Variable Persistence of Non-Suppressible Viremia on Antiretroviral Therapy

473

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BACKGROUND:

- Non-suppressible viremia (NSV) on antiretroviral therapy (ART) originates from infected T-cell clones rather than viral replication
- The variation and longitudinal persistence of NSV have not been well defined. To address this knowledge gap, we enrolled a longitudinal cohort of persons with NSV on stable ART [AIDS Clinical Trials Group (ACTG), Protocol A5321]

HYPOTHESIS: NSV will show variable persistence over time because of dynamic nature of infected cells clones

RATIONALE:

- Understand the natural history of NSV to aid in patient management
- Provide insight on how to develop interventions that target clones causing NSV (i.e. bnAbs or anti-proliferative agents)

METHODS and ANALYSES:

- The NSV cohort enrolled 31 participants of which 22 were selected for the current analysis meeting the following criteria: i) complete RNA data from weeks 0 (entry), 24 and 48 weeks; and ii) no interruptions/changes in ART from week 0 through 48
- All on-study plasma HIV-1 RNAs were quantified by the Abbott M2000 assay with a lower limit of quantification of 40 copies/mL. Results <40 copies/mL were reported as target detected (<40 copies/mL) or target not detected (TND)
- Participants were categorized into three patterns of plasma HIV-1 RNA: 1) all RNAs <40 (not considering TND vs. detected); 2) mix of RNAs <40 and ≥40; 3) all RNAs ≥40
- Characteristics that were compared between HIV-1 RNA categories were: i) pre-ART HIV-RNA, ii) pre-ART CD4 & entry CD4, iii) entry CD8, iv) entry CD4/CD8, v) years from first ART use at week 0, and vi) proportion of RNAs ≥40 copies/mL during the 24 months prior to study entry

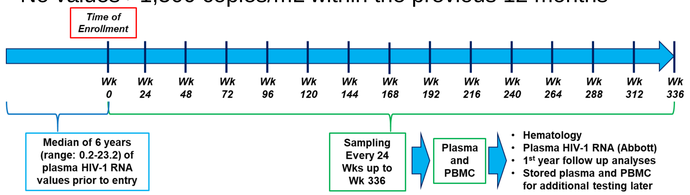
RESULTS:

- No significant differences in participant characteristics between the entire population (n=31) and the subpopulation analyzed and presented here (n=22) (***data not shown***)
- Median years of detectable HIV-1 RNA, plasma HIV-1 RNA at entry (≥40 c/mL)), and participants with quantifiable HIV-1 RNA are 1.5 years, 78 copies/mL, and 41%, respectively (**Table 1**)
- HIV-1 RNA was detected (<40 copies/mL) or TND in 36% or 23% of participants, respectively (**Table 1**)
- 1 of the participants was female and there were no significant associations between persistent NSV and participant age, sex, pre-ART HIV RNA, pre-ART CD4 or years on ART (**Table 2**)
- Participants in the more viremic category during follow-up were also more viremic during the 24 months pre-study/on-ART (**Table 2 and Figure 2**)

Figure 1. A5321 Non-Suppressible Viremia Cohort Inclusion Criteria, Testing Schema, and Primary Objectives

Inclusion Criteria:

- Persistent low-level viremia at least 12 months prior to entry
- On uninterrupted fully active ART regimen
- At least 2 HIV-1 RNA values 20-1,500 copies/mL within previous 24 months
- At least 1 HIV-1 RNA values 20-1,500 copies/mL within the previous 12 months
- No values >1,500 copies/mL within the previous 12 months



Sample Size:

- 31 participants enrolled
- 22 participants analyzed

Primary Objective: Analyses of participant characteristics comparing 3 categories of non-suppressible viremics by age, sex, gender, pre-ART plasma HIV-1 RNA (log_{10} copies/mL), pre-ART and entry $CD4^+$ T-cell count (cells/mm^3), entry $CD8^+$ T-cell count (cells/mm^3), entry CD4:CD8 ratio, years on ART at entry, and the proportion of RNAs ≥40 copies/mL during 24 months on ART prior to entry.

We enrolled a cohort of participants with non-suppressible viremia despite ART. After the first year of follow-up, the main findings are:

i) Non-suppressible viremia was dynamic. In only 14% of participants did it persist at ≥40 copies/mL from enrollment through week 48

ii) Participants with more persistent viremia in follow-up had more frequently detected viremia in the 24 months before cohort entry

iii) These results are consistent with variable persistence of clones producing virus with the minority being stable, and the majority declining in size and/or producing less virus over time

Table 1. Clinical and Virologic Characteristics of the ACTG A5321 Non-Suppressible Viremia Cohort Analysis Population

PATID	Years Living with HIV	Years on ART	Years of Detectable Viral HIV-1 RNA	Plasma HIV-1 Viral RNA at A5321 Entry (Copies/mL)[A]
1	27.2	15	4.5	93
2	24.6	22.4	1.2	<40[B]
3	32.2	11.1	0.1	78
4	38.7	3.7	0.3	TND[C]
5	26	25	0.3	TND
6	10.8	15.8	0.1	TND
7	8.3	7.3	1.2	280
8	3.3	3.3	2	45
9	34.3	26.8	0.2	<40
10	4.5	4.5	0.5	<40
11	3.3	3.3	1.1	49
12	13.9	11.4	0.2	TND
13	23.1	23	5.1	69
14	10.9	9.8	7.9	77
15	3	2.9	2.8	<40
16	8.1	8	3	167
17	14.5	11.3	5.5	<40
18	14.1	13.8	1.7	<40
19	3.8	3.8	2.1	170
20	5.8	5.8	0.4	TND
21	9.2	9.1	9	<40
22	32.2	8.2	6.1	<40
Median	12.4	9.5	1.5	<40 and among 9 participants with ≥ 40: median 78

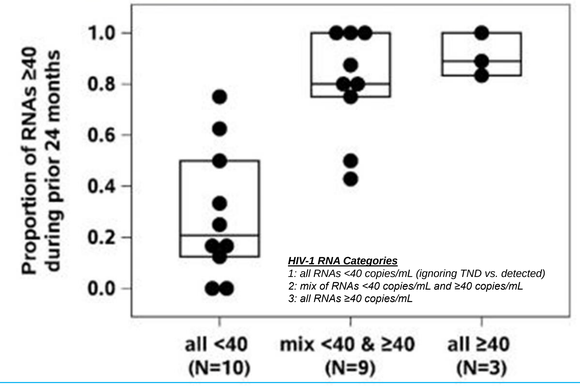
[A] Plasma HIV-1 RNA copies/mL at time of entry determined by the FDA-approved Abbott assay with a lower limit of 40 copies/mL; [B] <40 = less than 40 copies/mL which is detectable, but not quantifiable; [C] TND = Target Not Detected;

Table 2. Comparison of Baseline Characteristics by the 3 Categories of HIV-1 RNA Detection During Follow-up

Characteristics		Analyses Category (3 Levels)			
		Category 1 (N=10)	*Category 2 (N=9)*	*Category 3 (N=3)*	*P-Value*
Age at A5321 Entry (Years)	Median (Q1, Q3)	59 (55, 70)	56 (52, 60)	61 (58, 66)	
	N	10	9	3	
Sex	Male	9 (90%)	9 (100%)	3 (100%)	
	Female	1 (10%)	0 (0%)	0 (0%)	
Gender	Male	9 (90%)	9 (100%)	3 (100%)	
	Female	1 (10%)	0 (0%)	0 (0%)	
Pre-ART Plasma HIV-1 RNA (log_{10}cps/mL)	Median (Q1, Q3)	5.3 (4.0, 6.7)	5.5 (5.1, 5.8)	5.4 (5.4, 5.4)	0.93
	N	6	4	1	
Pre-ART CD4+ T-Cell Count (cells/mm^3)	Median (Q1, Q3)	98 (96, 275)	121 (101, 197)	164 (164, 164)	0.87
	N	5	4	1	
A5321 Entry CD4+ T-Cell Count (cells/mm^3)	Median (Q1, Q3)	820 (450, 912)	426 (368, 946)	479 (319,506)	0.60
	N	10	9	3	
A5321 Entry CD8+ T-Cell Count (cells/mm^3)	Median (Q1, Q3)	933 (591, 1051)	784 (624, 889)	852 (642, 1138)	0.74
	N	10	9	3	
A5321 Entry CD4:CD8 Ratio	Median (Q1, Q3)	0.9 (0.6, 1.2)	0.8 (0.4, 1.0)	0.4 (0.4, 08)	0.41
	N	10	9	3	
Years on ART at A5321 Entry	Median (Q1, Q3)	12.6 (5.8, 22.4)	8.2 (4.5, 11.1)	7.3 (3.7, 23.0)	0.52
	N	10	9	3	
Number of RNAs During 24 Months Prior to Entry	Median	2, 8	4, 8	6, 12	
Proportion of RNAs ≥40 during 24 Months Prior to Entry	Q1, Q3	0.21	0.80	0.89	0.001
	N	0.00, 0.75	0.43, 1.00	0.83, 1.00	

*Kruskal-Wallis Test; 1. *all RNAs <40 copies/mL (ignoring TND vs. detected); 2: mix of RNAs <40 copies/mL and ≥40 copies/mL; 3: all RNAs ≥40 copies/mL; TND = Target not Detected*

Figure 2. Proportion of RNAs ≥40 During the 24 Months Prior to Study Entry, by the Three Categories of HIV-1 RNA Detection During Follow-up (p=0.001 across categories)



CONCLUSIONS:

- NSV was dynamic and persisted ≥40 copies/mL at weeks 0-48 in only 14% of participants
- Persistence of NSV over 48 weeks was only associated with the proportion of RNAs ≥40 copies/mL prior to entry
- We did not detect associations between NSV persistence and age, sex, pre-ART HIV RNA, pre-ART CD4 or years on ART
- These results are consistent with variable persistence of clones producing virus with the minority being stable, and the majority declining in size and/or producing less virus
- Studies are in progress to differentiate the mechanisms of persistent NSV from NSV that spontaneously resolves.

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