IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME DURING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN ADVANCED HIV-INFECTED PATIENTS

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ABSTRACT

Background: The overall incidence of immune reconstitution inflammatory syndrome (IRIS) in antiretroviral therapy (ART) naïve patients has been scarcely reported in Thailand, especially in adults.

Patients and Methods: This retrospective cohort study was conducted in Chonburi Hospital, Thailand. The medical records of 174 ART-naïve HIV-infected patients, who started highly active antiretroviral therapy (HAART) between December 2004 and December 2005, were reviewed to determine the incidence, timing, risk factors and outcomes of IRIS.

Results: 11 of 174 patients whose median CD4 count was as low as 37 cells/mm^3, developed IRIS; the incidence of IRIS was 6.3% (4.21/100 patient-years HAART). Six mild post-HAART herpes zoster episodes were excluded. Most IRIS cases were TB or TB/NTM related (81.8%), primarily presenting as newly emerging or worsening pulmonary or LN (cervical, intra-abdominal) TB (89%). Skin TB (44%) and brain tuberculoma (11%) were also diagnosed. One case each of IRIS associated with CMV retinitis and cryptococcal meningitis were observed.

The median time between starting HAART and onset of IRIS was 22 (range 14-231) days.

Patients with IRIS were more likely to be younger ($p=0.022$) with a median age of 29 (range 23-68) years. Gender, baseline CD4 count and its increase, ART regimen and previous history of OI were not related to development of IRIS. IRIS was not associated with the outcomes of 1 year-ART except for an increase in the median number of admissions ($p<0.001$). All patients with IRIS were successfully managed by OI treatment. Steroids were used with 3 patients.

In case of TB, ART was initiated at a median duration of 5.8 (range 1-24) months after starting anti-TB treatment and 31% of patients developed new infections during the delay in ART initiation.

Conclusion: This study detected a relatively low incidence of IRIS in advanced HIV-infected patients. This might be due to the strategy of deferring ART while OIs are active. On the other hand, a few patients experienced new OIs while deferring ART. Physicians should not delay HAART once patients are stabilized.

KEY WORDS: IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME/ HIV/ HAART/ INCIDENCE/ TB/ THAILAND
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LIST OF ABBREVIATIONS

Abbreviation or symbol	Term
ADI	AIDS defining illness
AFB	Acid-fast bacillus
AIDS	Acquired immunodeficiency syndrome
Alb	Albumin
ALT	Alanine Aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Asparate transaminase
AZT	Zidovudine
BMI	Body Mass Index
BW	Body Weight
CD	Cluster of differentiation
CDC	Center for Disease Control and Prevention
CM	Cryptococcal meningitis
CMV	Cytomegalovirus
CMVR	Cytomegalovirus retinopathy
CSF	Cerebrospinal fluid
DTH	Delayed-type hypersensitivity
d4T	Stavudine
EB	Ethambutol
EFV	Efavirenz
GPO	Government Pharmaceutical Organization
HAART	Highly active antiretroviral therapy
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHV	Human herpesvirus
HIV	Human immunodeficiency virus

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LIST OF ABBREVIATIONS (cont.)

HREZ	Isoniazid+Rifampicin+Ethambutol+Pyrazinamide
HSV	Herpes simplex virus
HZ	Herpes zoster
IDV	Indinavir
IDV/r	Indinavir/ritnavir
IGT	Impaired glucose tolerance
INH	Isoniazid
IRIS	Immune reconstitution inflammatory syndrome
IVDU	Intravenous drug user
LN	lymph node
MAC	*Mycobacterium avium* complex
MTB	*Mycobacterium tuberculosis*
NIAID	National Institute of Allergy and Infectious Disease
NNRTI	Non nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSAID	Non steroidal anti-inflammatory drug
NTM	Nontuberculous mycobacterium
N/V	Nausea/vomiting
NVP	Nevirapine
OI	Opportunistic infection
PGL	Persistent generalized lymphadenopathy
PML	Progressive multifocal leukoencephalopathy
PI	Protease inhibitor
PS	Performance status
pVL	Plasma viral load
RFP	Rifampicin
TB	Tuberculosis
TMP/SMX	Trimethoprim/Sulfamethoxazole
3TC	Lamivudine
USA	United States of America

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CHAPTER I

INTRODUCTION

HAART has been widely used for the treatment of HIV-infected patients, and dramatically decreased mortality by restoring protective immune responses against a wide variety of pathogens. In the mid-1990s, clinicians noticed that certain patients deteriorated after starting HAART despite having favorable responses such as decreasing HIV-1 RNA levels and rising CD4 cell counts. In these patients, receipt of HAART result in a pathological inflammatory response to either previously treated infections or sub-clinical infections. This inflammation could result in deteriorating clinical outcomes, such as necrotizing lymphadenitis or culture-negative meningitis. It has been labeled as immune reconstitution disease (IRD) or immune reconstitution inflammatory syndrome (IRIS). Sarcoidosis and autoimmune diseases also have been reported during immune recovery after HAART initiation, although less common.

In Thailand, HIV-infected patients often present late with advanced AIDS and major opportunistic infections (OIs). The incidence of OI-associated IRIS is high in advanced HIV-infected patients with low CD4 cell counts and concurrent OI, especially tuberculosis. Previous case reports and retrospective studies of IRIS have offered information about its incidence, clinical features, outcomes, and probable risk factors, although sometimes there are discrepancies between studies that could be due to different patient backgrounds or different definitions of IRIS. Although range of 3 to 25% incidence of IRIS was reported in children and in patients with concurrent OIs, there has been limited data regarding overall IRIS incidence especially in adults.

For better patient management, it is important to make a diagnosis of IRIS as accurately as possible and to understand its epidemiology and characteristics in different situations. Therefore we would like to determine the incidence of IRIS among ART-naïve, HIV-infected adult patients in Chonburi Regional Hospital, Thailand.

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CHAPTER II

REVIEW OF LITERATURE

2.1 Definition of IRIS

It has been challenging to develop a clinically useful definition because of the wide variety of presentations of IRIS, but several attempts have been made to diagnose IRIS systematically. The general concepts of proposed infectious IRIS diagnostic criteria include 1) presence of distinct inflammatory reaction against external antigen during immune restoration, 2) atypical clinical course that is not consistent with re- or newly infected OI, or drug toxicity (Shelburne et al., 2005). It is possible to make a rational diagnosis of IRIS in many cases utilizing those criteria and supportive tests, but some cases remain difficult to distinguish from conditions such as newly acquired infections, especially in resource-limited settings.

Not only infectious IRIS but also sarcoid and autoimmune IRIS cases have been reported. Some authors defined IRIS as “a pathologic inflammatory response to preexisting microbial, host, or other antigens that results in clinical deterioration in HIV-infected persons after initiating HAART” (Lehloenya and Meintjes, 2006).

2.2 Incidence

It is estimated that 10-25% of patients who start HAART experience IRIS according to previous studies from the U.S., Australia and Europe. (Ratnam et al., 2006)

For patients with an underlying OI, reported incidence is higher than this, between 15 and 45%. A recent retrospective study in USA reported high incidence of IRIS (31.7% or 15.1/100 patient-years HAART) in patients co-infected with MTB, MAC or *Cryptococcus neoformans* (Shelburne et al., 2005).

In Thailand, overall incidence of IRIS in advanced HIV infected-children was reported as 25% (Sirisanthana et al 2004). Other reports were mainly for patients with underlying OI. Twenty-three percent of patients treated for cryptococcal

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meningitis developed OI during immune restoration associated with HAART, which is suggestive IRIS (Sungkanuparph et al., 2003). Meanwhile only 1 of 29 HIV patients (3%) with active MTB, experienced paradoxical worsening in a small study. (Sungkanuparph et al., 2006).

In a recent study, MTB associated IRIS was observed 13% of 167 HIV/TB co-infected patients (Manosuthi et al., 2006). The reported incidences of MTB-associated IRIS in Thailand tend to be lower than those of other studies. This may be explained by a strategy of deferred ART to reduce the possibility of adverse effects, genetic polymorphism, racial differences or nature of retrospective study.

2.3 Mechanism

Initial descriptions showed that activated memory cells account for the early incremental phase of CD4 cell recovery following effective HAART. Recovery of lost responses to specific antigens also occurs during this early phase, probably because of cellular redistribution rather than a *de novo* specific CD4 cell proliferation, as naïve activated CD4 cells do not recover for months to years after HAART. The nature and strength of this antigen-specific immune response may be responsible for the early-onset cases of IRIS. Alternatively, CD4 count increase has been removed from the AIDS Clinical Trials Group definition of IRIS, as cases of IRIS occurring prior to increase in CD4 and perhaps as a consequence of pVL reduction are common (Robertson et al., 2006).

Whether IRIS is the result of a response to a high antigen burden, an excessive response by the recovering immune system, exacerbated production of pro-inflammatory cytokines or a lack of immune regulation due to inability to produce regulatory cytokines remains to be determined. (Shelburne et al., 2005)

2.4 Clinical manifestation

The inflammatory response of IRIS results in a spectrum of presentations ranging from clinical worsening of a treated OI, atypical appearance of unrecognized OI, or sarcoid-like or autoimmune diseases. MTB, MAC, CMV and cryptococcus are the most important causes of IRIS. Most cases of IRIS occur in the first 3 months of HAART (Shelburne et al., 2006).

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2.4.1 Infectious IRIS

Mycobacterium IRIS

The fact that mycobacterial organisms and their cell wall components persist in host tissues for weeks after initiation of antimycobacterial treatment is probably an important factor contributing to the high frequency of IRIS developing in association with this group of organisms. (Lawn et al., 2005)

For MTB-associated IRIS, common presenting features are severe fever, intra-thoracic and cervical lymphadenopathy and worsening of pulmonary infiltrates. In a past study, 67% of MTB-IRIS patients had fever, 57% had lymph node enlargement and 38% had both. (Manosuthi et al., 2006) It presents within the first 2 months, usually in the first few weeks. Extra-thoracic diseases such as meningitis are less common. (French et al 2004) A recent report of cystic lung lesions as an IRIS phenomenon in HIV/TB highlights the difficulty in conclusively excluding the presence of another OI, in this case, possible *Pneumocystis jirovecii* infection. (Lipman et al., 2006)

The observation of atypical presentation of MAC disease in patients treated with AZT monotherapy was the first indication that restoring pathogen-specific immune responses can cause immunopathology (French et al., 1992). In MAC associated IRIS, disease tends to be localized rather than disseminated. Patients can develop huge, fistular lymphadenitis, cutaneous or muscular abscesses, osteomyelitis, nephritis or meningitis. Cutaneous DTH responses to mycobacterial antigens are characteristic. MAC-IRIS usually occurs during the first 3 months of HAART in patients with pre-therapy CD4 cell counts < 100/mm^3.

CMV IRIS

CMV retinitis may be seen either in patients with a prior history of CMV retinitis or in patients with no previous evidence of retinitis, while CMV vitritis and uveitis are seen exclusively in people with previous CMV retinitis who responded to ARV therapy (Surjushe et al., 2006). Inflammatory CMV retinitis with vitreitis is a form of IRIS that may lead to visual impairment. It can be described as a distinct syndrome, differing significantly from course of CMV retinitis seen in the pre-HAART era. Neovascularization endangers vision even after resolution. CMV uveitis

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as IRIS may occur within months of ART initiation, but typically is a late complication. It often results in macular edema, epiretinal membrane formation and/or cataracts, which can lead to permanent vision loss. Inflammatory CMV manifestations are not limited to the retina and may involve other organs.

Cryptococcal IRIS

Culture negative cryptococcal meningitis is occasionally a result of IRIS and is associated with increased intracranial pressure. There is low value for *C. neoformans* antigen in the CSF and elevated CSF WBC counts compared with typical cases of AIDS-associated cryptococcal meningitis (Shelburne et al., 2005). The MRI usually shows choriomeningitis with significant enhancement in the choroid plexus. As well as meningitis, lymphadenitis can occur.

Herpes virus IRIS

Mucocutaneous HSV disease may occur more frequently and be more severe in patients responding to HAART. Ratman et al (2006) were strict in their definition: "herpes simplex virus infection, recurrent disease was defined as an IRIS event only if there was documented evidence of a significant increased frequency, severity, or poor treatment response in the 6 months after initiation of HAART."

The occurrence or recurrence of herpes zoster in patients recently commencing HAART has been reported as IRIS in several articles. Although the clinical manifestations described have not been atypical or more inflammatory in nature, it has been suggested that immune reconstitution plays a role because herpes zoster occurs more commonly in the period after HAART initiation and there are reports of its occurring despite acyclovir prophylaxis (Lehloenya and Meintjes, 2006). However, Robertson et al (2006) excluded all cases of herpes zoster from consideration in their recent study of this syndrome.

Progressive multifocal leukoencephalopathy (PML) IRIS

Clinical symptoms are often more fluminant in initially than those of PML during the pre-HAART era, but patients usually have better prognosis.

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Other infection

Hepatitis B or C episodes also occur on HAART, particularly during the first weeks. HHV-8 associated Kaposi's sarcoma, and pre-existing skin disease can worsen on HAART (Hoffmann, 2005).

2.4.2 Sarcoid IRIS

Granulomatous inflammation of the lungs, which has the characteristics of sarcoidosis, has been described in patients responding to HAART. Granulomatous inflammation of other organs has also been described, including skin, kidneys, liver and duodenum. Sarcoid IRIS is associated with the intense CD4 T-cell alveolitis and a CD4 T-cell infiltrate in granulomas (French et al., 2004).

2.4.3 Autoimmune IRIS

Patients with systemic lupus erythematosus, polymyositis or rheumatoid arthritis usually present during the first few months therapy. Grave's disease is an uncommon but well-recognized complication of immune reconstitution in advanced HIV patients. It presents later than other autoimmune disease and probably has different pathogenic mechanism. (French et al 2004)

2.5 Risk Factors

Not a few things have been reported as risk factors of IRIS, which include male gender, ARV-naïve, close interval between OI diagnosis and HAART initiation, rapid decline in pVL and increase in CD4 count (Sheburne et al., 2005), younger age, low baseline CD4 cell count, low CD4/CD8 ratio (Ratnam et al., 2006), higher number of prior OIs, higher baseline CD8 cell counts, lower baseline ALT and Hb (Robertson et al., 2006), active or subclinical OI, disease susceptibility genes (French et al., 2004). In general, the poorer the immune status, the higher the danger of IRIS is.

2.6 Management

Many previous studies have shown, especially in mycobacterial and cryptococcal infections, that IRIS occurs more frequently if HAART is given early, in the presence of large quantities of antigen. This suggests that delaying HAART until

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the antigen load has been reduced by effective antimicrobial therapy will reduce the incidence of IRIS. The major guidelines recommend deferring HAART for 2 to 8 weeks in MTB co-infected patients with CD4 counts $\leqq 200/mm^3$ (A possible exception is CD4 counts $\leqq 50mm^3$). This strategy may be helpful to avoid IRIS, but the risk of other AIDS-defining illnesses may increase (Gillian et al., 2001, Dheka et al., 2004), even if HAART is delayed for a few weeks. Physicians face the dilemma of deferring HAART because of risk of IRIS or starting ART immediately to prevent further AIDS-related events, since the optimal time to commence HAART in co-infected patients with low CD4 cell counts remains to be established. A study of immediate versus deferred initiation of HAART for HIV-infected patients treated with TB with CD4 counts $\leqq 200/mm^3$, is now being conducted by National Institute of Allergy and Infectious Disease (NIAID).

Once IRIS has occurred, the first step is to exclude, as far as possible, drug toxicity, progressive disease due to poor compliance, viral resistance to ARV, malabsorption or inadequate blood drug levels due to drug-drug interactions.

The key features in the management of mycobacterial IRIS are: 1) appropriate deferral of HAART, 2) anti-mycobacterial therapy, and 3) anti-inflammatory therapy. In early herpes virus-associated IRIS, effective anti-herpes viral therapy appears to be important. Worsening of cerebral or mediastinal disease is likely to cause compression of vital structures should be treated with systemic corticosteroids. Palpable lymph node swelling can be treated corticosteroids and repeated needle aspiration (Lipman et al., 2006).

2.7 Prognosis

In most of cases IRIS may be mild and resolves without treatment. A current retrospective study has reported that there was no significant mortality difference between IRIS and non-IRIS advanced HIV patients after 24 months of HAART. (Shelburne et al., 2005)

Deaths, however, have been reported particularly in cases in which there is CNS involvement with progressive multifocal leukencephalopathy or infection with Cryptococcus species or *Mycobacterium tuberculosis*.

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CHAPTER III

OBJECTIVES

1. To determine the incidence of IRIS in HIV-infected patients who have newly initiated HAART at the Chonburi Regional Hospital in Thailand.
2. To determine risk factors for developing IRIS.
3. To determine clinical spectrum of IRIS.
4. To determine the estimated time to develop IRIS after HAART initiation.
5. To determine the outcome of IRIS.

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CHAPTER IV

MATERIALS AND METHODS

4.1 Study site and study design

This retrospective cohort study was carried out at the Chonburi Regional Hospital, which is located in 70 km southeast of Bangkok. Chonburi province has one of the highest rates of HIV infection in Thailand and the Chonburi Regional Hospital is a center providing HAART to more than 1000 HIV-infected patients in the area.

4.2 Population

All HIV-infected patients who started HAART between 1 December 2004 and 1 December 2005 were the target population.

INCLUSION CRITERIA

1) HIV-infected patients ≧ 15 year of age
2) ARV naïve patients who started HAART between 1 December 2004 and 1 December 2005
3) Patients had baseline measurement of the CD4 cell count and had at least one follow-up CD4 cell count after being prescribed HAART.

EXCLUSION CRITERIA

Patients who had never returned for follow-up after first prescription of HAART

4.3 Sample size

Previous studies in Thailand (Sirisanthana et al., 2004) showed that the incidence of IRIS among advanced HIV-infected children on HAART was about 25 %. Younger age was reported as a risk factor for developing IRIS. Our population (adults) was expected to have lower risk for IRIS than this. However we did not know

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how much the risk was, so we assumed that the incidence of IRIS in our population would be not more than 25%.

$n=z^2\times p\times(1-p)/d^2$

$n=1.96^2\times 0.25\times(1-0.25)/0.05^2$

$n=288$

Where, n=calculated sample size, z=1.96 (ά=0.05), p=expected incidence of IRIS, d= error allowance 5%

The estimated sample size of this study is 288.

4.4 Methodology

All available records of patients who met the inclusion criteria were reviewed from the time of diagnosis with HIV until the patient was lost to follow-up, or the end of study, 5 January 2007. Data on demographic characteristics, HIV status, concurrent and previous OI status were obtained in every patient to identify risk factors for IRIS. Interval between OI treatment and initiation of HAART, the rate of CD4 count increase were also analyzed as possible risk factors. Any clinical events after initiation of HAART were identified, and the diagnosis of IRIS was carefully made according to the IRIS diagnostic criteria, which was a modified version of the previously published definition (Shelburne et al, 2002).

In IRIS cases, the incidence, timing (interval between HAART and onset of IRIS), causative pathogen, clinical manifestation, treatment and outcomes were determined. We evaluated the outcomes after 12 months of HAART, including patient status, outcome of HAART in both IRIS and non-IRIS group.

4.5 Definition

HAART

HAART is defined as a combination of at least three drugs that typically includes either a protease inhibitor (PI) or a non-nucleoside-analogue reverse-transcriptase inhibitor (NNRTI) and two nucleoside-analogue reverse-transcriptase inhibitors (NRTIs). In Thailand, national ARV regimen includes GPO VIR S® and GPO VIR Z® which are generic fixed dose combination of Stavudine (d4T) or

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Zidovudine (AZT), Lamivudine (3TC) and Nevirapine (NVP) as first line regimens. In case of allergy and side effects, the combination of d4T (or AZT), 3TC and Efavirenz (EFV) or of d4T (or AZT), 3TC and Indinavir (IDV) /Ritonavir (RTV) is a choice of therapy.

OI co-infection

Confirmed MTB co-infection is defined by a positive culture of *M.tuberculosis.* Possible co-infection cases included those who had positive AFB smear, compatible clinical features, or empiric response to anti-TB treatment. In this study, disseminated TB was defined by one or more of following: (1) blood culture positive, (2) miliary infiltration in chest x-ray(±smear AFB positive) and favorable response to TB treatment, (3) 2 or more than 2 sites of involvement except lung(± smear AFB positive) and remission with TB treatment.

A presumptive diagnosis of NTM infection was made in an advanced patient with very low CD4 count (≦100/mm³), by clinical manifestations such as prolonged fever, weight loss, chronic diarrhea or hepatosplenomegaly. Definite diagnosis was obtained by blood culture.

Diagnosis of cryptococcosis was made by blood culture positive with *C. neofprman*, a positive *C. neoforman* antigen or a positive India ink test from the CSF.

IRIS

Previously published criteria for the diagnosis of IRIS (Shelburne et al., 2002) are as follows:

1) HIV-positive
2) Receiving HAART
   -Decrease in HIV-1 RNA level from baseline
   -Increased in CD4 cells from baseline (may lag HIV-1 RNA decrease)
3) Clinical symptoms consistent with inflammatory process
4) Clinical course not consistent with:
   -Expected course of previously diagnosed OI
   -Expected course of newly diagnosed OI
   -drug toxicity

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As a general concept, cases of IRIS need to have an inflammatory component occurring in the setting of immune reconstitution that cannot be explained by drug toxicity or newly acquired OI. In this study, diagnosis of IRIS was based on this concept and the modified criteria.

Modified diagnostic criteria of IRIS

(1) Evidence of immune restoration such as CD4 cell count increase or others

(2) Evidence of viral suppression which is reduction of plasma viral load

(3) Clinical improvement before worsening

(4) Inflammatory responses such as high fever, lymphadenitis, abscess and others

(5) Exclusion of alternative reasons

Definite IRIS: criterion (1) or (2) and all (3)-(5) are fulfilled

Probable IRIS: 1 or 2 criteria out of 5 are missed, but there is high suspicion of IRIS.

Possible IRIS: Only 1 or 2 criteria are fulfilled, but IRIS is clinically suspected.

The clinicians should describe the rationale in support of probable or possible IRIS diagnoses. If there is uncertainty in the diagnosis of IRIS, at least one HIV specialist's agreement is needed.

Laboratory data such as HIV-1 RNA level (viral load) are not always affordable for many patients in Chonburi Hospital, so we used increased CD4 cell count as supportive data. The check list was used to make a diagnosis of IRIS in case record form (Appendix A).

4.6 Statistical methods

Data was entered into a file using the Microsoft Excel and analyzed using Epi Info version 3.3.2. For numerical data with normal distributions, mean (SD) was used to summarize data, while median (range) was used for data that was not normally distributed. We used frequency (percentage) for categorical data.

The Mann-Whitney test was used for analysis of data (e.g., CD4 count, CD4%) that was not normally distributed. Categorical data were analyzed by using the chi-square test or Fisher exact test as appropriate.

A p-value of <0.05 was considered statistically significant.

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CHAPTER V

RESULTS

5.1 Demographics

In Chonburi regional hospital, more than 2,000 HIV-infected patients have been followed up in the anonymous clinic and internal medicine clinic. Only the medical records from the anonymous clinic were reviewed during the 2 months of data collection.

A total of 174 medical records which met the inclusion criteria were reviewed. Sixteen other records which might meet the criteria according to the ART start date, but we could not find those records including two dead cases. Ninety-two out of 174 patients (53%) were covered by a government program called “National Access to Antiretroviral Program for People living with HIV/AIDS (NAPHA)” from the time of HAART initiation. Others were supported by social insurance.

Baseline characteristics of the 174 cases are shown in Table 2. Median age of patients was 35.5 years old (range: 18-68), and 56.9% were male. Sexual contact and intravenous drug abuse were main mode of transmission in the known cases, 85.9% and 14.1%, respectively.

The mean baseline body weight and BMI were 52.6kg (SD: 9.3) and 19.7 (SD: 2.7) respectively. The median baseline CD4 count and CD4% were low, 37cells/mm^3 and 3%, but performance status(PS) scores in all patients at the time of ARV prescription were $\geqq$ 70, median score was 90 (Appendix B). This good PS for our patients could be explained by physicians’ policy that ART should be prescribed after stabilization of a patient. Most patients were started ART in the outpatient clinic after improvement or cure of any illnesses. Only 3 patients with CMV retinitis (2) or chronic oral ulcer (1) were prescribed ARV drugs during their hospitalizations.

Among 174 patients, 89.1% were categorized as CDC category A3 (5.2%), B3 (27.6%) or C3 (56.3%), implying that most patients had baseline CD4 counts less than 200 cells/mm^3. And 91.4% patients were defined as AIDS (A3, B3 and C1-3)

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before HAART initiation (Table 1). Baseline plasma viral load (pVL) was not performed in most cases except 3 patients, and baseline CD8 was available in only 30 patients, of which the median was 738 cells/mm^3 (range: 50-2246).

Twenty-four out of 173 patients had history of drug allergy (not shown in the Table 2) before ART initiation. Sixteen (66.7%) experienced allergic reactions due to trimethoprim/sulfamethoxazole(TMP/SMX), including 1 Stevens-Johnson syndrome (SJS) and 1 toxic epidermal necrolysis (TEN) case. There were some allergic episodes, 7 from anti-TB drugs, 4 from sulfa drugs (not specified), 5 from other antibiotics.

Table 1. Baseline CDC category* (n=174)

CD4 count (cells/mm^3)	A Asymptomatic No. (%)	B Symptomatic No. (%)	C ADI** No. (%)	Total
1. >500	A1: 0 (0)	B1: 0 (0)	C1: 0 (0)	0 (0)
2. 200-499	A2: 8 (4.6)	B2: 7 (4)	C2: 4 (2.3)	19 (10.9)
3. <200	A3: 9 (5.2)	B3: 48 (27.6)	C3: 98 (56.3)	155 (89.1)
Total	17 (9.8)	55 (31.6)	102 (58.6)	174(100)

*CDC category (Appendix C), **ADI: AIDS defining illness

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Table2. Baseline characteristics of the 174 studied patients

Characteristics	***No. of cases (%)***	***Median (range)***
Age (year)		35.5 (18-68)
Gender Male	99(56.9)	
Female	75(43.1)	
Occupation		
Employee	123 (70.7)	
Government officer	6 (3.4)	
Merchant	23 (13.2)	
Unemployed	8 (4.6)	
Housewife	6 (3.4)	
Others (soldier, monk, farmer etc.)	8 (4.6)	
Chronic health problem (n=45)		
Drug abuse	16 (35.5)	
Hypertension	5 (11.1)	
Chronic hepatitis	4 (8.9)	
Alcoholism	4 (8.9)	
Diabetes Melitus	3 (6.7)	
Thalassemia	3 (6.7)	
Psychosis	2 (4.4))	
Asthma	2 (4.4)	
COPD	2 (4.4)	
Others	11 (24.4))	
Mode of transmission (n=78)		
Sexual contact	67(85.9)	
Heterosexual	62 (79.5)	
Homosexual	4 (5.1)	
Bisexual	1 (1.3)	
IVDU	11 (14.1)	
HBV Ag+ (n=58)	6 (10.3)	
HCV Ab+ (n=38)	9 (23.9)	
Body weight (kg)		52.6 (9.3)*
BMI (n=173)		19.7 (2.7)*
Karnofsky PS		90 (70-100)
CD4 count (cells/mm^3)		37 (0-360)
CD4%		3 (0-28)

*mean (SD)

COPD: chronic obstructive pulmonary disease, IVDU: intra-venous drug user,

BMI: body mass index, PS: performance status

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5.2 Opportunistic infections (OIs)

5.2.1 Previous or concurrent OIs

In total, 136 patients (78.2%) had previous or concurrent opportunistic infections before starting HAART. The most common OIs were TB (44.9%), oral candidiasis (56.6%), PCP (29.4%) and herpes zoster infection (22.8%). (Table 3)

Table 3. Previous or concurrent opportunistic infections (n=136, 281 episodes)

Opportunistic infections (OIs)	*No. of cases (%)*
AIDS-defining infections	
Tuberculosis	61 (44.9)
Peumocystis pneumonia (PCP)	40 (29.4)
Cryptococcosis	12 (8.8)
Nontuberculous mycobacterium	10 (7.4)
Esophageal candidiasis	9 (6.6)
Cytomegalovirus retinitis	8 (5.9)
Salmonellosis	5 (3.7)
Histoplasmosis	3 (2.2)
Toxoplasmosis	2 (1.5)
Penicilliosis	1 (0.7)
Other OI	
Oral candidiasis	77 (56.6)
Herpes Zoster	31 (22.8)
Skin abscess	8 (5.9)
Herpes simplex	5 (3.7)
Vaginal candidiasis	3 (2.2)
pneumonia	4 (2.9)
GNB sepsis	1 (0.7)
Strongiloidiasis	1 (0.7)

GNB: gram negative bacillus

Tuberculosis

Sixty one patients had history of TB at the time of HAART initiation. Six of them were just recorded as relatively remote past histories or past TB without detailed information. Recent or concurrent TB was observed in 55 patients.

Majority of the patients had clinical diagnosis of TB except one culture-confirmed case. Twenty-six patients were diagnosed as TB from clinical presentation alone: prolonged fever, weight loss, lymphadenopathy and/or abnormal chest x-ray. Seven patients had biopsies from pleura, lymph node or appendix, from which

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pathologic findings were compatible with TB and were AFB positive. The sites of TB are shown in Table 4. Among 53 patients, 23(43.4%) patients had extrapulmonary TB, of which 8 (15.1%) cases were disseminated TB.

All 55 patients with active TB improved after anti-TB treatment, although 7 of them experienced relapses before starting ART due to poor compliance. Six patients had completed TB treatment and were supposed to reach presumptive cure before ART initiation. Two patients had incomplete treatment because they were lost to follow up after months of TB treatment. The other 47 patients were on TB drugs at the time of ART initiation.

Table 4. Site of TB (n=53)

Site of TB	***No. of cases (%)***
Pulmonary TB	30 (56.6)
Extrapulmonary TB	23 (43.4)
Pleura	2 (3.8)
Cervical LN	10 (18.9)
Abdominal LN	1 (1.9)
Appendix	1 (1.9)
Peritoneum	1 (1.9)
Disseminated	8 (15.1)

LN: lymph node

Nontuberculous mycobacterium (NTM)

Ten patients received NTM treatment before HAART initiation; 2 patients had blood culture proven; 8 patients had very low CD4 count with NTM suggestive symptoms (e.g. prolonged fever, weight loss, chronic diarrhea, hepatosplenomegaly with/without increased liver enzyme) and were empirically treated as NTM without microbiological evidences. Three of them received TB treatment concomitantly.

All patients were prescribed Clarithromycin and Ethambutol with the addition of Rifampicin, Isoniazid or Ofloxacin in 6 patients.

They were all on NTM treatment at the time of ART initiation.

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Pneumocystis pneumonia

Forty (29.4%) patients were diagnosed as PCP from clinical manifestations such as cough, dyspnea, low SaO_2 and chest x-ray findings. Of 35 patients whose treatment regimen records were available, 18 patients were treated by TMP/SMX or alternatives (Clindamycin+Prymaquine) with steroids, and 17 patients without steroids. One patient needed an intrathoracic catheter for the treatment of pneumothorax which was thought to be a complication of PCP.

Four cases relapsed, one of them was proved as PCP by bone marrow biopsy which was conducted as work-up for pancytopenia. All patients were cured after treatment.

Cryptococcosis

There were 12 patients diagnosed as cryptococcosis. Initial presentations of Cryptococcosis included meningitis (9), meningitis plus lymphadenopathy (1), disseminated disease without CNS involvement (skin 1, Coryptococcemia 1). They were treated by Amphotericin B intravenously or Fluconazole orally, and clinically improved. Among these 12 patients, 5 patients (41.7%) had a relapse of Cryptococcal meningitis after initial treatment. They received fluconazole suppression for prevention of further relapse.

CMV retinitis

All 8 patients were diagnosed by fundoscopic findings, and 6 of them were treated by intravenous ganciclovir, others were sent to other hospitals for treatment. Symptoms (blurred vision) of 2 patients did not improve after treatment.

Histoplasmosis

Three patients had Histoplasmosis by biopsy (bone marrow, hypopharynx), skin scraping, or blood culture. Patients were treated by amphotericin B and/or itraconazole, and impoved.

Esophageal candidiasis and other OIs

Among 9 cases of esophageal candidiasis, 4 patents were proved by gastroscopy. Oral candidiasis and herpes zoster were commonly seen, but most cases cured by anti-fungal drugs and acyclovir, respectively. In some patients, oral candidiasis recurred before initiation of ART because of low immunity.

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5.2.2 Duration between initiation of OI treatment and ART

The median duration between initiation of important OIs and ART are showed in Table 5.

Table 5. Duration between initiation of OI treatment and ART

Opportunistic infections	*Number of cases*	*Duration between initiation of OI treatment and ART(days) Median (range)*
Tuberculosis	54	174.5 (27-737)
NTM	10	98 (34-319)
Pneumocystis pneumonia	35	113 (21-594)
CMV retinitis	8	30.5 (0-78)
Cryprococcosis	12	91 (37-472)

The median duration between initiation of TB treatment and ART was 174.5 (range 27-737) days. In 50 out of 55 patients (91%), ART was prescribed more than 2 months after initiation of anti-TB treatment, primarily after completing 2 or more months of initial intensive TB regimen. For 6 patients, ART was started after they had totally completed 6-9 month-TB regimen.

During this interval without ART, 17 of 55 TB patients (all except one had ART deferred more than 2 months after anti-TB initiation), experienced 20 new episodes of other infections which included: PCP(1), Cryptococcus meningitis(2), CMV retinitis(3), Salmonella sepsis(1), pneumonia(1), Histoplasmosis(1), esophageal candidiasis(3), Strongyloidiasis(1), Herpes zoster(4), HSV(1), scabies(1), skin abscess (1). Visual disturbance remained in 2 patients even after CMV retinitis treatment. Timing of new infections after starting anti-TB (before ART initiation) is shown in Table 6. Severe AIDS defining infections appeared after 2 months. All CMVR cases were observed 5 months after of TB treatment without ART. Most patients who developed these subsequent infections had very low baseline CD4 count. Sixteen out of 17 patients were less than 100 cells/mm^3 and the median was 13 (range: 0-200) cells/mm^3. For 11 cases who developed AIDS defining illnesses, all had baseline CD4 count less than 50 cells/mm^3.

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Table 6. New infections prior to ART after starting TB treatment (n=20 episodes)

Duration from initiation of anti-TB	***New infections (No. of cases)***
1 month	Esophageal candidiasis (EC)* (2), Herpes Zoster(HZ) (1), HSV (1), PCP* (1)
2 months	Cryptococcal meningitis(CM)* (1)
3 months	EC* (1), HZ (2)
4 months	Histoplasmosis* (1), Strongyloidiasis (1), skin abscess (1)
5 months	CM* (1), CMV retinitis* (2), HZ (1)
>6 months	CMVR* (1), scabies (1), salmonella sepsis*(1), pneumonia (1)

*AIDS defining infections

5.3 Antiretroviral therapy

5.3.1 ART regimen

Initial HAART regimens for ART-naïve patients are listed in the Table 7. Boosted PI regimen (d4T, 3TC, IDV+RTV) was more frequently prescribed (42%) as a first ART regimen for patients with lower CD4 count.

EFV based regimen and NVP based regimen (GPOvir S: d4T, 3TC, NVP) were started in 57 patients (32.8%) and 44 patients (25.3%), respectively.

Changes of regimen were mainly due to side effects. Other reasons included cost, avoidance of side effects after HAART (e.g. lipodystrophy due to d4T). NVP was switched to EFV in case a patient needed simultaneous TB treatment including rifampicin.

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Table 7. Initial regimens of HAART (n=174)

ART regimen	**No. of cases (%)**	**CD4 count Median (range)**	**AIDS No.(%)**
NVP based GPOvir	44 (25.3)	124.5 (4-360)	34 (77.3)
EFV based	57 (32.7)	43 (0-288)	53 (92.9)
d4T, 3TC, EFV	42 (24.1)		
AZT, 3TC, EFV	13 (7.5)		
ddI, 3TC, EFV	2 (1.1)		
PI based d4T, 3TC, IDV/r	73 (42)	22 (3-235)	72 (98.6)

5.3.2 Adverse effects of ART

One-hundred and six patients (66.7%) experienced adverse effects from ART during their follow-up period [Median: 16 months (5 - 24 mo)].

Fifty one (32%) out of 159 patients who had been initially treated with d4T, developed lipodystrophy after about 11 months [median: 341 days (56 - 688)] of ART initiation. Of these 51 patients, 45 had changed the regimen from d4T to AZT because of this complication and 7 out of 45 patients had subsequently changed from AZT to ddI. Two patients were observed by d4T dose reduction only.

Hyperlipidemia was observed in 25 patients (14.4%), about 8 months after the prescription [median: 254days (28 - 565)]. Of these 25 patients, 16 patients had treatment changed from d4T or IDV/r to others. Some patients needed anti-lipid drugs to control their hyperlipidemia.

Gastrointestinal symptoms were observed in 30 patients (17.2%), including nausea/vomiting (18 cases), appetite loss (5 cases), diarrhea (3 cases) and dyspepsia (4 cases).

Skin rash was observed in 23 patients and mainly caused by NVP and EFV. One patient developed SJS due to NVP. One case developed skin rash due to EFV, and ART was interrupted for about 2 months. Seventeen out of 23 patients had regimen changed.

Fourteen patients out of 20 patients with neuropathy were considered to be due to d4T, and managed by d4T dosage reduction and/or regimen change.

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Hepatotoxicity was observed in 13 (7.5%) patients. ART was stopped temporally in one patient.

Seven patients developed anemia due to AZT. In the most severe case, hemoglobin (Hb) was 3.1 mg/dl and the patient had leukopenia simultaneously. Another patient had both anemia and leucopenia. Three patients, including these 2, needed packed red blood cells transfusions. All 7 patients had treatment changed from AZT to others.

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Table 8. Side effects of HAART (n=116)

Side effects	No. (%) of cases	Duration from causative ART initiation (days) Median (range)	Management ART change(No. of cases)
Lipodystrophy	52(44.8)	341(56-688)	d4T to others (49) d4T reduction (2) AZT to ddI (1)
Gastrointestinal		---	
Nausea/vomiting	18(15.5)		d4T, AZT, NVP, EFV, IDV/r to others
Appetite loss	5 (4.3)		
Diarrhea	3 (2.6)		
Dyspepsia	4 (3.4)		
Hyperlipidemia	25(21.6)	254(28-565)	d4T to AZT (9) IDV/r to NVP (6) IDV/r to EFV (1) EFV to NVP (1)
Skin rash	23(19.8)	28 (7-283)	NVP to others (10) EFV to others (5) d4T to AZT (1)
Neuropathy	20(17.2)	261 (174.1)*	d4T reduction (5) d4T to others (9)
Hepatotoxicity	13(11.2)	140 (14-315)	NVP to EFV (4) NVP reduction (1) IDV/r to EFV (1) ART interruption (1) Other (1)
Hematological			AZT to others (7)
Anemia	7 (6.0)	84 (56-173)	transfusion (PRC) (3)
Leukopenia	2 (1.7)	77 (70, 84)	
Dizziness	3 (2.6)	14 (9-41)	no change (EFV) (3)
Symptomatic hyper-lactemia	2 (1.7)	357(268, 446)	d4T to AZT (2)
Others			
DM	1 (0.9)	397	no change (metformin was started) (1)
Acute renal failure	1 (0.9)	21	IDV/r to EFV (1)
Ingrowing nail	1 (0.9)	335	IDV reduction (1)
Joint pain	1 (0.9)	---	d4T to AZT (1)
Myalgia	1 (0.9)	54	d4T to ddI (1)
Hair loss	1 (0.9)	84	no change (1)
Oral ulcer	1 (0.9)	14	NVP to IDV/r (1)

Note. PRC: Packed red blood cells

*mean (SD)

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5.4 IRIS

5.4.1 Opportunistic infections after HAART

After HAART initiation, 24 episodes of opportunistic infections were diagnosed in 22 patients during follow-up period (median 16 months). Eleven out of 24 episodes were considered IRIS. OIs after HAART are shown in Table 9.

There were 10 TB cases, 7 were considered TB IRIS, and 3 were related to their poor compliance of ART or to drug resistant of TB.

Among 3 cases of cryptococcal meningitis, two were excluded from IRIS diagnosis because they had poor compliance of ART and preventive therapy (fluconazole) or an insufficient previous cryptococcemia treatment.

There were first episodes of 2 HSV and 6 herpes zoster infections after HAART. All presented as localized skin lesions without fever and could not be distinguished from the ordinary patterns of herpes infections. In this study, all herpes infection cases were excluded from IRIS diagnosis because these episodes were fairly possible due to their residual immune deficiency after HAART. However, mild herpes zoster episodes after HAART have been reported as IRIS in several articles, characteristics of herpes zoster cases of present study are described in the last (5.4.4) for reference.

Table 9. Opportunistic infections after HAART (n=24 episodes)

Opportunistic infections	***No. (%)***
TB	10 (41.7)
MTB/NTM	2 (8.3)
Cryptococcosis	3 (12.5)
CMV retinitis	1 (4.2)
HSV (genital)	2 (8.3)
Herpes zoster	6 (25.0)

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5.4.2 Overview of IRIS cases

Eleven out of 174 patients developed IRIS, the incidence of IRIS was 6.3% (4.21/100 patients-years HAART) in this study.

Clinical characteristics of each IRIS case are shown in the Table 10. Only 1 patient was diagnosed as definite IRIS and 3 cases as probable IRIS according to the proposed diagnostic criteria in this study. Seven patients were suspected IRIS by HIV specialists from clinical presentation, but they met only one or two proposed criteria for IRIS. (Table 11)

Nine out of 11 IRIS cases were mycobacterium infection-related. There was 1 CMV-related IRIS and 1 cryptococcal meningitis related IRIS. Sarcoid or autoimmune IRIS was not observed during study period.

Five patients with TB IRIS had previous or concurrent TB. They presented as worsening or relapsing of TB symptoms; two cases of increasing pulmonary infiltrates, one case of intra-abdominal lymphadenopathy/abscess, one case of cervical lymphadenopathy, and new skin manifestations and brain tuberculoma were also observed. Two patients with TB IRIS and both patients with TB/NTM IRIS had new manifestations of disease, presented as new pulmonary infiltrations (2 cases), cervical lymphadenopathy (1 case), pleural effusion (1 case). Both CMV and CM IRIS cases experienced relapse of symptoms.

For the 11 patients who developed IRIS, the duration between the initiation of HAART and the onset of IRIS is shown in Fig. 1. The median time between starting HAART and onset of IRIS was 22 days, with the shortest time being 14 days and the longest 231 days.

All IRIS patients received OI treatment, 3 of them with steroids. NSAIDs were not used. Seven patients completed treatment and were considered presumptive cures. Three patients were still receiving MTB±NTM therapy at the time of data collection, and had no symptoms after starting treatment. One patient with brain tuberculoma improved after the operation and was still on anti-TB treatment. ART was not interrupted in any case.

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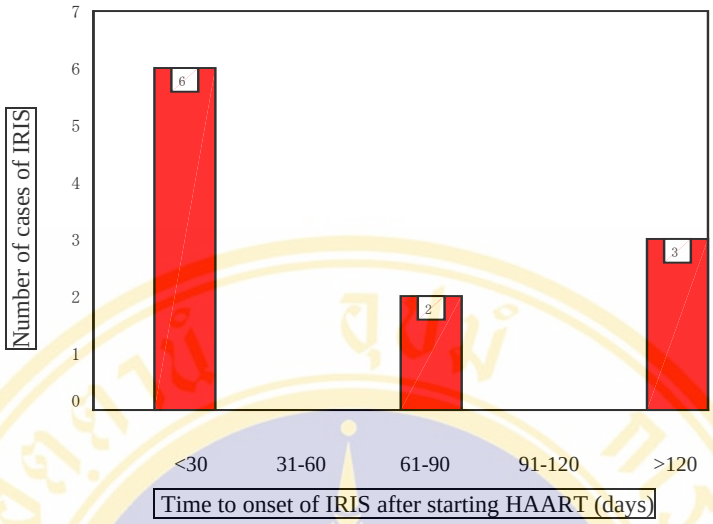

Fig. 1. Time to onset of IRIS after starting HAART (n=11)

5.4.3. Description of cases

TB related IRIS

Five out of 7 TB IRIS patients had recent or concurrent TB infections, which means that 5 (8.3%) of 61 patients who had TB history developed IRIS. Median time to develop MTB IRIS was 22 (range 14 - 231) days.

Definite case (case No.1 in table 10&11) was 25 year-old male who had history of amphetamine and intravenous drug abuse. Before starting HAART, he had a diagnosis of pulmonary TB (sputum AFB3+) and treated by IRZE for 4months and IRE for 1month. After 5 months (164 days) of TB treatment, his symptoms (dyspnea, weight loss) and chest x-ray finding improved. HAART (d4T, 3TC, IDV/r) was initiated. About 8 months later (still on INH and EB), he developed intermittent fever, cough, weight loss. Chest x-ray showed worsening of right lung infiltration, and TB treatment was intensified. Sputum culture was negative for MTB. After further 4 months, he complained headache, vertigo, nausea, vomiting, and contrast CT revealed a ring enhancing 4 cm mass at the left cerebellum. He was referred to another hospital for craniotomy and abscess removal. Twenty milliliters of pus were drained, and the patient was diagnosed as cerebellar tuberculoma with a positive TB-PCR. The culture was mycobacterium positive, pending for confirmation of MTB or NTM. His drug compliance was good, and CD4 count increased from 7(1%) to 91 (4%). pVL was less than 50 copies/ml at the time of IRIS development. CD4 count increased to 148(12%)

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just prior to the development of symptoms from the brain tuberculoma. His symptoms improved after the operation and TB treatment.

Case 2 is 26 year-old male who had previous pleural TB (pleural biopsy: AFB+) and was treated with IRZE for 2 months and IR for 4 or 5 months. After 4 - 5 months of TB treatment, he was lost to follow-up for about 5 months. When he returned to clinic, his chest x-ray was normal, but a physician added one month IR therapy and started HAART after finishing TB treatment. 5 months later, he complained weight loss, fever, dyspnea and the chest x-ray showed bilateral reticulonodular infiltration and right lower lobe infiltration. The serial sputum AFB was negative, but he developed left arm skin abscess. MTB was cultured from the pus. Anti-TB drugs were started, and he gained about 9 kg within 1 month. Other symptoms and x-ray findings also improved after treatment.

Case 3 is 28-year old female who had an acute abdomen and exploratory laparotomy one month before ART. It revealed an ilioceacal abscess and abdominal lymphadenopathy that was AFB positive. After one month of IRZE symptoms improved and HAART was added. After 18 days she developed fever, severe nausea, vomiting and abdominal pain. Abdominal ultrasonography showed splenic microabscesses and enlarged necrotic nodes in the peripancreatic region. From these findings, IRIS was suspected and same anti-TB regimen was continued. NSAIDs and steroids were not used in this patient. Two months after TB treatment was started, she had no complaints and abdominal ultrasound follow-up did not reveal significant abnormalities.

Case 4 had no AIDS defining illness before ART but had some episodes of skin infections such as impetigo. 2 weeks after the HAART initiation, this 31 year-old patient complained fever, cough, dyspnea and nausea, vomiting and chest x-ray showed new infiltration in perihilar left upper lobe. Sputum AFB was negative at that time, but ant-TB drugs were given empirically. 2 specimens of blood cultures grew *S. epidermidis* which was thought to be caused by skin infection, and intravenous antibiotics were also given for 2 weeks. Sputum AFB became positive after 2 months of TB treatment, but culture of the same sample was negative. Symptoms improved soon after the TB treatment, but x-ray findings took several months to improve in this case.

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Case 5 developed left cervical node swelling of 4 cm diameter after about 5 months of HAART. LN aspiration was done and culture grew RFP resistant MTB. She had a previous history of cervical lymphadenopathy (AFB+), and a relapse because of her poor compliance. After she complied with the 9 month-TB regimen, her symptoms resolved before starting HAART. The event after ART was suspected IRIS although it is impossible to exclude a relapse due to drug-resistant or insufficient previous TB treatment.

Case 6 is 42 year old female who developed massive left pleural effusion after about 2 months of HAART. Pleural effusion AFB was negative but biopsy of pleura was compatible with TB pleuritis. She received 9 months of anti-TB treatment and the manifestations resolved.

Case 7 was diagnosed as pulmonary TB from abnormal chest x-ray findings and symptoms. After 1.5 month of treatment, left upper lobe infiltration improved and HAART was prescribed. 22 days later, he developed left calf skin abscess which culture was negative for mycobacterium and bacteria, but AFB smear was positive. He received antibiotics for 10 days and anti-TB treatment was continued.

MTB/NTM related IRIS

Case 8 is 68 year old male who had no previous mycobacterium infection history. Soon after HAART initiation, he complained of dyspnea, cough, fever and skin rash (erythema nodosum). Chest x-ray showed bilateral upper lobe infiltration. Skin AFB was positive although sputum AFB was negative, he was treated as pulmonary TB and TB skin. Clarithromycin was added to cover NTM when x-ray showed worsening of right lung infiltration about 1 month anti-TB therapy.

Case 9 is 34 year old male who developed fever, weight loss, nausea and vomiting soon after HAART initiation. Because of his low baseline CD4 count and liver enzyme abnormality that might suggest infiltrative liver disease (increase of ALP), he was treated as TB/NTM infection with INH, RFP, EB, ofloxacin, clarithromycin. Two months further later, he developed right cervical node swelling of 3 cm diameter. The drainage from this LN was AFB positive, and improved by same regimen for total 8 months.

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CMV related IRIS

Case 10 had a previous history of bilateral CMV retinitis, and treated by intravenous ganciclovir for 1 month. After 2month of HAART, he complained right blurred vision, and fundoscopy revealed right active CMV retinitis with uveitis which was compatible with CMV IRIS. Ganciclovir and predonisolone were given, and his symptom improved.

CM related IRIS

Case 11 is 25-year old female who had previous disseminated cryptococcosis (blood culture positive, CSF India ink positive). Intravenous amphotericin B was given for 2 weeks followed by fluconazole 300mg for 10 weeks. HAART was started after clinical improvement, and the dose of fluconazole was changed to 200mg as suppression therapy. She developed low grade fever and headache 2 weeks later. The physician gave the patient predonisolone with suspicion of CM IRIS and also increased the dose of fluconazole to treating dose (400mg) in case of relapse and followed her up carefully. CSF was not evaluated at that time. Her symptoms soon improved.

5.4.4 Herpes zoster after HAART

During one year prior to ART initiation, there were at least 12 episodes of herpes zoster(HZ), and the episodes of HZ decreased to 6 after HAART (median follow-up period: 16 months) in this study.

All 5 patients did not have history of herpes zoster and not on acyclovir prophylaxis. They presented as uncomplicated dermatomal zoster and responded acyclovir therapy. The median age and baseline CD4 count was 37 (28-45) years old and 43 (3-65) cells/mm^3, respectively. Two patients developed HZ within 1 month after HAART initiation, the others had HZ after 4-12 months of ART. The median duration between initiation of ART and HZ onset was 112(19-357) days (Table 12).

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Table 10. Immune reconstitution inflammatory syndrome after HAART

No.	Age, gender	OIs	Diagnosis of IRIS	manifestation	Duration(days)		CD4 count (%)		Treatment of IRIS	Hp*	outcome of IRIS	ART**
					OI-ART	ART-IRIS	baseline	nearest to IRIS				
1	25, M	pul TB	TB IRIS (D)	skin abscess, pul TB brain tuberculoma	164	231	7(1)	91(4)	intensification of TB Tx surgical mass removal	3	anti-TB continue improve	S, L, Ir
2	26, M	pleural TB, OC	TB IRIS (P)	skin abscess, pulmonary	364	154	53(7)	76(17)	TB Tx : 12HREZO+3HR	1	anti-TB continue no complaint:NC	S, L, N
3	28, F	TB-LN PCP	TB IRIS (P)	intra-abdominal LN, spleen micro-abscess	27	18	43(6)	101(10)	continue TB Tx: 6HREZ	1	Tx.complete:NC AUS: no LN	S, L, E
4	31, F	None	TB IRIS (O)	pulmonary	---	14	9(1)	129(3)	TB Tx : 4HREZ+5HR	1	Tx.complete:NC	S, L, E
5	23, F	TB-LN OC	TB IRIS (O)	cervical LN	166	171	2(0)	431(16)	PSL: 10mg(3w),5mg(8w) intensification of TB Tx	0	anti-TB continue NC	S, L, E
6	42, F	OC	TB IRIS (O)	lt.pleural effusion	---	73	209(13)	331(17)	TB Tx : 3HREZ+6HR	1	Tx.complete:NC	Z, L, E
7	35, M	pul TB HSV	TB IRIS (O)	lt.calf abscess	49	22	53(9)	131(14)	continue Tb Tx: 4HREZ+ 9HR, oral ABx(10d)	0	Tx.complete:NC	S, L, E
8	68, M	OC	TB/NTM IRIS(O)	erythema nodosum, pulmonary	---	19	82(15)	141(21)	TB/NTM Tx	0	Tx.complete:NC	D, L, E
9	34, M	None	TB/NTM IRIS(O)	cervical LN	---	19	37(5)	74(17)	TB/NTM Tx: 8HREOK+ 8HREK	1	Tx.continue: NC	S, L, Ir
10	29, M	CMVR OC	CMV IRIS (P)	CMV retinitis, uveitis	7	62	10(2)	85(12)	PSL:30mg(4d),20mg(6d) Ganciclovir iv. (12d)	1	Tx.complete:NC	S, L, E
11	25, M	CM(diss) OC,HZ	CM IRIS (O)	headache, low grade fever	77	14	37(4)	100(7)	PSL:10(4w),5(4w),2.5(4 w), flu 400mg (6m)	0	Tx.complete:NC	S, L, E

Note: (D) definite, (P) probable, (O) possible, NC: no complaint, AUS: abdominal ultra sonography, OC: oral candidiasis, diss. CC: disseminated cryptococcosis *Hp: Hospitalization (times) **S: Stavudine (d4T), L: Lamivudine (3TC), Z: Zidovudine (AZT), D: Didanosine (ddI), N: Nevirapine (NVP), E: Efavirenz (EFV), Ir: Indinavir+ritonavir (boosted PI)

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Table 11. Fulfilled criteria for the diagnosis of IRIS

No.	Proposed five diagnostic criteria for IRIS					Diagnosis (fulfilled No. out of 5 criteria)
	(1)Immune restoration CD4 increase	(2)Viral suppression	(3)Improve-ment before IRIS	(4)Inflammato-ry responses	(5)Exclude other reasons	
1	Yes: 7(1%) to 91(4%)	pVL<50	BW increase, improve OI	abscess	Yes	Definite IRIS(5/5)**
2	Yes: 53(7%) to 76(17%)	NR*	improve OI, well being	abscess	No: insufficient Tx	Probable IRIS (3/5)
3	NR: nearest data 10 wks from onset	NR	improve OI, well being	high fever, intra abdominal LN & abscess	Yes	Probable IRIS (3/5)
4	NR: nearest data 5 mo from onset	NR	No	high fever	No: new OI	Possible IRIS (1/5)
5	NR: nearest data 6 mo from onset	NR	well being	painful LN	No: insufficient Tx drug resistant	Possible IRIS (2/5)
6	NR: nearest data 6 mo from onset	NR	No	high fever	No: new OI	Possible IRIS (1/5)
7	NR: nearest data 3 mo from onset	NR	improve OI	abscess	No: expected course of OI	Possible IRIS (2/5)
8	NR: nearest data 4.5mo from onset	NR	NR	High fever	No: new OI	Possible IRIS (1/5)
9	NR: nearest data 9 wks from onset	NR	No	fever	No: new OI	Possible IRIS (1/5)
10	NR: nearest data 7 wks from onset	NR	improve OI	uveitis	Yes	Probable IRIS (3/5)
11	NR: nearest data 4.5mo from onset	NR	BW increase	fever	No: relapse	Possible IRIS (2/5)

*NR: no record, **5/5 means 5 items are fulfilled out of 5 criteria

Table12. Herpes zoster after HAART

Age, gender	Duration(days) ART-HZ	CD4 count (CD4 %) baseline	nearest to HZ	Comments
(1) 28, F	112	43(6)	101(10)	TB IRIS (Case No.3)
(2) 43, M	19	51(4)	137(5)	CD4 f/u: 6mo after HZ onset
(3) 37, M	28	3(0)	118(6)	CD4 f/u: 2 mo after HZ onset
(4) 35, M	357	18(3)	171(9)	--------
(5) 45, F	299, 494 (2 episodes)	65(4)	139(7)	VL<50 copies/ml

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5.5 Risk factors of developing IRIS

5.5.1 Baseline demographics, ART regimen and IRIS development

The association between baseline demographics and subsequent development of IRIS is shown in Table 13.

There was no difference based on gender, baseline weight and BMI, performance status at initiation of HAART, baseline CD4 count and percentage. As an additional analysis, CD4 count was stratified into two groups: <100 cells/mm^3 and ≧100 cells/mm^3, and the result was not significant. History of OI before starting ART and history of TB were also not related to IRIS (Not shown in Table 13). However, patients who developed IRIS tended to be younger than those who did not (p=0.022), and patients younger than 30 years old were more likely to develop IRIS. The initial ART regimen and compliance with ART were not related to development of IRIS.

5.5.2 Comparison of duration between initiation of OI treatment and ART

There was no difference in the duration between initiation of OIs (TB, CMV and CM) treatment and ART. It was not significant when the duration between initiation of TB treatment and ART was compared separately. For CMV and CM cases, the duration was not able to be compared between patients with IRIS and without IRIS because of only 1 case for each IRIS group (Table 14).

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Table 13. The relation between baseline demographics, ART and IRIS development

Variables	total No.	Patients with IRIS	Patients without IRIS	P value
Baseline				
Age(years) *	174	29 (23-68)	36 (18-65)	0.022 †
age < 30 y.o. No. (%)	37	6 (16.2)	31 (83.8)	
age ≧30 y.o No. (%)	137	5 (3.6)	132 (96.4)	0.013‡
Gender				
Male No. (%)	99	6 (6.1)	93 (93.9)	1.000‡
Female No. (%)	75	5 (6.7)	70 (93.3)	
Baseline BW (kg) *	174	51(36-60)	52(30-76)	0.498 †
Baseline BMI *	173	18.3(14.4-25.5)	19.7(12.3-29.1)	0.121 †
Baseline Karnofsky score*	174	80 (70-100)	90 (70-100)	0.057 †
Baseline CD4 count (cells/mm^3)*	174	37 (2-209)	36 (0-360)	0.621 †
CD4 count <100 No. (%)	129	10 (7.8)	119 (92.2)	0.293‡
CD4 count≧100 No. (%)	45	1 (2.2)	44 (97.8)	
Baseline CD4%*	171	5 (0-15)	3 (0-28)	0.512 †
ART				
ART regimen No. (%)				
GPOvir (d4T,3TC,NVP)	44	1 (2.3)	43 (97.7)	0.294 † †
EFV based	57	7 (12.3)	50 (87.7)	
PI based (d4T,3TC,IDVr)	73	3 (4.1)	70 (95.9)	
Compliance of ART No.(%)				
good compliance	156	11 (7.1)	145 (92.9)	0.607‡
poor compliance	18	0 (0)	18 (100)	

*Median (range), † Calculated by Mann-Whitney test
‡ Calculated by Fisher's exact test, † † GPOvir vs pooled EFV and PI based regimen, calculated by Fisher's exact test

Table 14. Comparison of duration between initiation of OI treatment and ART

Variables	Patients with IRIS	Patients without IRIS	P value
Duration Between initiation of OI treatment and ART (days)*	n=7 77 (7-491)	n=62 120.5 (0-472)	0.585 †
Duration between initiation of anti-TB and ART (days)*	n=5 164 (27-491)	n=49 175 (44-737)	0.731 †
Duration between initiation of CMV treatment and ART(days)*	n=1 7	n=7 32 (0-78)	---
Duration between initiation of CM treatment and ART(days)*	n=1 77	n=12 91 (37-472)	---

* median (range), † Calculated by Mann-Whitney test

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5.5.3 Comparison of CD4 count and CD4% change after HAART

Serial CD4 count, CD4% and increase of those are shown in Table 15. CD4 count and its increase at 3months after HAART prescription were significantly higher in those of patients without IRIS. In contrast, CD4% and its increase at 3 months tended to be higher a little in those of patients with IRIS, although it is not statistically significant.

Table 15. Comparison of the serial CD4 count andCD4% increase from baseline

	Patients with IRIS (n=11)		**Patients without IRIS (n=163)**		**P value †**
	No.	**median(range)**	**No.**	**median(range)**	
CD4 count (/mm³)					
baseline	11	37 (2-209)	163	36 (0-360)	0.621
CD4 count increase					
3 months	6	47.5 (23-78)	85	95(−192-457)	0.027
6 months	6	73.5 (55-122)	103	101(−188-433)	0.212
9 months	6	88.5 (59-295)	69	129(−169–371)	0.245
12 months	5	141 (104-429)	75	162 (7-604)	0.835
CD4 %					
baseline	11	5 (0-15)	160	3 (0-28)	0.512
CD4 % increase					
3 months	6	7.5 (1-12)	74	4 (−9-14)	0.109
6 months	6	3.5 (2-12)	102	5 (−8-13)	0.819
9 months	6	5 (2-13)	69	6 (−8 - 21)	0.702
12 months	5	11 (2-16)	74	7 (0-20)	0.189

† Calculated by Mann-Whitney test

Figure 2 shows time course of CD4 count increase in both IRIS and non-IRIS patients. IRIS group had a slower increase compared with the non-IRIS group. However the IRIS group reached a similar level of CD4 increase after 1 year of ART.

Time course of median CD4 % increase is shown in Fig. 3. There was no statistically significant difference in CD4% increase between IRIS and non-IRIS group.

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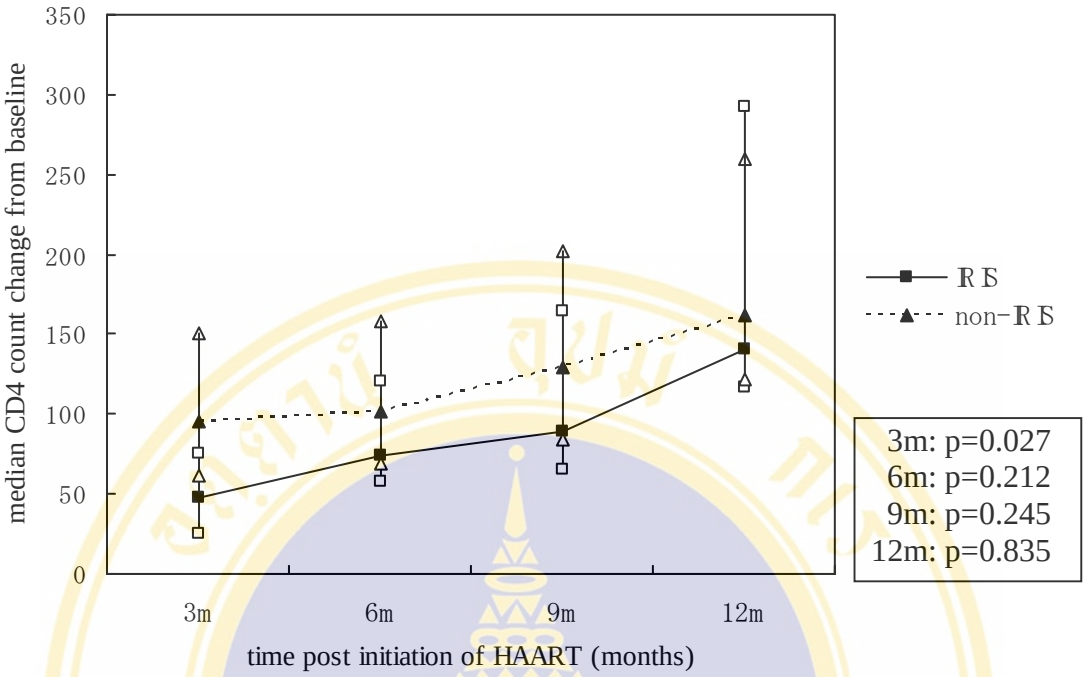

Fig. 2. Time course of CD4 count increase in response to HAART
Vertical bars represent 25-75th percentiles.

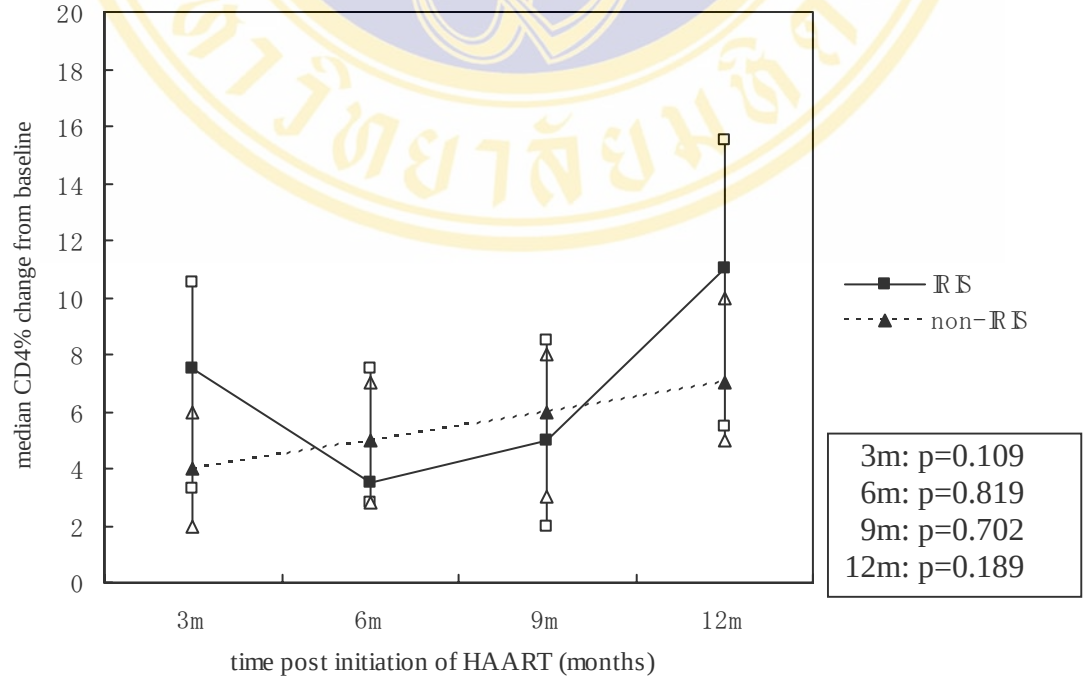

Fig. 3. Time course of CD4% increase in response to HAART
Vertical bars represent 25-75th percentiles.

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5.6 Relation between IRIS and outcomes after 1 year-HAART

Outcomes after 1 year-ART are evaluated by treatment success, weight, BMI, number of admissions, CD4 count and percent, and plasma viral load (Table 16). The results showed no difference between two groups except the number of admissions which was higher in IRIS group.

Table 16. The relation between IRIS and outcomes after 1 year-HAART

Variables	**Patients with IRIS**	**Patients without IRIS**	P value
Outcome of 1-yr ART	n=11	n=163	1.000 † † †
Treatment success (total 159)	10 (6.3%)	149 (93.7%)	
Treatment failure (total 3)	0 (0%)	3 (100%)	
Poor compliance		1	
Virologic failure		2	
Lost to follow up (total 12)	1 (8.3%)	11 (91.2%)	
Refer out		2	
Drop out		9	
Total admission No. during 1 yr-ART (times)*	n=10 1 (0-2)	n=152 0 (0-5)	<0.001 †
BW after 1yr-ART (kg)*	n=10 61 (42-68)	n=152 57 (38-81)	0.376 †
BW increase rate from baseline (%)*	n=10 14.8 (6.7-31)	n=152 8.0(-15.8-62.9)	0.064 †
BMI after 1yr-ART *	n=10 21.9 (16.8-29.4)	n=151 21.7 (15.6-30.6)	0.992 †
pVL after 1 yr-ART	n=4	n=56	1.000 ‡
<50 (copies/ml) (total 57)	4 (7%)	53 (93%)	
≧50 (total 3)	0 (0%)	3 (100%)	
CD4 count (cells/mm^3) after 1 yr ART*	n=5 165(148-431)	n=75 224(12-635)	0.372 †
CD4% after 1 yr-ART*	n=5 12 (7-22)	n=75 11.5 (2-34)	0.579 †

*Median (range), †Calculated by Mann-Whitney test, ‡Calculated by Fisher's exact test, † † †Treatment success vs pooled treatment failure and lost to follow-up, calculated by Fisher's exact test,

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5.7 CDC category after 1 year-HAART

Fig. 4 shows changes in CDC clinical categories before and after 1 year – HAART. The percentage of patients with CD4 count less than 200 cells/mm³ decreased from 89.1% to 35.6%. After 1 year of ART, most patients were asymptomatic, including patients categorized as C (Once a category C condition occurred, the person remained category C).

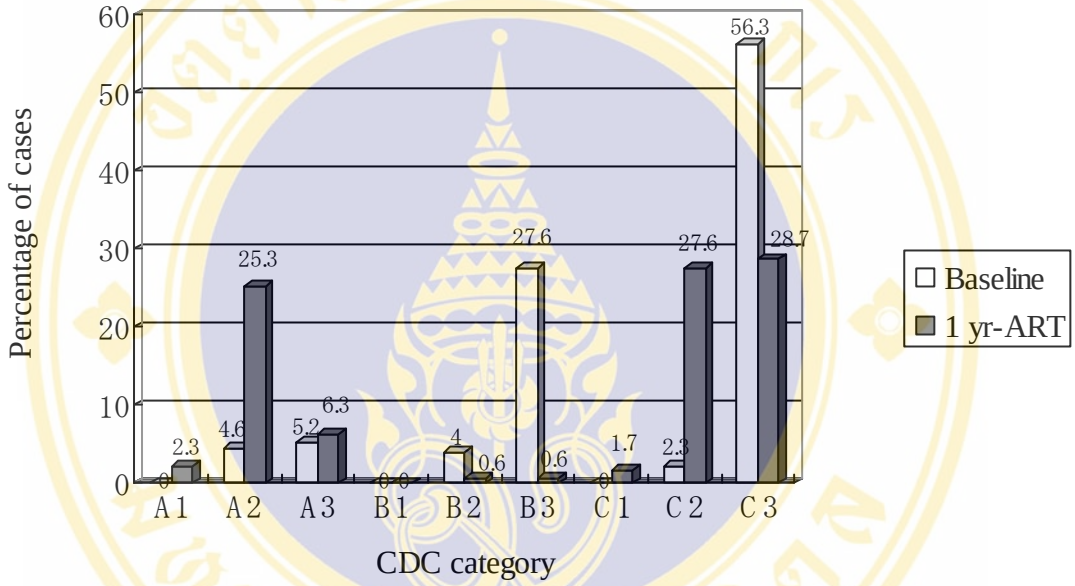

Fig. 4. CDC clinical categories before and 1 year after HAART
(Before ART: n=174, after ART: n=162)

5.8 Outcome of TB and NTM

Among 55 patients who had had active TB, 45 completed TB treatment (Cure with AFB conversion: 1, Presumptive cure 44). Six were still on treatment at the time of data collection. One patient was lost to follow up before treatment completion. Among those who completed therapy 4 patients had 6 months course of anti-TB therapy, and 41 patients had 9 months or more than 9 months therapy (10 and 31 patients, respectively).

For NTM patients, 7 patients completed treatment, and 3 were still continuing their therapy. Excluding the latter, median duration of treatment was 17 (range: 11-20) months.

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CHAPTER VI

DISCUSSION

6.1 Studied population

The total of 174 records of patients who initiated ART between December 2004 and December 2005 were reviewed in this study. Because of our inclusion criteria, patients who experienced ART including during antenatal care (ANC) and who had no baseline CD4 count or CD4 follow-up, were not included in the study.
A subject who died was excluded because there was no CD4 follow-up after HAART. This very advanced AIDS patient had concurrent TB/NTM (presumptive clinical diagnosis) and history of PCP, cryptococcal meningitis, Salmonella sepsis. He developed aseptic meningitis after 1 month-HAART and brain CT showed basal enhancement. On a suspicion of IRIS, TB/NTM regimen was intensified but died at his home after 5 months.

6.2 Sample size

Our study sample size was calculated from the reported incidence of IRIS in HIV-infected Thai children (poster presentation, international AIDS conference 2004). This previous prospective study of children was recently published (Puthanakit et al., 2006) with more cases and extended follow-up period (48 weeks), reporting an IRIS incidence of 19%. If this number is used to recalculate the sample size, it should be 236 patients. We did not collect the calculated number, because the number of patients who met the inclusion criteria in the anonymous clinic was less than this.

Considering that the incidence of TB IRIS among TB co-infected adult patients (high risk group for IRIS) was 13% (Monosuthi et al, 2006), previous rate used for calculation of sample size seems to be an overestimation. If we expect our population has an incidence no more than 13 %, sample size would be 174.

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6.3 Baseline Demographics

Proportion of males was slightly higher (56.9%) than that of females. This is partially explained by exclusion of female patients who had ART during antenatal care (ANC).

Injection drug abuse was an important mode of transmission, and not surprisingly HCV infection was very common in this group. Six out of 11 injection drug users who had HCV Ab records, were all positive.

Most of patients were very advanced at the time of ART initiation. Many patients presented late after developing symptoms, or some had been lost to follow-up for a long time since first HIV diagnosis until they became very sick.

Performance status at the time of ART prescription was not recorded on a chart but was estimated it from information of patient's condition. In most cases, HAART was started after improvement or cure of illnesses, baseline PS scores were relatively good.

6.4 Opportunistic infections (OIs)

Reflecting the advanced immune deficiency in our cohort, nearly 80 % of patients experienced 281 episodes of OIs prior to HAART.

Twenty episodes observed in 17 TB co-infected patients during the duration between initiation of anti-TB treatment and ART. These patients were severely immunocompromised at the time of HAART initiation, 16 patents had baseline CD4 count less than 100 cells/mm^3. For 11 patients who developed AIDS defining illnesses, all had CD4 less than 50 cells/mm^3.

In our study, 5 out of 55 TB patients were started HAART within 2 months after initiation of TB treatment but one of 5 patients had esophageal candidiasis during this period. Meanwhile, 16 (32%) of 50 patients who delayed HAART more than 2 months from initiation of TB therapy had experienced 19 episodes of infections including Cryptococcus meningitis, PCP, CMV retinitis, Histoplasmosis, Salmonella sepsis, Herpes zoster, and esophageal candidiasis. Severe AIDS defining infections occurred after 2 months and all CMV retinitis were observed after 5 months.

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Gilliam et al. (2002) reported that 39 % of patients with low CD4 count (<100cells/mm^3) who were receiving anti-TB drugs without ART developed further AIDS defining illnesses. They recommend starting HAART early for advanced patients with CD4 counts less than 100 cells/mm^3. It might be difficult to follow this recommendation, because our population was more immunocompromised and more likely to present with complications and to take time to be stabilized. Limitation of drug choice to avoid drug interactions (e.g. rifabutin) and social problems might relate to delayed ART initiation. However delaying ART more than 4 or 5 months from anti-TB treatment initiation might be not beneficial in terms of risk of severe OIs that may cause sequelae such as visual disturbance from CMV retinitis and also may contribute to a vicious cycle of infections that further delays HAART.

There were no fatal cases in our study and most improved after OI treatment, but morbidity from diseases and hospitalizations might degrade patients' quality of life.

6.5 ART and adverse effects

Considering that more than 90% of patients started d4T containing regimens initially, it is understandable that lipodystrophy from d4T was the most common adverse effect. Skin rash and hepatotoxicity were also common, usually not severe, but interruption of ART was needed in 2 patients.

6.6 IRIS

6.6.1 Diagnosis

Using our proposed criteria for IRIS diagnosis was not practical in the real setting. It was not possible to demonstrate immunological recovery or ART effectiveness by specific testing in many patients. Because of financial limitation, many patients can not afford frequent blood tests including plasma viral load and CD4 count in the anonymous clinic. No IRIS patient had a baseline pVL, and only one patient had pVL data at the time of IRIS onset. CD4 counts at IRIS onset were available in 2 patients, others had CD4 tests relatively remote from IRIS onset, after 2 months or more. In this situation, presumptive diagnosis of IRIS was made by considering following factors; 1) CD4 count or CD4% increase in proximity IRIS

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diagnosis (no evidence of treatment failure), 2) close relation between initiation of HAART and worsening /new symptoms, 3) clinical improvement before developing IRIS, 4) atypical inflammatory presentations and 5) the absence of other more reasonable explanations such as deterioration from poor ART compliance or insufficient previous OI treatment. Seven patients were diagnosed possible IRIS from these considerations. Although IRIS was suspected in these patients, it is difficult to exclude other conditions such as new OI, because of lack of laboratory evidence of immune recovery at the time of IRIS onset. Therefore, it is possible that we overestimated the rate of IRIS development.

6.6.2 Incidence

There were 24 episodes of OIs in 22 patients (12.6%) after initiation of HAART. This frequency was lower than the incidence of 23.3% reported in AIDS patients who had successful treatment for cryptococcal meningitis (Sungkanuparph et al., 2003). Higher rates of OI for the latter might be explained by more frequent occurrence of sub-clinical OI in patients with more advanced AIDS (in this case, recent CM patients) that might be unmasked with immune recovery after HAART.

Among 22 patients, 11 cases were diagnosed as IRIS. The incidence of IRIS in this study was 6.3%, which is one third of the incidence reported in HIV-infected Thai children (Puthanakit et al., 2006). Since younger age has been reported as an IRIS risk factor in previous studies, this might be age-related differences. Another point is a difference in IRIS definition. In the previous study of children, IRIS was defined as a disease event caused by microorganisms or conditions previously reported in association with IRIS in patients having immunologic and/or virologic response to HAART. A single episode of uncomplicated herpes zoster with typical dermal distribution after ART was counted as IRIS in 7 cases. Meanwhile such patients were excluded from IRIS diagnosis in this study, because it is difficult to differentiate them from natural course of the disease and they may affect the results of other IRIS when analyzed together. If these HZ patients were counted as possible IRIS in our study, the incidence would be 8.6% (15 out of 174 patients) which is still lower than the previous study.

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When compared with other studies from Europe and USA that reported rates of 10-25%, our incidence was also lower. Many factors might be related to this, for examples, the differences of genetics, ART regimens, timing of HAART initiation or the IRIS definition itself.

Mycobacterium related IRIS was most commonly observed in IRIS cases (81.8%). Among 9 TB or TB/NTM IRIS cases, 5 patients had preexisting TB history. One of them had completed TB treatment before HAART, the other 4 cases were receiving anti-TB and HAART concomitantly. There were 46 patients receiving both treatments at the time of ART initiation, and 8.7% developed IRIS after starting ART in this study. This figure is much lower than the incidence reported from USA which was 30.2% (Shelburne et al. 2005) but consistent with data from India which was 7.6%. (Kumarasamy et al, 2004), suggesting that differences in genetics, the ART regimens, or timing of ART might be related to this discrepancy.

In Thailand, the recently reported rate of MTB IRIS in patients co-infected with HIV and TB was 13% (Monosuthi et al, 2006). Characteristics of patients were similar except the duration between initiation of TB treatment and ART. Median duration was 2.2 months in previous study, and 5.8 months in our study. Longer delay in ART initiation may be related to our lower incidence of IRIS.

6.6.3 Timing

As described previously, the majority of IRIS episodes (72.7%) occurred within the first 90 days of HAART.

6.6.4 Risk factors

Younger age was considered a risk factor to develop IRIS in our patients. One definite and 3 probable IRIS cases were all in their twenties. Low baseline CD4 count, close interval between initiation of TB treatment and ART were not suggested as risk factors of IRIS. It might be explained by equality of low baseline CD4 count, most (74%) of whose CD4 counts were less than 100 cells/mm^3 and by delaying ART in patients with active TB to avoid drug interactions, side effects and IRIS.

In a previous study, significantly greater increase of CD4 counts after 3 month-ART and rapid initial fall of pVL were reported in IRIS patients, which

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suggests that greater immune recovery and rapid viral suppression relate to the development of IRIS. (Shelburne et al. 2006) In our study, increase of CD4 count in IRIS patients was low and significantly less than that of non-IRIS patients at the time of 3 month-ART, although at 12 month-ART, there was no difference between them. We do not know why absolute CD4 count and its increase of IRIS patients were significantly less at 3 month therapy, it might suggest that intensity of CD4 count increase might be not so useful to predict IRIS.

6.6.5 Outcomes

Patients with IRIS had an increased number of hospitalization compared with non-IRIS patients. Six out of 11 IRIS patients needed invasive procedures such as surgery, needle aspiration, tissue biopsy for diagnosis and treatment. Although there might be such short-term morbidity associated with IRIS, all patients were successfully managed without HAART cessation. IRIS and non-IRIS patients achieved similar CD4 counts, CD4 percent, body weight and BMI at one year of therapy.

6.7 Herpes zoster after HAART

In patients who have recently started HAART, herpes zoster (HZ) has been reported to occur in 0.8% to 12%, with a reported incidence of 6.2 to 22.9 episodes per 100 person-years (Lehloenya and Meintjes, 2006). The incidence of present study was lower than this, 2.2 episodes per 100 person-years, and all cases were uncomplicated dermatomal HZ infections. According to Dunic et al. (2005) advanced HIV-infected patients with lower CD4 count had more risk to develop HZ after HAART initiation, and our population was considered a risk group. We do not know the reason why we had low incidence of HZ despite having a high risk, but this may be due to the difference of genetics and of CD4 or CD8 T-response after HAART.

HZ after HAART can be explained by reactivation of latent infection from immune reconstitution, and many cases have been reported as IRIS. However it is difficult to exclude the possibility of disease occurrence due to residual low immunity rather than IRIS, especially in patients without atypical inflammatory presentations.

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Whether each HZ with mild presentation is true IRIS or not may be a minor problem for clinicians in terms of patient management. Further studies to determine risk factors developing complicated HZ infection (e.g. disseminated skin pattern, encephalitis, myelitis, keratitis) after HAART are more needed.

6.8 Limitation of study

The limitations of our study included its retrospective character and subjective nature of IRIS diagnosis. We attempted to minimize this issue by having more than two medical doctors (including HIV specialists) agree on the diagnosis. Because of the small number of IRIS patients, our results may not necessarily reflect the real situation of IRIS in this population. For example, correlation to CD4 count increase in response to HAART may be different if sample size were larger.

As mentioned before, because of resource and budget limitation, many opportunistic infections (including IRIS cases) were diagnosed presumptively without definitive evidence. This might cause over-diagnosis and treatment or vice versa.

We missed 2 records in cases that had died and might have met our criteria. If these 2 cases were related to IRIS, the mortality could have been significantly poorer in IRIS patients.

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CHAPTER VII
CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusions

1. In this retrospective cohort study, 6.3% of ART-naïve patients developed IRIS after starting HAART. The incidence of IRIS in the total cohort was 4.12/100 patient-years HAART. The relatively low incidence of IRIS in advanced HIV-infected patients might be related to the strategy of delaying ART while opportunistic infections were active.

   On the other hand, 31 % of TB patients (17 out of 55) developed other infections while deferring ART. Severe AIDS defining infections occurred after 2 months TB treatment without ART.

2. Median age at starting HAART of patients with IRIS was significantly younger than that of patients without IRIS. Young age is possible risk factor of IRIS.

3. The median time between the initiation of HAART and the onset of IRIS was 22 days, with shortest time being 14 days and the longest 231 days. Presentation was within 30 days for 6 (54.5%) and within 90 days for 8 (72.7%) of beginning HAART.

4. Most IRIS cases were MTB or MTB/NTM related (81.8%), presenting as newly emerging or worsening pulmonary or LN (cervical, intra-abdominal) TB. Skin, pleural TB, cerebellar tuberculoma, splenic abscess were also observed.

5. All patients with IRIS were successfully managed appropriate treatment. Steroids were used in 3 patients. Some patients needed invasive procedures such as needle aspiration and surgery.

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6. IRIS did not influence the outcome of ART at one year except that the number of admissions was higher in the group with IRIS.

7.2 Recommendations

1. Although delaying ART is considered to be effective in preventing IRIS, physicians should start HAART as soon as possible once patients are stabilized to avoid further opportunistic infections especially in patients with very low CD4 counts (<100 cells/mm^3).
2. Early initiation of HAART, early patient intervention including drug counseling or other support may be needed.
3. The optimal time to start HAART for co-infected patients with low CD4 counts should be determined by a well designed prospective study.

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APPENDIX

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APPENDIX A

PATIENT CASE RECORD FORM

1. Patient's general information

1.1 HN._____ ID No._____

NAPHA No._____ Data Collection ____/_____/ _____

1.2 Age ☐☐☐ yrs (at the point of ARV initiation)

1.3 Gender ☐(1) Male ☐(2) Female

1.4 Occupation _____

1.5 Past history of drug allergy ☐(1) Yes ☐(2) No

If , Yes 1)……..→Event……..

2)……..→ ……..

3)……..→ ……..

1.6 Infection status

(1)HBV ☐(1) Yes ☐(2) No ☐ (9) No record

(2)HCV ☐(1) Yes ☐(2) No ☐ (9) No record

(3)Others: Specify:……

1.7 History of chronic illness ☐(1) Yes ☐(2) No

If Yes, what? ……. Time of diagnosis……..

Treatment .....

1.8 Baseline Karnofsky PS ☐☐☐ /100

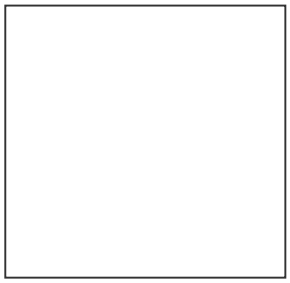
1.9 BMI ☐☐. ☐ (Height ☐. ☐☐ m , BW☐☐. ☐ kg)

1.10 Chest x-p at Baseline

…….

…….

…….



2. HIV infection

2.1 Date of diagnosis ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

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2.2 Rout of transmission ☐(1) Heterosexual ☐(2)Homosexual ☐(3)Bisexual ☐(4)IVDU ☐(5)Blood transfusion ☐(6)Tattoo ☐(7)Others :Specify:……. ☐ (9) No record

2.3 Baseline laboratory findings (* If, available)

2.3.1 CD4 counts _____cells/mm^3(☐☐/☐☐/☐☐☐☐)

2.3.2 CD4 percentage _____ %

2.3.3 CD8 percentage *_____ %

2.3.4 CD4:CD8 (%) ratio* _____

2.3.5 pVL *_____copies/ml (☐☐/☐☐/☐☐☐☐)

2.4 Baseline CDC clinical categories ☐A ☐B ☐C ☐1 ☐2 ☐3

Specify symptoms & illness……

2.5 Date of initiation of HAART ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

2.6 Treatment regimen ☐ (1)GPO-vir (d4T/3TC/NVP)

☐ (2)Other: ……

2.7 Adverse effects ☐(1) Yes ☐(2) No

If Yes, which events?

	Date	ART change	New Regimen
☐(1)Lipodystrophy		☐(1)Yes☐(2)No	
☐(2)Lactic acidosis		☐(1)Yes☐(2)No	
☐(3)Hepatotoxicity		☐(1)Yes☐(2)No	
☐(4)IGT		☐(1)Yes☐(2)No	
☐(5)Hyperlipidemia		☐(1)Yes☐(2)No	
☐(6)Neuropathy		☐(1)Yes☐(2)No	
☐(7)Leukopenia		☐(1)Yes☐(2)No	
☐(8) Skin rash		☐(1)Yes☐(2)No	
☐ (9)Nausea&vomiting		☐(1)Yes☐(2)No	
☐(10)Others…….. ……		☐(1)Yes☐(2)No	

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2.8 Compliance ☐1)good ☐2)poor (<95% adherence)

If Poor, why? ……..

2.9 CD4 count

	1st f/u	2nd f/u	3rd f/u	4th f/u	5th f/u	6th f/u
Date						
CD4 count						
CD4%						

3. Concurrent or previous recent OI ☐(1) Yes →3.1-8 ☐(2) No→ 3.8

3.1 Type of OI and Treatment

OI	Diagnosis Date	Treatment	Date start	Date stop
☐(1)MTB				
☐(2)MAC				
☐(3)CMV				
☐(4)*C.neoformans*				
☐(5)HSV				
☐(6)Oral candidiasis				
☐(7)PCP				
☐(8)Others ……. …….				

If (1) MTB, duration between initiation of TB therapy and HAART→_____days

3.2 Methods of diagnosis …….....

……

3.3 Clinical manifestation ……

……

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3.4 Radiological findings

☐Chest x-p……..

☐CT……

☐Others ……..

3.5 Drug Resistance ☐(1) Yes ☐(2) No ☐ (9)No record

If Yes, culture results for drug susceptibility ……..

…….

Any change of regimen? ☐(1) Yes ☐(2) No

……..

3.6 Adverse effects ☐(1) Yes ☐(2) No

If Yes, specify: ……

Any change of regimen? ……

3.7 Outcome ☐(1)Cure ☐ (2)Treatment completed ☐(3)Treatment failure

☐4)Relapse ☐5)Others……

If (3) or (4) in detail: ……

3.8 Prophylaxis ☐(1) Yes ☐(2) No

If Yes, regimen: ……

4. IRIS ☐(1) Yes ☐(2) No

4.1 Diagnosis: ☐probable ☐definite _____IRIS

***4.1.1 or 4.1.2 and all 4.1.3-5 criteria should be fulfilled to diagnose definite IRIS**.

4.1.1 Evidence of immune restoration--- ☐(1) Yes ☐(2) No ☐ (9)No record

If Yes, which data or clinical sign?

☐(a) Increase in CD4 cell count

_____cells/mm^3(%) →_____cells/mm^3(%)(☐☐/☐☐/☐☐☐☐)

☐(b) Others: …….

4.1.2 Evidence of response to HAART: Viral suppression (If available)

---☐(1) Yes ☐(2) No ☐ (9)No record

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☐Reduction in pVL _____log_{10} copies/ml

_____copies/ml→_____copies/ml (☐☐/☐☐/☐☐☐☐)

4.1.3 Clinical improvement before worsening---☐(1) Yes ☐(2) No

☐ (9)No record

If Yes, specify.

☐(a)Increase BW ☐(b) Improve symptoms of co-infected OI

☐(c)Well being ☐(d) Others: ……

4.1.4 Clinical symptoms consistent with inflammatory process

---☐(1) Yes ☐(2) No ☐ (9)No record

If Yes, specify.

☐(a) High fever ☐(b) Lymphadenopathy ☐(c)Abscess

☐(d) Others:…….

4.1.5 Exclude other condition (Tick the (a)-(d) box, if excluded)

---☐(1) Yes ☐(2) No

☐(a)Expected course of previously diagnosed OI ☐(b)New OI

☐(c)Drug toxicity ☐(d) Others……..

If any uncertainty on diagnosis of IRIS, in details……...

……..

……..

If probable IRIS, in details……...

……..

……..

4.2 Date of onset ☐☐/☐☐/☐☐☐☐

Duration after HARRT initiation _____ days

4.3 Type of IRIS ☐ (1)Worsening co-infected OI ☐(2)Unmasking OI

☐(3)Others……

If (1) or (2) which OI?.....

4.4 Clinical manifestation ……

……..

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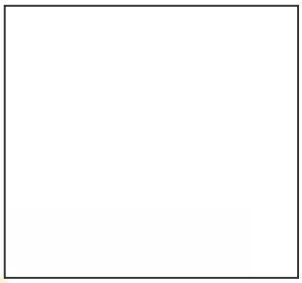
4.5 Radiological findings



4.6 Laboratory findings

4.6.1 Culture …….. Site ……

4.6.2 Antigen detection ……...

4.6.3 Others …….

4.7 Pathological findings ……...

…….

4.8 Treatment

	Drug	Dose	Duration
☐(1)NSAIDs			
☐(2)Steroid			
☐(3)Intensification of OI therapy			
☐(4) Others: ……			
☐(5)None			

If ☐(6) Mechanical procedure (e.g. aspiration, drainage) is needed, in detail……..

……

4.9 Hospitalization due to IRIS ☐(1) Yes ☐(2) No

If Yes, how many times? _____ times

4.10 Intensive care ☐(1) Yes ☐(2) No

If Yes, in detail, …….

……

……

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4.11 HAART discontinuation ☐(1) Yes ☐(2) No

If Yes, duration of cessation ☐☐/☐☐/☐☐☐☐-☐☐/☐☐/☐☐☐☐

4.12 Outcome of IRIS ☐(1) Cure ☐(2) Improve ☐(3) Relapse

☐(4) Worsening ☐ (5) Death ☐(6) Others……..

Clinical course: ……..

……

5. Outcome after 12 months-ART

☐(1) Treatment success → **5.1**

☐(2) Treatment failure → **5.1-2**

☐(3) Lost to follow-up → **5.3**

☐(4) Death → **5.4**

☐(5) Others…….

5.1 Patient status

5.1.1 BMI ☐☐. ☐ (Height ☐. ☐☐ m , BW☐☐. ☐ kg)

5.1.2 CD4 counts _____cells/mm^3(☐☐/☐☐/☐☐☐☐)

5.1.3 CD4 percentage _____ %

5.1.4 pVL* _____copies/ml (☐☐/☐☐/☐☐☐☐)

5.1.5 Clinical categories ☐A ☐B ☐C ☐1 ☐2 ☐3

Specify symptoms & illness……...

5.1.6 Total hospital admissions (0-12 months) _____ times

5.2 Treatment failure

5.2.1 Occurrence or recurrence of an HIV-related event after ≧3 months therapy (must exclude IRIS) ☐(1) Yes ☐(2) No

If Yes, diagnosis (Date)…..……(☐☐/☐☐/☐☐☐☐)

5.2.2 Virologic failure ☐(1) Yes ☐(2) No ☐ (9)No record

If Yes, in detail: ……

……..

……..

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5.2.3 Cause of failure ☐(1) Resistance ☐ (2) Inadequate adherence

☐(3) Altered metabolism ☐ (4) Drug interaction ☐(5) Others…….

In detail: ……...

……..

……..

5.3 Lost to follow-up ☐1) Referred to other hosp. ☐2) Drop out

☐3) Others……

5.4 Death

Cause: ……

Date of death ☐☐/☐☐/☐☐☐☐

6 Total follow-up duration after HAART _____months

Comment: ……...

……..

……..

……..

……..

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APPENDIX B

KARNOFSKY PERFORMANCE STATUS
(O'Dell WW et al. 1995)

Able to carry on normal activity; no special care is needed	100 Normal 90 Normal activity; some signs or symptoms of disease 80 Normal activity with efforts; some sighs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70 Cares for self; unable to carry on normal activity or to do active work 60 Requires occasional assistance but able to care for most needs 50 Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutions or hospital care; disease may be progressing rapidly	40 Disabled; requires special care 30 Severely disabled; hospitalization is indicated although death is not imminent 20 Very sick; hospitalization is necessary; active supportive treatment is necessary 10 Moribund, fatal process progressing rapidly 0 Dead

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APPENDIX C

CDC CLASSIFICATION

Clinical categories of the CDC classification system in HIV-infected persons	
Category A Asymptomatic HIV infection Acute (primary) HIV infection with accompanying illness or history of acute HIV infection Persistent generalized lymphadenopathy Category B Symptomatic conditions* that are not included among conditions listed in clinical Category C. Examples include, but are not limited to: Bacillary angiomatosis Candidiasis, oropharyngeal (thrush) Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy Cervical dysplasia (moderate or severe)/cervical carcinoma in situ Constitutional symptoms, such as fever (38.5° C) or diarrhea lasting longer than 1 month Hairy leukoplakia, oral Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome Idiopathic thrombocytopenic purpura Listeriosis Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess Peripheral neuropathy	Category C - AIDS-defining illnesses** Candidiasis of bronchi, trachea, or lungs Candidiasis, esophageal Cervical cancer, invasive* Coccidioidomycosis, disseminated or extrapulmonary Cryptococcosis, extrapulmonary Cryptosporidiosis, chronic intestinal (greater than 1 month's duration) Cytomegalovirus disease (other than liver, spleen, or nodes) Cytomegalovirus retinitis (with loss of vision) Encephalopathy, HIV-related Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (greater than 1 month's duration) Kaposi's sarcoma Lymphoma, Burkitt's (or equivalent term) Lymphoma, immunoblastic (or equivalent) Lymphoma, primary, of brain *Mycobacterium avium complex* or *M. kansasii*, disseminated or extrapulmonary Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary) Mycobacterium, other species or unidentified species, disseminated or extrapulmonary Pneumocystis pneumonia Pneumonia, recurrent* Progressive multifocal leukoencephalopathy

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	Salmonella septicemia, recurrent Toxoplasmosis of brain Wasting syndrome due to HIV

* These conditions must meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

** Once a Category C condition has occurred, the person will remain in Category C.

The CD4+ T-lymphocyte categories
Category 1: >500 CD4+ T-cells/mm³
Category 2: 200-499 CD4+ T-cells/mm³
Category 3: <200 CD4+ T-cells/mm³

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Clinical Categories

Clinical / CD4 count (%)	A	B	C
	Asymptomatic, or Acute HIV Infection	Symptomatic (not A or C)	AIDS Indicator Condition
>500(≧ 29%)	A1	B1	C1
200-499(14-28%)	A2	B2	C2
<200(<14%)	A3	B3	C3

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BIOGRAPHY

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