A Decade of Combination Antiretroviral Treatment in Asia: The TREAT Asia HIV Observational Database Cohort

The TREAT Asia HIV Observational Database (TAHOD) Network¹

Abstract

Asian countries have seen the expansion of combination antiretroviral therapy (cART) over the past decade. The TREAT Asia HIV Observational Database (TAHOD) was established in 2003 comprising 23 urban referral sites in 13 countries across the region. We examined trends in treatment outcomes in patients who initiated cART between 2003 and 2013. Time of cART initiation was grouped into three periods: 2003–2005, 2006–2009, and 2010–2013. We analyzed trends in undetectable viral load (VL; defined as VL <400 copies/ml), CD4 changes from pre-cART levels, and overall survival. Of 6,521 patients included, the overall median CD4 count at cART initiation was 120 cells/ μ l (interquartile range: 38–218). Despite an increase over time, pre-cART CD4 counts remained <200 cells/ μ l. Adjusted analyses showed undetectable VL was more likely when starting cART in later years [2006–2009: odds ratio (OR)=1.76, 95% confidence interval (CI) (1.45, 2.15); and 2010–2013: OR=3.04, 95% CI (2.33, 3.97), all $p < .001$, compared to 2003–2005], and survival was improved [2006–2009: subdistribution hazard ratio (SHR)=0.41, 95% CI (0.27, 0.61), 2010–2013: SHR=0.29, 95% CI (0.17, 0.49), all $p < .001$, compared to 2003–2005]. No differences in CD4 response was observed over time. Age and CD4 levels prior to cART initiation were associated with all three treatment outcomes, with older age and higher CD4 counts being associated with undetectable VL. Survival and VL response on cART have improved over the past decade in TAHOD, although CD4 count at cART initiation remained low. Greater effort should be made to facilitate earlier HIV diagnosis and linkage to care and treatment, to achieve greater improvements in treatment outcomes.

Introduction

RESOURCE-LIMITED COUNTRIES in Asia and Africa have seen a massive scale-up in combination antiretroviral therapy (cART) delivery in the past decade. The improved access to cART is partly due to the World Health Organization (WHO) public health promotion strategies beginning in 2001.^{1,2} In 2006, the WHO launched a standardized simplified treatment protocol and decentralized service delivery to enable access to cART to HIV-infected adults and children in both public and private sectors.² HIV-infected patients in many countries in Asia have since been provided with antiretroviral (ARV) drugs free of charge or at a minimal cost.

Despite the scale-up, cART coverage in Asia reached only 33% of those living with HIV compared to 37% in the African region in 2013.³ The TREAT Asia program of amfAR (The Foundation for AIDS Research), established the TREAT Asia HIV Observational Database (TAHOD) in 2003, aimed at evaluating the impact of HIV disease, coinfections, and cART management on clinical outcomes in the

Asia-Pacific, to inform HIV care and treatment practices and policies in the region. TAHOD⁴ is a prospective observational database and adult cohort study that has collected data from 23 sites in 13 countries and territories in Asia. All TAHOD sites are major referral centers in urban cities. In 2012, TAHOD expanded to include data captured from the TREAT Asia Studies to Evaluate Resistance–Monitoring Study (TASER-M)⁵, which had active patient recruitment between 2006 and 2011. In 2014, TAHOD Low Intensity Transfer (TAHOD-LITE⁶) was established with the aim of creating a surveillance mechanism for some of the TAHOD participating sites.

As the oldest, longitudinal regional HIV observational cohort in Asia, TAHOD facilitates the evaluation of trends and key treatment outcomes, offering important insights into the past decade of cART delivery in Asia, and informing further improvement of cART services. According to the WHO 2015 guidelines,⁷ the majority of countries with site participation in TAHOD initiated ART at CD4 $\leq$ 350 cells/ μ l with Thailand being the only country in South-East Asia that

¹The members of the TAHOD Steering Committee and study teams are listed in the Acknowledgments.

has adopted the “treat all” approach. Furthermore, a recently published TAHOD study has found that 72% of patients have presented late with older age, injecting drug users and male sex being risk factors for late presentation into care.⁸

In this study, we investigated time trends and factors associated with CD4 changes, undetectable viral load (VL) and mortality in TAHOD patients initiating cART between 2003 and 2013. Outcomes were not compared across sites or countries as these data are published elsewhere.⁶

Methods

Patients enrolled in TAHOD from the September 2013 data transfer were included if they initiated cART from 2003 onward. Patients with prior mono/dual ARV exposure were excluded. Year of cART initiation was divided into three periods corresponding to changes in WHO treatment guidelines^{9,10}: 2003–2005, 2006–2009, and 2010–2013. All analysis follow-up time were censored at 3 years from cART initiation to allow comparison of treatment outcomes over the three study periods, as this reflects the maximum follow-up time for those initiating cART between 2010–2013. VL, CD4, and mortality outcomes were those that occurred in the first 3 years from start of cART.

Undetectable VL

Patients included in this sub-analysis were those with at least one VL test available in the first 3 years of cART initiation. Time from cART initiation was divided into 6-monthly intervals to reflect our twice-yearly data transfers: 0–0.5, 0.5–1.0, 1.0–1.5, 1.5–2.0, 2.0–2.5, and 2.5–3.0 years. If there were multiple VL tests in each time interval, the VL closest to the end of that interval was used. Undetectable VL was defined as VL <400 copies/ml. Repeated measures logistic regression models fitted using Generalized Estimating Equations (GEE) were used to estimate the association between clinical characteristics and undetectable VL.

Changes in CD4 cell count

Patients were selected if they had at least one pre-cART CD4 and one post-cART CD4 count available in the first 3 years after treatment initiation. As with the analysis for undetectable VL, time from cART initiation was likewise divided into 6-monthly intervals. If more than one CD4 test was available in each follow-up time interval, the CD4 closest to the end of that interval was used. CD4 change was defined as the difference between the post-cART and the pre-cART CD4 counts. Factors associated with CD4 changes were analyzed using repeated measures linear regression GEE models.

Overall survival

Patients were included if they had at least one follow-up day after the start of cART, or after cohort enrolment for those who enrolled in TAHOD after having already initiated cART. Risk of mortality began from cART initiation and ended on the date of death, however, those who started cART prior to enrolment into TAHOD were included with risk time left truncated at cohort entry date. Fine and Gray's¹¹ competing risk analysis was used to analyze survival time with lost to follow-up (LTFU) cases treated as competing risk. All other patients were censored at the last visit date or 3 years

from cART initiation, which ever occurred first. The effect size was presented as the subdistribution hazard ratio (SHR) that represents the hazard ratio (HR) for mortality in the presence of competing risk, and can be interpreted in a similar way as Cox regression model HRs. LTFU was defined as patients not being seen for more than 12 months, excluding deceased and transferred patients. Cumulative incidence curves were plotted for mortality in the presence of competing risks.

Patient characteristics were compared using the chi-squared test for categorical variables and Kruskal–Wallis test for continuous variables. Covariates adjusted in the regression models were year of cART initiation, age, sex, mode of HIV exposure, pre-cART CD4 and VL, initial regimen, hepatitis B/C coinfection, prior AIDS diagnosis, and time from cART initiation. To account for site differences, such as frequency of VL testing, all regression models were adjusted for individual sites and fitted using backward stepwise selection process. Variables significant at $p < .10$ in the univariate models were chosen for inclusion in the multivariate models. Covariates with $p < .05$ were considered statistically significant in the final multivariate models.

Data transfers from clinical sites were aggregated at The Kirby Institute, UNSW Australia, at 6-monthly intervals in March and September. Ethics approvals were obtained from the local ethics committees of each TAHOD-participating site and the coordinating center (TREAT Asia/amfAR) and the UNSW Australia Ethics Committee. All data management and statistical analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC) and Stata software version 13.1 (Stata Corp., College Station, TX).

Results

A total of 6,521 TAHOD patients from Cambodia, China and Hong Kong SAR, India, Indonesia, Japan, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam met the inclusion criteria and received cART between 2003–2013. The median follow-up time from start of cART was 4.1 years [95% confidence interval (95% CI) (2.4, 6.6)]. Their baseline characteristics are described in Table 1. cART initiation was more common between 2006–2009 (45.4%) than in 2003–2005 (25.4%) or 2010–2013 (29.2%). The high proportion of patients initiating cART in 2006–2009 is attributed to active enrolment for the TASER-M cohort. The median age was 35 years [interquartile range (IQR) 29–41], with the majority of patients being male (69.5%) and reporting heterosexual HIV exposure (62.7%). The initial cART regimen mostly consisted of two nucleoside reverse transcriptase inhibitors (NRTI) and a non-NRTI (NNRTI), with stavudine- and zidovudine-based regimens being the most common.¹² These characteristics are also reported by individual country and can be seen in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/aid).

Undetectable VL

A total of 4,735 patients had at least one VL result available in the first 3 years of cART. Figure 1a indicates that the proportion of TAHOD patients with undetectable VL from 6 months of cART onward has remained steady at ~80%–90% for all time periods of cART initiation.

TABLE 1. PATIENT CHARACTERISTICS

	Total (%) n=6,521 (100)	Year of cART initiation			p-Value
		2003–2005 (%) n=1,657 (25.4)	2006–2009 (%) n=2,961 (45.4)	2010–2013 (%) n=1,903 (29.2)	
Age (years)					
Median [IQR]	35 [29–41]	35 [30–41]	35 [29–41]	34 [29–41]	.012
≤30	1,993 (30.6)	459 (27.7)	907 (30.6)	627 (32.9)	.027
31–40	2,758 (42.3)	749 (45.2)	1,226 (41.4)	783 (41.1)	
41–50	1,250 (19.2)	316 (19.1)	585 (19.8)	349 (18.3)	
>50	520 (8.0)	133 (8.0)	243 (8.2)	144 (7.6)	
Sex					
Male	4,534 (69.5)	1,127 (68.0)	2,062 (69.6)	1,345 (70.7)	.224
Female	1,987 (30.5)	530 (32.0)	899 (30.4)	558 (29.3)	
HIV mode of exposure					
Heterosexual exposure	4,087 (62.7)	1,134 (68.4)	1,895 (64.0)	1,058 (55.6)	<.001
Homosexual exposure	1,334 (20.5)	292 (17.6)	586 (19.8)	456 (24.0)	
Injecting drug use	617 (9.5)	74 (4.5)	291 (9.8)	252 (13.2)	
Other/unknown	483 (7.4)	157 (9.5)	189 (6.4)	137 (7.2)	
Pre-cART CD4 (cells/ μ l)					
Median [IQR]	120 [38–218]	92 [32–184]	127 [40–213]	134 [39–251]	<.001
≤50	1,722 (26.4)	446 (26.9)	759 (25.6)	517 (27.2)	<.001
51–100	809 (12.4)	215 (13.0)	367 (12.4)	227 (11.9)	
101–200	1,419 (21.8)	336 (20.3)	726 (24.5)	357 (18.8)	
>200	1,653 (25.3)	277 (16.7)	739 (25.0)	637 (33.5)	
Missing	918 (14.1)	383 (23.1)	370 (12.5)	165 (8.7)	
Pre-cART VL (copies/ml)					
Median [IQR]	100,000 [31,000–280,195]	117,000 [28,600–381,000]	100,000 [34,800–258,000]	95,963 [26,700–280,195]	.050
<100,000	1,616 (24.8)	248 (15.0)	855 (28.9)	513 (27.0)	.216
≥100,000	1,676 (25.7)	289 (17.4)	891 (30.1)	496 (26.1)	
Missing	3,229 (49.5)	1,120 (67.6)	1,215 (41.0)	894 (47.0)	
Initial cART regimen					
NRTI+NNRTI	5,721 (87.7)	1,327 (80.1)	2,674 (90.3)	1,720 (90.4)	<.001
NRTI+PI	736 (11.3)	311 (18.8)	258 (8.7)	167 (8.8)	
Other combination	64 (0.98)	19 (1.1)	29 (1.0)	16 (0.8)	
Hepatitis B status					
Negative	4,572 (70.1)	1,005 (60.7)	2,212 (74.7)	1,355 (71.2)	.448
Positive	529 (8.1)	120 (7.2)	241 (8.1)	168 (8.8)	
Not tested	1,420 (21.8)	532 (32.1)	508 (17.2)	380 (20.0)	
Hepatitis C status					
Negative	3,978 (61.0)	974 (58.8)	1,851 (62.5)	1,153 (60.6)	<.001
Positive	785 (12.0)	121 (7.3)	352 (11.9)	312 (16.4)	
Not tested	1,758 (27.0)	562 (33.9)	758 (25.6)	438 (23.0)	
CDC category					
A	3,247 (49.8)	754 (45.5)	1,375 (46.4)	1,118 (58.7)	<.001
B	800 (12.3)	197 (11.9)	508 (17.2)	95 (5.0)	
C	2,474 (37.9)	706 (42.6)	1,078 (36.4)	690 (36.3)	

p-Values for categorical variables exclude missing or not tested value.

cART, combination antiretroviral therapy; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-NRTI; PI, protease inhibitor; VL, viral load.

Table 2 shows factors associated with undetectable VL in the univariate model were year of cART initiation ($p < .001$), age ($p < .001$), mode of HIV exposure ($p = .011$), pre-cART VL ($p < .001$) and CD4 count ($p < .001$), hepatitis C coinfection ($p = .080$), prior AIDS diagnosis ($p = .042$), and time from cART initiation ($p < .001$).

In multivariate analyses, achieving undetectable VL was more likely if cART was initiated in later years [2006–2009: odds ratio (OR)=1.76, 95% CI (1.45, 2.15), $p < .001$; and 2010–2013: OR=3.04, 95% CI (2.33, 3.97), $p < .001$] compared to 2003–2005. Older age [41–50 years: OR 1.35, 95% CI (1.07, 1.71), $p = .011$; and >50 years: OR=1.57, 95% CI

(1.14, 2.17), $p = .006$] compared to age ≤30 years, high pre-cART CD4 count of >200 cells/ μ l [OR=1.49, 95% CI (1.18, 1.89), $p = .001$] compared to ≤50 cells/ μ l, and longer time since cART initiation [0.5–1.0 years: OR=2.14, 95% CI (1.82, 2.52); 1.0–1.5 years: OR=2.01, 95% CI (1.70, 2.38); 1.5–2.0 years: OR=2.24, 95% CI (1.88, 2.68); 2.0–2.5 years: OR=2.36, 95% CI (1.94, 2.87); and 2.5–3.0 years: OR=3.12, 95% CI (2.52, 3.88), all $p < .001$, compared to 0.0–0.5 years] were also associated with achieving VL suppression. Patients who started cART with VL ≥100,000 copies/ml were less likely to show undetectable VL in the first 3 years [OR=0.74, 95% CI (0.60, 0.91), $p = .004$].

FIG. 1. (a) Proportion of undetectable viral load; (b) median changes in CD4 count; and (c) cumulative incidence of mortality.

Changes in CD4 cell count

There were 5,244 patients with a CD4 cell count available before and after cART initiation. Figure 1b illustrates that there has been a continued increase in the median CD4 gain over time, with very little differences between periods of cART initiation. The median increase from pretreatment values reached ~ 250 cells/ μ L at 3 years from cART.

Table 3 shows that year of cART initiation was the only variable not associated with changes in CD4 in both the univariate and multivariate regression analyses. The adjusted model shows that characteristics associated with higher mean CD4 increase over 3 years were female sex [difference = 17 cells/ μ L compared to male, 95% CI (9, 26), $p < .001$], homosexual contact [difference = 20 cells/ μ L compared to heterosexual exposure, 95% CI (7, 32), $p = .002$], high pre-cART VL of $\geq 100,000$ copies/ml [difference = 32 cells/ μ L, 95% CI (22, 42), $p < .001$], protease inhibitor (PI)-based regimen [difference = 28 cells/ μ L compared to NNRTI-based regimen, 95% CI (6, 50), $p = .013$], prior AIDS diagnosis [difference = 10 cells/ μ L, 95% CI (1, 19), $p = .025$], and increasing time on cART compared to the first 6 months (all $p < .001$).

The mean CD4 increase for patients in the 41–50 year old age group was 19 cells/ μ L less than the increase for the ≤ 30 year old group [95% CI (–30, –8), $p < .001$]. The CD4 gain was smaller for those aged above 50 years [difference = –25 cells/ μ L, 95% CI (–42, –9), $p < .001$].

Other covariates associated with smaller increases compared to the reference group were pre-cART CD4 > 200 cells/ μ L [difference = –16 cells/ μ L, 95% CI (–28, –4), $p = .008$], positive hepatitis B coinfection [difference = –17 cells/ μ L, 95% CI (–28, –5), $p = .004$], and positive hepatitis C coinfection [difference = –15 cells/ μ L, 95% CI (–28, –3), $p = .015$].

Overall survival

Among 5,653 patients with follow-up, there were 191 deaths in the first 3 years of cART, with a crude mortality rate of 1.6 per 100 person-years [100 pys; 95% CI (1.39, 1.85)]. The number of patients who were considered LTFU was 478 patients. The overall rate of LTFU was 4.02 per 100 pys [95% CI (3.67, 4.39)]. By country, the LTFU rates ranged from 0.22 to 8.80 per 100 pys, with 7/13 countries having rates < 2.00 per 100 pys. By year of cART initiation, the LTFU rates ranged from 2.51 to 5.00 per 100 pys. Table 4 shows that in the presence of competing risk, the hazard for mortality decreased for later years of cART initiation. Other variables associated with better survival in the unadjusted model were age ($p < .001$), sex ($p < .018$), mode of HIV exposure ($p = .002$), pre-cART VL ($p = .017$), pre-cART CD4 count ($p < .001$), hepatitis C coinfection ($p = .018$), and prior AIDS diagnosis ($p < .001$).

The multivariate model shows CD4 count of > 200 cells/ μ L was associated with improved survival [SHR = 0.54 compared to CD4 ≤ 50 cells/ μ L, 95% CI (0.33, 0.89), $p = .016$]. Survival was better in later periods of cART with the hazards reducing for more recent years [2006–2009: SHR = 0.41, 95% CI (0.27, 0.61); and 2010–2013: SHR = 0.29, 95% CI (0.17, 0.49), all $p < .001$, compared to 2003–2005]. This can also be seen in Figure 1c where the cumulative incidence curve for mortality for 2003–2005 was much higher than the other two time periods. The 2010–2013 curve was lowest, remaining below 10% over 3 years.

Covariates associated with poorer survival were age > 50 years [SHR = 4.93 compared to age ≤ 30 years, 95% CI (3.19, 7.62), $p < .001$], positive hepatitis C coinfection [SHR = 1.72, 95% CI (1.10, 2.68), $p = .017$], and prior AIDS diagnosis [SHR = 2.35, 95% CI (1.64, 3.36), $p < .001$].

Supplementary Figure S1 is an extension of Figure 1, which shows graphical illustrations of proportions with undetectable VL, median changes in CD4 count, and mortality up to 10 years after cART initiation. This figure shows that proportions with undetectable VL remained high, with increasing median CD4 changes. Survival probability at 10 years for those in the 2003–2005 group was above 80%.

Discussion

The past decade of TAHOD showed that cART initiation in later years was associated with more frequent undetectable VL and improved survival. No association was seen with the magnitude of CD4 changes over time. There was a positive overall increase in the proportion of patients with VL suppression and increase in CD4 count gains over the 3 years from cART initiation. Additionally, the cumulative mortality incidence was noticeably higher for patients who started prior to 2006.

TABLE 2. UNDETECTABLE VIRAL LOAD OVER 3 YEARS FROM COMBINATION ANTIRETROVIRAL THERAPY INITIATION

Total of 4,735 patients	Univariate			Multivariate		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Year of cART initiation			<.001			<.001
2003–2005	1			1		
2006–2009	1.94	1.60, 2.35	<.001	1.76	1.45, 2.15	<.001
2010–2013	3.00	2.30, 3.90	<.001	3.04	2.33, 3.97	<.001
Age at cART initiation			<.001			.001
≤30	1			1		
31–40	1.13	0.94, 1.36	.183	1.10	0.92, 1.33	.298
41–50	1.39	1.11, 1.74	.004	1.35	1.07, 1.71	.011
>50	1.56	1.14, 2.14	.006	1.57	1.14, 2.17	.006
Sex						
Male	1					
Female	0.88	0.73, 1.06	.195			
HIV exposure			.011			
Heterosexual contact	1					
Homosexual contact	1.28	1.00, 1.63	.047			
Injecting drug use	0.73	0.55, 0.97	.032			
Other/unknown	0.97	0.72, 1.31	.858			
Pre-cART VL (copies/ml)						
<100,000	1			1		
≥100,000	0.69	0.56, 0.84	<.001	0.74	0.60, 0.91	.004
Missing						
Pre-cART CD4 (cells/μl)			<.001			<.001
≤50	1			1		
51–100	0.98	0.76, 1.27	.890	0.98	0.76, 1.27	.900
101–200	1.15	0.92, 1.45	.225	1.17	0.93, 1.47	.181
>200	1.56	1.24, 1.97	<.001	1.49	1.18, 1.89	.001
Missing						
Initial cART regimen			.864			
NRTI+NNRTI	1					
NRTI+PI	0.99	0.76, 1.28	.917			
Other combination	0.85	0.46, 1.55	.588			
Hepatitis B coinfection						
Negative	1					
Positive	0.96	0.72, 1.28	.784			
Not tested						
Hepatitis C coinfection						
Negative	1					
Positive	0.80	0.62, 1.03	.080			
Not tested						
Prior AIDS diagnosis						
No	1					
Yes	0.84	0.71, 0.99	.042			
Time from cART initiation, years			<.001			<.001
0.0–0.5	1			1		
0.5–1.0	2.13	1.82, 2.49	<.001	2.14	1.82, 2.52	<.001
1.0–1.5	1.95	1.65, 2.29	<.001	2.01	1.70, 2.38	<.001
1.5–2.0	2.15	1.81, 2.56	<.001	2.24	1.88, 2.68	<.001
2.0–2.5	2.18	1.80, 2.63	<.001	2.36	1.94, 2.87	<.001
2.5–3.0	2.82	2.27, 3.51	<.001	3.12	2.52, 3.88	<.001

Global *p*-values for age and CD4 are tests for trend. All other global *p*-values are tests for heterogeneity excluding missing values.

p-Values in *bold* represent significant covariates in the final model.

CI, confidence interval; OR, odds ratio.

The odds of achieving undetectable VL was tripled if cART was initiated in 2010–2013 and almost doubled for 2006–2009, compared to prior 2006. This is consistent with findings from a South African study, which showed reduced risk for virological failure in later years of cART initiation.¹³ However, due to the limited availability of VL testing in resource-poor countries in the early time periods of our

study,¹⁴ the differences we observed may reflect more targeted VL testing to confirm failure, rather than suboptimal treatment response in the early years of cART. The WHO now recommends VL testing every 12 months after starting cART if VL testing is routinely available.¹⁵ Our TAHOD sites consist mainly of low to middle-income country settings, with the majority reporting VL testing being done on

TABLE 3. CD4 CHANGES FROM OVER 3 YEARS FROM COMBINATION ANTIRETROVIRAL THERAPY INITIATION

Total of 5,244 patients	Univariate			Multivariate		
	Diff	95% CI	p-Value	Diff	95% CI	p-Value
Year of cART initiation			.444			
2003–2005	Ref					
2006–2009	4	–7, 15	.470			
2010–2013	–4	–16, 8	.537			
Age at cART initiation			<.001			<.001
≤30	Ref			Ref		
31–40	–4	–14, 6	.404	–4	–14, 6	.434
41–50	–19	–30, –8	.001	–19	–30, –8	.001
>50	–28	–44, –12	.001	–25	–42, –9	.002
Sex						
Male	Ref			Ref		
Female	15	7, 23	<.001	17	9, 26	<.001
HIV exposure			.005			.007
Heterosexual contact	Ref			Ref		
Homosexual contact	11	–1, 24	.075	20	7, 32	.002
Injecting drug use	–19	–33, –6	.004	–9	–25, 6	.223
Other/unknown	7	–9, 23	.414	10	–6, 26	.224
Pre-cART VL (copies/ml)						
<100,000				Ref		
≥100,000	36	25, 46	<.001	32	22, 42	<.001
Missing						
Pre-cART CD4 (cells/μl)			<.001			.008
≤50	Ref			Ref		
51–100	5	–5, 16	.328	5	–5, 15	.303
101–200	–2	–11, 7	.641	–1	–11, 9	.843
>200	–22	–32, –12	<.001	–16	–28, –4	.008
Initial cART regimen			.006			.014
NRTI+NNRTI	Ref			Ref		
NRTI+PI	32	10, 54	.004	28	6, 50	.013
Other combination	–9	–44, 27	.636	–11.85	–47, 23	.503
Hepatitis B coinfection						
Negative	Ref			Ref		
Positive	–17	–29, –5	.004	–17	–28, –5	.004
Not tested						
Hepatitis C coinfection						
Negative	Ref			Ref		
Positive	–22	–33, –11	<.001	–15	–28, –3	.015
Not tested						
Prior AIDS diagnosis						
No	Ref			Ref		
Yes	13	6, 21	.001	10	1, 19	.025
Time from cART initiation, years			<.001			<.001
0.0–0.5	Ref			Ref		
0.5–1.0	45	41, 49	<.001	45	41, 49	<.001
1.0–1.5	90	85, 94	<.001	90	85, 94	<.001
1.5–2.0	120	115, 125	<.001	120	115, 125	<.001
2.0–2.5	141	136, 147	<.001	141	136, 147	<.001
2.5–3.0	165	160, 171	<.001	165	159, 171	<.001

Global *p*-values for age and CD4 are tests for trend. All other global *p*-values are tests for heterogeneity excluding missing values. *p*-Values in **bold** represent significant covariates in the final model.

average less than once per year.¹⁶ Although site has been adjusted in the analyses to account for any heterogeneity across sites, the effects of different cART initiation periods on VL outcomes should be interpreted with caution. Additionally, the results are only representative of those who were included in the analyses and not of the entire cohort.

The overall median CD4 count at time of cART initiation was 120 cells/μl with patients starting in 2003–2005 having the lowest median CD4 of 92 cells/μl, and those starting

cART in 2010–2013 showing a median CD4 count of 134 cells/μl. These values are comparable to those found in Sub-Saharan Africa where the mean CD4 count at cART initiation in 2002 was 152 cells/μl with no significant increase over time until 2013.¹⁷ Although the proportion of late cART starters in TAHOD has decreased over time, there is still a significant number of HIV-infected individuals presenting at later stages of disease, which is associated with reduced effectiveness of cART.¹⁸ Furthermore, our results indicate that

TABLE 4. MORTALITY OVER 3 YEARS FROM COMBINATION ANTIRETROVIRAL THERAPY INITIATION

	No. of patients	Follow-up (years)	No. of deaths	Mortality rate (/100 pys)	95% CI	Univariate			Multivariate		
						SHR	95% CI	p-Value	SHR	95% CI	p-Value
Total	5,653	11,921.42	191	1.6	1.39, 1.85						
Year of cART initiation								<.001			<.001
2003–2005	1,352	2,750.48	58	2.11	1.63, 2.73	1			1		
2006–2009	2,598	5,963.95	76	1.27	1.02, 1.60	0.35	0.24, 0.52	<.001	0.41	0.27, 0.61	<.001
2010–2013	1,703	3,206.98	57	1.78	1.37, 2.30	0.24	0.14, 0.39	<.001	0.29	0.17, 0.49	<.001
Age at cART initiation								<.001			<.001
≤30	1,710	3,493.88	37	1.06	0.77, 1.46	1			1		
31–40	2,382	5,049.37	72	1.43	1.13, 1.80	1.41	0.94, 2.11	.099	1.29	0.86, 1.94	.212
41–50	1,093	2,389.3	38	1.59	1.16, 2.19	1.56	0.98, 2.47	.059	1.50	0.94, 2.38	.090
>50	468	988.87	44	4.45	3.31, 5.98	4.79	3.06, 7.48	<.001	4.93	3.19, 7.62	<.001
Sex											
Male	3,939	8,325.07	147	1.77	1.50, 2.08	1					
Female	1,714	3,596.35	44	1.22	0.91, 1.64	0.64	0.45, 0.93	.018			
HIV exposure											
Heterosexual contact	3,492	7,381.67	120	1.63	1.36, 1.94	1					
Homosexual contact	1,157	2,604.39	21	0.81	0.53, 1.24	0.40	0.22, 0.72	.002			
Injecting drug use	557	976.81	30	3.07	2.15, 4.39	1.45	0.87, 2.40	.152			
Other/unknown	447	958.54	20	2.09	1.35, 3.23	1.28	0.74, 2.22	.376			
Pre-cART VL (copies/ml)											
<100,000	1,511	3,441.2	35	1.02	0.73, 1.42	1					
≥100,000	1,535	3,505.64	66	1.88	1.48, 2.40	1.65	1.09, 2.49	.017			
Missing	2,607	4,974.58	90	1.81	1.47, 2.22						
Pre-cART CD4 (cells/ μ l)								<.001			.034
≤50	1,488	3,076.88	81	2.63	2.12, 3.27	1			1		
51–100	692	1,461.89	26	1.78	1.21, 2.61	0.68	0.44, 1.06	.092	0.80	0.52, 1.25	.330
101–200	1,223	2,641.86	36	1.36	0.98, 1.89	0.55	0.36, 0.82	.004	0.74	0.47, 1.16	.189
>200	1,475	3,214.98	25	0.78	0.53, 1.15	0.32	0.20, 0.50	<.001	0.54	0.33, 0.89	.016
Missing	775	1,525.8	23	1.51	1.00, 2.27						
Initial cART regimen								.464			
NRTI+NNRTI	4,973	10,437.89	174	1.67	1.44, 1.93	1					
NRTI+PI	623	1,356.24	14	1.03	0.61, 1.74	1.04	0.52, 2.08	.915			
Other combination	57	127.29	3	2.36	0.76, 7.31	2.06	0.66, 6.48	.216			
Hepatitis B coinfection											
Negative	3,995	8,580.24	124	1.45	1.21, 1.72	1					
Positive	455	994.02	14	1.41	0.83, 2.38	0.94	0.53, 1.64	.819			
Not tested	1,203	2,347.15	53	2.26	1.73, 2.96						
Hepatitis C coinfection											
Negative	3,430	7,491.58	103	1.37	1.13, 1.67	1			1		
Positive	701	1,304.09	33	2.53	1.80, 3.56	1.70	1.10, 2.62	.018	1.72	1.10, 2.68	.017
Not tested	1,522	3,125.74	55	1.76	1.35, 2.29						
Prior AIDS diagnosis											
No	3,474	7,416.78	66	0.89	0.70, 1.13	1			1		
Yes	2,179	4,504.63	125	2.77	2.33, 3.31	3.08	2.25, 4.22	<.001	2.35	1.64, 3.36	<.001

Global *p*-values for age and CD4 are tests for trend. All other global *p*-values are tests for heterogeneity excluding missing values. *p*-Values in *bold* represent significant covariates in the final model.
pys, person-years; SHR, subdistribution hazard ratio.

achieving cART initiation at the WHO recommended threshold of <500 cells/ μ l¹⁵ may not be feasible in many settings in the Asia-Pacific region without more successful HIV testing programs and immediate linkage to care.

CD4 recovery from pretreatment values continued over time, with an average increase of ~250 cells/ μ l after 3 years

on cART. The changes in CD4 were positively associated with treatment duration, although the cART initiation time periods had no effect on the CD4 increase, as has been shown in other studies.^{19–21}

Mortality rates in TAHOD have decreased across different periods of cART initiation. With LTFU as a competing risk,

the adjusted SHR in the first 3 years decreased as time of cART initiation advanced. This was to be expected due to advances in treatment guidelines over the past decade.^{1,15,22} These findings are similar to observations from other resource-limited settings where the HR for mortality has also been shown to decrease over time.^{23,24}

The rate of LTFU in TAHOD (4.02 per 100 pys) is relatively low compared to those seen in routine care programs in African countries, where proportions of LTFU as high as 39% have been reported.²⁵ This is possibly due to the TAHOD recruitment processes where consecutive samples of patients who were likely to remain in care were chosen. Factors associated with LTFU in TAHOD have been reported in previous literature, with younger age, HIV VL >500 copies, shorter history of HIV infection, no prior mono or dual therapy, and those receiving PI-based regimen being associated with LTFU.²⁶ It has been shown that there is an association between mortality and LTFU in the African region, where mortality is likely to have occurred within 3 months of being LTFU.^{27–29} In TAHOD, however, the risk of death in those LTFU remains unclear. A linkage study of the Australian HIV Observational Database (AHOD), which has an LTFU rate similar to that of TAHOD, revealed that being LTFU was not associated with increased risk of mortality.^{30,31}

Overall, the effects of other adjusted characteristics in the regression models are consistent with previous findings.^{4,12,16,32,33} Age and CD4 count were both significantly associated with the three treatment outcomes. Older age showed an association with lower CD4 increase and an increased risk of mortality. Achieving undetectable VL, however, was more likely in older patients. Patients initiating cART at high CD4 count had better survival, smaller increases in CD4 count, and were more likely to be virologically suppressed. Hepatitis C coinfection was associated with poorer survival and lower CD4 changes. However, it is important to note that there may be a high correlation between injecting drug use and hepatitis C coinfection, thus making it difficult to determine the underlying association.

The positive outcomes of homosexual HIV exposure and PI-based regimens on changes in CD4 count could be attributed to socioeconomic factors and other confounders that could not be adjusted for in this study. A published study³⁴ has shown that patients with these two characteristics were more likely to show good cART adherence, which could in turn lead to better treatment responses. Moreover, a previous TAHOD analysis has also shown that approximately two-thirds of TAHOD patients with CD4 < 200 cells/ μ L were taking pneumocystis prophylaxis, mainly co-trimoxazole and this was found to be a significant factor in lowering mortality rates,³⁵ another potential confounder in our analyses.

Our study was limited by the shorter maximum follow-up time available from those who initiated cART in 2010–2013. Although patients initiating cART in earlier years had longer follow-up time, we limited our analyses to 3 years to be able to compare treatment outcomes across multiple initiation time periods. However, graphical illustrations have been extended to include follow-up time of 10 years in Supplementary Figure S1. Another limitation of the study was that cART adherence information in TAHOD did not form part of routine data collection until 2011, however, risk factors for suboptimal adherence have been reported previously in

TASER-M, with sites that assessed adherence less frequently being associated with suboptimal adherence.³⁴ It is known that suboptimal adherence to cART compromises treatment response and is associated with VL failure, poor CD4 recovery, and the development of HIV drug resistance mutations.^{36–38} Therefore, our results must be interpreted with caution due to the absence of adherence data. In addition, as TAHOD sites are primarily urban referral centers, our findings may not be representative of the 13 countries and territories where they are located or of the broader Asia-Pacific region.

Conclusions

Over a decade of cART use in TAHOD, we found that virological response and survival improved over time in our cohort. Median CD4 count prior to treatment initiation has remained lower than targets set by international guidelines, and changes in CD4 count after starting cART were similar across all time periods. Although TAHOD patients have benefited from the increasing availability of cART and advances in HIV treatment options, HIV-infected patients in Asia continue to be linked to treatment at late stages of their disease. Greater effort to ensure earlier HIV diagnosis so that patients can be referred into treatment is required to control the regional epidemic.

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References

- World Health Organization: Scaling up anti-retroviral therapy in resource-limited settings: Guidelines for a public health approach. Available at <http://apps.who.int/medicinedocs/en/d/Js2888e/>, accessed February 14, 2014.
- Gilks CF, Crowley S, Ekpin R, *et al.*: The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet* 2006;368:505–510.
- World Health Organization: Global update on the health sector response to HIV. Available at www.who.int/hiv/pub/progressreports/update2014/en/ (2014), accessed January 22, 2015.
- Zhou J, Kumarasamy N, Ditangco R, *et al.*: The TREAT Asia HIV Observational Database: Baseline and retrospective data. *J Acquir Immune Defic Syndr* 2005;38:174–179.
- Sungkanuparph S, Oyomopito R, Sirivichayakul S, *et al.*: HIV-1 drug resistance mutations among antiretroviral-naïve HIV-1-infected patients in Asia: Results from the TREAT Asia Studies to Evaluate Resistance-Monitoring Study. *Clin Infect Dis* 2011;52:1053–1057.
- TAHOD-LITE: Antiretroviral treatment for adult HIV infection in Asia, 1998 to 2013. Available at <http://kirby.unsw.edu.au/publications/tahod-lite-antiretroviral-treatment-adult-hiv-infection-asia-1998-2013>, accessed January 22, 2016.
- World Health Organization: Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis on HIV. Available at http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf (2015), accessed January 22, 2016.
- Jeong SJ, Italiano C, Chaiwarith R, *et al.*: Late presentation into care of HIV disease and its associated factors in Asia: Results of TAHOD. *AIDS Res Hum Retroviruses* 2016;32:255–261.
- World Health Organization: Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach. Available at www.who.int/hiv/pub/guidelines/artadultguidelines.pdf (2006 revision), accessed February 17, 2015.
- World Health Organization: Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach. Available at http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf (2010 revision), accessed February 17, 2015.
- Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- Boettiger DC, Kerr S, Ditangco R, *et al.*: Trends in first-line antiretroviral therapy in Asia: Results from the TREAT Asia HIV observational database. *PLoS One* 2014;9:e106525.
- Boulle A, Van Cutsem G, Hilderbrand K, *et al.*: Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. *AIDS* 2010;24:563–572.
- Calmy A, Ford N, Hirschel B, *et al.*: HIV viral load monitoring in resource-limited regions: Optional or necessary? *Clin Infect Dis* 2007;44:128–134.
- World Health Organization: Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection: Recommendations for a public health approach. Available at http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf (June 2013), accessed January 8, 2014.
- Oyomopito R, Lee MP, Phanuphak P, *et al.*: Measures of site resourcing predict virologic suppression, immunologic response and HIV disease progression following highly active antiretroviral therapy (HAART) in the TREAT Asia HIV Observational Database (TAHOD). *HIV Med* 2010;11:519–529.
- Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC: Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002–2013: A meta-analysis. *Clin Infect Dis* 2015;60:1120–1127.
- Kiertiburanakul S, Boettiger D, Lee MP, *et al.*: Trends of CD4 cell count levels at the initiation of antiretroviral therapy over time and factors associated with late initiation of antiretroviral therapy among Asian HIV-positive patients. *J Int AIDS Soc* 2014;17:18804.
- Crawford K, Wakabi S, Magala F, Kibuuka H, Liu M, Hamm T: Evaluation of treatment outcomes for patients on

- first-line regimens in US President's Emergency Plan for AIDS Relief (PEPFAR) clinics in Uganda: Predictors of virological and immunological response from RV288 analyses. *HIV Med* 2015;16:95–104.
20. Smit M, Smit C, Geerlings S, *et al.*: Changes in first-line cART regimens and short-term clinical outcome between 1996 and 2010 in the Netherlands. *PLoS One* 2013;8: e76071.
 21. Nglazi MD, Lawn SD, Kaplan R, *et al.*: Changes in programmatic outcomes during 7 years of scale-up at a community-based antiretroviral treatment service in South Africa. *J Acquir Immune Defic Syndr* 2011;56:e1–e8.
 22. World Health Organization: Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. Available at www.who.int/hiv/pub/arv/adult2010/en/index.html (2010 revision), accessed January 16, 2013.
 23. Grimsrud A, Balkan S, Casas EC, *et al.*: Outcomes of antiretroviral therapy over a 10-year period of expansion: A multicohort analysis of African and Asian HIV programs. *J Acquir Immune Defic Syndr* 2014;67:e55–e66.
 24. Boulle A, Schomaker M, May MT, *et al.*: Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America: A collaborative analysis of prospective studies. *PLoS Med* 2014;11:e1001718.
 25. Rosen S, Fox MP, Gill CJ: Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review. *PLoS Med* 2007;4:e298.
 26. Zhou J, Tanuma J, Chaiwarith R, *et al.*: Loss to followup in HIV-infected patients from Asia-Pacific region: Results from TAHOD. *AIDS Res Treat* 2012;2012:375217.
 27. Van Cutsem G, Ford N, Hildebrand K, *et al.*: Correcting for mortality among patients lost to follow up on antiretroviral therapy in South Africa: A cohort analysis. *PLoS One* 2011; 6:e14684.
 28. Yu JK, Chen SC, Wang KY, *et al.*: True outcomes for patients on antiretroviral therapy who are “lost to follow-up” in Malawi. *Bull World Health Organ* 2007;85:550–554.
 29. Cornell M, Lessells R, Fox MP, *et al.*: Mortality among adults transferred and lost to follow-up from antiretroviral therapy programmes in South Africa: A multicenter cohort study. *J Acquir Immune Defic Syndr* 2014;67:e67–e75.
 30. McManus H, Petoumenos K, Brown K, *et al.*: Loss to follow-up in the Australian HIV observational database. *Antivir Ther* 2015;20:731–741.
 31. Guy R, Wand H, McManus H, *et al.*: Antiretroviral treatment interruption and loss to follow-up in two HIV cohorts in Australia and Asia: Implications for ‘test and treat’ prevention strategy. *AIDS Patient Care STDS* 2013;27: 681–691.
 32. Falster K, Choi JY, Donovan B, *et al.*: AIDS-related and non-AIDS-related mortality in the Asia-Pacific region in the era of combination antiretroviral treatment. *AIDS* 2009; 23:2323–2336.
 33. Fatti G, Mothibi E, Meintjes G, Grimwood A: Antiretroviral treatment outcomes amongst older adults in a large multicentre cohort in South Africa. *PLoS One* 2014; 9:e100273.
 34. Jiamsakul A, Kumarasamy N, Ditangco R, *et al.*: Factors associated with suboptimal adherence to antiretroviral therapy in Asia. *J Int AIDS Soc* 2014;17:18911.
 35. Lim PL, Zhou J, Ditangco RA, *et al.*: Failure to prescribe pneumocystis prophylaxis is associated with increased mortality, even in the cART era: Results from the Treat Asia HIV observational database. *J Int AIDS Soc* 2012; 15:1.
 36. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE: Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clin Infect Dis* 2003;37:1112–1118.
 37. Bastard M, Pinoges L, Balkan S, Szumilin E, Ferreyra C, Pujades-Rodriguez M: Timeliness of clinic attendance is a good predictor of virological response and resistance to antiretroviral drugs in HIV-infected patients. *PLoS One* 2012;7:e49091.
 38. Brennan AT, Maskew M, Sanne I, Fox MP: The importance of clinic attendance in the first six months on antiretroviral treatment: A retrospective analysis at a large public sector HIV clinic in South Africa. *J Int AIDS Soc* 2010;13:49.

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