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REVIEW

Cutaneous Drug Reactions in HIV-Infected Patients in the HAART Era

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Abstract. The introduction of highly active antiretroviral treatment (HAART) in 1996 radically changed the clinical course of human immunodeficiency virus (HIV) infection as it led to a dramatic reduction in mortality in these patients. However, these treatments have their limitations, including adverse effects, therapeutic failure, pharmacokinetic interactions, the development of resistance, and abnormal immune responses. In this article we review the current situation of cutaneous drug reactions in HIV-infected patients.

Key words: TARGA, VIH, HAART, HIV, cutaneous drug reactions.

REACCIONES CUTÁNEAS ADVERSAS A FÁRMACOS EN LOS PACIENTES CON INFECCIÓN POR EL VIH EN LA ERA TARGA

Abstract. La introducción del tratamiento antirretroviral de gran actividad (TARGA) en 1996 supuso un cambio radical en la historia natural de la infección por el virus de la inmunodeficiencia humana (VIH) al lograr reducir drásticamente la mortalidad en estos pacientes. No obstante, estos tratamientos no están exentos de limitaciones que incluyen efectos adversos, fracaso del tratamiento, interacciones farmacocinéticas, aparición de resistencias y respuestas inmunes anómalas. En este artículo se revisa la situación actual de las reacciones cutáneas adversas a fármacos en los pacientes con infección por el VIH.

Palabras clave: TARGA, VIH, efectos cutáneos adversos.

Introduction

Since 1996, the acronym HAART has been used to describe the combination of drugs that make up highly active antiretroviral therapy. This combination includes 2 nucleoside reverse transcriptase inhibitors (NRTI), with at least 1 third drug, generally a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI).

After the introduction of HAART, the outcome of infection by human immunodeficiency virus (HIV) underwent a radical change. For the first time, mortality fell markedly, consumption of hospital resources shrank, and the incidence of HIV-related neoplasm and opportunistic infections decreased.[1-3] Antiretroviral therapy alone was able to control infections and processes that had previously been refractory to treatment. These included oral candidiasis, molluscum contagiosum, cryptosporidiasis/microsporidiasis, infection by *Mycobacterium avium* complex, progressive multifocal leukoencephalopathy, Kaposi sarcoma, and lymphoma.[4] Similarly, the introduction of HAART was also accompanied by a fall in the incidence of *Pneumocystis jiroveci* pneumonia, esophageal candidiasis, and infections by mycobacteria, cytomegalovirus, and toxoplasmosis.[5,6]

Nevertheless, the proven efficacy of HAART in reducing HIV-associated morbidity and mortality does have some notable limitations: side effects that are sometimes so severe that treatment must be suspended; failure of treatment due to nonadherence; pharmacokinetic interactions; and resistance, which is often a consequence of poor adherence. Also important is the development of abnormal immune responses in some patients during the first weeks of HAART, with exacerbations or reactivations of infectious processes, which present with unusual clinical manifestations.[7,8] Such is the case of inflamed lymph nodes caused by *M avium* complex,[9] paradoxical tuberculosis reactions,[10] uveitis caused by cytomegalovirus,[11] exacerbation of cryptococcosis,[12] and worsening of progressive multifocal leukoencephalopathy.[13,14] This setting has also witnessed

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Table 1. Nucleoside Reverse Transcriptase Inhibitors (I): Zidovudine, Didanosine, Zalcitabine, and Stavudine

Generic name	*Zidovudine, AZT*	*Didanosine, ddI*	*Zalcitabine, ddC*	*Stavudine, d4T*
Proprietary name	Retrovir, Zidovudine Combinopharm, *Combivir, **Trizivir	Videx	Hivid	Zerit
Recommended dose	250-300 mg bid	<60 kg: 250 mg qd or 125 mg bid; >60 kg: 400 mg qd or 200 mg bid	0.75, mg tid	<60 kg: 30 mg bid; > 60 mg: 40 mg bid

Taken from López-Aldeguer J et al.[17]

Table 2. Nucleoside Reverse Transcriptase Inhibitors (II): Lamivudine, Emtricitabine, Abacavir, and Tenofovir

Generic name	*Lamivudine, 3TC*	*Emtricitabine, FTC*	*Abacavir, ABC*	*Tenofovir disoproxil fumarate, TDFT*
Proprietary name	Epivir, *Combivir, ** Trizivir, ***Kivexa	Emtriva, ****Truvada	Ziagen, **Trizivir, ***Kivexa	Viread, ****Truvada
Recommended dose	150 mg bid; 300 mg qd	200 mg qd	300 mg bid	300 mg qd

Taken from López-Aldeguer J et al.[17]

Table 3. Non-nucleoside Reverse Transcriptase Inhibitors

Generic name	*Nevirapine*	*Efavirenz*
Proprietary name	Viramune	Sustiva
Recommended dose	200 mg qd × 14 d, followed by 200 mg bid	600 mg qd

Taken from López-Aldeguer J et al.[17]

the development of autoimmune phenomena, such as transient thrombocytopenia,[15] hyperthyroidism,[12] or cryoglobulinemia,[16] which can be interpreted as the result of improved immune response.

Tables 1 to 5 present currently available antiretroviral drugs together with their commercial names and the recommended doses.[17] The classic drugs that can be used in HAART have been complemented with a new agent, enfuvirtide. This peptide antiretroviral agent is the first fusion inhibitor to be approved and the only antiretroviral drug to be routinely administered parenterally (subcutaneous route). It is active against resistant HIV-1 strains, although it must be administered as part of carefully designed regimens in order to minimize the risk of drug resistance.[18]

Toxicoderma in HIV-Infected Patients

Toxicoderma is extremely common in HIV-infected patients (3%-22% according to the series).[19-23] On the one hand, this is because of the large number of drugs these patients are exposed to (eg, antiretroviral drugs, other antiviral agents, antibiotics, chemotherapy drugs, antineoplastic drugs, anticonvulsants). On the other hand, HIV-infected patients seem to be particularly predisposed to developing adverse drug reactions, the incidence of which grows as immunodeficiency worsens. Polyclonal

Table 4. Protease Inhibitors (Part I): Indinavir, Ritonavir, Saquinavir, Nelfinavir, Amprenavir

Generic name	*Indinavir*	*Ritonavir*	*Saquinavir*	*Nelfinavir*	*Amprenavir*
Proprietary name	Crixivan	Norvir	Invirase (I); Fortovase (F)	Viracept	Agenerase
Dose	800 mg tid	600 mg bid (=7.5 mL bid)	(I) Not recommended without ritonavir. (I) 1000 mg + 100 mg ritonavir bid (F) 1200 mg tid	750 mg tid or 1250 mg bid	1200 mg bid (caps)

Abbreviation: caps, capsules. Taken from López-Aldeguer J et al.[17]

Table 5. Protease Inhibitors (Part II): Fosamprenavir, Lopinavir/Ritonavir, Atazanavir, Tipranavir

Generic name	*Fosamprenavir*	*Lopinavir/ritonavir*	*Atazanavir*	*Tipranavir*
Proprietary name	Telzir	Kaletra	Reyetaz	(Soon to be commercially available)
Dose FOS-APV/RTV	700/100 mg every 12 h	400/100 mg bid 300/100 mg every 24 h or 400 mg every 24 h	Caps 250 mg	Caps 250 mg
Recommendation	With or without meals	With meals	With meals	
Commercial presentation	Caps 700 mg	Caps 133/33 mg Oral solution 80/20 mg/mL	Caps 100, 150, and 200 mg	Caps 250 mg

Taken from López-Aldeguer J et al.[17] Abbreviations: caps, capsules; FOS-APV/RTV, fosamprenavir-amprenavir/ritonavir.

hypergammaglobulinemia, which usually accompanies HIV-infection, could favor drug hypersensitivity reactions. Infections by Epstein-Barr virus and cytomegalovirus, which are extremely prevalent in HIV-infected patients, could play a similar role to the one they play in rash induced by ampicillin and other aminopenicillins in patients with infectious mononucleosis.[19-23]

Trimethoprim-sulfamethoxazole (also known as cotrimoxazole), other sulfonamides, and β-lactam antibiotics are the drugs that most commonly cause toxicoderma in HIV-infected patients.[19-23] PIs inhibit cytochrome P450 enzymes and can increase the plasma level of several drugs that are metabolized by this pathway, thus favoring the onset of adverse events. Other antimicrobial agents, such as the aminopenicillins (Figure 1), clindamycin, and rifampicin, also induce toxicoderma more commonly in HIV-infected patients than in other groups, although this association is less widely reported than with sulfonamides. Doses of anticonvulsants (eg, carbamazepine and phenytoin), which cause very severe toxicoderma such as toxic epidermal necrolysis, should be strictly adjusted according to plasma levels in patients taking PIs. Furthermore, in much the same way as other cytochrome P450 inducers (ketoconazole, trimethoprim-sulfamethoxazole, macrolides), these drugs increase PI levels and may favor the onset of adverse events.[19-23]

Table 6 shows the main types of toxicoderma affecting HIV-infected patients.

Cutaneous Adverse Events Caused by HAART

HAART has generally been associated with 3 main cutaneous effects: lipodystrophy syndrome, retinoid-like effect, and immune reconstitution dermatosis, all of which are discussed below.

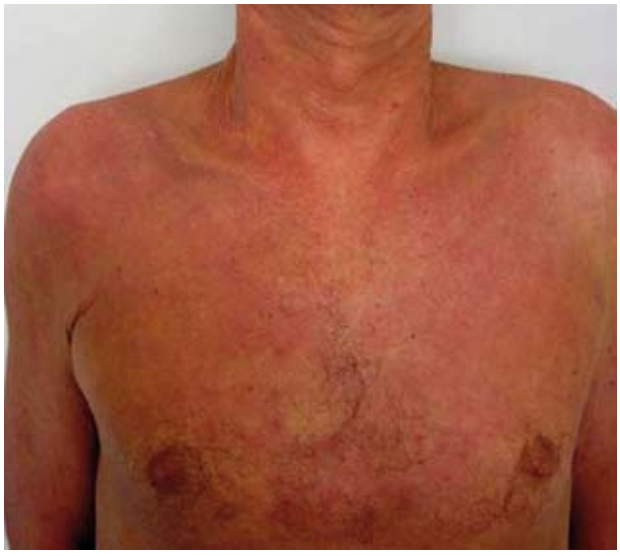

Figure 1. Maculopapular rash after starting therapy with amoxicillin-clavulanate in a patient infected with the human immunodeficiency virus.

Lipodystrophy Syndrome

In the summer of 1997, about 1 year after the introduction of PIs in the United States, anecdotic reports of abdominal obesity in patients taking these drugs began to appear on some web pages, mainly those aimed at HIV-infected patients (www.pinkpage.com and www.thebody.com). The same year in *The Lancet*, Hengel et al[24] reported a case of benign symmetric lipomatosis, which they associated with indinavir, and Herry et al[25] published the case of a patient with hypertrophy of the breasts, which they also attributed to indinavir. New cases of abnormal body fat

Table 6. Relevant Types of Toxicoderma in HIV-Infected Patients[19-23]

Drug	*Toxicoderma*
Trimethoprim-sulfamethoxazole Aminopenicillins Clindamycin Rifampicin	Rash (Figure 1), SJS, TEN
Pentamidine	Rash
Ganciclovir Foscarnet	Rash, phlebitiss Oral and genital ulcers, phlebitis
Thalidomide	Rash
Anticonvulsants	Hypersensitivity syndrome (DRESS), rash, SJS, TEN
Dapsone	Rash, SSJ, sulfone hypersensitivity syndrome

DRESS: *drug reaction with eosinophilia and systemic symptoms;* Abbreviations: SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

distribution were reported in HIV-infected patients taking antiretroviral therapy until 1998, when this entity was formally denominated lipodystrophy syndrome.[26] It was then rapidly identified as one of the main drawbacks of long-term antiretroviral therapy.

Lipodystrophy is characterized by a redistribution of body fat involving the loss of subcutaneous fat (lipoatrophy), which mainly affects the face (Figures 2 and 3), buttocks, and limbs. There may also be an increase in abdominal visceral fat and dorsocervical fat (buffalo hump), and hypertrophy of the breasts (Figure 4). Other associated metabolic abnormalities include diminished glucose tolerance (47%), diabetes with or without insulin resistance (1%), and disorders involving triglycerides and cholesterol (60%), which increase the risk of atherogenesis and vascular disease.[27,28]

Visceral fat accumulation usually appears before peripheral fat accumulation. Both are painless, although the patient may complain of a feeling of fullness and abdominal distension. The loss of subcutaneous fat on the legs makes superficial veins and muscles more prominent (pseudoathletic appearance); on the face, atrophy of the buccal, parotid, and preauricular fat pads makes the zygomatic arch prominent and could necessitate a differential diagnosis with the cachectic states associated with opportunistic diseases and wasting syndrome.[27,28]

Hypertriglyceridemia is the most common metabolic disorder. Hypercholesterolemia presents the characteristics that are traditionally associated with cardiovascular risk (high low-density lipoprotein values and low high-density lipoprotein values). Insulin resistance, which is pathophysiologically related to hypertriglyceridemia, is demonstrated in DRESS, drug reaction with eosinophilia

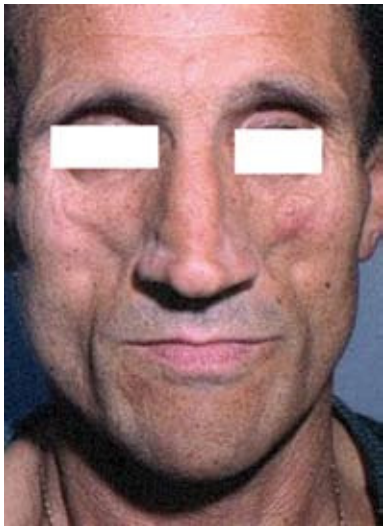

Figure 2. On the face, atrophy of the buccal, parotid, and preauricular fat pads leads to prominence of the zygomatic arch and could require a differential diagnosis with the cachectic states associated with opportunistic diseases and wasting syndrome.

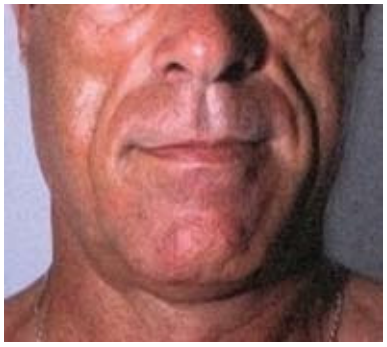

Figure 3. Facial lipoatrophy can be marked and lead to stigmatization in patients with this condition.

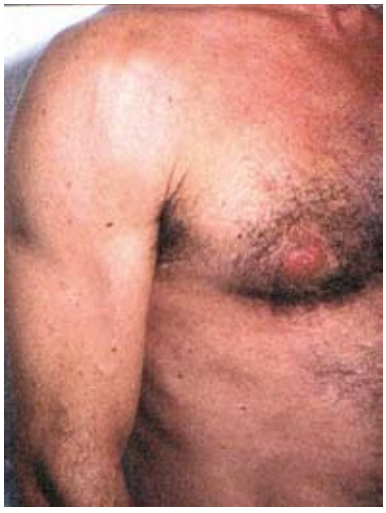

Figure 4. Lipodystrophy syndrome often involves increased abdominal visceral fat and hypertrophy of the breasts.

and systemic symptoms; laboratory tests by an increase in serum insulin and C-peptide levels and, occasionally, by glucose intolerance or frank type 2 diabetes mellitus.[27,28]

At present, there are no established objective criteria for the diagnosis of HIV-related body fat redistribution syndrome. Diagnosis is based mainly on the patient's subjective impression and on the doctor's physical examination, which may be complemented by anthropometric measurements such as the waist-hip ratio.

Although the syndrome was associated with PIs in the initial description,[29] its pathogenesis remains unclear and may be multifactorial. Various factors have been proposed, including PI-induced lipid metabolism disorders and retinoic acid abnormalities, mitochondrial toxicity induced by NRTI (especially stavudine), immune reconstitution, HIV infection itself, and the interaction between cytokines and hormones.[30-33] Other factors that contribute to the development of this syndrome are race, sex, duration of HAART and HIV infection, and changes in viral load.[27]

The consequences for patients include altered perception of physical appearance and stigmatization. Duran et al[34] analyzed several factors associated with adherence to therapy, and lipodystrophy symptoms reported by patients were seen to be an independent factor associated with poor adherence.

There is no efficacious treatment for body fat alterations. In the best of cases, the measures set out below have proven partially effective, and some of them are not free of risk.[17] They include the following:

1. General measures (diet, physical exercise). Patients must avoid changes of more than 5% of their acceptable body weight. Furthermore, aerobic physical exercise improves metabolic abnormalities and intra-abdominal fat accumulation.
2. Switching antiretrovirals (PIs, nucleoside analogs). Discontinuation of PIs can improve metabolic abnormalities and intra-abdominal fat accumulation; similarly, discontinuation of thymidine analogs improves lipoatrophy.
3. Use of drugs with metabolic effects (metformin, glitazones, growth hormone). Pioglitazone (30 mg/d) has been reported to be efficacious. Growth hormone can reduce intra-abdominal fat accumulation, although this effect can be achieved equally well with other simpler and cheaper methods.
4. Plastic surgery. Facial filling in cases of lipoatrophy, reduction surgery in the case of accessible fat deposits. This is the only currently available treatment with clear results. Facial filling can be performed with autologous fat (generally abdominal subcutaneous fat) or with synthetic materials (eg, polyacrylamide, polyalkylimide, and polylactic acid).

Oral Retinoid–Like Effect

In a letter to *The Lancet* in April 1998, Zerboni et al[35] reported 12 HIV-infected patients with paronychia on the fingers (Figure 5) and toes. Cultures for fungi and bacteria were negative. The authors interpreted this condition as an adverse effect of lamivudine, since this was the only drug common to all 12 patients in the previous 3 months. In August of the same year, Bouscarat et al[42] reported patients with paronychia and onychocryptosis of the great toe during a 1-year period in 2 French hospitals. In 28 patients, this condition was accompanied by intense cutaneous xerosis. The authors attributed these disorders to indinavir and drew attention to their similarity to the adverse effects of oral retinoids. In 6 of these patients, discontinuing indinavir for different reasons led to total or partial resolution of the nail and skin lesions.[36]

Several cases of paronychia on the fingernails and toenails were subsequently published, and most were related to indinavir or lamivudine and indinavir, although PIs other than indinavir, such as ritonavir, were also involved.[37-42] Other retinoid-like phenomena reported in connection with antiretroviral drugs, especially indinavir, include mucocutaneous xerosis (Figure 6), asteatotic eczema, pruritus, desquamative or erosive cheilitis, curling of previously straight hair, and hair loss on the body or scalp.[37,41]

There is some confusion in the literature about which drugs are responsible for this clinical picture and about how the symptoms should be classified. (At the first international conference on lipodystrophy held in San Diego, USA, in 1999, nail disorders and cheilitis were considered part of the lipodystrophy syndrome.) Furthermore, attributing an association of a drug with phenomena as common as dry skin, pruritus, or onychocryptosis often seems arbitrary

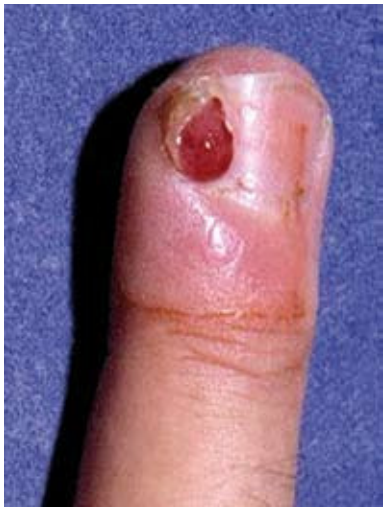

Figure 5. Pyogenic granulomatous lesions are a retinoid-like phenomenon that has been reported in association with antiretroviral treatment, especially indinavir.

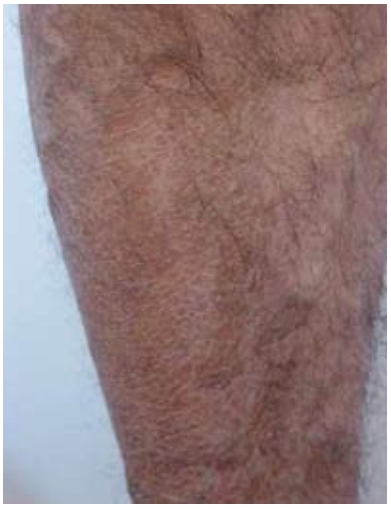

Figure 6. Cutaneous xerosis is another phenomenon that presents in patients infected by human immunodeficiency virus, and it is often linked with antiretroviral treatment.

Table 7. Dermatoses Related to the Immune Reconstitution Syndrome[43-49]

Herpes zoster (most frequent)
Herpes simplex
Eosinophilic folliculitis
Other types of folliculitis
Atypical mycobacteriosis
Tuberculous leprosy
Autoimmune diseases
Universal alopecia areata (1 case associated with *Graves-Basedow disease)*
Tumid lupus erythematosus
Sarcoidosis
Lipodystrophy (?)

(in fact, some of the cases of indinavir-associated alopecia reported in nondermatology journals clearly correspond to alopecia areata).

The pathogenesis of the retinoid effect is unknown. Symptoms mimic the adverse effects of oral retinoids, the most common manifestations being desquamative cheilitis and—cutaneous xerosis.[37] Hyperlipidemia has been described as a component of this syndrome. To date, other well-known effects of oral retinoids—myalgia, headache, and pyogenic granulomatous lesions at sites other than the perionychium—have not been reported in relation to the retinoid effect induced by antiretroviral drugs.

Immune Reconstitution Dermatosis

Recovery of the immune system after starting HAART can lead to the onset or reactivation—seemingly paradoxical—of infections and diseases that were not previously apparent, possibly because the inflammatory response is necessary for the disease to appear.[43-46] Dermatoses related to immune reconstitution are presented in Table 7.[43-49]

Diseases induced by immune recovery appear between a few weeks and 3 months after starting HAART and are associated with a reduction in viral load and recovery of the CD4 lymphocyte count. They show the typical clinical characteristics of these diseases in immunocompetent patients, instead of the atypical characteristics that are usually associated with severe immunodepression. Thus, the herpes zoster that appears in immune reconstitution affects a single dermatome, has a mild uncomplicated course, and does not become chronic or present atypical forms (chronic verrucous, ecthymatous, affecting several dermatomes) that are usually present in immunodepressed patients with high viral loads and a low CD4 lymphocyte count.

HAART-Induced Toxicoderma

Several adverse reactions have been described in patients receiving HAART, and the causative agent has been identified in some cases. Similarly, some patterns of cutaneous reaction are more commonly associated with certain antiretroviral drugs. These are set out below.

Toxicoderma Induced by NRTI

Zidovudine

Zidovudine was the first NRTI to be approved; its cutaneous side effects are well documented, especially mucocutaneous and ungual hyperpigmentation. Several patterns of zidovudine-related hyperpigmentation of the nails have been reported, including complete pigmentation, multiple longitudinal bands, and transverse bands (Figure 7). Involvement of the nails varies as follows: incomplete involvement of fingernails and toenails, complete involvement of fingernails with sparing of the toenails, complete involvement of fingernails and toenails, or involvement of the toenails only. Pigmentation varies in color from light blue to dark grayish-blue and brown,[50-56] is proximal, and extends until it involves the whole nail in a few months. Hyperpigmentation can appear less than 1 month after the start of therapy.[51]

There have also been reports of skin hyperpigmentation related to zidovudine. Greenberg and Berger[51] reported

isolated hyperpigmentation of the forehead and abdomen, as well as generalized hyperpigmentation that was more pronounced in flexural areas and the knuckles. Bendick et al[52] observed the onset of brown hyperpigmented macules on the palms and soles, and well-defined hyperpigmented macules on the volar aspect of the fingers and toes. Hyperpigmentation of the mucosa presented as spotted hyperpigmented brown macules on the lateral aspects of the tongue.[52]

Hyperpigmentation associated with zidovudine is similar to patterns seen with other drugs, especially cytostatic agents. The pigmentation is reversible, selective, and relatively dose-dependent. Mucocutaneous and ungual hyperpigmentation is caused by an increase in melanin levels, which appears to be due to greater production and dispersion of melanosomes by a normal number of melanocytes after these are stimulated by zidovudine.[51,57]

There have also been reports of hypertrichosis after starting treatment with zidovudine. Sahai et al[58] and other authors[51] observed a marked increase in the length of the hair on the dorsum of the hand and darkening of pubic hair (from grey to black). Similarly, zidovudine-induced hypertrichosis of the eyelashes has been reported,[59] although the mechanism is unknown. Zidovudine-induced hypertrophy of the follicular cells remains hypothetical.

There have also been reports of zidovudine-related leukocytoclastic vasculitis[60] and increased response to insect bites.[61] In the 3 patients studied by Diven et al,[61] these increased responses occurred between a few weeks and 3 months after starting treatment with zidovudine. There has been speculation that these reactions could reflect the increased T-cell response after the introduction of treatment.[61]

Didanosine

Didanosine is a pyrimidine nucleoside analog that is activated upon conversion to its triphosphate form. It has been associated with pancreatitis and peripheral neuropathy, although few cutaneous reactions have been reported. Herranz et al[62] observed leukocytoclastic vasculitis after 4 days of treatment. The lesions disappeared when the drug was discontinued. Stevens-Johnson syndrome has also been reported in a 35-year-old patient.[63] Didanosine has been involved as the causal agent in a case of papuloerythroderma of Ofuji, which is characterized by solid and pruriginous papules and erythrodermic lesions that usually spare the face and skin folds. The systemic manifestations of papuloerythroderma of Ofuji include lymphadenopathy, eosinophilia, high immunoglobulin E level, and low CD4 lymphocyte count.[64-66]

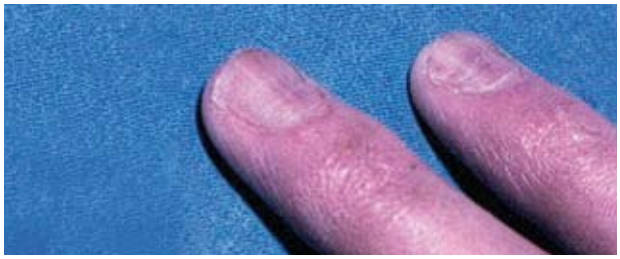

Figure 7. Hyperpigmentation of the nails associated with zidovudine can present as longitudinal bands.

Lamivudine

Lamivudine is used not only to treat HIV infection but also to inhibit replication of hepatitis B virus.[67] It is used widely in combination therapy due to its ability to delay the onset of resistance to zidovudine. There has been 1 report of allergic contact dermatitis. After prolonged contact with this drug, the patient experienced an erythematous vesicular rash on the proximal palm. This extended to the wrist. The results of patch testing with the drug were positive.[68] Allergic contact dermatitis seems to be very uncommon and does not predict future reactions. Lamivudine has also been involved in alopecia[69] and in paronychia.[70]

Zalcitabine

Zalcitabine is more effective when used in combination with zidovudine. Reported side effects include oral and esophageal ulcers, liver toxicity, and, particularly, peripheral neuropathy.[23] Phase I studies have shown that skin lesions in the form of generalized erythematous maculopapules presented in 70% of patients treated with high-dose intravenous zalcitabine.[71-73] At the standard dose, skin rash was observed in only 2%.[74] The skin lesions were transient in 60% of patients, and resolved when the drug was discontinued.[75] Similarly, 2 cases of zalcitabine-related hypersensitivity syndrome (drug reaction with eosinophilia and systemic symptoms) were observed between 2 and 6 weeks after starting treatment.[76,77]

Abacavir

Hypersensitivity reactions induced by this agent appear in around 5% to 8% of adult patients,[78,79] although their pathogenesis is unknown. The reaction is characterized by fever, rash (generally maculopapular and less commonly urticaria-like), gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain), arthralgia and myalgia, paresthesia, weakness, respiratory symptoms (cough, dyspnea), hypertransaminasemia, and leukopenia.[77,80-82] There have also been reports of rhabdomyolysis[83] and disseminated intravascular

coagulation.[84] Hypersensitivity reaction is more severe, and can even prove fatal after successive rechallenge.[85] There have also been reports of toxic epidermal necrosis associated with abacavir.[86]

Stavudine

There has been 1 report of neutrophilic eccrine hidradenitis in an HIV-infected patient with hemophilia.[87]

Tenofovir

Maculopapular and urticarial rash and vesiculobullous and lichenoid lesions have been reported.[88,89]

Emtricitabine

Skin pigmentation abnormalities have been reported in association with emtricitabine.[90] They generally involve hyperpigmentation of the palms and soles. Maculopapular and urticarial rash, and vesiculobullous and pustular reactions have also been reported.[88]

Toxicoderma Induced by PI

Indinavir

Indinavir is the PI with the greatest number of documented cutaneous manifestations. It has been reported to be the causal agent of acute porphyria,[91] hypersensitivity syndrome,[92] Stevens-Johnson syndrome,[93] maculopapular rash,[94] and gynecomasty.[95,96]

The 2 best known skin manifestations associated with this agent are alopecia[97,98] and paronychia with pyogenic granulomatous lesions.[99-101] The patterns of alopecia include diffuse hair loss, well-defined circular bald patches, and thinning of the hair on the legs, thighs, pubic region, and axillary or thoracic region. Hair loss progresses during the first 6 months of treatment. Two possible explanations are that the immune system attacks the hair follicles during immune reconstitution and that indinavir enhances the action of retinoids.[97,98]

Paronychia associated with indinavir seems to be idiosyncratic, occasionally recurrent, and dose-independent, and it resolves when the drug is discontinued. Most cases appear between 1 and 9 months after starting treatment and affect the fingernails and toenails. The clinical picture includes onychocryptosis and formation of hypertrophic granulation tissue. Possible interference of indinavir in the endogenous metabolism of retinoids has been suggested as a pathogenic mechanism. This same mechanism would account for other findings associated with indinavir, such as cutaneous xerosis, asteatotic eczema, acquired ichthyosis, hair loss on the body and scalp, hair curling, and desquamative and erosive cheilitis.[99-101]

Ritonavir

The cutaneous manifestations of ritonavir include medication-induced rash, hypersensitivity reactions, spontaneous bleeding (joints, soft tissue on the palms and soles, and muscle), and hematoma. Skin biopsy performed on these patients suggests an immunoglobulin A–mediated hypersensitivity reaction. As for spontaneous bleeding, although most commonly observed with ritonavir, it has also been detected with other PIs. The underlying mechanism of this bleeding remains unknown, although the scant efficacy of the clotting factors administered suggests that it is not directly related to the action of factors VIII or IX.[102-104]

Lopinavir/Ritonavir

Low-dose lopinavir with ritonavir significantly improves the pharmacokinetic properties and activity of lopinavir against HIV-1 protease. This combined formulation was created for easier administration and to ensure that both agents were taken together, in combination with other antiretroviral drugs. One of the most common adverse effects in adults is diarrhea, followed by other gastrointestinal disturbances, asthenia, headache, and skin rash. There have been reports of pruriginous maculopapular rash caused by this combination. Histopathology reveals a nonspecific inflammatory infiltrate made up of neutrophils and lymphocytes, but with no eosinophils or capillary dilation in the papillary dermis.[105,106] Similarly, a patient who was taking lopinavir/ritonavir as postexposure prophylaxis to HIV experienced exanthematous pustulosis.[107]

Nelfinavir

Nelfinavir is a commonly used PI in children, and its adverse effects include diarrhea, nausea, and asthenia. As far as the skin is concerned, there have been reports of generalized maculopapular rash and urticaria. Maculopapular rash affects 3% to 28% of patients depending on the series, and it usually appears between 5 and 9 days after the start of treatment. Urticaria is observed 8 to 10 days after the start of treatment.[108]

Saquinavir

Saquinavir was the first PI approved by the US Food and Drug Administration; however, its complex administration schedule means that its role in combination therapy is limited. Bioavailability has improved with the introduction

of the soft-gel capsule presentation.[109] The most frequent adverse effects include abdominal pain, diarrhea, and nausea. There have been reports of fixed drug eruption (2 cases)[110] and gynecomasty,[111] although it is not clear whether gynecomasty is yet another facet of lipodystrophy syndrome or an independent finding.

Atazanavir

Atazanavir was the first PI that could be administered in a single daily dose. Its most notable side effects are asymptomatic hyperbilirubinemia, nausea, vomiting, diarrhea, abdominal pain, headache, and peripheral neuropathy. Maculopapular rash has also been described.[112,113]

Amprenavir

Amprenavir is generally well tolerated. Nevertheless, it leads to cutaneous hypersensitivity reactions—mainly maculopapular rash—in more than 28% of patients, and treatment must be discontinued in 3% of cases. Desensitization has been reported with dose titration, thereby improving tolerance to the drug.[114]

Fosamprenavir

Fosamprenavir is an oral prodrug of amprenavir. In clinical trials where it has been administered with or without ritonavir in combination with abacavir and lamivudine, the most common side effects were diarrhea, nausea, vomiting, abdominal pain, and maculopapular rash.[115]

Tipranavir

Tipranavir has been approved for use in combination with ritonavir. Side effects such as urticarial rash, maculopapular rash, and possible photosensitivity have been reported.[88]

Toxicoderma Caused by NNRTI

Nevirapine

The main toxic effect of nevirapine is maculopapular rash, which usually appears after 4 to 6 weeks of treatment. Incidence ranges from 9% to 32% depending on the series, and the drug must be discontinued in 6% to 7% of cases. Nevirapine has also been associated with erythema multiforme (Figures 8 and 9) and Stevens-Johnson syndrome in approximately 1% of patients.[116] A case of hypersensitivity syndrome with eosinophilia and systemic symptoms has been reported after 2 to 6 weeks of treatment.[117]

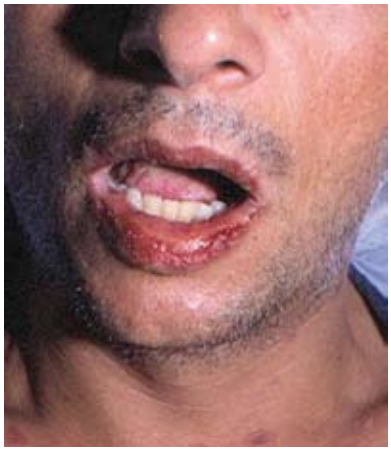

Figure 8. Involvement of the oral mucosa in a case of Stevens-Johnson syndrome induced by nevirapine.

Delavirdine

The incidence of maculopapular rash in patients taking delavirdine is 18% to 50%, according to the series. There has also been a report of a case of Stevens-Johnson syndrome associated with this agent.[118]

Efavirenz

Generalized maculopapular rash,[119,120] leukocytoclastic vasculitis,[121] and severe hypersensitivity reaction with renal failure and liver and lung involvement with no skin alterations and blood eosinophilia[122] have been reported with efavirenz. There have also been reports of photosensitivity reaction and Stevens-Johnson syndrome.[88]

Toxicoderma Caused by Enfuvirtide

The only adverse effect reported with enfuvirtide is injection site reaction, which is generally mild to moderate and may require discontinuation.[18] Reports of hypersensitivity reaction are less common.[88]

Conclusion

There can be no doubt that HAART has many benefits. However, much ground remains to be covered, mainly in terms of how side effects are managed, especially those that are foreseeable, such as lipodystrophy, the retinoid-like effect, or immune reconstitution reactions. These effects can lead to poor adherence to treatment, and, eventually, failure thereof. In addition, knowledge of adverse reactions to antiretroviral drugs is necessary, as is reporting of new ones. This information will enable physicians to detect

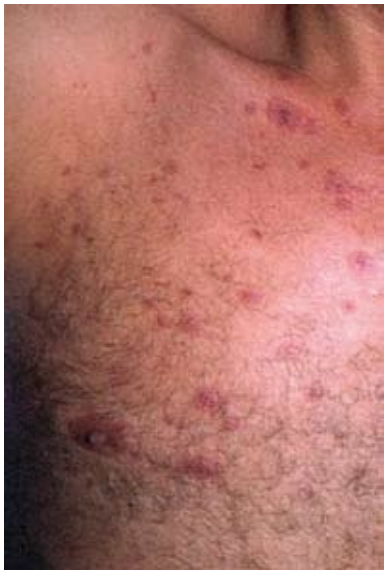

Figure 9. Target lesions characteristic of the Stevens-Johnson syndrome. Symptoms appeared after initiation of nevirapine.

symptoms quickly and prevent an increase in morbidity among HIV-infected patients.

Conflict of Interest
The authors declare no conflicts of interest.

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ADDENDUM

Borrás-Blasco et al[88] recently published a review focused on adverse skin reactions associated with the newest antiretroviral drugs. Some of them were not included in the initial version of our article, as they were not commercially available at the time of writing. They are listed briefly below:

Etravirine (*TMC125, Intelence*) Etravirine is an NNRTI. Early-onset mild maculopapular rash has been described during the first weeks of treatment with this drug, although they usually resolve without the need to discontinue treatment. *Darunavir* (*Prezista*) Darunavir is a PI. Mild to moderate maculopapular rash has been reported. This is generally self-limiting. A case of Stevens-Johnson syndrome has been reported in clinical trials. *Maraviroc* (*Celsentri*) Maraviroc is a member of a new family, the CCR5 antagonists. Adverse skin reactions have not been described. *Raltegravir* (*MK-0518, Isentress*) Raltegravir belongs to a new family, the integrase inhibitors. Mild maculopapular rash and diaphoresis have been reported.