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Toxoplasmosis in HIV/AIDS Patients - A Living Legacy

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1. Introduction

The coccidian *Toxoplasma gondii* (*T. gondii*) is a ubiquitous, intracellular, protozoan parasite that causes toxoplasmosis, a cosmopolitan zoonotic disease. *Toxoplasma* infections are reported in approximately half of the world's population but most are asymptomatic. *T. gondii* may serve as one factor that can enhance the immunodeficiency found after HIV-1 infections. Co-infection with other pathogens in humans infected with HIV-1 may enhance the progression of the disease to AIDS (Lin & Bowman, 1992). In concurrence with HIV infection, cerebral toxoplasmosis (CT) occurs primarily due to reactivation of latent *Toxoplasma* infection and is one of the most frequent opportunistic infections, particularly in patients with full-blown AIDS. CT is the most common clinical presentation of toxoplasmosis (Luft & Remington, 1992), and is one of the most frequent causes of focal intracerebral lesions that complicates AIDS (Nissapatorn et al, 2004). CT is undoubtedly a serious life-threatening disease but it is treatable when there is a timely diagnosis and prompt treatment, and there are no other concurrent co-infections. When HIV-infected patients develop CT this poses many diagnostic and therapeutic challenges for clinicians (Israelski & Remington, 1992), particularly in developing countries where the infrastructure is limited but the number of patients infected with HIV is increasing. This chapter focuses on the clinico-epidemiological aspects of toxoplasmosis in HIV/AIDS patients at the time of transition to treatment with highly active anti-retroviral therapy (HAART). The course of toxoplasmosis in HIV/AIDS patients should be able to provide us with a better understanding of the clinical scenario and future management of this so-called "enigmatic parasite" of the tropics.

2. Pathogenesis - from source to host defense mechanism

2.1 Morphology

T. gondii is a coccidian, that is ubiquitous and an obligate intracellular parasite with a complex life cycle and felids are the definitive hosts. There are three infectious stages of *T. gondii* in the environment. Tachyzoites (or endozoites), crescent to oval in shape, are seen in an active infection. They can be transmitted through the placenta from mother to fetus, by blood transfusion, or by organ transplantation. Tissue cysts, containing thousands of bradyzoites, the terminal life cycle stage, are transmitted by eating infected meat or organs, and may persist life-long in an intermediate host. In this stage, they are associated with

latent infections, but reactivation occurs in persons who lose their immunity. Bradyzoites (or cystozoites) are less susceptible to chemotherapy and the presence of this infective stage in host tissues is of clinical significance, particularly in immunosuppressed individuals. The oocyst stage, is excreted in the cat's feces, and this most tolerant form of *T. gondii*, is ubiquitous in nature, is highly resistant to disinfectants and environmental influences, as well as playing a key role in transmission through the fecal-oral route.

2.1.1 Life cycle and transmission

The life cycle of *T. gondii* was described in 1970, before it was determined that members of the family Felidae, including domestic cats, were the definitive hosts and warm-blooded animals including most livestock and humans serve as intermediate hosts (Figure 1). In contrast to other protozoans, *T. gondii* is a parasite that can parasitize all mammals. *T. gondii* has a large host range; this parasite can be found throughout the world. *T. gondii* is a common infection in humans; it becomes more important in the field of veterinary and medical infectious diseases. *T. gondii* is a potential organism causing a serious public health hazard due to infected meat-producing animals and a severe economic loss to the livestock owners. *T. gondii* can be transmitted (Figure 2) through one of the following routes (Tenter et al, 2000; Derouin et al, 2008).

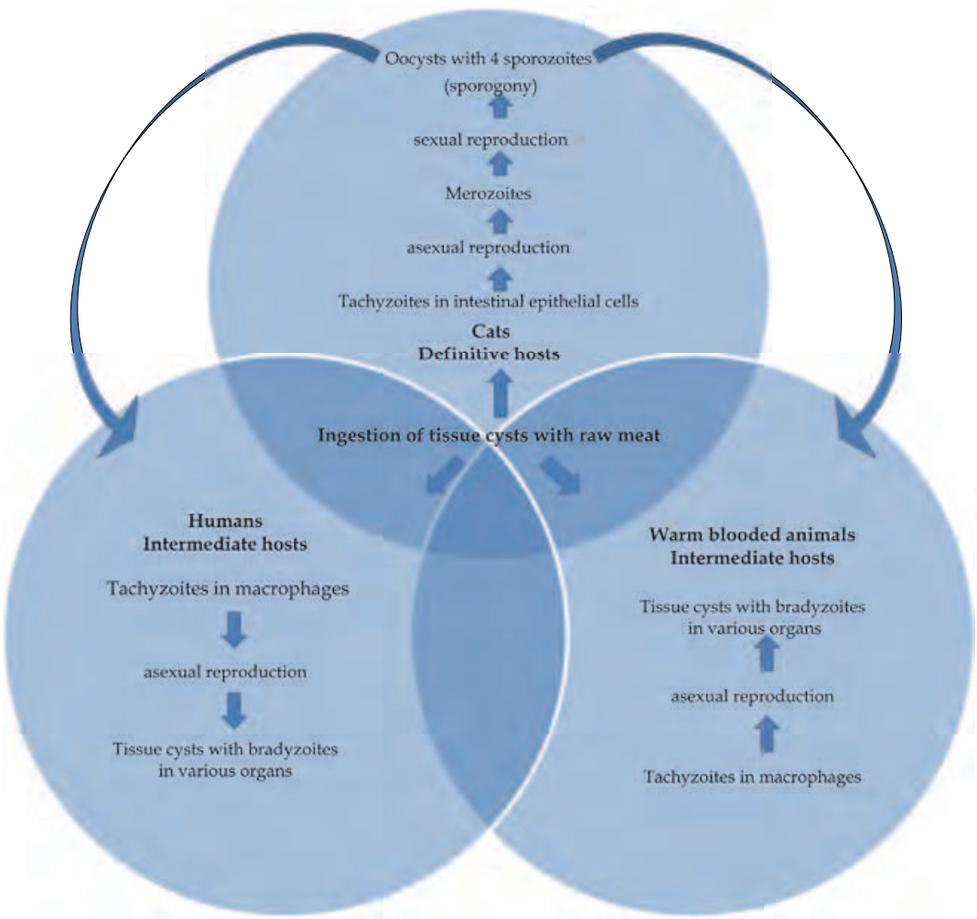

Fig. 1. The life cycle of *T. gondii*.

In the definitive hosts, infection with *T. gondii* occurs following not only ingestion of tissue cysts in under-cooked meat but also after ingesting the rapidly-multiplying tachyzoite forms or the oocysts shed in feces. The cyst wall of *T. gondii* is dissolved by the proteolytic enzymes of both stomach and small intestine, releasing the slowly-multiplying bradyzoite form. The asexual cycle begins after the invasion of *T. gondii* into the epithelial cells of the small intestine. While, the sexual cycle is very specific and occurs only in the gut epithelial cells of feline species. The oocyst forms are produced by gamete fusion and are then shed in the feces of the definitive hosts. These oocysts are highly infective to other definitive and intermediate hosts once they are in contact with a susceptible environment (Frenkel, 1973). The oocysts of *T. gondii* are less infective and pathogenic in the definitive host (cat) as compared with intermediate hosts (mice, pigs, humans) (Dubey, 1998).
In intermediate hosts, *T. gondii* undergoes two phases of asexual development. The infective stages (sporozoites or bradyzoites) transform into tachyzoites following *Toxoplasma* infection of the intestinal epithelial cells. In the first phase, tachyzoites multiply rapidly by repeated endodyogeny in an intracellular parasitophorous vacuole in many different types of host cells. The second phase develops from the tachyzoites of the last generation and results in tissue cysts (Tenter et al, 2000). Within the tissue cyst, bradyzoites multiply slowly by endodyogeny. Tissue cysts have a high affinity for neural and muscular tissues and are located mainly in the central nervous system (CNS), eye, skeletal and cardiac muscles as well as other visceral organs (Dubey et al, 1998). Tissue cysts break down periodically, with bradyzoites transforming into tachyzoites that reinvade host cells and again transform to bradyzoites within new tissue cysts (Dubey, 1998).

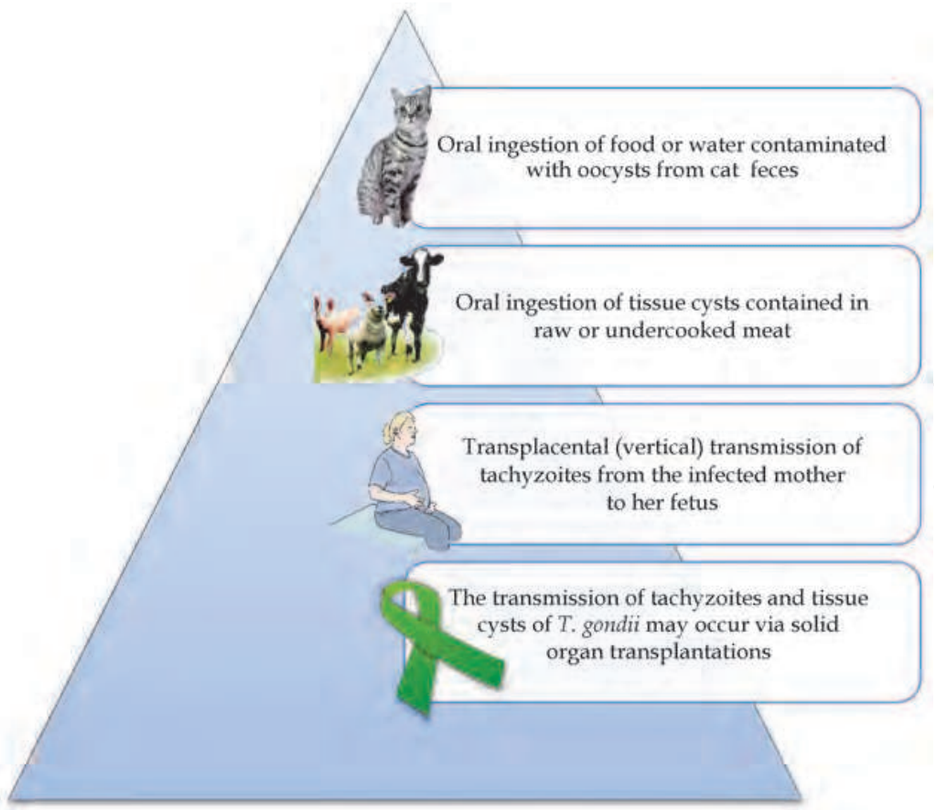

Fig. 2. The different routes of *T. gondii* transmission.

2.1.2 *T. gondii* antigens, host defense mechanisms and cerebral toxoplasmosis

In patients with AIDS, tissue cysts rupture and the released bradyzoites may multiply locally and spread to other organs. Infected patients may have serious complications or even death from symptomatic toxoplasmosis. The pathology of *Toxoplasma* infection is due to the invasion process initiating the lytic cycle that consequently leads to cell and tissue destruction. In the host cell cytoplasm, *T. gondii* induces the formation of a parasitophorous vacuole that contains secretions of both parasite and host proteins that normally promote phagosome maturation, , and thereby prevent lysosome fusion (Dubey et al, 1998; Carruthers, 2002). Despite this rapid, dynamic and significant process, there are very few secretory proteins that have so far been discovered (Zhou et al, 2005). These proteins (antigens) are essential components for low-grade stimulation that boosts the immune system. These antigens have been shown to stimulate antibody production as well as a T-cell response (Carruthers, 2002).

T. gondii excretory/secretory antigens (ESAs) represent the majority of the circulating antigens in host sera of patients with acute toxoplasmosis (Pereira-Chioccola et al, 2009). ESAs include the tachyzoite, sporozoite and encysted bradyzoite stages (Tilley et al, 1997). The secretions by the bradyzoite cysts maintain a long-lasting immunity to *T. gondii* (Cesbron-Delauw & Capron, 1993). The ESAs released by tachyzoites are highly immunogenic (Prigione et al, 2000; Carruthers, 2002) and may induce either antibody dependent or cell mediated immunity (Costa-Silva et al, 2008). Anti-ESA antibodies develop in high titers when circulating blood tachyzoites are present in AIDS-associated CT patients (Meira et al, 2008). *Toxoplasma* infection results in pathological changes such as inflammation and is usually followed by necrosis. This parasitic infection also induces strong type 1 polarized innate and adaptive immune responses. It is known that the host defense mechanism to infection with *T. gondii* is mediated by production of pro-inflammatory cytokines, including IL-12, IFN-γ and TNF-α (Suzuki et al, 1989). The important sources of IFN-γ in response to *Toxoplasma* infection are CD4-T lymphocytes, CD8-T lymphocytes, natural killer cells and T cells responding to IL-12 (Yap et al, 2000). These major mechanisms prevent rapid replication of tachyzoites and subsequent pathological changes (Denkers, 2003). Of these, T lymphocytes are a crucial source of IFN-γ during the first 2-3 weeks after infection, as demonstrated in antibody-mediated T-cell depletion experiments that resulted in reactivation of *Toxoplasma* infection (Denkers, 2003). In the chronic phase, the tissue cysts can persist indefinitely in the brain and muscle, developing lifelong protective immunity against re-infection (Dubey, 1998; Montoya & Liesenfeld, 2004). There are re-infections in some cases because slightly different genotypes of *T. gondii* strains have been found in the same patients (Ferreira et al, 2008). In the clinical phase, tissue cysts are periodically ruptured, but the bradyzoites released are normally destroyed by the host immune response. At the time when asymptomatic individuals become immune deficient, secondary reactivation of latent/chronic infection may occur, culminating in the conversion of bradyzoites to the active and rapidly replicating tachyzoites, as a result of tissue injury which is often fatal. As the cysts have a predilection for neural, muscle tissue and the eye, most cases reactivate chorioretinitis or, more frequently, cerebral toxoplasmosis, which is the predominant manifestation in patients with AIDS. Apart from these mechanisms, the development of cerebral toxoplasmosis has recently been studied and shown to have a

significant correlation with the HLA genes (class I and class II) in HIV-infected patients. The MHC is one of the most polymorphic genetic systems in humans and controls the adaptive immune response by class I (HLA-A, HLA-B, HLA-Cw) and class II (HLA-DRB1, HLA-DQB1, HLA-DPB1) against both intra-and extracellular microorganisms as well as it being correlated with infection susceptibility or resistance. Class I HLA-B35 antigen was associated with retinochoroiditis (Veronese Rodrigues et al, 2004). Class I HLA-B8 and class II HLA-DRB1*17 antigens were associated with cerebral toxoplasmosis (Castro Figueiredo et al, 2000). The presence of class II HLA-DQB1*0402 and DRB1*08 alleles (Habegger de Sorrentino et al, 2005) and the HLA-DR52 haplotype represent risk factors to the development of cerebral toxoplasmosis, whereas the HLA-DR53 haplotype was associated with resistance to *Toxoplasma* infection (Pereira-Chioccola et al, 2009).

Among patients with AIDS, CT is a multifocal process that occurs spontaneously. The use of the highly sensitive technique of magnetic resonance imaging (MRI) reveals that >80% of patients will have multiple lesions (Ciricillo & Rosenblum, 1990). With this technique, the percentages are probably an underestimation of the multifocal pathological process that may be occurring as they will be below its resolution. The spontaneous and simultaneous development of multifocal brain lesions strongly indicates that although CT arises because of reactivation of a latent infection, the multiple areas of the brain that are involved are likely a result of the hematogenous spread of the parasite, and involvement of the brain is due to the particular proclivity of *T. gondii* for causing disease in the CNS (Luft & Remington, 1992). The latter is likely due to the fact that the brain is an immunologically original site rather than an actual site of the organism. This supposition is further supported by the observation that patients who relapse after receiving an adequate course of therapy often develop new lesions in areas of the brain previously free of infection (Leport et al, 1989).

3. Epidemiology - from source to gene

The high rates of latent *Toxoplasma* infection (41.9–72%) were reported in South America and in approximately half of the studies (≥ 40%) from the Asian continent. In North America, however, the rate of *Toxoplasma* infection was low. Surprisingly, only 8 of the 50 studies were conducted on HIV-infected pregnant women and 2 of those studies, interestingly, reported a very high seroprevalence of toxoplasmosis of 53.7% in Thailand and 72% in Brazil. Latent toxoplasmosis is still prevalent as an infection that coexists with HIV infection. The level of anti-*Toxoplasma* (IgG) antibodies was, interestingly, unaffected by either antiretroviral drugs or therapeutic regimes/prophylaxis used for toxoplasmosis in these patients (Machala et al, 2009). Supporting these epidemiological studies, screening for *Toxoplasma* infection should be included in routine investigations in order to monitor primary infections even though it is not very common in such patients. It may also prevent secondary reactivation of latent infections, especially in HIV-infected patients with limited resource settings where the majority are unable to access primary chemoprophylaxis and/or antiretroviral therapy.

How do the plausible risk factors play their roles in association with *Toxoplasma* infection in HIV-infected patients? Age and race/ethnicity, among other demographic characteristics, were shown to have a positive interaction with this parasite. A study from the United States

demonstrated that *Toxoplasma* prevalence rates reported in HIV-infected women aged ≥ 50 years were significantly higher compared to those who were younger (Falusi et al, 2002). This was dissimilar to a study from Malaysia which reported that HIV-infected patients in the younger age group had higher *Toxoplasma* seroprevalence rates than the older age group although it was not statistically significant (Nissapatorn et al, 2001). Based on these findings, *Toxoplasma* infection is acquired irrespective of age, and preventive measures are needed to curb the prevalence rate especially in areas where the parasite is highly endemic. The study by Falusi and colleagues in 2001 further pointed out that those women born outside the U.S. were more likely to have higher rates of latent toxoplasmosis although race did not affect *Toxoplasma* seroprevalence between black and white women in that country (Falusi et al, 2002). In a country like Malaysia, a higher rate of *Toxoplasma* infection was more likely to be found among Malays, the predominant ethnic group in this region compared to others including Chinese and Indian (Nissapatorn et al, 2007). Traditionally, Malays keep cats as pets, which could explain this association. Based on these studies, demographic characteristics certainly make significant contributions to the epidemiological surveillance of *Toxoplasma* infection in a given population, such as HIV/AIDS patients.

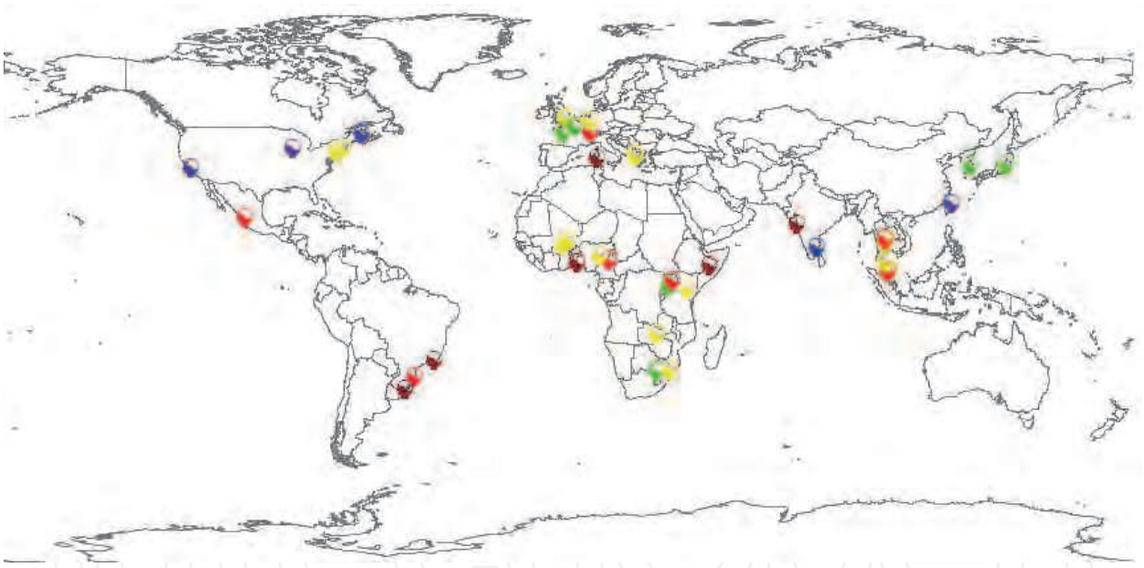

Fig. 3. Global status of latent *Toxoplasma* infection in HIV-infected patients.

Dark red equals prevalence above 60%, light red equals 40-60%, yellow 20-40%, blue 10-20% and green equals prevalence <10%. White equals absence of data. (Courtesy of Dr. Rattanasinchaiboon O and Dr Phumkokrux S, Bangkok, Thailand.)

There are not many studies on how the T-cell response could affect *Toxoplasma*-seropositive patients. It has been recognized that T-helper (CD4) cells, among several types of T-cell responses, are involved in *Toxoplasma* infection by stimulating T-cytotoxic cells which are then able to lyse tachyzoites directly and participate in the activation of B-cells which then go on to produce antibodies against *Toxoplasma* (Ho-Yen, 1992.). An earlier study showed that there is a greater likelihood of problems with *Toxoplasma* infection in situations in which there is a reduction of T-cell function (Pendry et al, 1990). Supporting this literature, a U.S.

study demonstrated a significant association between CD4 counts of 200-499 cells/mm^3 and *Toxoplasma*-seropositivity in patients (Falusi et al, 2002). The authors were unable to provide an explanation for this association except that patients with low CD4 counts were more likely to be foreign born. So far, similar findings have not been reported from previous studies (Nissapatorn et al, 2001; Nissapatorn et al, 2002). Looking at other possible risk factors such as a history of close contact with cats, consumption of contaminated meat, and receiving blood transfusions from *Toxoplasma*-seropositive patients, there was however no significant association found from studies reported earlier (Wallace et al, 1993; Nissapatorn et al, 2001; Nissapatorn et al, 2002). This possibly explains that these patients had been constantly exposed to *Toxoplasma* infections (with no definite time frame) before acquiring HIV infection. The other reason is that patients acquired *Toxoplasma* infection from other sources such as eating raw vegetables or drinking contaminated water, risk factors that were not included in these studies. However, primary behavioral practice such as avoiding close contact with cats, consumption of clean and properly cooked foods is necessary and advisable for HIV-infected patients regardless of *Toxoplasma* serostatus. Interestingly, patients with *Toxoplasma*-seropositivity were more likely to develop CT and tended to be patients receiving HAART (Nissapatorn et al, 2007). From this observation, primary chemoprophylaxis or antiretroviral drugs including HAART (if available) should be instituted to these patients after clinical evaluation.

Apart from the host immune status, the genotype of the infecting parasites may influence the course of disease (Lindström et al, 2006). Genetic analyses have shown that the vast majority of all *T. gondii*-strains typed to date fall into one of three clonal lineages, type I, II, and III (Howe & Sibley, 1995), which differ in virulence but do not show clear host or geographic boundaries (Lindström et al, 2006). Studies from different parts of the world have produced similar findings in which the genotyping of the SAG2-locus revealed that the type II allele was the most disease-causing strain (reactivation of chronic infections) found in immunocompromised individuals (Dardé et al, 1992; Howe and Sibley, 1995; Howe et al, 1997; Fuentes et al, 2001; Lindström et al, 2006; Ajzenberg et al, 2009).

This high prevalence of type II strains in human toxoplasmosis may simply reflect the source of the strains that led to human infections (Howe et al, 1997). Also, the low level of gamma interferon and other factors related to the immune system in these patients might increase the possibility of reactivation of the infective forms of the parasite by developing bradyzoites and increasing the formation of cysts in the brain (Gross et al, 1997). During this same period, a few studies have reported on uncommon type I strains (Khan et al, 2005), type I/III (Genot et al, 2007), and a high rate of genetic polymorphism (Ferreira et al, 2008) in *T. gondii* strains isolated from immunocompromised patients. Despite these differences, genotyping studies could serve as an important mile-stone for improving the diagnosis and management of human toxoplasmosis, in addition, for the development of novel drugs and vaccines. Surprisingly, genotyping studies on *T. gondii* strains have not been reported from HIV-infected patients in the Asian continent even though there are a number of these patients, in endemic areas for latent *Toxoplasma* infections (Subsai et al, 2006; Nissapatorn et al, 2007), and cases of clinical toxoplasmosis detected in AIDS patients (Subsai et al, 2006; Lian et al, 2007). Future studies are recommended to elucidate the distribution of genotypes and to establish any correlations between genotyping of *T. gondii* strains and human toxoplasmosis in Asian HIV patients.

Based on these findings, it certainly poses a question as to whether there is an association between genotyping of *T. gondii* strains and human toxoplasmosis. One study interestingly indicates that the type of infecting parasitic strain does not predominantly influence the pathogenesis of toxoplasmosis in immunocompromised patients and fully support the need for specific prophylaxis in patients infected by *T. gondii*, regardless of the strain genotype (Honoré et al, 2000). In addition, other host factors are more involved than parasite factors in patients' resistance or susceptibility to toxoplasmosis in immunocompromised hosts (Ajzenberg et al, 2009).

A total of 50 studies have been reported from different parts of the world including Asia, Europe, North America, South America and Africa (Table 1). The varying seroprevalence of toxoplasmosis (latent/chronic infection) interestingly showed low to high rates of infection being >60% (9 studies), 40-60%, (12 studies), 20-40% (21 studies), 10-20% (3 studies), and <10% (5 studies).

Study (Ref)	City, Country	No. of HIV/AIDS patients	Seroprevalence in %
Asia			
Wongkamchai et al, 1995	Bangkok, Thailand	40	42.5
Meisheri et al, 1997	Bombay, India	89	67.8
Yoong and Cheong, 1997	Kuala Lumpur, Malaysia	49	59.0
Chintana et al, 1998	Bangkok, Thailand	253 (pregnancy)	21.1
Sukthana et al, 2000	Bangkok, Thailand	190	23.2
Oh et al, 1999	Seoul, South Korea	173	4.0
Nissapatorn et al, 2001	Bangkok, Thailand	183	22.4
Shivaprakash et al, 2001	Pondicherry, India	216	11.5 (IgM)
Wanachiwanawin et al, 2001	Bangkok, Thailand	838 (pregnancy)	53.7
Shamilah et al, 2001	Kuala Lumpur, Malaysia	729	31.3
Nissapatorn et al, 2002	Kuala Lumpur, Malaysia	100	21.0
Nissapatorn et al, 2003	Kuala Lumpur, Malaysia	406	51.2
Nissapatorn et al, 2004	Kuala Lumpur, Malaysia	505	44.8
Hung et al, 2005	Taipei, Taiwan	844	10.2
Nissapatorn et al, 2005	Kuala Lumpur, Malaysia	162	35.8 and 14.8 (IgM)
Naito et al, 2007	Tokyo, Japan	56	5.40
Nissapatorn et al, 2007	Kuala Lumpur, Malaysia	693	43.85
Nissapatorn et al, [In print]	Songkhla, Thailand	300	36.3
Europe			
Holliman, 1990	London, UK	500	26.6 and 1.4 (IgM)
Sykora et al, 1992	Prague, Czechoslovakia	67	29.8

Study (Ref)	City, Country	No. of HIV/AIDS patients	Seroprevalence in %
Zufferey et al, 1993	Lausanne, Switzerland	715	50.0
Oksenhendler et al, 1994	Villejuif, France	499	25.4
Raffi et al, 1997	Nantes cedex, France	186	97
Bossi et al, 1998	Paris, France	399	97
Letillois et al, 1995	Grenoble, France	37	64.9
Reiter-Owona et al, 1998	Bon, Germany	183	33.3 (in 1987) and 36.6 (in 1995)
Millogo et al, 2000	Burkina Faso, France	1,828	25.4
Machala et al, 2009	Prague, Czech Republic	626	33.2
North America			
Grant et al, 1990	New York, USA	411	32.0
Israelski et al, 1993	California, USA	1,073	11.0
Minkoff et al, 1997	Brooklyn, USA	138	20.2
Ruiz et al, 1997	Rhode Island, USA	169 (pregnancy)	22.0
Falusi et al, 2002	Chicago, USA	1,975	15.1
South America			
Wainstein et al, 1993	RS, Brazil	516	65 and 49 (CSF)
Galván Ramirez et al, 1997	Universidad de Guadalajara, Mexico	92	50.0 and 1.0 (IgM)
Cruz et al, 2007	RJ, Brazil	767 (pregnancy)	74.0
Lago et al, 2009	Rio Grande do Sul, Brazil	168 (pregnancy)	72.0
Africa			
Brindle et al, 1991	Kenya, Nairobi	94	22
Zumla et al, 1991	Zambia and Uganda	373 (186-Uganda and 187-Zambia)	34 (Ugandan) and 4 (Zambian)
Woldemichael et al, 1998	Addis Ababa, Ethiopia	127	74.2
Maïga et al, 2001	Bamako, Mali	?	22.6 and 60
Uneke et al, 2005	Jos, Nigeria	219	38.8
Lindström et al, 2006	Kampala, Uganda	130	54
Hari et al, 2007	Johannesburg, South Africa	307	8
Ouermi et al, 2009	Burkina faso, agadougou	138 (pregnancy)	31.9 and 3.6 (IgM)
Akanmu et al, 2010	Lagos, Nigeria	380	54
Sitoe et al, 2010	Maputo, Mozambique	58 (pregnancy)	31.3
Oshinaike et al, 2010	Lagos, Idi Araba, Nigeria	83	85.5

Table 1. Summary of studies on seroprevalence of toxoplasmosis in HIV-infected patients.

4. Toxoplasmosis - from epidemiology to clinical implication

4.1 Congenital toxoplasmosis

Seven of the 50 studies were conducted on HIV-infected pregnant women, 2 reported a high seroprevalence, 53.7% in Thailand (Wanachiwanawin et al, 2001) and 74% in Brazil (Cruz et al, 2007). Considering these epidemiological studies (Table 1), geographical location, environment, socio-economic, clinical and diagnostic methods are among the factors that can pin point the differences of *Toxoplasma* infections between these affected areas. Latent toxoplasmosis is still prevalent and coexists with HIV infections. The level of anti-*Toxoplasma* (IgG) antibodies does not appear to be affected by antiretroviral drugs or therapeutic regimes/prophylaxis used to treat toxoplasmosis in these patients (Machala et al, 2009). Given the results of these epidemiological studies, screening for *Toxoplasma* serostatus should be carried out among HIV-infected women in the prenatal period even though it is not a common practice. It may also prevent secondary reactivation of latent toxoplasmosis during pregnancy, especially among HIV-infected women in limited resource settings where the majority of these patients are unable to access primary chemoprophylaxis and/or antiretroviral therapy.

In HIV-infected pregnant women, a secondary reactivation of chronic *Toxoplasma* infection may occur during pregnancy particularly in those who are severely immunocompromised. There are cases of cerebral toxoplasmosis reported in HIV-infected pregnant women and congenital toxoplasmosis in the fetus of these infected mothers but it is found only at a low incidence (Dunn et al, 1997). A case of CT was earlier reported in an HIV-infected pregnant woman who responded well with a standard regimen of pyrimethamine and sulfadiazine, with a normal fetal outcome (Hedriana et al, 1993). Another case of CT was confirmed in an HIV-infected pregnant woman during the puerperium with her CD4 count being < 200 cells/cumm (Biedermann et al, 1995). A prophylactic treatment was recommended to prevent maternal reactivation and congenital transmission of toxoplasmosis in such a case. In recent years, an HIV-infected pregnant woman with CT who was at risk for transmitting HIV (low CD4 and high viral load) and *Toxoplasma* infections to her fetus; she responded well to anti-*Toxoplasma* therapy and HAART (Nogueira et al, 2002). In this case, the combined *Toxoplasma* therapy (pyrimethamine and sulfadiazine) and HAART were benefitial not only to the mother but also prevented transmission to the fetus. Despite this evidence of success in most cases, there have been reports of poor outcomes when an HIV-infected mother has CT during pregnancy, with vertical transmission of one or both infections to the fetus and an increase of morbidity and mortality in the mother (Mitchell et al, 1990; O'Riordan & Farkas, 1998; Fernandes et al, 2009). Maternal-fetal transmission of toxoplasmosis due to reactivation of chronic infection during pregnancy occurs in mothers with a very low CD4 cell counts (Minkoff et al, 1997) or in the presence of other immunological disorders (Montoya & Liesenfeld, 2004). A case of severe congenital toxoplasmosis was reported from an HIV-infected mother with moderate immunosuppression as a result of reactivation (Bachmeyer et al, 2006). This indicates that a routine screening for not only children from HIV-infected mothers should be used to detect congenital toxoplasmosis but also in pregnant women to confirm an early diagnosis of a reactivation of a chronic *Toxoplasma* infection. The first case of congenital toxoplasmosis was reported in Brazil, this was from an HIV-infected mother with a high titer of IgG but negative for IgM antibodies (Cruz et al, 2007). This highlights the special attention needed

for analysis of maternal titers of anti-*Toxoplasma* antibody during HIV prenatal care. Two years later, a contrasting study reported a case of congenital toxoplasmosis in an HIV-infected pregnant woman with a low titer of IgG to *T. gondii* and a negative result for IgM antibodies (Lago et al, 2009). It is important to keep this in mind that a high titer for IgG antibody is fairly common in HIV-infected mothers. This phenomenon is not significantly associated with an increased risk of congenitally acquired toxoplasmosis during pregnancy. Compliance to antiretroviral therapy is a medical challenge which led to a rare case of congenital toxoplasmosis from a severely immunosuppressed HIV-infected woman as a result of reactivation (Fernandes et al, 2009). Under this circumstance, prophylaxis is required in addition for strict adherence to therapy in pregnant women infected with HIV. The most recent cases of congenital toxoplasmosis were reported from HIV-infected mothers who had a high titer for IgG and were negative for IgM antibodies (Azevedo et al, 2010). Due to the increasing number of HIV- infected women in childbearing age worldwide, the possibility of maternal-fetal transmission from mothers infected with chronic *Toxoplasma* infection is more likely to occur and may have a huge impact on public health perspectives, especially in those endemic areas with *Toxoplasma* infection. It is surprising that there has been no reported case of clinically confirmed congenital toxoplasmosis or CT in HIV-infected pregnant women from Asian countries. In fact, HIV infection is fast growing in this region compared to other parts of the world. This could be explained either because of the overall low prevalence of toxoplasmosis in HIV-infected women or those cases of toxoplasmosis are under-reporting. Therefore, clinicians should be more aware of this parasitic infection to establish an early diagnosis and better management in both qualities of care and treatment among HIV-infected pregnant women in this continent. To conclude, HIV and *Toxoplasma* infections are common in developing countries with resource limited settings, it is therefore imperative that drugs related to both infections are easily accessible particularly for pregnant women living in low-socio-economic conditions. Due to the effectiveness of anti-*Toxoplasma* therapy and increasing global availability of HAART in HIV-infected pregnant women, the incidence of congenital toxoplasmosis should decline or even disappear.

4.2 Cerebral toxoplasmosis

Neurological complications of AIDS patients are often due to opportunistic infections (OIs) in the central nervous system (CNS). Toxoplasmosis is one of the most common CNS-OIs and causes high rates of morbidity and mortality in patients with advanced HIV infection. With the advent of the HIV pandemic, epidemiological studies have shown CT to be one of the most common OIs in AIDS patients and the most commonly reported CNS-OIs on 5 continents: Asia (India, Malaysia and Thailand), Europe (France, United Kingdom and Germany), North America (USA), South America (Brazil and Mexico), and recently from South Africa (Amogne et al, 2006; Oshinaike et al, 2010). The incidence of CT varies according to geographical locations and the prevalence of *Toxoplasma* infections in the general population. Other factors such as the mode of transmission, gender, ethnicity, severe immunodeficiency, and differences in genotypes of *T. gondii* isolates are also found to influence the occurrence of CT (Richards et al, 1995; Khan et al, 2005). In the pre-HAART era, ~25% of AIDS patients from France had CT compared to ~10% in some cities from the USA (Dal Pan & McArthur, 1996). The rate of CT was found to vary from between 16-40%

in the USA and UK, ~60% in Spain, 50-80% in Brazil, 75-90% in France (Pereira-Chioccola et al, 2009), and <20% in Asian countries including India (Sharma et al, 2004), Malaysia (Nissapatorn et al, 2003-2007), or Thailand (Anekthananon et al, 2004; Subsai et al, 2004). CT is frequently diagnosed in adults but rarely occurs in children with AIDS; the infection accounted for 0.86% of AIDS-defining illnesses (Richards et al, 1995) or <1.0 per 100 person years (Dankner et al, 2001; Gupta et al, 2009). CT is the most common cause of focal intracerebral lesion(s) in patients with AIDS. More than 95% of CT is caused by the reactivation of latent (chronic) *Toxoplasma* infection as a result of the progressive loss of cellular immunity in AIDS patients (Luft & Remington, 1988). In clinical practice, the incidence of CT patients is related both to *Toxoplasma* IgG seropositivity and the CD4 cell count. The risk of developing CT among seropositive patients with AIDS was 27 times that of seronegative ones (Oksenhendler et al, 1994). AIDS patients who are *Toxoplasma* seropositive, have CD4 count of <100 cells/cumm, and failure to receive prophylaxis are among the identified risk of developing CT (Luft and Remington, 1992; Nascimento et al, 2001; Nissapatorn et al, 2004). The clinical presentations of CT depend on the number of lesions and location. Headache, hemiparesis and seizure (Nissapatorn et al, 2004; Vidal et al, 2005a) are among the most common neurological presentations found in CT patients. Other clinical manifestations include disarthria, movement disorders, memory and cognitive impairments and neuropsychiatric abnormalities. These neurological deficits remain in surviving patients even after good clinical response to therapy (Hoffmann et al, 2007). More than 50% of CT patients may have focal neurological findings. CT is a life-threatening but treatable condition provided there is early diagnosis and treatment. CT can be prevented by primary behavioral practices in avoiding acquisition of *Toxoplasma* infection such as consumption of well cooked meat, avoiding close contact with stray cats, contaminated soil and/or water, and receiving unscreened blood transfusions. Compliance to both therapeutic regimens for treatment and prophylaxis of toxoplasmosis is an imperative to prevent relapse of CT in areas where HAART is not fully accessible for people living with HIV/AIDS. This ultimately reduces the number of hospital admissions as well as the mounting medical care cost of AIDS-associated CT patients, particularly in limited resource settings.

There are atypical/unusual clinical manifestations reported in AIDS-associated CT patients. Ventriculitis and obstructive hydrocephalus, characteristics of congenital toxoplasmosis, are rarely seen in adult AIDS-associated CT. Ventriculitis has so far been reported in nine adult AIDS patients (Cota et al, 2008), accompanied by hydrocephalus, occurred as the primary manifestations of toxoplasmosis or as complications of a preexisting, recognized cerebral toxoplasmosis. In addition, hydrocephalus without mass lesions was the only abnormal finding from a computed tomography (CAT) scan in an adult AIDS patient (Nolla-Salas et al, 1987). It is very rare for patients with CT to present as a neuropsychiatric illness with an acute psychosis followed by a rapid mental and somatic decline, however one case has been reported in a patient with AIDS (Ilniczky et al, 2006). Extrapyramidal movement disorders are one of the atypical clinical manifestations reported in AIDS patients. Toxoplasmosis is one of the main underlying opportunistic infections and causes movement disorders in AIDS patients. These movement disorders are becoming well known and increasingly recognized as a potential neurological complication in AIDS patients (Tse et al, 2004). In hyperkinetic movements, holmes (also known as rubral or midbrain tremor) tremor is the earliest reported symptom of CT and might present with other focal neurological signs that

indicates a midbrain localization (Koppel & Daws, 1980). The appearance of hemichorea-hemiballism is considered as a pathognomonic of CT and is most commonly associated with a subthalamic abscess (Navia et al, 1986; Maggi et al, 1996). The presence of hemichorea-hemiballism in CT patients is low (7.4% of cases) compared to the pathological studies which show 50% of *Toxoplasma* abscesses occur in the basal ganglia (Navia et al, 1986; Maggi et al, 1996). Generalized chorea may occur as a result of bilateral abscesses of toxoplasmosis (Gallo et al, 1996). Myoclonus, is generalized and elicited by sudden auditory stimuli that resembles a startled response, has also been described in AIDS-associated CT patients (Maher et al, 1997). A case of focal dystonia of the left arm and hand has been reported in an AIDS patient due to the right lenticular nucleus and thalamic abscesses of toxoplasmosis (Tolge & Factor, 1991). A few cases with parkinsonian features, hypokinetic movement disorders, due to toxoplasmosis were also described in patients with AIDS (Carrazana et al, 1989; Murakami et al, 2000). Movement disorders in AIDS patients and particularly in countries with a high prevalence of toxoplasmosis, should indicate the possibility of CT (Noël et al, 1992). In AIDS patients, opportunistic infections may affect endocrine organs. Diabetes insipidus (DI) is uncommon but has also been reported in relation to CT. Imaging studies may demonstrate pathological situations and assist in the diagnosis (Brändle et al, 1995). A case of CT with massive intracerebral hemorrhage leading to a fatal vehicular crash was also reported in a patient with AIDS (Gyori & Hyma, 1998). Cerebellar toxoplasmosis is another infrequent complication of HIV/AIDS that should prompt a high index of clinical suspicion and early institution for presumptive therapy in poor resource settings (Emeka et al, 2010). These unusual neurological presentations of AIDS patients associated toxoplasmosis have rarely been reported in Asia (Chaddha et al, 1999; Nissapatorn et al, 2004; Subsai et al, 2006; Nissapatorn et al, 2007).

4.3 Extracerebral toxoplasmosis

Overall, the prevalence of extracerebral toxoplasmosis (ECT) in patients with AIDS is estimated to be 1.5%-2% (Rabaud et al, 1994) which is far less common than CNS toxoplasmosis. Ocular toxoplasmosis (OT) is the most common form of ECT associated with CT, being detected in 50% of ECT in AIDS patients and has the best prognosis (Rabaud et al, 1994; Zajdenweber et al, 2005). OT, in contrast to intracranial disease, is uncommon in patients with AIDS (Lamichhane et al, 2010). However, OT is a serious eye problem in HIV-infected patients, especially in developing countries (Chakraborty, 1999). OT is an important disorder and may be the first manifestation of life-threatening intracranial or disseminated *T. gondii* infections. Accurate diagnosis may allow early referral to a neurologist and infectious diseases specialist (Holland et al, 1988). Generally, OT tends to cause retinochoroidal scars with less retinal pigment epithelium hyperplasia (Arevalo et al, 1997). It has no association between the ocular findings and a positive titer of toxoplasmosis (Mansour, 1990.). However, the presence of IgM antibodies may support this diagnosis, although antibody levels in AIDS patients may not reflect the magnitude of the disease (Gagliuso et al, 1990). OT was first reported in 2 of 34 AIDS patients with a 'cotton wool' spot as one of the most common retinal manifestations (Schuman & Friedman, 1983). It is also characterized by several features, including single or multifocal retinal lesions in one or both eyes or massive areas of retinal necrosis. These lesions that are not associated with a pre-existing retinochoroidal scar indicate a manifestation of acquired rather than congenital

disease (Gagliuso et al, 1990). A unique pattern of bilateral retinitis due to OT was observed in a patient in the late stages of AIDS in which the recognition of this pattern is important for providing the appropriate treatment of an immunosuppressed patient (Berger et al, 1993). Toxoplasmosis should therefore be considered in the differential diagnosis in an AIDS patient with necrotizing retinitis (Moorthy et al, 1993). There have been few studies reported on toxoplasmosis as being one of the most common causes of neuro-ophthalmological disorders in neurologically symptomatic HIV-infected patients such as palsy involving the sixth and third cranial nerves (Mwanza et al, 2004). Thus, clinicians should be more aware of this pathogen to avoid consequences, such as damaging visual pathways leading to visual impairment or blindness in these patients. With more affordable and accessibility of HAART, the prevalence of ocular toxoplasmosis will decline over time.

Toxoplasmosis is known to cause widely disseminated and extracerebral disease which is less common and more difficult to diagnose in AIDS patients. *Toxoplasma*-induced cystitis or pseudoneoplastic bullous cystitis is rarely detected in these patients. The diagnosis may be difficult because this condition is associated with misleading radiologic and endoscopic findings (Welker et al, 1994). With these studies, the diagnosis was eventually confirmed by the presence of *Toxoplasma* cysts on histopathological examination of bladder biopsies (Hofman et al, 1993). Therefore, disseminated toxoplasmosis should be considered in the differential diagnosis of AIDS patients with culture-negative cystitis (Welker et al, 1994). For unclear reasons, gastrointestinal involvement is exceedingly rare and occurs only in the context of severe immunosuppression and disseminated disease (Merzianu et al, 2005). Gastric toxoplasmosis has been reported in AIDS patients. It presents as diarrheoa and other nonspecific GI symptoms. Biopsy shows the presence of *Toxoplasma* trophozoites in the forms of tachyzoites, bradyzoites, and pseudocysts which are mandatory for definite diagnosis. It responds well to anti-*Toxoplasma* therapy (Alpert et al, 1996; Merzianu et al, 2005). It is of interest, that disseminated toxoplasmosis with sepsis has also been found in AIDS patients and should be considered in patients with sepsis of unknown origin (Artigas et al, 1994). ECT has also been diagnosed in the heart (Guerot et al, 1995; Chimenti et al, 2007), lung (Touboul et al, 1986; Kovari et al, 2010), liver (Mastroianni et al, 1996), and spinal cord (Harris et al, 1990; Kung et al, 2011). ECT has a low incidence in AIDS patients. Many HIV-infected patients lack access to primary chemoprophylaxis and antiretroviral therapy, in limited resource settings hence, more cases are reported in this group.

5. Neuropathology of toxoplasmosis: from pre to HAART era

Toxoplasmosis is an important opportunistic infection, causing short-term and chronic mortality (Neuen-Jacob et al, 1993; Kumarasamy et al, 2010). Multifocal necrotizing encephalitis is the predominant neuropathological finding of CT in AIDS patients. Localization of multiple with ring enhancing lesions on neuroimaging in basal ganglia, frontoparietal cortex and thalamus suggests haematogenous spread. The predilection of *T. gondii* in the basal ganglia can result in a variety of movement disorders (Nath et al, 1993). The cerebral edema, encephalitic process and tissue destruction are significant and responsible for majority of neurological morbidity in HIV-infected patients presenting with focal brain lesion (Ammassari et al, 2000). Rupture of tissue cysts in AIDS- associated CT patients result in multiplication of bradyzoites into tachyzoites, which causes severe

inflammatory reaction. Three morphological patterns of brain lesions in patients with CT are produced based on the stage of infection and degree of tissue reaction (Shankar et al, 2005): (i) In the acute stage (less than a few weeks duration): appearance of a necrotizing abscess or encephalitis seen as poorly circumscribed necrotic foci with variable degrees of haemorrhage, perifocal edema, acute and chronic inflammation, macrophage infiltration, with numerous *T. gondii* tachyzoites and encysted bradyzoites along the periphery. Also common are vascular thrombosis/fibrinoid necrosis of vessel walls, with polymorph infiltration, hypertrophy and the presence of tachyzoites in the hypertrophie arterial wall. (ii) A chronic lesion (weeks to months) : organized abscesses are found in CT cases treated for ≥ 2 weeks and seen as well circumscribed foci of central necrosis with a rim of congestion. In contrast to the acute phase, the central foci of an acellular necrosis is surrounded by a granulomatous reaction, with macrophages containing tightly packed lipid and haemosiderin, prominent hypertrophic occlusive arteritis with dense lymphocytic cuffing, and only a few organisms. (iii) Patients treated for ≥ 1 month show chronic abscesses in CT appear as small cystic cavities or linear orange-yellow scars and macrophages containing lipid and haemosiderin surrounded by a dense gliotic reaction. Calcification of vessels occurs and organisms are rarely found. In addition, a CAT scan can present as a diffuse, non-necrotizing, rapidly progressive encephalitis. The histological appearance seen as nodules of micrioglial cells with encysted bradyzoites and dispersed tachyzoites within the nodules.

Autopsy findings confirm the presence of the parasite and demonstration of *Toxoplasma* cysts is diagnostic of disseminated toxoplasmosis in AIDS patients (Holch et al, 1993). Despite the effectiveness of HAART, involvement of the brain in patients with AIDS remains a frequent autopsy finding (Masliah et al, 2000). AIDS-associated CT continues to be the major cause of mortality in the era of HAART (Rajagopalan et al, 2009; Kumarasamy et al, 2010). The expansion of earlier access to HAART could substantially reduce mortality, particularly in limited resource settings (Mzileni et al, 2008; Rajagopalan et al, 2009).

The seroprevalence of toxoplasmosis is generally high in HIV-infected patients and approximately 10% of CT is reported in AIDS patients. There has been no report of such neuropathological findings related to toxoplasmosis found in AIDS patients from Malaysia and its neighboring countries in the Southeast Asian region such as Thailand. This may be due to the fact it is not a common practice to conduct an autopsy in HIV/AIDS patients that could give the actual prevalence of AIDS-associated CT being underestimated. CT is one of the most common opportunistic infections of the CNS (Wadia et al, 2001; Nobre et al, 2003) as reported in an autopsy series conducted in India (Lanjewar et al, 1998a; Lanjewar et al, 1998b) and in other clinical settings (Petito et al, 1986; Souza et al, 2008). The majority of AIDS-related diseases diagnosed at autopsy had not been clinically diagnosed or suspected antemortem (Eza et al, 2006). The importance of an autopsy in evaluating clinical management and diagnosis (Eza et al, 2006) should be periodically done; particular in areas of high endemic toxoplasmosis where antiretroviral drugs, such as HAART, cannot be fully accessed.

There is scanty data about AIDS-associated neuropathological findings during the HAART era in Asia and Sub-Sahara Africa. This is mainly due to delayed introduction of these agents to these regions. It is expected that more autopsy studies will be carried out in this part of the world in the near future. The incidence of toxoplasmosis in autopsy studies has

declined since the introduction of HAART in various countries, such as the USA (Langford et al, 2003) and France (Vallat-Decouvelaere et al, 2003). These studies show that autopsy findings can be a valuable means for determining the range and relative frequency of infectious diseases in these patients (Lucas et al, 1993). In addition, this can potentially have an immediate impact on patient care by enabling appropriate interventions, based on the results obtained (Lucas et al, 1993).

6. Diagnostic approaches - from conventional to advanced technology

Among patients with AIDS, cerebral involvement is more common and more serious than extracerebral toxoplasmosis. The definitive diagnosis is crucial for CT patients by directly demonstrating the presence of the tachyzoite form of *T. gondii* in the cerebral tissues. The presumptive diagnosis for CT, including the clinical presentations, radio-imaging findings, molecular and sero-diagnosis for *Toxoplasma* infection, and good response to anti-T*oxoplasma* therapy are widely accepted in clinical practice. The favorable outcome of CT is the improvement of clinical and radiological features after 2 to 3 weeks of initiated empirical therapy. The clinical diagnosis is a dilemma due to CT mimics with other brain diseases making it difficult to diagnose. Differential diagnosis of AIDS-associated CT is extremely important and the local neuroepidemiology and the degree of immunosuppression in the host are two key factors involved (Vidal et al, 2008). Primary CNS lymphoma is the main differential diagnosis of CT reported from developed countries (Manzardo et al, 2005). While, focal forms of cerebral tuberculosis (tuberculoma and, less likely tuberculous brain abscess) allow for differential diagnosis of CT mainly in developing countries (Trujillo et al, 2005). Primary CNS lymphoma usually presents with a CD4 count of less than 50 cells/cumm, CT occurs below 100 cells/cumm, and cerebral TB is more frequently present with a CD4 count above 200 cells/cumm (Vidal et al, 2004a; Vidal et al, 2005a; Vidal et al, 2005b). In addition to these more common neurological diseases, the differential diagnosis of CT includes other opportunistic infections such as progressive multifocal leucoencephalopathy, herpes simplex encephalitis, and cryptococcal meningitis; AIDS-and non-AIDS-associated tumors such as metastases of disseminated lymphoma and glioblastoma multiforme, respectively; and vascular diseases. Overall, a rapid and accurate diagnosis of CT is necessary, as the earlier the treatment the better the clinical outcome and survival rate of these patients.

6.1 Radiological diagnosis

Radio-imaging findings, either by computed tomography (CAT scan) or magnetic resonance imaging (MRI), are useful tools for the presumptive or empirical diagnosis of CT. CT usually causes unifocal, and more frequently multifocal lesions, and less likely diffuse encephalitis. These findings are however not pathognomonic of CT. Radiological diagnosis (Vidal et al, 2005a) can be classified as typical findings of hypodense lesions with ring-enhancing and perilesional edema, are observed in ~80% of CT cases. A typical pattern of hypodense lesions found without contrast enhancing and with an expansive effect, CT patients without focal lesions and MRI demonstrating focal lesions, and diffuse cerebral encephalitis without visible focal lesions, are shown in ~20% of these cases. An unusual but highly suggestive image of patients with CT is the 'eccentric target sign', which is a small

asymmetric nodule along the wall of the enhancing ring (Pereira-Chioccola et al, 2009). Figure 2 shows the main radiological features of AIDS-associated CT patients. A CAT scan seems to be a sensitive diagnostic method for patients with focal neurological deficits; however it may underestimate the minimal inflammatory responses seen during early disease (Gill et al, 1986).

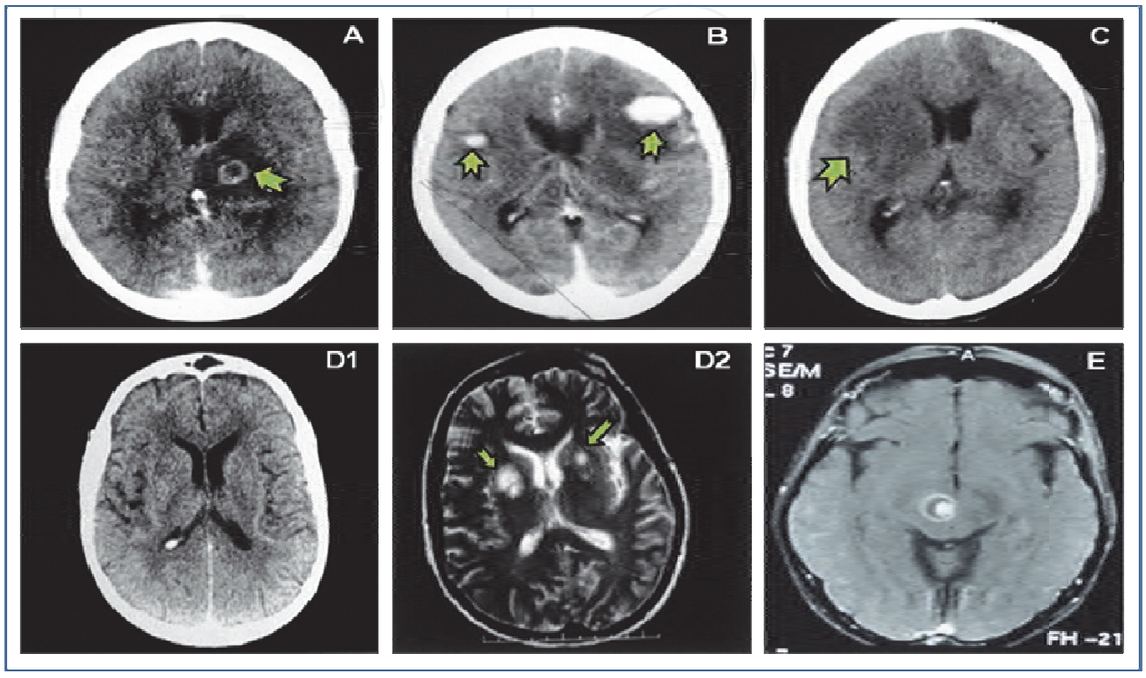

Fig. 4. Computed tomography images showing the spectrum of radiological findings of cerebral toxoplasmosis in HIV-infected patients.

Hypodense lesion with ring-enhancing and perilesional edema **(A)**; nodular enhancing and perilesional edema **(B)**; without contrast enhancing and with expansive effect **(C)**. A CAT scan with contrast enhancement showed no abnormalities **(D1)** and corresponding T2-weighted MRI showed multiple basal ganglia focal lesions, with high-intensity signals **(D2)**. T1-weighted MRI showed a ring-enhancing lesion with a small, enhancing asymmetric nodule along the wall of the lesion **(E)** ('the eccentric target sign'). The arrows show the abnormalities. (Courtesy of Dr. Pereira-Chioccola VL and Dr. Vidal JE, São Paulo, Brazil.)

MRI is recommended to be performed in patients with; neurological symptoms and positive serology to anti-*Toxoplasma* antibodies whose CAT scans show no or only a single abnormality, or persistent or worsening focal neurological deficits of disease if results of the initial procedure were negative (Luft & Remington, 1992). A CAT scan or MRI is useful for assessment of patients who had responded to initial empirical treatment. There may be a worsening of radiographic appearance in patients with a clinically improved condition before 3 weeks, and complete resolution of cerebral lesions seen on a CAT scan may vary from 3 week to 6 months after initiation of therapy (Luft & Remington, 1992). An evidence of either clinical or radiographic improvement within 3 weeks of initial therapy provides a confirmed diagnosis of patients with CT.

6.2 Serological diagnosis

Cerebral toxoplasmosis poses a diagnostic problem that relies on classical serological methods to detect anti-*Toxoplasma* immunoglobulins because clinical blood samples from patients with immunodeficiency can fail to produce sufficient titers of specific antibodies. Sero-evidence of *Toxoplasma* infection, independent of antibody levels, is generally seen in all patients before developing CT (Carme et al, 1988). Most CT patients have high titers of anti-*Toxoplasma* IgG antibodies with high IgG avidity that provides serological evidence of infection (Raffi et al, 1997; Vidal et al, 2005a), and this also supports a conclusion that this is the result of a secondary reaction of latent or chronic *Toxoplasma* infection (Dardé, 1996). Therefore, it is important to determine the *Toxoplasma* serostatus in all HIV-infected patients in order to define the population at risk for CT. At the onset of CT, significant rises in anti-*Toxoplasma* antibody titers are found in only a minority of these patients (Carme et al, 1988). The level of rising titers may occur before the onset of CT and it does not seem to predict the occurrence of CT. Anti-*Toxoplasma* IgM antibody, as measured by the indirect fluorescent or ELISA tests, is rarely found in CT patients (Luft & Remington, 1992). In cases of CT, a negative or low titer of serological results or even the absence of anti-*Toxoplasma* antibodies does not exclude positive diagnosis and the initiation of anti-*Toxoplasma* therapy should be immediately started without delay if clinical and radiological presentations are consistent with CT (Luft & Remington, 1992; Nissapatorn et al, 2004). A positive serology result seems to be even less useful in areas where there is a high prevalence of toxoplasmosis in the general population (Pereira-Chioccola et al, 2009). While, a negative result does have a high negative predictive value (Vidal et al, 2008) Determination of an increase of intrathecal anti-*Toxoplasma* IgG antibody production is normally characterized by the presence of *T. gondii* oligoclonal bands (OCBs) of IgG antibody in CT patients (Potasman et al, 1988). Immunological diagnosis using other clinical samples such as cerebrospinal fluid (CSF) is of limited use because of the sensitivity and specificity being only about 60-70% (Collazos, 2003). *T. gondii* excretory/secretory antigens (ESAs) are an excellent serological marker for the diagnosis of CT in AIDS patients (Pereira-Chioccola et al, 2009). ESAs are produced by *T. gondii* tachyzoites, the form responsible for disease dissemination, which plays an important role in stimulating humoral and cellular immunities in order to control *Toxoplasma* infection (Carruthers & Sibley, 1997; Cérède et al, 2005). Anti-ESA IgG antibodies are also present in CSF sample of AIDS patients with CT which can be determined by ESA-ELISA and immunoblot techniques and these samples are clearly distinguishable from AIDS patients who are *Toxoplasma* seropositive but with other brain diseases (Pereira-Chioccola et al, 2009).

6.3 Molecular diagnosis

Since the serological status is solely useful to recognize whether the patient is at risk for reactivation, the direct detection of *T. gondii* DNA in biological specimens by polymerase chain reaction (PCR) has provided a major breakthrough for the diagnosis of toxoplasmosis (Reischl et al, 2003). Over a period of two decades, these molecular methods based on PCR and specific genetic markers have been developed for routine use in assisting serology for the diagnosis of CT patients. PCR techniques are suitable for patients with AIDS because these methods do not depend on the host immune responses and allow for direct detection of *T. gondii* DNA from a variety of clinical samples. In addition, these methods are rapid, sensitive, specific, less time consuming, and can be used to replace invasive procedures such

as stereotactic brain biopsy. The sensitivity and specificity of the PCR reactions depends on the types of reagents, protocols for DNA extraction, storage of clinical samples, and the timing between the start of a specific therapy and collection of clinical samples, which can make the interpretation of results difficult (Pereira-Chioccola et al, 2009). Among clinical/biological samples, blood and CSF are the most frequently used for the detection of *T. gondii* DNA in patients with CT. To yield a better result, clinical samples should be collected before or up until the first 3 days of anti-*Toxoplasma* therapy because the diagnostic sensitivity will be reduced after the first week of this specific treatment (Vidal et al, 2004b). In CSF samples, the varying sensitivity of the PCR technique ranges from 11.5% to 100% but a high specificity (96-100%) has been reported using CSF specimens (Novati et al, 1994; Dupon et al, 1995; Vidal et al, 2004b). The collection of CSF sample is invasive and is not recommended for patients with multiple brain lesions (Pereira-Chioccola et al, 2009). PCR in blood samples, as an alternative approach, has been reported with a wide range of sensitivities of between 16% and 86% (Dupouy-Camet et al, 1993; Dupon et al, 1995). A quantitative real-time PCR (qrtPCR), is a recent development among molecular methods, and accelerates the detection of *T. gondii* DNA in most positive samples and allows for amplification and simultaneous detection of DNA in 1 hour (Hierl et al, 2004). Its advantages over conventional and nested PCR include rapid, improved sensitivity, a broad dynamic range of targets, DNA quantitation and reduction of contamination. Despite these advantages, in some patients with low parasite load particularly in CSF samples; there is still the need for comparative results of both conventional nested and real-time quantitative PCR methods (Bretagne, 2003; Hierl et al, 2004; Apfalter et al, 2005). Future prospect on the diagnosis of patients with CT is more likely to rely on the development of molecular methods based on qrtPCR which provides quantitative results and is less time-consuming in preparation. However, this technique needs to have improved specificity and more importantly a reduction of the high cost of the necessary equipment.

6.4 Other diagnostic methods

There is a need for more specific or invasive approaches that will assist confirmation of the diagnosis of CT. Brain biopsy is generally reserved for those patients who present with a diagnostic dilemma or do not fulfill the criteria for presumptive treatment and for those patients who fail to improve clinically or radiologically over the succeeding 10-14 days after being empirically treated for toxoplasmosis initially so they do warrant a stereotactic brain biopsy (SBB) in order to institute specific and appropriate therapy (Luft & Remington, 1992). For patients with expansive brain lesions who fail to respond to empirical treatment initiated for CT within 14 days, SBB should be seriously considered relatively early in the course of treatment, with or without change in therapy (Pereira-Chioccola et al, 2009). Surprisingly, SBB is not commonly used for the diagnosis of CT or CT-associated other opportunistic CNS diseases in Asian countries (Yeo et al, 2000) compared to other settings where CT cases have been reported in patients with AIDS. Brain biopsies do not influence survival of CT patients (Sadler et al, 1998). SBB is an efficient, safe and important diagnostic procedure. In selected patients even expensive investigations should be undertaken before considering specific therapy and cost effective homecare (Armbruster et al, 1998). This procedure should be performed early during the patient's evolution in order to achieve a prompt and accurate diagnosis and to guide the therapeutic scheme for AIDS patients with FBL (Corti et al, 2008).

Recently, genotyping analysis of *T. gondii* strains isolated from clinical samples has been conducted in HIV-infected patients from different settings. However, it remains doubtful on how to ascertain the association between *T. gondii* strains and human toxoplasmosis since the majority of infected individuals are chronic and without any clinical symptoms, and it is difficult to isolate *T. gondii* strains from these patients. Therefore, a larger sample size should be carried out in human patients to identify specific *T. gondii* strains using high resolution typing methods such as multiplex nested PCR-RFLP which can genotype some DNA samples extracted directly from infected tissues. Serotyping of *T. gondii* strains has proved to be a promising tool using serum samples to overcome the diagnostic challenge (Kong et al, 2003; Peyron et al, 2006; Morisset et al, 2008; Sousa et al, 2008; Sousa et al, 2009). However, due to the limitation of serotyping it is not possible to differentiate type II from non-type II strains particularly in South America where there is a high diversity of *T. gondii* strain types. At present, this requires further developments of typing analyses to facilitate and be incorporated into the routine diagnosis of patients with CT.

7. Therapeutic approaches: from specific treatment to HAART

7.1 Anti-*Toxoplasma* therapy

One of the keys after diagnoses is how patients respond to the different therapeutic regimens used for treating this opportunistic disease. Most patients with CT respond well to anti-*Toxoplasma* agents as demonstrated by findings from studies in various settings. However, about 10% of CT cases died despite what was thought to be adequate treatment (Vidal et al, 2005a). There are few options other than anti-*Toxoplasma* regimens used as first-choice initial therapy; 6 weeks with sufadiazine (1.0-1.5 g per oral [PO] every 6 h) with pyrimethamine (100-200 mg PO loading dose, then 50 mg PO daily) and folinic acid (10-20 mg PO daily) that can reduce the hemato-toxicities related to pyrimethamine (Portegies et al, 2004). This standard combination has been successfully used in treating CT but has been associated with high toxicities such as Lyell's syndrome or Steven-Johnson syndrome (Katlama et al, 1996a; Torre et al, 1998). The other regimen is trimethoprim/sulfamethoxazole (Co-trimoxazole, 5/25 mg/kg PO or intravenous (IV) every 12 h for 4-6 weeks) (Canessa et al, 1992). This therapeutic regimen has been confirmed for its efficacy and safety in a single available randomized clinical trial (Canessa et al, 1992; Torre et al, 1998; Dedicoat & Livesley, 2006; Béraud et al, 2009). Several alternative therapies, principally used in patients who are intolerant to this combination, have been reported to be effective, including clindamycin and pyrimethamine or sulfadiazine (Katlama et al, 1996a; Tsai et al, 2002), clarithromycin and pyrimethamine (Fernandez-Martin et al, 1991), clindamycin and 5-fluoro-uracil (Dhiver et al, 1993), azithromycin and pyrimethamine (Saba et al, 1993; Jacobson et al, 2001), clindamycin and fansidar (Nissapatorn et al, 2004), sulfadoxine and pyrimethamine (Amogne et al, 2006), and atovaquone (Torres et al, 1997). There was no superior regimen among the three following combinations: pyrimethamine plus sulfadiazine, pyrimethamine plus clindamycin (Katlama et al, 1996a), and pyrimethamine plus sulfadiazine with Co-trimoxazole (Torre et al, 1998) that were reported in a recent review of comparative studies (Dedicoat & Livesley, 2006).

There is one case of toxoplasmosis resistant to standard combination therapy (pyrimethamine and sulfadiazine) that was improved with clindamycin and pyrimethamine (Huber et al, 1995). The other case was an AIDS patient with toxoplasmic myelopathy and myopathy

resistant to standard anti-*Toxoplasma* therapy due to the possibility of immune reconstitution of the inflammatory syndrome, was reported (Kung et al, 2011). Another study suggested atovaquone as being effective in AIDS cases with resistant toxoplasmosis (Lafeuillade et al, 1993). This helps to identify drugs that are effective and may act synergistically (McFadden et al, 2001). Relapses of CT are frequently observed in AIDS patients non-compliant to therapy or prophylaxis, and in those who develop adverse drug effects (Luft & Remington, 1992; Nissapatorn et al, 2004; Béraud et al, 2009). There has been no evidence of treatment-induced resistance so far reported that have contributing to a relapse of CT. Few studies have arrived at a solution of how to prevent relapses. Pyrimethamine and sulfadoxine twice a week appears to give promising results for prevention of CT. Allergic reactions are usually mild and disappear on continuation, but may limit the value of this regimen (Ruf et al, 1993). Daily doses of pyrimethamine and sulfadiazine are more effective as maintenance therapy for preventing relapses of CT (4.4 compared to 19.5 per 100 patient-years; incidence rate ration, 4.36; p=0.024) than twice weekly administration (Podzamczer et al, 1995). Pyrimethamine and clindamycin has been shown to be a valuable alternative for treatment but is less effective, particularly for the long term prevention of relapses (Katlama et al, 1996a). Azithromycin and pyrimethamine have been used as alternative therapy, but maintenance with this combination or oral azithromycin alone is associated with relapses (Jacobson et al, 2001).

Atovaquone is a unique naphthoquinone with broad-spectrum antiprotozoal activity. It has been found to be effective against tachyzoites in vitro and may kill bradyzoites within cysts at a higher concentration. Atovaquone is frequently used in combination with other agents in treating CT. Experimental studies have shown that the efficacy of atovaquone was enhanced when other agents were added, such as pyrimethamine, sulfadiazine, clindamycin, or clarithromycin (Guelar et al, 1994). An intravenous preparation is highly effective in murine models with reactivated toxoplasmosis (Schöler et al, 2001; Dunay et al, 2004). In AIDS patients, the only study to report failure with atovaquone during treatment found that a high temperature may induce inactivation of the product in the absence of food intake (Duran et al, 1995). Atovaquone has consistently been found to be a promising therapeutic for salvage therapy in CT patients who were intolerant to or who failed standard regimens (Guelar et al, 1994; Katlama et al, 1996a; Torres et al, 1997; Chirgwin et al, 2002). However, the role of atovaquone in the treatment and prophylaxis of CT in AIDS patients is not well defined and more studies are required before a firm recommendation can be made (Baggish & Hill, 2002). The treatment of choice is often directed by the available therapy, particularly in resource-poor settings. An important question is whether the incidence of secondary reactivation or relapse cases of CT may begin to rise in the future. This depends on how the efficacy of the current treatment regimens and new novel drugs, especially those that can destroy cyst/bradyzoite forms of the *Toxoplasma* parasite. Another important factor is increasing resistance to antiretroviral drugs in HIV-positive patients and the subsequent decline in CD4 cell counts (Kuritzkes et al, 2000) which has been reported in the recent years.

7.2 Primary and secondary chemoprophylaxis

Toxoplasmosis is one of the leading CNS-OIs, that causes morbidity and mortality in advanced stages of HIV-infected patients. Effective primary and secondary prophylaxis has been formulated to prevent the occurrence of CT (Katlama et al, 1996a; Bucher et al, 1997). Before the era of HAART, co-trimoxazole played an important role as a primary prophylactic agent in preventing the reactivation of toxoplasmosis in HIV-positive patients

(van Oosterhout et al, 2005). CT was still reported in HIV-infected patients with or without prophylaxis (Nissapatorn et al, 2004; Nissapatorn et al, 2007). To be consistent with previous reports and present situations in most resource limited settings, a current guideline recommends the use of a daily dose of a double-strength tablet of co-trimoxazole in *Toxoplasma*-seropositive patients who have a CD4 cell count below100 cells/cumm (CDC, 2009). For AIDS patients who survive their first episode of CT, the risk of relapse is between 30% and 50% if lifelong suppressive therapy is not provided (Leport et al, 1988; de Gans et al, 1992). Discontinuation of maintenance therapy (secondary/ suppressive therapy) for established CT patients is not recommended (USPHS/IDSA Prevention of opportunistic infections working group, 1997). In the pre HAART era, relapse rates of CT after discontinuation of maintenance therapy was approximately 50% (Katlama et al, 1996b). There are few regimens that have been used for secondary prophylaxis for CT patients; the combination of pyrimethamine (25-50 mg/day) plus sulfadiazine (500 mg every 6 h) plus leucovorin (10-20 mg/day) is a highly effective treatment. The use of this combined thrice-weekly regimen (Podzamczer et al, 1995) or the same doses of sulfadiazine twice a day (Jordan et al, 2004) is an alternative option among non-compliance patients. The recommendation is for pyrimethamine plus clindamycin (600 mg clinidamycin every 8 h) for patients who are intolerant to sulfa drugs (CDC, 2009). Co-trimoxazole (960 mg twice daily) is another potential drug used in secondary prophylaxis for patients with CT (Duval et al, 2004). This agent (2.5/12.5 mg/kg PO every 12 h) is considered as safe, cheap and effective and can be an alternative choice (Pereira-Chioccola et al, 2009) to increase drug adherence in areas where other maintenance therapies are not available.

7.3 Highly active anti-retroviral therapy (HAART)

For more than two decades now, the use of HAART in HIV-infected patients has resulted in an improved quality of life and an increase in the length of time that patients remain free from opportunistic infections (Mocroft et al, 1998; Palella et al, 1998). A higher CNS Penetration-Effectiveness (CPE) score of antiretroviral drugs is increasing the survival rate of CT patients (Lanoy et al, 2011). In CT cases, there is no recommendation for the timing of HAART when CT is present in antiretroviral-naïve patients. However, HAART should be started at least 2 weeks after an anti-*Toxoplasma* regimen was initiated in these patients (Manzardo et al, 2005; Pereira-Chioccola et al, 2009). In HIV-infected patients receiving HAART, primary prophylaxis for CT can be safely discontinued in patients whose CD4 cell counts increase to >200 cells/mm^3 (CDC, 2009). It is a medical challenge to decide whether secondary prophylaxis should be continued while HIV-infected patients are receiving HAART. If maintenance therapy is stopped, recurrence of toxoplasmosis may allow for permanent damage to cerebral and visual functions which is potentially harmful to an affected person (Stout et al, 2002). While maintenance therapy is still essential, evaluation of *T. gondii*-specific immune responses might be the other important step for improving estimates of the individual risk of CT and CT relapse (Hoffmann et al, 2007). Otherwise, secondary prophylaxis can be safely discontinued in CT patients receiving HAART with CD4 cell count of > 200 cells/cumm after 6 months (Pereira-Chioccola et al, 2009). This same prophylaxis should be reintroduced in patients with CD4 cell count of < 200 cells/cumm (CDC, 2009). While, primary and secondary prophylaxis against CT can also be safely discontinued after the CD4 cell count has increased to ≥ 200 cells/cumm for more than 3 months in HIV-infected patients receiving HAART (Miro et al, 2006). These strategies can

help in reducing the toxicity, pill overload, and expense associated with complicated therapeutic regimens. Considering that CT patients have a high chance of early death, HAART should be immediately initiated after CT diagnosis and prophylaxis should be maintained in these patients who fail to respond to antiretroviral therapy.

8. Immune Reconstitution Inflammatory Syndrome (IRIS) - from past to future concerns

Anti-retroviral therapy partially restores the immune function of HIV-infected patients, thereby remarkably reducing morbidity and mortality of opportunistic infections in general and CT in particular. The incidence of opportunistic infections, including CT and ECT has decreased, particularly in areas where antiretroviral therapy, including HAART, is accessible (Kaplan et al, 2000; Subsai et al, 2006; Lian et al, 2007). HAART has reduced relapse in cases of toxoplasmosis and has improved survival in these HIV-infected patients. This may be due to the successful suppression of virus replications followed by an increase in CD4+ lymphocytes, a partial recovery of T-cell specific immune responses and decreased susceptibility to both local and systemic opportunistic pathogens (Silva & Araújo, 2005). HIV-associated IRIS is the clinical worsening of opportunistic infections that result from enhancement of pathogen-specific immune responses among patients responding to antiretroviral treatment (Lawn & Wilkinson, 2006). IRIS has been widely recognized in CT patients following initiation of HAART and development of a paradoxical clinical deterioration despite an increased CD4 cell count and decreased HIV viral load which leads to the rapid restoration of the immune system (Gray et al, 2005). So far, more than 20 cases of IRIS-associated CT have been reported in the literature (Table 2). A low CD4 cell count has been identified as a significant risk factor in AIDS patients with CT (Tsambiras et al, 2001; de Boer et al, 2003; Sendi et al, 2006; Chen et al, 2009; Caby et al, 2010; Kung et al, 2011) due to impaired proliferative response to *Toxoplasma* antigen (Belanger et al, 1999), a decreased production of interferon γ (Ullum et al, 1997), and it is found to be more common that IRIS develops in HIV-infected patients (Jevtović et al, 2005). Therefore, monitoring of CD4/CD8 T cells in patients on HAART might serve as a better marker for the restoration of *T. gondii*-specific immune responses than the total number of CD4 cells count (Furco et al, 2008). Immune reconstitution under HAART has been associated with a restoration of immune responses against *T. gondii* (Fournier et al, 2001). In the case where IRIS is suspected in CT patient, close observation for 7-15 days, a higher steroid dose to control IRIS (Venkataramana et al, 2006), uninterrupted HAART, and continued treatment for toxoplasmosis can resolve this problem without biopsy (Tremont-Lukats et al, 2009). Based on reported cases of CT-associated IRIS from different studies, this could verify its association that it can develop in a substantial numbers of HIV-infected patients receiving HAART. No case of IRIS-related toxoplasmosis has ever been reported among AIDS patients in Malaysia even though CT was one of the most common systemic opportunistic infections in AIDS patients (Nissapatorn et al, 2004; Lian et al, 2007). Toxoplasmosis is a common neurological opportunistic infection in industrialized countries for which HAART is often initiated fairly early compared to developing or resource-limited settings. As for the increasing use of HAART worldwide, the care for patients receiving HAART will need to incorporate monitoring for and treating complications of IRIS (Agmon-Levin et al, 2008), including impaired CD4-cell immune reconstitution upon HIV therapy in patients with CT

Reference	Country	No. of cases	Clinical presentation	Baseline CD4 cell count/μL
Rodríguez-Rosado et al, 1998	Spain	3	Cerebral toxoplasmosis	-
González-Castillo et al, 2001	Spain	1	Cerebral toxoplasmosis	456
Tsambiras et al, 2001	USA	1	Cerebral toxoplasmosis	83
de Boer et al, 2003	The Netherlands	1	Cerebral toxoplasmosis	43
Jevtović et al, 2005	Serbia & Montenegro	1	Cerebral toxoplasmosis	<100
Sendi et al, 2006	Switzerland	1	Immune recovery vitritis with isolated toxoplasmic retinochoroiditis	11
Subsai et al, 2006	Thailand	2	Cerebral toxoplasmosis	-
Huruy et al, 2008	Ethiopia	2	Cerebral toxoplasmosis	-
Chen et al, 2009	USA	1	Cerebral toxoplasmosis	29
Klotz et al, 2009	Ethiopia	7	Cerebral toxoplasmosis	50-100
McCombe et al, 2009	Canada	1	Cerebral toxoplasmosis	2
Tremont-Lukats et al, 2009	USA	1	Cerebral toxoplasmosis	14
Cabral et al, 2010	Brazil	1	Cerebral toxoplasmosis	276
Caby et al, 2010	France	1	Placental IRIS	7 (pregnancy)
Martin-Blondel et al, 2010	France	3	Cerebral toxoplasmosis	9, 25, 23
Kung et al, 2011	USA	1	Toxoplasmic myelopathy and myopathy	67
Shah, 2011	India	1 (child)	Cerebral toxoplasmosis	-

Table 2. Summary on reported cases of immune reconstitution inflammatory syndrome (IRIS) associated toxoplasmosis in HIV-infected patients.

(Kastenbauer et al, 2009). As the number of AIDS-associated CT cases treated with HAART increases, the complications of IRIS-CT may become more common and easily recognizable, particularly in areas where toxoplasmosis is endemic. Therefore, increased awareness of IRIS is importance to clinicians along with early diagnosis and appropriate treatment in managing AIDS patients.

9. Conclusion

Despite a decline in both morbidity and mortality in HIV-infected patients in developed countries including the United States and Europe, toxoplasmosis remains an important disease and is unlikely to be eradicated. Toxoplasmosis still occurs in those not diagnosed with HIV and not receiving medical care, those not receiving prophylaxis, and those not taking or not responding to HAART. There are very few reports regarding resistance to the drugs used for toxoplasmosis. Resistance in HIV cases and the action of anti-retroviral therapy with or without IRIS may contribute to an increase in the incidence of CT. In developing countries where anti-retroviral therapy is still lacking, HIV-infected patients are at high risk for CT, these regions include China, India, South America, Southeast Asia and most importantly sub-Saharan Africa. A better understanding of the clinico-epidemiology of toxoplasmosis, and improved efforts in prevention, diagnosis and treatment, are needed. The role of infections with this parasite requires further study, including as to whether infections, such as CT have an impact on HIV/AIDS patients.

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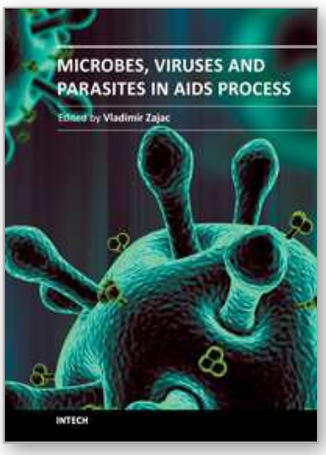

Microbes, Viruses and Parasites in AIDS Process

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The main goal in compiling this book was to highlight the situation in Africa in terms of AIDS and opportunistic diseases.Â Several chapters reveal great poverty, an apocalyptic situation in many parts of Africa.Â Global migration of people resulted in their exposure to pathogens from all over the world. This fact has to be acknowledged and accepted as African reality. New, unconventional hypotheses, not determined by established dogmas, have been incorporated into the book, although they have not yet been sufficiently validated experimentally.Â It still applies that any dogma in any area of science, and medicine in particular, has and always will hinder progress. According to some biologists, in the future, AIDS is very likely to occur in a number of variations, as a direct result of the ongoing processes in the global human society. Thus, we urgently need a comprehensive solution for AIDS, in order to be ready to fight other, much more dangerous intruders.

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