



Correlations of undetectable HIV DNA 96 weeks after ART Initiation during Acute HIV

Gunn Pungpapong¹, Phillip Chan², Denise Hsu^{3,4}, Carlo Sacdalan², Somchai Sriplienchan², Peeriya Prueksakaew², Suteeraporn Pinyakorn^{3,4}, Bohyung Yoon^{3,4}, Sandhya Vasani^{3,4}, Sodsai Tovanabutra^{3,4}, Nittaya Phanuphak², Robert Paul⁵, Nicolas Chomont⁶, Serena Spudich⁷, on behalf of the RV254/SEARCH 010 Study Team

¹ Imperial College London, London, UK, ² SEARCH, Institute of HIV Research and Innovation, Bangkok, Thailand, ³ United States Military HIV Research Program; Walter Reed Army Institute of Research, Silver Spring, MD, USA ⁴ The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA, ⁵ Missouri Institute of Mental Health, St. Louis, MO, USA, ⁶ Université de Montréal, Montréal, Canada, ⁷ Department of Neurology, Yale University, New Haven, CT, USA

BACKGROUND

In chronic HIV, a larger HIV reservoir (measured by cell associated HIV-DNA) associates with worse cognition despite antiretroviral therapy (ART) (Ref 1-3).

We evaluated:

- Whether HIV-DNA measured in peripheral blood mononuclear cells (PBMC) 96 weeks after ART started during acute HIV infection (AHI), associates with neuropsychiatric outcomes.
- Pre-ART predictors of undetectable HIV-DNA at 96 weeks.

METHODS

RV254 cohort participants in Thailand initiated ART within 4 days after AHI diagnosis. They underwent regular blood sampling and NP assessment during pre-ART AHI (week 0) and follow-up visits at weeks 24, 48 and 96.

Neuropsychiatric assessment included:

- Patient Health Questionnaire-9 (PHQ-9) for depression symptoms
- A 4-test cognitive battery that included Color Trails 1 and 2, Trail making A, and non-dominant hand Grooved Pegboard test
- Demographically adjusted Z-scores of the 4 tests based on local Thai norms were averaged to generate composite NPZ-4 scores.

HIV-DNA measurement:

- Total HIV-DNA, measured by ultrasensitive LTR-gag real-time PCR in PBMC at weeks 0, 24, 48 and 96.

Statistical Analysis:

- Multivariable logistic regression determined week 0 factors correlated with undetectable HIV-DNA at week 96.

RESULTS

124 RV254 participants had HIV-DNA measurements at week 0; 118 (95%) were male, with median age 26; 59 (48%) presented at Fiebig stage I-II (**Table 1**).

83 virally suppressed participants had HIV-DNA measurement at week 96. Proportion of participants with detectable HIV-DNA in PBMC decreased from 89% (110/124) at week 0 to 70% (66/94) at week 24, 67% (62/93) at week 48, and 52% (43/83) at week 96.

NPZ-4 and PHQ-9 scores at wk 96 were statistically similar between those with detectable and undetectable HIV-DNA in PBMC (**Table 2**).

Week 0 factors associated with undetectable HIV-DNA at week 96 in univariable analysis (Table 3):

- Early Fiebig stage (I-II)
- Lower plasma HIV RNA
- Higher CD4/CD8 ratio

Week 0 factors associated with undetectable HIV-DNA at week 96 in multivariable analysis (Table 3):

- Lower plasma HIV RNA
- Higher CD4/CD8 ratio

Predictors of undetectable week 96 HIV-DNA included:

- Lower blood plasma HIV-1 RNA
- Higher blood CD4/CD8 ratio

No association between neuropsychiatric outcomes and detection of HIV-DNA at week 96

Table 1. Participants' Characteristics at Weeks 0 & 96

	Week 0 (Acute HIV) (n=124)	Eligibility Week 96 (n=83)
Age	26 (23-31)	28 (24-32)
Sex, n(%)		
Male (Ref)	118 (95.2)	77 (92.8)
Female	6 (4.8)	6 (7.2)
Fiebig Stage at Week 0		
I-II (Ref)	59 (47.6)	37 (44.6)
III-V	65 (52.4)	46 (55.4)
Log ₁₀ Plasma HIV-1 RNA	5.6 (5.0 -6.5)	1.3 (1.3-1.7)
Log ₁₀ Plasma HIV-1 RNA>5, n(%)	93 (75.0)	0 (0)
CD4+ T-cell count	373 (278-529)	644 (526-869)
CD4+ T-cell count>350, n(%)	69 (55.7)	83 (100.0)
CD8+ T-cell count	482 (255-784)	589 (460-758)
CD8+ T-cell count>500, n(%)	79 (63.7)	76 (91.6)
CD4/CD8 ratio	0.8 (0.5-1.4)	1.1 (0.9-1.4)
CD4/CD8 ratio>1, n(%)	52 (41.9)	54 (65.1)
HIV-DNA level in PBMC	186 (21.5-775.5)	4.0 (0.0-21.0)
Detectable Total HIV DNA, n(%)	110 (89)	43 (52)

Table 2. Parameter Comparisons between Detectable & Undetectable HIV-DNA Groups

Parameter at week 0	Detectable HIV-DNA (n=43)	Undetectable HIV-DNA (n=40)	P-value
Age at W0	28 (24-30)	28 (23-32)	0.902
Sex, n (%)			
Male (Ref)	42 (97.7)	35 (87.5)	0.101
Female	1 (2.3)	5 (12.5)	
Fiebig Stage at W0			
I-II	14 (32.6)	23 (57.5)	0.028
III-V	29 (67.4)	17 (42.5)	
Log ₁₀ Plasma HIV-1 RNA	5.76 (5.45-6.69)	5.62 (4.82-6.23)	0.067
HIV RNA >5 log ₁₀	39 (90.7)	27 (67.5)	0.013
Total HIV-DNA at week 0	623 (190-1967)	26 (3.5-103)	<0.001
CD4+ T-cell count	341 (266-532)	402 (301-536)	0.161
CD4+ T-cell count>350, n(%)	21 (48.8)	27 (67.5)	0.120
CD8+ T-cell count	558 (304-917)	419 (239-659)	0.175
CD8+ T-cell count>500, n(%)	30 (69.8)	24 (60.0)	0.368
CD4/CD8 ratio	0.68 (0.38-1.08)	1.02 (0.57-1.47)	0.026
CD4/CD8 ratio>1, n(%)	12 (27.9)	21 (52.5)	0.027
NPZ-4 score	-0.37 (-0.68 to -0.09)	-0.12 (-0.57 to 0.22)	0.311
PHQ-9 score	10 (7.5-16)	9 (6-15)	0.570

CONCLUSIONS

- Though half of individuals had undetectable HIV-DNA at week 96, this was not associated with neuropsychiatric outcomes including NPZ-4 and PHQ-9 scores.

- Predictors of undetectable HIV-DNA at week 96 included lower pre-ART plasma HIV RNA and higher CD4/CD8 ratio, suggesting that early events impact HIV reservoir trajectory.

REFERENCES

- Cysique, Lucette A., et al. "Peripheral blood mononuclear cells HIV DNA levels impact intermittently on neurocognition." *PLoS One* 10.4 (2015): e0120488.
- de Oliveira, Michelli Faria, et al. "Circulating HIV DNA correlates with neurocognitive impairment in older HIV-infected adults on suppressive ART." *Scientific reports* 5.1 (2015): 1-9.
- Ruhanya, Vurayai, et al. "Clinical relevance of total HIV DNA in peripheral blood mononuclear cell compartments as a biomarker of HIV-associated neurocognitive disorders (HAND)." *Viruses* 9.11 (2017): 324.

Table 3. Factors Associated with Undetectable HIV-DNA 96 weeks after ART Initiation during Acute HIV

	Odds ratio (95%CI)	p-value	Adjusted Odds ratio (95%CI)	p-value
Age	1.01 (0.95 - 1.07)	0.74		
Sex				
Female	6.00 (0.67 – 53.79)	0.109		
Male	Ref.			
Fiebig stage				
I-II	2.80 (1.15 – 6.85)	0.024		
III-IV	Ref.			
HIV RNA at week 0				
≤ 5 log ₁₀ copies/mL	4.69 (1.38 – 15.95)	0.013	4.67 (1.10 – 7.34)	0.016
> 5 log ₁₀ copies/mL	Ref.		Ref.	
Total HIV-DNA at week 0				
Detectable	Ref.			
Undetectable	10.5 (1.25 - 88.28)	0.03		
CD4 T cells at week 0				
CD4 ≤ 350 cells/mm ³	Ref.			
CD4 > 350 cells/mm ³	2.18 (0.89 - 5.31)	0.088		
CD8 T cells at week 0				
CD8 ≤ 500 cells/mm ³	1.54 (0.62 – 3.81)	0.352		
CD8 > 500 cells/mm ³	Ref.			
CD4/CD8 ratio at week 0				
≤ 1	Ref.		Ref.	
> 1	2.86 (1.15 - 7.1)	0.024	2.84 (1.10 - 7.34)	0.031
ART regimen				
HAART	1.69 (0.71 – 4.04)	0.238		
MegaHAART	Ref.			

Acknowledgements

We would like to thank the study participants who committed so much of their time for this study. The participants were from the RV254/SEARCH 010, which is supported by cooperative agreements (WW81XWH-18-2-0040) between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of Defense (DOD) and by an intramural grant from the Thai Red Cross AIDS Research Centre and, in part, by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institute of Health (DAIDS, NIAID, NIH) (grant AAI20052001). Antiretroviral therapy for RV254/SEARCH 010 participants was supported by the Thai Government Pharmaceutical Organization, Gilead Sciences, Merck and Viiv Healthcare. This study was additionally supported by R01MH113560, R01MH095613, R01MH106466, and additional funds contributed by the US NIH/National Institute of Mental Health.

Disclaimers

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, the National Institutes of Health, the Department of Health and Human Services, or the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. The investigators have adhered to the policies for protection of human subjects as prescribed in AR-70-25.