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Toxoplasmic Encephalitis

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1. Introduction

Toxoplasmic encephalitis (TE), a life-threatening disease in HIV/AIDS infected individuals, is an inflammation of the brain caused by the reactivation of latent infection of the protozoa *Toxoplasma gondii*. Immunocompetent host when infected with *T. gondii* is almost always unnoticeable or develops mild and non-specific signs and symptoms, then tissue cysts are the consequence harbored in those infected persons life-long, quietly without any problem. However, when host immunity is suppressed by any cause but mostly by HIV/AIDS, the previously quiescent protozoa become active and the aggressive stage, tachyzoite, causes severe clinical manifestations in the Central Nervous System (CNS) such as encephalitis or abscess.

In the early 1980s, at the beginning of AIDS pandemic, there were many alarming case-reports threatening the world medical community with increasing numbers of unknown causes and severe diseases presented in homosexual men, hemophiliacs and Haitian. TE was one of the most common opportunistic infections of this immunocompromised host. Huge efforts have been put on to combat with TE including budget, manpower and research on diagnostic methods, prophylaxis, treatment and prevention. The incidence of TE is now decreasing due to primary and secondary prophylaxis as well as immune restoration because of the HAART (Highly active antiretroviral therapy), but some old problems still exist and new ones have surfaced.

This chapter will focus on all aspects of TE including the etiologic organism, epidemiology, clinical manifestations, diagnostic methods, management and outcome as well as prophylaxis and prevention. Evidences from our research on *T. gondii* and literature review will be used as an input. With those frameworks, an extensive perspective on this fascinating disease will be forthcoming.

2. Etiologic organism: *Toxoplasma gondii*

T. gondii was discovered since 1908 simultaneously by 2 groups of researchers. Firstly, Charles J. H. Nicolle (1866-1936) and Louis H. Manceaux (1865-1943) from the Pasteur Institute in Tunisia isolated a new parasite from the African rodent, *Ctenodactylus gundi*, and differentiated it from *Leishmania*. Secondly, the Italian researcher namely Alfonso Splendore (1871-1953) who worked at Sao Paulo, Brazil identified this protozoan from the liver of rabbit (Dubey et al., 1970; Sukthana, 2006). *T. gondii* was named a year later by Nicolle and Manceaux according to its bow-like shape (Toxoplasma is from a Greek word: toxos means bow or arc; plasma means life) and gondii may result from a misspelling of the scientific

name of its original host, the gundii (Ferguson, 2009a). The first congenital case of toxoplasmosis was described in 1923 and the first adult case was diagnosed in 1940 (Frenkel & Fishback, 2000). It was not until 1969 when its life cycle was completely known with cats and other felids as the only definitive host in which sexual reproduction takes place to produce infective oocysts. Human, warm-blooded domestic animals, birds, and rodents including wild and marine mammals are intermediate hosts that harbor tissue cysts in their bodies (Hutchison et al., 1969; Dubey et al., 1970; Dubey, 2007; Ferguson, 2009b). *T. gondii* was classified as coccidian belonging to the phylum Apicomplexa which is an intracellular organism (Dubey et al., 1970).

2.1 Life cycle and mode of transmission of *T. gondii*

There are 3 infective stages of *T. gondii* i.e. 1) oocysts produced and shed by cat and felid animals, 2) an active, rapidly dividing tachyzoite form and 3) an inactive dormant bradyzoite harbored in tissue cysts. Tachyzoite and bradyzoite, sized 2 x 9 µm, cannot be differentiated by light microscope, while the mature oocyst is an oval shape, sized 9 x 13 µm containing 2 sporocysts with 4 sporozoites in each.

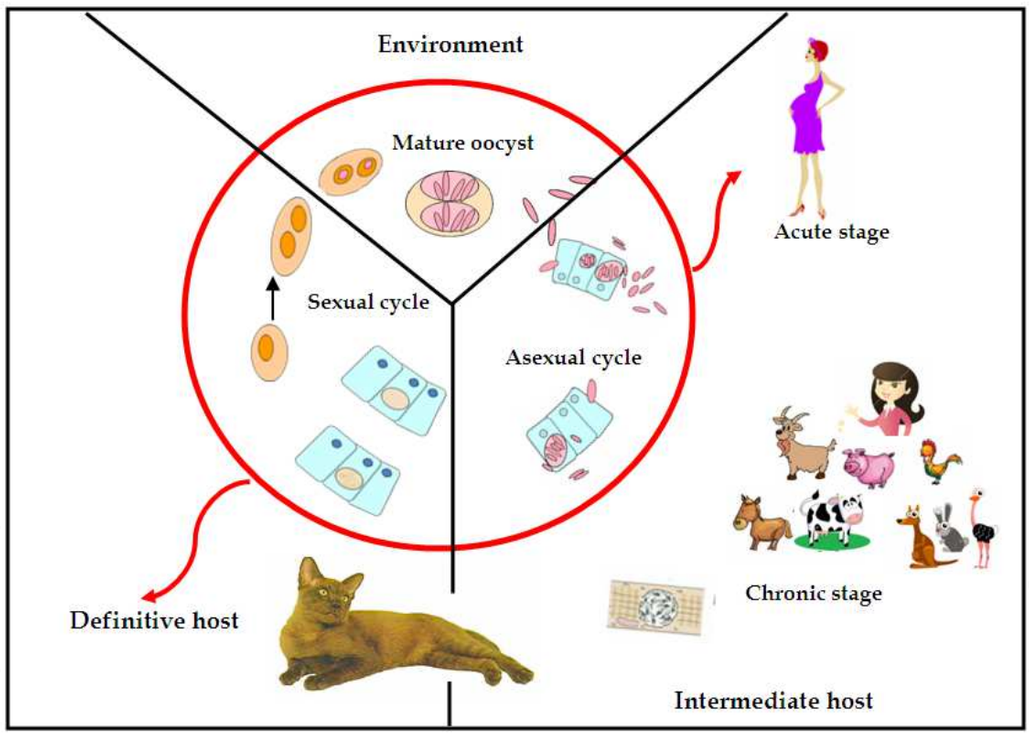

Fig. 1. Life cycle of *Toxoplasma gondii*: Cat and felids are only definitive host where *T. gondii* completes its life cycle. Intermediate hosts are human, warm-blooded domestic animals, bird and rodent including wild and marine mammals. Immature oocysts develop in the environment before becoming infected mature oocysts. Acute stage of infection occurs in both definitive and intermediate hosts, but turns to be chronic and develops as a tissue cyst in the intermediate host. Sexual reproduction occurs in cat producing immature oocysts.

When mature oocysts are ingested by hosts, sporozoites are released after exposure to gastric enzymes and invade enterocytes, whereas in asexual multiplication, multiple

fissions, occurs resulting in many tachyzoites causing cell rupture and subsequently they invade other enterocytes producing the active stage of infection (Figure 1). In intermediate host tachyzoites will shortly transform to be inactive bradyzoites and reside silently in tissue cyst for the whole life of the infected host. Thus the chronic stage of infection occurs. On the contrary, tachyzoites in definitive host modify to be macrogametocyte and microgametocyte and sexual reproduction occurs producing immature oocysts which when shed with cat's fecaes, need about 2-5 days to develop in the environment until mature as infective stage.

Toxoplasma is transmitted to human by 3 routes. The most common two are ingesting contaminated food or water with mature oocysts and consuming undercooked, infected meat where bradyzoites harbor in tissue cysts. The least frequent route is transplacental transmission which occurs only when the mother acquires primary infection during pregnancy. A European multicenter study including cities in Western Europe identified the consumption of undercooked meat as the strong risk factor for acquiring a *T. gondii* infection, whereas in Central and South America it is related with large numbers of stray cats that have access to the outdoor environment of which the climate favours and prolongs the survival of oocysts (Sukthana, 2006). Toxoplasmosis transmitted by cat excreta is not straight forward in Southeast Asia. Due to the religious belief, Malaysian and Indonesian Muslims prefer cats to dog as pet, while lots of stray cats are left in Buddhist temples in Thailand. Those settings should promote cat's excreta as a strong risk factor in that region. Noteworthy, human *Toxoplasma* seroprevalence in Thailand is much lower than in those two countries (21.9% vs. 44.8% and 58%) and correlated with cat seroprevalence (Konishi et al., 2000; Nissapatorn et al, 2004a; Sukthana, 2006). This might be due to high humidity and more rainfall in the latter countries suggesting that ground temperature is an important determinant of oocyst survival.

3. Epidemiology and risk factor

About 20% to 40% of individuals with AIDS develop TE from the reactivation of a latent *T. gondii* infection when the CD4 cell count falls below 100/mm^3 (Luft & Remington, 1992; Sukthana, 2000; Ajzenberg, 2009). The incidence of TE is thus directly proportional to the prevalence of antibodies to *Toxoplasma* in any given population. Before the advent of HIV/AIDS epidemic in 1981, toxoplasmosis was occasionally reported in immunocompromised patients, mostly in those with malignancies of the reticuloendothelial system and cardiac transplant recipients with lesions mostly outside the CNS. But, TE has become one of the commonest causes of focal brain lesions in Western Europe and North America due to AIDS pandemic (Luft & Remington, 1988). Since then, more and more TE cases in HIV/AIDS individuals were diagnosed worldwide. Nearly three decades from that point, nowadays to get a clearer picture of its epidemiology and clinical course, herein, three periods could be divided as: 1) TE during the beginning of AIDS pandemic period (1980s), 2) TE during prophylaxis period (1990s) and 3) TE during HAART period (1997-present).

3.1 TE during the beginning of AIDS pandemic period (1980s)

At the beginning of the 1980s, more and more of the mysterious cases with severe manifestations and fatal outcomes presented in homosexual men, hemophiliacs and Haitian. HIV was subsequently identified as the cause that impaired host immunity causing acquired immunodeficiency syndrome (AIDS) and opportunistic infections. In November 1982, the Centers for Disease Control (CDC) reported 19,744 AIDS cases from the United States, with

287 deaths and 54 cases have been reported from foreign countries (Gapen, 1982). Neurological involvement was seen in three out of four AIDS patients and TE was one of the most common neurological complications. Luft and colleagues (1983) reported acute encephalitis caused by *Toxoplasma* in 10 patients from Belgium, USA and Canada who had no underlying history associated with toxoplasmosis. All patients had a prodrome which varied from one week to 18 months. Three patients had disseminated toxoplasmosis with several organs affected (Table 1). Half of them had concomitant infections including tuberculosis, pneumocystosis, cytomegalovirus infection (CMV) and candidiasis. Other studies revealed similar pictures which reported neurological complications ranging from 20% to 41% with TE as the most or the second most common neurological disorders in HIV/AIDS patients (Luff, et al, 1983; Levy, et al, 1985; Berger, et al, 1987).

A 10-year observational studies from USA (Luft, & Castro, 1991; Richards et al, 1995) revealed at the end of 1989, there were 5,614 cases of toxoplasmosis reported to the CDC as the AIDS indicator disease and it increased to 14,059 (5.1%) of 274,150 adults and adolescents in the United States. The risk factors were observed as black male, intravenous drug users (IVDU), homosexual men, immigrants, Haitian and different geographic location. Richards and colleagues demonstrated that TE was more common among black males than white (5.2% vs. 4.2%, $P < .0001$) and was also more common among IVDU than among men with male sex partners (5.9% vs. 4.6%, $P < .0001$). Immigrants to the USA from Africa, Latin America and Haiti were three to four times more likely to develop TE than American-born (Luft, & Castro, 1991). The rate of TE was higher in the northeastern and southern states of America (5.6% vs. 5.5%) than in the north-central and western states (4.4% vs. 4.1%, $P < .0001$) this was related to the *Toxoplasma* IgG seroprevalence which was observed twice higher in the northern and northeastern regions than those in the western and southwestern regions (Richards et al, 1995).

In Africa, Europe, and South America, where the prevalences of chronic *T. gondii* infection were as high as 60%-75%, patients with AIDS who developed TE were three to four times greater than that in the United States whereas HIV-infected adults with latent *T. gondii* infection was less than 40%, only one-third of those patients developed TE (Luft & Remington, 1992). In France, 11% of AIDS-defining illness was due to TE in 1987, and rose to 23% in 1992 (Oksenhendler et al, 1994). Studies from France and Brazil in 1985 to 1990 reported the prevalence of TE in AIDS patients at 17% and 13% by presumptive diagnosis compared with 22% by definite diagnosis, respectively (Ragnaud et al, 1993; Wainstein et al, 1993). In Asia, the seroprevalence of toxoplasmosis was low, from 4% to 42.5% in Japan, Korea, Taiwan and Thailand, but was higher in India, Malaysia and Indonesia as 22.4% to 67.8% (Nissapatorn, 2009). The first documented case of TE reported in an international journal was from Thailand in 1992 (Sukthana, 2000), but a report in a local textbook showed 9.7% of cerebral toxoplasmosis as AIDS-defining illnesses from 1987 to 1994 and increased to 10.5% in 2001 and to 14.8% in 2002 (Chankrachang, 2004).

3.2 TE during prophylaxis regimen period (1990s)

In the 1990s, numerous TE cases as one of the common opportunistic infections in HIV/AIDS individuals were being diagnosed; medical researchers thus developed a clearer picture of its epidemiology and clinical features. For example, the incidence of TE was found to be 20.5 per 100 patient-years in France (Bossi et al., 1998), 15.9 per 100 patient-years in Swiss HIV Cohort study group (Furrer et al, 1999) and 4.0 per 100 patient-years in nine US cities (Jones et al, 1996). Khetsuriani and colleagues (Khetsuriani et al, 2002) studied the

Study period [References]	Study Location	Patients	Risk factors	TE Prevalence	Clinical features	Diagnostic procedures
1981-1982 [Luft et al, 1983]	Research Institute, Palo Alto Medical Foundation, USA	10 patients with acute encephalitis from Belgium, USA and Canada	Host immune deficiency by unknown cause in homosexual men, IVDU and Haitians.	All developed TE with disseminated toxoplasmosis	1wk-18 mo prodromic period Brain involvement with other organs affected such as lung, retina and heart	Serology (IgG and all negative IgM) Mice inoculation
1980-1984 [Berger et al, 1987]	Jackson Memorial Hospital, Miami, Florida, USA	132 AIDS patients with symptomatic AIDS (including : 55%Haitian, 27%homo-sexual men and 11%IVDU)	Haitian	39%	Fever Headache Alteration of semsorium Hemiparesis Ataxia	Histological diagnosis by Biopsy or Autopsy Immuno-peroxidase staining CT showing multiple enhanced ring-shaped lesions
1985-1990 [Ragnaud et al, 1993]	Bordeaux Regional Hospital, France	428 AIDS patients with initial CD4= 72 cell/mm^3	M:F= 2.8:1 Mean age 36.2 yrs 43% homo-sexual men 30% IVDU	17%	62% focal neurological deficit 58% fever 47%headache 45% altered consciousness 18% seizures	CT findings: focal mass 60% with and 40% without ring enhancement 59% multiple lesions 58% with brain edema
1985-1999 [Wainstein et al, 1993]	Hospital de Clinicas de Porto Alegre, Brasil	516 AIDS patients	-	13% by presumptive diagnosis and 22% by definite diagnosis	Fever with 92% sen and 56% spec Neurological focal signs with 59% sen and 82% spec Headache with 41% sen and 69% spec	65% by blood serology with 95% sen and 30% spec 49% by CSF serology with 77% sen and 56% spec By CT with 65% sen and 82% spec 125 patients by Autopsy

Study period [References]	Study Location	Patients	Risk factors	TE Prevalence	Clinical features	Diagnostic procedures
1981-1990 [Richards et al,1995]	San Francisco, USA	Homosexual men, with AIDS	IVDU, Homo-sexual men, Black male, geographic difference	0.05 cases/person-year of observation	-	-

Table 1. Summary of the data from studies on epidemiology and clinical course of toxoplasmic encephalitis (TE) during the beginning of AIDS pandemic period (1980s). IVDU = Intravenous drug user, mo = month(s), sen = sensitivity, spec = specificity, wk = week(s).

burden of encephalitis in USA from 1988 to 1997 and revealed TE accounted for the majority of 34.1% known causes of hospitalization due to encephalitis (21,504 hospitalizations; SE, ± 2,583). More than 97% of TE had been reactivated from the chronic quiescent *Toxoplasma* infection, nevertheless, few TE cases developed as acute infection (Richards et al, 1995). Only 30%-50% of HIV-positive patients with chronic *T. gondii* infection developed TE when their immune system became severely compromised. These were because host factors or virulence among different strains of *Toxoplasma* played a role in predisposing those patients to recrudescence of active clinical symptoms and signs (Luft & Remington, 1992). The research questions in that period was focused on when and what caused the reactivation to occur and how patients could be taken care of.

There were various retro- and prospective studies on the prevalence of TE, risk factors and prophylaxis worldwide (Table 2). To combat aggressive opportunistic infections (OIs) in HIV/AIDS patients including PCP, CMV infection and toxoplasmosis, medical researchers have unanimously agreed in giving primary prophylaxis to the population at risk of those OIs in suitable time. Primary prophylaxis should be given to prevent OIs when immune deficiency occurs and secondary prophylaxis would be continuously prescribed after acute opportunistic infections subsided. In general, HIV/AIDS individuals were mostly prescribed penthamedine, cotrimoxazole and dapsone as the prophylaxis of PCP and CMV infection which were more aggressive and occurred earlier than toxoplasmosis, when their CD4 were < 200 cell/mm^3. The matters had arisen whether those medications were also preventing TE and were good candidate regimens of appropriate dosage with acceptable adverse effect and adherence or compliance of the patients. In the case of TE, there were two things to be considered for primary prophylaxis which were HIV/AIDS infected person who was also seropositive of *T. gondii* antibody and CD4 was lower than 100 cell/mm^3 (Oksenhendler et al, 1994; Richards et al, 1995; Leport et al, 1996).

Table 2 summarized the data from studies which were carried out in the 1990s concerning TE epidemiology, prophylaxis regimens and outcomes. Cotrimoxazole or trimethoprim-sulfamethoxazole (TMP-SMZ) was the most popular regimen for TE primary prophylaxis, while Fansidar (pyrimethamine-sulfadiazine) was prescribed at the beginning of 1990 when CD4 was lower than 200 cell/mm^3 (Carr et al, 1992; Köppen et al, 1992). However, it was not recommended for the primary prophylaxis of TE because of its side-effects especially rash and allergy. Thus patients discontinued the prophylaxis and had higher TE reactivation. Pyrimethamine had bone marrow toxicity. When patients received without leucovorin supplement the survival rate reduced (Jacobson et al, 1994). Even though pyrimethamine

was not recommended as a first-line regimen for primary prophylaxis of TE, some medical researchers considered pyrimethamine for patients who were intolerant to TMP-SMZ, especially in high risk patients with CD4 <100 cell/mm^3 (Leport et al, 1996).

TMP-SMZ was the drug of choice for prophylaxis for both PCP and toxoplasmosis (Carr et al, 1992; Richards et al, 1995). Therefore, there were various regimens ranging from 1 double-strength[1] (DS) tablet twice daily to 1 DS tablet 3 times weekly (14 DS tablets to 3 DS tablets per week) have been used. Ribera and colleagues (1999) found that since 1992, patients received either one of the following 5 regimens of TMP-SMZ for TE prophylaxis i.e.1 DS tablet daily (7DS tab/wk), 2 DS tablets daily 3 times weekly (6 DS tab/wk), 1 DS tablet 5 times weekly (5 DS tab/wk), 1 DS tablet 3 times weekly (3 DS tab/wk), and 1 single-strength (SS) tablet daily (3.5 DS tab/wk), they noticed the more frequent doctors began prescribing low doses of TMP-SMZ the higher number of patients receiving TMP-SMZ prophylaxis developed TE. Therefore, they studied to assess the efficacy of the various doses of TMP-SMZ as primary prophylaxis for TE and concluded that patients receiving low dose TMP-SMZ (<4 DS tab/wk) had a higher risk of developing TE than those who received high dose TMP-SMZ indicating 89% protective efficacy for high doses. An insufficient concentration of the low dose TMP-SMZ within the CNS may be an additional problem in the prevention of toxoplasmosis. Moreover, they also studied the potential interactions between rifampin and TMP-SMZ and hypothesized that rifampin may reduce the efficacy of TMP-SMZ.

Dapsone combined with pyrimethamine (200/75 mg once weekly) was more effective in the primary prophylaxis of TE than aerosolized pentamidine (300 mg every 4 weeks) and had the advantage of a lower cost and easier administration (Torres et al, 1993; Opravil et al, 1995). Girard and colleagues (1993) revealed dapsone plus pyrimethamine prevented first episodes of TE better, but they were more toxic than aerosolized pentamidine (42 patients discontinued dapsone plus pyrimethamine while only 3 patients stopped aerosolized pyrimethamine, $p<0.001$)

In conclusion, primary prophylaxis was the important strategy to prevent TE occurrence in the 1990s period. TMP-SMZ was the drug of first choice which was prescribed when HIV/AIDS seropositive to *T. gondii* antibody had low CD4 <200 cell/mm^3. By this practice, the prevalence of TE was reduced from 19% in 1988 to 6% in 1994 (Katlama, 1995). The incidence of TE was 3.9 cases/100 person-years (95% CI, 3.7–4.1 cases/100 person-years), patients who discontinued TMP-SMZ increased the risk of TE (Abgrall et al, 2001).

3.3 TE during HAART period (1997-present)

Since 1997, protease inhibitor, an antiretroviral drug, had been widely available, HIV-infected persons have lived longer and healthier lives. Since then, in the period of 15 years, that development was considered one of the great success stories of modern medicine. The death rate from HIV disease was reduced by 50 to 80% and changed from a fatal and hopeless illness to what is now a manageable chronic disease. The simultaneous combination of three or more different antiretroviral drugs was known as Highly Active Antiretroviral Therapy or HAART (Cooper 1996). It significantly delayed the onset of AIDS in HIV-infected individuals as well as reduced almost all opportunistic infections. The

[1] double-strength (DS) tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole, while single-strength (SS) contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole.

incidence of TE was, with no exception, decreased from 3.9 cases per 100 person-years in the period before the availability of HAART to 1.0 case per 100 person-years in the HAART era (Sacktor et al, 1990; Abgrall et al, 2001). However, TE remained the most prevalent CNS disorder, accounting for one-fourth of all documented cases in both antiretroviral-treated

Study Design [References]	Drug Regimens	Outcomes	Significance
Cohort study in 83 AIDS patients comparing primary and secondary prophylaxis to prevent TE with follow up duration of 3-41 mo (median = 8 mo) [Köppen et al, 1992]	Aerosolized Pentamidine (AP) IAP: Primary prophylaxis IIAP: Secondary prophylaxis Fansidar (pyrimethamine/sulfadiazine PY/S) Ib: Primary prophylaxis IIb: Secondary prophylaxis	TE occurrence • 73% in IAP • 30.9% in IIAP • 5% in IPY/S • 2.3% in IIPY/S	Fansidar (PY/S) was recommended for use as prophylaxis when AIDS patients with ≤ 100 cell/mm^3 , if CD_4 100-200 /mm^3 AP was recommended
Retrospective study in 155 AIDS patients who were referred to tertiary referral teaching hospital after PCP for following up of the TE complication within 3 year periods [Carr et al, 1992]	TMP-SMZ: 60 patients received trimethoprim 160 mg + sulfamethoxazole800 mg Low-dose i.e. 2 tab twice a week AP or P: Pentamidine (AP) and 17 patients received intravenous Pentamidine (P)	No TE occurred in patient who received TMP-SMZ with 1,153 days follow up 33% TE occurred in patients who received AP or P (95% CI, 19% - 51%, P=0.008) and TE occurred even patients have already received prophylaxis for 460 days	Low-dose TMP-SMZ was more effective (P<.008) than AP in preventing TE in HIV-infected patients with previous PCP
Randomized trial in AIDS patients who had CD_4 < 200 cell/mm^3 with the 539 days follow up period [Girard et al, 1993]	D/PY: 173 patients received Dapsone 50 mg(D) plus Pyrimethamine 50 mg (PY) AP: 176 patients received aerosolized Pentamidine 300 mg (AP)	TE occurred 10.9% in D/PY gr. (19 out of 173) and 18.2% in AP gr. (32 out of 176) Patients receiving AP had 1.81 times higher risk of TE than those receiving D/PY (95%, CI; 1.12 – 2.94, p= 0.02) Patients infected by *T. gondii*, TE risk was 2.37 times (95% CI, 1.3 -4.4, P =0.006)	D/PY prevents first episodes of TE better, but more toxicity than AP (42 patients discontinued D/PY while only 3 patients stopped AP, p<0.001)
Prospective study in 278 AIDS patients who had CD_4 <250 cell/mm^3 and follow up TE occurrence for 42-44 wks [Torres et al, 1994]	D: patients received Dapsone 100 mg, twice per wk AP: 176 patients received aerosolized Pentamidine 100 mg every 2 wk	6 TE events occurring among those receiving AP, compared to none among those taking D (p = 0.01).	D was more effective in the primary prophylaxis of TE and has the advantage of a lower cost and easier administration.
Multicenter, double-blind randomized clinical trial in 378 AIDS patients who had CD_4<200 cell/mm^3 with 2.5 yrs follow up period [Jacobson et al, 1994]	PY: 264 patients received Pyrimethamine 25 mg (PY) trice per wk Placebo: 132 patients received placebo	Patients received PY had higher death rate (RR, 2.5; 95% CI, 1.3-4.8; p=.006) No difference between two groups of TE occurrence, this may be due to concomitant PCP prophylaxis with TMP-SMZ in both groups	PY had bone marrow toxicity when patients received without leucovorin supplement will reduce the survival rate, thus primary prophylaxis for TE with PY was not recommended.

Study Design [References]	Drug Regimens	Outcomes	Significance
The placebo-controlled study, randomized, double-blind trial. 554 HIV-infected patients who had CD4 < 200 cell/mm^3 were recruited in France, USA and Spain. [Leport et al, 1995]	PY: 50 mg three time a week after a 100-mg loading dose on the first day plus folinic acid 15 mg three time a week Placebo: the similar in appearance and taste to PY plus folinic acid 15 mg three time a week	TE occurrence • 12% in PY gr. • 13%in placebo (RR 0.9; 95% CI, 0.6-1.4), The survival rate was similar, 85% and 80% (RR, 0.9; 95% CI, 0.7-1.2).	PY was not recommended as a primary prophylaxis of TE, but it should be considered for patients who are intolerant to TMP-SMZ, especially in high-risk patients with < 100 CD4 cells/mm3.
Randomized, open label, prospective trial in 197AIDS patients who had CD_4<200 cell/mm^3 and no history of previous PCP or TE [Antinori et al, 1995]	AP: aerosolized Pentamidine 300 mg/mo TMP-SMZ: trimethoprim 160 mg and sulfamethoxazole 800 mg every alternative day D/PY: dapsone-pyrimethamine 100 mg/ wk and pyrimethamine 25 mg every 2wk	TE occurred • 25.6/100 person-year in AP gr. • 8.9/100 person-year inTMP-SMZ gr. • 9.4/100 person-year in D/PY gr.	Intermittent TMP-SMZ was more effective preventing TE than low-dose D/PY and AP D/PY was associated with a shorter survival.
Case-control study in 521 HIV-infection cohort study from 1993 – 97 by selecting 32 TE cases compared with 64 non-TE cases who were matched by CD4 and *Toxoplasma gondii* serostatus. [Ribera et al, 1999]	Low doses TMP-SMZ:< 4 DS (8SS) tab/wk (i.e. 3 DS tablets per week and 7 SS tablets per week) H igh doses TMP-SMZ: 14 DS/wk (7, 6, and 5 DS tablets per week).	Patients receiving low dose TMP-SMZ had a higher risk of developing TE than those patients receiving high dose TMP-SMZ (estimated protective efficacy for high doses, 89%).	High doses of TMP-SMZ were more effective than low doses for lowering the risk of TE in HIV-infected patients. Patients receiving concomitant rifampin treatment, rifampin may reduce the efficacy of TMP-SMZ.

Table 2. (cont.) Data from the studies on toxoplasmic encephalitis during prophylaxis regimen period (1990-1997). AP = aerosol pentamidine, D = dapsone, DS = double-strength, gr. = group, mo. = month(s), P= pentamidine, PY/S = pyrimethamine/sulfadiazine, PCP = *Peumocystis carinii* pneumonia, RR = relative risk, SS = single-strength, Tab = tablet, TMP-SMZ = trimethoprim + sulfamethoxazole, TE= Toxoplasmic Encephalitis, wk. = week(s)

and untreated HIV-infected persons, especially among severe immunodeficients and in the absence of prophylaxis (Antinori et al, 2004). The significant risk factors for TE occurrence were identified as decreased CD4 count and lack of prophylaxis against infection with *Toxoplasma* species. As demonstrated by Abgrall and colleagues (2001), patients who discontinued TMP-SMZ prophylaxis, received before and after HAART period, had 4.8 and 4.2 times increased risk of TE respectively. During HAART, patients whose CD4 cell counts increased to >200 cells/mm^3, the incidence of TE was only 0.1 case/100 person-years (95% CI, 0.0–0.2) and TE was not increased even with the discontinuation of TMP-SMZ. On other hand, in HIV-infected individuals whose CD4 was lower than 50 cell/mm^3, TE occurred in 12.6/100 person-years, the most common opportunistic infection followed by PCP at 11.4/100 person-years (Yazdanpanah et al, 2001). Other problems affecting TE occurrence even with the widespread use of HAART were patients unaware of their HIV serostatus and those who lacked exposure to HAART or prophylaxis. Thus they presented more with TE as AIDS defining illness than the pre HAART era. In cases who were accessible to HAART, the issues of patients' adherence, drug resistance, failure and cross-resistance were major risks for the development of TE (Yazdanpanah et al, 2001; Antinori et al, 2004).

The decreased incidence of TE and other OIs in HIV-infected patients from HAART raised the issue of discontinuation of primary prophylaxis preventing those OIs and secondary

prophylaxis against opportunistic diseases. Furrer et al (1999) demonstrated no case of *P. carinii* pneumonia (PCP) and TE in patients receiving a combined antiretroviral therapy and their primary prophylaxis were discontinued after CD4 increased to >200 cells/mm^3 for at least 12 weeks, plus 14% of the total lymphocyte count. They also calculated the upper 99% confidence limits for the incidence of PCP at 1.93/100 patient-years, while it was 4.20/100 patient-years for TE. They thus recommended stopping primary prophylaxis against PCP, but not TE, in HIV-infected patients who received HAART and had a sustained increase (longer than 12 weeks) in their CD4 counts to >200 cells/mm^3 and to at least 14% of total lymphocytes. Because the number of TE patients who had been assessed were insufficient to recommend stopping prophylaxis, the same researcher group thus extended their study by accommodating more patients who were seropositive to *T gondii* with longer follow-up (up to 272 person-years) period. They reassured that stopping primary prophylaxis was safe in HIV- and *T gondii*-infected patients who responded to potent antiretroviral treatment with a sustained elevation in immunological markers (14% of peripheral lymphocyte count and the CD4 count remaining higher than 200 cell/mm^3 for at least 12 weeks), especially in the regions where the prevalence of *Toxoplasma* infection was high as in central and western Europe (Furrer et al, 2000).

Because of high toxicity, the discontinuation of secondary or maintenance prophylaxis of CMV infection and PCP were evaluated first and revealed safety discontinuing for patients receiving HAART whose their CD4 count was increased to >200 cells/mm^3 (Zeller et al, 2002). It was known that the risk of relapse after a TE episode was as high as 50% - 80% among patients who did not receive secondary/maintenance prophylaxis and survived more than 6-12 months (Miro et al, 2006). Studies were later undertaken to evaluate the safety of TE secondary/maintenance prophylaxis discontinuation. Concomitant results supported the recommendations of the US Public Health Service (USPHS) guidelines which suggested that secondary prophylaxis for TE can be discontinued for patients receiving HAART in whom either their CD4 counts remained >200 cells/mm^3 for 3–6 months or CD4 counts were >100 cells/mm^3 with their plasma HIV RNA loads were <500 copies/mL (Soriano et al, 2000; Zeller et al, 2002). However, those studies were primarily aimed at evaluating PCP prophylaxis discontinuation in the patients' CD4 threshold of <200 cells/mm^3. Miro and the GESIDA study group conducted a randomized, multicenter clinical trial by stratified HIV-infected patients according to the high risk of TE reactivation as CD4 count of <100 cell/mm^3. They found no episode of TE during a median follow-up of 25 months (409 person-years). Thus, they recommended discontinuation of primary prophylaxis in patients with sustained increase in the CD4 count of >200 cell/mm^3 for at least 3 months and advised to resume primary prophylaxis when the CD4 count was decreased to <100 cells/mm^3 (Miro et al, 2006). This group also followed 20 patients who developed acute TE and received HAART. It revealed the majority of their T cell responded to *T. gondii* antigen, interferon (IFN)-γ production and CD4 count of >200 cell/mm^3 were restored after at least 1 year of HAART. They concluded that the criteria for safely stopping TE secondary/maintenance prophylaxis should be when patients were on HAART for at least 1 year with an increase in CD4 count to >200 cell/mm^3 and with totally (<5,000 copies/mL) or partially (<10,000 copies/mL) suppressed viral replication for at least 3-6 months. Similar to primary prophylaxis, reintroducing secondary/maintenance prophylaxis whenever the CD4 count was decreased to <200 cell/mm^3 was a prudent practice.

It has been nearly 15 years since HAART was widely administered in advanced AIDS. Many benefits were well recognised and appreciated. However, there were reports of TE relapse after discontinuation of maintenance prophylaxis despite high CD4 count (Tsambiras et al,

2001; Ghosn et al, 2003). TE patients, from two large HIV centres in Germany, receiving HAART was studied regarding the restoration of *T. gondii*-specific immune response and IFN-γ as well as the longitudinal clinical characteristics/outcomes of TE (Hoffmann et al, 2007). Patients were grouped according to the date of TE diagnoses i.e. period 1, 1990-1993; period 2, 1994-1996; period 3, 1997-1999 considered as early HAART period and period 4, 2000-2004 as late HAART period (figure 2). The data from that study indicated several characteristics of TE that have changed since the availability of HAART such as a marked increase in 5-year survival rate as 7% in period 1 compared to 78% in period 3 ($p < 0.0001$). However, accumulative survival in the late HAART era was significantly lower than in the early HAART era (Figure 2). TE was found to be the first AIDS-defining illness more frequently than in earlier periods, therefore, patients who were co-infected with HIV and TE in HAART era did not receive antiretroviral therapy or any prophylaxis. More interestingly, persistent neurological deficits caused by TE such as hemiparesis, seizures, cognitive or other deficits were present in TE patients who survived during HAART higher than in pre HAART era (45% and 37%).

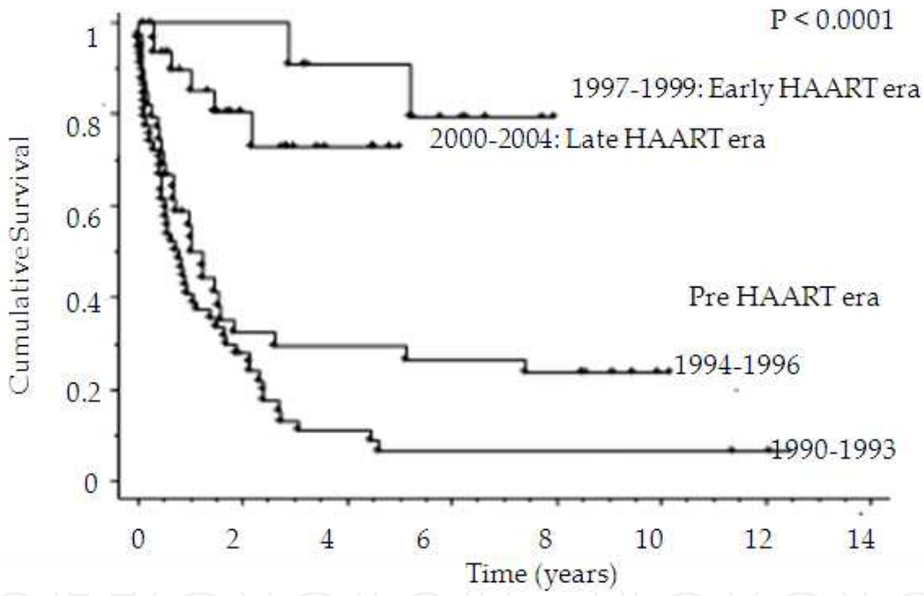

Fig. 2. Comparing cumulative survival of toxoplasmic encephalitis (TE) patients during pre-, early- and late-HAART eras (Hoffmann et al, 2007)

Hoffmann and colleagues found significant decrease in the *T. gondii*-specific immune response and IFN-γ (IL-12 and IL-15) in patients with acute episodes or relapses of TE more than in those who did not relapse even when maintenance therapy was discontinued. The latter was an adequate restoration group, while the former was a poor one in whom TE developed even on HAART and plasma HIV RNA level was below the detection limit for >6 months and their CD4 count were >200 cell/mm^3. There were evidences showing that functional immune restoration during HAART in advanced AIDS patients may be incomplete because quantitative increased CD4 count may not always reflect the quality of antigen-specific responses (Hoffmann et al, 2007; Furco et al, 2008). A multicentre study conducted by Spanish *Toxoplasma gondii* Study Group proposed whether *in vitro* lymphocyte

proliferative response (LPR) and IFN–γ production in response to *T. gondii* soluble antigen extract (SATg) could be used as a useful biomarker indicating immune restoration in AIDS patients receiving HAART. They found that severe immunosuppressed patients whose CD4 count <200 cells/mm^3 with experience in current or previous TE did not develop immune restoration indicated by almost absent of SATg-specific LPR and IFN-γ production. Those biomarkers were found in patients receiving successful HAART and in immnunocompetent asymptomatic patients who did not receive TE prophylaxis, however, they may be absent in HIV-1–uninfected and *T. gondii*-positive healthy subjects. Therefore, they cannot be used as biomarkers to detect the status of immune protection against *T. gondii* reactivation. Nevertheless, the discontinuation of TE prophylaxis, especially secondary prophylaxis, can be safely withdrawn after successful HAART as shown by CD4 count >200 cells/mm^3 and a sustained reduction in viral load (Lejeune et al, 2011).

3.3.1 Immune reconstitution inflammatory syndrome (IRIS)

The administration of HAART in HIV-infected patients restores protective immune responses against a wide variety of pathogens and dramatically decreases mortality. An immune restoration process occurs by the suppression of HIV-1 viral replication followed by an increasing CD4 count. In some patients, however, during the initial institution of HAART, the restoration process may be complicated by immune reconstitution inflammatory syndrome or IRIS leading to worsening of clinical, laboratory and/or radiological features. Its histology showed an intense inflammatory reaction against intact subclinical pathogens or residual antigens of opportunistic infections and non-infectious agents. It occurs either by disclosure of occult subclinical infection or enhanced inflammatory response to a treated infection. The former is named "unmasking IRIS" while the latter is called "paradoxical IRIS". About 10-25% of patients on HAART may develop IRIS, particularly in those patients with profound immune suppression, which may occur days to months after starting HAART, but normally within the first 2 months (Howard & Manji, 2009).

The common neurological IRIS had been reported in cryptococcosis, tuberculosis, and mycobacteriosis (Murdoch et al, 2007). Despite TE being the most common opportunistic neurologic disease in HIV-infected patients, neurological IRIS associated with cerebral toxoplasmosis was rarely reported and has been doubted regarding insufficient clinical details challenging the diagnosis of IRIS. In contrast, Subsai and colleagues showed that TE and other abnormalities such as stroke, progressive multifocal leukoencephalopathy (PML), and cytomegalovirus (CMV) retinitis were among the commonest kinds of neurological IRIS in northern Thai AIDS patients (Subsai et al, 2006). Their findings were TE-IRIS accounting for 0.29 and 0.59 per 100 person-years in the first and second year follow-up, respectively. Moreover, they found the incidence rate of TE-IRIS lower than the previous incidence during pre-HAART era.

Sungkanuparpha and colleagues from 4 medical centres in Thailand reported one fatal case of toxoplasmosis after initial HAART institution in HIV-infected patient with very low median (range) CD4 count as 9 (0–147) cells/mm^3. In their study, 20% developed unmasking OIs and tuberculosis was the most common followed by cryptococcal meningitis. They thus proposed that immune reconstitution response to occult pathogens may explain those phenomena (Sungkanuparpha et al, 2002). Researchers from Toulouse University, France reported 9 unmasking TE-IRIS cases; 3 out of 65 TE cases from their institution with a study period of 9 years and the 6 remaining cases from published

documents (Martin-Blondel et al, 2010). Their findings with other suggestion (Shelburbe et al, 2006) were proposed as a definition of unmasking TE-IRIS as 1) absence of neurological features related to TE in patients before starting HAART but presented afterwards; 2) at the onset of TE-IRIS, patients' CD4 counts were higher than when starting HAART and their viral load were decreased > 1 $\log_{10}$; 3) histological features showed a profound inflammatory response with predominantly CD8 lymphocytes and 4) symptoms and signs were not due to other newly acquired infections, the expected TE course or drug toxicity.

Paradoxical TE-IRIS cases, in which an exacerbation of a past known and usually treated TE occurred, were also reported (Pfeffer et al, 2009; Tremont-Lukats et al, 2009; Cabral et al, 2010). Two HIV-infected known cases, without antiretroviral treatment, developed TE when their CD4 count was low. They thus received specific TE treatment and HAART and their immune status was restored as indicated by lowering of viral load and increased CD4 count. One and 3 months later, they presented with deterioration of clinical signs and symptoms related to TE. Imaging studies showed significant increase in size and stronger enhancement of the lesions as well as appearance of new nodular areas. Pathological study found an intense perivascular inflammatory infiltration, predominated by CD8 lymphocytes. One case (Pfeffer et al, 2009) showed both stages of cysts containing *Toxoplasma* bradyzoites and few tachyzoites, but negative in another (Cabral et al, 2010). Tremont-Lukats and colleagues (2009) reported a case of paradoxical TE, but was argued by another group (Martin-Blondel et al, 2009) because of finding abundant tachyzoites on brain biopsy, which is an active viable form of *T. gondii*, but not bradyzoite. Also, there was no evidence of an immune response of the affected tissues, so they suggested that the case might be due to an unfavourable course of a previously diagnosed toxoplasmosis than a TE-IRIS.

Despite toxoplasmosis-associated IRIS being a very rare phenomenon, nevertheless, it occurs. Low metabolism of intracellular *Toxoplasma* bradyzoites with less expression of immunogenic surface proteins hides it from the host's immunity, immune reconstitution during HAART is thus attenuated. The patients at highest risk are those with low CD4 count, HAART-naïve, of young age and starting HAART close to a recent diagnosis of opportunistic infections (Shelburne et al, 2006). If TE-IRIS is suspected, close observation is recommended within 2 weeks. The use of magnetic resonance imaging in association with clinical and laboratory data can reduce the number of unnecessary cerebral biopsies (Cabral et al, 2010). A high steroid dose to control IRIS (Venkataramana et al, 2006), uninterrupted HAART, and ongoing treatment for toxoplasmosis could resolve the problem.

4. Clinical features

Toxoplasmic encephalitis (TE) is the most common cause of focal brain lesion (FBL) in HIV/AIDS individuals with profound immune deficiency. Clinical presentations of TE depended on the location, number and size of the lesions. It may present with generalized cerebral dysfunction or focal signs and symptoms of the central nervous system (CNS) or with psychiatric abnormalities (Table 3). The majority of patients present with a combination of generalized and focal CNS abnormalities (Table 1) such as headache, fever, alteration of consciousness, confusion, cognitive impairment, hemiparesis, facial nerve palsy and convulsion (Berger et al, 1987; Ragnaud et al, 1993; Wainstein et al, 1993, Sukthana et al, 2000; Anrinori et al, 2004; Nissapatorn et al, 2004b; Chankrachang, 2004; Miro et al; 2006; Hoffmann et al, 2007; Ho et al, 2008). Headache was a more frequent symptom than fever ranging from 47% to 100%, while fever was found 45.6% to 64.5%. However, Ragnaud and

colleagues (1993) demonstrated that fever was more sensitive than headache when used as diagnostic criteria (92% v. s. 41%sensitivity).

TE has an insidious onset presenting initially by non-focal features such as headache, lethargy, cognitive impairment or confusion followed by focal neurological deficits which develop over a period of days to weeks (up to 4-6 weeks). The common focal neurological deficits are hemiparesis, ataxia and cranial nerve palsies (Mariuz & Steigbigel, 2001; Chankrachang, 2004). Convulsion was found to be the initial manifestations in 14%-39% of TE cases (Nissapatorn et al, 2004b; Chankrachang, 2004).

Neurological manifestations	**Clinical presentations**
Generalized CNS dysfunction	Alteration of consciousness
	Confusion
	Coma
	Cognitive impairment
	Stiffness of neck
	Headache
	Fever
Focal neurological deficits	Hemiparesis, hemiplegia
	Convulsion
	Cranial nerves deficit
	Dysphasia, Aphasia, Dysarthria
	Hemisensory deficit
	Papilledema
Psychiatric abnormalities	Dementia
	Anxiety
	Psychosis
	Personality changes

Table 3. Neurological manifestations and clinical presentations of toxoplasmic encephalitis

Neuropsychiatric abnormalities occasionally dominate the clinical picture (Mariuz & Steigbigel, 2001). Thus the diagnosis will be missed if those were not borne in mind. Meningeal involvement is rare, so that meningeal irritation is unusual on physical examination. However, nearly half of Thai TE patients had positive neck stiffness (Chankrachang, 2004; Mootsikapun et al, 2004). Diffuse form, without focal deficit, of TE showed rapidly progressive generalized cerebral dysfunction which was usually fatal. In such cases, histological study revealed numerous diffuse microglial nodules with *T. gondii* tachyzoites and cysts, hence brain CT scans were negative (Mariuz & Steigbigel, 2001).

Toxoplasmosis of the spinal cord is a rare manifestation and is usually associated with multiple lesions in the brain. Sites of involvement include the cervical, thoracic and lumbar spine. Few cases did not have brain lesions showing myelitis and myelopathic symptoms including a sensory level deficit, paraparesis, incontinence and changes in the deep tendon reflexes (Vyas, & Ebright, 1996; Kung et al, 2011). Kung and colleagues (2011) reported the first case of toxoplasmosis with myelitis in the absence of encephalitis and the diagnosis can be made pre-mortem by muscle biopsy showing multiple *Toxoplasma* bradyzoites and tachyzoites. Ajzenberg et al (2009) found a significantly higher TE occurrence in patients with AIDS than in patients whose immunosuppression was due to other causes than HIV infection (75% v.s. 27,8%). Patients with TE had a better outcome than those whose infection was non-cerebral, whereas pulmonary involvement was more frequently associated with death.

5. Diagnosis

There are no obvious or non-specific clinical manifestations of toxoplasmosis in competent hosts which are unique to the disease. Most of the time, infections are overlooked. Thus, it is not straightforward to diagnose. Serological testing in such patient is the main identifying evidence of specific antibody. In TE reactivation, clinical features are more helpful than serological testing in term of diagnostic criteria.

Centre for Disease Control and Prevention (CDC), the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America recommend that making a definitive diagnosis of TE requires 1) compatible clinical features; 2) single or multiple mass lesions by computerized tomography (CT), magnetic resonance imaging (MRI), or other radiographic testing; and 3) the most important is detection of the organism in a clinical sample. This requires a brain biopsy performed by a stereotactic CT-guided needle biopsy. Organisms are demonstrable with hematoxylin and eosin stains and immunohistochemistry staining by experienced laboratories might increase sensitivity (CDC 2009). However, these are always impracticable due to patients' conditions. For clinically suspected TE cases, CDC criteria should be applied for a presumptive diagnosis i.e. 1) the recent onset of a focal neurological abnormality that is consistent with intracranial disease or reduced consciousness; 2) evidence from brain imaging of a lesion with mass effect and ring enhanced appearance after injection of a contrast medium; and 3) positive serum antibody to *T. gondii* or successful response to anti-toxoplasmic treatment (Sukthana, 2006). By using these presumptive diagnostic criteria, the positive predictive value is achievable in approximately 80% (Cohn et al, 1989; Katlama, 1992; Luft et al, 1993).

On brain imaging, most of TE lesions occur in the basal ganglia, thalamus and corticomedullary junction (Lee et al, 2009). MRI is more sensitive than CT, Weenink and colleagues reported a TE patient who showed a normal contrast-enhanced CT scan, but MRI revealed clear abnormalities in the basal ganglia (Weenink et al, 2009). TE usually appears as multiple nodular or ring enhanced lesions with edema and mass effect. However, 14% of cases showing a solitary lesion which need to be differentiated from CNS lymphoma that more commonly presented as a single mass than toxoplasmosis (Legrand et al, 2010). Several techniques such as a diffusion weighted imaging; single-photon emission CT (SPECT) and positron-emission tomography (PET) could provide a more precise diagnosis (Sukthana, 2006; Legrand et al, 2010). Weighted MRI shows a peripheral hyperintensity of

TE mass lesion that is a feature helping to distinguish it from lymphoma. In comparison with TE and other infections, lymphoma displays high thallium uptake on SPET image. The rate of detection will be as high as 100% sensitivity and 89% specificity when the lesion is larger than 2 cm; otherwise it drops significantly if the lesion is smaller than 2 cm. PET imaging need more studies to determine its effectiveness (Lee et al, 2009). Among those techniques, none has high specificity and they are only useful when used in combination (Legrand et al, 2010). Moreover, they are costly and not widely available especially in resource-poor settings (Sukthana, 2006).

Routine laboratory tests of the cerebrospinal fluid (CSF) are not helpful for TE diagnosis because they are usually normal or non-specifically altered. Increased protein level could be seen in about 65% of patients, low glucose level in 8-52% and pleocytosis, predominantly mononuclear cells, in 27-40% (Collazos, 2003). Intrathecal level of *T. gondii* antibody is always low and of limited value for diagnosis because its sensitivity and specificity is about 60-70% (Collazos, 2003; Sukthana, 2006). Parasitic isolation from CSF is very rarely successful. Tachyzoites were seen in only 2 out of 6,090 examined ventricular CSF specimens and only 5 cases existed in the literature where a direct identification of *T. gondii* was possible by cytologic examination (Palm et al, 2008), however, those researchers reported a tachyzoites and bradyzoites of *T. gondii* directly seen in lumbar CSF cytology.

Most patients with TE have an evidence of past infection showing a low titre of *T. gondii* antibody, but it helps the diagnosis. The absence of the antibody thus argues against TE diagnosis (Collazos, 2003; Sukthana, 2006). Nevertheless, it is not impossible since 3-5% of patients with TE have negative serological finding (Collazos, 2003). DNA-amplification-based techniques greatly contribute to the diagnostic improvement. Blood PCR as a single test is not sensitive. CSF PCR produced disappointing results with low sensitivity (50%), although specificity is high (96%-100%) and the results usually are negative once specific anti-toxoplasmic therapy has been started (Collazos, 2003; Sukthana, 2006; CDC, 2009). Repeated testing and combining both CSF and blood PCR enhance sensitivity. Tachyzoite-bradyzoite stage-specific primers could provide a more precise diagnosis of reactivated toxoplasmic encephalitis, especially in recurrent cases (Contini et al, 2002; Cultrera et al, 2002; Mahittikorn et al, 2010). Sukthana used duplex reverse transcriptase PCR (RT-PCR) technique containing tachyzoite (SAG1) and bradyzoite (BAG1) specific genes developed by our colleagues (Mahittikorn et al, 2010) to diagnose Thai TE cases. It was found that RT-PCR technique is simple, easy to perform, and provides 85% positive predictive value when compared with CDC diagnostic criteria (to be published).

6. Treatment

The standard treatment of toxoplasmic encephalitis is a combination of pyrimethamine and sulfadiazine (PY+S). They provide synergistic action, pyrimethamine being an inhibitor of dihydrofolate reductase while sulfadiazine inhibiting dihydrofolic acid synthetase, an enzyme involved in folic acid metabolism. Dose-related bone marrow suppression, thrombocytopaenia and anemia by this combination could occur. Hence, oral folinic acid (leucovorin) is routinely given to prevent those effects without inhibiting the action of pyrimethamine (Petersen & Liesenfeld, 2007). Dose, duration and adverse effects of those drugs are shown in table 4. Serum levels of pyrimethamine on a dose of 25-75 mg/day ranging from 1 to 4.5 mg/l and its CSF level is 10-25% of the serum level. Sulfadiazine is well absorbed with good penetration into CSF (Petersen & Liesenfeld, 2007).

Treatment with PY+S has some limitations including 1) poor compliance due to side effects, particularly sulfadiazine; 2) the large number of pills needed; 3) unavailability in some countries; 4) high cost and 5) lack of an intravenous form. Nearly half of treated patients develop adverse effects such as gastrointestinal upset or rashes (Table 4) and require a change of therapy. Clindamycin is an alternative drug in the case of intolerance to sulfa-compounds. A 600 mg every 6 hours for 3-6 weeks by oral or intravenous route is recommended (Mariuz & Steigbigel, 2001; Sukthana, 2006; Dedicoat & Livesley, 2008). The efficacy and adverse effects of the combination between pyrimethamine and clindamycin (PY+C) seem to be comparable with pyrimethamine and sulfadiazine (PY+S) combination (Table 5). However, when using PY+C as a maintenance regimen, the relapse rate was twice higher (P = .02) than those who received PY+S (Katlama et al, 1996). Diarrheoa was more frequent on PY+C, while skin rash and fever were more commonly encountered in the PY+S group. More drug discontinuation occurred in the PY+S than in PY+C group (11 vs. 30%, p=.001). Therefore, Katlama et al (1996) suggested that a combination of pyrimethamine and clindamycin is a good alternative for acute treatment but is less effective for long-term prevention of the relapses.

Drug	Dosing/duration of treatment	Adverse effects
Pyrimethamine	100 mg orally twice for 1 day, (loading dose) then 50-75 mg orally daily for 3-6 weeks	Gastro-intestinal (GI) upset Rash Cytopaenias
Sulfadiazine	100 mg/kg (4-8 gm in four divided doses) orally daily for 3-6 weeks	GI upset Rash (including Stevens-Johnson syndrome) Cytopaenias Interstitial nephritis Crystalluria Encephalopathy
Or Clindamycin	600 mg every 6 hours for 3-6 weeks, orally or IV use	GI upset Rash Diarrheoa Pseudomembranous colitis
Folinic acid	10-20 mg orally daily for 3-6 weeks	

Table 4. Recommended dose, duration and adverse effects of the standard and alternative drug regimens for toxoplasmic encephalitis (Modified from Mariuz & Steigbigel, 2001).

Cotrimoxazole or trimethoprim-sulfamethoxazole (TMP-SMZ) is another regimen that has been studied and recommended as an alternative treatment in particular areas that pyrimethamine and sulfadiazine are not available especially in developing world (Torr et al, 1998; Béraud et al, 2009). Its efficacy was as high as 70-85.5%, while the mortality rate was low (Table 5). TE relapse occurrence was around one-third of the patients and successfully re-treated by TMP-SMZ. Rash and neutropaenia were the most common side effects which occurred in 12-13.8% of patients but only half required treatment discontinuation. With its low cost, availability in parenteral form with excellent diffusion into the CNS and wide availability in developing countries, TMP-SMZ thus could be the first-line drug regimen for

curative treatment and prophylaxis of TE, especially in resource-poor settings (Torr et al, 1998; Dedicoat & Livesley, 2008; Béraud et al, 2009).

Atovaquone was studied as salvage therapy in AIDS patients with TE who were intolerant or failed PY+S or PY+C therapy (Torres et al, 1997). With a dose of 750 mg four times daily, 52% and 37% of patients were clinically and radiologically improved during the acute-therapy phase (the first 6 weeks), respectively, while 26% and 15% remained clinically or radiologically improved by week 18. Few patients' adverse effects that were associated with and resulted in discontinuation of atovaquone were severe rash, fever, hepatomegaly, and toxic epidermal necrolysis. Commonly reported adverse events that did not result in discontinuation of therapy were fever, headache, diarrhea, nausea, and rash.

Outcome		**Drug Regimen [Reference]**			
		PY+C [Mariuz & Steigbigel, 2001]	PY+C vs. PY+ S [Dedicoat & Livesley, 2008]	TMP-SMZ vs. PY+ S [Dedicoat & Livesley, 2008]	TMP-SMZ [Bérau et al, 2009]
Mortality rate		6-20% during the first 3 wk	19% vs. 6% (RR 3.17,95% CI 0.67-15.06)	0% vs. 0%	3.2%
Complete response	clinical response	18-55%	46.2%vs. 48.5% (RR 0.95,95% CI 0.55-1.64)*	70% vs. 70% (RR 1.0, 95% CI 0.74-1.33)*	85.5%
	neurological response	71% by day 7 and 91% by day 14			ND
	radiological response	25%	72-73% vs. 61 - 80%	68% vs. 62%	ND
Partial response		68-95%	-	-	TE relapsed in 30% of patients
Not response		5-12%	ND	ND	7.4%
Adverse effect		40%	60-62% vs. 58-60%	12% vs. 22%	13.8% (only 7.4% required treatment interruption)

Table 5. Outcome of TE cases after receiving different drug regimens therapy. *including complete or partial response defined as a resolution of TE or a greater than 50% improvement in the graded neurological examination. C = clindamycin; ND = no data; PY = pyrimethamine; S = sulfadiazine; TMP-SMZ = trimethoprim-sulfamethoxazole; vs. = versus; wk = week(s).

6.1 Clinical response and outcome

A complete response to standard therapy includes absence of neurological sequelae expected within 10-14 days. Luft and colleagues found that 50%, 86% and over 90% of

patients had a clinical response after 5, 7 and 14 days of treatment (Luft et al, 1993). Seizures and headache could not be used to assess the clinical response to therapy. Complete radiological response was defined as disappearance of all initial lesions and the absence of any new lesion. Those who showed clinical response, neuroradiographic abnormalities were also improved within 2-6 weeks in 91% (Mariuz & Steigbigel, 2001). Since patients may have more than one complication, follow-up brain imaging was recommended 10-14 days after starting therapy in each case (Chang et al, 1995). Brain biopsy should be considered in patients who clinically deteriorated after 3 days of treatment or showed no clinical improvement after 10-14 days of therapy. Treatment failure occurs if there is progression of either relevant symptoms and signs or new abnormalities developed within the first 10 days. Many patients died or still had neurological dysfunctions despite receiving standard or alternative therapy as well as developing adverse effects (Table 5).

6.2 Maintenance (secondary) and primary prophylaxis

Life-long maintenance/secondary prophylaxis, after acute-therapeutic phase, using half the dose of therapeutic drugs to prevent TE recurrence is necessary because the available drugs are ineffective against the tissue cyst that could later be reactivated (Sukthana, 2006). The use of highly active antiretroviral therapy (HAART) suppresses the HIV viral load and improves the CD4 count, followed by a strong reduction of opportunistic infections, including TE. It has been confirmed in randomized, controlled clinical trials that maintenance/secondary prophylaxis could be safely discontinued after HAART administration and immune restoration successfully occurred. Table 2 and sections 3.3 entitled 'TE during HAART period' provide more details.

HIV-infected patients with CD4 count <200 cell/mm^3 and positive *T. gondii* antibody is indicated to receive primary prophylaxis preventing toxoplasmosis reactivation. Drug regimens, outcomes and recommendation provided in Table 2 and section 3.2 entitled 'TE during prophylaxis regimen period'. Serological study identifying the past infection is prudent in HIV-infected individual, appropriate primary prophylaxis should thus be administered.

7. Preventive measures

Prevention of *Toxoplasma* infection comprise two important measures i.e. infected-meats and contamination by oocyst from cat excreta. HIV-infected persons with negative *T. gondii* antibody should be recommended to consume only well-cooked meats or those frozen for at least 24 hours. Properly cooked until the internal temperature is over 60°C, correctly smoked or cured in the brine are safe, but microwave cooking is not (Mariuz & Steigbigel, 2001). Noteworthy, increasing animal-friendly production systems might increase *T. gondii* prevalence if cooking practice is not proper. Chumpolbanchorn et al (2009) demonstrated 64.03% *T. gondii* antibody in Thai free-range chickens, while low prevalence (2.3%) was found in animal-friendly pig production systems in the Netherlands (Kijlstra et al, 2004).

Limiting exposure to cats, their litter and soil contamination with cat fecaes are things to be practised as well as avoiding infective oocysts by daily disposal cat litter and thorough hand washing, keeping cats indoor and feeding with canned or well-cooked food.

8. Conclusion

Toxoplasmic encephalitis is the most common cause of focal CNS infections in people with AIDS. Its incidence has been reduced after prophylaxis was widely advocated, but the dramatic reduction occurred since HAART introduction. Although HAART restores immune status and improves the quality of life, some patients were complicated by immune reconstitution inflammatory syndrome (IRIS) with clinical and radiological deterioration. However, TE-IRIS rarely occurs. Clinical features of TE comprise focal and generalized CNS dysfunctions or with psychiatric abnormalities. Its insidious onset and clinical presentations depend on the location, size and number of focal lesions, which is usually multiple. The majority of cases were diagnosed presumptively including clinical relevance to CNS abnormalities, suggestive brain imaging and serological showing past *T. gondii* infection or response to anti-toxoplasmic therapy. Standard treatment is a combination of pyrimethamine and sulfadiazine for 3-6 weeks followed by either life-long maintenance prophylaxis or HAART to prevent TE relapse. Despite the efficacy of currently available drug regimens, the mortality and adverse effects continue to be problems for the responsible physician. Primary prophylaxis should be given to HIV-infected persons whose CD4 count is <200 cell/mm^3 to prevent TE reactivation. HIV-infected individuals with negative *T. gondii* antibody should be instructed on preventing *Toxoplasma* transmission by avoiding either consuming infected meat or ingesting contaminated food and water by oocysts from cat excreta.

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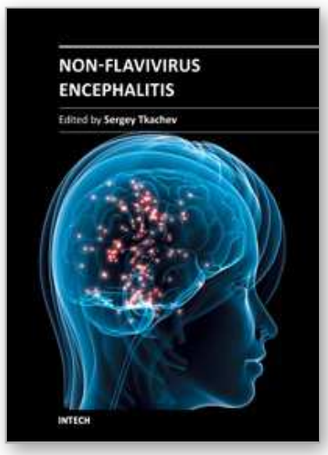

Non-Flavivirus Encephalitis
Edited by Dr. Sergey Tkachev

ISBN 978-953-307-720-8
Hard cover, 360 pages
Publisher InTech
Published online 16, November, 2011
Published in print edition November, 2011

This book covers the different aspects of non-flavivirus encephalitises of different ethiology. The first section of the book considers general problems of epidemiology such as study of zoonotic and animal vectors of encephalitis causative agents and methods and approaches for encephalitis zoonoses investigations. The members of different virus species are known to be the causative agents of encephalitis, so the second section of the book is devoted to these viral pathogens, their epidemiology, pathology, diagnostics and molecular mechanisms of encephalitis development by such viruses as HIV/SIV, herpes simplex virus type 1 and equine herpesvirus 9, measles virus, coronaviruses, alphaviruses and rabies virus. The next section of the book concerns the study of protozoan pathogens such as toxoplasma and amoebae. The last section of the book is devoted to multicellular pathogen as human Filaria Loa Loa - a filarial worm restricted to the West Africa.

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