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# Loss to follow-up trends in HIV-positive patients receiving antiretroviral treatment in Asia from 2003 to 2013

**Nicole L. De La Mata**[§,1], **Penh Sun Ly**[2], **Kinh Van Nguyen**[3], **Tuti Parwati Merati**[4], **Thuy Thanh Pham**[5], **Man Po Lee**[6], **Jun Yong Choi**[7], **Jeremy Ross**[8], **Matthew G. Law**[1], and **Oon Tek Ng**[9]

[1]Kirby Institute, UNSW Australia, Sydney, NSW, Australia [2]National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia [3]National Hospital for Tropical Diseases, Hanoi, Vietnam [4]Faculty of Medicine Udayana University & Sanglah Hospital, Bali, Indonesia [5]Bach Mai Hospital, Hanoi, Vietnam [6]Queen Elizabeth Hospital, Hong Kong, China [7]Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, Severance Hospital, Seoul, South Korea [8]TREAT Asia, amfAR - The Foundation for AIDS Research, Bangkok, Thailand [9]Tan Tock Seng Hospital, Singapore

## Abstract

**Introduction—**Over time there has been substantial improvement in antiretroviral treatment (ART) programmes, including expansion of services and increased patient engagement. We describe time trends in, and factors associated with, loss to follow-up (LTFU) in HIV-positive patients receiving ART in Asia.

**Methods—**Analysis included HIV-positive adults initiating ART in 2003-2013 at seven ART programmes in Asia. Patients LTFU had not attended the clinic for ≥180 days, had not died or transferred to another clinic. Patients were censored at recent clinic visit, follow-up to January 2014. We used cumulative incidence to compare LTFU and mortality between years of ART initiation. Factors associated with LTFU were evaluated using a competing risks regression model, adjusted for clinical site.

[§]Corresponding author: Nicole L. De La Mata, The Kirby Institute, UNSW Australia, Wallace Wurth Building, Sydney, 2052, Australia, (02) 9385 9012, ndelamata@kirby.unsw.edu.au.

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TAHOD-LITE study members: PS Ly and V Khol, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia;
MP Lee, PCK Li, W Lam and YT Chan, Queen Elizabeth Hospital, Hong Kong, China;
N Kumarasamy, S Saghayam and C Ezhilarasi, Chennai Antiviral Research and Treatment Clinical Research Site (CART CRS), YRGCARE Medical Centre, VHS, Chennai, India
TP Merati, DN Wirawan and F Yuliana, Faculty of Medicine Udayana University & Sanglah Hospital, Bali, Indonesia;
OT Ng, PL Lim, LS Lee and R Martinez-Vega, Tan Tock Seng Hospital, Singapore;
JY Choi, Na S and JM Kim, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea;
TT Pham, DD Cuong and HL Ha, Bach Mai Hospital, Hanoi, Vietnam;
KV Nguyen, HV Bui, DTH Nguyen and DT Nguyen, National Hospital for Tropical Diseases, Hanoi, Vietnam;
AH Sohn, J Ross and B Petersen, TREAT Asia, amfAR - The Foundation for AIDS Research, Bangkok, Thailand;
NL De La Mata, A Jiamsakul, DC Boettiger and MG Law, The Kirby Institute, UNSW Australia, Sydney, Australia.

**Authors' contributions**: NLD and ML contributed to the concept development. PSL, OTN, KVN, TPM, TTP, MPL and JYC contributed data for the analysis. NLD performed the statistical analysis and wrote the first draft of the manuscript. All authors commented on the draft manuscript and approved of the final manuscript.

**Results—**A total of 8,305 patients were included. There were 743 patients LTFU and 352 deaths over 26,217 person-years (pys), a crude LTFU and mortality rate of 2.83 (2.64-3.05) per 100 pys and 1.34 (1.21-1.49) per 100 pys, respectively. At 24 months, the cumulative LTFU incidence increased from 4.3%(2.9-6.1%) in 2003-05 to 8.1%(7.1-9.2%) in 2006-09, then decreased to 6.7%(5.9-7.5%) in 2010-13. Concurrently, the cumulative mortality incidence decreased from 6.2%(4.5-8.2%) in 2003-05 to 3.3%(2.8-3.9%) in 2010-13. The risk of LTFU reduced in 2010-13 compared to 2006-09 (adjusted subhazard ratio=0.73, 0.69-0.99).

**Conclusions—**LTFU rates in HIV-positive patients receiving ART in our clinical sites have varied by the year of ART initiation, with rates declining in recent years while mortality rates have remained stable. Further increases in site-level resources are likely to contribute to additional reductions in LTFU for patients initiating in subsequent years.

### Keywords

Asia; HIV; epidemiology; retention in care; loss to follow-up; ART

## Introduction

The expansion of antiretroviral treatment (ART) has had substantial impact on the outcomes of HIV-positive patients. However, HIV care requires lifelong ART which causes a considerable burden on ART programmes to retain patients in-care. Many ART programmes and cohort studies have shown large numbers of patients lost to follow-up (LTFU) following ART initiation. Studies in Sub-Saharan Africa have reported high rates of LTFU within 6 months following ART initiation[1]. More than half the patients receiving ART in two care and treatment centres in Tanzania were LTFU within 3 months of ART initiation[2]. While a systematic review of patient retention in sub-Saharan Africa after ART initiation found that LTFU exceeded death as the cause of patient attrition (59% vs 41%)[3].

In addition, there are significant clinical implications for patients who are LTFU. Patients who are LTFU often have high mortality rates, particularly from low-income countries[4-8]. Unreported deaths in LTFU patients can also bias findings from analyses, particularly in time-to-event analyses[9,10]. There is also a risk that LTFU patients will discontinue or interrupt ART. One study in Malawi reported that of the 2 183 LTFU patients who had initiated ART, 1 250 (57.3%) had either stopped or interrupted ART after being LTFU[11]. These treatment interruptions are concerning as they may lead to viral rebound and an increased chance of HIV transmission and drug resistance[12]. CD4 cell count restoration and overall prognosis are also hindered during periods of ART interruption[13-15]. Hence, there is a strong need to retain patients in care to achieve better patient outcomes and reduce the transmission of HIV through sustained viral suppression.

There have been substantial improvements in ART programmes globally to retain HIV-positive patients in long-term care[16,17]. Previous studies have highlighted that the use of support services offered by HIV programmes is associated with increased engagement in-case[18,19]. The HIV cascade of care describes how patients move between stages of care, from HIV diagnosis, to linkage and retention in care, to ART initiation and viral load suppression[20]. The cascade of care highlights the importance of all stages of HIV care and,

ideally, 90% or more of patients will achieve each stage[21]. However, disparities in the continuum of care do occur and, as ART scale-up continues, there may be an increased proportion of patients LTFU[22]. As patients receiving ART continue to increase, HIV programmes have a limited capacity to maintain the quality of care provided and retention in long-term care becomes more challenging[23]. Over the past decade, treatment coverage in Asia has substantially increased from 19% in 2010 to 41% in 2015, with an estimated 2.1 million people receiving ART[16]. Yet, Asia is a diverse region with the HIV epidemic considered as concentrated in particular high risk populations and countries including India and Cambodia[24]. Monitoring patient retention rates in Asia is important to ensure the long-term success of HIV treatment services in the region. Our study objective was to analyse and describe time trends in and factors associated with LTFU in HIV-positive patients receiving ART in Asia.

## Methods

### Data collection and Participants

We used observational patient data collected in the TREAT Asia HIV Observational database Low Intensity TransfEr (TAHOD-LITE), a sub-study of the TREAT Asia HIV Observational database (TAHOD), member cohorts of the International Epidemiology Databases to Evaluate AIDs (IeDEA)[25]. Currently, TAHOD collects prospective data on a subset of patients attending 20 treatment sites in Asia and TAHOD-LITE collects retrospective data on all patients seen at 8 of the 20 treatment sites, including one each in Cambodia, Hong Kong, India, Indonesia, Singapore, and South Korea, and two in Vietnam. A more detailed description of TAHOD-LITE has been previously described[26]. Briefly, routine patient data collected at the treatment site are anonymized and then electronically transferred for data management and analysis at the Kirby Institute, UNSW Australia. Patient data are limited to demographics, hepatitis serology, ART history and HIV-related laboratory results. TAHOD-LITE was granted ethics approvals from Institutional Review Boards (IRB) at each participating site, the University of New South Wales and the coordinating center at TREAT Asia/amfAR.

This analysis was limited to only 7 of the 8 sites that were able to distinguish LTFU from patient transfers to another clinical site for ongoing care. Hence, patient data were used from 7 sites representing 6 countries in Asia. Patients were eligible for inclusion if aged over 18 years, they had initiated an ART regimen consisting of three or more antiretroviral drugs from 01 January 2003 to 31 December 2013, and they had at least one subsequent follow-up visit after ART initiation.

### Statistical analyses

Patients were defined as LTFU if they had not attended the clinic for at least 180 days and had not been transferred to another clinic or died. Sites determined whether patients had transferred to another clinic, either through clinic referral or self-referral to another clinic. Sites conducted their own patient tracing methods, according to local standards of practice, to identify patients who missed appointments and attempt to re-engage them into care or identify if they had been transferred to another clinic. No additional post-LTFU patient

tracing was conducted as part of this study. The 180 day cut-off was selected as this has previously been validated in our cohort to achieve the highest sensitivity and specificity for determining LTFU patients[27,28]. Re-engagement into care after the first LTFU event was not considered. Hence, once patients were LTFU, subsequent follow-up was not included in the analysis. Follow-up was from the start of ART initiation to the date of death or most recent clinic visit, whichever occurred first. Patient follow-up was censored at 01 January 2014. We used a quasi intention-to-treat approach where changes to treatment after ART initiation were ignored.

Pre-ART laboratory results were defined as the result closest to and within 6 months prior to ART initiation. Patients were censored at most recent clinic visit and death was considered as a competing event. We used the observed cumulative incidence of LTFU to compare between year periods of ART initiation. Fine and Gray methods [29] for competing risks regression models were used to evaluate factors associated with LTFU, adjusted by clinical site. Covariates selected *a priori* only included age at ART initiation, sex, mode of HIV exposure, time-updated CD4 cell count (cells/μL), time-updated HIV viral load (copies/mL), first ART regimen, hepatitis B (HBV) and hepatitis C co-infection (HCV).

Data were analysed using Stata version 14 (Stata Corporation, College Station, Texas, USA) and SAS software (Version 9.4 for Windows).

## Results

A total of 8 382 patients from the seven eligible sites were aged over 18 years and had initiated ART between 1 January 2003 and 31 December 2013. Of these, 77 patients (0.9%) were excluded as they did not have subsequent visits after ART initiation. The remaining 8 305 patients were included in our analysis.

### Patient Characteristics

Overall, patients were male (69%), initiated ART in more recent year periods (2003-05: 9%; 2006-09: 33%; 2010-13: 58%) and had heterosexual contact as their reported mode of HIV exposure (66%). The median age was 35 years (interquartile range [IQR]: 30-44). The majority of patients had been tested at least once for HBV and HCV, and 9% and 12%, respectively, had ever tested positive. The median pre-ART CD4 cell count and pre-ART HIV viral load was 117 cells/μL (IQR: 32-239) and 105 000 copies/mL (IQR: 30 589-358 000), respectively. Most patients did not have previous mono/dual therapy (98%) and had initiated an ART regimen consisting of nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitor (NNRTI) (92%). The largest proportion of patients were from Cambodia (30%), followed by Singapore (22%), Vietnam (19%), Indonesia (13%), Hong Kong (10%) and South Korea (6%) (Table 1).

### Cumulative LTFU and mortality rates

The median duration of follow-up was 34 months (IQR: 15-62 months). Of the 8 305 patients, 743 patients were LTFU over 26 217 person-years (pys), giving a crude LTFU rate of 2.83 (95% CI: 2.64-3.05) per 100 pys (Table 2). In addition, there were 352 deaths with a crude death rate of 1.34 (95% CI: 1.21-1.49) per 100 pys.

The cumulative LTFU incidence at 6, 12 and 24 months of follow-up for patients initiating ART: in 2003-05 was 1.5% (95% CI: 0.8-2.8%), 2.8% (95% CI: 1.7-4.4%) and 4.3% (95% CI: 2.9-6.1%); in 2006-09 was 2.9% (95% CI: 2.3-3.6%), 4.9% (95% CI: 4.2-5.8%) and 8.1% (95% CI: 7.1-9.2%); in 2010-13 was 2.1% (95% CI: 1.7-2.5%), 4.0% (95% CI: 3.4-4.6%) and 6.7% (95% CI: 5.9-7.5%), respectively (Figure 1).

The cumulative mortality incidence at 6, 12 and 24 months of follow-up for patients initiating ART: in 2003-05 was 2.7% (95% CI: 1.6-4.2%), 4.3% (95% CI: 2.9-6.0%) and 6.2% (95% CI: 4.5-8.2%); in 2006-09 was 2.1% (95% CI: 1.6-2.8%), 2.6% (95% CI: 2.1-3.3) and 3.4% (95% CI: 2.8-4.1%); in 2010-13 was 2.0% (95% CI: 1.6-2.4%), 2.7% (95% CI: 2.3-3.3%) and 3.3% (95% CI: 2.8-3.9%), respectively (Figure 1).

The cumulative LTFU and mortality incidence has also been shown by country (Appendix 1). Three of the six countries displayed similar trends to the overall results, where the cumulative incidence of LTFU was high and mortality was low during 2006-09. However, the cumulative LTFU incidence reduction was less pronounced or even higher in 2010-13. Two of the six countries had consistent mortality and LTFU cumulative incidence during all time periods. One of the six countries only had data available for one time period (2010-13).

## Factors associated with LTFU

The multivariate competing risks regression model, adjusted by clinical site, suggested that LTFU was associated with year of ART initiation, when adjusting for other relevant covariates (Table 2). Patients initiating in 2003-05 and 2010-13 had a subhazard ratio (SHR) of 0.73 (95% CI: 0.56-0.95; p value=0.021) and 0.83 (95% CI: 0.69-0.99; p value=0.034), respectively, compared to those initiating in 2006-09, adjusting for clinical site and other covariates.

Age at ART initiation was also significant in the multivariate model (p value=0.003), where those who were aged above 50 years were 31% less likely to be LTFU compared to those aged 30 or below (SHR: 0.69, 95% CI: 0.53-0.90, p value=0.007). Patients with homosexual contact or injecting drug use as the mode of HIV exposure were 36% (SHR: 1.36, 95% CI: 1.05-1.76, p value=0.021) and 65% (SHR: 1.65, 95% CI: 1.19-2.30, p value=0.003) more likely to be LTFU compared to patients with heterosexual contact, respectively.

Patients with a higher current CD4 cell count were also less likely to be LTFU (p value <0.001). Those with a current CD4 count above 200 cells/μL were 67% less like to be LTFU compared to those with a current CD4 cell count ≤50 cells/μL (SHR: 0.32, 95% CI: 0.25-0.41, p value<0.001). Patients ever having a positive HCV antibody test were 54% more likely to be LTFU than those that had never contracted HCV (SHR: 1.54, 95% CI: 1.16-2.05, p value=0.003). Clinical site was significantly associated with LTFU in the multivariate model (p value <0.001). The two larger sites, Cambodia and Singapore, had a higher risk of LTFU compared to the other sites.

## Discussion

Our findings have shown that the rate of LTFU has varied by year of ART initiation in this cohort of 8 305 HIV-positive patients receiving ART in Asia. The LTFU rate was lowest for those initiating in 2003-05, reaching 4.3% at 24 months of follow-up. The mortality rate was highest during this period of ART initiation, with a cumulative incidence of 6.2% at 24 months of follow-up. However, in 2006-09, there was a rapid increase in the LTFU rate to 8.1% at 24 months of follow-up while the mortality rate nearly halved to 3.4% at 24 months of follow-up. During 2010-13, the LTFU rate decreased compared to the previous period to 6.7% at 24 months of follow-up, while the mortality rate remained stable at 3.3% at 24 months of follow-up. The mortality rate surpassed LTFU rates only during the first 4 months of follow-up for those initiating ART in 2006-09 and 2010-13.

Since the UNAIDS initiative to scale-up universal access to ART, there has been a substantial increase in the expansion of services and HIV-positive people receiving ART in Asia as well as other regions [30-32]. Significant improvements in the survival of patients receiving ART followed, likely as a result of a combination of factors including greater access to ART, earlier initiation of ART and, more tolerable and convenient ART regimens[26]. However, the rapid growth within the programs may also be accompanied by poorer patient retention and higher rates of LTFU[33]. There was some indication in our findings to suggest that sites with more patients tended to have higher LTFU rates than other sites. Recently, there has been greater attention on reducing LTFU rates to ensure patients are retained in care, maintain adherence and achieve better long term outcomes[5,34]. Treatment programmes in Asia commonly conduct at least one form of outreach and tracking for adults receiving ART who have missed clinic visits[19]. Most report phone call as the method of contact, but other methods include sending letters, home visits, consulting with pharmacies and checking hospital records. ART adherence support services, such as one-on-one counselling and reminder tools, are also offered at a vast majority of treatment programmes. Hence, increased support services and other resources at the site-level to engage patients in long-term care may have contributed to the decreasing LTFU seen in recent years[35].

Similar trends have been reported in a multiregional analysis where the LTFU rate at 12 months after ART initiation increased from 9.3 per 100 pys (95% CI: 8.7-9.9) in 2004 to 14.6 per 100 pys (95% CI: 14.1-15.2) in 2010 [36]. Concurrently, the mortality rate at 12 months from ART initiation decreased from 11.8 per 100 pys (95% CI: 11.1-12.6) to 5.1 per 100 pys (95% CI: 4.8-5.4) in 2010. Other studies have reported a less prominent increase in LTFU rates after scale-up[37]. Our cumulative LTFU incidence ranged between 4.3-8.1% at 24 months, depending on year of ART initiation. This was relatively low compared to other HIV cohorts within the region which may be reflective of our ART programmes generally being better resourced tertiary referral sites. The LTFU incidence in India and China was 14% and 16%, at 24 months, for patients initiating ART in 2007-11 and 2005-10, respectively[38,39]. Outside of the region, in Rwanda, the cumulative LTFU rate for patients initiating ART in 2005-10 was low at 4.4% (95% CI: 4.4-4.5%) at 24 months. However, the cumulative mortality rate was nearly double our mortality rate at 6.3% (95% CI: 6.2-6.4%) [40]. While in South Africa, both LTFU and mortality rates are much higher at 24

months, ranging from 13.4% (95% CI: 12.0-14.9%) to 26.5% (95% CI: 23.8-29.2%) and 7.4% (95% CI: 6.4-8.5%) to 15.4% (95% CI: 13.2-17.6%), respectively, for patients initiating in 2005-2010 at three different HIV programmes[41].

Our findings also highlight that lower CD4 count is strongly associated with a greater risk of LTFU. Previous studies have also shown a similar association[42-44]. As LTFU patients have a high mortality rate, the lower CD4 count may reflect the association with mortality arising from unreported deaths rather than LTFU from a lack of engagement in care. It may also relate to suboptimal adherence, where those patients less engaged with care also have lower ART adherence, leading to lower CD4 counts and subsequently LTFU[45,46].

The risk of LTFU was highest among those aged ≤30 years at ART initiation. This is consistent with Africa cohorts where retention in care is lowest among the ≤30 age group and highlights the need to engage adolescents and young adults[47]. In contrast with European and US HIV studies, we did not see greater retention in those aged >50 years at ART initiation[48]. Patients with HCV co-infection, homosexual contact or injecting drug use as the mode of HIV exposure were associated with a higher risk of LTFU. These populations are often marginalized and faced with stigma and discrimination, subsequently impacting on their engagement with health services[49-52].

There were limitations to our study. Some patient data had large proportions of missing data, such as HIV viral load. Subsequently, the association with LTFU should not be over interpreted. In addition, while our study had a relatively large patient sample size, our data was obtained from seven clinical sites across six countries from Asia, where most countries had one contributing site. Hence, our analysis is not necessarily representative of trends occurring within the given country or the region. There is also the potential for site-level differences in the resources available that can dictate the level of patient care provided, the type of ART and other unmeasurable confounders that could influence the results. Disengagement from the clinic may be influenced by cultural or social factors that vary between the countries, such as stigma and discrimination[53]. Hence, it is difficult to make direct comparisons of LTFU between our clinical sites. However, we have adjusted for clinical site in the multivariate model, as well as providing figures by clinical site, to account for heterogeneity between the sites and produce more reliable estimates.

Another limitation is the bias arising from our chosen LTFU definition[27]. Previous studies have used definitions ranging from 90 days [7] to 365 days [54] with no clinic visit. We have attempted to minimize error in the determining patients LTFU by using validated definitions that achieve optimal specificity and sensitivity for LTFU, both in our own TAHOD cohort[28] and supported by other studies[55]. Transient gaps between clinical visits can also introduce bias in identifying LTFU patients who have recently initiated ART. As patients who initiate ART recently have less time to return to care, they are more likely to be incorrectly classified as LTFU following a temporary interruption in care. However, this tends to overestimate LTFU rates in patients with recent ART initiation[56]. Therefore, our observed LTFU rates are likely to be conservative of the true LTFU rate and there is potentially a greater difference between the LTFU rates in 2006-09 and 2010-13.

Patient deaths were ascertained through hospital records and, in some cases, through further tracing to national death registries or verbal autopsy, but this was site dependent and practices may have varied over time. Hence, there is possible bias in the underreporting of deaths, where some patients may have been incorrectly classified as LTFU. In particular, the increasing number of patients presenting for care may have contributed to under-recording of deaths in recent years. However, our mortality rate was consistent between 2006-09 and 2010-13, and our observed LTFU rate could be overestimating the true LTFU and underestimating mortality rates.

In conclusion, we have shown that the LTFU rates in HIV-positive patients receiving antiretroviral therapy in our cohort have varied by the year of ART initiation. With an increasing number of patients initiating ART, the mortality rate in 2003-05 halved in subsequent years while the LTFU rate markedly increased. Those initiating in 2010-13 have reduced LTFU rates compared to 2006-09, while maintaining the same low mortality rate. Further increases in site-level resources to improve adherence counselling and support services would be needed to reduce LTFU and promote retention as HIV care increasingly transitions to a chronic disease management model[35,57,58].

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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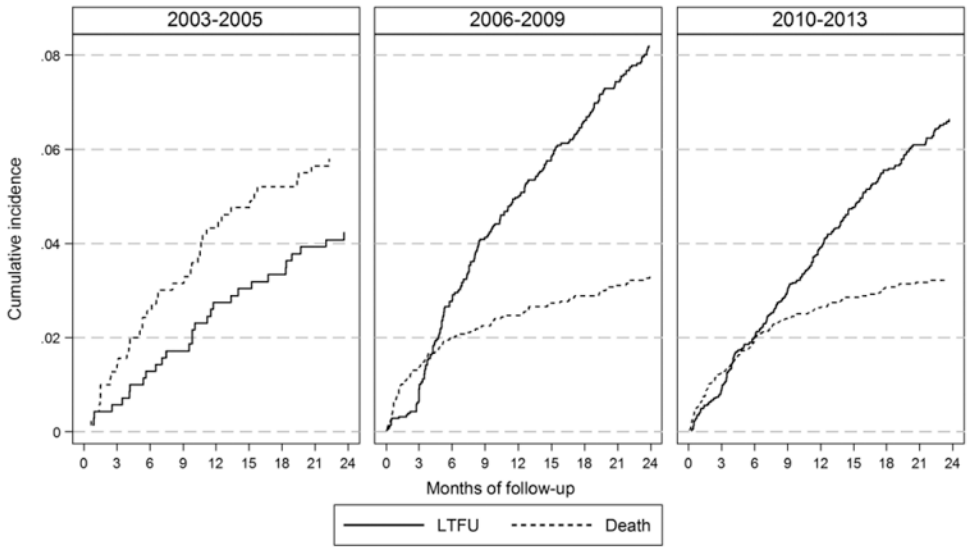


**Figure 1. Cumulative incidence of LTFU and death across all countries, by year of ART initiation**

**Table 1**

**Summary of the patient characteristics across all countries**

| | LTFU | | In care | | Deaths | | All patients | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| **Total** | 743 | | 7210 | | 352 | | 8305 | (100) |
| **Year of ART initiation** | | | | | | | | |
| 2003-05 | 67 | (9) | 564 | (8) | 75 | (21) | 706 | (9) |
| 2006-09 | 396 | (53) | 2240 | (31) | 124 | (35) | 2760 | (33) |
| 2010-13 | 280 | (38) | 4406 | (61) | 153 | (43) | 4839 | (58) |
| **Age** | | | | | | | | |
| ≤30 | 245 | (33) | 1986 | (28) | 69 | (20) | 2300 | (28) |
| 31-40 | 255 | (34) | 2950 | (41) | 131 | (37) | 3336 | (40) |
| 41-50 | 150 | (20) | 1399 | (19) | 68 | (19) | 1617 | (19) |
| 51+ | 93 | (13) | 875 | (12) | 84 | (24) | 1052 | (13) |
| Median [IQR] | 35 | [29, 44] | 35 | [30, 43] | 39 | [32, 50] | 35 | [30, 44] |
| **Sex** | | | | | | | | |
| Male | 503 | (68) | 4929 | (68) | 280 | (80) | 5712 | (69) |
| Female | 240 | (32) | 2276 | (32) | 69 | (20) | 2585 | (31) |
| Transgender | 0 | (-) | 5 | (0) | 3 | (1) | 8 | (<0.2) |
| **Mode of HIV exposure** | | | | | | | | |
| Heterosexual | 503 | (68) | 4805 | (67) | 213 | (61) | 5521 | (66) |
| Homosexual contact | 106 | (14) | 1113 | (15) | 34 | (10) | 1253 | (15) |
| Injecting drug user | 65 | (9) | 584 | (8) | 66 | (19) | 715 | (9) |
| Other/Unknown | 69 | (9) | 708 | (10) | 39 | (11) | 816 | (10) |
| **HCV (ever)** | | | | | | | | |
| Negative | 499 | (67) | 5387 | (75) | 237 | (67) | 6123 | (74) |
| Positive | 73 | (10) | 819 | (11) | 68 | (19) | 960 | (12) |
| Not tested | 171 | (23) | 1004 | (14) | 47 | (13) | 1222 | (15) |
| **HBV (ever)** | | | | | | | | |
| Negative | 519 | (70) | 5634 | (78) | 271 | (77) | 6424 | (77) |
| Positive | 59 | (8) | 634 | (9) | 40 | (11) | 733 | (9) |

| | LTFU | | In care | | Deaths | | All patients | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Not tested | 165 | (22) | 942 | (13) | 41 | (12) | 1148 | (14) |
| **Pre-ART CD4 (cells/μL)** | | | | | | | | |
| ≤50 | 239 | (32) | 2104 | (29) | 174 | (49) | 2517 | (30) |
| 51-100 | 100 | (13) | 839 | (12) | 74 | (21) | 1013 | (12) |
| 101-200 | 154 | (21) | 1295 | (18) | 48 | (14) | 1497 | (18) |
| >200 | 194 | (26) | 2316 | (32) | 29 | (8) | 2539 | (31) |
| Not tested | 56 | (8) | 656 | (9) | 27 | (8) | 739 | (9) |
| Median [IQR] | 108 | [30, 217] | 126 | [34, 246] | 45 | [16, 97] | 117 | [32, 239] |
| **Pre-ART viral load (copies/mL)** | | | | | | | | |
| ≤10^5 | 75 | (10) | 1138 | (16) | 42 | (12) | 1255 | (15) |
| >10^5 | 56 | (8) | 1177 | (16) | 67 | (19) | 1300 | (16) |
| Not tested | 612 | (82) | 4895 | (68) | 243 | (69) | 5750 | (69) |
| Median [IQR] | 62000 | [20303,264000] | 105 000 | [30 500,362 400] | 151 900 | [70 500,380 840] | 105000 | [30589,358000] |
| **First ART regimen** | | | | | | | | |
| NRTI+NNRTI | 700 | (94) | 6618 | (92) | 313 | (89) | 7631 | (92) |
| NRTI+PI | 41 | (6) | 505 | (7) | 37 | (11) | 583 | (7) |
| Other | 2 | (0) | 87 | (1) | 2 | (1) | 91 | (1) |
| **Previous mono/dual therapy** | | | | | | | | |
| No | 728 | (98) | 7061 | (98) | 329 | (93) | 8118 | (98) |
| Yes | 15 | (2) | 149 | (2) | 23 | (7) | 187 | (2) |
| **Clinical Site** | | | | | | | | |
| Cambodia | 323 | (44) | 2115 | (29) | 97 | (28) | 2535 | (30) |
| Hong Kong | 14 | (2) | 704 | (10) | 76 | (22) | 794 | (10) |
| Indonesia | 114 | (15) | 954 | (13) | 29 | (8) | 1097 | (13) |
| Singapore | 222 | (30) | 1529 | (21) | 50 | (14) | 1801 | (22) |
| Vietnam | 33 | (4) | 1467 | (21) | 92 | (26) | 1592 | (19) |
| South Korea | 37 | (5) | 441 | (6) | 8 | (2) | 486 | (6) |

**Table 2**

**Factors associated with permanent LTFU, defined as no clinic visit for 180 days, among all patients under follow-up**

| | Events | / | pys | Rate per 100 pys (95% CI) | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SHR | 95% CI | p value | SHR | 95% CI | p value |
| | 743 | / | 26217 | 2.83 (2.64, 3.05) | | | | | | |
| **Year of ART Initiation** | | | | | | | 0.595 | | | 0.746 |
| 2003-2005 | 67 | / | 4531 | 1.48 (1.16, 1.88) | 0.74 | (0.57, 0.96) | 0.023 | **0.73** | **(0.56, 0.95)** | **0.021** |
| 2006-2009 | 396 | / | 12734 | 3.11 (2.82, 3.43) | 1.00 | | | **1.00** | | |
| 2010-2013 | 280 | / | 8952 | 3.13 (2.78, 3.52) | 0.90 | (0.77, 1.07) | 0.231 | **0.83** | **(0.69, 0.99)** | **0.034** |
| **Age at ART initiation (years)** | | | | | | | 0.005 | | | **0.003** |
| ≤30 | 245 | / | 6694 | 3.66 (3.23, 4.15) | 1.00 | | | 1.00 | | |
| 31-40 | 255 | / | 10721 | 2.38 (2.10, 2.69) | 0.67 | (0.56, 0.80) | <0.001 | **0.67** | **(0.56, 0.80)** | **<0.001** |
| 41-50 | 150 | / | 5548 | 2.70 (2.30, 3.17) | 0.73 | (0.59, 0.91) | 0.004 | **0.72** | **(0.58, 0.89)** | **0.002** |
| 51+ | 93 | / | 3254 | 2.86 (2.33, 3.50) | 0.71 | (0.55, 0.92) | 0.008 | **0.69** | **(0.53, 0.90)** | **0.007** |
| **Sex** | | | | | | | | | | |
| Male | 503 | / | 18147 | 2.77 (2.54, 3.02) | 1.00 | | | 1.00 | | |
| Female | 240 | / | 8070 | 2.97 (2.62, 3.38) | 1.05 | (0.89, 1.25) | 0.546 | 1.13 | (0.94, 1.36) | 0.186 |
| **Mode of HIV Exposure** | | | | | | | <0.001 | | | **0.005** |
| Heterosexual contact | 503 | / | 18139 | 2.77 (2.54, 3.03) | 1.00 | | | 1.00 | | |
| Homosexual contact | 106 | / | 3893 | 2.72 (2.25, 3.29) | 1.21 | (0.95, 1.54) | 0.130 | **1.36** | **(1.05, 1.76)** | **0.021** |
| Injecting drug use | 65 | / | 1786 | 3.64 (2.85, 4.64) | 1.89 | (1.41, 2.55) | <0.001 | **1.65** | **(1.19, 2.30)** | **0.003** |
| Other/unknown | 69 | / | 2400 | 2.88 (2.27, 3.64) | 1.16 | (0.89, 1.52) | 0.269 | 1.11 | (0.85, 1.44) | 0.440 |
| **Time-updated CD4 (cells/μL)** | | | | | | | <0.001 | | | **<0.001** |
| ≤50 | 117 | / | 1175 | 9.96 (8.31, 11.93) | 1.00 | | | 1.00 | | |
| 51-100 | 61 | / | 1098 | 5.56 (4.32, 7.14) | 0.60 | (0.43, 0.82) | 0.001 | **0.59** | **(0.43, 0.82)** | **0.001** |
| 101-200 | 144 | / | 3679 | 3.91 (3.32, 4.61) | 0.50 | (0.39, 0.65) | <0.001 | **0.48** | **(0.37, 0.62)** | **<0.001** |
| 201+ | 369 | / | 16883 | 2.19 (1.97, 2.42) | 0.34 | (0.27, 0.44) | <0.001 | **0.32** | **(0.25, 0.41)** | **<0.001** |
| Not tested | 52 | / | 3382 | 1.54 (1.17, 2.02) | 0.21 | (0.15, 0.30) | <0.001 | **0.19** | **(0.14, 0.28)** | **<0.001** |

| | Events | / | pys | Rate per 100 pys (95% CI) | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SHR | 95% CI | p value | SHR | 95% CI | p value |
| **Time-updated HIV viral load (copies/mL)** | | | | | | | | | | |
| ≤100000 | 177 | / | 8500 | 2.08 (1.80, 2.41) | 1.00 | | | 1.00 | | |
| >100000 | 14 | / | 462 | 3.03 (1.80, 5.12) | 0.83 | (0.47, 1.48) | 0.535 | 0.58 | (0.32, 1.05) | 0.072 |
| Not tested | 552 | / | 17256 | 3.20 (2.94, 3.48) | 0.96 | (0.78, 1.18) | 0.699 | 0.84 | (0.67, 1.04) | 0.114 |
| **First ART regimen** | | | | | | | 0.333 | | | 0.390 |
| NRTI+NNRTI | 700 | / | 23879 | 2.93 (2.72, 3.16) | 1.00 | | | 1.00 | | |
| NRTI+PI | 41 | / | 2127 | 1.93 (1.42, 2.62) | 1.01 | (0.70, 1.46) | 0.965 | 1.03 | (0.71, 1.49) | 0.873 |
| Other | 2 | / | 211 | 0.95 (0.24, 3.8) | 0.36 | (0.09, 1.40) | 0.140 | 0.38 | (0.10, 1.55) | 0.178 |
| **Hepatitis B co-infection** | | | | | | | | | | 0.170 |
| Negative | 519 | / | 20693 | 2.51 (2.3, 2.73) | 1.00 | | | 1.00 | | |
| Positive | 59 | / | 2362 | 2.50 (1.94, 3.22) | 1.04 | (0.80, 1.37) | 0.755 | 1.01 | (0.77, 1.33) | 0.936 |
| Not tested | 165 | / | 3162 | 5.22 (4.48, 6.08) | 1.89 | (1.53, 2.34) | <0.001 | 1.43 | (0.99, 2.08) | 0.060 |
| **Hepatitis C co-infection** | | | | | | | | | | **0.002** |
| Negative | 499 | / | 20472 | 2.44 (2.23, 2.66) | 1.00 | | | 1.00 | | |
| Positive | 73 | / | 2364 | 3.09 (2.46, 3.88) | 1.79 | (1.39, 2.31) | <0.001 | **1.54** | **(1.16, 2.05)** | **0.003** |
| Not tested | 171 | / | 3382 | 5.06 (4.35, 5.87) | 2.00 | (1.62, 2.46) | <0.001 | **1.50** | **(1.04, 2.18)** | **0.030** |
| **Clinical Site** | | | | | | | <0.001 | | | **<0.001** |
| Cambodia | 323 | / | 9706 | 3.33 (2.98, 3.71) | 1.00 | | | 1.00 | | |
| Hong Kong | 14 | / | 3110 | 0.45 (0.27, 0.76) | 0.14 | (0.08, 0.23) | <0.001 | **0.11** | **(0.06, 0.20)** | **<0.001** |
| Indonesia | 114 | / | 3128 | 3.64 (3.03, 4.38) | 1.02 | (0.82, 1.27) | 0.848 | **0.53** | **(0.40, 0.70)** | **<0.001** |
| Singapore | 222 | / | 5485 | 4.05 (3.55, 4.62) | 1.06 | (0.89, 1.27) | 0.480 | 1.00 | (0.78, 1.27) | 0.975 |
| Vietnam (Site 1) | 4 | / | 1533 | 0.26 (0.10, 0.70) | 0.06 | (0.02, 0.15) | <0.001 | **0.04** | **(0.01, 0.11)** | **<0.001** |
| Vietnam (Site 2) | 29 | / | 1274 | 2.28 (1.58, 3.28) | 0.45 | (0.30, 0.66) | <0.001 | **0.29** | **(0.18, 0.45)** | **<0.001** |
| South Korea | 37 | / | 1980 | 1.87 (1.35, 2.58) | 0.64 | (0.45, 0.90) | 0.009 | **0.56** | **(0.35, 0.89)** | **0.013** |

^ Global p-values are test for linear trend while all other global p-values are test for heterogeneity.

Note that global p-value test was not conducted if there were only two categories when using test for heterogeneity or three categories where one was ‘Not tested’ when using test for linear trend.

[1]Multivariate model was adjusted for year of ART initiation, age at ART initiation, sex, mode of HIV exposure, time-updated CD4 count, time-updated HIV viral load, first ART regimen, hepatitis B co-infection, hepatitis C co-infection and clinical site.

[2]NRTI = nucleoside reverse transcriptase inhibitor.

[3]NNRTI = nonnucleoside reverse transcriptase inhibitor.

[4]PI = protease inhibitor.

[5]Includes all other antiretroviral drug regimen combinations.



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