabine (FTC)	• Hyperpigmentation (primarily of palms and/or soles but may include tongue, arms, lip and nail; generally mild and non progressive without associated local reactions as pruritus or rash) • Rash, Pruritus
	Zalcitabine (DDC)	• Morbilliform eruption • Hypersensitivity syndrome
	Didanosine (DDI)	• Leukocytoclastic vasculitis • SJS • Papuloerythroderma of Ofuji • Acute gouty arthritis • Alopecia
	Abacavir (ABC)	• Rash • Hypersensitivity reaction, SJS, TEN
NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NtRTIs)	Tenofovir (TDF)	• Rash • Pruritus or urticaria
NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)	Nevirapine (NVP)	• Rash (most common toxicity; occurs most frequently within first 6 weeks of therapy; women may be at higher risk than men). • SJS, TEN
	Delaviridine	• Drug eruption
	Efavirenz (EFV)	• Rash • Pruritus • Erythema multiforme, nail disorder, skin discoloration, SJS
	Etravirine (ETV) Rilpivirine (RPV)	• Skin rash

ENTRY INHIBITORS	Enfuvirtide (T-20)	• Injection site reaction
	Maraviroc	• Rash, pruritus, skin neoplasms(benign; 3%), • Erythema
INTEGRASE INHIBITORS	Raltegravir (RAL)	• Rash, pruritus • SJS
	Elvitegravir (EVG)	• Ongoing clinical trials
MATURATION INHIBITORS	Bevirimat (PA-457,DSB)	• Ongoing clinical trials



Figure 5.11: Efavirenz induced Gynaecomastia

HIV-associated cutaneous changes must be distinguished from drug reactions. The associated changes occur more frequently when the CD4 cell count is below 350/ μ l. They include HPV-induced changes (condylomata acuminata, verrucae), changes induced by human herpes viruses (herpes simplex infections, herpes zoster, oral hair leukoplakia) and mycotic infections (oral candidoses, pityrosporum folliculitis) [7].

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