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Title

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Journal

AIDS, 35(13)

ISSN

0269-9370

Authors

Fajnzyblber, Jesse

Sharaf, Radwa

Hutchinson, John N

et al.

Publication Date

2021-11-01

DOI

10.1097/qad.0000000000002978

Peer reviewed



Published in final edited form as:

AIDS. 2021 November 01; 35(13): 2225–2227. doi:10.1097/QAD.0000000000002978.

Frequency of Post Treatment Control Varies by ART Restart and Viral Load Criteria

Jesse Fajnzylber^a, Radwa Sharaf^a, John N. Hutchinson^b, Evgenia Ag^{a,b}, Ronald J. Bosch^b, Wendy Hartogensis^c, Jeffrey M. Jacobson^d, Elizabeth Connick^e, Paul Volberding^c, Daniel J. Skiest^f, David Margolis^g, Michael C. Sneller^h, Susan J. Littleⁱ, Roy M. Gulick^j, John W. Mellors^k, Rajesh T. Gandhi^l, Robert T. Schooleyⁱ, Keith Henry^m, Pablo Tebasⁿ, Steve Deeks^c, Tae-Wook Chun^h, Ann C. Collier^o, Frederick M. Hecht^c, Jonathan Z. Li^a, CHAMP study team

^aBrigham and Women's Hospital, Harvard Medical School

^bHarvard T.H. Chan School of Public Health, Boston, Massachusetts

^cUniversity of California, San Francisco, San Francisco, California

^dCase Western Reserve University, Cleveland, Ohio

^eUniversity of Arizona, Tucson, Arizona

^fUniversity of Massachusetts- Baystate, Springfield, Massachusetts

^gUniversity of North Carolina, Chapel Hill, North Carolina

^hNational Institute of Allergy and Infectious Diseases, Bethesda, Maryland

ⁱUniversity of California, San Diego, San Diego, California

^jWeill Cornell Medicine, New York, New York

^kUniversity of Pittsburgh, Pittsburgh, Pennsylvania

^lMassachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

^mUniversity of Minnesota, Minneapolis, Minnesota

ⁿUniversity of Pennsylvania, Philadelphia, Pennsylvania

^oUniversity of Washington, Seattle, Washington, USA

Abstract

Clinical trials including an analytical treatment interruption (ATI) are vital for evaluating the efficacy of novel strategies for HIV remissions. We briefly describe an interactive tool for predicting viral rebound timing in ATI trials and the impact of post-treatment controller (PTC) definitions on PTC frequency estimates. A 4-week viral load threshold of 1,000 cps/mL provides

Corresponding Author: Jonathan Li, MD, Brigham and Women's Hospital, 65 Landsdowne Street, Rm 421, Cambridge, MA 02139, jli@bwh.harvard.edu.

A list of the CHAMP study team contributors is provided in the Supplementary Appendix

Conflicts of Interest

There are no conflicts of interest.

both high specificity and sensitivity for PTC detection. PTC frequency varies greatly based on the definition of a PTC.

Analytical treatment interruption (ATI) is an essential strategy to determine the effectiveness of HIV cure strategies. Although previous work has demonstrated that ATI does not lead to an increase in the reservoir size [1,2], minimizing unnecessary prolonged exposure to viremia is an important consideration for all studies. Historically, there has been little concordance in antiretroviral therapy (ART)-restart criteria among ATI studies and our understanding of how different ART-restart criteria influence viral rebound dynamics remains incomplete [3]. The interactive viral rebound calculator (<http://jonathanlilab.bwh.harvard.edu/rebound-calc/>) was created as a pooled analysis of plasma viral loads (pVLs) of >700 participants from 12 ATI trials to predict HIV rebound after stopping ART [4].

The tool allows the user to set the ART-restart criteria to predict the percentage of 1) all participants, 2) post-treatment non-controllers (NCs), 3) and post-treatment controllers (PTCs) that would remain off therapy from week 1 through week 48. The interactive tool also allows the user to set an absolute pVL threshold or a multiweek threshold (e.g., pVL>1,000 for a duration of 4 weeks) as well as customize results based on: the timing of ART initiation, frequency of pVL measurements, ART regimens, therapeutic intervention arms, and PTC frequency (the default is the frequency identified in the CHAMP study of post-treatment controllers (PTCs) based on the criteria: pVL<400 cps/mL at 2/3 time points for 24 weeks post-ATI [3]). We also assessed how varying the threshold of suppressed time points and pVLs affected the frequency of PTC identification.

During ATI, investigators aim to balance safety issues of prolonged viremia with characterizing the effect of cure interventions such as: time to viral rebound, HIV viral set point and identification of PTCs. Although the time to viral rebound and set point data are easily quantifiable, PTC frequency calculations remain elusive as ART is often restarted before confirming controller status. Here, we compared the impact of several commonly used threshold pVL ART restart criteria (1,000 pVL, 1,000 pVL for 2 weeks, 1,000 pVL for 4 weeks [5], and 50,000 pVL for 4 weeks) on the ability of an ATI trial to detect PTCs as defined by the CHAMP definition [4]. The calculator applies the user's ART restart criteria to the dataset containing the 700+ participants pVL data to estimate the proportion of participants experiencing viral rebound and remaining off ART after treatment discontinuation (see Supplemental methods). In the CHAMP study, PTCs frequently had an early viral load peak before subsequent viral control off ART. Some of these PTCs may be missed depending on the ART restart criteria, which would have mandated the resumption of ART prior to demonstrating their natural ability to suppress virus. Our calculator predicted that these criteria would fail to identify 47%, 18%, 0%, and 0% of PTCs, respectively, due to premature ART restart. Of the four criteria, the 1,000 pVL for 1-week criterion had high specificity (99%), but low sensitivity (53%), while the 50,000 pVL for 4-week criterion had low specificity (12%), but high sensitivity (100%). The 1,000 pVL for 4-weeks criterion achieved a balance with 90% specificity and 100% sensitivity for identifying PTCs.

The definition of posttreatment control remains fluid and not yet standardized within the field. In addition to the calculator's ability to predict the number of CHAMP-defined PTCs identified by each ART restart criteria, we also evaluated five alternative PTC definitions, each changing one aspect of the CHAMP criteria (Supplemental Table 1): 1) VL suppression for 100% of timepoints; 2) VL suppression for 90% of timepoints; 3) VL threshold of 200 cps/mL; 4) VL threshold of 1,000 cps/mL; 5) Suppression for 48 weeks (Figure 1). Significantly fewer PTCs were identified in both the chronic and early-treated arms in definition 1, (100% suppression < 400 pVL, $p = .04$ and $.01$, respectively) and significantly more PTCs were identified in the chronic-treated arm in definition 4 (2/3 suppression < 1,000 pVL, $p = .03$). PTCs were more frequently identified in early-treated participants compared with chronic-treated participants in every iteration except for the final case, suppression for 48 weeks. Importantly, key characteristics (pre-ART VL, CD4 decline, baseline CD4+ count, peak VL, and peak VL week) remained comparable for the PTCs regardless of the specific PTC definition used (Supplemental Table 2).

One limitation of this analysis was the heterogeneity in frequency of viral load measurements during the ATI among studies, with some studies using weekly viral load monitoring, but other studies using less frequent monitoring. We also excluded participants on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy as it has been shown to impact viral rebound timing, likely due to the prolonged half-life of NNRTIs [6–8].

In summary, the results provide insights on the chances of identifying PTCs given different ART restart criteria and demonstrate that the expected frequency of post-treatment control is highly dependent on the viral load definitions used. The online calculator provides an interactive tool for estimating viral rebound outcomes and for supporting the design of ATI trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the participants, investigators, and site staff for all of the included studies.

Funding Statement

This work was supported in part by the Harvard University Center for AIDS Research (to Drs. Li and Gandhi, NIAID 5P30AI060354-08); National Institutes of Health (NIH) grants UM1 AI068634 (Statistical and Data Management Center of the AIDS Clinical Trials Group), UM1 AI068636 (AIDS Clinical Trials Group), subcontract from UM1 AI106701 to the Harvard Virology Support Laboratory (to Dr. Li).

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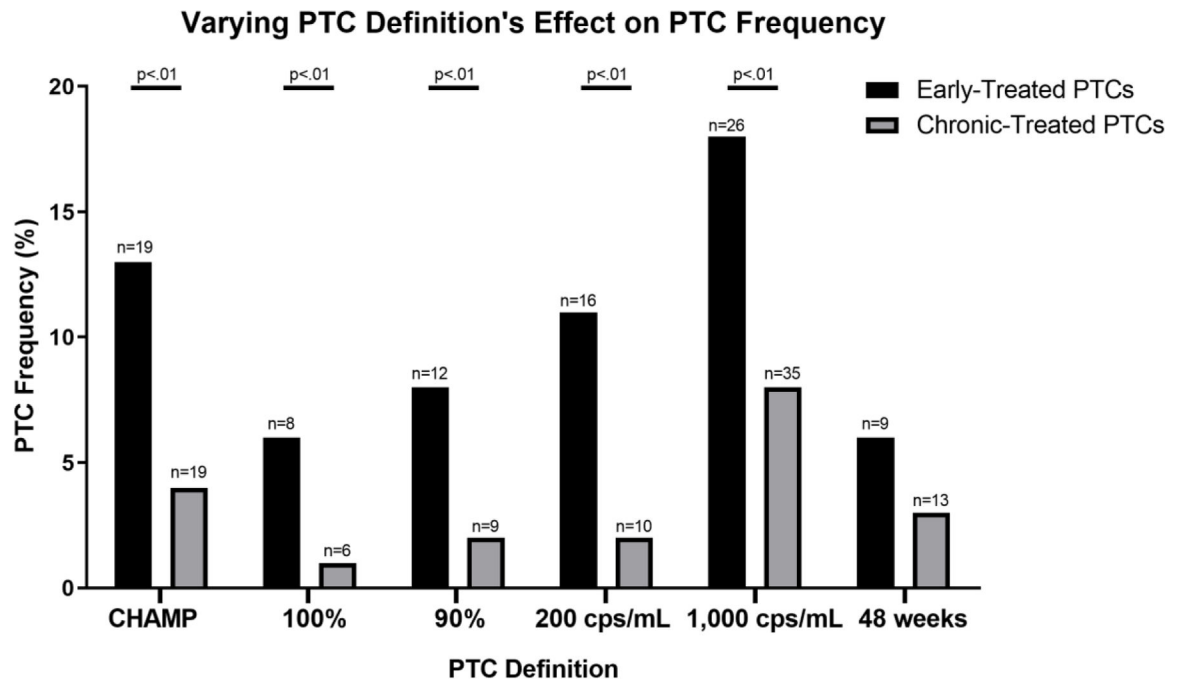


Figure 1. Effect of post-treatment controller definitions on estimated frequency of control. “CHAMP” refers to the post-treatment controller (PTC) criteria used in the CHAMP study: pVL<400 cps/mL at 2/3 time points for 24 weeks post-ATI. “100%” criteria = pVL<400 cps/mL at 100% of time points for 24 weeks post-ATI. “90%” criteria = pVL<400 cps/mL at 90% of time points for 24 weeks post-ATI. “200 cps/mL” criteria = pVL<200 cps/mL at 2/3 of time points for 24 weeks post-ATI. “1,000 cps/mL” criteria = pVL<1,000 cps/mL at 2/3 of time points for 24 weeks post-ATI. “48 weeks” criteria = pVL<200 cps/mL at 2/3 of time points for 48 weeks post-ATI. Frequencies were compared using Fishers exact test. n, refers to the number of PTCs identified in each condition.