

## Activity of antiretroviral drugs in human infections by opportunistic agents

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Highly active antiretroviral therapy (HAART) is used in patients infected with HIV. This treatment has been shown to significantly decrease opportunist infections such as those caused by viruses, fungi and particularly, protozoa. The use of HAART in HIV-positive persons is associated with immune reconstitution as well as decreased prevalence of oral candidiasis and candidal carriage. Antiretroviral therapy benefits patients who are co-infected by the human immunodeficiency virus (HIV), human herpes virus 8 (HHV-8), Epstein-Barr virus, hepatitis B virus (HBV), parvovirus B19 and cytomegalovirus (CMV). HAART has also led to a significant reduction in the incidence, and the modification of characteristics, of bacteremia by etiological agents such as *Staphylococcus aureus*, coagulase negative staphylococcus, non-typhoid species of *Salmonella*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis*. HAART can modify the natural history of cryptosporidiosis and microsporidiosis, and restore mucosal immunity, leading to the eradication of *Cryptosporidium parvum*. A similar restoration of immune response occurs in infections by *Toxoplasma gondii*. The decline in the incidence of visceral leishmaniasis/HIV co-infection can be observed after the introduction of protease inhibitor therapy. Current findings are highly relevant for clinical medicine and may serve to reduce the number of prescribed drugs thereby improving the quality of life of patients with opportunistic diseases.

**Uniterms:** Highly active antiretroviral therapy. Antiretroviral drugs/activity. Opportunist infections/treatment.

A terapia HAART (terapia antirretroviral altamente ativa) é usada em pacientes infectados pelo vírus da imunodeficiência humana (HIV) e demonstrou diminuição significativa de infecções oportunistas, tais como as causadas por vírus, fungos, protozoários e bactérias. O uso da HAART está associado com a reconstituição imunológica e diminuição na prevalência de candidíase oral. A terapia antirretroviral beneficia pacientes co-infectados pelo HIV, vírus herpes humano 8 (HHV-8), vírus Epstein-Barr (EBV), vírus da hepatite B (HBV), parvovírus B19 e citomegalovírus (CMV). A HAART também apresentou redução significativa da incidência e modificou as características da bacteremia por agentes etiológicos, tais como *Staphylococcus aureus*, espécies não-tifóides de *Salmonella*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*. A HAART é capaz de modificar significativamente a história natural da criptosporidiose e microsporidiose. HAART pode efetivamente restaurar a imunidade da mucosa, levando à erradicação de *Cryptosporidium parvum*. Semelhante restauração da resposta imune ocorre em infecções por *Toxoplasma gondii*. O declínio na incidência de co-infecção leishmaniose visceral/HIV pode ser observada após a introdução da terapia com inibidores da protease. Os resultados atuais são altamente relevantes para a medicina clínica e podem proporcionar diminuição no número de prescrições medicamentosas e, conseqüentemente, melhor qualidade de vida para pacientes com doenças oportunistas.

**Unitermos:** Terapia antirretroviral altamente ativa. Medicamentos antirretrovirais/atividade. Infecções oportunistas/tratamento.

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## INTRODUCTION

Combined antiretroviral (ARV) drugs have improved survival rates in acquired immune deficiency syndrome (AIDS) patients. Early antiretroviral drugs caused only temporary gains due to low efficiency in the recovery of immune competence of the patient and to the limited effects in reducing viral load. The use of new ARV classes (protease inhibitors and non-nucleoside reverse transcriptase inhibitors) from the mid-1990s proved highly successful in HIV-infected persons through highly active antiretroviral therapy (HAART). A significant fall in AIDS morbidity and mortality rates were reported (Delpierre *et al.*, 2008).

In developed countries, HAART has achieved significant results in the suppression of HIV viral load and restoration of immunity, coupled with improvements in qualitative and quantitative CD4+ T-cells counts and with significant decreases in opportunist infections such as those caused by viruses, fungi and particularly, protozoa. Standout medicines include reverse transcriptase nucleosides inhibitors and protease inhibitors (WHO, 2006).

Protease inhibitors block the activity of the aspartyl protease of the HIV and may affect the growth of other micro-organisms besides blocking virus multiplication (Abbenante, Fairlie, 2005). The activity of HIV protease inhibitors in *Leishmania* spp. (Savoia, Aliche, Tovo, 2005), *Toxoplasma gondii* (Deuoin, Santillana-Hayat, 2000), *Plasmodium* spp. (Andrews *et al.*, 2006; Parikh *et al.*, 2005; Redmond *et al.*, 2007), *Cryptosporidium parvum* (Mele *et al.*, 2003; Pozio, Morales, 2005), *Candida albicans* (Falkensammer *et al.*, 2007), and *Mycobacterium* spp. (Kabbesh *et al.*, 2005), among others, has been previously shown. Reverse transcriptase inhibitors may also affect organisms such as *Trypanosoma cruzi* (Nakajima-Shimada, Aoki, 1998).

The current systematic review identifies and analyzes original articles published in the literature on the activity of antiretroviral drugs in human infections by opportunist agents.

## METHODS

A systematic review of the databases PubMed (U.S. National Library of Medicine), SciELO (Scientific Electronic Library Online) and LILACS (Latin American and Caribbean Center on Information in Health Sciences) was undertaken from February to April 2008. This study focused on articles retrieved in English, French, Italian, Spanish and Portuguese languages, published between January 1998 and December 2007. Additional articles

besides those identified in the systematic review were included in the discussion of the data.

## Search strategy and quality assessment

The search strategy on PubMed consisted of employing the MeSH Database for the term 'antiretroviral agents' coupled to 'fungi', 'bacteria', 'viruses', 'protozoa', 'opportunist infections', using the limits of the methodological filter to identify original publications of clinical trials, randomized controlled trials, case reports, classical articles, comparative studies and journal articles. Although a free term search strategy was employed on the SciELO and LILACS databases, coupling 'antiretroviral drugs' and 'fungus', 'bacteria', 'virus', 'protozoa', 'opportunist infections', no reference was extant.

The first stage involving the bibliography focused on sample quality and quality of the analysis among identified publications. Two researchers independently undertook the same task on the electronic databases in order to increase search precision.

The second stage consisted of an analysis of potential articles by four independent researchers. This entailed examination of each article's predefined contents, namely, aim, opportunist agent, study design, antiretroviral drugs, conclusion. Publications were chosen at random and allocated to the four researchers for analysis. In addition, an additional search for relevant articles identified from the list of references of the initially retrieved papers was performed.

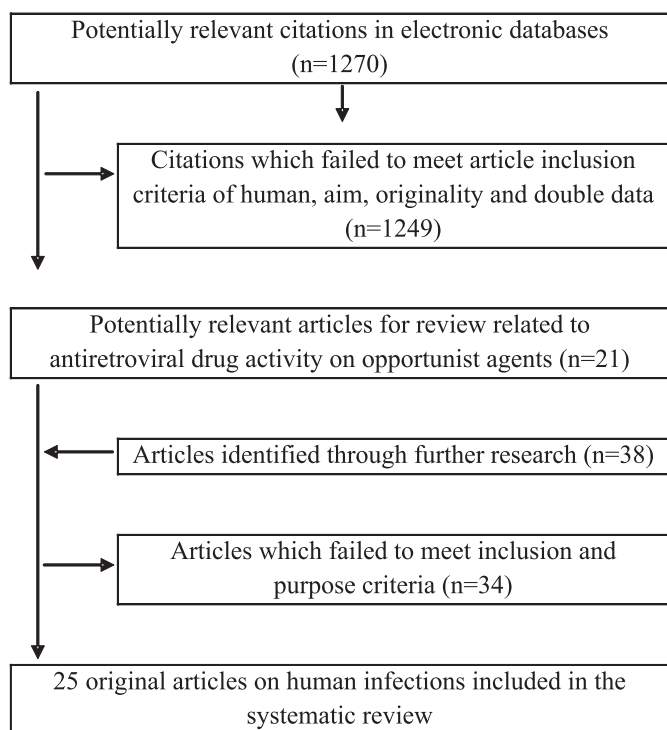
The third stage involved a further final randomized selection of article handed out to three researchers, or 'independent judges,' for verification of the total percentage of agreement with regard to contents from each article versus the four researchers' predefined items.

## Behavioral data

Figure 1 shows the potential publications for analysis by the current study. The 25 articles identified only on the PubMed database using the key word antiretroviral agent and the terms fungi, viruses, bacteria, protozoa were combined in 6, 9, 5 and 5 publications, respectively. Antiretroviral combinations and opportunist infections/infectious were automatically classified for the respective opportunist agent group. Total percentage concordance among the three judges with regard to the four independent researchers was calculated as 72.7% (8/11), 75.0% (3/4) and 77.8% (7/9).

## Antiretroviral drugs and fungal agents (Table I)

HAART has produced satisfactory results in HIV



**FIGURE 1** - Flow of studies for systematic review.

patients also infected by *Candida* spp. Since oral candidiasis (OC) is a particularly common infection in this patient group, it is noteworthy that HAART significantly decreases the amount of fungi in the oral cavity (Macura *et al.*, 2002). A decrease in the prevalence of OC has also been coupled with a rise in CD4+ T-cell counts (Yang *et al.*, 2006). The diminished exposure to *Candida* spp. was accompanied by decreases in levels of *Candida*-specific secretory immunoglobulin A (Pomarico, 2009).

In addition, the importance of secreted aspartic protease (SAP), an important virulence factor of *Candida* spp, has also been emphasized. HIV protease inhibitor, a common component of HAART, is an inhibitor of HIV protease, the enzyme required for correct processing of HIV's retroviral precursor proteins. Previous research has evaluated the inhibitory activity of protease inhibitors (PI) for SAP during OC manifestations. The anti-SAP effect of PI-HAART (indinavir and ritonavir) has been associated with the clinical resolution of OC but not with late and inconstant recovery of anticandidal cellular immunity (Cassone *et al.*, 2002). Although oral candidal isolates secrete protease, ritonavir does not inhibit all protease-secreting oral yeast isolates. Nevertheless, it decreases the percentage of *Candida* spp. isolates, particularly *C. albicans*, which is resistant to anti-fungal agents (amphotericin B, fluorocytosine, fluconazole, ketoconazole and itraconazole). This is perhaps due to the synergic effect between

these drugs and antiretrovirals (Migliorati *et al.*, 2004).

Antiretroviral treatment, including protease inhibitors, in patients with advanced HIV infection, has a positive impact on the natural history of oropharyngeal candidiasis (OPC). This positive impact appears to be correlated with improved immunological function in spite of constant HIV replication (Arribas *et al.*, 2000). Consequently, decrease in colonization and oral manifestations has been reported in patients, with high CD4+ T-cell counts reported after PI employment (Hoegl *et al.*, 1998).

The same protease inhibitors can act directly on SAPs 1, 2 and 3, but not on SAPs 4, 5 and 6, inhibiting several relevant biological processes of *C. albicans*, such as growth and adhesion to mammalian cells (Bektic *et al.*, 2001; Blanco *et al.*, 2003; Borg-von Zepelin *et al.*, 1999; Braga-Silva *et al.*, 2010; Cassone *et al.*, 1999; Falkensammer, Pilz, Bektic, 2007; Gruber *et al.*, 1999; Korting *et al.*, 1999; Monod *et al.*, 1999). Braga-Silva *et al.* (2010) showed that amprenavir reduced the expression of surface mannose- and sialic acid-rich glycoconjugates also inhibited esterase activity, sterol content and biofilm formation in *C. albicans*. The adhesion of *Candida* sp. may be related to surface glycoprotein or ion-bridging, especially with calcium ions, given these physical factors may be affected differentially by different protease inhibitors (Tsang, Hong, 2009).

In summary, it is possible to conclude that the use of antiretroviral therapy in HIV-positive was associated with immune reconstitution as well as decreases in the prevalence of OC and candidal carriage. According to Pomarico *et al.* (2009), the protease inhibitors might have had an anti-candidiasis effect, resulting not only from immune reconstitution, but also from direct anti-yeast mechanisms.

## Antiretroviral drugs and viral agents (Table II)

Antiretroviral therapy benefits patients who are co-infected by HIV, HHV-8 (Harrington *et al.*, 1997; Hocqueloux *et al.*, 2001; Lebbe *et al.*, 1998; Wit, Sol, Renwick, 1998), EBV (Hocqueloux *et al.*, 2001), HBV (Benhamou *et al.*, 2001; Deal *et al.*, 2002; Perillo *et al.*, 2000), parvovirus B19 (Mylonakis *et al.*, 1999; Ware, Moore, 2001) and CMV (Borges *et al.*, 2001; Deayton *et al.*, 1999; Li *et al.*, 1999).

It has been shown that HIV stimulates HHV-8 replication *in vitro* (Harrington *et al.*, 1997) and strong suppression of HIV replication by antiretroviral agents may thus indirectly suppress HHV-8. After 94 weeks of HAART treatment, a case report detected absolute cure from Kaposi sarcoma (KS), DNA clearance of HHV-8 in peripheral blood mononuclear cells and plasma, and an

**TABLE I** - Characteristics of studies included in the systematic review, on antiretroviral agents and fungi

Source	Aim	Study design	Drug groups	Patients (n)	Conclusion
Macura <i>et al.</i> <i>Folia Med.</i> <i>Cracov.</i> , 2002.	Evaluate impact of antiretroviral therapy on development of oral mucosa mycosis in HIV patients.	Controlled clinical trial	PI NNRTI	75	ARV in HIV patients significantly reduced the number of fungi present in oral cavity.
Yang <i>et al.</i> BMC <i>Infectious Disease</i> , 2006.	Determine effect of prolonged HAART on oropharyngeal candidiasis and colonization with <i>Candida</i> species in Taiwan.	Prospective	HAART	142	HAART was highly effective for decreasing oral candidiasis in association with a rise in CD4+ T-cell count.
Cassone <i>et al.</i> <i>J. Infect. Dis.</i> 2002.	Compare effects of IP and NNRTIs in SAP in <i>C. albicans</i> .	Cross-sectional and longitudinal.	PI NNRTI	60	PIs apply an early, immune reconstitution-independent effect on <i>Candida</i> virulence in oral cavities of HIV-positive subjects.
Migliorati <i>et al.</i> <i>Oral Surg.</i> <i>Oral Med.</i> <i>Oral Pathol.</i> <i>Oral Radiol.</i> <i>Endod.</i> , 2004.	Evaluate ritonavir's anti-fungal activities, principally in oral candidal isolates that secrete protease.	Clinical trial	PI	19	Ritonavir does not inhibit all protease-secreting oral yeast isolates.
Arribas <i>et al.</i> AIDS, 2000.	This study determined the relationship between antiretroviral therapy and changes in prevalence and amount of oropharyngeal candidiasis (OPC) and skin test reactivity for delayed hypersensitivity type.	Observational cohort	PI NRTI	99	In patients with advanced HIV infection, antiretroviral therapy including a protease inhibitor has a positive impact on natural history of OPC.
Hoegl <i>et al.</i> <i>Mycoses</i> , 1998.	Evaluate the effects of treatment with an HIV protease inhibitor (PI) on oral candidiasis.	Retrospective and prospective	PI NRTI	62	Absence of <i>Candida</i> colonization and manifest oral candidiasis was observed only in patients with elevation of CD4+ T-cells after PI.

Protease inhibitor (PI); Nonnucleoside reverse-transcriptase inhibitors (NNRTI); Nucleoside analog reverse-transcriptase inhibitors (NRTI), Highly active antiretroviral therapy (HAART); Antiretroviral therapy (ARV).

improvement in the patient's immunological condition (Wit, Sol, Renwick, 1998). A cohort study with ten patients also showed KS/ DNA clearance of HHV-8 in HIV patients after immune reconstitution with antiretroviral therapy containing a protease inhibitor. Antiretroviral therapy has been effective in KS regression and HHV-8 viraemia negation condition (Lebbe *et al.*, 1998).

Primary effusion lymphoma (PEL) is a rare HIV-associated cancer which may be caused by HHV-8 and EBV infection. A case report of a HAART-treated AIDS patient showed complete PEL clearance and decrease in HHV-8-DNA and EBV-DNA to negligible levels. When chemotherapy is contraindicated, HAART becomes a vi-

able alternative (Hocqueloux *et al.*, 2001).

There is evidence that the AZT (azidothymidine) and valganciclovir association design targeting cells with lytic Kaposi sarcoma herpes virus (KSHV) replication also has activity in KSHV-associated multicentric Castleman disease (MCD) (Uldrick *et al.*, 2011). AZT and interferon-alpha (IFN- $\alpha$ ) induced apoptosis in HHV-8+/EBV- PEL cells in culture, by induction of a tumor necrosis factor-related apoptosis inducing ligand (TRAIL) mediated suicide program (Wu *et al.*, 2005).

EBV-associated immunoblastic lymphoma occurs in immunocompromised patients such as those with AIDS where Dewan *et al.* (2009) observed that ritonavir induced

**TABLE II** - Characteristics of studies included in the systematic review, on antiretroviral agents and virus

Source	Aim	Study design	Drug groups	Patients (n)	Conclusion
Wit <i>et al.</i> <i>AIDS</i> , 1998.	Describe a case of complete regression of AIDS-related KS and clearance of HHV-8 DNA after initiation of ARV.	Case report	NRTI	1	Clearance of HHV-8 DNA from both peripheral blood mononuclear cells and plasma after initiation of antiretroviral therapy.
Lebbé <i>et al.</i> <i>AIDS</i> , 1998.	Correlate clinical and biological response of IP with HIV-associated Kaposi's sarcoma.	Prospective	NRTI PI	10	Antiviral therapy with protease inhibitors is clinically effective in HIV-associated Kaposi's sarcoma.
Hocqueloux <i>et al.</i> <i>AIDS</i> , 2001.	Analyze remission of primary lymphoma effusion in HAART-subjected patient.	Case report	PI NRTI NNRTI	1	Complete remission of primary effusion lymphoma.
Deal <i>et al.</i> <i>Ann. Biol.</i> <i>Clin.</i> , 2002.	Evaluate treatment with lamivudine in HIV patients co-infected by HBV.	Controlled clinical trial	NRTI	34	Long-term efficacy of lamivudine in HBV-infected patients was proven.
Mylonakis <i>et al.</i> <i>Am. J.</i> <i>Hematol.</i> , 1999.	Report on remission of parvovirus B-19-infected patient with aplasia, prior to HAART treatment.	Case report	PI NRTI	1	CD4+ T-cells count progressively increased, and DNA polymerase chain reaction for parvovirus B19 became undetectable.
Ware, Moore. <i>Clin. Infect.</i> <i>Dis.</i> , 2001.	Describe solution of chronic parvovirus B-19-infected patient with AIDS when HAART is employed.	Case report	PI NRTI	1	Serologic evidence of eradication of parvovirus after having received effective treatment for human immunodeficiency virus infection.
Deayton <i>et al.</i> <i>AIDS</i> , 1999.	Determine effect of HAART on cytomegalovirus viraemia and retinitis.	Prospective	NRTI PI	16	HAART including a protease inhibitor can result in complete suppression of CMV viraemia.
Borges <i>et al.</i> <i>Int. J. STD</i> <i>AIDS</i> , 2001.	Evaluate effectiveness of ARV on cytomegalovirus viraemia in AIDS patients.	Prospective	PI NRTI	70	HAART induces immunological improvement and can be associated with negativity of CMV antigenaemia.
Li <i>et al.</i> <i>J. Acquir.</i> <i>Immune</i> <i>Defic.</i> <i>Syndr. Hum.</i> <i>Retrovirol.</i> , 1999.	Report improvement of an HIV and cytomegalovirus patient after treatment with ARV.	Case report	PI NRTI	1	Negative result of CMV blood culture with restoration of CD4+ T-cell reactivity to CMV after HAART.

Protease inhibitor (PI); Nonnucleoside reverse-transcriptase inhibitors (NNRTI); Nucleoside analog reverse-transcriptase inhibitors (NRTI), Highly active antiretroviral therapy (HAART), Antiretroviral therapy (ARV).

cell-cycle arrest at the G1-phase as well as apoptosis through down-regulation of cell-cycle gene cyclin D2 and antiapoptotic gene survivin. Furthermore, ritonavir suppressed transcriptional activation of nuclear factor-kappaB (NF-κB) in these cells. AZT inhibits NF-κB and up-regulates EBV gene expression in primary Epstein-

Barr virus-positive Burkitt lymphoma (EBV-BL) lines (Kurokawa *et al.*, 2005).

Lamivudine (3TC), a nucleoside analogue reverse transcriptase inhibitor of HIV and HBV DNA polymerase, is used in the long-term treatment of HBV chronic hepatitis because of its effectiveness and good tolerability. Research

with HBV-DNA detection-sensitive techniques has demonstrated the effectiveness of lamivudine in co-infected HIV patients over a long period of time (Deal *et al.*, 2002). However, resistant mutants occur during treatment and also for HIV, corresponding to changes of methionine for isoleucine and valine in the YMDD domain C sequence of the enzyme (Deal *et al.*, 2002). Other drugs such as tenofovir and adefovir dipivoxil can show beneficial associations with HAART in the treatment of lamivudine-resistant hepatitis B (Benhamou *et al.*, 2001; Perillo *et al.*, 2000). There are potentially more effective drugs or combination therapies, which can reduce intrahepatic covalently closed circular DNA (cccDNA) effectively in chronic B hepatitis patients (Kumar *et al.*, 2011; Reijnders *et al.*, 2010; Shinkai *et al.*, 2006; Sung *et al.*, 2005).

Other studies report virus clearance by parvovirus B19 in HIV-infected people after HAART application. The first case report showed the clearance of parvovirus B19 in a patient with red blood aplasia and severe anemia some two months after the start of antiretroviral therapy, that was not eradicated after conventional treatment with intravenous immunoglobulin (IVIG) (Ware, Moore, 2001). The second study showed that overall clearance in the serum of a parvovirus B19-chronic anemia case occurred after 14 months of HAART. Thus, antiretrovirals can be effective and possibly eliminate transfusions and IVIG therapy in HIV co-infected individuals (Mylonakis *et al.*, 1999). This may be associated with the immune reconstitution syndrome (IRS). In 2005, the first case of IRS associated with B19-induced chronic pure red cell aplasia during highly active antiretroviral therapy was described (Intalaporn *et al.*, 2005).

HAART use, coupled with PI, may require complete suppression of CMV. This response was correlated with protection against CMV retinitis in a group of patients featuring high risk for the development of the disease (Deyaton *et al.*, 1999). Antiretroviral therapy may also result in negative antigenemia and culture for CMV, immunological improvement through increased CD4+ T-cell count, increase in reactivity of CD4+ T-cells for CMV antigens and reduction in HIV load (Borges *et al.*, 2001; Li *et al.*, 1999). Criteria for discontinuation of treatment for CMV when the patient is receiving HAART for several months requires further investigation by prospective studies (Li *et al.*, 1999). To our knowledge, there are no articles describing the direct activity of antiretroviral drugs on CMV.

### Antiretroviral drugs and bacterial agents (Table III)

Respiratory tract bacterial (pyogenic and non-pyogenic) infections in human immunodeficiency

virus-infected patients are the most frequent respiratory disease but other sites may also be compromised. In the pre-HAART era the incidence of most common opportunistic infections such as bronchitis and pneumonia could be partially prevented by the use of prophylaxis (Mayaud, Parrot, Cadranet, 2002). According to these authors the main pyogenic bacteria responsible for pneumonia in these patients were *Streptococcus pneumoniae* and, to a lesser degree, *Haemophilus influenzae*, in adults as well as children in both developed and developing countries. In the HAART era, some studies have observed a decrease in the number of cases of bacterial pneumonia (Mayaud, Parrot, Cadranet, 2002), while other authors (Tumbarello *et al.*, 1999) have shown that this decrease was mainly observed for nosocomial pneumonia and remained nonsignificant for community-acquired pneumonia.

HAART has also led to a significant reduction in the incidence, and in changes of characteristics, of bacteremia by etiological agents such as *Staphylococcus aureus* (28%), coagulase negative *Staphylococcus* (13%), nontyphoid (NT) species of *Salmonella* (11%), *Streptococcus pneumoniae* (11%), *Pseudomonas aeruginosa* (11%) (Tumbarello *et al.*, 2000). The incidence of Non-typhoidal *Salmonella* (NTS) and *Campylobacter* have declined since the introduction of HAART (Larsen *et al.*, 2011). A decline in incidence of nosocomial bacterial pneumonia (NBP) caused by *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumoniae* in HIV-infected individuals was observed after the introduction of HAART. *S. aureus* and *P. aeruginosa* were the leading causes of NBP, but the frequency of pneumococcal pneumonia was also significant (Franzetti *et al.*, 2006).

A study carried out at a central hospital in Malawi (Africa) during the period of national scale-up of antiretroviral therapy and cotrimoxazole prophylaxis, demonstrated a downward trend in invasive pneumococcal disease (IPD) (Everett *et al.*, 2011). Although HAART has been associated with significant decline in IPD morbidity and mortality, HIV-infected African children with access to HAART remain a high-risk group for IPD (Nunes *et al.*, 2011).

HIV increases the risk of immediate tuberculosis (TB) progress soon after infection or re-infection with *Mycobacterium tuberculosis* (MTB) and of reactivating a latent MTB. HAART decreased the incidence of MTB infections and death among patients with AIDS, although some patients experienced temporary worsening of TB (Leone *et al.*, 2010). This phenomenon termed Immune Reconstitution Inflammatory Syndrome (IRIS) is caused by the introduction of HAART, where immune recovery may result in immunological reactions and clinical dete-

**TABLE III** - Characteristics of studies included in the systematic review, on antiretroviral agents and bacteria

Source	Aim	Study design	Drug groups	Patients (n)	Conclusion
Kirk <i>et al.</i> <i>Am. J. Respir. Crit. Care Med.</i> , 2000.	Evaluate effectiveness of HAART in <i>Mycobacterium tuberculosis</i> and <i>M. avium</i> -infected HIV patients.	Cohort	HAART	7,000	Decrease in TB was associated with introduction of HAART and changes in CD4 <sup>+</sup> T-cell count.
Tumbarello <i>et al.</i> <i>Eur. J. Clin. Microbiol. Infect. Dis.</i> , 2001.	Evaluate effectiveness of HAART on infection spread by <i>Mycobacterium avium</i> in HIV patients.	Case-control	HAART	81	MAC infections are less frequent in HAART era, but remain responsible for cases of severe disease.
Tumbarello <i>et al.</i> <i>J. Acquir. Immune Defic. Syndr.</i> , 2000.	Evaluate incidence of bacteremia in HIV-infected subjects after introduction of HAART and describe patients' characteristics.	Case-control	PI NRTI	174	HAART promotes a significant reduction in the incidence, and in changes of characteristics, of bacteremia.
Paech <i>et al.</i> <i>Clin. Infect. Dis.</i> , 2002.	Evaluate effectiveness of HAART treatment by <i>M. haemophilum</i> co-infection.	Case report	PI NRTI	1	A local <i>M. haemophilum</i> skin infection resolved as a result of successful antiretroviral therapy only.
Drona <i>et al.</i> <i>Rev. Clin. Esp.</i> , 2000.	Describe patient with <i>Mycobacterium xenopi</i> lung infection.	Case report	PI NRTI	1	A possible latent infection was expressed clinically after immune reconstitution induced by the treatment.

Protease inhibitor (PI); Nucleoside analog reverse-transcriptase inhibitors (NRTI), Highly active antiretroviral therapy (HAART). MAC: *Mycobacterium avium* complex.

rioration in patients with TB (Lawn, Bekler, Meller, 2000). Baalwa *et al.* (2008) discussed a possible limitation in the protective effects of HAART against TB recurrence and reiterated the need to consider TB chemoprophylaxis as a supplement to reduce TB in patients from endemic regions.

The initiation of HAART after starting TB treatment involves many variables such as drug tolerance, drug co-toxicities, pharmacokinetic drug interactions, polypharmacy impacts on adherence, high pill burden, and the immune reconstitution inflammatory syndrome (IRIS), thus complicating the management of co-infected individuals (Piggott, Karakousis, 2011; Wood, 2010). Perturbations of the innate and adaptive immune response to *M. tuberculosis* before and during antiretroviral therapy (ARV) may contribute to the immunopathology of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) (Oliver *et al.*, 2010; Tadokera *et al.*, 2011). Hypercytokinaemia appears to be involved with TB-IRIS, because higher interleukin (IL)-18, IL-6 and tumour necrosis factor (TNF) (Oliver *et al.*, 2010; Tadokera *et al.*, 2011) and type 1 effector T cell responses are noted in ARV-associated tuberculosis (Elliott *et al.*, 2009).

Relevant reduction in the incidence of other mycobacteria such as *Mycobacterium avium complex* (MAC) has been reported among HIV-infected patients. The introduction of HAART, although partially explaining some of the decrease in MAC during a certain period, a significantly lower risk of MAC than expected remained (Kirk *et al.*, 2000). A study showed that a 74% reduction in the rate of new MAC infections occurred following widespread use of HAART (Tumbarello *et al.*, 2001). The use of protease inhibitor-containing regimens was associated with a decreased risk of bacterial pneumonia (risk ratio [RR] 0.55, 95% CI 0.31 to 0.94) (Sullivan *et al.*, 2000).

*Mycobacterium haemophilum* was identified as the local agent of skin infection in an AIDS patient, and clinical cure was achieved only after reconstitution of immunity by HAART, although this has not been observed in clinical outcomes of patients with the invasive form of the disease (Paech *et al.*, 2002). However, clinical manifestation was observed in patients presenting latent infection with *Mycobacterium xenopi* (Bachmeyer *et al.*, 2002; Drona *et al.*, 2000; Manfredi *et al.*, 2003) and *Mycobacterium kansasii* (Ito *et al.*, 2009) after reconstitution

of immunity by antiretroviral therapy. The isolation of pulmonary *M. xenopi* in an HIV-1 infected population is usually associated with severe immune suppression and the presence of other pathogens. In most cases, patients in use of HAART have potent immune reconstitution that is sufficient, dispensing with the need for antimycobacterial drugs. Mortality rates among these patients seems to be significantly lower than previously reported (Kerbioui *et al.*, 2003).

HIV-*Mycobacterium leprae* interaction is different from that described above. HIV infection has not been reported to increase susceptibility to leprosy or have a significant effect on the pathogenesis of neural or skin lesions. On the other hand, the initiation of HAART in HIV-leprosy patient has been reported to be associated with activation of subclinical infection and exacerbation of existing leprosy lesions. Chow *et al.* (2009) reported a case of IRIS in a patient co-infected with HIV and *M. leprae*, presenting as an exacerbation of Hansen's Disease where the patient's skin lesions progressed from borderline tuberculoid to lepromatous leprosy following ARV initiation. Other publications have also reported the presence of IRIS in HIV-*Mycobacterium leprae* patients (Couppie *et al.*, 2004; Lawn, Wood, Lockwood, 2003; Pignatato *et al.*, 2004; Visco-Comandini, *et al.*, 2004).

#### Antiretroviral drugs and protozoa agents (Table IV)

Combination antiretroviral therapy has been able to modify the natural history of opportunistic diseases, such as cryptosporidiosis and microsporidiosis (Maggi *et al.*, 2000). AIDS-related *Enterocytozoon bieneusi* and *Cryptosporidium parvum* may be cured following successful antiretroviral therapy (Miao *et al.*, 2000), but infection eradication might not always be possible (Maggi *et al.*, 2000). Protease inhibitors may be capable of eradicating *Microsporidium* and/or *Cryptosporidium*, which are refractory to other treatments, and this effect may involve partial restoration of immune function due to the inhibition of HIV replication (Bobin *et al.*, 1998). Miao *et al.* (2000) prospectively followed up HIV-positive patients with diarrheal symptoms caused by cryptosporidia or microsporidia and observed that patients who responded successfully to HAART eradicated both organisms promoting improved symptoms within one month of therapy. Complete eradication of the organisms however, was only observed after 6 months of treatment. Combination antiretroviral therapy that includes a PI may restore immunity and result in complete clinical, microbiological, and histological responses to *Enterocytozoon bieneusi* and *Cryptosporidium parvum* in HIV-1 infected individuals

(Carr *et al.*, 1998). Findings show rapid repopulation of the intestinal mucosa with CD4+ T cells after initiation of HAART, which can effectively restore mucosal immunity, leading to the eradication of *Cryptosporidium parvum* (Carr *et al.*, 1998). Indinavir directly affects the cycle of *C. parvum*, evidenced by marked reduction in oocyst shedding and number of intracellular parasites on *in vitro* and *in vivo* models (Mele *et al.*, 2003).

In 2001, Casado *et al.* determined the evolution of visceral leishmaniasis (VL) in 10 consecutive patients co-infected with HIV, taking into account the decline in the incidence of opportunistic infections after the introduction of protease inhibitor therapy. Giudice *et al.* (2002) estimated the incidence of HIV-*Leishmania* coinfections in a French hospital, and showed a decreased from  $11.6 \pm 1.2$  per 10,000 persons-years before 1996 to  $6.3 \pm 0.7$  per 10,000 persons-years after 1996, the year when HAART was introduced in France. Factors other than restoration of immune function might also account for the decline in the incidence of VL. PIs have shown antimicrobial properties, such as anticandidal and antitoxoplasmic activities, *in vitro*.

Some studies have reported antiprotozoal activity of HAART in *Leishmania* (Araújo *et al.*, 2011; Kumar *et al.*, 2008; Santos *et al.*, 2009; Savoia, Alice, Tovo, 2005; Valdivieso *et al.*, 2010). AZT significantly decreased the number of *Leishmania* parasites due to its toxicity and caused morphometric alterations such as an increase in width of the body, cytoplasmic granulation and vacuolization (Araújo *et al.*, 2011). PIs such as ritonavir, indinavir and saquinavir have reduced the number of *Leishmania* promastigotes *in vitro* (Savoia, Alice, Tovo, 2005). Furthermore, PIs seem to reduce the intracellular growth of *Leishmania* parasites in human primary monocyte-derived macrophages (MDMs) coinfecting with HIV-1 (Trudel *et al.*, 2008) and can also induce oxidative stress-mediated, caspase-independent apoptosis in *Leishmania* amastigotes (Kumar *et al.*, 2010). Valdivieso *et al.* (2010) reported an antiproliferative effect on *Leishmania* sp. promastigotes, axenic amastigotes and co-infected HIV/*Leishmania* monocytes and amastigotes of *Leishmania* per macrophage by saquinavir mesylate and nelfinavir. This outcome appears to be the result of cell division block. In addition, PIs can promote profound changes in *Leishmania* ultrastructure such as cytoplasm shrinking, increase in the number of lipid inclusions with some cells presenting the nucleus closely wrapped by endoplasmic reticulum resembling an autophagic process, as well as chromatin condensation, suggestive of apoptotic death (Santos *et al.*, 2009).

Analysis of therapy-induced changes in the mucosal



**TABLE IV** - Characteristics of studies included in the systematic review, on antiretroviral agents and protozoa

Source	Aim	Study design	Drug groups	Patients (n)	Conclusion
Miao <i>et al.</i> <i>JAIDS</i> , 2000.	Determine whether the parasites cryptosporidia and microsporidia were effectively eradicated or supply suppressed after HAART.	Prospective	NRTI PI	6	AIDS-related cryptosporidiosis and microsporidiosis can be cured following successful antiretroviral therapy
Bobin <i>et al.</i> <i>Path. Biol.</i> , 1998.	Evaluate ARV effect on evolution of diarrhea caused by <i>Microsporidium</i> and <i>Cryptosporidium</i> in HIV patients.	Prospective	PI	20	PI may be capable of eradicating <i>Microsporidium</i> and/or <i>Cryptosporidium</i> infection refractory to other treatments.
Carr <i>et al.</i> <i>Lancet</i> , 1998.	Demonstrate that combination PI and NRTIs may improve immunity with regard to <i>E. bienewisi</i> and <i>C. parvum</i> .	Prospective	NRTI PI	9	This combination can restore immunity to <i>E. bienewisi</i> or <i>C. parvum</i> in HIV-1 infected individuals.
Schmidt <i>et al.</i> <i>Gastroenterology</i> , 2001.	Evaluate effectiveness of HAART with PI against <i>C. parvum</i> .	Case report	NRTI PI	1	HAART has led to clinical recovery and eradication of cryptosporidiosis. This could be due to decreased HIV RNA below the detection limit and increase in CD4 T cells.
Maggi <i>et al.</i> <i>Eur. J. Clin. Microbiol. Infect. Dis.</i> , 2000.	Evaluate response to antimicrobial treatment of HIV-1 associated microsporidiosis and cryptosporidiosis in patients with or without previous antiretroviral treatment.	Retrospective	NRTI PI	50	Combination antiretroviral therapy may be able to greatly modify the course of these diseases in patients infected with HIV-1.

Protease inhibitor (PI); Highly active antiretroviral therapy (HAART); Nucleoside analog reverse-transcriptase inhibitors (NRTI); Antiretroviral therapy (ARV).

immune response of these patients may provide significant clues to the mechanisms involved in the control of enteric opportunistic agents (Schmidt *et al.*, 2001). Similarly, persistent CD8<sup>+</sup> T-cells and macrophage infiltrate plus the rapid relapse time in patients with declining CD4<sup>+</sup> T-cells counts suggest that neither infection was eradicated (Carr *et al.*, 2000).

Restoration of immune responses to *Toxoplasma gondii*, a major opportunistic pathogen in patients with AIDS, has also been reported in patients receiving HAART (Derouin and Santillana-Hayat, 2000). Pozio and Morales (2005) have reported that the use of PIs resulted in marked decrease in toxoplasmic encephalitis among HIV-positive individuals.

Furco *et al.* (2008) showed that specific immune reconstitution against *T. gondii* occurred in most HIV-infected patients with a low baseline CD4<sup>+</sup> T-cell count after 12 months of HAART. However, a significant proportion of these patients did not present a normal lymphoproliferative

response or IFN- $\gamma$  production to the *Toxoplasma* antigen. These data will also promote better understanding of the determinants of restoration of *T. gondii*-specific immune responses in patients with AIDS starting on HAART. Derouin and Santillana-Hayat (2000) showed that nucleoside analogs had no effect on *T. gondii* growth *in vitro*, whereas ritonavir and nelfinavir were inhibitory for *Toxoplasma*.

## CONCLUDING REMARKS

Current findings are highly relevant for clinical medicine and may serve to reduce the number of prescribed drugs thereby improving the quality of life of patients with opportunistic diseases. The present systematic review identified several opportunistic agents of the oral cavity subjected to the positive activities of HAART thus decreasing the number of fungi, favoring SAP inhibition, and improving laboratory and immunological parameters. In the case of viruses, antiretroviral therapy may be

beneficial for patients co-infected by HIV, HHV-8, EBV, HBV, parvovirus B19 and CMV. The incidence of *Mycobacterium tuberculosis*, *Mycobacterium avium complex*, *Microsporidium* and/or *Cryptosporidium*, refractory to other treatments was significantly reduced. Protease inhibitors are of paramount importance among those drugs currently used in HAART.

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