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Incidence and Risk Factors of Opportunistic Infections in HIV-Infected Adults on Antiretroviral Therapy

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ABSTRACT

Although the majority of people living with HIV in Thailand receive antiretroviral therapy, which helps suppress the replication of virus and improve the immune system, the mortality rate for people living with HIV remains high. Opportunistic infections are found to be the leading cause of morbidity and mortality in this population. This research aimed to study the incidence and risk factors of opportunistic infections in HIV-infected adults receiving the highly effective antiretroviral therapy (HAART) who visited Takhli Hospital, Nakhon Sawan from January 2005 - September 2019. After obtaining human ethics approval, medical records of the study population were retrieved from the Takhli Hospital database (HOSxP database) and were reviewed. Incidence rates of opportunistic infections were analyzed by the Kaplan-Meier method and multifactorial variables were assessed using the Cox regression model. Of the 280 HIV-infected adults, 50.7% were male, and the median age at HAART initiation was 36.8 years (interquartile range: 30.4 - 43.9 years). The incidence of opportunistic infections was 14.08 per 1,000 person-years (95% Confidence Interval [95% CI]: 10.06 - 19.71). The risk factors for opportunistic infections in HIV-infected adults were receiving efavirenz antiretroviral drug (Adjusted Hazard Ratio [HR_{adj}] = 3.07, 95% CI: 1.44-6.50) and having a CD4 lymphocyte count ≤350 cells/mm^3 (HR_{adj} = 5.43, 95% CI: 2.08-14.17). Overall, our findings suggest that caution should be exercised when initiating the antiretroviral therapy for newly infected HIV patients, particularly with the efavirenz-based regimen, and the CD4 lymphocyte numbers should be taken into consideration to minimize the occurrence of opportunistic infections.

Keywords: AIDS; Antiretroviral therapy; HIV; Opportunistic infections

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1. Introduction

HIV-infection and AIDS continues to be a major health problem in all countries around the world. In 2018, there were an estimated 37.9 million people living with HIV (PLHIV). In Thailand, it is estimated that there are 480,000 PLHIV, with approximately 360,000 (75%) receiving treatment and 18,000 deaths from AIDS [1].

Thailand aims to implement the National Strategic Plan on Ending AIDS Problems 2017-2030 to address the problem of HIV/AIDS according to the guidelines of the World Health Organization (WHO) and the United Nations AIDS Program. There are three goals for implementation following the 90-90-90 principle: Goal 1 is that 90 percent of HIV-infected individuals will know their status; Goal 2 is that 90 percent of people diagnosed with HIV will be treated with antiretroviral therapy (ART); and Goal 3 is that 90 percent of PLHIV who receive ART will have viral suppression [2]. In Thailand, the Reach-Recruit-Test-Treat-Retain (RRTTR) measure has been implemented and is aimed at achieving the 90-90-90 goals so that PLHIV can receive effective ongoing care leading to healthy longevity [3].

The main therapeutics for PLHIV/AIDS include a Highly Active Antiretroviral Therapy (HAART) which is a regimen that combines three or more antiretroviral drugs. It aims to reduce the amount of virus in the bloodstream to an undetectable level (below 40 copies/mL) and, simultaneously, to restore the CD4 lymphocyte count to a normal level (500-1,500 cells/mm^3), thereby reducing the risk of mortality and morbidity from AIDS complications. Nevertheless, the mortality rate of HIV/AIDS is still high, and opportunistic infections (OIs) are a major cause of death. Some common OI pathogens included *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Candida* spp., *Pneumocystis jirovecii*, Cytomegalovirus, *Toxoplasma gondii* and *Penicillium marneffei* [4-6].

Despite taking HAART, PLHIV may still acquire OIs. Previous studies have found factors associated with increased risk of OIs among PLHIV who take HAART; these include gender (i.e., female [7], and male [8]), patients whose marital status is single [9], being on an antiretroviral regimen with efavirenz [10], having a CD4 lymphocyte count <350 cells/mm^3 [11], WHO clinical stage 3 and 4 disease [12, 13], an increased HIV RNA load per 1 $\log_{10}$ copies/mL [14] and receiving OI prophylaxis [12].

According to the Thailand National Guidelines on HIV/AIDS Treatment and Prevention in 2014, OIs were the most common cause of death in PLHIV [15]. These infections included tuberculosis (50%), Pneumocystis pneumonia (26.3%) and cryptococcal meningitis (8.3%) [15]. Nakhon Sawan Province has the highest number of PLHIV receiving treatment in Health Region 3, with a mortality rate after treatment at 16% in 2019 [16]. A previous study analyzing the causes of death in Nakhon Sawan Province revealed that infectious diseases were the second most common cause of death, and HIV/AIDS was ranked as the most frequent cause (accounting for 60.6%) among all infectious diseases [17]. Data from the 2019-2020 National AIDS Program in Thailand study showed that the most common cause of death in PLHIV in Nakhon Sawan Province was OIs [16]. Moreover, it reported that Takhli District had an increasing trend of HIV infection in 2020 (from 13.3% to 14.0%) [16]. Among OIs, the three leading causes of death in PLHIV were pulmonary tuberculosis (42.86%), cryptococcal meningitis (14.29%) and Pneumocystis pneumonia (14.29%) [16]. Therefore, this study aimed to investigate the incidence and risk factors associated with the development of OIs in PLHIV who received HAART at Takhli Hospital.

2. Materials and Methods

2.1 Ethical considerations

This study was approved by the Human Research Ethics Committee of Thammasat University (No.044/2564).

2.2 Study design

This retrospective cohort study collected important variables from the HOSxP database. The inclusion criteria were: (1) patient was naïve to antiretroviral therapy (ART) and attended the Takhli Hospital; (2) patient began HAART between 1 January 2005 and 30 September 2019; and (3) patient had received HAART for more than 15 months. The exclusion criteria were: PLHIV who were under 18 years old, a history of OIs before treatment initiation, or imprisonment during the investigation period. All patients were followed up with until 31 December 2020, at which point data collection was halted for purposes of analysis. Patient disposition is outlined in Fig. 1.

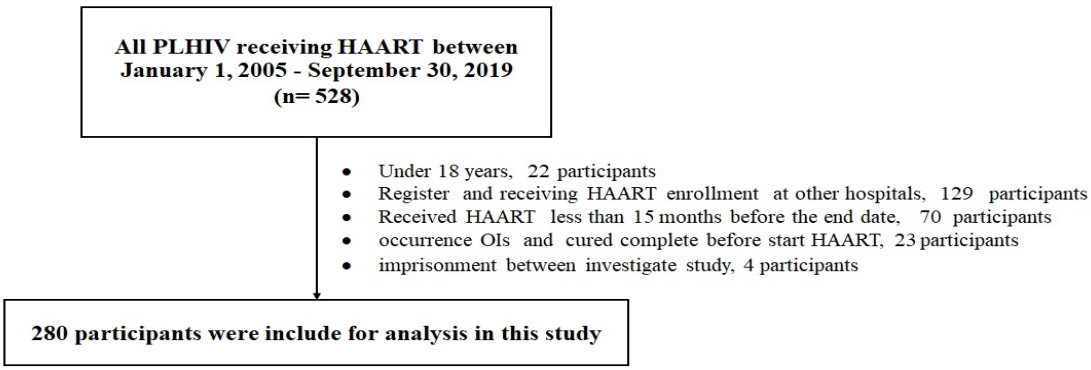

Fig. 1. Patient's disposition.

2.3 Data collection

Data from all patients with ongoing regimens, including those who were lost during follow-up, were censored on the date of the patients' last contact with the clinic. Baseline characteristics and laboratory values were determined at the time of initiation of the first regimen for each patient (range, -6 months to treatment initiation). OI events were defined as the first OI after treatment initiation. OIs were defined as infection with *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, *Cryptococcus neoformans*, *Candida* spp., *Toxoplasma gondii*, *Penicillium marneffei*, *Histoplasma capsulatum*, Cytomegalovirus or *Mycobacterium avium* complex.

2.4 Statistical analysis

The first part of the analysis was based on data from patients with their first OI diagnosed anytime during the study period. Continuous variables including age, body mass index, CD4 lymphocyte count and HIV RNA Load were assessed for their normality using Shapiro-Wilk test. Variables with a non-normal distribution are presented as median and interquartile range (IQRs), whereas categorical variables are presented as frequencies and percentages. A high/low CD4 lymphocyte count in relation to being an OI risk factor was defined as >350/≤ 350 cells/mm^3 (as suggested by Mohammadi et al. [18]). In addition, a detectable/undetectable HIV RNA Load in relation to being an OI risk factor was defined as >40/≤ 40 copies/mL as suggested by Ekwaru et al. [19]. Cumulative OI rates at 6 months, and 1, 2, 3, 4, 5, 10 and 15 years after treatment initiation were estimated by using Kaplan-Meier curves. Risk factors associated with OIs were identified by using

Cox proportional hazard regression models. Clinically relevant variables or potential associated factors with p-values of less than 0.25 in the univariable analyses (i.e., sex, age, marriage status, antiretroviral regimen based, CD4 lymphocyte count, HIV RNA load, comorbidity and receiving/not receiving prophylaxis) were included in a multivariable analysis with backward elimination [20]. WHO staging was also included in the Cox regression analyses. Covariances that were collinear were excluded from the multivariable model. All analyses were performed using Stata version 15 (StataCorp, College Station, Texas, USA).

3. Results

3.1 Participants demographic

In total, 280 participants, mostly male (142, 50.7%), median age 36.8 years (IQR: 30.4–43.9) initiated HAART (Table 1). Demographic and clinical characteristics of all 280 participants at treatment initiation are summarized in Table 1.

Table 1. Demographic and clinical characteristics of participants (*n*=280).

Characteristic	Frequency	Percent
Sex		
male	142	50.7
female	138	49.3
Age (years)		
18-29	63	22.5
30-39	111	39.6
40-49	73	26.1
≥50	33	11.8
Median (IQR)	36.8(30.4-43.9)	
Body Mass Index (kg/m^2)		
thin (<18.5)	20	7.1
normal (18.5-22.9)	137	49.0
overweight (23.0-24.9)	40	14.3
obese (≥25.0)	83	29.6
Median (IQR)	22.4 (20.4-25.7)	
Marriage status		
single	61	21.8
married/couple	156	55.7
widowed/divorced	63	22.5
Antiretroviral regimen based		
NVP-based	218	77.9
EFV-based	60	21.4
PIs-based	2	0.7
CD4 lymphocyte count (cells/mm^3)		
<200	56	20.0
200-350	53	18.9
351-500	76	27.1
>500	95	34.0
Median (IQR)	416.5 (245.5-569.5)	
HIV RNA Load (copies/mL)		
≤40	254	90.7
41-1,000	12	4.3
>1,000	14	5.0
Median (IQR)	40 (40-40)	
WHO stage		
Asymptomatic	186	66.4
Symptomatic	34	12.2
AIDS	60	21.4
Comorbidity		
no	277	99.0
yes	3	1.0
hepatitis B	1	33.3
hypertension	2	66.7
Prophylaxis		
not receive	193	68.9
receive	87	31.1
Cotrimoxazole	82/87	94.3
Fluconazole	73/87	83.9
Azithromycin	40/87	46.0
Dapsone	4/87	4.6
Itraconazole	1/87	1.2

IQR, interquartile range; NVP, nevirapine; EFV, efavirenz; PI, protease inhibitor.

3.2 Incidence of opportunistic infections.

From the 280 participants included in this study, 34 (12.14%) developed OIs. Of these, 15 (44%) patients had tuberculosis, (26%) had candidiasis, 6 (18%) had Pneumocystis pneumonia, 1 (3%) had cryptococcosis, 1 (3%) had Mycobacterium avium complex infection, 1 (3%) had Talaromycosis and 1 (3%) had toxoplasmosis.

The cumulative OI rates after treatment initiation of the 280 patients are shown in Figure 2. OI incidence was 14.08 per 1,000 person-years (95% CI: 10.06 - 19.71). The OI rates at 6 months, 1, 2 and 5

years after treatment initiation were 4.64% (95% CI: 2.72-7.86), 5% (95% CI: 2.99-8.30), 6.10% (95% CI: 3.84-9.63) and 8.13% (95% CI: 5.42-12.10), respectively (Table 2). Of the 13 of 34 patients who were diagnosed with OIs at 6 months post-initiation, 2 of these 13 patients developed OIs which were tuberculosis and pneumocystis pneumonia with severe symptoms and were defined as unmasking immune reconstitution inflammatory syndrome.

3.3 Factors associated with OIs among PLHIV who received HAART.

In the univariable analysis, male gender (Crude hazard ratio [HR_{crude}] = 2.26; 95% CI: 1.10-4.64; *p*-value = 0.024), receiving Efavirenz (HR_{crude} = 4.91; 95% CI: 2.40-10.06; *p*-value < 0.001), CD4 lymphocyte count ≤ 350 cells/mm^3 (HR_{crude} = 8.16; 95% CI: 3.53-18.85; *p*-value <0.001), HIV RNA load >1,000 copies/mL (HR_{crude} = 5.66; 95% CI: 2.13-13.89; *p*-value = 0.007), comorbidity (HR_{crude} = 14.51; 95% CI: 3.34-62.98; *p*-value = 0.008) and prophylaxis use (HR_{crude} = 4.41; 95% CI: 2.19-8.86; *p*-value < 0.001) were associated with OIs (Table 3).

In the multivariable analysis, OIs were independently associated with efavirenz-based regimen (Adjusted hazard ratio [HR_{adj}] = 3.07; 95% CI: 1.44-6.50), and CD4 lymphocyte count ≤ 350 cells/mm^3 (HR_{adj} = 5.43; 95% CI: 2.08-14.17) after adjusting for prophylaxis use and WHO stage (Table 4).

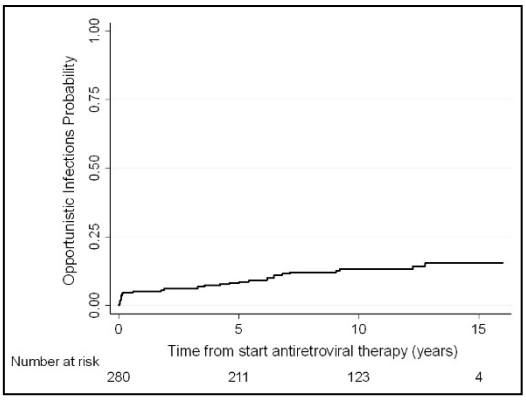

Fig. 2. Kaplan-Meier curve showing OIs in PLHIV on HAART.

Table 2. The cumulative probability of OIs after receiving HAART.

Duration between HAART start to OI occurrence	OI frequency (*n*)	Cumulative probability of OIs	95% CI
6 months	13	4.64	2.72-7.86
1 years	1	5.00	2.99-8.30
2 years	3	6.10	3.84-9.63
3 years	0	6.10	3.84-9.63
4 years	3	7.29	4.76-11.07
5 years	2	8.13	5.42-12.10
10 years	10	13.22	9.46-18.30
15 years	2	15.39	10.93-21.44

Table 3. Results of univariable proportional hazards analyses of OI risk.

Risk factors	Frequency of OIs *n*/N (%)	HR_{Crude} (95% CI)	*p*-value
Sex			0.024
female	11/138 (8.0)	1.00	
male	23/142 (16.2)	2.26 (1.10-4.64)	
Age (years)			0.060
18-29	9/63 (14.3)	1.00	

Table 3. Results of univariable proportional hazards analyses of OI risk (continuous).

Risk factors	Frequency of OIs *n*/N (%)	HR_{Crude} (95% CI)	*p*-value
30-39	10/111 (9.0)	0.55 (0.22-1.37)	
40-49	7/73 (9.6)	0.61 (0.23-1.66)	
≥50	8/33 (24.2)	2.04 (0.78-5.31)	
Body Mass Index (kg/m^2)			0.820
normal	18/137 (13.1)	1.00	
thin	3/20 (15.0)	1.30 (0.38-4.43)	
overweight	4/40 (10.0)	0.78 (0.26-2.33)	
obese	9/83 (10.8)	0.75 (0.33-1.67)	
Marriage status			0.193
married/couple	16/156 (10.3)	1.00	
single	11/61 (18.0)	2.03 (0.94-4.38)	
widowed/divorced	7/63 (11.1)	1.02 (0.42-2.50)	
Antiretroviral regimen based			<0.001
NVP-based/Protease Inhibitor	20/220 (9.2)	1.00	
EFV-based	14/60 (23.3)	4.91 (2.40-10.06)	
CD4 lymphocyte count (cells/mm^3)			<0.001
> 350	7/171 (4.1)	1.00	
≤ 350	27/109 (24.8)	8.16 (3.53-18.85)	
HIV RNA Load (copies/mL)			0.007
≤ 40	26/254 (10.2)	1.00	
41-1,000	2/12 (16.7)	1.57 (0.37-6.63)	
> 1,000	6/14 (42.9)	5.66 (2.31-13.89)	
WHO stage			0.300
Asymptomatic	24/186 (12.9)	1.00	
Symptomatic and AIDS	10/94 (10.6)	0.67 (0.32-1.41)	
Comorbidity			0.008
no	32/277 (11.6)	1.00	
yes	2/3 (66.7)	14.51 (3.34-62.98)	
Prophylaxis			<0.001
not received	14/193 (7.3)	1.00	
received	20/87 (23.0)	4.41 (2.19-8.86)	

HR_{crude} = Crude hazard ratio; 95% CI = 95% confidence interval; *n* =number of PLHIV occurred OIs; N = number of PLHIV.

Table 4. Results of multivariable proportional hazards analyses of OI risk.

Risk factors	HR_{adj}	95% CI	*p*-value
Antiretroviral regimen based			0.003
Nevirapine/Protease Inhibitor	1.00		
Efavirenz	3.07	(1.44-6.50)	
CD4 lymphocyte count (cells/mm^3)			0.001
>350	1.0		
≤350	5.43	(2.08-14.17)	
Prophylaxis			0.301
not received	1.00		
received	1.52	(0.68-3.38)	
WHO stage			0.716
Asymptomatic	1.00		
Symptomatic and AIDS	0.86	(0.39-1.87)	

HR_{adj} = adjusted hazard ratio; 95% CI = 95% confidence interval.

4. Discussion

The present study found that the incidence rate of OIs in PLHIV after initiation of HAART was 14.08 cases/1,000 person-years. This incidence rate was similar to the rate reported from Arba Minch, Ethiopia which was 11.59 cases/1,000 person-years [21]. However, this incidence rate was lower than that found in Vietnam and Uganda which were 46.7 and 59.4 per 1,000 person-years, respectively [14, 22]. The reason for the lower OI incidence rate in our study could possibly be because the majority of PLHIV participating in this study were in the asymptomatic stage, had relatively high CD4 lymphocyte counts and lower HIV RNA loads at the onset of ART, compared to other studies [23]. Moreover, ethnic and cultural differences may have had an influence on these findings.

In our study, PLHIV developed OIs during the first 6 months after taking ART. As the duration of ART increased, the incidence of acquiring OIs lessened. This finding is consistent with studies in Taiwan and France, where PLHIV developed OIs within the first 90 days (HR_{adj} = 6.92; 95% CI = 5.28-9.08) and the first 2 months (HR_{adj} = 2.6; 95% CI = 1.2-5.5) after starting the antiretroviral therapy, respectively [24, 25]. Similarly, a study from Ethiopia revealed the incidence of OIs was 39% during the first 6 months and 35% within 12 months after starting ART [26]. It is likely that the CD4 lymphocyte count was a factor contributing to the positive effect on the patients' clinical status, especially during the first 6 months after the treatment began, as CD4 lymphocyte count increased rapidly, especially during the first 3-6 months, then decreased and stabilized [27].

Of the 13 PLHIV who developed OIs in the first 6 months after receiving HAART, 2 developed OIs which were tuberculosis and pneumocystis pneumonia with severe symptoms and were defined as unmasking immune reconstitution inflammatory syndrome (IRIS) [28]. This unmasking IRIS can occur in PLHIV who have a low CD4 lymphocyte count initially and subsequently have an improvement in their CD4 lymphocyte count after HAART initiation [29]. IRIS can be serious and can cause mortality in PLHIV, especially for those who have a CD4 lymphocyte count of less than 100 cells/mm^3 at the start of ART [30]; furthermore, tuberculosis is among one of the most common IRIS [31]. Most IRIS occurs within the first 30 days after starting ART, and following this trend, the 2 patients in the present study developed this condition within their first month of treatment.

The results of this study revealed a statistically significant increase in the incidence of OIs in PLHIV with a low CD4 lymphocyte count at the start of HAART. The risk of developing OIs was 5.43 times higher in PLHIV with CD4 lymphocyte counts ≤ 350 cells/mm^3 than it was in those with CD4 lymphocyte counts > 350 cells/mm^3. This finding is consistent with reports from other studies: the study in Ethiopia showed that PLHIV with CD4 lymphocyte counts less than 350 cells/mm^3 at the start of ART were 3.38 times more likely to get an OI [11]. Similarly, a study of PLHIV/AIDS in Iran found that patients with CD4 lymphocyte counts of less than 350 cells/mm^3 had a 2.2 times increased risk of OI (HR_{adj} = 2.21; 95% CI = 1.84-2.64) [18]. A systematic analysis also demonstrated that PLHIV with CD4 lymphocyte counts greater than 350 cells/mm^3 had a reduced risk of OIs by 57% (HR_{adj} = 0.35; 95% CI = 0.30-0.63) [32].

In addition, this study found that ART regimens were a risk factor for OIs. PLHIV who received efavirenz had a 3.17 times higher risk of OIs compared to those who received nevirapine or protease inhibitors. This result was intriguing us. Therefore, we further tested if this finding was affected by confounding bias, namely CD4 lymphocyte counts. It was found that PLHIV receiving an efavirenz based regimen had significantly

lower CD4 lymphocyte count (median 252; IQR 106 - 452 cells/mm^3) compared to PLHIV receiving a nevirapine/protease inhibitor regimen (median 433; IQR 310 - 780 cells/mm^3) (p-value < 0.001). However, after Cox regression analysis (as shown in Table 4), it was demonstrated that when the CD4 lymphocyte count was controlled for, efavirenz still posed a greater risk for OIs than a nevirapine/protease inhibitor regimen. This finding was also unchanged when other variables (i.e., OI prophylaxis and WHO stage) were controlled for. Although efavirenz and nevirapine are both non-nucleoside reverse transcriptase inhibitors, efavirenz is more favorable as it has less liver toxicity.

The finding that the efavirenz regimen is associated with a risk of acquiring OIs in this study corresponds to studies in Tanzania, where PLHIV who received nevirapine had a lower risk of OIs by 64%. Efavirenz was also associated with discontinuation of treatment due to adverse drug events [31]. However, a previous study in Uganda found that efavirenz reduced the incidence of OIs over the long-term throughout antiretroviral therapy [11]. Efavirenz is recommended for the treatment of PLHIV in Thailand due to it having a lower toxicity than nevirapine [32].

Prophylaxis is effective for reducing the development of OIs. The effectiveness of prophylaxis for preventing infection found in this study has also been found in previous reports [11-13, 33]. However, when confounding factors were controlled for and analyzed with multivariable analysis, no association was found between prophylaxis and OI rate (HR_{adj} = 1.52; 95% CI = 0.68-3.38). A previous study of PLHIV in Ethiopia found no statistically significant difference with/between OIs among those who took co-trimoxazole and/or isoniazid prophylaxis and those who did not take the prophylaxis. Receiving cotrimoxazole and/or isoniazid prophylaxis was not found to be associated with reducing the development of OIs [34]. The univariate analysis in the present study also found that HIV RNA load was a risk factor for OIs (p-value=0.007); however, it was found that this factor was with CD4 lymphocyte count in the multivariate analysis.

5. Conclusion

This study found that the incidence of OIs in PLHIV who received HAART was 14.08 per 1,000 person-years, highest during the first 6 months of treatment when OIs were found in 4.64% of the studied population. PLHIV who are receiving efavirenz or who have a low CD4 lymphocyte count (≤ 350 cells/ mm^3) are at a higher risk of getting OIs. In line with the results from this study, the latest Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2021/2022 has suggested that healthcare providers should implement monitoring processes (i.e. screenings for OIs, which include chest X-rays, tuberculin skin tests, and serum cryptococcal antigen detection, as well as monitoring CD4 lymphocyte count) when starting antiretroviral therapy, especially during the first 6 months of treatment with efavirenz, even if PLHIV are given OI prophylaxis. Screening for OIs in PLHIV who are about to begin efavirenz treatment or who have a low CD4 lymphocyte count should reduce the risk of OIs and lower the mortality rate of PLHIV.

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