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Early Suboptimal ART Adherence Was Associated with Missed Clinical Visits In HIV-infected Patients in Asia

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Conflicts of interest

There are no conflicts of interest.

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Abstract

Missed clinic visits can lead to poorer treatment outcomes in HIV-infected patients. Suboptimal antiretroviral therapy (ART) adherence has been linked to subsequent missed visits. Knowing the determinants of missed visits in Asian patients will allow for appropriate counselling and intervention strategies to ensure continuous engagement in care.

A missed visit was defined as having no assessments within six months. Repeated measures logistic regression was used to analyse factors associated with missed visits.

A total of 7100 patients were included from 12 countries in Asia with 2676 (37.7%) having at least one missed visit. Patients with early suboptimal self-reported adherence <95% were more likely to have a missed visit compared to those with adherence ≥95% (OR=2.55, 95% CI(1.81–3.61)). Other factors associated with having a missed visit were homosexual (OR=1.45, 95% CI(1.27–1.66)) and other modes of HIV exposure (OR=1.48, 95% CI(1.27–1.74)) compared to heterosexual exposure; using PI-based (OR=1.33, 95% CI(1.15–1.53)) and other ART combinations (OR=1.79, 95% CI(1.39–2.32)) compared to NRTI+NNRTI combinations; and being hepatitis C co-infected (OR=1.27, 95% CI(1.06–1.52)). Patients aged >30 years (31–40 years OR=0.81, 95% CI(0.73–0.89); 41–50 years OR=0.73, 95% CI(0.64–0.83); and >50 years OR=0.77, 95% CI(0.64–0.93)); female sex (OR=0.81, 95% CI(0.72–0.90)); and being from upper middle (OR=0.78, 95% CI(0.70–0.80)) or high-income countries (OR=0.42, 95% CI(0.35–0.51)), were less likely to have missed visits.

Almost 40% of our patients had a missed clinic visit. Early ART adherence was an indicator of subsequent clinic visits. Intensive counselling and adherence support should be provided at ART initiation in order to optimise long term clinic attendance and maximise treatment outcomes.

Keywords

Asia; adherence; missed visit; HIV

Introduction

Continuous engagement in care after HIV diagnosis often maximises responses to ART and increases viral load (VL) suppression (Mugavero et al., 2012). Missed clinical visits or “no show” have shown to be associated with higher mortality rates in both resource-rich and resource-limited settings (Horberg et al., 2013; Y. Zhang et al., 2012). The risk for mortality also increases with higher frequency of missed visits in patients retained in care (Mugavero et al., 2014). Predictors of missed visits often include female sex, younger age, injecting drug users (IDU), and lower CD4 cell count (Horberg, et al., 2013; Y. Zhang, et al., 2012).

Little is known about missed visits in HIV-infected population in Asia. In loss to follow-up (LTFU) studies, it has been reported that ART adherence levels can be an important predictor of LTFU, in addition to other patient and clinical characteristics (Tran et al., 2013; Zhou et al., 2012). Although patients having missed clinical visits would most likely return for further clinical care, early ART adherence levels may be a good indicator of future clinic attendance.

The TREAT Asia HIV Observational Database (TAHOD) is a prospective cohort consisting of 20 sites in 12 countries in Asia (TAHOD, 2016; Zhou et al., 2005). Determining the extent of missed visits in this cohort, where ART combinations are often limited, will not only allow for appropriate intervention strategies to be implemented, but will enable health care providers to establish long term treatment plan to ensure that optimal treatment responses can be achieved.

Methods

Study population

Patients enrolled in TAHOD in the September 2015 data capture who had initiated ART were included in the analyses. Countries within TAHOD include Cambodia, China and Hong Kong SAR, India, Indonesia, Japan, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam.

Definitions

ART adherence was obtained from the WHO endorsed (Obermeyer et al., 2009) self-reported 30-day adherence visual analogue scale (Jiamsakul et al., 2014) (VAS). ART adherence used in this study was the assessment recorded in the first six months of ART initiation categorised (Obermeyer, et al., 2009) as (i) <95%, (ii) 95%, and (iii) Not done. We chose adherence levels in the first six months as our previous study suggests that suboptimal adherence occurred in highest proportions in the first 6 months of ART, and decreased thereafter (Jiamsakul, et al., 2014).

Analysis follow-up time began from the latter of ART initiation date or cohort entry date. Follow-up time was divided into six-monthly intervals, up to a maximum of five years. As the TAHOD database does not record scheduled or cumulative clinic visit attendances, a missed visit in this study was defined as having no clinical or laboratory attendance/assessments in each of the six-monthly intervals.

Patients were considered at risk of having a missed visit after six months from analysis start time as all patients in the study were expected to have a clinic visit in the first six months due to our endpoint definition and inclusion criteria. LTFU patients were categorised as having missed visits for 12 months after their last visit date, after which they were censored from the analysis datasets.

Statistical analyses

Factors associated with missed visits were analysed using repeated measures logistic regression (generalised estimating equations, GEE), using exchangeable correlation structure. Regression models were fitted using backward stepwise procedures. A sensitivity analysis was performed by restricting the study population to patients who had an adherence assessment available in the first six months.

Ethics approvals were obtained from respective local ethics committees of all TAHOD-participating sites, the data management and biostatistical center (UNSW Sydney Ethics Committee), and the coordinating centre (TREAT Asia/amfAR). All data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata software version 14.2 (Stata Corp., College Station, TX, USA).

Results

Of the 7100 patients included, 2676 (37.7%) had at least one missed visit. Of those who have had a missed visit, 845 (31.6%) patients subsequently became LTFU. Table 1 shows characteristics of the patient group consisting of mostly male patients (70.0%), with an overall median age of 34 years (IQR: 29–41). Adherence in the first six months after ART initiation was reported in 35.8% of patients. The median CD4 cell count prior to ART initiation was 128 cells/ μ L (IQR: 41–255), and median VL was 97100 copies/mL (IQR: 28400–280000).

Factors associated with missed visit events are presented in Table 2. In multivariate analyses, adjusting for follow-up time, patients reporting suboptimal ART adherence <95% in the first six months were more likely to have subsequent missed visits compared to those with adherence $\geq$ 95% (OR=2.55, 95% CI (1.81–3.61), $p<0.001$). Other clinical characteristics associated with having missed visits were homosexual HIV mode of exposure (OR=1.45, 95% CI (1.27–1.66), $p<0.001$) and other/unknown (OR=1.48, 95% CI (1.27–1.74), $p<0.001$), compared to heterosexual mode of exposure; initiating on a nucleoside reverse transcriptase inhibitor (NRTI) plus protease inhibitor (PI) (OR=1.33, 95% CI (1.15–1.53), $p<0.001$), and other combinations (OR=1.79, 95% CI (1.39–2.32), $p<0.001$) compared to a non-NRTI (NNRTI) -based regimen; and being hepatitis C co-infected (OR=1.27, 95% CI (1.06–1.52), $p=0.011$). Factors associated with decreased odds of having missed visits were age >30 years (31–40 years: OR=0.81, 95% CI (0.73–0.89), $p<0.001$, 41–50 years: OR=0.73, 95% CI (0.64–0.83), $p<0.001$, and >50 years: OR=0.77, 95% CI (0.64–0.93), $p=0.006$); female sex (OR=0.81, 95% CI (0.72–0.90), $p<0.001$); and being from upper middle-income (OR=0.78, 95% CI (0.70–0.86), $p<0.001$) and high-income countries (OR=0.42, 95% CI (0.35–0.51), $p<0.001$) compared to low and lower middle-income countries.

The differences in ART adherence levels and their association with missed visits are illustrated in Figure 1. Proportion of patients with missed visits over five years were consistently higher for those who reported adherence <95% in the first six months. Missed visits in those with adherence ≥95% slightly increased over time from 3% to 7%, while the proportions fluctuated between 8% and 15% in the suboptimal adherence group.

When we restricted our study population to patients who had an adherence measurement available in the first six months after ART initiation, we found that adherence has maintained its association with missed visits. We found that among the 2541 patients with adherence available, patients who had adherence <95% were at least two times more likely to have a subsequent missed visit during follow-up (OR=2.40, 95% CI (1.65–3.48), $p<0.001$).

Discussion

Missed visits occurred in almost 40% of our patient group. Patients with suboptimal adherence were more likely to have subsequent missed visits compared to patients with adherence ≥95%. Other factors associated with missed visits included homosexual and other/unknown mode of HIV exposure, PI-based and other ART combination first-line regimen, and being hepatitis-C positive. Factors showing decreasing likelihood of missed visits were older age, female sex, and being from upper middle- and high-income countries.

Our study suggests that ART adherence was an important factor in determining subsequent clinic attendance, which was consistent with findings from other resource-rich settings (Woodward et al., 2015). The significant association between adherence and missed visits in both the main and sensitivity analyses indicate that adherence levels should be carefully monitored, particularly immediately after ART initiation, to ensure that life-long HIV treatment schedules can be maintained and adhered to. Socioeconomic and psychosocial risk factors (Ayer et al., 2016; Wawrzyniak et al., 2015), have been reported to affect clinic attendance. TAHOD, however, does not routinely collect socioeconomic risk factors, but the decreasing odds of missed visits with higher country income levels signal the underlying socioeconomic barriers to continuous engagement in care in our patient group.

There is limited literature investigating the association of other clinical characteristics with missed visits, especially in resource-limited settings. However, our results are comparable to reported studies which showed that younger patients, males, and those with hepatitis C co-infection were more likely to have discontinuous engagement in care (Asiimwe, Kanyesigye, Bwana, Okello, & Muyindike, 2016; Mburu et al., 2016; Megerso et al., 2016; Rachlis et al., 2016; F. Zhang et al., 2014). We also found that PI-based first-line regimen was associated with increased odds of missed visits, which could be due to the toxicities associated with PI drugs (Zhou, et al., 2012). Heterosexual mode of exposure has been shown in different studies to be associated with an increased risk of missed visits or LTFU (McManus et al., 2015; Rachlis, et al., 2016). This is contrast to our findings where the association was seen in homosexual HIV exposure group. This may reflect the stigma and discrimination faced by this population potentially leading to disengagement in care.

A limitation of this study includes the nature of the data collection in TAHOD where scheduled or cumulative visit dates were not captured. We could not ascertain scheduled clinic appointments in each of the six-monthly intervals and therefore the reported missed visits may not represent the true proportion. Another limitation is the high percentage (64.2%) of patients without an adherence assessment in the first six months of ART initiation. This is because adherence information was not routinely collected in TAHOD until 2011. The sensitivity analysis, however, reported a significant association between suboptimal adherence and missed visits, thus indicating the importance of ART adherence in determining future clinic attendance. Lastly, as we did not control for site in the regression analysis due to potential collinearity with country-income level, we were not able to determine the association between site-level effects with missed visits.

Conclusions

This study found that patients with early suboptimal ART adherence were at increased risk of not attending future clinic appointments. Patients with poor adherence should be targeted in order to improve retention in care. Appropriate support should be provided at ART initiation to maximise treatment uptake in the first six months.

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Figure 1: Proportion of missed visits over time by ART adherence levels in the first six months.

*Follow-up time is time from ART initiation or cohort entry.

Table 1:

Patient characteristics

	Total patients (%) N = 7100 (100.0)	Patients with at least one missed visit (%) N = 2676 (37.7)
ART adherence in the first six months		
95%	2383 (33.6)	478 (17.9)
<95%	158 (2.2)	50 (1.9)
Not done	4559 (64.2)	2148 (80.3)
Age at ART initiation (years)		
	Median = 34 (IQR: 29–41)	Median = 33 (IQR: 28–40)
30	2238 (31.5)	963 (36.0)
31–40	3022 (42.6)	1116 (41.7)
41–50	1308 (18.4)	428 (16.0)
>50	532 (7.5)	169 (6.3)
Sex		
Male	4967 (70.0)	1978 (73.9)
Female	2133 (30.0)	698 (26.1)
HIV mode of exposure		
Heterosexual contact	4506 (63.5)	1598 (59.7)
Homosexual contact	1545 (21.8)	638 (23.8)
Injecting drug use	531 (7.5)	202 (7.5)
Other/Unknown	518 (7.3)	238 (8.9)
Pre-ART viral Load (copies/mL)		
	Median = 97100 (IQR: 28400–280000)	Median = 100000 (IQR: 27968–310000)
50000	1195 (16.8)	431 (16.1)
50001–250000	1303 (18.4)	452 (16.9)
>250000	912 (12.8)	353 (13.2)
Not done	3690 (52.0)	1440 (53.8)
Pre-ART CD4 (cells/μL)		
	Median = 128 (IQR: 41–225)	Median = 145.5 (IQR: 51–233)
50	1729 (24.4)	511 (19.1)
51–100	840 (11.8)	263 (9.8)
101–200	1510 (21.3)	573 (21.4)
>200	1863 (26.2)	701 (26.2)
Not done	1158 (16.3)	628 (23.5)
Initial ART Regimen		
NNRTI-based	6032 (85.0)	2214 (82.7)
PI-based	976 (13.7)	420 (15.7)
Other combination	92 (1.3)	42 (1.6)
Hepatitis B co-infection		
Negative	4906 (69.1)	1635 (61.1)
Positive	562 (7.9)	168 (6.3)

	Total patients (%) N = 7100 (100.0)	Patients with at least one missed visit (%) N = 2676 (37.7)
Not tested	1632 (23.0)	873 (32.6)
Hepatitis C co-infection		
Negative	4309 (60.7)	1230 (46.0)
Positive	759 (10.7)	281 (10.5)
Not tested	2032 (28.6)	1165 (43.5)
pre-ART AIDS Diagnosis		
No	4457 (62.8)	1673 (62.5)
Yes	2643 (37.2)	1003 (37.5)
Country income		
Low and lower middle	2975 (41.9)	1264 (47.2)
Upper middle	2658 (37.9)	980 (36.6)
High	1467 (20.7)	432 (16.1)

Table 2:

Factors associated with missed visits.

#Total Missed Visits			Univariate		Multivariate	
	OR	95% CI	* p-value	OR	95% CI	* p-value
ART adherence in the first six months						
95%	912	1		1		
<95%	99	2.15 (1.53, 3.01)	<0.001	2.55 (1.81, 3.61)		<0.001
Not done	5189					
Age at ART initiation						
30	2237	1	<0.001	1		<0.001
31–40	2657	0.81 (0.73, 0.89)	<0.001	0.81 (0.73, 0.89)		<0.001
41–50	933	0.66 (0.57, 0.75)	<0.001	0.73 (0.64, 0.83)		<0.001
>50	373	0.65 (0.54, 0.79)	<0.001	0.77 (0.64, 0.93)		0.006
Sex						
Male	4581	1		1		
Female	1619	0.81 (0.73, 0.89)	<0.001	0.81 (0.72, 0.90)		<0.001
Hepatitis B co-infection						
Heterosexual contact	3792	1	<0.001	1		<0.001
Homosexual contact	1403	1.08 (0.97, 1.20)	0.146	1.45 (1.27, 1.66)		<0.001
Injecting drug use	393	1.08 (0.91, 1.28)	0.390	0.87 (0.70, 1.08)		0.197
Other/Unknown	612	1.50 (1.29, 1.75)	<0.001	1.48 (1.27, 1.74)		<0.001
Pre-ART viral Load (copies/mL)						
50000	983	1	0.633			
50001–250000	1058	0.95 (0.82, 1.11)	0.548			
>250000	791	1.03 (0.88, 1.21)	0.719			
Not done	3368					
Pre-ART CD4 (cells/μL)						
50	1186	1	0.001			
51–100	614	1.10 (0.93, 1.31)	0.277			

	#Total Missed Visits	Univariate			Multivariate		
		OR	95% CI	*p-value	OR	95% CI	*p-value
101–200	1368	1.34	(1.17, 1.54)	<0.001			
>200	1601	1.29	(1.13, 1.47)	<0.001			
Not done	1431						
Initial ART Regimen							
NNRTI-based	5097	1		0.008	1		<0.001
PI-based	985	1.04	(0.92, 1.17)	0.509	1.33	(1.15, 1.53)	<0.001
Other combination	118	1.63	(1.19, 2.23)	0.002	1.79	(1.39, 2.32)	<0.001
Hepatitis B co-infection							
Negative	3513	1					
Positive	383	0.92	(0.76, 1.11)	0.379			
Not tested	2304						
Hepatitis C co-infection							
Negative	2469	1			1		
Positive	544	1.49	(1.28, 1.73)	<0.001	1.27	(1.06, 1.52)	0.011
Not tested	3187						
pre-ART AIDS Diagnosis							
No	3869	1					
Yes	2331	1.03	(0.94, 1.13)	0.556			
Country income							
Low and lower middle	3097	1		<0.001	1		<0.001
Upper middle	2212	0.77	(0.70, 0.85)	<0.001	0.78	(0.70, 0.86)	<0.001
High	891	0.50	(0.44, 0.56)	<0.001	0.42	(0.35, 0.51)	<0.001

Total missed visits include all repeated missed visits. A patient can have more than one missed visit during follow-up.

* Global p-values are test for heterogeneity excluding missing values.

Multivariate model is adjusted for follow-up time.