

## Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome and Tropical Diseases: a Brazilian Perspective

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*The paper summarizes recent findings on the epidemiology and pathogenesis of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/Aids), highlighting the role of co-infections with major tropical diseases. Such co-infections have been studied in the Brazilian context since the beginning of the Aids epidemic and are expected to be more frequent and relevant as the Aids epidemic in Brazil proceeds towards smaller municipalities and the countryside, where tropical diseases are endemic. Unlike opportunistic diseases that affect basically the immunocompromised host, most tropical diseases, as well as tuberculosis, are pathogenic on their own, and can affect subjects with mild or no immunosuppression. In the era of highly active anti-retroviral therapies (HAART), opportunistic diseases seem to be on decrease in Brazil, where such medicines are fully available. Benefiting from HAART in terms of restoration of the immune function, putative milder clinical courses are expected in the future for most co-infections, including tropical diseases. On the other hand, from an ecological perspective, the progressive geographic diffusion of Aids makes tropical diseases and tuberculosis a renewed challenge for Brazilian researchers and practitioners dealing with HIV/Aids in the coming years.*

Key words: human immunodeficiency virus/acquired immunodeficiency syndrome-HIV/Aids - co-infections - Brazil

### THE HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME (HIV/AIDS) EPIDEMIC: AN OVERVIEW

The HIV is one of the most important emergent pathogens of this century. Based on phylogenetic analyses, it was estimated that HIV emerged in 1931 (range 1915-1941), becoming a worldwide public health challenge fifty years later (Korber et al. 2000).

As recently reviewed by the Joint United Nations Programme on HIV/Aids (UNAIDS 2000), since the description of the first cases at the early beginning of 80' in USA and Europe, more than 18 million deaths have been occurring due to HIV/Aids. Thirty-four million individuals, adults and children, are estimated to be living with HIV/Aids worldwide. Latin America contributes with almost 4% of such cases. HIV/Aids was the cause of 4.2%

of the deaths in the world in 1999. Moreover, HIV is the fifth cause of death worldwide and is now believed to cause more deaths than malaria.

Aids has deeply affected young adults all over the world, with multiple adverse consequences, such as growing numbers of orphaned children and disruption of the local economy and community life, especially in developing countries, particularly affected by the epidemic and other health and social problems (UNAIDS 2000). In the cities of São Paulo and Rio de Janeiro, Aids has been one of the leading causes of death in young adults, and has deeply affected young women in recent years, despite the undeniable improvement of clinical evolution due to free-access to highly active anti-retroviral therapy (Lowndes et al. 2000).

Only in 1999, 5.4 million adults and children were estimated to become infected worldwide, with 15,000 new infections a day. Around 95% of these new cases occurred in developing countries, roughly 11% in children under 15, and 90% in people aged 15-49, of whom almost 50% are women and about 50% are 15-24 years old. In selected African countries with high HIV prevalence, reduction in the life expectancy is being observed overtime, and major public health achievements

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of the past decades (e.g. reduction in child mortality in different African countries) have been strikingly reversed (Garnett & Anderson 1993).

#### AIDS IN BRAZIL

As of November 1999, 179,541 Aids cases have been reported to the National Coordination of HIV/Aids of the Brazilian Ministry of Health (1999), and it is estimated that around 550,000 individuals are living with HIV/Aids in the country. According to the UNAIDS, Brazil ranks among the first four countries in the world with the largest number of reported cases. However, considering the relative incidence, its position in the world falls to the 40th to 50th (Brazilian Ministry of Health 1998).

The Brazilian Aids epidemic has as a distinctive characteristic: its deep heterogeneity, with "hot spots" deeply affected by the epidemic, especially the metropolitan areas of the Southeast, and areas where the epidemic is still in its beginning phase. Over the years, the epidemic has grown all over the country, and currently has been observed in roughly half of the 5,000 Brazilian municipalities (Szwarcwald et al. 2000).

The evolution of the epidemic in the country is matched by a clear change in the profile of the main types of exposure. Whereas in the eighties the majority of the reported cases concerned homosexual/bisexual individuals (around 70% in 1984-1988), the relative participation of this category has progressively decreased over time, reaching 23.3% in 1998/1999. In contrary, transmissions by heterosexual intercourse, which corresponded to 3-8% in 84/88, increased to almost 40% of the reported cases in 1998/99 (Brazilian Ministry of Health 1999).

Due to the rapid introduction of blood screening and inactivation of blood products, the transmission by blood transfusion rapidly declined in the beginning of the Aids epidemic in Brazil. However, blood transmission among injecting drug users increased rapidly, from 3-5% in 1984/1986 to 20% in 1990, and has been maintained around this value (20-25%) so far, keeping parenteral transmission as a core route for HIV continuous spread in Brazil.

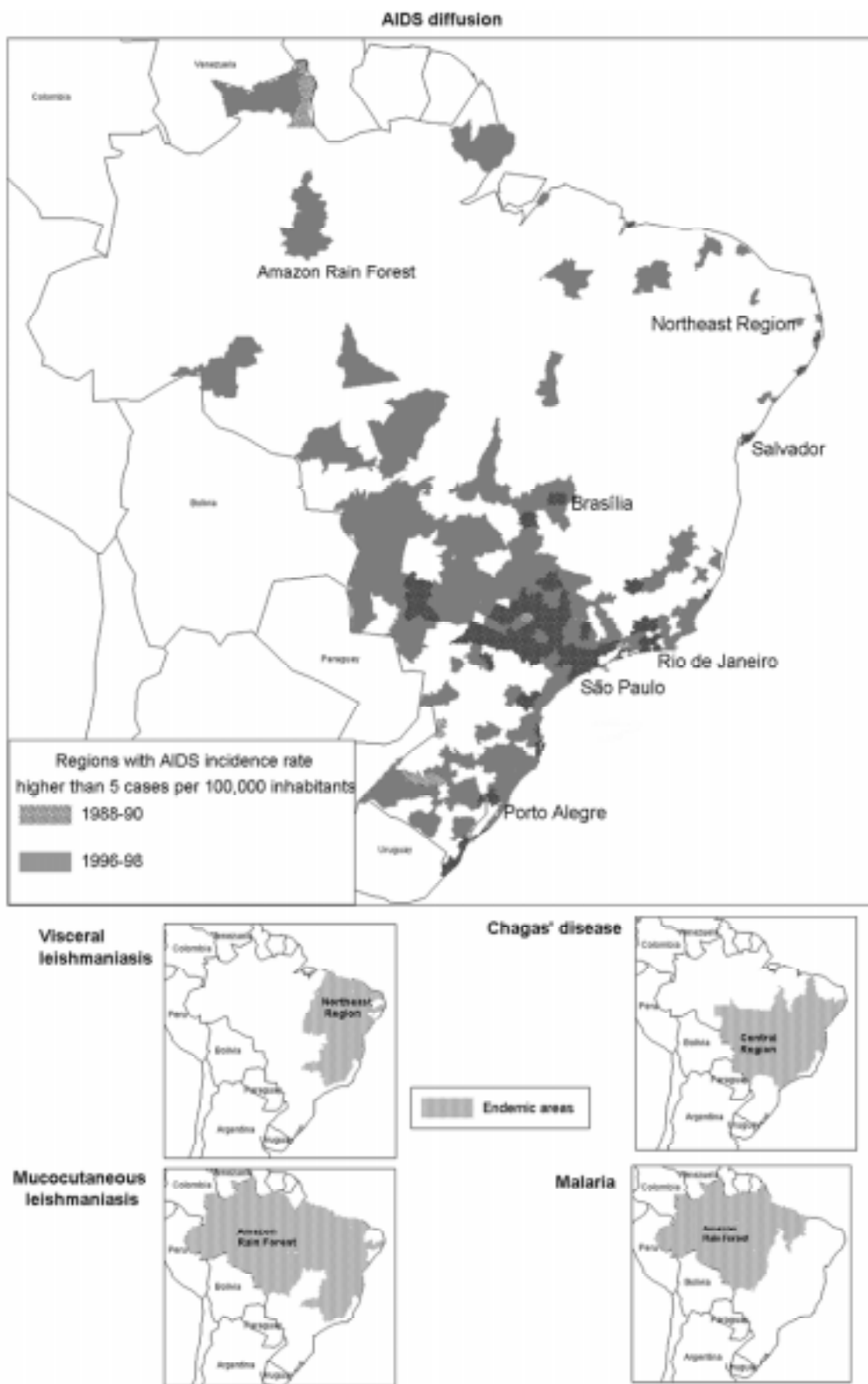
It is important to point out that the participation of the different exposure categories in the Aids epidemic varies along the regions of the country, with net difference from the North/Northeast profile, where transmission due to injection drug use has been negligible (exception made to Bahia), to South/Southeast where transmission by unprotected heterosexual intercourse and by injection drug use have been pivotal (Szwarcwald et al. 2000). Moreover, the sex ratio has also changed over time, with the male:female ratio dropping from 24:1 in 1985 to 2:1 in 1998/1999. The increased

role of the women in the Brazilian Aids epidemic has important consequences in perinatal transmission, accounting for 90% of the registered cases of children under 13 years old in 1998/1999 (Brazilian Ministry of Health 1999).

The first Aids cases were notified in 1982 in the Southeast region (exception made to a single case retrospectively notified in São Paulo, in 1980) and, considering the latency period of HIV infection, it is possible to infer that the virus was probably introduced at the beginning of the 70's, initially becoming disseminated in the main metropolitan areas of the central-south region, spreading to other areas at the beginning of the 80's (Szwarcwald et al. 2000). Although cases have been registered in all Brazilian states and in the Federal District, most of them are still concentrated in the Southern region, with 124,797 reported to the Ministry of Health by November 1999, corresponding to about 70% of the cases already reported since the beginning of the epidemic.

In addition to the internal migrations, leading HIV infection from one region to another, as it is the case, for instance, of people involved in farming and mining activities, truck drivers and seasonal workers (Bastos & Barcellos 1995), the progressive dissemination of HIV infection towards smaller municipalities and the countryside, overlapping endemic areas of infectious and parasitic diseases (Figure), has increased the number of co-infections, which may modify the natural history of such diseases, as well as HIV/Aids spread and clinical course.

This overlapping area has both individual and ecological dimensions. Individuals can be doubly infected by HIV and different pathogens, especially in areas where both agents are prevalent. Due to the very dynamic nature of Brazilian social geography, unusual co-infections have been observed, such as outbreaks of malaria among HIV-infected injecting drug users in non-malarigenic areas of São Paulo (Bastos et al. 1999). Renewed public health challenges such as the combined diffusion of Aids and tuberculosis (TB) (Ferrazoli et al. 2000), or the aforementioned malaria outbreaks among HIV-infected persons, have been more frequent in recent years, due to the progressive intensification of communication between different regions of the country, as a consequence of the increase of interstate and Latin American Southern Cone regional commerce (free-trade zone), changes in the nature and occupation of the working force and opening of alternative economic opportunities far from main metropolitan areas (Bastos et al. 1999), affected by economic reform and structural unemployment and violence (Szwarcwald et al. 1999).



Acquired immunodeficiency syndrome (Aids) diffusion and endemic areas for visceral and mucocutaneous leishmaniasis, malaria and Chagas disease in Brazil. For the major endemic diseases, gray areas represent states reporting at least one case during the period (Cenepi, Brazilian Ministry of Health, 1997-1999) and incidence rates above the median.

Beyond the individual dimension, the overlapping of different infections also has a deep impact upon herd immunity (i.e. the immunity of communities taken as an integrated and interactive unity) and the global health status of communities, as has been made clear in the reemergence of tuberculosis in developed countries (Frieden et al. 1993), as well as the emergence of strains that resist usual prophylaxis and therapeutic regimens (Frieden et al. 1993, Fandinho et al. 1999).

#### **HIV AND CO-INFECTIONS: IMPLICATIONS FOR PATHOGENESIS**

The main immunological alterations observed along the evolution to Aids have been thoroughly described, which are characterized by the severe reduction of the CD4<sup>+</sup> T helper cells over time, impairment of the T helper cell activity, chronic immune activation, apoptosis of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, B cell polyclonal activation and deactivation of macrophage functions, among others (Fauci 1996, Cohen et al. 1997, Lane 1999). The consequent immunosuppression renders the HIV positive individuals more susceptible to opportunistic diseases as well as to the reactivation of endogenous infections. Conversely, HIV infection might modify the natural history of some parasitic infections, facilitating parasite replication due to the limited immunological control.

Worldwide, many different infectious agents have affected HIV-infected patients. Some of them are prevalent in different contexts, even in patients with mild immunological dysfunction such as the infection with *Mycobacterium tuberculosis* (Whalen et al. 2000), others are typical opportunistic agents, such as Cytomegalovirus, affecting basically severely immunosuppressed patients (Deayton et al. 2000). The latter class of infectious agents have become less common in recent years in settings where highly active anti-retroviral therapy (HAART) has been made available and a certain degree of immunological reconstitution has been observed in a sizeable number of patients (Deayton et al. 2000).

In the Brazilian context, where HAART has been fully available since 1996, most opportunistic infectious diseases associated to HIV/Aids, have been on decrease, some of the most prevalent, such as candidiasis, neurotoxoplasmosis and *Pneumocystis carinii* pneumonia (for which efficient prophylaxis was made available much earlier), in a significant extent (Guimarães 2000). As therapeutic regimens become more efficient in terms of restoration of the immune system and/or prevention of immunological dysfunction, opportunistic diseases, in settings where the best medical practices are available, tend to become each day more

and more rare. On the other hand, for agents with a relevant infectivity and pathogenicity in immunologically non-compromised individuals, such as *M. tuberculosis* and other infectious parasites, much has to be done, especially in hiperendemic areas.

*Tuberculosis* - TB is one of the most important Aids-associated infectious diseases worldwide, with 15.3 million people estimated to be infected with HIV and *M. tuberculosis* at the end of 1997 (WHO 2000). Recurrence rates may be higher than in HIV-negative persons through relapse or re-infection. Although patients with HIV-associated TB mostly have typical clinical patterns, their frequency of atypical manifestations is increased, making diagnosis more difficult. Worsening of the clinical and immunological features have also been thoroughly described in the HIV-TB co-infection (reviewed by Bonecini-Almeida et al. 1998). As described for other co-infections, *M. tuberculosis* accelerates the HIV infection and disease progression (Pape et al. 1993, Whalen et al. 1995, 1997).

*Leishmaniasis and other endemic prevalent diseases* - As reviewed previously by Ferreira (1996), its important to point out that some infectious diseases endemic in Brazil do not have their epidemiological and clinical course changed in function of the co-infection with HIV-1, others, however, like leishmaniasis, Chagas disease, strongyloidiasis, histoplasmosis, and paracoccidioidomycosis have important changes in its clinical-evolutive pictures. Indeed, reactivation of Chagas disease with central nervous system and cardiac involvement have already been described in Aids patients (Rocha et al. 1994, Ferreira et al. 1997, Silva et al. 1999). Moreover, several studies have demonstrated that HIV/Aids patients living in *Leishmania*-endemic areas are at high risk to develop leishmaniasis and this association accelerates the progression to Aids (WHO 1997). However, few data concerning the immunopathogenic mechanisms involved in *Leishmania*-HIV co-infection are available and were recently reviewed by Wolday et al. (1999). Increased viral load and immune activation associated with the Th2 cytokine pattern have also been described in HIV-*Leishmania* co-infection (Preiser et al. 1996). Cases of disseminated American cutaneous (Coura et al. 1987) and muco-cutaneous (Machado et al. 1992) leishmaniasis have been described in Brazilian co-infected Aids patients, which were probably associated with the inability of the T cell-mediated immune response to control the spread of *Leishmania* infection in immunosuppressed HIV-1 positive individuals (Da Cruz et al. 1992). Based on an extensive review of published cases from 1986 to 1999, Rabelo et al. (1999) identified an increased number of HIV-*Leishmania* co-infections in Brazil (54) in

the last decade, corresponding to 33.3% of visceral, 27.8% of mucocutaneous, 7.4% of mucosal and 31.5% cutaneous leishmaniasis. Proactive surveillance is being suggested by the experts, to assess new cases of leishmaniasis/HIV co-infection.

*Malaria* - The malaria/HIV co-infection has been a significant challenge in sub-Saharan Africa (Bloland et al. 1995), but a rare event in Brazil so far, due to the fact the overlapping between malarigenic areas and the areas where HIV infection is more prevalent is a quite recent occurrence, although a consistent trend (Bastos & Barcellos 1995, Szwarcwald et al. 2000). The clinical relationship between the two infections remains controversial (Chandramohan & Greenwood 1998), although some authors point to higher recrudescence rates of *P. falciparum* and a longer fever clearance time among Aids patients (Same-Ekobo & Monny-Lobe 1994), as well as reduced humoral immune response to malaria (Wabwire-Mangen et al. 1989) and poorer clinical prognosis (Niyongabo et al. 1994), especially in advanced Aids cases. Moreover, higher viral load was observed in *P. falciparum*/HIV-1 co-infected individuals when compared to those infected with HIV, which could be partially reduced with antimalarial therapy (Hoffman et al. 1999).

Most authors agree on a key finding: there is an enhanced effect of both infections (HIV-1 and *P. falciparum*) on perinatal transmission of malaria, with increased post-neonatal mortality (Bloland et al. 1995). This finding is of concern in the African context, where the measures directed to the prevention of the mother-to-child transmission of HIV have been erratically adopted or not adopted at all. In Brazil, where the mother-to-child transmission of HIV has been prevented with the comprehensive use of the best available clinical and laboratorial practices, the possibility of HIV and malaria co-infection in pregnant women should be carefully evaluated in the areas where malaria is prevalent and among women from these areas, to minimize the chance to reverse the significant gains Brazil has obtained in this field so far.

*Retroviruses co-infection: HIV and HTLV* - HTLV infection has been described in the most different settings and groups of patients in Brazil (Carneiro-Proietti et al. 1998, Pombo-de-Oliveira et al. 1999), although there is a clear concentration of such infection in populations under double risk of parenteral and sexual transmission, e.g. injection drug users (IDUs) (Carvalho et al. 1996, Andrade et al. 1999), and specific regions of the country, such as the state of Bahia (Gomes et al. 1999). IDUs, far from being a segregated population, as ordinarily thought, seem to exacerbate background infection patterns prevailing in the so called general popula-

tion, probably due to transmission of HTLV through unprotected sex between injecting drug users and their non-injecting sexual partners.

HIV/HTLV-I/II co-infection can pose problems in the field of clinical research and therapeutics, as was demonstrated by former studies (Schechter et al. 1994). The higher CD4+ lymphocyte counts observed in HIV/HTLV-I/II co-infection do not provide an immunological benefit, and may rather reflect HTLV-I associated nonspecific lymphocyte proliferation. Moreover, increased viral load has been described in HIV/HTLV-I/II co-infected individuals (Brites et al. 1998), but not in HIV/HTLV-I co-infected ones (Harrison et al. 1997). Thus, although evidences have been supported the role of HTLV co-infection as a potential co-factor to disease progression, this point is still unclear.

*Prospects for the future* - The field of HIV/Aids has experienced a permanent revolution, both from the perspective of the basic sciences and from the point of view of the many applications of the new scientific findings in the prevention of new HIV infections and treatment of the already HIV-infected patients. In recent years, great achievements have been made in the understanding of the pathogenesis of HIV infection. These achievements have been quite immediately translated in brand new therapeutic alternatives, with the consequent significant improvement in the lives of people living with HIV and Aids. Another recent breakthrough was the development of preventive strategies once systematically applied could effectively curb the spread of HIV from pregnant women to their offspring.

The face of the Aids epidemic has been changing in a fast pace, many times for better, but, unfortunately most of the times for worst. The recent explosive epidemics in South Africa or in the recently independent eastern European countries and parts of the former USSR are of deep concern, given the paucity of preventive and therapeutic alternatives in those contexts.

Brazil has in this global picture an intermediate position. Due to its deep social heterogeneity and its huge size, the Brazilian epidemic is still diffusing towards formerly spared regions and populations. Some areas now experiencing a fast diffusion of HIV are areas traditionally affected by endemic diseases such as malaria, Chagas disease and the leishmaniasis. In this sense, Brazil needs to ask for its accumulated expertise in the field of Aids and tropical diseases, and to have a strong political commitment to prevent and treat such putative new co-infections.

A continuous effort to improve adherence and the maintenance of the current politics of free access to anti-retroviral therapies constitute essen-

tial measures, in order to keep opportunistic diseases associated to HIV-infection under sustained decrease, as made evident by epidemiological and clinical studies.

The simultaneous diffusion of HIV/Aids and TB poses a formidable challenge for Brazilian scientists, physicians and public health officials, due to the need to address current problems and unsuspected trends such as the low-adherence to long-term anti-tuberculosis prophylactic and therapeutic regimens or the emergence of resistant strains.

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