Any Level of Detectable Viremia is Associated with Serious Non-AIDS Events

Anuradha Ganesan, MBBS, MPH [1,2,3], Hsing-Chuan Hsieh MPH [1,3], Xiuping Chu MS [1,3], Rhonda E Colombo MD [1,3,4], CDR Catherine Berjohn MD [1,5], Tahaniyat Lalani MBBS [1,3,6], MHS, COL Jason Blaylock MD [1,2], Col Jason Okulicz MD [1,7] and Brian Agan MD [1,3]

1- Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD. 2 - Walter Reed National Military Medical Center, Bethesda, MD 3- Henry M Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, 4- Madigan Army Medical Center, Tacoma, WA 5-Naval Medical Center San Diego, San Diego, CA, 6- Naval Medical Center Portsmouth, Portsmouth, VA, 7- Brooke Army Medical Center, San Antonio, TX

Presentation #689

Abstract

Background: A proportion of HIV-infected persons on antiretroviral therapy [ART] have detectable viral loads [VL] at low levels without ever meeting criteria for virologic failure [VF]. The clinical consequences of this low level viremia [LLV] are not well understood. In this study, we examined the association between detectable VL and serious non-AIDS events (SNAEs).

Methods: We used data from the US Military HIV Natural History Study (NHS). The NHS is comprised of military beneficiaries who are enrolled early in infection and have access to care and medications. NHS participants who initiated ART after 1996 were included if they had two or more VLs measured using an assay with a lower limit of detection of ≤50 copies/mL, ≥ 6 months after ART initiation. VLs were categorized as LLV [51-199 copies/mL], high level viremia [HLV-200-999 copies/mL], VF [≥200 copies/mL on 2 or more successive determinations or a single VL≥1000 copies/mL] and virologic suppression [VS- ≤50 copies/mL on all determinations and blips]. SNAEs evaluated are footnoted on Table 1. We examined the first occurrence of a SNAE from any category. Factors significant at a p <0.05 in the univariate model were included in the multivariable Cox proportional hazards models. We adjusted for gender, race, time to ART start; Age, VL category, ART regimen and CD4 count were analyzed as time updated variables.

Results: 2815 participants [94% male, 40% Caucasian, 43% African American] were followed for a median of 10.1 years [IQR 4.8 to 18.2]. A total of 489 [17.4%] SNAEs were recorded {106 [3.7%] malignancies, 155 [5.5%] cardiovascular events, 205 [7.3%] cases of chronic kidney disease and 23 [0.8%] cases of cirrhosis}. A third of the participants had one or more episodes of VF. LLV was noted in 7.9% and HLV in 4.3 %. We observed an association with LLV, HLV, VF and SNAEs with a graded hazard by level of viremia, Table 1. Other factors associated with SNAEs were older age, female gender, Caucasian race, delays in ART initiation and regimen type. In comparison with boosted PI, InSTIs and NNRTIs were protective, whereas unboosted PI use had a greater risk. Higher CD4 counts were protective.

Conclusion: The results of this study add to a growing body of literature that suggest detectable viremia including LLV could have adverse clinical consequences. We confirm previously observed negative clinical consequences of delays in ART initiation and lower CD4 counts. The association with race gender and ART categories, need further evaluation.

Background

- Low-level viremia (LLV) refers to viral loads (VL) that are detectable but <200 copies/mL.
- LLV is common, between 3 and 10% of HIV infected persons will experience LLV.
- The consequence of having LLV are unclear, whereas the deleterious consequences of higher levels of LLV (hLLV) are more agreed upon.
- Having hLLV has been associated with a greater risk of serious non-AIDS events (SNAEs) and virologic failure (VF).
- A single study suggests LLV is associated with a greater hazard of death but not SNAEs.
- This study was designed to examine the effects of LLV on development of SNAE.

Methods

Definitions for the primary exposure of interest

- **Non-suppressed viremia**
  - A single VL ≥ 1000 copies/mL, OR
  - VL ≥ 200 copies/mL on two or more consecutive determinations at least 3 months apart
- **High-level viremia:** VL of 200-999 copies/mL, that does not meet the criteria for a blip or non suppressed viremia
- **Low-level viremia:** VL of 51-199 copies/mL which do not met criteria for a blip
- **Virological suppression**
  - VL ≤ 50 copies/mL OR
  - Blips: Isolated VL of 51-999 copies/mL which is preceded and followed by a VL ≤ 50 copies/mL

Highest Viremia Status	Overall (n=2815)	No SNAEs (n-2326)	SNAEs (n=489)
VS	1220 (43.3)	1094 (47)	126 (25.8)
Blips	325 (11.5)	266 (11.4)	59 (12.1)
LLV	221 (7.9)	194 (8.3)	27 (5.5)
hLV	122 (4.3)	102 (4.4)	20 (4.1)
NS	927 (32.9)	670 (28.8)	257 (52.6)

Table 1- Categorization of Viral loads Based on Highest viremia status

Methods (Contd.)

SNAE Type	Description (Frequency)
Cancer	Anal Cancer (26)
	Breast Cancer (5)
	Colon Cancer (2)
	Leukemia (1)
	Lung Cancer (3)
	Lymphoma, Hodgkin's (7)
	Multiple Myeloma (1)
	Melanoma (13)
	Other Cancer (25)
	Prostate Cancer (23)
Heart	Cardiomyopathy (10)
	Congestive Heart Failure (5)
	Pericardial Effusion (1)
	Pericarditis (9)
Vascular	Myocardial infarction (MI) (25)
	Cerebrovascular Disease (19)
	Coronary Heart Disease without MI (54)
	Peripheral Artery Disease (6)
	Deep Vein Thrombosis (26)
Renal	Stage 3 CKD (205)
Liver	Cirrhosis (23)

Table 2- List of Serious Non -AIDS Events (SNAEs) With Frequencies

Statistical Consideration

- Descriptive statistics are presented as medians with interquartile ranges (IQRs) for continuous variables and counts with proportions for categorical variables.
- For group comparisons, Kruskal-Wallis test and $\chi 2$/Fisher exact test were used to calculate 2-sided p- values for continuous and categorical variables, respectively.
- We analyzed time to the first SNAE. NHS subjects without SNAEs were censored at their last study visit.
- Viremia was categorized as defined previously, and was time updated to the highest category.
- The multivariate model was adjusted for time updated age, gender, race, time-updated measure of viremia, time from HIV diagnosis to ART initiation, time updated CD4 counts and ART regimen type.
- All reported p-values are 2-sided with a p-value <0.05 considered to indicate statistical significance.
- Several different sensitivity analysis were completed, including one restricted to those who initiated ART after 2006.

Results

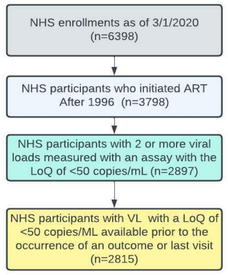


Figure 1- NHS participants selected for the analysis

# Of SNAEs	# Of Participants	Proportion
0	2213	78.61
1	383	13.61
2	124	4.4
3	55	1.95
4	19	0.67
5	14	0.5
6	4	0.14
7	3	0.11

Table 3- Distribution of Number or SNAEs per Participant

	Overall N = 2815	No SNAE n = 2326 (82.6%)	SNAE n = 489 (17.4%)	p value
Demographics				
Gender				0.0006
Male	2636 (93.6)	2195 (94.4)	441 (90.2)	
Female	179 (6.4)	131 (5.6)	48 (9.8)	
Race				<.0001
Caucasian	1125 (40.0)	882 (37.9)	243 (49.7)	
African American	1203 (42.7)	1020 (43.9)	183 (37.4)	
Hispanic/Other	487 (17.3)	424 (18.2)	63 (12.9)	
Age at HIV Dx (yrs)	28.8 [24.4-35.2]	28.1 [23.9-33.8]	33.7 [28.0-40.7]	<.0001
Age at AI (yrs)	32.5 [26.9-39.0]	31.1 [26.0-37.4]	39.2 [34.3-45.9]	<.0001
Age at SNAE/LV (yrs)	42.0 [32.9-51.8]	39.7 [31.5-49.2]	51.8 [45.0-58.4]	<.0001
HIV related				
Year of ART initiation (AI)	2005 [1998-2011]	2007 [1998-2012]	1998 [1997-2004]	<.0001
Time from HIV dx to AI	1.0 [0.2-5.2]	0.7 [0.1-4.0]	4.9 [0.9-9.0]	<.0001
First ART Regimen				
Unboosted PI	889 (31.6)	615 (26.4)	274 (56.0)	<.0001
Boosted PI	244 (8.7)	205 (8.8)	39 (8.0)	
NNRTI	1119 (39.8)	984 (42.3)	135 (27.6)	
PI+NNRTI+NRTI	75 (2.7)	52 (2.2)	23 (4.7)	
INSTI	478 (17.0)	461 (19.8)	17 (3.5)	
ART at SNAE/Last visit				
Unboosted PI	159 (5.6)	114 (4.9)	45 (9.2)	<.0001
Boosted PI	381(13.5)	266 (11.4)	115 (23.5)	
NNRTI	843 (29.9)	708 (30.4)	135 (27.6)	
PI+NNRTI+NRTI	70 (2.5)	49 (2.1)	21 (4.3)	
3 NRTI	1 (0.0)	1 (0.0)	0 (0.0)	
InSTI	1155 (41.0)	1055 (45.4)	100 (20.4)	
Other Combination	177 (6.3)	127 (5.5)	50 (10.2)	
CD4 at HIV Dx (cells/ul)	459 [328-616]	458 [328-614]	474 [333-630]	0.5356
CD4 at AI (cells/ul)	370 [255-504]	376 [263-513]	327 [194-462]	<.0001
VL at AI (copies/mL)	32173 [7255-94610]	33279 [7933-95832]	23622 [4056-80623]	0.0062

Table 4- Demographic and HIV specific characteristics of those with and without SNAEs

Results (cont.)

	Unadjusted HR	95%CI		P	Adjusted HR	95% CI		P
Time updated viral load categories (Reference: VS)								
LLV	1.68	1.571	1.797	<.0001	1.249	1.161	1.343	<.0001
hLV	2.119	1.977	2.272	<.0001	1.566	1.453	1.689	<.0001
NS	2.69	2.599	2.784	<.0001	1.713	1.641	1.788	<.0001
Gender								
Female vs. Male	1.373	1.305	1.444	<.0001	1.355	1.28	1.436	<.0001
Race (Referent: Caucasian)								
African American	0.652	0.631	0.673	<.0001	0.699	0.674	0.724	<.0001
Hispanic/Other	0.652	0.621	0.684	<.0001	0.81	0.767	0.855	<.0001
Time updated age (per 10-year increase)	1.698	1.671	1.724	<.0001	1.631	1.601	1.661	<.0001
log(VL) at ART initiation (copies/ml)	0.967	0.951	0.982	<.0001	1.02	1.003	1.037	0.0242
Time from HIV dx to ART initiation (per year increase)	1.07	1.067	1.073	<.0001	1.017	1.013	1.021	<.0001
Time updated CD4 counts (per 100 cells increase/ul)	0.861	0.856	0.866	<.0001	0.939	0.933	0.945	<.0001
Time updated ART regimen (ref: InSTI)								
Boosted PI	5.131	4.706	5.593	<.0001	3.718	3.375	4.096	<.0001
NNRTI	3.115	2.863	3.389	<.0001	2.679	2.441	2.941	<.0001
Other Combinations	7.674	7.027	8.381	<.0001	4.396	3.98	4.855	<.0001
Unboosted PI	6.601	6.064	7.186	<.0001	4.744	4.309	5.222	<.0001

N = 2777. SNAE cases, n = 483.

Table 5- Factors associated with SNAEs in the primary analysis

	Adjusted HR	95% CI		P
Time updated viral load categories (Referent: VS)				
LLV	1.299	0.983	1.717	0.0656
hLV	1.959	1.21	3.172	0.0062
NS	2.565	1.84	3.576	<.0001
Gender				
Female vs. Male	2.528	2.12	3.015	0.2168
Race (Referent Caucasian)				
African American	0.537	0.468	0.616	<.0001
Hispanic/Other	1.056	0.918	1.214	0.4455
Time updated age for every 10 year increase	2.263	2.139	2.396	<.0001
log(VL) at ART initiation (copies/ml)	0.913	0.867	0.961	0.0005
Time from HIV dx to ART initiation (per year increase)	1.001	0.99	1.011	0.8744
Time updated CD4 counts (per 100 cells increase/ul)	1.023	1.001	1.045	0.0404
Time updated ART regimen (Ref: InSTI)				
Boosted PI	2.409	2.005	2.894	<.0001
NNRTI	1.823	1.578	2.106	<.0001
Other Combinations	2.808	2.122	3.715	<.0001
Unboosted PI	3.37	2.13	5.334	<.0001

N = 1,322. SNAE case, n = 99.

Table 6-Sensitivity analysis examining factors associated with SNAEs among those initiating ART after 2006

	Adjusted HR	95% CI		P
Time updated viral load categories (Referent: VS)				
LLV	1.239	1.141	1.346	<.0001
hLV	1.691	1.556	1.837	<.0001
NS	1.686	1.606	1.771	<.0001
Gender				
Female vs. Male	1.047	0.974	1.125	0.2168
Race (Referent:Caucasian)				
African American	0.705	0.677	0.734	<.0001
Hispanic/Other	0.707	0.662	0.755	<.0001
Time updated age (per 10-year increase)	1.544	1.511	1.577	<.0001
log(VL) at ART initiation (copies/ml)	1.025	1.005	1.046	0.0136
Time from HIV dx to ART initiation (per year increase)	1.033	1.029	1.038	<.0001
Time updated CD4 counts (per 100 cells increase/ul)	0.913	0.905	0.92	<.0001
Time updated ART regimen (Ref: InSTI)				
Boosted PI	5.535	4.828	6.347	<.0001
NNRTI	4.29	3.756	4.901	<.0001
Other Combinations	7.85	6.842	9.007	<.0001
Unboosted PI	8.302	7.254	9.501	<.0001

N = 2,765. SNAE case, n = 384.

Table 7- Factors associated with SNAEs in an analysis in which CKD was defined as stage 4 or lower

Discussion

- About 1 in 5 NHS participants had at-least one SNAE.
- SNAEs occurred more frequently in women and those who self-identified as Caucasians; these differences remained even after adjustment.
- While we confirm previously observed associations with hLLV, the association with LLV have not been previously reported.
- At the time they were diagnosed with a SNAE most NHS participants were immune reconstituted with an undetectable viral load. However, higher VL at ART initiation, lower CD4 counts, any level of detectable viremia, and waiting longer to initiate ART were associated with SNAEs.
- To limit confounding and to better delineate the association with ART class and SNAEs we restricted the analysis to those initiating ART after the advent of single pill regimens (2006 and later). Even in this sensitivity analysis, the protective effect of the INSTI class and the deleterious effect of LLV were observed; though the association with LLV was marginal (likely related to smaller sample size).
- CKD was the most frequently observed first SNAE. Since serum creatinine forms the basis for eGFR calculation and can be artifactually increased by ART regimens. we used a stringent definition for CKD (i.e., an eGFR ≤ 30 ml/min). Even in this secondary analysis the association with LLV remained, further strengthening our observation.
- Our results need confirmation, nevertheless, we believe, at a minimum, the presence of LLV should necessitate an assessment of adherence and closer follow-up.

Conclusions

- In an adjusted analysis, we observed an association with any level of detectable viremia and SNAEs. Confirmation of these results would argue for a lower VL threshold for defining VF in the US. This study provides more evidence that the WHO defined VL threshold virologic failure should be lowered from the current 1000 copies/mL to 200 copies/mL.

Acknowledgments

This project was conducted by the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed by the Uniformed Services University of the Health Sciences (USU) through a cooperative agreement with The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This projected has been supported with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter-Agency Agreement Y1-AI-5072, the Defense Health Program, U.S. DoD, under award HU0001190002.

Disclaimer. The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Uniformed Services University of the Health Sciences, Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., National Institutes of Health and Department of Health and Human Services, Department of the Navy, Army, Department of Defense, nor the U.S. Government. This research has been approved by USU IRB.

Correspondence

Anuradha Ganesan, Email: Anuradha.Ganesan.ctr@health.mil