Published in final edited form as:

Antivir Ther. 2016 ; 21(8): 725–730. doi:10.3851/IMP3052.

HIV viral suppression in TREAT Asia HIV Observational Database enrolled adults on antiretroviral therapy at the Social Health Clinic, the National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia

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To the editors

Introduction

The World Health Organization (WHO) recommends viral load (VL) monitoring over CD4 cell count and clinical monitoring as it is the most sensitive means of detecting antiretroviral therapy (ART) failure.¹ Rapid detection of ART failure is important for the prevention of HIV drug resistance accumulation and optimization of clinical outcomes. However, access to VL testing is uncommon in resource-limited settings.²

In Cambodia, it is estimated that 71% of the 70,885 adults infected with HIV are currently accessing treatment³ and a 2011 study based in Phnom Penh found that approximately 4% of patients receiving ART had a VL >1000 copies/ml⁴. The Social Health Clinic at the National Center for HIV/AIDS, Dermatology & STDs (SHC-NCHADS) has been operating since 2004 with support from the national HIV treatment program and has provided care to over 3,500 patients in Cambodia.⁵ A random selection of those 18 years old seen at SHC-NCHADS contributes data to the TREAT Asia HIV Observational Database (TAHOD). TAHOD collects information on HIV-infected patients in routine care services across Asia⁶, however, very few SHC-NCHADS patients have a history of VL monitoring.⁵ This is despite the current national guidelines recommending routine VL testing every 12 months.⁷

We conducted a cross-sectional evaluation of HIV VL in TAHOD-enrolled SHC-NCHADS patients on ART to determine the proportion of patients experiencing virological failure and to identify factors associated with virological failure in this population.

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The authors report no conflicts of interest.

Methods

All TAHOD-enrolled patients at SHC-NCHADS who had been using their current first- or second-line ART regimen for 6 months were eligible. First-line ART was defined as the first antiretroviral combination containing 3 drugs. Second-line ART was defined as therapy initiated after a drug class change to first-line ART that occurred after treatment failure. Treatment failure on first- or second-line ART was only considered after 6 months of using that regimen and was defined as: a VL >1000 copies/ml (virological failure); a CD4 cell count <100 cells/mm³ confirmed by re-testing within 6 months, or a CD4 cell count less than that documented at current regimen initiation (immunological failure); or diagnosis of a WHO stage III/IV illness or death (clinical failure).

VL testing was conducted between January and September 2014, and test results were combined with routinely collected data from TAHOD. Patients who were not tested in the VL testing period could contribute their latest VL result if one was available and those who died or were lost-to-follow-up before the testing period or did not have a VL performed despite presenting during the testing period were considered to be experiencing virological failure at their latest clinic visit. Patients were regarded as lost-to-follow-up if they did not have a record of being transferred, did not have a prior VL and did not attend the clinic during the testing period. Those that were transferred to another clinic prior to VL testing were considered to be on a virally suppressive regimen at their final visit to SHC-NCHADS.

The outcomes analyzed were virological failure (inclusive of death, lost-to-follow-up and not having a VL performed despite presenting during the testing period), virological failure in the absence of immunological or clinical failure, and immunological failure in the absence of virological failure. The latter two outcomes were only evaluated in individuals with a VL test result available. The window period for assessing immunological and clinical failure in relation to virological failure (or the absence of virological failure) was within 3 months of VL testing.

Factors associated with virological failure were evaluated by logistic regression. Co-variables available and considered important for analysis included age, sex, mode of HIV exposure, hepatitis B and C status, CD4 cell count, history of WHO stage III/IV illness, history of mono/dual ART, ART regimen (first- or second-line), historical and latest self-reported ART adherence (based on the 30-day self-reported adherence visual analogue scale⁸) and years on current ART regimen. Patients with missing covariate data were included in all analyses but odds ratios for missing categories are not reported. Two-sided p-values <0.05 were considered statistically significant. Stata version 14.1 (Stata Corp., College Station, TX, USA) was used for all statistical analysis.

SHC-NCHADS participation in TAHOD is approved by the Cambodia National Ethics Committee for Health Research. Individual patient informed consent is not required by the local institutional review board for entry of anonymized routine care data into TAHOD.

Results

As of September 2014, 463 individuals from SHC-NCHADS with a history of 6 months on their latest ART regimen had been enrolled into TAHOD and were therefore eligible for this

analysis. Table 1 describes the characteristics of the study population at the time of VL testing/the latest clinic visit. Zidovudine, stavudine and abacavir were being used by 65.7%, 11.9% and 11.0% of patients, respectively. Among those on first-line ART (n=443), nevirapine was being used by 74.3% and efavirenz was being used by 19.2%. All patients on second-line ART (n=20) were using a protease inhibitor-based regimen. The last documented assessment of ART adherence occurred a median of 4 (IQR 2–10) days prior to VL testing/the last clinic visit and was 100% in all except three patients; one reported 70% adherence and the other two were missing this information. Sixty two (13.4%) individuals had a history of <100% ART adherence.

Before the testing period began and without having received a prior VL test, 10 (2.2%) patients were transferred to another clinic, 9 (1.9%) patients were lost-to-follow-up, 4 (0.9%) patients died due to AIDS-related causes, and 4 (0.9%) patients died due to non-AIDS-related causes. One (0.2%) patient did not undergo a VL test despite being eligible and having attended the clinic within the testing period. Table 2 summarizes the final visit characteristics of those who died, were lost-to-follow-up, or did not have VL testing performed despite attending during the testing period. The remaining 435 (94.0%) patients received a VL test; 28 tests took place a median of 6.0 years (interquartile range [IQR] 2.3–6.4) before the testing period began.

Of those that underwent VL testing, 419 (96.3%) patients had a VL <400 copies/ml, 6 (1.4%) patients had a VL between 400–1000 copies/ml and 10 (2.3%) patients had virological failure. When combined with the 18 patients we considered to have failed prior to the VL testing period, the overall rate of virological failure was 28/463 (6.0%). The median VL amongst those with virological failure was 9,633 copies/ml (IQR 4,386–84,600). Concurrent immunological or clinical failure was present in 2 patients with a VL 1000 copies/ml. Eleven patients had immunological failure without documented virological failure.

Table 3 shows that shorter duration on current ART regimen (odds ratio [OR] 23.5 for <2 years vs. >5 years, 95% confidence interval [CI] 7.3–74.9, $p<0.01$), lower CD4 at VL testing/last clinic visit (OR 12.9 for <350 cells/mm³ vs. >500 cells/mm³, 95%CI 1.6–104.5, $p=0.02$), and a history of <100% ART adherence (OR 4.4 vs. no history of <100% adherence, 95%CI 1.5–13.0, $p<0.01$) were significantly associated with virological failure in our final multivariate model.

Discussion

This study describes the positive outcomes of ART provided under the national HIV treatment program at SHC-NCHADS. Despite a high prevalence of advanced HIV disease at regimen initiation, only 2.3% of patients were experiencing virological failure at the time of VL assessment and 6.0% of patients met our extended definition of virological failure. This is consistent with most patients having a long history of good ART adherence. Others have reported similar rates of virological failure and adherence in Cambodia.^{4,9,10} Pujades-Rodriguez *et al* (2011) described virological outcomes in 349 adults receiving ART for 4 years under the Médecins Sans Frontières-supported HIV program in Phnom Penh.⁴ Even though 29% of this cohort was using stavudine at the time of VL assessment, 83.3% reported being fully adherent to ART in the month prior and only 4% had a VL >1000

copies/ml. These positive results were attributed to the frequent use of fixed-dose ART combinations and a dedicated team of counsellors supporting the program. Such methods to optimize adherence are also well-established at SHC-NCHADS.

Our analysis of factors associated with virological failure was limited by the low number of events observed. Nevertheless, in our final model, shorter time on ART regimen, low CD4 cell count and a record of suboptimal adherence were the strongest predictors of virological failure. Earlier work from Cambodia and elsewhere has reported the association between virological failure and poor adherence, and between virological failure and CD4 cell count.^{10–13} The apparent role of treatment duration on viral control is most likely explained by the time-dependent attrition of poorly adherent patients¹⁴ and switching of failing patients onto alternative regimens.

The poor correlation we observed between VL >1000 copies/ml and other means of detecting ART failure is consistent with earlier work.^{10,15} This highlights the importance of introducing routine VL testing in Cambodia. Compared with immunological and clinical monitoring, virological monitoring allows for an earlier, more accurate determination of the need to switch ART, thereby reducing the accumulation of drug-resistance mutations and improving clinical outcomes. In settings with limited resources, the WHO suggests targeted VL testing as a less costly alternative to routine testing.¹ Researchers at Sihanouk Hospital Centre of HOPE in Phnom Penh have created a clinical prediction tool that uses routinely collected data to identify patients at elevated risk of virological failure.^{9, 16–18} However, this tool remains in development.

There were several limitations to this investigation. As SHC-NCHADS is a well-resourced clinic located in central Phnom Penh, our findings may not be broadly generalizable to ART centers elsewhere in Cambodia. Further, the small number of patients from this clinic that contribute data to TAHOD limited the power of our study. Nevertheless, the recent TAHOD-LITE report shows that demographic, clinical, ART, patient retention and mortality data for the entire SHC-NCHADS cohort is similar to what we have reported in our sub-population⁵, suggesting that our results are at least generalizable to patients seen within SHC-NCHADS. Since virological failure was determined by a single VL, it is possible that a proportion of patients meeting our definition would have had undetectable VL with a repeat measurement. Given almost all patients reported 100% adherence at the time of testing, this seems unlikely, although we cannot rule out the possibility that patients overestimated their true adherence level. Unfortunately, we were not able to perform resistance testing and prior resisting testing data were not available. Resistance estimates from other centers in Cambodia are also lacking.

The national HIV treatment program at SHC-NCHADS is delivering a high rate of viral suppression. Future work should focus on phasing-in routine VL monitoring in Cambodia.

Acknowledgments

TAHOD study members at participating sites:

CV Mean, V Saphonn, and K Vohith, National Center for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia; AH Sohn, N Durier, B Petersen, and T Singtoroj, TREAT Asia, amfAR - The Foundation for AIDS

Research, Bangkok, Thailand; DA Cooper, MG Law, A Jiamsakul, and DC Boettiger, The Kirby Institute, UNSW Australia, Sydney, Australia.

Sources of support:

The TREAT Asia HIV Observational Database is an initiative of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Cancer Institute, as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; U01AI069907). TREAT Asia is also supported by ViiV Healthcare. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, UNSW Australia. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above.

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Table 1

Characteristics of patients on antiretroviral therapy attending the Social Health Clinic, the National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh (N=463)

Age, years	
Median [IQR]	42.1 [37.1 – 47.3]
Male	246 (53.1)
Mode of HIV exposure	
Heterosexual	457 (98.7)
MSM	3 (0.7)
IDU	0 (0.0)
Other	3 (0.7)
Hepatitis C antibody status, n=451	
Negative n (% tested)	425 (94.2)
Positive n (% tested)	26 (5.8)
HBsAg status, n=452	
Negative n (% tested)	399 (88.3)
Positive n (% tested)	53 (11.7)
Current CD4 count, cells/mm³, n=335	
Median [IQR]	445 [311 – 590]
Prior WHO stage III/IV illness	412 (89.0)
ART regimen	
First-line	443 (95.7)
Second-line	20 (4.3)
Time on current regimen, years	
Median [IQR]	7.9 [6.0 – 8.3]
Last adherence measurement, %, n=461	
Median [IQR]	100 [100 – 100]
History of <100% ART adherence	62 (13.4)
Received mono/dual therapy prior to current regimen initiation	4 (0.9)
CD4 at current regimen initiation, cells/mm³, n=434	
Median [IQR]	101 [34 – 208]

Values presented are n (% total) unless otherwise specified.

IQR = interquartile range; MSM = men who have sex with men; IDU = intravenous drug use; HBsAg = hepatitis B virus surface antigen; WHO = World Health Organization; ART = antiretroviral therapy

Table 2

Last visit characteristics of patients attending the Social Health Clinic, the National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh who died or were lost-to-follow-up before viral load testing, or were not tested despite attending during the testing period* (N=18)

Patients	Final visit	Age, years	Sex	Hepatitis C antibody status	HBsAg status	Latest CD4 count, cells/mm ³	Prior WHO stage III/IV illness	Time on current regimen, years	Last adherence measurement, %	History of <100% adherence	CD4 at current regimen initiation, cells/mm ³
1	AIDS death	38.1	M	Negative	Positive	35	Yes	1.2	100	No	14
2	AIDS death	26.3	M	Negative	Negative	10	Yes	0.5	100	No	10
3	AIDS death	45.6	F	Negative	Negative	66	Yes	0.5	100	No	66
4	AIDS death	39.5	M	Negative	Negative	334	Yes	5.8	100	No	42
5	Non-AIDS death	46.1	F	Negative	Negative	116	Yes	1.4	100	No	42
6	Non-AIDS death	22.5	M	Negative	Negative	22	Yes	0.5	100	Yes	22
7	Non-AIDS death	40.2	M	Negative	Negative	84	Yes	0.7	100	No	?
8	Non-AIDS death	41.1	M	Negative	Negative	152	Yes	1.7	100	No	14
9	LTFU	39.3	F	Negative	Negative	207	Yes	1.1	100	Yes	61
10	LTFU	45.1	M	Negative	Negative	149	Yes	1.9	100	No	47
11	LTFU	28.4	F	Negative	Negative	383	Yes	2.2	100	Yes	266
12	LTFU	40.8	M	Positive	Negative	395	Yes	4.7	100	No	346
13	LTFU	32.6	F	Negative	Negative	92	Yes	0.5	100	No	92
14	LTFU	45.5	F	Negative	Positive	563	Yes	2.1	100	No	153
15	LTFU	63	M	Positive	Negative	394	Yes	1.4	?	Yes	278
16	LTFU	30.9	M	Negative	Negative	437	Yes	3.1	100	No	221
17	LTFU	33.2	M	?	?	374	Yes	7.1	?	Yes	620
18	Missed VL test	46.3	M	Negative	Negative	337	No	0.8	100	No	?

* All patients were exposed to HIV via heterosexual contact, all were using first-line ART at the time of their last visit, and none received mono/dual therapy prior to starting their last known regimen.

HBsAg = hepatitis B virus surface antigen; WHO = World Health Organization; LTFU = lost-to-follow-up; VL = viral load; M = male; F = female; ? = unknown

Table 3

Factors associated with virological failure in patients on antiretroviral therapy attending the Social Health Clinic, the National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh (N=463)

	N	Virological failures (%N)	Univariate odds ratio (95%CI)	p	Multivariate odds ratio (95%CI)	p
Times on current regimen, years						
<2	35	14 (40.0)	30.4 (11.5 – 80.5)	<0.01	23.5 (7.3 – 74.9)	<0.01
2–5	55	6 (10.9)	5.6 (1.9 – 16.8)	<0.01	7.0 (2.2 – 22.4)	<0.01
>5	373	8 (2.1)	1.0		1.0	
Current CD4 count, cells/mm³						
>500	132	1 (0.8)	1.0		1.0	
350–500	93	6 (6.5)	9.0 (1.1 – 76.4)	0.04	9.8 (1.1 – 88.8)	0.04
<350	110	18 (16.4)	25.6 (3.4 – 195.4)	<0.01	12.9 (1.6 – 104.5)	0.02
Missing	128	3 (2.3)	-		-	
History of <100% ART adherence						
No	401	20 (5.0)	1.0		1.0	
Yes	62	8 (12.9)	2.8 (1.2 – 6.7)	0.02	4.4 (1.5 – 13.0)	<0.01
Age, years						
<40	181	14 (7.7)	1.0			
40–50	206	11 (5.3)	0.7 (0.3 – 1.5)	0.34		
>50	76	3 (4.0)	0.5 (0.1 – 1.8)	0.27		
Sex						
Male	246	16 (6.5)	1.0			
Female	217	12 (5.5)	0.8 (0.4 – 1.8)	0.66		
Hepatitis C antibody status						
Negative	425	24 (5.7)	1.0			
Positive	26	2 (7.7)	1.4 (0.3 – 6.2)	0.67		
Missing	12	2 (16.7)	-			
HBsAg status						
Negative	399	23 (5.8)	1.0			

	N	Virological failures (%N)	Univariate odds ratio (95%CI)	p	Multivariate odds ratio (95%CI)	p
Positive	53	3 (5.7)	1.0 (0.3 – 3.4)	0.98		
Missing	11	2 (18.2)	-			
Prior WHO stage III/IV illness						
None known	51	2 (3.9)	0.6 (0.1 – 2.6)	0.50		
Yes	412	26 (6.3)	1.0			
CD4 at current regimen initiation, cells/mm³						
>200	115	8 (7.0)	1.0			
100–200	103	4 (3.9)	0.5 (0.2 – 1.9)	0.33		
<100	216	14 (6.5)	0.9 (0.4 – 2.3)	0.87		
Missing	29	2 (6.9)	-			

Patients that died, were lost-to-follow-up, or did not undergo a viral load test during the testing period despite presenting for care were considered to be using a failing regimen at their latest clinic visit. Patients with missing covariate data were included in all models but odds ratios for missing categories are not shown.

N = total number of patients in category; CI = confidence interval; ART = antiretroviral therapy; MSM = men who have sex with men; HBsAg = hepatitis B virus surface antigen; WHO = World Health Organization.