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Trends in follow-up visits among people living with HIV - results from the TREAT Asia and Australian HIV Observational Databases (TAHOD and AHOD)

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Abstract

Background—Less frequent follow-up visits may reduce the burden on people living with HIV (PLHIV) and health facilities. We aimed to assess trends in follow-up visits and survival outcomes among PLHIV in Asia and Australasia.

Settings—PLHIV enrolled in TAHOD or AHOD from 2008–2017 were included.

Methods—Follow-up visits included laboratory testing and clinic visit dates. Visit rates and survival were analysed using repeated measure Poisson regression and competing risk regression, respectively. Additional analyses were limited to stable PLHIV with VL <1000 copies/mL and self-reported adherence ≥95%.

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Conflicts of interest

All authors stated that they have no conflicts of interest.

Results—We included 7707 PLHIV from TAHOD, and 3289 from AHOD. Visit rates were 4.33 per person-years (/PYS) in TAHOD, and 3.68/PYS in AHOD. Both TAHOD and AHOD had decreasing visit rates in later calendar years compared to years 2008–2009 (p<0.001 for both cohorts). Compared to PLHIV with 2 visits, those with ≥4 visits had poorer survival: TAHOD ≥4 visits: sub-hazard ratio (SHR)=1.88, 95%CI 1.16–3.03, p=0.010; AHOD ≥4 visits: SHR=1.80, 95%CI 1.10–2.97, p=0.020; while those with ≤1 visit showed no differences in mortality. The association remained evident among stable PLHIV: TAHOD ≥4 visits: SHR=5.79, 95%CI 1.84–18.24, p=0.003; AHOD ≥4 visits: SHR=2.15, 95%CI 1.20–3.85, p=0.010, compared to 2 visits.

Conclusions—Both TAHOD and AHOD visit rates have declined. Less frequent visits did not affect survival outcomes, however poorer health possibly lead to increased follow-up and higher mortality. Reducing visit frequency may be achievable among PLHIV with no other medical complications.

Background

In the early antiretroviral therapy (ART) era, people living with HIV (PLHIV) in low- and middle- income countries often presented to HIV care with advanced disease. Clinic appointments were often scheduled at monthly intervals to facilitate more intensive monitoring and clinical care[1]. As treatment guidelines have evolved, increasing numbers of PLHIV are now initiating ART at higher CD4 cell counts and less advanced disease. Many PLHIV are achieving and maintaining viral load suppression over time as HIV transitions to become a manageable chronic disease.

Frequent HIV clinic visits can be inconvenient and represent financial burden on PLHIV [2], which can lead to poor adherence and reduced retention[3,4]. There is currently no accepted gold standard on how often HIV monitoring should occur. Previous studies have shown that by extending clinic appointment intervals, patients were less likely to miss their scheduled appointments, and this was often associated with better treatment outcomes[5,6].

The World Health Organization (WHO) now recommends less frequent clinical visits for PLHIV on stable ART[1]. The reduction in visit frequency is expected to reduce the cost burden for both PLHIV and health care services, especially in resource-limited settings such as the Asia-Pacific region which is home to an estimated 5.8 million PLHIV in 2019, more than any other region outside of sub-Saharan Africa[7,8].

The TREAT Asia HIV Observational Database (TAHOD)[9,10] consists of sites from high, upper-middle and lower-middle income countries across Asia, with ongoing patient recruitment since 2003. The Australian HIV Observational Database (AHOD)[11], established in 1999, is a cohort comprised of sites within Australia and New Zealand, both high-income countries. TAHOD and AHOD are observational cohorts which longitudinally capture routine HIV clinical care data, such as patient demographics, ART regimen, CD4 cell count, plasma viral load (VL), and other laboratory measurements. Follow-up visits are conducted as per clinical guidance with no scheduled visits mandated by the study protocol.

Previously, patients in AHOD were reported to have CD4 and VL testing up to 4 times per year, in contrast to up to twice per year for TAHOD low-income sites[12]. In addition,

combined CD4 and VL testing frequency in TAHOD fell from 2 per person-years in 2003–2005 to 1.5 per person-years in 2014–2015[13]. It is not known if the overall follow-up visit frequency has also fallen over the years in both cohorts.

The aim of this study was to investigate follow-up frequencies among the general TAHOD and AHOD population over the past decade, and the association of the number of visits occurring in the past year with survival outcomes. Additional analyses were conducted among those considered to be adhering to care and clinically stable.

Methods

Study population

PLHIV enrolled in TAHOD and AHOD in follow-up and on ART for at least one year from 2008 to 2017 were included. Patients who became lost to follow-up (LTFU), transferred out, or died prior to 2008 were excluded from the study. Sites in TAHOD are all urban HIV referral centres spanning across World Bank[14] lower-middle to high income countries in Asia. AHOD sites consist of sexual health clinics, high HIV caseload general practitioners and public HIV clinics in Australia and New Zealand.

Definitions

As TAHOD and AHOD do not collect cumulative visit dates, i.e. only the latest visit date is captured in the dataset, we defined a follow-up visit or contact as any of the clinic visit dates, CD4, VL or other laboratory testing dates recorded in the database. Other laboratory testing dates include but not limited to hepatitis serology testing and routine bloods.

Follow-up visit rates

Analysis time started from the later of cohort entry date or six months after ART initiation to minimise bias caused by the higher number of visits expected in the first six months after initiation of ART. Follow-up rates occurring between 2008 and 2017 were plotted across calendar years and analysed using repeated measure Poisson regression with random effects on patient.

Survival time

Survival time were plotted using the Kaplan-Meier (KM) curve, and analysed using Fine and Gray's competing risk regression, with LTFU included as a competing risk. LTFU was defined as those not seen in the previous 12 months excluding transfers or deaths. Risk time for mortality was left truncated either at one year after cohort entry date, one year from date of ART initiation or at the beginning of our follow-up period in 2008, whichever occurred last. Patients who were alive, transferred out, became LTFU or died after 2017 were all censored at the end of our follow-up period of 31st December 2017. Proportional hazards (PH) assumption was assessed using Schoenfeld residuals method.

Covariates

Time fixed covariates included age at ART initiation, sex, mode of HIV exposure, initial ART regimen, hepatitis B/C co-infection, and World Bank Country Income grouping[14]

for TAHOD sites, which was adjusted a priori in the multivariate analysis. Time-updated covariates included calendar year of follow-up categorised according to changes in WHO treatment guidelines [1,15,16], VL, CD4, AIDS illnesses and self-reported ART adherence using the WHO endorsed 30 day visual analogue scale[17]. ART adherence was not collected in AHOD. In the survival analysis, a visit frequency variable was added to the model. This time-updated variable measures the number of follow-up visits occurring in the past 12 months. We chose 2 visits as the reference category to be consistent with the previously published average CD4 cell and VL testing frequency in TAHOD[12].

Regression models were fitted using backward stepwise selection process using Wald's test for heterogeneity or test for trend. With the exception of World Bank Country Income in TAHOD which was adjusted a priori, other covariates with $p<0.10$ in the univariate analysis were included in the multivariate model selection. Covariates with $p<0.05$ were considered statistically significant.

Stable PLHIV

To further explore whether similar trends were present among PLHIV deemed clinically stable, we limited our analyses to PLHIV with VL <1000 copies/mL between 2008 and 2017 in both cohorts. We additionally excluded patients with at least one self-reported ART adherence <95% in the TAHOD cohort as routine VL testing is not performed at all TAHOD sites. These definitions were derived from WHO[18,19] and adapted to our cohorts.

Ethics approvals for TAHOD were obtained from the local ethics committees of all participating sites, the data management and biostatistical program (The Kirby Institute, UNSW Sydney), and the coordinating centre (TREAT Asia/amfAR). Ethics approval for AHOD was obtained from the respective local ethics committees of all participating sites and the Kirby Institute, UNSW Sydney. Data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata software version 16.1 (Stata Corp., College Station, TX, USA).

Results

A total of 7707 TAHOD patients were included from Cambodia (7%), China (3%), Hong Kong SAR (5%), India (10%), Indonesia (10%), Japan (3%), Malaysia (8%), the Philippines (5%), Singapore (3%), South Korea (3%), Taiwan (7%), Thailand (26%), and Vietnam (9%). AHOD contributed 3289 patients from sites in Australia (93%) and New Zealand (7%). Table 1 shows TAHOD patients were younger at enrolment (median age = 34 years (interquartile range (IQR) 29–41)) compared to AHOD (median age = 39 years (IQR 33–47)). The main mode of HIV exposure for TAHOD was heterosexual contact (63%), while men who have sex with men (MSM) was the main mode of exposure for AHOD (70%). TAHOD patients had lower CD4 count prior to ART initiation (TAHOD median CD4 = 135 cell/μL, IQR (44–238)); AHOD median CD4 = 310 cell/μL (IQR 189–480).

Follow-up visit rates

From 2008 to 2017 the overall visit rate for the TAHOD was 4.33 per person-years (/PYS); for AHOD it was 3.68/PYS. Figure 1 illustrates the visit rates for each cohort across

calendar years. The figure shows a strong downward trend in visit rates for AHOD, while TAHOD showed a gradual decrease in follow-up visits.

In the Poisson analysis for TAHOD, all covariates were significant in the univariate analysis: calendar year, age at ART initiation, sex, mode of HIV exposure, viral load, CD4, initial ART regimen, hepatitis B/C co-infection, AIDS illnesses, ART adherence, and World Bank Country Income level, all p<0.001. Figure 2a is a forest plot of the multivariate regression model for TAHOD. Not tested/unknown values were analysed as a separate category, but excluded from test for heterogeneity and omitted from the forest plot.

From Figure 2a, there was a decrease in visit rates for later calendar years of follow-up: 2013–2015: incidence rate ratio (IRR)=0.94, 95% confidence interval (CI) (0.92–0.95), p<0.001; and 2016–2017: IRR=0.95, 95% CI (0.93–0.96), p<0.001); compared to years 2008–2009. Those with higher CD4 count also showed decreases in visit rates: 201–350 cells/μL (IRR=0.83, 95% CI (0.82–0.85), p<0.001), 351–500 cells/μL (IRR=0.76, 95% CI (0.75–0.78), p<0.001) and >500 cells/μL (IRR=0.72, 95% CI (0.70–0.73), p<0.001) compared to ≤200 cells/μL. An increase in visit rates was seen in older age 41–50 years (IRR=1.05, 95% CI (1.02–1.08), p=0.002, and age >50 years (IRR=1.10, 95% CI (1.05–1.14), p<0.001) compared to age ≤30 years; higher VL 401–1000 copies/mL (IRR=1.12, 95% CI (1.07–1.18), p<0.001) and VL >1000 copies/mL (IRR=1.34, 95% CI (1.30–1.37), p<0.001), compared to VL ≤400 copies/mL. Other factors associated with increased visit rates compared to the reference category were injecting drug users, having an AIDS illness, hepatitis B co-infection, female sex and being from high income countries. Those associated with lower visit rates were MSM and other/unknown mode of HIV exposure, initiating on an nucleoside reverse transcriptase inhibitor (NRTI)+ protease inhibitor (PI) regimen and being from upper-middle income countries.

In AHOD, we also observed decreased visit rates at later calendar years of follow up (Figure 2b). The follow-up visit rate in 2008–2009 was 4.59/PYS, decreasing to 3.12/PYS in 2016–2017. Compared to 2008–2009, the adjusted IRRs for other years were: 2010–2012: IRR=0.81, 95% CI (0.79–0.82), p<0.001; 2013–2015: IRR=0.71, 95% CI (0.69–0.73.), p<0.001; and 2016–2017 IRR=0.65, 95% CI (0.63–0.67), p<0.001. Similar to TAHOD we observed an increase in visit rates for older age and higher VL, while higher CD4 cell counts were associated with decreased visit rates. Compared to MSM, AHOD patients with heterosexual mode of exposure (IRR=0.91, 95% CI (0.86–0.97), p=0.003), and those with other/unknown mode of exposure (IRR=0.93, 95% CI (0.87–0.99), p=0.018) had less frequent follow-up. Those with an AIDS defining illness and those who initiated with combination regimens other than NRTI+non NRTI (NNRTI) had more frequent follow-up visits.

Survival time

A total of 7495 TAHOD and 3147 AHOD patients were included in the survival analysis. Mortality rates during 2008–2017 were 0.55/100PYS for TAHOD and 0.79/100PYS for AHOD. All variables satisfied PH assumption. Figures 3a and 3b are KM curves for survival time according to the frequency of follow-up visits in the previous year. Visit frequency of ≥4 times in the past year had overall lower survival probabilities than those who were

seen twice. However, we also observed that the KM curve for ≤1 visit was also lower than our reference curve of 2 visits, but this association was not significant after controlling for confounders as shown in Figures 4a and 4b. TAHOD patients (Figure 4a) with ≥4 follow-up visits had higher hazard for mortality compared to those with 2 visits (sub-hazard ratio (SHR)=1.88, 95% CI (1.16–3.03), p=0.010). There were no differences in survival for those who had 3 visits (p=0.148) or ≤1 visit (p=0.223). A similar association can also be seen in AHOD (Figure 4b) where those with ≥4 follow-up visits was associated with poorer survival time (SHR=1.80, 95% CI (1.10–2.97), p=0.020), while visit frequency of ≤1 had no effect on survival (p=0.611). Other factors associated with increased mortality for both cohorts were older age, VL >1000 copies/mL, hepatitis C-coinfection and AIDS illnesses. Those with hepatitis B co-infection in TAHOD and those who initiated with NRTI+PI regimen in AHOD had increased mortality. Higher CD4 cell count was associated with improved survival in both TAHOD and AHOD.

Stable PLHIV

We conducted additional analyses by limiting our study group to those deemed clinically stable. There were 4658 TAHOD and 2575 AHOD PLHIV included. Supplementary Figures 1a and 1b show that the results are similar to the main analyses, with decrease in visit rates for later years of follow-up.

Supplementary Figures 2a and 2b indicate that similar patterns in survival outcomes remained evident for both cohorts. There was an association of frequent follow-up visits ≥4 times in the past 12 months with mortality: TAHOD: SHR=5.79, 95% CI (1.84–18.24), p=0.003; AHOD: SHR=2.15, 95%CI 1.20–3.85, p=0.010, while having 3 or ≤1 visit did not affect survival time compared to 2 visits. TAHOD showed wide 95% CIs suggesting more sample size is needed.

Collinearity was assessed and presented as correlation matrices in Supplementary Figure 3. There was no collinearity observed between variables.

Discussion

Visit rates during 2008–2017 was 4.33/PYS for TAHOD, and 3.68/PYS for AHOD. We observed decreased visit rates in both cohorts in later years of follow-up. Having ≥4 visits in the last 12 months was associated with poorer survival outcomes, while ≤1 visit did not have an impact on survival. Once PLHIV without evidence of stable disease were excluded from the study population, we continued to observe a decrease in visit rates across calendar years, without changes in patterns of survival outcomes.

The 2016 WHO guidelines[1] recommend less frequent clinical visits and medication pick-ups at 3–6 month intervals for PLHIV with stable disease. Along with the introduction of Treat All strategies, low- and middle-income countries have begun to extend clinic visit intervals to optimise patient retention and relieve the potential burden on the health care system. Within the Asia-Pacific region, clinically stable PLHIV in the Philippines are seen at the clinic every six months. However, a stand-alone satellite clinic has begun offering e-consultations to stable PLHIV with ART refills couriered to their home thus reducing

the requirement for a face-to-face visit[20]. In Vietnam, the recent successful registration of 90 and 180 count ART pill bottles has allowed for three to six month ART dispensing to qualified patients[21]. In high-income countries such as Australia, PLHIV who have reached virological suppression are recommended to come for VL monitoring once every 3–6 months[22].

Amongst the general TAHOD and AHOD population, as well as those deemed clinically stable, a decreasing trend in follow-up visits in later calendar years were observed for both cohorts. From our previous TAHOD study[23], PLHIV with suboptimal ART adherence were shown to be more likely to miss clinic appointments. Similarly, other studies have shown that PLHIV with indicators of disease progression, such as low CD4 cell count and recent hospitalisation were more likely to miss their visit appointments[24,25]. It is important to note that our study did not capture missed clinic appointments, but rather attended visits. A South African study comparing visit rates among PLHIV with stable disease and those receiving failing ART has shown that those failing ART were seen more frequently compared to those deemed clinically stable[26]. By excluding PLHIV without stable disease from our study population, we observed a greater decrease in follow-up visit rates among those adhering and responding to treatment.

Survival time in both cohorts was not affected by less frequent follow-up. There was an increase in hazard for mortality, however, for those having four or more visits in the previous 12 months. Once we limited the analyses to stable PLHIV, the association remained evident in both cohorts. These findings may appear counterintuitive as various studies have found that more consistent engagement in care were associated with decreased mortality, while having multiple missed visits after ART initiation substantially increased the risk for all-cause mortality[27–30]. It can also be argued that those with higher number of visits are sicker with shorter survival time, and those who disengage in care with fewer visits are at increased risk of mortality. Our survival curves somewhat illustrate this with the effect more evident in TAHOD. That is, there appeared to be higher risk for mortality among those with lowest and highest number of visits compared to our reference group (2 visits), however, the association was not significant except for those with ≥4 visits.

PLHIV with other health conditions such as those with adverse drug reactions, co-morbidities or co-infections are more likely to seek frequent medical care. A study of African and Caribbean PLHIV immigrants in Ontario, Canada found higher rates of health service usage for certain non-communicable diseases, e.g. chronic pulmonary disease, hypertension, diabetes and mental health illnesses[31]. Our data also suggest that those with hepatitis B/C co-infection had higher follow-up visit rates compared to those without the co-infection. This is likely due to the more frequent monitoring among those who are hepatitis B/C positive. Therefore, the association between higher number of visits and mortality illustrates that PLHIV with co-morbidities are perceived to be at greater risk of serious morbidity and mortality, and are subsequently being monitored more closely.

Although better VL control and greater increases in CD4 cell counts have been associated with more frequent visits[32], recent studies suggest that reduced clinic visit frequency does not have an impact on treatment outcomes in both high income and low- and middle-

income settings[6]. There was no association seen between three, four and six month visit intervals and virological suppression among PLHIV enrolled in six clinics across the USA[33]. Similarly, an analysis from South Africa comparing ART pharmacy pick-ups every two months vs. every four months did not find a significant association between ART dispensing frequency and virological suppression rates among PLHIV with stable disease[34]. This suggests that clinicians may consider extending clinic visit intervals among PLHIV who are well and who have demonstrated good adherence to ART with sustained virological control.

The limitations of the study include not having all retrospective clinic visit dates. Both TAHOD and AHOD cohorts do not record all previous clinic visits, therefore we defined follow-up visits as a combination of all possible laboratory and assessment dates. If a patient attended a clinic appointment without any laboratory testing, we would not have been able to capture this visit in our analysis, unless it was the latest visit date collected in the dataset. This may introduce a bias in the study whereby those who are stable may come in for a clinic visit without any laboratory testing resulting in lower number of visits recorded compared to those who are sick requiring frequent blood testing. However, as VL and CD4 testing are often performed as part of HIV routine clinical visits, even among stable PLHIV, we believe the number of visits without any laboratory testing that is not captured in our analyses is minimal. Another limitation of the study is the definition of stable PLHIV. As ART adherence is not collected in AHOD, we were not able to define stable AHOD PLHIV based on adherence levels. We did not exclude those with adverse drug reactions requiring regular monitoring, or those with current illnesses or pregnancy as per WHO's definition[18,19] due to limited data collected in both of our cohorts. A previous linkage study in AHOD has found that LTFU status was not associated with mortality. This was possibly due to re-engagement in care with other health providers[35]. The mortality estimate among LTFU patients in TAHOD is unknown. We have attempted to account for this by censoring LTFU as competing risk, although it is likely that the mortality rate for TAHOD was underestimated. Both TAHOD and AHOD did not collect transgender status consistently. As such, we were not able to assess its impact on the study outcomes. Lastly, as the TAHOD cohort is not representative of all PLHIV in Asia, the findings of the study are limited to our study groups, and not generalisable to the wider PLHIV population.

Conclusions

Less frequent visits in recent years were observed among PLHIV enrolled in TAHOD and AHOD. The increased risk in mortality with higher number of visits were most likely due to PLHIV with greater risk of mortality being monitored more frequently. Having fewer follow-ups did not affect survival outcomes, supporting recent WHO recommendations. The results indicate that across high-, middle- and lower-middle income countries in Asia and Australasia, health care providers may consider reducing follow-up appointments in otherwise healthy PLHIV maintaining virological control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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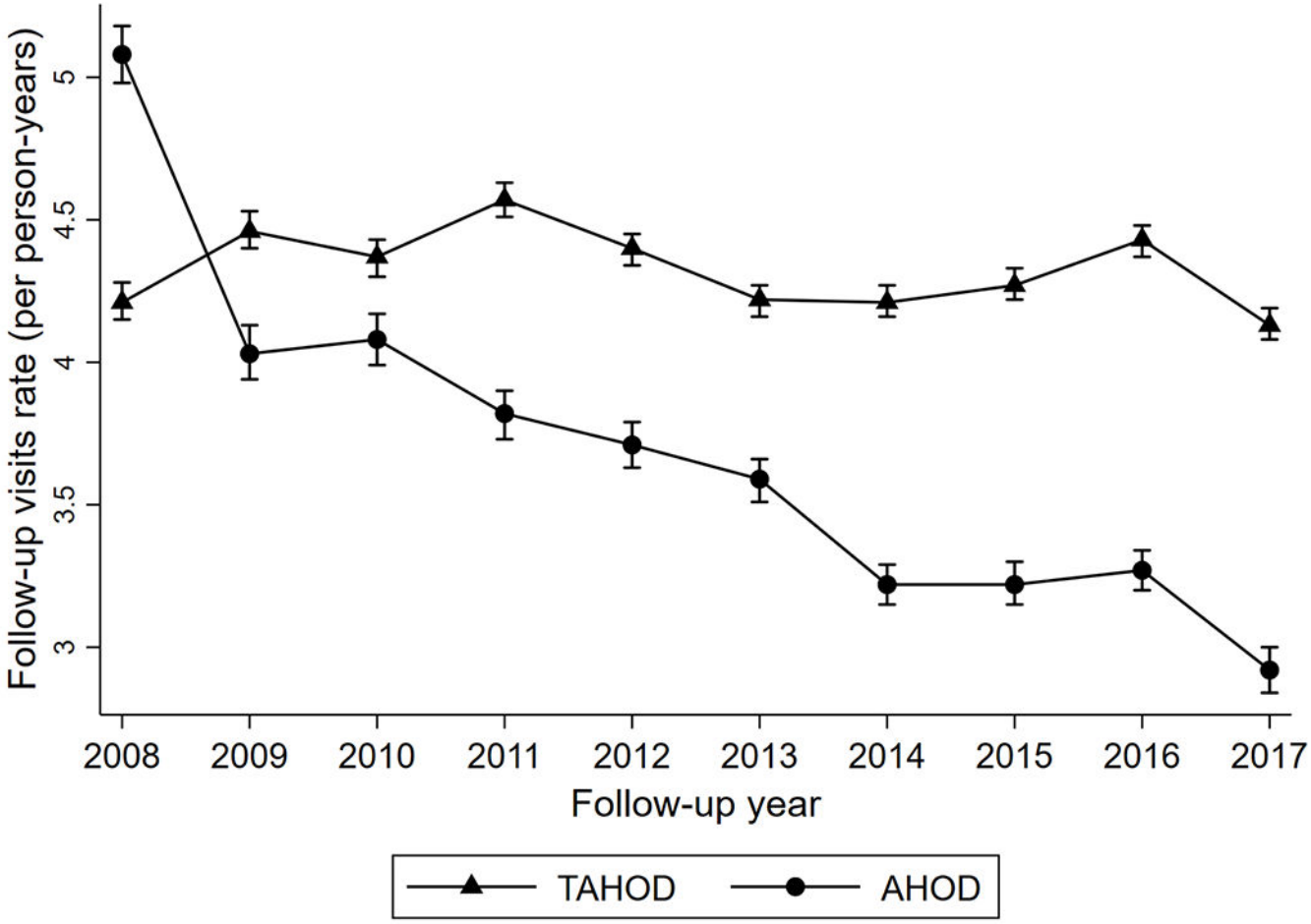

Figure 1:

Follow-up visits rates for TAHOD and AHOD during 2008–2017

Note: Each point on the graph corresponds to follow-up visit rate (per person-years) with associated 95% confidence interval.

Abbreviations: TAHOD – The TREAT Asia HIV Observational Database; AHOD – The Australian HIV Observational database.

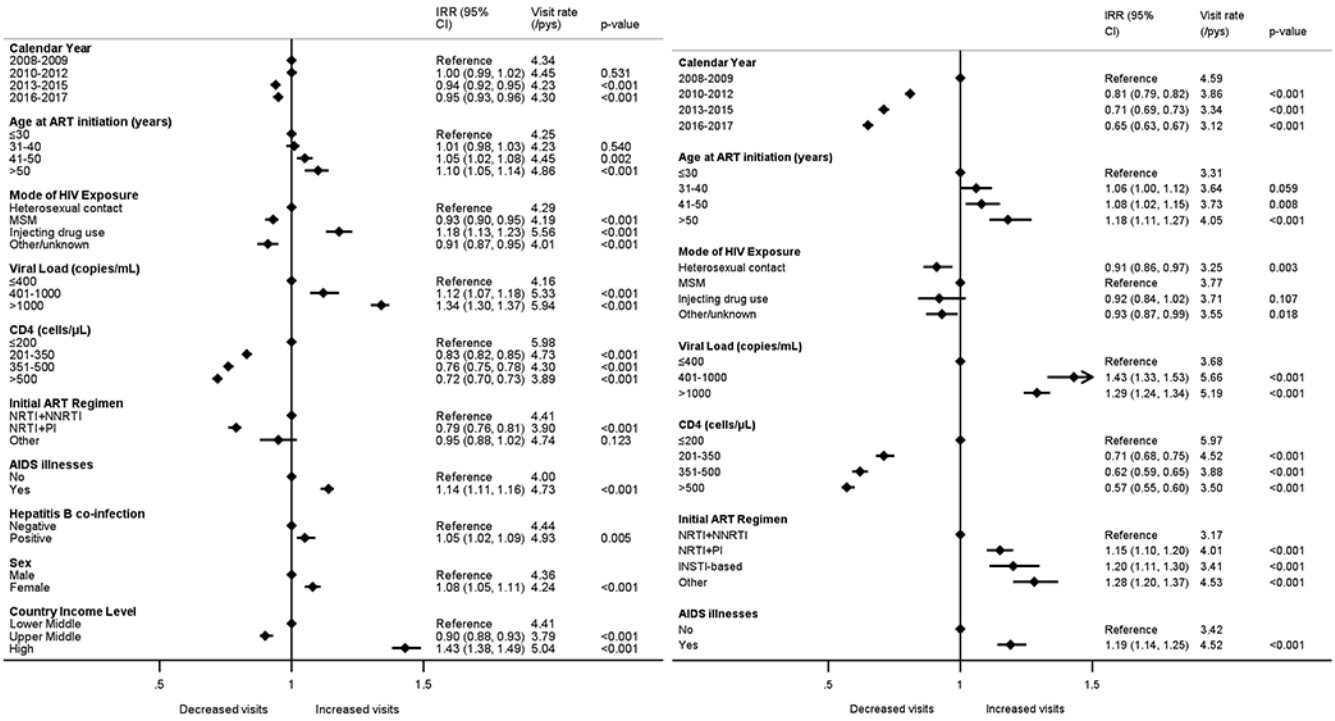

Figure 2:

Factors associated with follow-up visit rates in (a) TAHOD; and (b) AHOD

Not tested values were included in the analysis as a separate category but were excluded from test for heterogeneity, and omitted from the forest plot.

Global p-value for calendar year, age, viral load and CD4 were test for trend.

Calendar year, viral load, CD4 and AIDS illnesses were time updated variables.

Abbreviations: TAHOD – The TREAT Asia HIV Observational Database; AHOD – The Australian HIV Observational database; IRR – incidence rate ratio, CI – confidence interval; /pys – per person-years; ART – antiretroviral therapy; NRTI - nucleoside reverse transcriptase inhibitor, NNRTI – non NRTI; PI – protease inhibitor; INSTI – integrase inhibitor

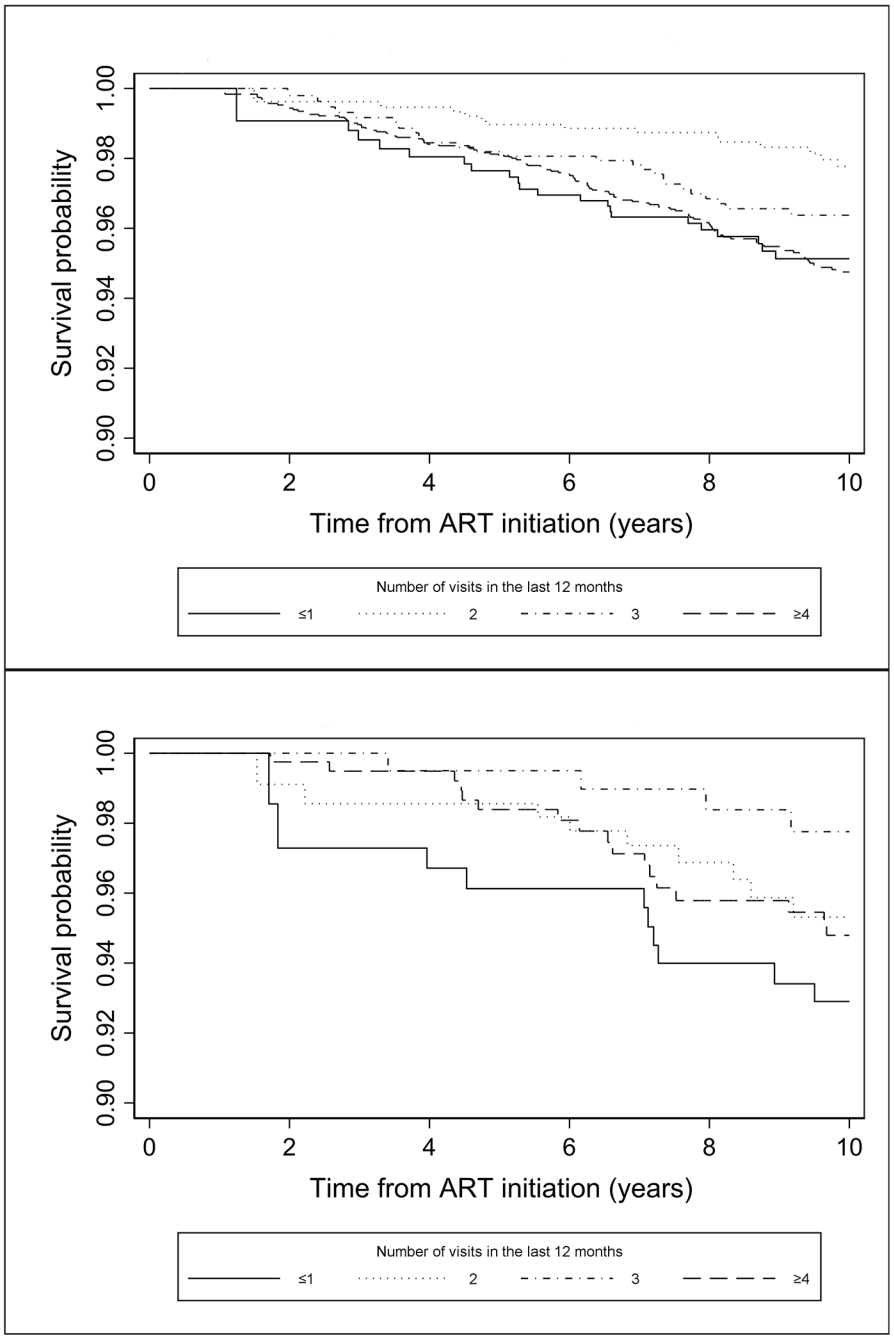

Figure 3:

Kaplan-Meier curves by frequency of follow-up visits in the past 12 months for (a) TAHOD; and (b)AHOD

Abbreviations: TAHOD – The TREAT Asia HIV Observational Database; AHOD – The Australian HIV Observational database; ART- antiretroviral therapy.

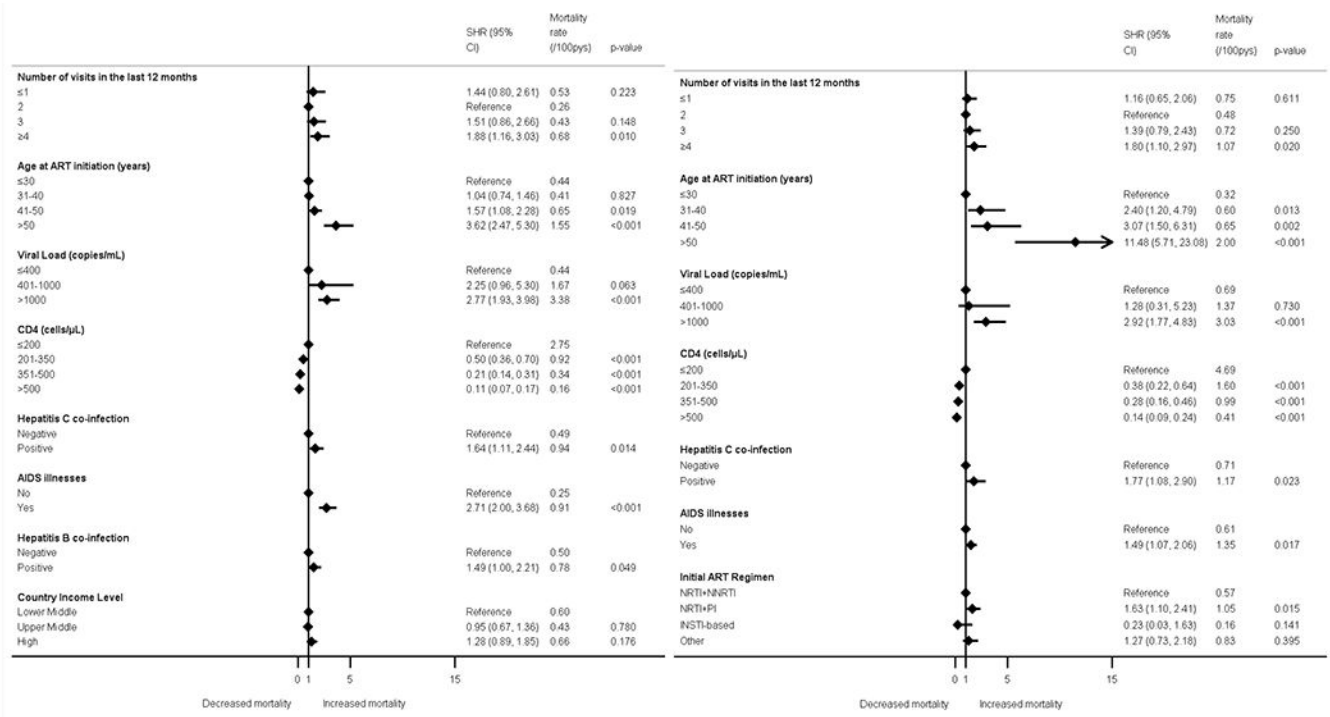

Figure 4:

Risk factors for mortality for (a) TAHOD; and (b) AHOD

Not tested values were included in the analysis as a separate category but were excluded from test for heterogeneity, and omitted from the forest plot.

Global p-value for calendar year, number of visits, age, viral load and CD4 were test for trend.

Number of visits, calendar year, viral load, CD4 and AIDS illnesses were time updated variables.

Abbreviations: TAHOD – The TREAT Asia HIV Observational Database; AHOD – The Australian HIV Observational database; SHR –sub-hazard ratio, CI – confidence interval; / 100pys – per 100 person-years; ART – antiretroviral therapy; NRTI - nucleoside reverse transcriptase inhibitor, NNRTI – non NRTI; PI – protease inhibitor; INSTI – integrase inhibitor

Table 1:

Patient characteristics

	TAHOD (%) N= 7707 (100)	AHOD (%) N =3289 (100)
Age at ART initiation (years)	Median = 34, IQR (29–41)	Median =39, IQR (33–47)
≤30	2389 (31)	605 (18)
31–40	3306 (43)	1217 (37)
41–50	1441 (19)	925 (28)
>50	571 (7)	542 (17)
Sex		
Male	5376 (70)	2971 (90)
Female	2331 (30)	318 (10)
Mode of HIV Exposure		482 (15)
Heterosexual contact		2290 (70)
MSM	4868 (63)	557 (7)
Injecting drug use	1733 (23)	143 (4)
Other/unknown	549 (7)	374 (11)
Pre-ART viral load (copies/mL)	Median = 84000, IQR (21304–250000)	Median = 46900, IQR (5790–140000)
≤100000	2058 (27)	1683 (51)
>100000	1689 (22)	728 (22)
Not tested	3960 (51)	878 (27)
Pre-ART CD4 (cells/μL)	Median = 135, IQR (44–238)	Median = 310, IQR (189–480)
≤50	1792 (23)	193 (6)
51–100	888 (12)	139 (4)
101–200	1564 (20)	375 (11)
>200	2198 (29)	1806 (55)
Not tested	1265 (16)	776 (24)
Initial ART Regimen		
NRTI+NNRTI	6359 (83)	1454 (44)
NRTI+PI	1167 (15)	1187 (36)
INSTI-based	72 (1)	332 (10)
Other	109 (1)	316 (10)
Hepatitis B co-infection		
Negative	5652 (73)	2434 (74)
Positive	644 (8)	112 (3)
Not tested	1411 (18)	743 (23)
Hepatitis C co-infection		
Negative	5022 (65)	2342 (71)
Positive	829 (11)	270 (8)
Not tested	1856 (24)	677 (21)
Country Income Level Lower Middle	3128 (41)	0 (0)
Upper Middle	2859 (37)	0 (0)
High	1720 (22)	3289 (100)