Antiretroviral drugs and therapy of the skin

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SUMMARY

The highly active antiviral therapy (HAART) has dramatically improved the prognosis of *Human immunodeficiency virus* infections. This therapy includes representatives of all the three main groups of antiviral drugs: Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs).
These drugs may cause serious side effects, especially in patients with impaired laboratory tests. Interactions with other drugs and various disturbances of metabolism are not rare. Clinicians should be familiar with the possible complications and use such drugs carefully.

KEY WORDS

HIV infection, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, side effects, drug reactions

Introduction

Highly active antiretroviral therapy (HAART) has dramatically improved the prognosis of HUMAN IMMUNODEFICIENCY VIRUS (HIV) disease, therefore AIDS case reports and AIDS deaths have been reduced in industrialized countries with the introduction of multidrug combination regimens (1).

These drugs may cause some serious side effects and may interact with an important number of medicines. To minimize potential problems, the clinician should consider clinical issues such as drug toxicity, laboratory abnormalities and drug interactions between antiretroviral regimens and other agents that often require dose modification or substitution of various drugs (2).

Dermatologists play a critical role in the physical examination of HIV-positive individuals because manifestations on the skin and mucous membranes occur in up to 90% of patients infected with the HIV. Skin diseases in the HIV-infected patient are important even though some disorders have decreased in incidence or have experienced complete remission following initiation of HAART. Mucocutaneous disorders can create both physical and psychological morbidity and mortality, for this reason they require adequate treatment (3).

Dermatologists should be familiar with the current knowledge of antiretroviral drugs and their interactions with different medicines used frequently in management of mucocutaneous disorders.

Antiretroviral drug therapy

The three main groups of antiretroviral drugs are **Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** and **Protease Inhibitors (PIs)** (Table 1).

The main mechanism of action of NRTIS is the inhibition of replication of retroviruses, including HIV, by interfering whit viral RNA-directed DNA polymerase (reverse transcriptase), NNRTIS also inhibit replication of HIV-1 by acting as a specific, non-competitive, reverse transcriptase inhibitor, by disrupting the catalytic site of the enzyme. PIs are selective and competitive inhibitors of HIV protease. This enzyme plays an essential role to prevent cleavage of protein precursors essential for HIV maturation, infection of new cells and replication.

The recommended antiretroviral drug regimens for initial treatment of established HIV infection including a PI with two NRTIs, an NNRTIs with two NRTIs, or a three NRTIs regimen (4).

Drug interactions may occur when antiretrovirals are co administered with a wide variety of other drugs, including classical dermatological therapies.

Antiretroviral drugs		
Group	Drugs	Trade name
NRTIs	Zidovudine	Retrovir
	Didanosine	Videx
	Zalcitabine	Hivid
	Stavudine	Zerit
	Lamivudine	Epivir
	Abacabir	Ziagen
NNRTIs	Nevirapine	Viramune
	Delavirdine	Rescriptor
	Efavirenz	Sustiva
PIs	Indinavir	Crixivan
	Ritonavir	Norvir
	Nelfinavir	Viracept
	Saquinavir	Invirase, Fortovase
	Amprenavir	Agenerase
	Lopinavir + Ritonavir	Kaletra

Table 1. Major groups of antiretroviral drugs.

Dermatological drugs in HIV-infected patients

Mucocutaneous diseases in the HIV-infected patient using combination drug regimens (HAART) often, have to be treated with systemic agents. Sometimes the treatment of dermatological manifestations in these patients becomes problematic due to pharmacological interactions.

The main groups of drugs used for the most common skin conditions that develop in HIV-infected individuals are antibiotics, oral antifungal agents, antihistamines, immunosuppressive drugs, thalidomide, retinoids and systemic glucocorticoids (5).

Antibiotics

Staphylococcus aureus is the most common microorganism causing cutaneous and systemic infections in HIV-infected patients. This bacterial pathogen can cause infections just below the stratum corneum, like impetigo, or in hair follicles, like folliculitis, furuncles or carbuncles that generally respond to treatment with dicloxacillin, amoxicillin plus clavulanic acid, cephalexin, erythromycin, clarithromycin, ciprofloxacin or clindamycin. Some experts recommend trimethoprim-sulfamethoxazole to treat skin infections caused by methicillin-resistant *Staphylococcus aureus.*

Erythromycin and doxycycline are appropriate agents to treat Bacillary angiomatosis. It is a bacterial infection caused by organisms of the genus *Bartonella* that occur more frequently in immunocompromized patients.

The penicillin continues to be the treatment of choice for all forms of infection with *Treponema pallidum* (6).

Oral antifungal agents

Oropharyngeal candidiasis is the most common infection in HIV-infected individuals. Oral imidazoles such as ketoconazole, fluconazole or itraconazole are effective for treatment of infections caused by yeast of the genus *Candida* (7). In the cases of resistance to imidazoles, amphotericin B is given.

After candidiasis cryptococcosis is the second most common fungal opportunistic infection and responds well to systemic treatment with intravenous amphotericin, oral fluconazole or itraconazole.

Terbinafine is an excellent antimycotic agent against dermatophytes.

Antihistamines

Antihistamines have been used in HIV-seropositive patients for the relief of pruritus caused by different conditions that include xerosis, eosinophilic folliculitis, atopic dermatitis, prurigo nodularis, scabies, and insect bites.

Immunosuppressive drugs

Cyclosporine is an effective immunosuppressive agent commonly used to treat refractory cases of psoriasis.

The use for psoriasis developed in HIV infected

Recommended regimens are comprised of one choice each from columns A and B		
Recommended	**Column A**	**Column B**
Strongly recommended	Efavirenz	Stavudine + Didanosine
	Indinavir	Stavudine + Lamivudine
	Nelfinavir	Zidovudine + Didanosine
	Ritonavir + Indinavir	Zidovudine + Lamivudine
	Ritonavir + Saquinavir	
Recommended as alternatives	Abacavir	Didanosine + Lamivudine
	Amprenavir	Zidovudine + Zalcitabine
	Delavirdine	
	Nelfinavir + Saquinavir	
	Nevirapine	
	Ritonavir	
	Saquinavir	
Non recommended: insufficient data	Hydroxyurea + other antiretroviral drugs	
	Ritonavir + Indinavir	
	Ritonavir + Nelfinavir	
Non recommended: should non be offered	Saquinavir	Stavudine + Zidovudine
		Zalzitabine + Lamivudine
		Zalzitabine + Stavudine
		Zalzitabine + Didanosine

Table 1. Recommended regimens for treatment of HIV infections.

patients is limited to selected cases, due the risk of causing increased immunosuppression and because elevated cyclosporine levels have been linked to nephrotoxicity and neurotoxicity.

Cyclosporine can be used also in cases of severe and refractory atopic dermatitis (8).

Thalidomide

Prurigo nodularis is a pruritic dermatosis in which treatment is problematic. The HIV-associated prurigo nodularis responds well to treatment with thalidomide.

Systemic therapy with thalidomide has been found to be an effective treatment in cases of aphthous ulcers of the mouth and oropharynx in AIDS and in some cases of Kaposi's sarcoma.

This drug has a potent anti-inflammatory activity, it also has antiangiogenic properties and at the same time thalidomide may inhibit HIV replication. The use in HIV-infected individuals is limited because it can increase the neuropathic effects of zalcitabine, stavudine and didanosine (9).

Retinoids

The oral retinoids can be safe and effective in cases of psoriasis that do not respond to topical treatment and in cases of eosinophilic folliculitis that have not responded to other therapies.

Retinoids produce hyperlipidemia and liver toxicity that may limit their use in patients receiving HAART particularly with protease inhibitors and NNRTIs whose metabolism involves the hepatic cytochrome p450 enzymatic pathway (10).

Systemic glucocorticoids

Skin manifestations in HIV-infected patients commonly treated with oral glucocorticoids include cutaneous drug-induced eruptions and urticaria/angioedema. The most common implicated agents are trimethoprim-sulfamethoxazole and amoxicillin-clavulanate.

The use of glucocorticoids is limited because they can cause hyperglycemia. Hyperglycemia, new onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of pre-existing diabetes mellitus are strongly associated with the use of protease inhibitors (11).

Interactions

Caution should be exercised when using of the frequent dermatological therapies in patients receiving

HAART. The risk of applying dermatological therapies must be weighed against the potentially favorable effects.

Knowledge of the pharmacokinetics of the antiretrovirals is an absolute necessity to understand how specific HIV-related medications interact with other drugs (12).

Nucleoside Reverse Transcriptase Inhibitors

NRTIs do not seem to be inducers or inhibitors of the cytochrome P450 system. All NRTIs, with the exception of zidovudine, are mostly eliminated through the urine. Zidovudine is conjugated by glucuronidation, and the conjugate is eliminated by renal excretion (10).

Amino glycosides, amphotericin B and cotrimoxazole are nephrotoxic, therefore these drugs should be used with caution during NRTIs therapy and the patients must be monitored accordingly.

Non-Nucleoside Reverse Transcriptase Inhibitors

NNRTIs are extensively biotransformed by the liver via cytochrome P450 metabolism. Nevirapine and efavirenz are inducers of hepatic cytochrome P450 3A4, and efavirenz inhibits also the CYP isoenzymes 2C9, 2C19, and 3A4. Delavirdine is an inhibitor of cytochrome P450 isoenzymes from the CYP 3A family.

- Ketoconazole inhibits some cytochrome P450 isozymes and subsequently increases plasma levels of nevirapine in 15-30 percent. Nevirapine decreases the concentration of ketoconazole in 63 percent because this NNRTI induces hepatic cytochrome P450 3A4. This association is contraindicated.
- Itraconazole has small affinity for the cytochrome P450 system, therefore simultaneous administration with NNRTIs is not contraindicated but may require liver enzymes monitoring.
- Clarithromycin is an inhibitor of cytochrome P450 isozymes from the CYP3A family, and in association with nevirapine elevates the plasma concentration in 26 percent. Instead clarithromycin plasma concentration is reduced in 30 percent. Therefore careful monitoring is recommended. Clarithromycin in association with efavirenz reduce clarithromycin plasma concentration in 39 percent. Therefore it will be better to choose other antibiotics in association with efavirenz.
- Astemizole and terfenadine are contraindicated because given concurrently with NNRTIs may result in higher plasma concentrations of those antihistamines promoting adverse effects like ventricular tachycardia (13, 14).

Protease Inhibitors

PIs are metabolized by the cytochrome P450 enzyme system. All are inhibitors of CYP3A4 and can impede the biotransformation of other drugs that undergo this isoenzyme metabolism. Ritonavir is the most potent 3A4 inhibitor and saquinavir is the weaker. Ritonavir and nelfinavir are also inducers of CYP3A4. Ritonavir inhibits also slightly 2D6, 2C9/10 and 2C19 isoenzymes and may induce CYP1A2. Nelfinavir is partially metabolized by the CYP2C19 isoenzyme (15).

- Astemizole and terfenadine are contraindicated because PIs are potent 3A4 inhibitors and given concurrently may promote adverse effects of this antihistamines like ventricular tachycardia.
- Loratadine is metabolized through the liver cytochrome P450 enzyme system in small quantity. The simultaneous administration with ritonavir, the most potent 3A4 inhibitor is not contraindicated but require close monitoring.
- The concentration of ketoconazole is increased three times if administrated with ritonavir. Ketoconazole should be used with caution and the limit-dose will be 200 mg daily. Ketoconazole increases three times the concentration of saquinavir, although no dose adjustment is required. Ketoconazole increases serum concentration of amprenavir in 31 percent and amprenavir increases the levels of ketoconazole in 44 percent. The significance of these findings is under investigation.
- Itraconazole and miconazole have a small affinity for the cytochrome P450 enzyme system. The concentration of these antifungal agents may be slightly increased by PIs simultaneous administration, therefore close monitoring is required.
- Clarithromycin levels are increased in 77 percent with ritonavir. A dose adjustment and close monitoring of the liver tests are required. Erythromycin and azithromycin levels are also increased. Concomitant administration of others PIs with clarithromycin does not require dose adjustment.
- Clindamycin is metabolized in the liver by the P450 isoenzyme CYP3A4 and co administration with PIs implicates a slight increase of serum concentration with elevated risk of diarrhoea.
- Cyclosporine is primarily metabolized by hepatic P450 3A4 isoenzyme. PIs are mainly inhibitors of this enzyme, therefore they will increase cyclosporine levels. Cyclosporine should be used in patients receiving PIs only if strictly necessary and with close monitoring (16, 17).

Conclusions

Little specific data are available on the drug interactions between antiretroviral drugs and dermatological therapies.

Significant drugs interactions occur during metabolism because many drugs are metabolized by CYP3A4, one of the major isoenzymes of the CYP 450 group, therefore some of these interactions could easily be predicted based on the knowledge of this isoenzyme (18).

The most important problem is the association with some H1-type antihistamines (terfenadine and astemizole) but currently their dermatological use is restric-

ted because in recent years others antihistamines with less side effects have been developed.

Associations with others drugs are, normally, non contraindicated but most of them require close monitoring.

Dermatologists frequently are faced with the need for management of cutaneous and mucous lesions in HIV infected patients. At the same time HAART therapy induces an arrest of progression of immunodeficiency and significant restoration of immune function. Therefore, antiretroviral therapy has the priority and the choice of others medicines will be done regarding the compatibility with those drugs (19).

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