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Time to antiretroviral therapy initiation in HIV-positive patients with opportunistic infections/AIDS-defining illness in Southern Thailand: a prospective cohort study

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Abstract

Introduction: Rapid antiretroviral therapy (ART) initiation is recommended for all people living with human immunodeficiency virus (HIV). Time to ART initiation in individual patients depends on several factors. The study objectives were to investigate the time to ART initiation in HIV-positive patients with opportunistic infections/AIDS-defining illnesses (OIs/ADI), and associated factors.

Material and methods: A prospective cohort study was performed among ART-naïve HIV patients with OIs/ADI. Time to ART initiation was defined as the time from being diagnosed with OIs/ADI to ART initiation.

Results: A total of 253 patients were included. The three most common OIs were tuberculosis (36.8%), *Pneumocystis jirovecii* pneumonia (26.1%), and candidiasis (19.0%). 39.9% of patients learned about their HIV-serostatus after OIs/ADI diagnosis. The median time from OIs/ADI diagnosis to ART initiation was 38 days (IQR, 23-71). From Cox regression model, the factor independently associated with a shorter waiting time to ART initiation was continuous engagement in HIV care (aHR = 2.42; 95% CI: 1.70-3.45%). On the other hand, the factors associated with a longer time to ART initiation were tuberculosis co-infection (aHR = 0.52; 95% CI: 0.36-0.75%), HIV diagnosis after OIs/ADI (aHR = 0.42; 95% CI: 0.30-0.57%), viral hepatitis B/C co-infection (aHR = 0.59; 95% CI: 0.39-0.89%), seeking care in general hospital and community hospital (aHR = 0.67; 95% CI: 0.49-0.93%, and aHR = 0.62; 95% CI: 0.44-0.86%, respectively), having more than one hospital admission in the past six months (aHR = 0.60; 95% CI: 0.44-0.81%), and history of missed appointments (aHR = 0.62; 95% CI: 0.42-0.91%).

Conclusions: To achieve maximal benefits of ART, strategies to improve HIV awareness, continuous care engagement, and timely ART initiation are required.

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Key words: antiretroviral therapy, opportunistic infections, AIDS-defining illnesses, co-infection, time to antiretroviral therapy initiation.

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Introduction

Antiretroviral therapy (ART) should be offered to all people living with human immunodeficiency virus (PLHIV) to reduce HIV-related morbidity and mortality, and prevent HIV transmission [1, 2]. The global coverage of ART had increased to 73% by the year 2020 [3]. However, it was reported that 26-40% of PLHIV had advanced HIV disease at ART initiation [4]. Late HIV diagnosis might partly contribute to this delay [5, 6].

Even though ART could potentially enhance the success of opportunistic infections (OIs) treatment, antiretroviral initiation in individuals with advanced HIV disease is challenging. Several factors should be considered, including types of opportunistic co-infections and patients readiness for treatment. ART might put patients with OIs at risk for several complications (i.e., immune reconstitution inflammatory syndrome [IRIS] and overlapping toxicities), and non-adherence [7]. Additionally, providers' perceptions and local healthcare system influence the decision regarding ART initiation [8, 9].

Previous studies had demonstrated that the time from diagnosis of OIs to ART initiation was different in various settings [10-14]. Factors associated with time to ART initiation after OIs diagnosis were CD4 count and types of OIs [10, 11, 14]. Patients with *Pneumocystis jirovecii* pneumonia (PCP) had a shorter waiting time to start ART than other treatable OIs [10, 12]. Although the delay of ART was decreasing after the implementation of HIV-TB guidelines [15, 16], patients with TB still have to wait longer to ART initiation than other OIs patients [10-12]. The risk of IRIS might increase in patients with central nervous system (CNS) infections and, hence, affect the time to ART initiation. A previous study reported that time to ART initiation after toxoplasma encephalitis was 32 days [10]. Additionally, ADI patients with no effective treatment, such as progressive multifocal leukoencephalopathy, cryptosporidiosis, and Kaposi's sarcoma, tend to have a shorter waiting time to starting ART [11]. By using different definitions in several studies, delay or deferred ART ranged from 48% to 67% [10, 11,14, 15, 17].

In Thailand, data regarding time to ART initiation after OIs/ADI diagnosis are limited. Therefore, this study aimed to investigate the time to ART initiation and their associated factors in ART-naïve patients with OIs/AIDS-defining illnesses (ADI) in the context of routine HIV care in the country.

Material and methods

The current study was a hospital-based prospective cohort study. Study settings were outpatient departments of public hospitals in Songkhla Province, Southern Thailand. There are three levels of public hospitals in the country: community hospital, general hospital, and regional hospital. Under the universal coverage scheme of the health insurance system, all public hospitals provide a comprehensive HIV care and treatment according to the national HIV treatment guidelines free of charge. Most HIV-diagnosed patients in public hospitals are registered and followed up at a HIV clinic. ART is offered by an infectious disease (ID) clinician in a regional or general hospital, but will be provided by a general practice physician in a community hospital. Among HIV-tuberculosis (TB) co-infected patients, ART may be started in HIV clinic, TB clinic, or integrated HIV-TB clinic.

Study population

Our eligible cohort consisted of ART-naïve patients with OIs or ADI, who were at least 18 years of age, sought care in outpatient departments, and were willing to provide written informed consent. Between October 2017 and April 2019, study participants were recruited from public hospitals (one regional hospital, one general hospital, and fourteen community hospitals) and were followed for at least six months after OIs/ADI diagnosis. Patients with drug-resistance TB or pregnant women were excluded from the study.

Data collection

At baseline visit, consecutive eligible patients were interviewed by a trained interviewer. Baseline information collected included demographic characteristics, HIV testing, signs and symptoms at HIV diagnosis, route of infection, duration of HIV infection, care engagement after HIV diagnosis, history of missed appointments, sexual behaviors, and beliefs in antiretroviral benefits. Information regarding date of HIV diagnosis, type of OIs/ADI and treatment, hepatitis B or C co-infection (HBV or HCV), CD4 count, and date of ART initiation were obtained from patients' medical records.

Variables

Outcome variable was the time to ART initiation after OIs/ADI diagnosis. Independent variables included demographic characteristics, timing of HIV diagnosis, linkage to care after HIV diagnosis, type of OIs/ADI, CD4 count before ART initiation, HBV/HCV co-infection, site of HIV care, history of hospital admission, history of missed appointments, serostatus of sexual partner, and beliefs regarding ART benefits.

Definitions

1. Time to ART initiation is the time from the first OIs/ADI diagnosis to ART initiation.

2. Opportunistic infections and/or AIDS-defining illness are defined by using 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults [18].

3. Continuous engagement in HIV care or linkage to care after HIV diagnosis are described in persons who registered

and regularly attend follow-up visits at a HIV clinic after being diagnosed with HIV infection until the start of ART.

Data analysis

Data were summarized by using descriptive statistics. In patients with multiple OIs, the most severe disease was considered as the type of first OI. Survival analysis was applied to explore ART initiation. Time was defined as the duration from OIs/ADI diagnosis to ART initiation, death, or loss to follow-up, depending on which came first. To identify predictors associated with the time to ART initiation, variables with a *p*-value of less than 0.20 from log-rank test and variables of interest, such as CD4 count, timing of HIV diagnosis, and serostatus of sexual partner, were considered covariates for Cox regression. Final model contained significant predictors and variables of interest. High adjusted hazard ratios (aHR) reflected shorter time between OIs/ADI diagnosis and ART initiation after adjustment for potential confounders. Schoenfeld's global test was used to check for evidence of a violation of proportional hazard assumption. A *p*-value of less than 0.05 was considered statistically significant. All statistic evaluations were performed using Stata version 14.1.

The current study was approved by the Committee for Research in Human Subjects at the Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand, and Institutional Review Boards of the study hospitals.

Results

Patients demographics and clinical characteristics

A total of 253 ART-naïve HIV patients with OIs or ADI were enrolled in the study. One hundred and fifty-five (61.3%) were males. The median age was 40 years (IQR, 33-47). Sexual contact was the major route of HIV infection (80.6%). 14.6% and 21.7% of the patients had a serodiscordant partner and an unknown serostatus partner, respectively. Nearly one-fifth (18.6%) of the patients believed that ART could cure HIV infection. 39.9% were HIV-diagnosed after OIs/ADI occurrences. Of these, 90.1% were diagnosed within 14 days, and 10 participants (9.9%) had access to HIV testing longer than 14 days after OIs/ADI diagnosis (median, 82 days; IQR, 32-107). For the patients already diagnosed with HIV at the time of OIs or ADI, 59.2%, 7.2%, 7.2%, 19.1%, and 7.2% had developed OIs within 1 month, > 1 month to 1 year, > 1 year to 5 years, > 5 years to 10 years, and more than 10 years after HIV diagnosis, respectively. One-fourth did not engage with care after HIV diagnosis. Other demographic and clinical characteristics of the study participants are presented in Table 1.

Before ART initiation, 42.7%, 40.7%, and 16.6% of the patients were diagnosed with one OI/ADI, two OIs/ADI, and more than two OIs/ADI, respectively. The most common diagnosed OI was tuberculosis (36.8%), followed by PCP (26.1%), candidiasis (19.0%), and bacterial pneumonia (6.3%). Other OIs/ADI were wasting syndrome (*n* = 9), toxoplasmosis (*n* = 8), cryptococcal meningitis (*n* = 8), cryptococcal septicaemia (*n* = 1), CMV retinitis (*n* = 1), herpes simplex virus infection (*n* = 1), salmonella septicaemia (*n* = 1), and rhodococcus pneumonia (*n* = 1).

Time to ART initiation after OIs/ADI diagnosis

After OIs/ADI diagnosis, two hundred and forty-three patients (96.0%) started ART. The remaining 10 patients did not initiate ART due to death (*n* = 5) and loss to follow-up (*n* = 5). The median CD4 count was 48 (IQR, 20-112) cells/mm^3 before ART initiation. Most patients (97.5%) initiated ART in an outpatient department, and only 6 participants started ART while they were admitted to a hospital. The median duration from OIs/ADI diagnosis to ART initiation was 38 days (IQR, 23-71). Tuberculosis, except for TB meningitis, had the longest duration of time to ART initiation (median, 61 days; IQR, 36-84), followed by CNS infections (median, 48 days; IQR, 38-61) and PCP (median, 28 days; IQR, 22-48), respectively. Among patients with CNS infection, the median time to ART initiation was 43 days (IQR, 38-50) for cryptococcal meningitis, and 41 days (IQR, 27-52) for toxoplasmosis. The two participants who were diagnosed with tuberculous meningitis started ART at 56 and 65 days after OIs/ADI diagnosis.

Factors associated with time to ART initiation after OIs/ADI diagnosis

From log-rank tests, factors associated with the time to ART initiation were the education level, type of health insurance, site of HIV care, history of missed appointments, linkage to care after HIV diagnosis, type of OI/ADI, and number of hospital admissions in the past six months (Table 1). Additionally, no association between the route of HIV infection and time of ART initiation was observed.

From Cox regression model (Table 2), factor independently associated with a shorter time to ART initiation was continued engagement in care after HIV diagnosis (aHR = 2.42; 95% CI: 1.70-3.45%). On the other hand, tuberculosis co-infection had a significantly longer waiting time to ART initiation (aHR = 0.52; 95% CI: 0.36-0.75%) compared with PCP. After adjustment for potential confounders, patients diagnosed with HIV after OIs/ADI diagnosis and patients with HBV or HCV co-infection had a statistically significant longer waiting time to ART initiation (aHR = 0.42; 95% CI: 0.30-0.57%, and aHR = 0.59; 95% CI: 0.39-0.89%, respectively). The site of HIV care was also an independent predictor for the time to ART initiation. Patients seeking care at a general hospital and community hospital were associated with a longer waiting time to ART initiation after OIs/ADI diagnosis (aHR = 0.67; 95% CI: 0.49-0.93%, and aHR = 0.62; 95% CI: 0.44-0.86%, respectively). Furthermore,

Table 1. Time to ART initiation according to demographic and clinical characteristics (*N* = 253)

Characteristics	*n* (%)	Time to ART initiation; median, days (IQR)	*p*-value[a]
Gender			
Female	98 (38.7)	36 (24-75)	0.644
Male	155 (61.3)	39 (23-71)	
Education level			
≤ Primary school	106 (41.9)	45 (27-84)	0.022
≥ Secondary school	147 (58.1)	35 (22-66)	
Having financial problems in HIV treatment			
No	165 (65.2)	38 (23-67)	0.282
Yes	88 (34.8)	37 (22-84)	
Type of health insurance			
Universal coverage scheme	175 (69.2)	43 (26-79)	0.024
Other	78 (30.8)	30 (20-56)	
Having underlying disease			
No	210 (83.0)	41 (26-75)	0.073
Yes	43 (17.0)	27 (19-66)	
Site of HIV care			
Regional hospital	120 (47.4)	29 (20-54)	0.003
General hospital	75 (29.7)	58 (30-94)	
Community hospital	58 (22.9)	47 (31-82)	
History of missed appointments			
No	213 (84.2)	35 (22-67)	0.002
Yes	40 (15.8)	62 (35-175)	
Serostatus of sexual partner			
HIV-positive	44 (17.4)	45 (27-80)	0.460
HIV-negative	37 (14.6)	30 (15-66)	
Unknown serostatus	55 (21.7)	35 (21-61)	
No partner	117 (46.3)	41 (27-77)	
Timing of HIV diagnosis			
Before OIs/ ADI diagnosis	152 (60.1)	39 (22-67)	0.369
After OIs/ ADI diagnosis	101 (39.9)	37 (26-92)	
Continue linkage to care after HIV diagnosis			
No	64 (25.3)	48 (25-180)	< 0.001
Yes	189 (74.7)	36 (23-65)	
Type of OIs/ADI			
PCP	66 (26.1)	28 (22-48)	0.006
TB (except for TB meningitis)	91 (36.0)	61 (36-84)	
Central nervous system infections[b]	18 (7.1)	48 (38-61)	
Other OIs/ADI	78 (30.8)	27 (15-62)	
CD4 count before ART initiation			
< 200 cells/mm^3	226 (89.3)	38 (23-71)	0.951
≥ 200 cells/mm^3	27 (10.7)	41 (22-75)	
HBV or HCV co-infection			
No	190 (75.1)	35 (22-67)	0.146
Yes	35 (13.8)	50 (25-84)	
Unknown	28 (11.1)	48 (26-103)	
Number of hospital admissions in the past six months			
0-1	189 (74.7)	33 (21-62)	< 0.001
> 1	64 (25.3)	62 (36-112)	
Believing that ART could cure HIV infection			
No	140 (55.3)	35 (23-66)	0.064
Yes	47 (18.6)	38 (23-93)	
Not sure	66 (26.1)	52 (27-75)	

[a] *– log-rank test;* [b] *– toxoplasmosis, cryptococcal meningitis, TB meningitis*

having a history of more than one hospital admission in the past six months was also associated with a longer time to ART initiation (aHR = 0.60; 95% CI: 0.44-0.81%). A group of patients with a history of missed appointments had a 38% lower hazard rate compared with those with no history of missed appointments. In addition, CD4 count and serostatus of sexual partner were not associated with the time to ART initiation after OIs/ ADI diagnosis.

Discussion

The current hospital-based cohort study provided evidence of the time to ART initiation in ART-naïve patients with OIs or ADI. Tuberculosis had the longest time to ART initiation after OIs/ADI diagnosis. Among our study participants, continued linkage with HIV care was associated with a shorter time to ART initiation. Conversely, the waiting time to ART initiation was significantly prolonged in those who were diagnosed with HIV after OIs/ADI diagnosis, having TB co-infection, HBV/HCV co-infection, several hospital admissions, and history of missed appointments. Patients who sought care at a general hospital and community hospital were independently associated with a longer waiting time to ART initiation.

Early HIV diagnosis and linkage with care are crucial for timely HIV treatment. Patient engagement in care is as-

sociated with better health outcomes and lower healthcare costs [19, 20]. However, our study found that a quarter of the patients did not engage in care after HIV diagnosis. A lack of care linkage was also reported in 26.2% of newly HIV-diagnosed patients in South Africa [21]. Related barriers included stigma, unawareness of the importance of early care engagement, poor organizational structure, overcrowded clinics, long waiting times, and inadequate resources [21, 22]. The results suggest that strategies to improve the establishment of care and early utilization of HIV treatment should be strengthened in routine HIV care in the country. To enhance retention in care, obstacles of continuous care engagement should also be explored.

Late HIV diagnosis remains in the era of universal access to ART. Similar to other studies [5, 6], a substantial proportion of our studied patients (39.9%) presented with advanced HIV disease, and HIV diagnosis was made after OIs/ADI. As the baseline CD4 is an important predictor of the magnitude of CD4 recovery [23, 24], routine HIV testing should be strongly encouraged among at-risk population in order to target the optimal benefits of ART.

Approximately one-fifth of our participants believed that ART could cure HIV infection. Misconceptions regarding ART efficacy might encourage the engagement of patients in risky behaviors. However, data from previous studies showed inconclusive results regarding the association of ART beliefs and sexual behaviors [25-27]. Although the risk behaviors among the studied sample was not explored in our study, misconceptions regarding ART benefits highlight the need for education programs tailored for this sub-population.

Not surprisingly, the awareness of HIV after OIs/ADI diagnosis is associated with a longer waiting time to ART initiation. Our observations were similar to the results of previous studies [15, 16]. Tweya *et al.* found that patients who learned about their HIV status before tuberculosis diagnosis had a shorter time to ART initiation [15]. On the other hand, for patients who presented late for care and HIV testing, a longer time to intensive counselling and follow-up of patients might be crucial. Furthermore, a sub-group of patients, in whom HIV diagnosis was made after 14 days of OIs/ADI could reflect a lack of formal linkage between voluntary counselling and testing (VCT) unit and patient care settings. Service systems that facilitate HIV testing and connect patients to treatment should be improved along with the increasing awareness of healthcare providers on HIV testing among at-risk populations.

Consistent with other studies [10, 11, 13, 14], the impact of type of OIs on time to ART initiation was found in our study. Tuberculosis co-infection patients had a significantly longer waiting time to ART initiation. Concerns regarding side effects of anti-tuberculous drugs and the potential for drug-drug interactions might partly explain this finding. Moreover, polypharmacy might put patients at difficulty with medication adherence, leading to poor treatment outcomes. Although TB patients had the longest waiting time to ART initiation, the median time of two months from TB diagnosis to ART was still in line with the current ART recommendations for TB patients [1, 28].

Table 2. Factors associated with time to ART initiation among HIV patients co-infected with OIs/ADI (*N* = 253)

Variables	Adjusted HR (95% CI)	*p*-value
Continue linkage to care after HIV diagnosis		
No	1	< 0.001
Yes	2.42 (1.70-3.45)	
Type of OIs/ ADI		
PCP	1	
TB (except for TB meningitis)	0.52 (0.36-0.75)	< 0.001
Central nervous system infections[a]	0.68 (0.40-1.18)	0.172
Other OIs	1.05 (0.74-1.50)	0.776
HBV or HCV co-infection		
No	1	
Yes	0.59 (0.39-0.89)	0.012
Unknown	0.79 (0.51-1.23)	0.299
Site of HIV care		
Regional hospital	1	
General hospital	0.67 (0.49-0.93)	0.016
Community hospital	0.62 (0.44-0.86)	0.004
Number of hospital admissions in the past six months		
0-1	1	0.001
> 1	0.60 (0.44-0.81)	
History of missed appointments		
No	1	0.016
Yes	0.62 (0.42-0.91)	
Timing of HIV diagnosis		
Before OIs/ADI diagnosis	1	
After OIs/ADI diagnosis	0.42 (0.30-0.57)	< 0.001
CD4 count before ART initiation		
< 200 cells/ mm3	1	0.236
≥ 200 cells/ mm3	1.30 (0.84-2.00)	
Serostatus of sexual partner		
HIV-positive	1	
HIV-negative	1.15 (0.72-1.83)	0.563
Unknown serostatus	1.41 (0.92-2.14)	0.114
No partner	1.08 (0.75-1.56)	0.675

[a] *– toxoplasmosis, cryptococcal meningitis, TB meningitis*

Patients with several hospital admissions had a significant delay in ART initiation. In our study settings, ART initiation was mostly provided in a HIV clinic of outpatient department. A lag time between hospital stay and first hospital appointment visit after discharge might delay patients' ART

initiation. A previous study showed that provision of ART in an in-patient department was associated with a shorter time to ART initiation [10]. Therefore, strategies to improve ART access among in-patients who are ready for antiretroviral treatment is required.

The influence of HBV or HCV co-infection on time to ART initiation was detected in the present study subjects. The finding of a longer waiting time to ART among HBV or HCV co-infected patients may reflect the provider's awareness of the risks of ART initiation (i.e., hepatitis flare from IRIS or hepatotoxicity as a result of non-nucleoside reverse transcriptase inhibitors-containing regimen, which is the recommended regimen in our country). To explore this issue, a qualitative study focusing on the healthcare providers' perspective is necessary.

In the present study, patients seeking care in a general hospital and community hospitals had a significantly longer waiting time to ART initiation. The differences of HIV service systems and resources among the settings might explain this finding. During the study period, the general hospital had only one ID physician, but none in the community hospitals. Approximately two-thirds of the studied participants in the community hospitals were referred to a higher level hospital for cryptococcosis and CMV screening, and one-third of patients for OIs treatment before ART initiation. Additionally, patients' acceptance and readiness for ART have been reported as an important factor related to the delay of ART initiation [9, 29]. In this study, a difference between the patients who reside in urban and those in rural areas regarding ART readiness and willingness to start the treatment was not investigated, and therefore require further research.

As in a previous study [30], the impact of history of missed appointments on time to ART initiation was detected in patients. Providers' concerns about ART non-adherence among patients with a history of missed appointments have been cited as the reasons for deferring ART [9, 29]. To shorten the waiting time to ART and maximize treatment benefits, the barriers of appointments' adherence should be identified, and strategies for improving adherence should be reinforced.

Since 2014, Thai HIV treatment guideline recommend ART for all HIV-positive individuals, regardless of CD4 cell count [28]. Despite the universal ART access, the low CD4 levels at the time of ART initiation of most studied patients emphasize the need to reinforce early HIV testing and continuous care retaining. To target the goals of "Treatment as Prevention", strategies with an emphasis on linking HIV-infected people to care is urgently required.

Several limitations of the current study should be acknowledged. First, the studied participants were outpatient in nature, data of patients who died or were lost to follow-up before entering a HIV clinic were not acquired. Second, the number of participants was less than expected, and may affect the statistical power to explore all possible associated factors. Third, the study results might also be influenced by the Hawthorne effect. Lastly, the provider's perspective can influence ART initiation, but was not explored in our study. Despite these concerns, to the best of our knowledge, this is the first report that reflects the time to ART initiation in ART-naïve patients co-infected with OIs/ADI in Thailand. In addition, this hospital-based prospective cohort study can indicate the need to access to HIV treatment in actual clinical settings, as the majority of HIV-infected population in the country seek care in the public hospitals.

Conclusions

Among HIV patients co-infected with OIs/ADI, a longer time to ART initiation remains in the era of universal access to ART. Our findings support the necessity of systems with well-organized structure for OIs/ADI treatment and HIV care. Strategies to improve HIV awareness, continuous care engagement, and early ART initiation are crucial.

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Conflict of interest

The authors declare no conflict of interest.

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