A Moving Target: Impacts of Lowering Viral Load Suppression Cutpoints on Progress Towards HIV Epidemic Control Goals

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Running Head: Lowering VLS Cutpoints in Rakai, Uganda

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Conflicts of Interest
The authors have no conflicts of interest to disclose.

Ethical Statement
The study was approved by the Uganda Virus Research Institute Research and Ethics Committee and the Johns Hopkins University School of Medicine Institutional Review Board. This project was reviewed in accordance with CDC human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes.

Word Count: 989/1,000

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

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1   **Summary**

2   Redefining viral load suppression (VLS) using lower cutpoints could impact progress towards

3   the UNAIDS 95-95-95 targets. We assessed impacts of lowering the VLS cutpoint on achieving

4   the 95-95-95 VLS target in the Rakai Community Cohort Study. Population VLS fell from 86%

5   to 84% and 76%, respectively, after lowering VLS cutpoints from <1,000 to <200 and <50

6   copies/mL. The fraction of viremic persons increased by 17% after lowering the VLS cutpoint

7   from <1,000 to <200 copies/mL.

8   **Key Words**: viral load suppression, viral load cutpoint, Fast-Track targets, population-based

9   study, Uganda

10   The 95-95-95 Fast-Track targets proposed by the Joint United Nations Programme on

11   HIV/AIDS (UNAIDS) are ambitious goals for HIV elimination by 2030.[1] To reach the "third

12   95", 86% of people living with HIV (95% of whom are receiving antiretroviral therapy (ART))

13   must achieve viral load suppression (VLS). The World Health Organization (WHO) defines VLS

14   as <1,000 RNA copies/mL,[2] a threshold associated with reduced HIV transmission risk.[3,4] This

15   definition is also used by national surveys in Africa, including the population-based HIV impact

16   assessments.[5]

17   A VLS cutpoint of <1,000 copies/mL, however, potentially underestimates the proportion

18   of individuals on ART experiencing negative consequences of viremia. A study in Lesotho

19   estimated that 94% of treatment-experienced persons with viral loads 80-999 copies/mL

20   harbored drug-resistant mutations.[6] Likewise, persistent low-level viremia (50-999 copies/mL

21   over ≥6 months) has been linked to subsequent virologic failure and drug resistance.[7] These

22   findings, coupled with rising levels of HIV drug resistance across Africa, have prompted calls to

23   redefine VLS using lower cutpoints.[8,9]

24   In addition to identifying persistent low-level viremia of potential clinical significance,

25   lowering VLS cutpoints will also result in the detection and escalated management of people

26   experiencing clinically insignificant transient viremia, or viral "blips". Emerging evidence also

27   suggests viremic blips of low magnitude (<500 copies/mL) unassociated with subsequent

28   virologic failure are common in persons with prolonged ART use.[10] Implementing more

29   conservative VLS cutpoints could, therefore, prompt unwarranted switching of suppressed

30   persons to second- or third-line ART regimens, which remain scarce in many higher-burden

31   countries.[11] Lowering existing VLS cutpoints could also increase the proportion of people on

32   ART requiring enhanced clinical monitoring and intensive adherence support, which could

33   further strain already under-resourced health systems in hyperendemic settings.

34   To assess the impact of using different VLS cutpoints in estimating progress towards the

35   95-95-95 targets, we used data from the Rakai Community Cohort Study (RCCS), an open,

36   population-based prospective study of 40 communities in south-central Uganda.[12] After

37   providing written informed consent, RCCS participants undergo rapid HIV testing using a

38   validated three-test algorithm followed by confirmatory enzyme immunoassays,[13] and viral load

39   testing is performed on stored plasma using the Abbott RealTi*m*e HIV-1 assay (Abbott

40   Molecular, Inc., Des Plaines, IL). We estimated VLS by calculating the proportion of persons

41   with undetectable viral loads or exhibiting viremia below specific cutpoints over three survey

42   intervals: February 2015 to September 2016 (midpoint: November 2015), October 2016 to May

43   2018 (midpoint: July 2017), and June 2018 to October 2020 (midpoint: August 2019).

44   First, we estimated population viral load among persons with detectable viremia ($\geq$50

45   copies/mL) and ART coverage (prevalence of self-reported ART use), respectively. We used

46   Wilcoxon rank-sum tests to evaluate whether observed changes in population viral load over

47   time were statistically significant ($p<0.05$). Next, to evaluate the impact of VLS cutpoints on

48   Fast-Track target achievement, we ascertained the sensitivity of population VLS estimates

49   against four different VLS cutpoints: <1,000, <400, <200, and <50 copies/mL (the latter

50   approaching the lower limit of detection for many viral load assays). Lastly, among persons with

51   detectable viremia, we examined the distribution of viral copy counts to estimate the relative

52   increase in the fraction of unsuppressed persons if VLS cutpoints were lowered.

53   Overall, 5,814 individuals (median age: 33 years, 63% women) contributed 10,418

54   observations over three survey intervals (2015: *n*=3,606, 2017: *n*=3,590, 2019: *n*=3,222). Across

55   cutpoints (**Figure 1A**), population VLS increased significantly over time, with detectable

56   viremia declining from a median of 9,136 copies/mL (interquartile range [IQR] 2,467-34,434) in

57   2015 to 2,516 copies/mL (IQR 150-22,101) in 2019 ($p<0.001$). These reductions in population

58   viremia coincided with substantial increases in ART coverage, from 67% (95% confidence

59   interval [CI] 65-68%) in 2015 to 85% (CI 83-86%) in 2019.

60   By 2019, population VLS met the 95-95-95 target using a cutpoint of <1,000 copies/mL

61   (86%, CI 85-87%). However, when using the most conservative cutpoint of <50 copies/mL,

62   population VLS declined to 76% (CI 74-77%). When restricted to persons reporting ART use

63   ($n=2,725$), population VLS remained below the 95% target (83%, CI 82-85%) when using a

64   cutpoint of <50 copies/mL. Among persons with detectable viremia in 2019 ($n=788$), lowering

65   the VLS cutpoint from <1,000 to <200 copies/mL would increase the proportion of unsuppressed

66   persons by 17% (**Figure 1B**).

67   Our study provides evidence that estimates of the "third 95" at a population level are

68   highly sensitive to VLS cutpoints. Relative to a more conservative clinical VLS cutpoint of <50

69   copies/mL, a cutpoint of <1,000 copies/mL, per WHO recommendations, overestimated 95-95-

70   95 Fast-Track target achievement in our sample by ~10% on an absolute scale. This relationship

71   persisted even after restricting population VLS measures to persons reporting ART use.

72   Lowering VLS cutpoints would, therefore, require reassessment of countries and subnational

73   units meeting the "third 95" using a <1,000 copies/mL cutpoint. Multilateral agencies and donors

74   must be prepared to articulate justifications for lowering VLS cutpoints and manage expectations

75   surrounding revisions to Fast-Track target achievement, ensuring investments in HIV treatment

76   programs are sustained, rather than abandoned, if progress towards the "third 95" is revisited.

77   Furthermore, we found that by lowering the VLS cutpoint from <1,000 to <200

78   copies/mL, the fraction of persons classified as unsuppressed increased by 17%. This would

79   represent a substantial population-level increase in the number of individuals requiring enhanced

80   clinical monitoring (e.g., intensive ART adherence support, increased care appointment

81   frequency). While vigilance around lower-level viremia may be clinically indicated, the abrupt

82   growth in persons requiring enhanced clinical support may be challenging for health systems to

83   manage without additional resources and investments. Updated clinical guidelines with

84   algorithms for switching individuals to second- or third-line ART in the context of persistent

85   lower-level viremia are also warranted.

86   Irrespective of VLS cutpoints, our findings highlight remarkable achievements in HIV

87   epidemic control, largely attributable to the scale-up of combination HIV interventions and

88   universal ART provision in south-central Uganda.[14] Continued transitioning of persons stable on

89   ART to differentiated service delivery models, coupled with promising testing and treatment

90   technologies in the development pipeline (i.e., long-acting ART, point-of-care viral load assays),

91   may accelerate momentum towards HIV elimination in this setting.

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Figure 1. Viral load suppression prevalence (Panel A) and the distribution of viral copy counts among viremic ($\geq$50 copies/mL) persons living with HIV (Panel B), by calendar period.

A

B