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Prevalence of Advanced HIV Disease, Cryptococcal Antigenemia, and Suboptimal Clinical Outcomes Among Those Enrolled in Care in Vietnam

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Background: People living with advanced HIV disease are at high risk of morbidity and mortality. We assessed the prevalence of cryptococcal antigenemia (CrAg) and clinical outcomes among patients newly presenting with CD4 ≤100 cells/μL in Vietnam.

Setting: Twenty-two public HIV clinics in Vietnam.

Methods: During August 2015–March 2017, antiretroviral therapy (ART)-naïve adults presenting for care with CD4 ≤100 cells/μL were screened for CrAg. Those who consented to study enrollment were followed up for up to 12 months and assessed for clinical outcomes.

Results: Of 3504 patients with CD4 results, 1354 (38.6%) had CD4 ≤100 cells/μL, of whom 1177 (86.9%) enrolled in the study. The median age was 35 years (interquartile range 30–40); 872 (74.1%) of them were men, and 892 (75.8%) had CD4 <50 cells/μL. Thirty-six patients (3.1%) were CrAg-positive. Overall, 1151 (97.8%) including all who were CrAg-positive initiated ART. Of 881 patients (76.5%) followed up for ≥12 months, 623 (70.7%) were still alive and on ART at 12 months, 54 (6.1%) had transferred to nonstudy clinics, 86 (9.8%) were lost to follow-up, and 104 (11.8%) had died. Among all 1177 study participants, 143 (12.1%) died, most of them (123, 86.0%) before or within 6 months of enrollment. Twenty-seven patients (18.9%) died of pulmonary tuberculosis, 23 (16.1%) died of extrapulmonary tuberculosis, 8 (5.6%) died of *Talaromyces marneffei* infection, and 6 (4.2%) died of opioid overdose. Eight deaths (5.8%) occurred among the 36 CrAg-positive individuals.

Conclusions: Late presentation for HIV care was common. The high mortality after entry in care calls for strengthening of the management of advanced HIV disease.

Key Words: advanced HIV, mortality, Vietnam, opportunistic infections, cryptococcal antigenemia

(*J Acquir Immune Defic Syndr* 2021;88:487–496)

INTRODUCTION

With a goal of ending AIDS by 2030, Vietnam has committed to the Joint United Nations Program on HIV and AIDS (UNAIDS) "95-95-95" strategy. In 2019, approximately 80% of the estimated 230,000 people living with HIV (PLHIV) in Vietnam were diagnosed, and, of them, 70% was on antiretroviral therapy (ART), of whom 66% was virally suppressed.[1] Since 2005, the Vietnam national ART program, largely supported by the President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria has widely scaled up ART across the country. However, despite remarkable progress in addressing the HIV epidemic, only 70% of PLHIV in the country is on treatment.[2]

The burden of advanced HIV disease (AHD) (defined as a CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4)[3] and associated opportunistic infections (OIs) among patients has not declined as expected because of limited access to services. Among patients enrolled in a randomized controlled trial who initiated ART between April 2011 and 2014 at a large HIV clinic in Hanoi, Vietnam, the median CD4 cell count at enrollment in HIV care was 130 cells/μL, and 35.5% (230/647) of participants had AIDS-defining OIs.[4] The high proportion of patients with advanced disease at the time of testing, delayed linkage to care, and late ART initiation all contribute to suboptimal clinical outcomes—lower retention rates, high loss to follow-up (LTFU), death, and OIs.[5] Cryptococcal disease is common among patients with advanced HIV and is an independent predictor of cryptococcal meningitis (CM) and death in HIV-infected individuals with advanced disease.[6] In Vietnam, Cryptococcosis was reported as the most common OI among HIV-infected persons in a study of patients presenting to a single hospital in Ho Chi Minh City in 2005.[7] In addition,

Received for publication June 13, 2021; accepted August 12, 2021.

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Supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the US Centers for Disease Control and Prevention (CDC) under the terms of grant number 3U01GH000758.

The authors have no conflicts of interest to disclose.

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stigma and discrimination toward PLHIV are common and affect health care–seeking behaviors and engagement in HIV care.[8–10]

In Vietnam[11,12] as elsewhere,[13,14] patients with AHD have higher mortality, often in the first 6 months of ART initiation, and more comorbidities, increasing the cost of care and treatment.[15] In the context of declining donor resources and widening HIV funding gap, understanding the extent of advanced disease and its associated outcomes is important to plan resources for the care and treatment of PLHIV and is critical for reducing AIDS-related deaths. For example, donor funding for HIV was projected to decline from $20 million to less than 5 million in 2016 and the resource gap to grow from $6.9 million in 2014 to $27.3 million in 2016.[16,17] Our study aimed to determine the proportion of patients who present for HIV care with very AHD (CD4 ≤100 cells/μL) and, among them, the prevalence of cryptococcal antigenemia (CrAg) and other reported OIs to determine clinical outcomes and to identify factors associated with mortality.

METHODS

Setting

In Vietnam, outpatient HIV care and treatment services are provided in outpatient clinics (OPCs) located either within health facilities or freestanding. In[18] 2015, when the study started, 95,752 patients were on ART in 312 OPCs throughout the country. OPCs with at least 60 ART patients were purposefully selected to reflect the following criteria: (1) district, provincial, or national level; (2) primary or tertiary care; (3) rural, peri-urban, and urban locations; (4) and the north and south of Vietnam. To fulfill those criteria and get a representative number of sites, 10 and 12 OPCs were selected from the northern and southern regions of the country, respectively. Our study was implemented in 22 (7.1%) of 312 OPCs that accounted for nearly a quarter of patients newly initiated on ART nationally in 2015.

Participants

ART-naïve persons aged 18 years or older who newly presented for HIV care during August 2015–March 2017 at any of the 22 study OPCs and who underwent CD4 testing were informed about CrAg screening and were potentially eligible for study enrollment. Reflex CrAg testing—using remnant plasma from routine CD4 testing—was conducted for patients with CD4 ≤100 cells/μL, consistent with national and WHO recommendations at the time of the study.[19–21] CD4 was conducted using flow cytometry, whereas CrAg testing was conducted using lateral flow immunochromatographic assay (LFA), Immy Diagnostics, Norman. Thus, separate consent for CrAg testing was not obtained. CD4 and CrAg results were returned from the laboratory to OPCs within 48 hours of sample receipt. At the time of CD4 and CrAg results delivery, patients with CD4 ≤100 cells/μL, regardless of CrAg results, were offered and consented for enrollment in a longitudinal follow-up study. Study participants were followed up longitudinally until the study ended (September 30, 2017). Patients with previous or current CM, those who had received systemic antifungal medication for more than 4 consecutive weeks within 6 months before study enrollment, or those who received ART for more than 4 consecutive weeks within the previous 12 months were excluded from study enrollment. The CrAg testing was not repeated in the follow-up visits among CrAg-negative patients.

Clinical Evaluation and Treatment

OPC staff assessed all patients at baseline according to standard OPC procedures and recorded clinical findings, including baseline CD4 and CrAg status, OIs, and any WHO staging illnesses and conditions, and assigned a WHO stage accordingly. PLHIV with presumptive TB were referred from HIV clinics to TB clinics for TB evaluation, using either AFB smear or Xpert MTB/RIF test. Diagnostic results were shared with the HIV clinics for documentation. Patients who were CrAg-negative were further counseled and started on ART according to national guidelines. CrAg-positive patients were assessed specifically for fever, headache, and stiff neck to exclude symptomatic meningitis. Those who did not have symptoms—asymptomatic CrAg-positive patients —received preemptive fluconazole at a dose of 900 mg daily for 2 weeks, followed by 450 mg daily for 8 weeks, and maintained at 200 mg daily until the CD4 exceeded 200 cells/μL for at least 6 months. We used a higher dose (900 mg/450 mg) than the WHO recommended 800 mg/400 mg because at the time of the study, the only available formulation in Vietnam was 150 mg tablets. Per national guidelines, lumbar punctures were not performed unless there were clinical signs of meningitis.[20] Other OIs were assessed according to standard practices.[20] In CrAg-positive patients, ART initiation was delayed by 2 weeks to enable completion of 2 weeks of preemptive therapy with fluconazole and prevent development of IRIS, especially because we were not able to exclude meningitis for lumbar punctures were not recommended in asymptomatic patients. All patients were initiated on ART based on national guidelines with tenofovir, lamivudine, and efavirenz.

Subsequent appointments for all patients were made 2 and 4 weeks after ART initiation and monthly thereafter per routine protocol for patients initiating ART.

Data Collection

Baseline data, including date of OPC registration, demographic, and clinical characteristics were abstracted from clinical records on the date of study enrollment and recorded in study case report forms; of note, risk factors such as injection drug use are not systematically collected in clinical records in Vietnam. Baseline OIs were defined as any OIs reported at the time of study enrollment or within 28 days after enrollment. Apart from CrAg screening, diagnosis of other OIs or other HIV-related conditions were made according to routine procedures and was based on diagnostic testing when reagents were available but was often presumptive. Hepatitis B and C serology was conducted routinely unless there were reagent stockouts.

Mortality information was collected from hospitalization records for those who died in the hospital or who were palliatively discharged. More detailed mortality information

was often obtained from family members when they contacted OPCs to obtain death certificates for the decedents or when the OPC contacted them to track missed appointments.

Study Outcomes

Study participants were followed up longitudinally. Clinical outcomes were documented at 12 months after study enrollment and included retained in care (alive and on ART), transferred, LTFU, undetermined, and death.

Patients who sought care from a nonstudy OPC during the follow-up period were considered to have transferred. Patients were considered retained in care if they had had a visit to a study OPC within 30 days of their 12-month appointment. According to the 2015 national HIV treatment guidelines, patients were considered LTFU if they did not return to the OPC for ART refills for 3 consecutive months (>90 days) from their last recorded appointment. After the end of the study, study staff contacted OPCs to determine the outcomes for patients who missed their 12-month clinic visit but did not yet meet the national criteria for LTFU. Patients for whom no subsequent information was available were considered to have an undetermined status.

The date of death was obtained from facility records or reports from family members. The cause of death was reviewed by an independent physician using the most recent hospitalization notes and communication with the treating doctor at the OPC where the patient was registered.

Statistical Analysis

The means, rates, and 95% confidence limits adjusted for within-OPC clustering for disease outcomes of interest were estimated using SAS PROC SURVEYFREQ, with differences between rates tested using Rao–Scott χ^2 tests. A P value of less than 0.05 was considered statistically significant. Mortality rates and 95% confidence limits were estimated and differences tested using a Poisson model in SAS PROC GENMOD, adjusting for OPC clustering using a generalized estimating equations error variance.

Time at risk was calculated from the date of study enrollment for all patients to the date of death or last clinic contact. Decedents were censored at the date of death, and patients who transferred to nonstudy OPC facilities or were LTFU were censored at the date of their last visit to the study OPC. Bivariate and multivariate Cox proportional hazards regression, adjusted for clustering within OPC using SAS PROC SURVEYPHREG, were used to identify factors associated with time to death and other outcomes 12 months after ART initiation. Variables with P values of ≤0.25 in bivariate analysis were included in the multivariate analysis. Unadjusted and adjusted hazard ratiosHRs, 95% confidence intervals (CIs), and P values are presented. Kaplan–Meier analysis was used to compare survival times using log rank tests among patients with CD4 <50 cells/μL vs CD4 ≥50 cells/μL. This stratification was made because mortality is highest in patients with CD4 <50 cells/μL.[22,23] Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc.) and IBM SPSS Statistics for Windows, version 24.0 (Armonk, NY IBM Corp.).

Ethics Statement

The study was approved by the institutional review boards at the US Centers for Disease Control and Prevention (CDC) Atlanta, National Hospital for Tropical Diseases (NHTD) in Hanoi, and Ho Chi Minh City Hospital for Tropical Diseases and registered on the ClinicalTrials.gov website (ClinicalTrials.gov Identifier: NCT02955862).

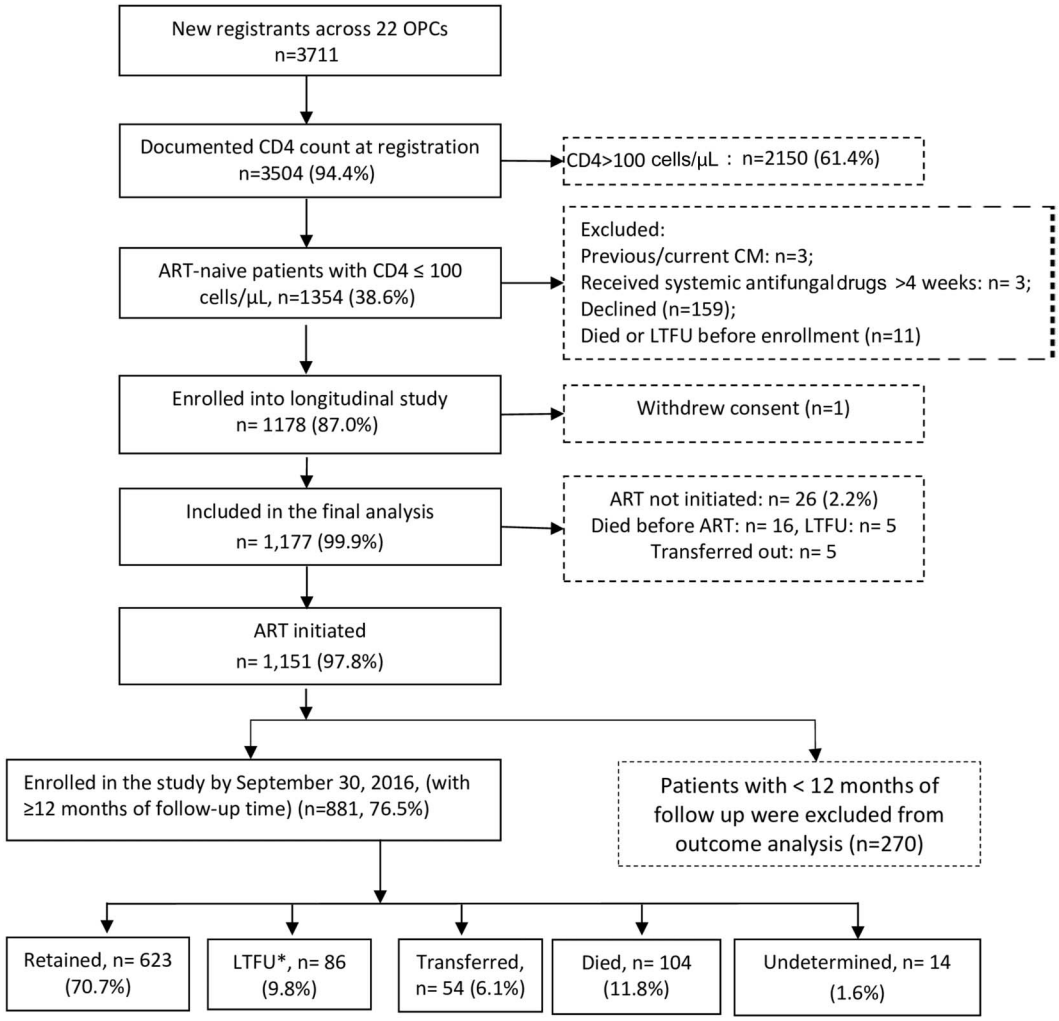
RESULTS

During August 2015–March 2017, 3711 adults with newly diagnosed HIV presented for HIV care at the 22 study OPCs in 10 provinces in Vietnam; 3504 (94.4%%) underwent CD4 testing (Fig. 1). Of those with a CD4 result, 1354 (38.6%) had a CD4 count ≤100 cells/μL. There were no major changes in the proportion with CD4<100 cells/μL observed by year of diagnosis over the study period (39.9%, 38.4%, and 39.1%, in 2015, 2016, and 2017, respectively). Of 1354 patients with CD4 counts ≤100 cells/μL, 6 did not meet study enrollment criteria (3 had previous CM and 3 had received systemic antifungal treatment for >4 weeks), 11 died or were lost before enrollment, and 159 declined study participation (Fig. 1). Of 1178 (87.0%) patients who consented to study enrollment, one subsequently withdrew consent after enrollment, leaving 1177 (86.9%) participants for follow-up. Baseline characteristics of study participants are summarized in Table 1.

CrAg Status and Prevalence of Opportunistic Infections

Among 1177 enrolled patients with CD4 ≤100 cells/μL, 36 (3.1%; 95% CI: 2.1% to 4.0%) were CrAg-positive. None had CM symptoms. CrAg prevalence was 3.4% (95% CI: 2.4% to 4.3%) for those with CD4 <50 cells/μL and 2.1% (95% CI: 0.4 to 3.8%) for those with CD4 50–100 cells/μL (P = 0.16), 3.2% (95% CI: 2.1 to 4.3) among men and 2.6% (95% CI: 1.0 to 4.3) among women (P = 0.53). The mean age of CrAg-positive patients was 34.8 (95% CI: 29.7 to 39.8) years vs. 38.1 (95% CI: 36.2 to 40.1) years for CrAg-negative patients (P = 0.23). All CrAg-positive patients received fluconazole for preemptive therapy. CrAg prevalence across 10 northern sites was 2.7% (95% CI: 1.6 to 3.7%) compared with 3.4% (95% CI: 1.7 to 5.1%) in the 12 southern sites (P = 0.44). The one OPC in An Giang, a province in southwestern Vietnam, had the highest CrAg prevalence with 7 of 86 (8.1%) patients being CrAg-positive. In 6 OPCs in 5 provinces, none of the 219 patients screened were CrAg-positive.

Among the 1177 study participants, 247 (21.0%; 95% CI: 15.1 to 26.8) patients were classified at study enrollment as WHO clinical stage 1; 121 (10.3%; 95% CI: 5.7 to 14.8) as stage 2; 526 (44.7%; 95% CI: 37.8 to 51.6) as stage 3; and 283 (24.0%; 95% CI: 16.4 to 31.7) as stage 4. The most prevalent WHO stages 3 and 4 conditions at enrollment were



** CM= cryptococcal meningitis; *The 2015 National HIV Guidelines defined loss to follow up as not returning to the clinic in >90 days since the last visit; 6 persons newly presented for care by March 31, 2017—such that they were eligible for the study (since inclusion criteria was based on date of presentation to the OPC), but they did not enroll in the study until after that date*

FIGURE 1. Flow chart of patients.

pulmonary (n = 304, 25.8%) or extrapulmonary (n = 121, 10.3%) tuberculosis (altogether, n = 397 or 33.7% had TB); persistent oral (n = 194, 16.5%) or oesophageal (n = 47, 4.0%) candidiasis; and *Pneumocystis jirovecii* pneumonia (n = 65, 5.5%); 99 (8.4%) patients had severe unexplained weight loss (Table 1).

Patients with any WHO clinical stage 3 or 4 illnesses at enrollment were more likely than those with WHO stages 1 and 2 conditions to have the following: CD4 counts <50 cells/μL (650/809 = 80.3% vs 242/368 = 65.8%, $P < 0.001$); moderate-severe anemia defined as hemoglobin 80–109 g/L (237/767 = 30.9% vs 44/351 =12.5%, $P < 0.001$); and lower mean BMI (18.3; 95% CI: 18.1 to 18.6 vs 19.7; 95% CI: 19.4 to 20.0, $P < 0.001$). There were no differences between patients with WHO clinical stage 3 or 4 illnesses and those with stage 1 or 2 illnesses regarding the proportion who were enrolled in a freestanding (rather than hospital-based) OPC (stage 3 or 4 illness, 43.9% vs. stage 1 or 2 illness, 42.4%, $P = 0.82$); sex (73.3% men, WHO stages 3 and 4 vs. 75.8% male, WHO stages 1 and 2, $P = 0.36$); or mean age (35.6 years, WHO stages 3 and 4 vs. 35.9 years, WHO stages 1 and 2, $P = 0.62$).

ART Initiation and 12-Month Retention

Of 1177 study participants, 1151 (97.8%; 95% CI: 96.6 to 99.0) initiated ART (Fig. 1). The median time from first clinic registration to ART initiation was 7 days [interquartile range (IQR) 3–14] for the 1116 CrAg-negative patients and 17 days (IQR 14–23) for the 36 asymptomatic CrAg-positive

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients With CD4 Count<100 Cells/μL, Vietnam (2015–2017)

	All Patients (N = 1177), n (%)
OPC type	
Freestanding	511 (43.4)
Hospital-based	666 (56.6%)
Region	
North	559 (47.5%)
South	618 (52.5%)
Sex	
Male	872 (74.1%)
Female	305 (25.9%)
Age, yrs	
18–35	657 (55.8%)
36–45	381 (32.4%)
≥46	139 (11.8%)
CD4 count at study enrollment (cells/μL)	
<50	892 (75.8%)
≥50	285 (24.2%)
ART initiation	
No ART	26 (2.2%)
ART	1151 (97.8%)
Currently living with spouse/partner	
Living alone	461 (39.2%)
Living with partner	716 (60.8%)
Currently employed	
Unemployed	167 (14.2%)
Currently employed	1010 (85.8%)
Education level	
From high school education and above	478 (40.6%)
Less than high school education	699 (59.4%)
Monthly income*	
Monthly income less than 68 USD	420 (35.7%)
Monthly income from more than 68 USD	757 (64.3%)
WHO clinical staging illnesses at enrolment	
Clinical stage 1 or 2	368 (31.3%)
Clinical stage 3 or 4	809 (68.7%)
BMI category (kg/m^2)	
<18.5	573 (48.7%)
≥18.5	604 (51.3%)
Anemia category	
Mild anemia or normo-anemia	837 (74.9%)
Moderate to severe anemia	281 (25.1%)
HBsAg status	
Negative	890 (87.2%)
Positive	131 (12.8%)
Anti-HCV status	
Negative	724 (71.3%)
Positive	291 (28.7%)
CrAg status	
Negative	1141 (96.9%)
Positive	36 (3.1%)
Cotrimoxazole prophylaxis	
No	236 (20.1%)
Yes	941 (79.9%)
Latent TB/TB treatment status	
INH prophylaxis	69 (5.9%)
No INH prophylaxis among eligible patients	703 (59.7%)
TB treatment	405 (34.4%)
WHO stage 3 or 4 defining OIs/conditions	
WHO stage 3 OIs/conditions†	686 (58.3%)
WHO state 4 OIs/conditions‡	295 (25.1%)

*Exchange rate by World Bank 2016 (1USD = 21,935 VND); Row (n/% or median/IQR). Levels of poor households and near-poor households applicable during 2016–2020.

†WHO Stage 3: pulmonary TB (304, 25.8%), persistent oral candidiasis (194, 16.5%), unexplained severe weight loss more than 10% of presumed or measured body weight (99, 8.4%), unexplained chronic diarhea >1 month (33, 2.8%), unexplained persistent fever (28, 2.4%), oral hairy leukoplakia (13, 1.1%), severe bacterial infections (8, 0.7%), and unexplained anemia, neutropenia, and/or chronic thrombocytopenia (7, 0.6%).

‡WHO Stage 4: extrapulmonary tuberculosis (121, 10.3%), *Pneumocystis* (*jirovecii*) pneumonia (65, 5.5%), oesophageal candidiasis (47, 4.0%), HIV wasting syndrome (31, 2.6%), central nervous system toxoplasmosis (31, 2.6%), extrapulmonary cryptococcosis, including meningitis (15, 1.3%), and cytomegalovirus infection (12, 1.0%).

patients who were treated with 2 weeks of preemptive fluconazole before ART initiation. Of the 1116 CrAg-negative patients who initiated ART, 606 (54.3%; 95% CI: 41.3 to 67.3) initiated ART within 7 days after clinic registration, 271 (24.3%; 95% CI: 16.7 to 31.8) initiated ART between 8 and 14 days, and 239 (21.4%; 95% CI: 13.2 to 29.7) initiated ART after 14 days of registration. The proportion of patients who initiated ART within 7 days of registration did not change significantly during 3 years of study enrollment ($P = 0.75$). Among the 1151 who initiated ART, 881 (76.5%) enrolled in the study by September 30, 2016, and had ≥12 months of follow-up (Fig. 1). At 12 months, 623 of the 881 (70.7%) were still in care (retained), 86 (9.8%) were LTFU, 54 (6.1%) were transferred out, and 104 (11.8%) died, and the status of 14 (1.6%) could not be determined (Fig. 1).

Mortality

Among 1177 study participants, 143 (12.1%; 95% CI: 8.9 to 15.4) had died by 12 months after study enrollment or their date of censoring. Of the 143 decedents, 16 (11.2%) died before ART initiation (including 1 patient who was CrAg (+) on preemptive treatment with fluconazole), 108 (75.5%) died within 6 months of ART initiation, and 19 (13.3%) died between 6 and 12 months after ART initiation. The median time from study enrollment to death was 6 days (IQR, 3–17)

for the 16 participants who died before ART initiation and 61 days (IQR, 30–130) among the 127 decedents who initiated ART. Commonly reported causes of mortality included pulmonary TB (n = 27, 18.9%), extrapulmonary TB (n = 23, 16.1%), *Talaromyces marneffei* infection (n = 8, 5.6%), and opioid overdose (n = 6, 4.2%) (Table 2). Eight (5.6%) deaths occurred among participants who had asymptomatic CrAg at enrollment (2 due to unknown causes, 2 due to extrapulmonary tuberculosis, and 1 each due to nonspecified cause, pneumonia, anemia, and CM), and the median duration on preemptive therapy with fluconazole among those died was 86 days (IQR 52–125 days). Fifty-one (87.9%) of the decedents were noted to have had HIV wasting syndrome at the time of death.

The total duration of follow-up from study enrollment was 927.2 person-years in all patients and 913.6 person-years in those who initiated ART. Overall, all-cause mortality was 15.4 per 100 person-years. The mortality rate in patients who were CrAg-positive, all of whom received fluconazole, was 31.6 per 100 person-years, compared with 14.9 per 100 person-years among CrAg-negative patients ($P = 0.10$). The mortality rate differed by CD4 count, being 7.9 per 100 persons-years among patients with CD4 count 50–100 cells/μL vs. 17.9 per 100 person-years among those with CD4 count <50 cells/μL ($P = 0.006$). Among patients who initiated ART, the mortality was higher among those with CD4 count <50 cells/μL ($P = 0.001$) (Fig. 2). Among patients who initiated ART, the mortality rate was 13.1 per 100 person-years in those who initiated ART within 7 days of clinic registration vs. 14.5 per 100 person-years in those who initiated after 7 days ($P = 0.56$).

Among all patients, factors independently associated with mortality in multivariate analysis included baseline CD4 count <50 cells/μL (adjusted HR [aHR], 1.75; 95% CI: 1.04 to 2.96), baseline WHO clinical stage 3 or 4 (aHR, 3.4; 95% CI: 1.97 to 5.88), baseline BMI <18.5 (aHR 1.59, 95% CI: 1.04 to 2.42), baseline positive HBsAg (aHR 1.87; 95% CI: 1.19 to 2.94), and not starting ART (aHR 27.81; 95% CI: 12.04 to 64.23) (Table 3).

TABLE 2. Causes of Death Among Patients With CD4 Count <100 Cells/μL, Vietnam (2015–2017)

*Cause of Death	All (n = 143), n (%)
Nonspecified cause	29 (20.3%)
Pulmonary tuberculosis	27 (18.9%)
Extrapulmonary tuberculosis	23 (16.1%)
Unknown	10 (7.0%)
Talaromyces marneffei	8 (5.6%)
Bacterial pneumonia	7 (4.9%)
Opioid overdose	6 (4.2%)
Pneumocystis jirovecii pneumonia	6 (4.2%)
Central nervous system toxoplasmosis	3 (2.1%)
Cirrhosis	3 (2.1%)
Renal failure	2 (1.4%)
Anemia	2 (1.4%)
Suicide	2 (1.4%)
Gastrointestinal bleeding	2 (1.4%)
Cytomegalovirus infection	2 (1.4%)
Hepatocellular carcinoma	2 (1.4%)
Unexplained chronic diarrhea	1 (0.7%)
Septicemia	1 (0.7%)
Fulminant hepatitis B	1 (0.7%)
Gastric cancer	1 (0.7%)
Diarrhea	1 (0.7%)
Cryptococcal meningitis	1 (0.7%)
Cancer of the nasal cavity	1 (0.7%)
Brain ischemia	1 (0.7%)
Meningitis	1 (0.7%)

*Irrespective of ART initiation status.

DISCUSSION

We report findings from a study evaluating clinical outcomes of patients presenting for care with advanced HIV in the first national rollout program for CrAg screening in Vietnam. A high proportion (38.6%) of patients newly presenting for care had very AHD with CD4 counts ≤ 100 cells/μL, and among them, the CrAg prevalence was 3.1%. Morbidity and mortality from OIs and HIV-associated conditions were high, with tuberculosis being the most prevalent—reported among 34.4% of all participants.

The 3.1% prevalence of CrAg in our study was lower than the 4% prevalence (95% CI: 2 to 7%) from a previous retrospective study on stored sera from patients with CD4≤100 cells/μL in Vietnam in 2009–2012.[6] We observed a wide variation in prevalence across clinics (0.0%–8.1), but unlike the study by Smith et al, we did not observe a significant regional variation, although prevalence was slightly higher in the South (3.4%) than in the North (2.7%). However, the prevalence of CrAg in our study was lower than in other countries in Southeast Asia, including Thailand (12.9% during 2003–2008)[24] and Cambodia (18% in 2004).[25] At the current estimated CrAg prevalence of 3.1% in Vietnam, the rollout of the cryptococcal antigen screening and preemptive treatment with fluconazole is warranted and will cost less than $190 per life-year gained if implemented in the context of the parameters used in the cost-effectiveness

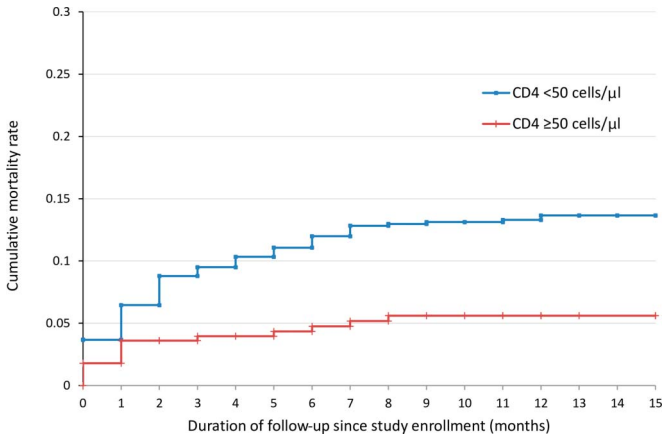


FIGURE 2. Cumulative all-cause mortality for study participants who initiated ART by baseline CD4 count. full color online

TABLE 3. Demographic and Clinical Characteristics Associated With Mortality Among Patients Who Presented for HIV Care With CD4 Count <100 Cells/μL, Vietnam (2015–2017)

	All Patients (N = 1177)	Died within 12 months of Enrollment	Unadjusted Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio (95% CI)*	*P* for Adjusted HR
OPC type						
Freestanding	511 (43.4%)	57/511 (11.2%)	1			
Hospital-based	666 (56.6%)	86/666 (12.9%)	1.18 (0.7 to 1.99)	0.5148		
Region						
North	559 (47.5%)	65/559 (11.6%)	1			
South	618 (52.5%)	78/618 (12.6%)	1.08 (0.64 to 1.8)	0.7649		
Sex						
Male	872 (74.1%)	105/872 (12.0%)	1			
Female	305 (25.9%)	38/305 (12.5%)	1.03 (0.67 to 1.57)	0.8957		
Age (yr)						
18–35	657 (55.8%	72/657 (11.0%)	1	0.2354	1	
36–45	381 (32.4%)	48/381 (12.6%)	1.16 (0.77 to 1.75)		1.17 (0.74 to 1.83)	0.4899
≥46	139 (11.8%)	23/139 (16.5%)	1.56 (0.93 to 2.6)		1.85 (1 to 3.44)	0.0516
CD4 count at study enrollment (cells/μL)						
<50	892 (75.8%)	124/892 (13.9%)	2.18 (1.36 to 3.51)	0.0027	1.75 (1.04 to 2.96)	0.0378
≥50	285 (24.2%)	19/285 (6.7%)	1		1	
ART initiation						
No ART	26 (2.2%)	16/26 (61.5%)	17.8 (7.36 to 43.05)	<0.0001	27.81 (12.04 to 64.23)	<0.001
ART	1151 (97.8%)	127/1151 (11.0%)	1		1	
Currently living with spouse/partner						
Living alone	461 (39.2%)	66/461 (14.3%)	1.36 (0.85 to 2.17)	0.1901	1.12 (0.76 to 1.64)	0.6988
Living with partner	716 (60.8%)	77/716 (10.8%)	1		1	
Currently employed						
Unemployed	167 (14.2%)	32/167 (19.2%)	1.93 (1.03 to 3.59)	0.0402	1.07 (0.46 to 2.49)	0.8761
Currently employed	1010 (85.8%)	111/1010 (11.0%	1		1	
Education level						
From high school education and above	478 (1010)	44/478 (9.2%)	1		1	
Less than high school education	699 (59.4%)	99/699 (14.2%)	1.59 (1.13 to 2.22)	0.0094	1.62 (1.97 to 2.71)	0.0635
Monthly income†						
≤68 USD	420 (35.7%)	70/420 (16.7%	1.81 (1.18 to 2.79)	0.0094	1.45 (0.81 to 2.6)	0.1959
>68 USD	757 (64.3%)	73/757 (9.6%)	1		1	
WHO clinical staging illnesses at enrollment						
Clinical stage 1 or 2	368 (31.3%)	17/368 (4.6%)	1		1	
Clinical stage 3 or 4	809 (68.7%)	126/809 (15.6%)	3.63 (2.05 to 6.4)	0.0001	3.40 (1.97 to 5.88)	0.0001
BMI category (kg/m^2)						
<18.5	573 (48.7%)	93/573 (16.2%)	2.06 (1.36 to 3.12)	0.0016	1.59 (1.04 to 2.42)	0.0337
≥18.5	604 (51.3%)	50/604 (8.3%)	1		1	
Anemia category						
Moderate to severe anemia	281 (25.1%)	60/281 (21.4% ()	2.51 (1.76 to 3.58)	<0.0001	1.56 (0.99 to 2.46)	0.0549
Mild anemia or normo-anemia	837 (74.9%)	79/837 (9.4%)	1		1	
HBsAg status						
Negative	890 (87.2%)	101/890 (11.3%)	1		1	
Positive	131 (12.8%)	21/131 (16.0%)	1.42 (0.91 to 2.21)	0.1163	1.87 (1.19 to 2.94)	0.0089
Anti-HCV status						
Negative	724 (71.3%)	82/724 (11.3%)	1			
Positive	291 (28.7%)	12.7% (37/291)	1.14 (0.79 to 1.65)	0.4724		
CrAg status						
Negative	1141 (96.9%)	11.8% (135/1141)	1		1	
Positive	36 (3.1%)	8/36 (22.2%)	1.93 (1.03 to 3.63)	0.0416	1.25 (0.65 to 2.43)	0.4869

(*continued on next page*)

TABLE 3. (*Continued*) Demographic and Clinical Characteristics Associated With Mortality Among Patients Who Presented for HIV Care With CD4 Count <100 Cells/μL, Vietnam (2015–2017)

	All Patients (N = 1177)	Died within 12 months of Enrollment	Unadjusted Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio (95% CI)*	*P* for Adjusted HR
Cotrimoxazole prophylaxis						
No	236 (20.1%)	35/236 (14.8%)	1	0.1204	1.01 (0.6 to 1.71)	0.9673
Yes	941 (79.9%)	108/941 (11.5%)	0.69 (0.43 to 1.11)		1	
Latent TB/TB treatment status						
INH prophylaxis	69 (5.9%)	4/69 (5.8%)	1	0.2342	1	
No INH prophylaxis among eligible patients	703 (59.7%)	80/703 (11.4%)	2.10 (0.61 to 7.17)		1.65 (0.53 to 5.14)	0.3686
TB treatment	405 (34.4%)	59/405 (14.6%)	2.71 (0.71 to 10.35)		1.26 (0.37 to 4.33)	0.7009

*Only variables with *P* value ≤ 0.25 were included in multivariate analysis.
†Exchange rate by World Bank 2016 (1USD = 21,935 VND); Row (n/% or median/IQR). Levels of poor households and near-poor households applicable during 2016–2020.

study conducted by Smith et al.[6] Routine screening for CrAg and preemptive treatment is recommended by WHO in patients with CD4 counts ≤100 cells/μL (strong recommendation) and also conditionally recommended for consideration for those up to a CD4 count ≤200 cells/μL.[20] Over the study period, national guidelines for ART eligibility evolved; in 2015, those with CD4 counts ≤500 cells/μL and WHO clinical stages 3 and 4 or severe chronic hepatitis B) were eligible. In 2016, vulnerable subpopulations (eg, aged 50 years or older; key populations (FSW, MSM, and PWID), those in sero-discordant relationships (ie, had HIV-uninfected partners); or those who resided in remote areas) became eligible irrespective of CD4 count or WHO stage. In 2017, all those who tested positive were considered eligible regardless of CD4 count or WHO clinical stage but would only be initiated after CD4 testing and screening for OIs.[19] Same-day ART initiation was not adopted until 2018. Still, current national guidelines do not comprehensively address AHD among patients with HIV.

In our study, 3 quarters of study participants initiated ART within 2 weeks of presentation to OPCs per WHO guidelines at the time.[26] The implementation of same-day ART in Vietnam will further shorten the duration from OPC presentation to ART initiation. However, given the substantial morbidity and mortality among patients with advanced disease, to maximize the benefits of same-day ART, earlier diagnosis will be necessary to reduce the proportion of patients presenting with advanced disease.

In the studied population, OIs and other HIV-associated conditions were common and similar to those reported from a 2010–2011 HIV cohort enrolled in Thailand and Vietnam in which 70% of ART-naïve, HIV-infected patients had CD4 count <100 cells/μL, but with a lower TB prevalence at 8.6%.[27] High TB case identification in our study not only could be because of improved routine screening for TB among HIV-positive patients (including the use of GeneXpert, which was introduced in 2012–2013) and HIV testing among patients with TB in accordance with the national policy, but may also reflect high prevalence of TB disease in those with advanced HIV.[28]

The 12-month retention rate of 70.7% in our study was lower than that for other Vietnamese cohorts that included patients with higher CD4 counts, suggesting that patients with AHD have lower retention rates. For example, data from monitoring HIV early-warning indicators of drug resistance in 27 OPCs in 2012 estimated a retention rate of 81.2% at 12 months.[29] On the other hand, in a retrospective study conducted between 2007 and 2012 in 2 OPCs that also participated in our study, the retention rate was 95.3% at 12 months (the baseline median CD4 count was 371 cell/μL).[30] In a systematic review of studies conducted between 2008 and 2013 in 42 low-income and middle-income countries, the retention rate at 12 months was 78% overall and 84% in the Asia region (the baseline median CD4 count was 110 cells/μL).[31] To address barriers to retention and strengthen follow-up, the 2017 WHO guidance for managing AHD recommends intensified adherence support for those presenting with AHD.[32]

The mortality rate of 15.4 per 100 person-years in our study was higher than that in other studies, but causes of mortality were similar. For example, in a randomized controlled trial evaluating the impact of peer support on treatment outcomes in 640 HIV-infected patients with a median CD4 count of 110 cells/μL from 2007 to 2010 in Vietnam, mortality was 9% in the first year of registration (mortality rate of 7.4/100 person-years), and TB was the most common cause of death among HIV-infected patients (24/49 or 40%), followed by *T. marneffei*, and *Mycobacterium avium complex* (each of 5/49 or 8%).[33] Similar to Faini et al,[34] we did not observe a statistically significant mortality difference between those who were CrAg-positive and -negative, probably because all patients in our study had very AHD.

Our study is subject to certain limitations. Aside from CrAg testing, which was systematically performed in all participants at enrollment, other OIs at baseline and follow-up were empirically diagnosed, with or without laboratory confirmation. Similarly, causes of death were not verified by autopsy. The clinical diagnosis of OIs in an advanced HIV cohort may be inaccurate and overestimate or underestimate the true OI prevalence.[35] In addition, our estimates of CrAg prevalence did not consider those with CM, potentially underestimating the true prevalence. Reporting of OIs in the medical records might have also been incomplete. Even among patients who were hospitalized before death, many

patients left the hospital before complete evaluation or treatment because of the cost of hospitalization and the Vietnamese tradition of dying at home. Patients LTFU in our study were not all accounted for, and this may have underestimated the mortality because LTFU is associated with high mortality.[36] In addition, the data from 22 OPCs may not be generalizable to each province, region, or to the country. Finally, our analysis was restricted to those with very advanced disease (CD4 count <100 cells/μL) and did not extend to those with CD4 count between 100 and 200 cells/μL who by WHO definition have AHD.

In conclusion, more than one-third of patients newly presenting for HIV care in Vietnam had very advanced HIV with CD4 count <100 cells/μL. Mortality was high among those who present for care with AHD, and most deaths occurred in the first 6 months after ART initiation. Achieving the 95-95-95 targets in Vietnam will be facilitated by intensified efforts toward early HIV diagnosis for and differentiated service delivery for AHD. Offering the WHO recommended package of interventions for AHD, which includes rapid ART in the absence of contraindications, intensive follow-up of patients with AHD, and prophylaxis and treatment of OIs, could improve outcomes.[3,37]

ACKNOWLEDGMENTS

The authors thank the study participants and data collectors at 22 study sites from provinces of An Giang; Binh Dương; Hanoi; Ho Chi Minh City; Nghe An; Quang Ninh; Son La; Thai Nguyen; Thanh Hoa; and Vinh Phuc. The authors appreciate the support of Drs Cao Thi Thanh Thuy (Clinton Health Access Initiative, CHAI Vietnam), Rachel Smith (CDC, Atlanta), Bui Thi Hien (CDC Vietnam), Dr. Jon Kaplan who provided critical support in designing and implementing the study. The authors also thank Nguyen Thi Thu Huong (CDC, Vietnam) and CRICS team for their hard work on project management.

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