Published in final edited form as:

J Acquir Immune Defic Syndr. 2013 June 1; 63(2): e84–e86. doi:10.1097/QAI.0b013e31828ed2e4.

Measuring the Unknown: Calculating Community Viral Load among HIV-Infected MSM Unaware of their HIV Status in San Francisco from National HIV Behavioral Surveillance, 2004-2011

Moupali Das, MD, MPH^{1,2}, H.Fisher Raymond, DrPH, MPH¹, Priscilla Chu, DrPH, MPH¹, Israel Nieves-Rivera, BS¹, Mark Pandori, PhD, HCLD(ABB)^{1,2}, Brian Louie, BS¹, Leah Rauch, CLS¹, Susan Scheer, PhD, MPH¹, Eric Vittinghoff, PhD², and Willi McFarland, MD, PhD, MPH, TM^{1,2}

¹San Francisco Department of Public Health;

²University of California, San Francisco

“Community viral load” (CVL), broadly defined as the mean, median, or total viral load (VL) of a population of persons living with HIV, has been posited as one measure that may provide both an indicator of burden of disease (e.g., higher proportions of patients virally suppressed by antiretroviral treatment [ART] will lower CVL, thus tracking treatment benefit) and as an indicator of potential epidemic propagation (e.g., more persons in a population with high VL point to increased likelihood of onward transmission for a given level of risky behavior).¹⁻³ CVL may be calculated for a clinic population,⁴ for persons participating in studies,^{5,6} or from public health surveillance case registries if VL data are systematically abstracted.¹⁻³ For example, we previously reported a mean CVL of 23,348 copies per mL for 2005-2008 using data from the San Francisco HIV/AIDS surveillance case registry, which contains an estimated 95% of all HIV-infected individuals diagnosed in the city.¹ However, a limitation of calculating CVL from surveillance data of reported cases as a measure of population-level viremic burden and transmission potential is the omission of people living with HIV who are not yet diagnosed and thus not reported to surveillance.^{1,7,8} Moreover, persons unaware of their HIV infection may have higher VLs by virtue of not being treated with ART and by the high viremia characteristic of acute/early infection.^{1,7,8}

The National HIV Behavioral Surveillance (NHBS) system provided an opportunity to fill one gap in our surveillance-derived estimation of CVL for men who have sex with men (MSM), who comprise 90% of HIV/ AIDS cases in San Francisco. The NHBS is a CDC-coordinated series of population-based, cross-sectional surveys among populations at risk for HIV in 21 US cities, and was conducted among MSM in San Francisco in three waves in 2004, 2008, and 2011.⁹ The survey methods comprised time-location sampling with random selection of venues where MSM congregate and recruitment of MSM attending the venues.

For correspondence and reprints, contact: Moupali Das, MD, MPH San Francisco Department of Public Health 25 Van Ness Avenue, Suite 500 San Francisco, CA 94102 Phone: (415) 437-6204 Fax: (415) 437-4693 dasm@php.ucsf.edu.

Meetings at which parts of the data were presented: None

Conflicts of Interest: None

Disclosures: None

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

A risk and preventive behavioral questionnaire was completed anonymously. Data included past HIV testing history and self-reported results of their most recent test. In the field, standard venipuncture was done for HIV testing and incidence testing. The present analysis focuses on HIV-positive MSM who reported being undiagnosed; that is, they tested positive in the NHBS survey but reported their most recent test was negative or that they had never previously been tested.

We measured plasma HIV-1 RNA copies/mL on remnant specimens from MSM who reported being undiagnosed using Abbott Real Time HIV-1 assay. From these results, we calculated median, mean, and log mean CVL and the percent of samples in which no virus was detected or was below the limit of detection at <40 copies/mL. Temporal trends across the three survey waves were assessed using linear and logistic models. We report interquartile ranges for the median CVL and confidence intervals (CIs) obtained using bootstrap procedures for the mean and log mean; we report exact binomial CIs for the proportions. The original protocols, including specimen banking for future analyses, were approved by the University of California, San Francisco Committee on Human Research.

From 2004 to 2011, there was a decline in the number of HIV-infected MSM in NHBS who reported being unaware of their infection from 21.7% [13.2-30.3] in 2004, to 18% [10.9-25.2] in 2008, and 7.5% [2.4-12.7] in 2011 ($p=0.025$).⁹ Over all three years, 23% (11/48) of the stored specimens did not contain sufficient quantity to measure VL. Median, mean, and log mean CVL are shown in the Table. Mean CVL was 23,013 copies/mL in the 2004 survey and 4,980 copies/mL in 2011; median CVL was 4,237 copies/mL in 2004 and 3,318 copies/mL in 2011. No trends in any of the CVL measures over time were statistically significant. Of note, no virus was detected in 25% (5/19) of the samples from MSM who reported being undiagnosed in 2004, 18% (2/11) in 2008, and 43% (3/7) in 2011. These numbers of persons with no detectable virus are higher than expected from persons with untreated HIV infection; possible explanations include the approximately 1 in 300 of HIV-infected individuals known as elite controllers who would be expected to be durably aviremic without ART,¹⁰ laboratory error, poor specimen, or persons on ART not being forthcoming about their HIV-infected status prior to the study test. As a sensitivity analysis for the latter possibility, we calculated mean CVL only among those with detectable VLs, which increased the estimates slightly, but these differences were not statistically significant.

The time captured by the three waves of NHBS coincides with a period of local efforts to expand coverage and frequency of HIV testing for MSM and other populations at risk for HIV and to promote earlier initiation of ART.^{1,4,9} The decline in the proportion of HIV-infected MSM who were unaware of their HIV status in our data appears to corroborate the impact of these efforts.

While our approach attempts to fill a gap in the calculation of CVL from case registry data for the population of MSM in San Francisco by evaluating CVL of those MSM who reported being un diagnosed, we recognize limitations that may bias results downward. First, the main limitation of our study is that the proportion of individuals testing HIV-positive without detected virus is unexpectedly high for a population purporting to not be on ART. Only 0.3% (1 in 300) of HIV-infected individuals are elite controllers who would be expected to be durably aviremic without ART; this is unlikely to explain the current results.¹⁰ The most likely explanation is that these MSM denied already knowing their HIV-positive serostatus when they were in fact aware of their diagnosis and undetectable because they were on ART. A key way to address this would have been to measure ART levels in specimens. Unfortunately, additional specimens were not available for ART level detection. The point estimates of CVL measures calculated excluding the undetectable specimens, as expected, were slightly higher, although within reasonable margins of error. Laboratory

error or deterioration of viral RNA in handling and storage could also reduce the count to undetectable levels for some specimens while yielding lower counts for others; however, our laboratory conducted quality control studies with comparable archived specimens with no indication of viral decay. Second, our study does not include persons in the acute phase of infection where their antibody test would be negative yet their VL is likely to be very high.^{7,8} This gap in the calculation of CVL will be very difficult to fill as such acutely infected persons will rarely be detected in population-based surveys. The challenge compounds interpretation of CVL as an indicator of transmission potential as persons acutely infected may account for a disproportionate number of onward infections.⁸ Third, there were very few MSM who reported being undiagnosed, particularly in the last year. While it is welcome information that the proportion of persons unaware of their infection is low and decreasing, the small sample size increases the uncertainty in our estimates of CVL. The challenges of small sample size, the absence of acutely infected individuals, and possible misclassification of undiagnosed individuals could be addressed by including the measurement of VL and ART levels and calculation of CVL across other cities involved in the NHBS, and the quality, handling, and storage of specimens collected specifically for RNA testing and ART levels could be improved in studies specifically designed to measure VL, ART use and to calculate CVL. The NHBS system was designed to track HIV prevalence and measures of risk for MSM and other populations between cities and over time in order to complete the picture of the epidemic outside of case reporting and surveillance. It has long been recognized that HIV case reporting and HIV prevalence are not sufficient measures to track the full burden of disease nor the full potential for further transmission, a point all the more true in the current era of wider use of ART and reduction in transmission due to ART-mediated virologic suppression.¹¹ The addition of VL and ART levels to calculate CVL and objectively measure ART use to the NHBS system would augment estimates of CVL from surveillance registries and add one more indicator to interpret epidemic trends that is well-suited to the high impact prevention era of expanded testing and ART. Moreover, direct measures of HIV incidence and acute infection also face logistical and theoretical challenges and are consequently rare on a population level. We recognize that CVL has limitations; nonetheless, taken in the context of expanded HIV testing, ART uptake, and linkage and engagement efforts to promote earlier and durable viral suppression, the measure provides additional insight into our efforts to mitigate the effects of HIV disease among those infected and thereby reduce transmission. Examining CVL trends in upcoming international individual and community cluster randomized trials of ART as prevention¹² will further refine our current understanding of the relationship between population-level viremic burden and HIV transmission.

Acknowledgments

Sources of support: Centers for Disease Control and Prevention

References

1. Das M, Chu PL, Santos GM, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS One*. 2010; 5(6):e11068. [PubMed: 20548786]
2. Castel AD, Befus M, Willis S, et al. Use of the community viral load as a population-based biomarker of HIV burden. *Aids*. Jan 28; 2012 26(3):345–353. [PubMed: 22008660]
3. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet*. Aug 14; 2010 376(9740):532–539. [PubMed: 20638713]
4. Geng EH, Hare CB, Kahn JO, et al. The effect of a “universal antiretroviral therapy” recommendation on HIV RNA levels among HIV-infected patients entering care with a CD4 count

greater than 500/muL in a public health setting. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Dec; 2012 55(12):1690–1697. [PubMed: 22955429]

5. Jain V, Liegler T, Kabami J, et al. Assessment of Population-Based HIV RNA Levels in a Rural East African Setting Using a Fingerprick-Based Blood Collection Method. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb; 2013 56(4): 598–605. [PubMed: 23243180]
6. Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ*. 2009; 338:b1649. [PubMed: 19406887]
7. Smith MK, Powers KA, Muessig KE, Miller WC, Cohen MS. HIV Treatment as Prevention: The Utility and Limitations of Ecological Observation. *PLoS Med*. Jul.2012 9(7):e1001260. [PubMed: 22802740]
8. Cohen MS, Dye C, Fraser C, Miller WC, Powers KA, Williams BG. HIV Treatment as Prevention: Debate and Commentary-Will Early Infection Compromise Treatment-as-Prevention Strategies? *PLoS Med*. Jul.2012 9(7):e1001232. [PubMed: 22802728]
9. A new trend in the HIV epidemic among men who have sex with men, San Francisco, 2004-2011. *Journal of acquired immune deficiency syndromes*. Jan.2013 17
10. Walker BD. Elite control of HIV Infection: implications for vaccines and treatment. *Top HIV Med*. Aug-Sep;2007 15(4):134–136. [PubMed: 17720999]
11. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11; 2011 365(6):493–505. [PubMed: 21767103]
12. Granich R, Gupta S, Suthar AB, et al. Antiretroviral therapy in prevention of HIV and TB: update on current research efforts. *Curr HIV Res*. Sep; 2011 9(6):446–469. [PubMed: 21999779]

Table

Measures of Community Viral Load (CVL) among HIV-infected MSM who reported being undiagnosed in San Francisco; 2004, 2008, and 2011.

Measure	MSM NHBS 1	MSM NHBS 2	MSM NHBS 3	p-value (trend)
Year	2004	2008	2011	
(Assayable samples/ Total N); % [95% CI]	(19/20); 95% [75-100%]	(11/21); 52% [30-4%]	(7/7); 100% [59-100%]	0.20
Median CVL (copies/mL); [Interquartile Range]	4,237; [1-40,234]	896; [47-6,860]	3,318; [1-8,211]	0.35
Mean CVL (copies/mL), [95% CI]	23,013; [(10,619-43,999)]	11,412; [1,690-32,574]	4,980; [782-11,184]	0.16
Mean CVL excluding undetectable, [95% CI]	31,231; [13,461-57,370]	13,947; [2,336-45,241]	8,713; [4,002-18,639]	0.17
Log Mean CVL; [95% CI]	6.73; [4.67, 8.53]	6.42; [3.92-8.26]	5.06; [0, 8.45]	0.43
(Suppressed/Assayable samples) %; [95% CI]	(5/19); 25% [9-51%]	(2/11); 18% [2-52%]	(3/7); 43% [10-82%]	0.61