Guidance on Community Viral Load:
A Family of Measures, Definitions, and Method for Calculation

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Contents

Executive Summary

The Division of HIV/AIDS Prevention at the Centers for Disease Control and Prevention (CDC) was charged by the National HIV/AIDS Strategy to provide "technical assistance to [HIV reporting] localities to collect data to calculate community viral load" [1]. ***Guidance on Community Viral Load: A Family of Measures, Definitions, and Method for Calculation*** represents the work of over 50 Workgroup members from more than 25 jurisdictions. This Guidance document introduces the concept of community viral load and provides definitions of, and methods for calculating, community viral load and related measures.

During the past few years, there has been great interest in the scientific literature and at scientific meetings about a new public health HIV measure called "community viral load." It is a population-based measure of HIV-infected individuals' concentration of plasma HIV-1 RNA (viral load). When viral loads are summed across a community and then divided by the number of HIV-infected persons in the community, the average HIV community viral load represents the level of viremia for a geographic area during a defined time. Having a single number that is an indicator of HIV transmission potential and quality of HIV care and treatment for a geographic area is extremely attractive.

For community viral load to be a robust measurement, it must reflect the viral loads of persons diagnosed with HIV, be a reliable measure that is also sensitive to viral load changes in the community, and reflect sexual behaviors or other HIV transmission risks in the community. This measure could be used by local HIV reporting jurisdictions each year to assess progress in treating HIV-infected persons with antiretroviral medications that would lower the community's viremia, which could—potentially—reduce transmission within the community. Community viral load may also have some utility in monitoring the progress of national HIV care and treatment objectives when assessed over time.

During the process of examining local and federal HIV surveillance activities and the data obtained from such activities, a number of issues were identified that may impact the ability of a jurisdiction to successfully and accurately estimate a population's viral load. These include:

- Population selection. A well-defined population should be chosen, possibly even a closed population, so that those who are at risk for transmitting HIV and those at risk for acquiring HIV can be identified and counted, all within a defined geographic area that may not correspond with jurisdictional boundaries.

- Varying definitions of "community viral load." There are many analyses that report "community viral load" and the methods and definitions used for each varies somewhat. The history of the community viral load concept and an inventory of community viral load analyses highlight these differences and the varying methods used to calculate community viral load (Appendix A and Table 2). Ideally, measures of community viral load and its related terms should use a common method that would, at a minimum, allow for periodic snapshots to assess changes over time by a jurisdiction, as well as allow for comparisons across localities.

- Complete and accurate surveillance/health data. Locations with universal health coverage or a common source of healthcare will fare better than those areas without such infrastructure because the latter will need to create composite data from disparate sources. In addition, jurisdictions have reported significant amounts of missing viral load results for HIV-infected persons, which may bias community viral load estimates. This

> may be due to a large proportion of HIV-infected persons being out of care in a jurisdiction, or data quality issues for a jurisdiction, or both.

This document proposes a family of viral load measurements, of which one is Community Viral Load (Figure 2); other measures include: Population Viral Load, In-Care Viral Load, and Monitored Viral Load. Technical guidance for estimating Community Viral Load, In-Care Viral Load, and Monitored Viral Load are provided. Analytic methods and tools (spreadsheet and SAS code) for calculating mean viral load, percentage with suppressed viral load (≤200 copies/mL), percentage with undetectable viral load (≤50 copies/mL), and for assessing a statistical difference between two mean viral load measures will be made available by CDC to HIV surveillance coordinators. While this Guidance document is intended primarily for HIV surveillance coordinators to be able to calculate Community Viral Load measures for their jurisdictions, it should be recognized that the ability to do so does not rest solely with the HIV surveillance system (see Appendix B for description of surveillance and viral load issues). Using viral load measures to monitor the epidemic is a function of policy, care and treatment, and surveillance as illustrated below:

Policy
- HIV treatment guidelines (when/how often viral load test recommended; see Appendixes C and D)
- Reporting policies for laboratory tests (vary by jurisdiction)
- Jurisdictional data sharing
  - Sharing surveillance data across jurisdictions
  - Facilities and institutions (private, federal) sharing data with surveillance

Practice
- Medical care practice of requesting viral load tests
- Laboratory reporting practices and number of laboratories in a jurisdiction
- Reach of HIV testing and linkage to care programs

Surveillance
- Entry/upload of laboratory reports
- Death ascertainment
- Deduplication of records (intra- and interstate)
- Missing data

The effective monitoring of Community Viral Load measures and ultimately documenting progress towards the National HIV/AIDS Strategy goals of reduced HIV incidence and improved health outcomes for persons living with HIV infection in the United States (see Appendix E) requires translation of concepts developed in a few jurisdictions to relevant measures that can be used in all jurisdictions. This document acknowledges the complexity of doing so and offers practical options for measurements under various scenarios where policy, practice, and surveillance intersect.

History of Community Viral Load

In early 2009, based on a mathematical model for South Africa, Granich et al. suggested that universal HIV testing and immediate treatment with antiretroviral medications among persons with heterosexually acquired HIV infection could lead to virtual elimination of HIV disease in 50 years [2]. The underlying mechanism by which this could be possible is to reduce the amount of virus circulating in a person's bloodstream (HIV plasma viral load) by consistent and early use of antiretroviral medications. As the level of viremia and viral shedding decreases, infectiousness also decreases, greatly reducing or eliminating the transmission of HIV [3,4]. A 2004 study in Taiwan demonstrated that free access to HIV antiretroviral medications for HIV-infected persons decreased HIV transmission [5].

The earliest use of "community viral load" occurred in 2008 at the Conference of Retroviruses and Opportunistic Infections by Ronald Stall [6]. Based on the work of Millett et al. [7], the high prevalence of untreated HIV infection was used to explain the disproportionately high rates of HIV infection among African American men who have sex with men (MSM). Due to lack of treatment and a resulting high viremia, the African American MSM community was described to have a much higher "community viral load" than other MSM communities, which accounted for more efficient transmission of HIV and higher infection rates.

One of the first cohort studies to examine HIV concentration levels in the blood of injecting drug users (IDUs) from Vancouver, Canada was published in 2009 [8]. Wood et al. studied a well-described population of IDUs that was followed every six months for more than 11 years. HIV viral loads, HIV diagnostic testing, and antiretroviral therapy were monitored for this population and community plasma HIV-1 RNA concentrations over time were ascertained. A statistically significant correlation between the median IDU community viral load and the incidence of new HIV infections was observed. Furthermore, in their analysis, Wood found that when the community viral load among IDUs decreased to <20,000 copies/mL, the association with HIV incidence ceased.

In June 2010, Das et al. published a paper on community viral load in San Francisco [9]. Das and colleagues found a significant association between a declining community viral load and a decline in new HIV diagnoses from 2004 to 2008. Additionally, the authors presented viral load data in novel ways that examined geographic distribution of mean viral load by demographic, risk, and socioeconomic factors. Montaner et al. (2010) published data that helped provide the final link in the mechanism that described viral loads and transmission [10]. Using the community of British Columbia, Canada, they demonstrated that, over time, increased use of antiretroviral therapy was associated with a decrease in the population's viral load and, ultimately, a decrease in new HIV infections.

Collectively, these papers have galvanized the HIV prevention and surveillance communities and spurred analyses exploring the relationship between community viral load and newly diagnosed and reported cases and estimated HIV incidence (see Appendix A, Inventory of VL Analyses).

In addition to ecological analyses suggesting benefits of reduction in community viral load for population-level HIV prevention, use of antiretroviral therapy by the HIV seropositive partner has been shown to be associated with lower HIV incidence in the seronegative partner [3, 11]. Data from the HIV Prevention Trials Network (HPTN) 052/AIDS Clinical Trials Group (ACTG) 5245 have also found that antiretroviral treatment of an HIV-infected partner reduced transmission to the uninfected partner [4]. These data lend support to the Test-and-Treat

strategy [12, 13] that proposes to decrease HIV transmission through the following two pathways:

- HIV testing identifies HIV-infected persons who, after learning their status, adopt safer behaviors, which decreases HIV transmission [14].

- HIV-infected individuals who initiate antiretroviral treatment, maintain high levels of adherence, and achieve viral suppression are less infectious, which decreases HIV transmission.

Figure 1. Test and Treat concept

To optimize health outcomes, however, expanded testing efforts must be coupled with initiatives that ensure the newly diagnosed and those already known to have HIV infection are effectively linked to HIV care [15], receive antiretroviral treatment as indicated, and achieve optimal adherence and suppression of viral replication. (See Appendix D.)
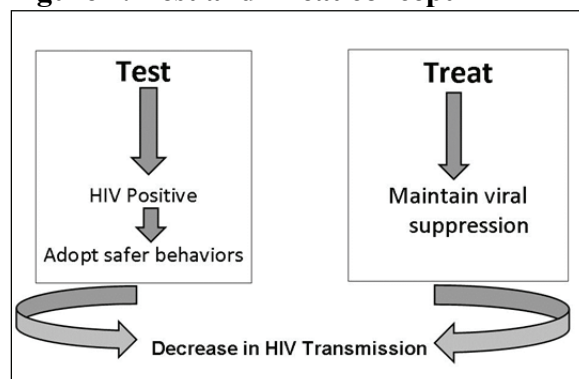
A recently launched National Institutes of Health (NIH) and CDC-supported study, HPTN065 (TLC-Plus), aims to evaluate the feasibility of an enhanced community-level test, link to care, plus treat strategy in the United States. The study is being conducted in two intervention communities (the Bronx, New York and Washington, D.C.) and four non-intervention communities (Chicago, Illinois; Houston, Texas; Miami, Florida; and Philadelphia, Pennsylvania). HIV test sites that identify new HIV-infected patients will be randomized to one of two interventions: 1) financial incentives or 2) standard-of-care. Each intervention will be assessed for success in linkage to HIV care and for achieving and maintaining viral suppression among these newly diagnosed patients. The study outcomes will be evaluated using jurisdictional and national HIV surveillance data. Results from this 3-year study are expected in 2013. Appendix F includes a list of Test and Treat clinical trials.

Given the interest in, and utility of, measurement of community viral load for monitoring HIV infections, it is critical to have guidelines so that various measures are comparable across time and across jurisdictions. These guidelines form the basis for CDC's evaluation of the National HIV/AIDS Strategy goals and can be used to evaluate local Test and Treat initiatives.
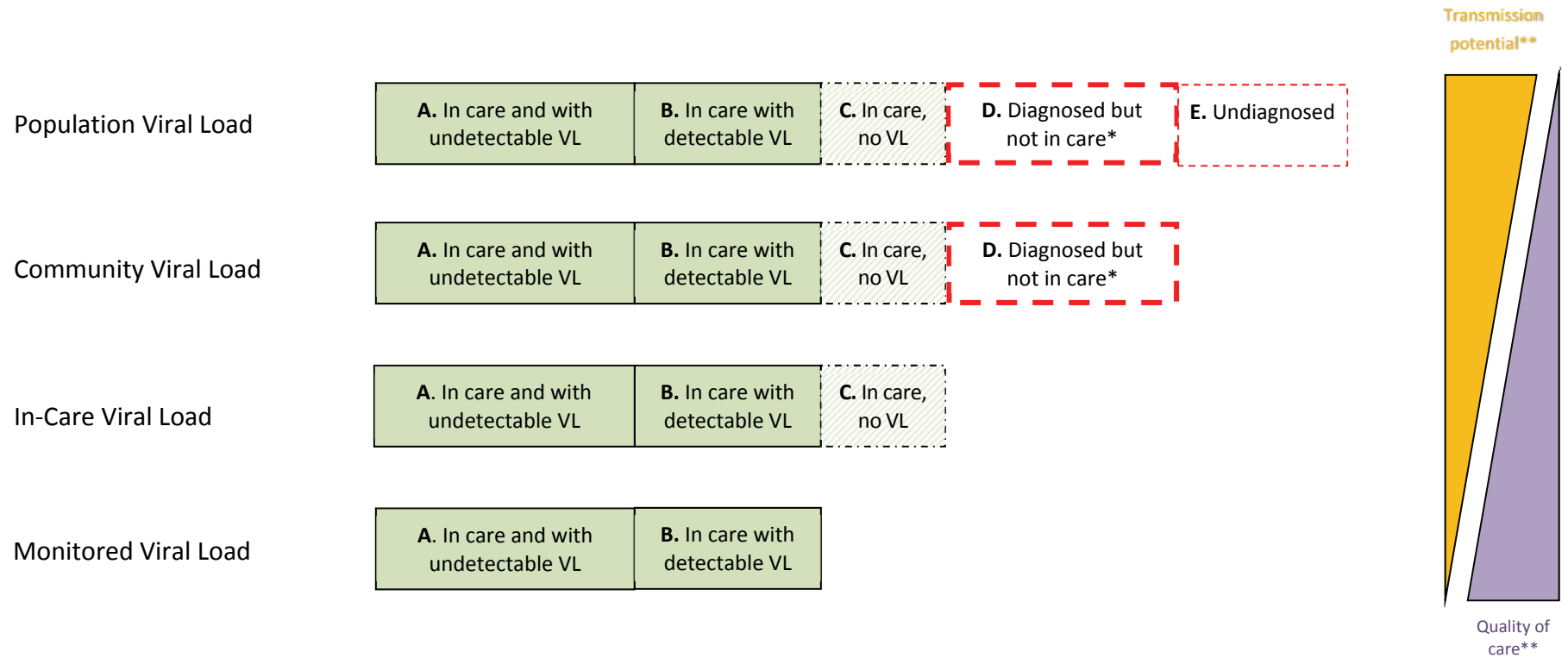
Establishing a Common Language

Researchers have interpreted community viral load differently (see Table 2 and Appendix A, Inventory of VL Analyses). Related community viral load terms and measures are being developed and it is not the intent of this document to catalogue each one. Instead, this document will propose some basic common language to encompass the original spirit and aspiration of HIV prevention, and suggest some measures or indicators from HIV surveillance that could be used by localities or by the nation, over time, as snapshots of primary, secondary, and tertiary HIV prevention efforts. Figure 2, Conceptual framework for viral load measurements among HIV-infected persons, depicts the four proposed Measures (capital M) of viral load (VL) for a given HIV-infected population and their component and categorical VL measures (lowercase m). Component VL measures include: A. In care and with undetectable VL; B. In care with detectable VL; C. In care, no VL; D. Diagnosed but not in care; and E. Undiagnosed. Categorical measures of viral load are described in the **Technical Guidance** section.

Population Viral Load is a conceptual Measure, unable to be directly calculated, that includes viral loads of <u>all HIV-infected persons</u> in the population, both those unaware of their HIV status (undiagnosed) and those who are aware of their HIV status (diagnosed), whether or not linked and retained in HIV care. Population Viral Load is the most comprehensive Measure of the HIV transmission potential for a given population. Population Viral Load Measure could apply, in principle, to the whole nation, individual states, and specific jurisdictions; however, viral load measurements for subgroups depicted in boxes C, D, and E in Figure 2 are typically not available in the local or national HIV surveillance databases. The shortcomings of available data and nascent methodology for its modeling (including data imputations for persons in boxes C–E in Figure 2), has precluded the estimation of Population Viral Load to date. An estimated 21% of HIV-infected Americans are living with undiagnosed HIV infection [16] (box E, Figure 2) and, thus, their HIV viral loads are unknown but are likely detectable and elevated in the absence of antiretroviral therapy. These persons, who may practice unsafe sex while unaware of their HIV infection, are thought to contribute to the majority of new, sexually acquired HIV infections in the United States [17].

Viral load data are not available for all persons that have been diagnosed with HIV infection. A significant proportion of such persons are not in care at a given point in time (either never linked to HIV care or not retained in continuous care) and, therefore, may not have HIV viral load monitoring performed (box D, Figure 2). It can be assumed that most of these persons have detectable/not suppressed viral loads as they are unlikely to be receiving continuous, effective antiretroviral therapy; however, the actual distribution of their viral loads is not known (in the absence of special studies). Finally, a fraction of persons that are in care may be missing HIV viral load in HIV surveillance for a variety of reasons, including: incomplete or delayed reporting of viral loads from laboratories to the surveillance system, undetectable viral loads not reportable, viral load results that have not been entered into the surveillance database, patient refusal of HIV disease monitoring, receiving medical care but out of HIV care, and no viral load testing (box C).

Figure 2. Conceptual framework for viral load (VL) measures among HIV-infected persons

Transmission potential**

Population Viral Load

| **A.** In care and with undetectable VL | **B.** In care with detectable VL | **C.** In care, no VL | **D.** Diagnosed but not in care* | **E.** Undiagnosed |

Community Viral Load

| **A.** In care and with undetectable VL | **B.** In care with detectable VL | **C.** In care, no VL | **D.** Diagnosed but not in care* |

In-Care Viral Load

| **A.** In care and with undetectable VL | **B.** In care with detectable VL | **C.** In care, no VL |

Monitored Viral Load

| **A.** In care and with undetectable VL | **B.** In care with detectable VL |

Quality of care**

* No current lab results, including viral load

** Relative indicator for each Measure

Estimates based on national projections and may vary across U.S. states and jurisdictions. Relative sizes of each box are approximated from Gardner et al., *Clin Infect Dis*, 2011 and Burns et al., *Clin Infect Dis*, 2010.

The VL of persons in care but lacking VL in surveillance data represent a heterogeneous group. Persons that are missing VL results because of surveillance processes (e.g., VL results that haven't been entered in the surveillance database) may have VL results similar to other persons in care and with VL results, whereas persons missing VL because they are refusing VL monitoring may have high VL, especially if they are also refusing antiretroviral therapy. To minimize the size and heterogeneity of persons in care but without VL, local health departments should work closely with the laboratories to assess, improve, and maintain the inflow of data and should promote policies for reporting of all detectable and undetectable HIV viral loads to surveillance systems.

Community Viral Load describes viral load of all <u>HIV-infected persons diagnosed</u> with HIV infection in a given population. As with "Population Viral Load," viral load measurements for persons that are 'diagnosed but not in care' (box D, Figure 2) are typically missing as is information for those 'in care, no VL' (box C). In order to estimate Community Viral Load as accurately as possible, local public health jurisdictions should implement programmatic activities to expand and routinize HIV testing [18] so that the proportion of 'undiagnosed' (box E) is as small as possible, and maximize linkage to and retention in care of HIV-diagnosed persons so that the proportion of 'diagnosed but not in care' (box D) is as small as possible. In jurisdictions where (i) the percentage of persons that are in care but have missing viral loads and persons that are diagnosed but not in care (boxes C and D, respectively) when combined is less than 25% of persons, and in particular, if (ii) additional data relating to care and health status are available (such as history of antiretroviral therapy, insurance status, opportunistic infections, and engagement in care), techniques such as multiple imputation may be considered in modeling Community Viral Load for the total diagnosed population (in and out of care). However, the limitations of multiple imputation and the lack of additional data make calculation of Community Viral Load not feasible for most jurisdictions at this time. Methodologies for such analyses are an active area of research.

In-Care Viral Load includes both the readily observable HIV viral loads of persons who have <u>accessed the healthcare system</u>, been diagnosed with HIV infection, and have viral load testing results reported to HIV surveillance (boxes A and B) and persons that may be in care, but as mentioned above, due to incomplete reporting or less frequent VL monitoring, do not have viral load data available (box C, Figure 2). Persons 'in care, no VL' are identified by HIV surveillance data as persons with CD4+ T-lymphocyte count or other test result but without any VL result. After refining surveillance data, persons that are in care but do not have a VL result should represent a small percentage of persons "in care" and may represent persons that are receiving health care but not HIV care, have declined HIV monitoring, or have inadequate VL monitoring. An example is persons not engaged in HIV care but who have received emergency department services in which a CD4+ T-lymphocyte count was obtained. Although the 'in care, no VL' group includes patients refusing HIV care for which they have the right, persons in this group may also represent missed opportunities to engage in HIV care. Because the U.S. HIV Treatment Guidelines recommend the ongoing monitoring of CD4+ T-lymphocyte and viral load, these persons identified by surveillance with only CD4+ T-lymphocyte counts are likely receiving suboptimal HIV care and their viral loads are likely not suppressed and may follow more closely the natural history of CD4+ T-lymphocyte count and viral load [19].

In-Care Viral Load may be used as a quality of care indicator for the general population engaged in care of a jurisdiction. If measured over time, it should reflect access to healthcare, acceptance and adherence to antiretroviral therapy, and adequate clinical monitoring of VL. For a particular healthcare system (e.g., an HMO, a U.S. veterans cohort), In-Care Viral Load can be used as a rough proxy Measure of access to antiretrovirals, level of antiretroviral medication adherence, patient compliance with disease monitoring, and quality of care delivered to a patient population.

Importantly, data on CD4+ T-lymphocyte count and supplemental data on antiretroviral treatment for included cases can greatly aid the interpretation and understanding of In-Care Viral Load. Entities interested in estimating In-Care Viral Load should expand efforts to minimize the proportion of persons in care who have underreported or otherwise missing viral load in their medical records and, ultimately, in the HIV surveillance system. However, the limitations of imputation for 'in care, no VL' and the lack of additional data make calculation of In-Care Viral Load not feasible for most jurisdictions at this time. Methodologies for such analyses are an active area of research.

Monitored Viral Load is limited to the readily observable HIV viral loads of persons who have been diagnosed with HIV infection, who are <u>receiving HIV medical care and disease monitoring</u> through viral load testing, and whose test results are reported to HIV surveillance (boxes A and B, Figure 2). This Measure excludes persons that may be in care, but as mentioned above for In-Care Viral Load, do not have viral load data available (box C) due to incomplete reporting or less frequent monitoring. As missing VL data for 'in care, no VL' become evident through improved surveillance data quality and adequate monitoring of HIV disease, this component measure will decrease in size, and the In-Care Viral Load Measure will approach the Monitored Viral Load Measure. After data refinement, the difference between the two surveillance Measures may be attributed to persons that may be refusing disease monitoring with VL testing and persons that are receiving inadequate VL monitoring. Monitored Viral Load may be used as a quality of care indicator for persons engaged in HIV care within a jurisdiction. If measured over time, it should reflect the combined access and adherence to antiretroviral therapy at a population-based level. For a particular healthcare system (e.g., an HMO, a U.S. veterans cohort), Monitored Viral Load can be used as a rough proxy Measure of access to antiretrovirals and level of antiretroviral medication adherence of a patient population.

Jurisdictions may consider calculating a variety of measures to describe Monitored Viral Load, including measures of central tendency and dispersion. One approach to examining the quality of HIV care, antiretroviral treatment uptake, and adherence and engagement in care is to determine the percent of persons virologically suppressed, or the percent that are undetectable (lowercase m, measurements). Among persons that are receiving antiretroviral treatment, the proportion that achieves viral suppression is referred to as maximal virologic suppression [16] and has been endorsed as a quality of HIV care measure by various national groups. Additional measures are discussed in the **Technical Guidance** section.

For jurisdictions with overlapping projects such as Test and Treat initiatives, Medical Monitoring Project (MMP), or other clinically oriented projects that capture use of antiretroviral medications, percent suppression is a useful population-based measure of the penetration of the U.S. HIV Treatment Guidelines. HIV care measures calculated from HIV surveillance and clinically collected data will help to evaluate suppression rates among different disproportionately affected populations as highlighted in the National HIV/AIDS Strategy.

Summary

It is challenging to estimate Population Viral Load, Community Viral Load, and In-Care Viral Load at this time. Jurisdictions able to address missing viral load data among diagnosed resident persons with HIV by using multiple imputation [9] have been able to calculate Community Viral Load as defined in this document. Those jurisdictions able to impute missing viral load data would also be able to calculate an In-Care Viral Load. For those jurisdictions that are unable to impute missing viral loads for diagnosed cases, they can calculate a Monitored Viral Load Measure.

Technical Guidance

This section provides guidance on analytic decisions and methodologic considerations for conducting viral load (VL) analyses and calculating VL Measures using HIV surveillance data. Estimation of Community VL, In-Care VL and Monitored VL, as described in **Establishing a Common Language,** will be the focus of this section. Each subsection topic will include a description, recommendation, or discussion if no recommendation is provided, and an explanation that follows the recommendation.

Selected standardized categorical VL measures are also defined so that comparisons across jurisdictions may be possible. These standardized measures and methodologic recommendations are enclosed within a grey box. An example of VL data to report is included in Figure 4 and a brief discussion of Population VL follows. Because of the variability in types of analyses, a checklist at the end of this section identifies key explanatory elements that should be described in the method section of any Community VL or related analysis.

Getting started

As described in Appendix B, Surveillance, a number of periodic, routine surveillance activities must occur to ensure HIV surveillance data are accurate and of sufficient quality. Those steps and others, which will be described in this section, provide the framework for Figure 3, Decision tree for conducting viral load analyses.

Note: Geographic analyses may be conducted as a subset of Community VL/In-Care VL or a subset of Monitored VL.

Inclusion criteria for cases

Depending on the type of analysis an HIV jurisdiction plans to conduct, the case inclusion criteria may differ. For the purposes of standardization, however, the following criteria for case selection as part of a cross-sectional Community VL, In-Care VL, or Monitored VL analysis is recommended:
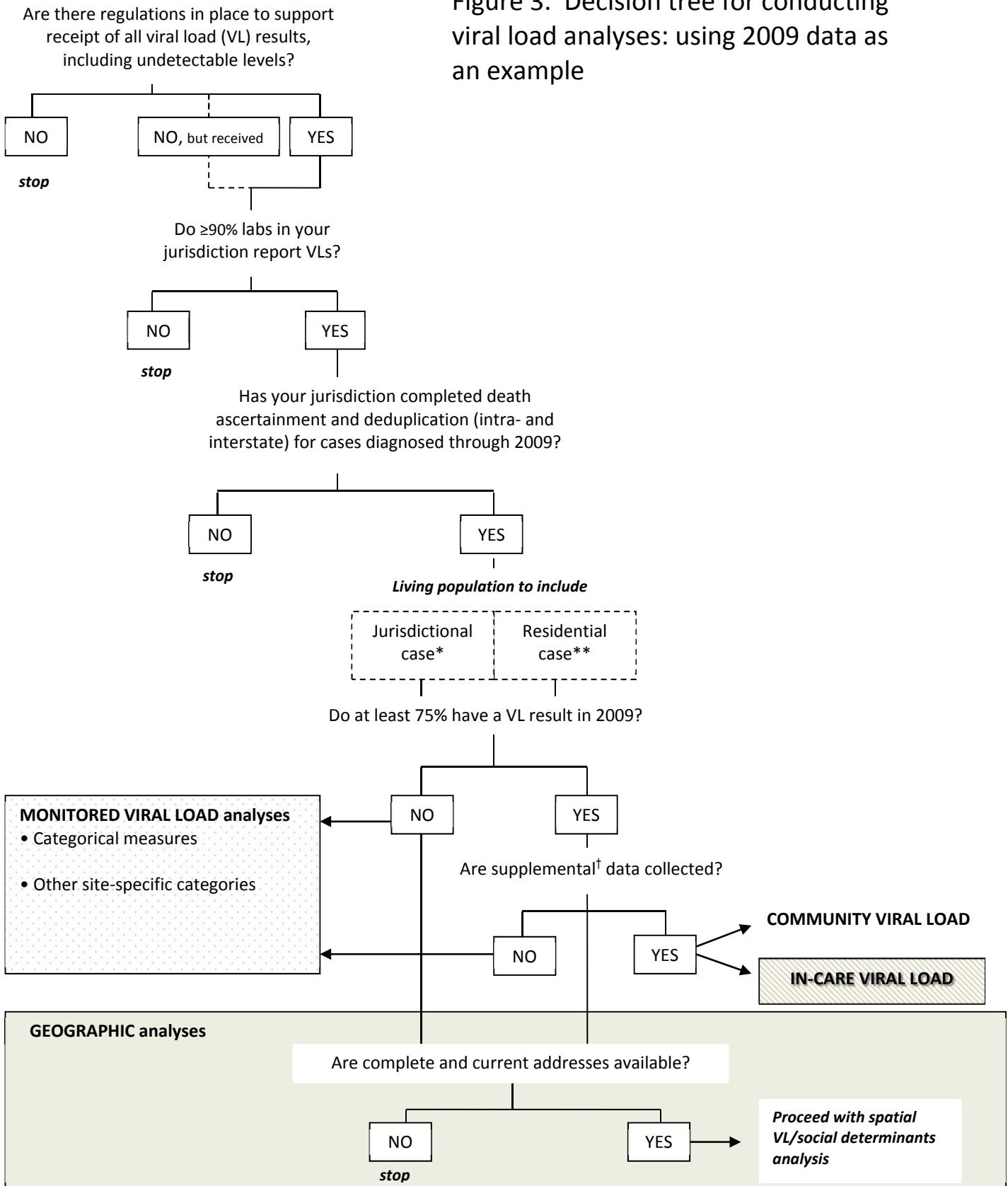
> **Inclusion Criteria** (for cross sectional review)
> Examine a single calendar year, allowing at least 12 months for data lag—2009 used as an example
> - Use data reported through December 2010
> - HIV-infected persons aged ≥13 years, alive on December 31, 2009, and diagnosed by December 31, 2009 or earlier
>   - Interstate and intrastate deduplication conducted recently (within 6 mo) for 2009
>   - Match to state vital registry and at least one National Death Registry through 2009, accounting for lag time of registry data
> - HIV surveillance sites may initially include only jurisdictional cases, but should make efforts to include and eventually report for residential cases

Explanation: HIV-infected adults and adolescents may transmit HIV through sex and injection drug use. At the time of this writing, the latest full calendar year that could be examined is 2009, allowing for the minimum 12-months lag time for cases to be reported (i.e., using data reported through December 2010), data to be found and entered, etc. Using a calendar year and including

Figure 3. Decision tree for conducting viral load analyses: using 2009 data as an example

Are there regulations in place to support receipt of all viral load (VL) results, including undetectable levels?

| NO | NO, but received | YES |

stop

Do ≥90% labs in your jurisdiction report VLs?

| NO | YES |

stop

Has your jurisdiction completed death ascertainment and deduplication (intra- and interstate) for cases diagnosed through 2009?

| NO | YES |

stop

Living population to include

| Jurisdictional case* | Residential case** |

Do at least 75% have a VL result in 2009?

| NO | YES |

MONITORED VIRAL LOAD analyses
• Categorical measures

• Other site-specific categories

Are supplemental[†] data collected?

| NO | YES |

COMMUNITY VIRAL LOAD

IN-CARE VIRAL LOAD

GEOGRAPHIC analyses

Are complete and current addresses available?

| NO | YES |

stop

Proceed with spatial VL/social determinants analysis

* diagnosed in jurisdiction and current resident (or no evidence moved out) of jurisdiction
** current resident of jurisdiction (in-migration) but diagnosed outside jurisdiction
[†] data from chart abstraction such as in HIV care, use of antiretroviral agents, etc.

persons alive at the end of that year is consistent with data requests from HRSA and most local HIV planners. For reporting cities within a state, those reporting jurisdictions will also need to conduct an intrastate deduplication process to determine which persons may have moved out of the jurisdiction but remain in the state. All states must participate in the interstate deduplication process. By the case inclusion criteria, HIV-infected persons who died during 2009 or earlier would be excluded. To keep track of those deaths, matching to state vital registry databases will help identify deaths among HIV-infected persons who died in state; matching to at least one national death registry (National Death Index or Social Security Death Index) is necessary to identify deaths that may have occurred out of state. Although each HIV surveillance jurisdiction has incentive to keep track of its jurisdictional cases, residential cases are more important to understanding current HIV transmission in a locality.

Sample size

The sample size needed to detect a 3-fold geometric mean (GM) difference[*] between mean viral loads depends on the desired power and standard deviation of the sample. Table 1a presents sample sizes needed with 80% power to detect a difference at the 0.5 level for various GM. The dark row lists the sample size needed to detect a difference of 3-fold in the GM; the sample size is the intersection of the row and column, standard deviation, *S*. The column of *S*=1.2 reflects the standard deviation observed in national VL data.

Table 1a. Minimum sample size for detecting GM ratio of *k* with α = 0.05 and *W* = 0.8

k	*S*					
	1	1.1	1.2	1.3	1.4	1.5
1.5	399	483	574	674	782	897
2	136	165	196	231	267	307
2.5	78	94	112	132	153	176
3	54	66	78	92	106	122
3.5	42	51	60	71	82	94
4	34	41	49	58	67	77
5	25	31	36	43	50	57
7	17	21	25	29	34	39
10	12	15	18	21	24	28

α = significance level
W = power
GM = geometric mean
S = standard deviation; 1.2 is the standard deviation of national VL data

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[*] From the U.S. HIV Treatment Guidelines, Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1–166. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Table 1b is the same as Table 1a except it uses power=90%. The statistical equations used for Tables 1a and 1b can be found in Appendix G.

Table 1b. Minimum sample size for detecting GM ratio of *k* with α = 0.05 and *W* = 0.9

k	*S*					
	1	1.1	1.2	1.3	1.4	1.5
1.5	552	668	795	933	1083	1243
2	189	229	272	319	370	425
2.5	108	131	156	183	212	243
3	75	91	108	127	147	169
3.5	58	70	83	98	113	130
4	47	57	68	80	93	106
5	35	42	50	59	69	79
7	24	29	35	41	47	54
10	17	21	25	29	34	39

α = significance level
W = power
GM = geometric mean
S = standard deviation; 1.2 is the standard deviation of national VL data

> Each jurisdiction will need to assess the standard deviation of their local VL data and then determine the appropriate sample size needed to assess VL.

Explanation: Sample size considerations must be taken into account when choosing the cases or study population to examine. For example, Monitored VL among African American men and women may be of great interest to evaluate by a jurisdiction, but if the sample size is inadequate to meet the recommended case inclusion criterion, an alternate method may need to be used, such as combining multiple years of data.

Jurisdictions may want to explore factors related to differences in means of viral loads, such as the difference in the proportion with undetectable or very low VL, which may be expressed as a categorical difference.

Crude viral load data and differences in lower limits of detection

With the advent of newer assays for quantifying HIV viral load, the lower limit of detection (LLD) of these assays has steadily decreased from <1000 copies/mL in the early 1990s to <400 copies/mL in the early 2000s to <50 copies/mL or fewer in most recent years. Most persons that receive and adhere to antiretroviral therapy will have a viral load below the LLD, and a question arises how to handle their viral loads in the analyses.

> We recommend that half of the LLD be used in the analyses of viral loads for persons who have VL below the limit of detection (whether numeric result provided or not) to approximate the likelihood of their actual viral load burden.

Explanation: The distribution of actual VL values below a test's LLD is unknown. Factors that may influence the VL distribution in a jurisdiction include the regimen of and adherence to antiretroviral therapy among the cohort, sensitivity of assay used in measuring these otherwise

undetectable VL results, and possibly the combination of patient demographics and clinical characteristics of HIV-infected persons at the time. Some researchers have used zero or the value LLD minus one as the VL value for undetectable results in VL analyses. We chose half the value of the LLD as a compromise and for its ease of use. As more data become available, it will be possible to more accurately establish a value for VL results currently classified as undetectable. Nevertheless, for our purposes of providing a uniform method that can be compared across sites or within a site over time, use of half LLD should be adequate. Consequently, when a viral load assay with LLD <50 copies/mL is used, undetectable viral load results should be replaced with 25 copies/mL for analysis.

When undertaking a calendar-time trend analysis, however, it may be necessary because of different viral load tests in use to truncate the lower limit of detection and possibly the upper limit of detection[†]. After examining local VL data by year, it should become apparent where those cut points are needed. As an example, if a jurisdiction had complete and refined data from 2005–2009, it may be found that viral load tests with a LLD <400 copies/mL were in wide use in 2005 and 2006, but then were replaced by a more sensitive test with LLD of 75 copies/mL by 2009. For such an example, test results of undetectable, 400 copies/mL or less would be collapsed into a single group and given a VL value of 200 (half LLD) for each year, 2005 through 2009. VL analyses for each year would then be conducted using this common LLD of 400. If a single year, 2009, as a point in time analysis was planned, however, it would be appropriate to use 75 copies/mL as the LLD and use 37.5 as the value for analysis when results of ≤75 copies/mL or undetectable were reported. In either situation, the LLD or range of VL results used in analysis should be stated.

Multiple imputation of missing viral load

Although only 15 of 26 jurisdictions responded to an informal survey conducted among Workgroup members, most jurisdictions reported missing VL information for more than 30% of their cases [20]. VL results may be missing for persons not in care, in care but without VL, and for persons who have died or moved away as described in Appendix B, Table B1. This discussion of multiple imputation of missing viral load for calculating Community VL and In-Care VL applies to data that have been refined after completing data management processes described in Appendix B, Surveillance.

> We recommend that imputation of missing VL data only be attempted if <25% of cases are missing VL AND jurisdictions are collecting supplemental clinical data.

Explanation: Two groups of HIV-infected persons have, by surveillance definition, missing VL results—those "in care, no VL" and those "diagnosed but not in care" (boxes C and D, respectively, Figure 2). After data refinement, if the number of persons "in care, no VL" is small, jurisdictions may want to conduct follow-up to better characterize these persons. This information may help inform approaches for data imputation for this group, "in care, no VL."

Jurisdictions that routinely collect supplemental information—such as use of antiretroviral medications, engagement in care, insurance, co-morbidities—may wish to explore data imputation using published methods [9] that would enable them to calculate a Community VL or

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[†] Sites should assess their data and determine if an upper limit of detection is needed. Because of the recommended methods, providing a uniform upper limit of detection is not warranted in most circumstances. If, however, sites have a significant percentage of high VL results, use of an upper limit of detection may be prudent.

In-Care VL. However, jurisdictions should carefully weigh the benefits and limitations of multiple imputation before embarking on such analyses.

> We recommend that calculation of Community VL and its related viral load Measures (see Figure 2) is performed after transformation of viral load results onto the logarithmic base 10 scale, followed by calculation of the mean.

Methods like multiple imputation that extrapolate from available surveillance VL data to the remainder of the population may not be appropriate for surveillance data. A fundamental requirement of imputation, that data are missing at random and that the distribution of values in the unknown group mirrors the distribution of values in the known, may not be satisfied. The fundamental problem for a "diagnosed case but not in care" identified from surveillance data (i.e., lacking VL data in a surveillance system that routinely receives fairly complete VL data from labs) is that the case is not in care or has moved out of jurisdiction. The viral load distribution of cases not in care cannot be modeled from the distribution of those that are in care. The Workgroup is not aware of any supplemental data available to the majority of surveillance jurisdictions at this time that could address this lack of information.

Even if supplemental information is available to support randomness or similarity (these would likely derive from research samples also reflecting patients in care), there is no clear cut-off for how much information may be imputed (e.g., the recommendation of 75% as the minimum threshold for data completeness). The usefulness of supplemental data for "filling in the blanks" depends on the relevance, completeness, and accuracy of the data; it also depends on the homogeneity of the population that is being modeled. Jurisdictions are advised to consult with statisticians familiar with the methodology when planning analyses that involve imputation.

Mean viral load

The early VL and prevention studies have used median viral load as the summary analytic measure for community viral load; others have used the mean of the VL results. Because successful clinical use of antiretroviral therapy results in viral suppression, jurisdictions that have successfully engaged HIV-infected persons in care may have over 75% of such persons with undetectable VL; the median would be undetectable, so the mean was used.

Explanation: The rationale for this logarithmic transformation is that it helps to normalize the distribution of viral load values and reduces the influence of outlying measurements for persons having extreme viremia (due to acute infection, advanced HIV disease, concurrent sexually transmitted infections, or random variability).[‡] Since the interpretation of viral load measurements is often more intuitive on a linear scale, we recommend calculation of geometric mean (GM) for viral load. The GM is thus calculated through log transformation by averaging the log transformed values and transforming the average back to the original (linear) scale. The base used for the log transformation has no effect on the final GM estimate. However, using log base 10 has an advantage by its relationship to the value on the original scale; for example, a value of 2 on the log10 scale is 100 on the original scale, 3 corresponding to 1000, 4 corresponding 10000, and so forth.

While our recommendation for calculating the mean viral load is limited to Population VL, Community VL, In-Care VL, and Monitored VL, jurisdictions may wish to calculate a mean VL

[‡] This is similar to using the median VL

for a subpopulation. In addition, a geometric mean could be useful in combination with categorical VL measurements (see below). For example, the population can be described in terms of the fraction with undetectable or suppressed VLs and the (geometric) mean of the remaining population.

Selection of viral load results for analysis

Once the time frame for analysis is decided, the handling of VL values for individuals that may have more than one VL result needs to be considered. Depending on the type of analysis, jurisdictions may want to average the VL results for each individual and then take the mean of those average VLs to compute the Community VL, In-Care VL, or Monitored VL. For other analyses, it may be more appropriate to use the highest, lowest, or most recent VL result. (See *Other viral load methods and analyses* later in this section.)

As part of the standard case inclusion criteria for a calendar year, the following VL should be selected for analysis:

> Use the most recent VL result per person for analysis—this would be for specimens obtained in 2009 that are the closest to December 31. If there is no VL specimen for a case in 2009, that case would be excluded and would belong to either the "In care, no VL" or "Diagnosed but not in care" boxes of Figure 2 (boxes C and D, respectively).

Explanation: The examination of a single VL result (most recent) is the least restrictive definition of 'being in-care.' Whereas other new measures or definitions of 'in-care' require at least two lab results within a specified timeframe of each other in a 12-months period, no such requirement is necessary for this standardized, point in time examination.

The Community Viral Load Workgroup has developed and tested an Excel spreadsheet that allows for calculation of mean viral load, proportion suppressed, proportion undetectable, and a Z-test to identify a statistically significant difference between two mean viral loads. This spreadsheet accommodates small datasets.

A generic SAS program that incorporates the methodologic guidelines and standards set forth in this document will also be available. The SAS code will be created so that large volumes of data from eHARS can be used for VL calculation by all HIV surveillance jurisdictions.

Categorical measures of viral load

Viral load results may be grouped into various clinically meaningful categories. Tracking VL categories for a population yearly (e.g., using histograms) may aid in the interpretation of changes in VL results in the population over time, concomitant with changes in proportion of patients receiving highly active antiretroviral therapy or adherence support, or due to other factors.

> We recommend use of three categorical VL measures: suppressed/not suppressed, undetectable, and high VL.

Although the VL cut points that define each of these categories may not meet all needs, given the nature of ever evolving VL test technology, we have proposed definitions so that all HIV jurisdictions can report using standard definitions of these measures. The three standardized measures that are proposed are as follows:

> Report percentage ≤200 copies/mL as suppressed as a categorical VL measure. Conversely, the percentage >200 copies/mL may be reported as not suppressed.

Explanation: A measurement that may be useful in describing the disease status of local PLWH is percentage of persons that have viral load below LLD or suppressed viral load, defined as VL ≤200 copies/mL by the latest U.S. HIV Treatment Guidelines [21]. Percentage of persons that have viral load suppression may serve as a rough proxy indicator of the combined access to and adherence to antiretroviral therapy in a given population.

> Report percentage ≤50 copies/mL as undetectable as a categorical VL measure.

Explanation: This measure can only be assessed in jurisdictions where recent sensitive assays (LLD of 50 copies/mL or lower) are consistently used by laboratories. While this measure is most informative for a clinical setting among persons on antiretroviral therapy, it could also be applied to populations receiving care from a specific facility or across all persons in care using surveillance data.

> Report percentage >100,000 copies/mL as high VL, in need of treatment as a categorical VL measure.

Explanation: To better characterize the spectrum of viral loads in the population, some jurisdictions may opt to quantify the proportion of VL results that are considered very high (i.e., >100,000 copies/mL), which may indicate high potential transmission risk for a group or the healthcare challenges facing a group in need of immediate antiretroviral therapy [21].

Another potential categorical measure that jurisdictions may want to examine is the proportion of HIV-infected persons that meet a standardized definition of in-care—e.g., at least two lab results obtained within a calendar year that are at least 60 days apart.

Categorical measures might be more informative than means and may also be more comprehensible to planners, evaluators, policy makers, and others. These measures provide the VL distribution and have the advantage of not implying a normal distribution of values (as means may be perceived by the public). The actual distribution of VL results in surveillance populations is highly skewed. A large proportion of the population has undetectable or very low values (e.g., <200 copies/mL), and the remainder of values are spread across a wide range. Distributions such as these are not well represented by a single measure, especially one that implies a normal distribution. Jurisdictions should examine their data to determine the local viral load distribution and the best measures to describe it, including outlier cutoff values, etc. Other measures are listed in Table 2. Such distributions can also be stratified by CD4+ T-lymphocyte count to reflect stage of illness and the U.S. HIV Treatment Guidelines recommendations on initiation of antiretroviral therapy.

Address and residency

For analyses that use address (geospatial analyses or linkage to Census geographic information on social determinants data), the current address, if available, should be used. Current address is also useful in establishing whether a jurisdictional case may have moved. While most jurisdictions use patient address from lab reporting, this information is useful only if the address is accurate. Patients with post office boxes or incomplete or inaccurate street addresses cannot be geocoded and placed with certainty on a map.

A timeframe in which current address should be updated could not be agreed upon by the Workgroup. Any analyses including cases by residence or using geographic analyses should specify when addresses were updated and the percentage of cases that could not be geocoded with a high level of confidence.

Population Viral Load

The **Technical Guidance** section provides methodologic recommendations for calculating Community VL, In-Care VL, and Monitored VL. Although Population VL is the best Measure for assessing HIV transmission, information is not available for its calculation. However, a component VL measure that is of interest includes an estimation of the number of undiagnosed HIV-infected persons. A back-calculation method estimated that almost 250,000 HIV-infected persons are undiagnosed (21% of the total number of HIV-infected persons) in the United States [16]. Efforts are underway to also estimate the relative proportion of undiagnosed HIV-infected persons by state or metropolitan statistical area. These methods will be available to state health departments in 2011.

VLs will vary greatly among undiagnosed persons, depending on how recently the person was infected. However, they may be assumed to not have suppressed VL.

Other viral load methods and analyses

Although this Guidance document suggests using one VL result (most recent) of possibly many VL results for a person and recommends a method for calculating VL Measures, viral loads may be analyzed differently. Table 2 includes different VL measures that have been calculated and reported. Each measure has particular strengths and uses. Appendix A lists the references associated with the VL analyses.

The mean viral load provides an estimate of the average level of viral burden and is the most useful for comparing subpopulations and neighborhoods in a jurisdiction. Comparing mean of most recent and total VLs at the geographic level may reflect disparities in access to and use of antiretroviral medications by neighborhood. Comparing means among different subpopulations within a jurisdiction can highlight disparities. The total VL is a useful measure for looking at the combination of HIV prevalence and viremia among prevalent cases.

Depending on the type of analysis that is being conducted, VL results other than the most recent may be appropriate to use. If the purpose of the analysis is to evaluate a new measure of quality of care, the researcher may choose to report the proportion of cases that were virologically suppressed for a calendar year; thus, cases with even a single VL result >200 copies/mL would not be considered suppressed for the year. If the focus of the analysis is on acute antiretroviral need and possible lapses of optimal antiretroviral use, then the proportion of cases that may have a single VL result >100,000 copies/mL may be used. Although we recommend the most recent (to December 31) VL within a calendar year be used to calculate a VL Measure that is a more

"current" snapshot, researchers may also want to use the mean of serial VL results obtained throughout the year for a person and then calculate the overall mean VL among all persons in a group for the year. Again, this document is not meant to be a comprehensive list of all possible VL analyses and measures but to point out ones in use and to recommend a common method for calculating VL Measures and reporting of component and a limited number of categorical VL measures.

Summary for data reporting—see Checklist on page 20

For each type of population-based analysis, Population VL, Community VL, In-Care VL, and Monitored VL, the study population should be described and its size should be reported. The size and relative percentage of each of the component VL measures (boxes A–E), as shown in Figure 2, that defines each VL Measure should also be reported.

Table 2. Types of viral load (VL) analyses and measures[†]

VL analysis/measure	How to calculate	What it tells you
Mean of most recent VL*	Determine the most recent VL for each case, total the values of those VLs, and divide by the number of cases with a VL.	The average number of virus particles in a population; can be influenced by large outliers; useful for comparisons between sub-populations (e.g., disparities)
Mean of most recent log transformed VL*	Log transform the most recent VL for each case, average the log transformed values, total the average values, and divide by the number of cases with a VL.	The log transformation will provide a stable estimate by reducing the influence of outliers; tightens the association of trend between decline in CVL and new diagnoses
Mean of mean VL*	Determine the mean VLs for each case, total the values of those mean VLs, and divide by the number of cases with a VL.	Provides an average of the average number of virus particles per case; this may reflect a greater influence of those individuals with multiple measurements and those who were started on ART and trended towards suppression within 1 year
Total VL	Sum of VLs for all cases.	The number of virus particles in the population who have a VL; affected by the number of cases; reflects both prevalence of HIV cases and burden of viremia
Percent suppressed (proportion with suppressed VL)*	The numerator is the number of cases whose most recent VL was suppressed; the denominator is the number of cases with a VL.	Maximal Virologic Suppression, or the percent virologically suppressed reflects ART uptake, adherence, and effectiveness in clinical settings; a quality of HIV care measure; in jurisdictions offering universal treatment, an important marker of uptake of universal ART guidelines

ART, antiretroviral treatment.
[†] Time needs to be defined for each calculation, usually a 12-month period. Pooling over a few years can increase VL completeness but is harder to interpret.
* The denominator includes all viral load results, including undetectable viral load.

It may not be possible for many jurisdictions, at this time, to calculate a Community VL or In-Care VL estimate because of an inability to estimate VLs for persons "Diagnosed but not in care" or "In care, no VL."

> Jurisdictions should report: 1) the component VL measures—e.g., percentage of persons "Diagnosed but not in care" in addition to the percentage, "In care and with undetectable[*] VL," "In care with detectable VL," and "In-care, no VL" when conducting In-Care VL Measurements; and 2) on categorical VL measures to describe the population that is in care and being monitored such as the percentage of persons with suppressed (i.e., ≤200 copies/mL), the percentage with high viral loads (i.e., >100,000 copies/mL), and the percentage undetectable (i.e., ≤50 copies/mL).

Explanation: In addition to standard component and categorical measures, jurisdictions may also choose to report alternate categorical VL measures that use other VL cut points that are meaningful to their area.

Examples for Data Reporting (bottom up)

Figure 4a: When VL LLD[†]=50 copies/mL (standard undetectable)

1. Report component and categorical VL measures for Jurisdiction X/Subgroup Y
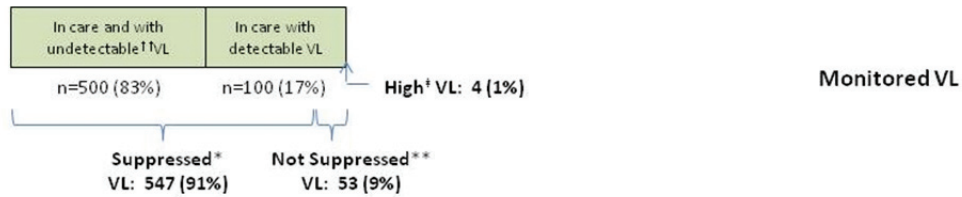
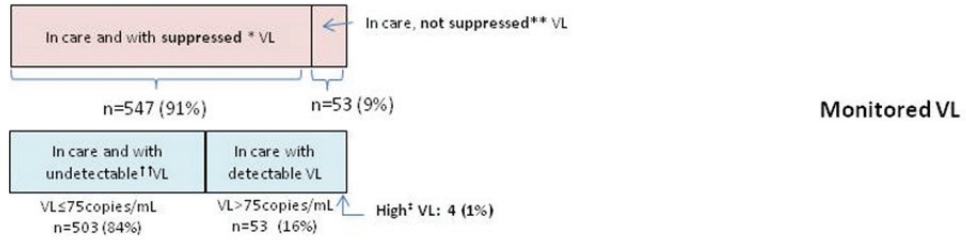2. Report Monitored Viral Load : GM VL=39 (log(10)=1.589[**])

3. Report remaining Community VL component measures for Jurisdiction X/Subgroup Y
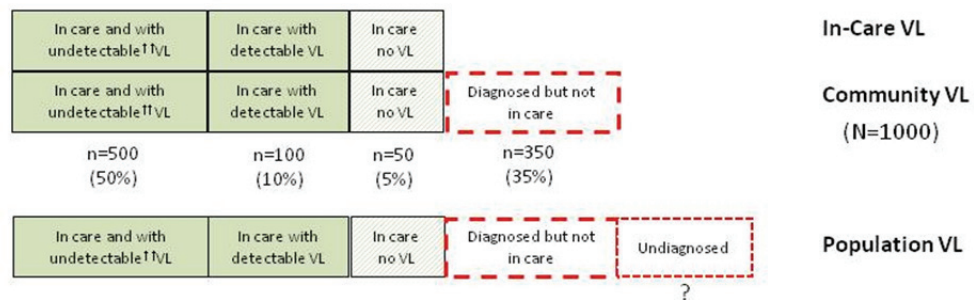
†VL test lower limit of detection; ††≤50 copies.mL; * ≤200 copies/mL; ** >200 copies/mL; †>100,000 copies/mL; ‡‡mean log(vl)
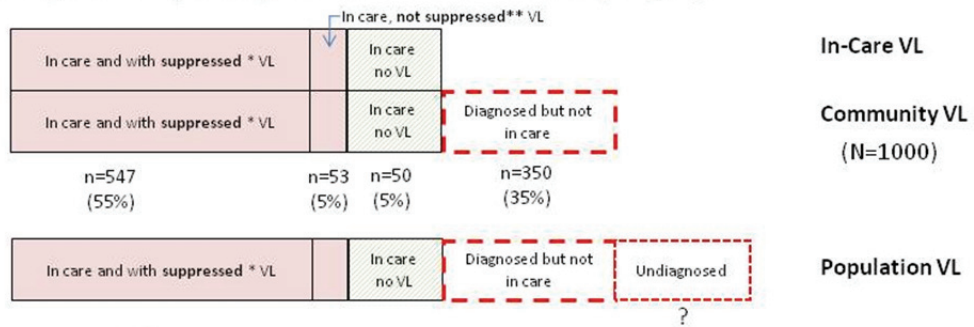
Figure 4b: When VL LLD[†]=75 copies/mL (less sensitive VL test)

1. Report categorical (and optional modified component) VL measures for Jurisdiction Y/Subgroup Z

2. Report Monitored Viral Load :   GM VL=54   (log(10)=1.734[††])

3. Report remaining Community VL component measures for Jurisdiction Y/Subgroup Z

[†]VL test lower limit of detection; [††]≤**75** copies.mL; * ≤200 copies/mL; ** >200 copies/mL; [‡]>100,000 copies/mL; [††]mean log(vl)

Checklist[§]: Items to include when reporting on Community VL or related analyses

Introduction

□ Describe the rationale for the analyses and specific objectives; e.g., estimating HIV transmission potential of the population, assessing quality of care indicator, monitoring the outcomes of programmatic interventions

Methods

Analysis design and measurements

□ Describe key elements of analysis design (cross-sectional, longitudinal), including relevant dates

□ Describe data sources and method for selection of persons and viral load measurements
(e.g., allowing ≥1 year reporting lag in data analyzed; Persons alive as of when? Handling of VLs for those who died in the year? Resident vs jurisdictional cases? Timeframe when residency last assessed)

□ Describe any data quality assurance processes and when conducted (matching to local vital statistics data, National Death Index, or Social Security Death Index, determination of patient residency through laboratory data, Routine Interstate Deduplication Review, intrastate review, etc.; see the **Technical Guidance** section)

□ Present n (%) of cases with missing viral load data or excluded for any reason (consider a flow diagram)

□ Define all outcomes and how computed; e.g., geometric mean of VLs, percentage of VLs <200 copies/mL, locally-defined VL categories, etc.

□ Define other variables; e.g., which address/ZIP Code used for geospatial analyses; how current? present n (%) of addresses that could not be geocoded

□ Specify what the VL lower limit of detection (LLD) was and how they were handled in the analyses (see Technical Guidance)

□ Justify categories chosen for categorical independent or outcome variables, as appropriate

Analyses

□ Describe all statistical methods (e.g., tests for trend; accounting for multiple observations per patient; data imputation and variables used in imputation, if used; geospatial analyses; multivariable modeling)

□ Describe sample size calculations if used (e.g., for comparison of VL Measures between 2 patient subgroups)

□ Describe any methods of adjustment for confounders (e.g., standardization, multivariable modeling)

□ Describe any efforts to address potential sources of bias due to missing data, sensitivity analyses (e.g., imputation).

Results

□ Give characteristics of the study population and univariate summaries of outcome measures

□ Report variability (e.g., standard deviation) and precision (e.g., 95% confidence intervals) around estimates

□ Present results from adjusted analyses, controlling for potential confounders

Discussion

□ Discuss limitations of the analyses, taking into account potential sources of bias or imprecision; discuss both direction and likely magnitude of the bias (e.g., under or over estimation of Community VL)

□ Interpret findings in the context of prior analyses—highlight differences and similarities

□ Discuss generalizability of the results

[§] Adapted from STROBE http://www.strobe-statement.org with checklist available at http://www.plosmedicine.org/

Acknowledgments

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Appendixes

Appendix A. Inventory* of Viral Load Analyses

Title	Author	Venue	Source	Population	VL analysis	Method/notes	Data presented
Longitudinal community plasma HIV-1 RNA concentrations & incidence of HIV-1 among IDUs: a prospective cohort study	E Wood (BC,Canada)	BMJ 2009	Article	cohort IDUs	Median VL	Spearman correlation, Cox proportional hazards regression; closed community	Correlated 6 mo CVL & incidence (& % ART); modeled time to HIV(+); covariates: 6 mo CVL and IDU risk
Geographic, demographic, and health-status related disparities in CVL	M Das (SF/UCSF)	CROI 2009	PP	PLWHA 2004–07	Mean of the means of individual VLs in period	K Wallis	Differences in CVL by demographic, risk category, clinical status, CVL geography
Population-level assessment of the geographic, demographic, and health status correlates of virologic suppression among all San Franciscans on ART, 2005–07	M Das (SF/UCSF)	CROI 2009	Poster	PLWHA w <350 CD4	Mean VL (75 & 400 cut points)	Wald adj OR + GEE	Two models, outcome1: VL <75 and outcome2: VL <400; covariates: demographics, clinical, access to care
CVL: Geographic, clinical and risk-related disparities in a novel population-based biomarker of HIV prevention and treatment	M Das (SF/UCSF)	IDSA 2009	PP	PLWHA 2005–07	Mean recent VL	K Wallis; floor: ≤75	Differences in CVL by demographics, risk category, clinical status, CVL geography
Decreases in CVL are accompanied by reductions in new HIV infections in San Francisco	M Das (SF/UCSF)	CROI 2010	PP	PLWHA 2004–08	Mean + total recent VL, % VL suppressed	K Wallis, Poisson regression; floor: ≤75, 26% missing VL imputed	Test & Treat parameters, '04 & '08; modeled new dx/incidence; total CVL, mean CVL, and % VL suppressed
Association of highly active antiretroviral therapy coverage, population viral load & yearly new HIV dx in British Columbia, Canada: a population-based study	J Montaner (BC, Canada)	Lancet 2010	Article	PLWHA in province	Log(10) highest yrly VL	Poisson log-linear; floor: ≤500, ceiling: ≥100K	Correlated HAART and incid, 3 time periods; modeled new dx; covariates: VL, HAART use, yr
Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco	M Das (SF/UCSF)	Plos 2010	Article	PLWHA 2004–08	Mean + total recent VL, % VL suppressed	K Wallis, Poisson regression; floor: ≤75, 26% missing VL imputed	Modeled new dx/incidence; examined total CVL, mean CVL, and % VL suppressed
Predictors for high HIV viral load (VL) among persons with HIV in Los Angeles County using lab surveillance & HARS	Y Hu (LACounty)	APHA 2010	Abstract	PLWHA w VL, 4/06–10/09	High VL (>10K)	Mixed model	Modeled high VL; covariates: demographics, SES, and behavioral factors

Appendix A. Inventory* of Viral Load Analyses

Title	Author	Venue	Source	Population	VL analysis	Method/notes	Data presented
Decline in community viral load is strongly associated with declining HIV incidence among IDUs	G Kirk (Hopkins)	CROI 2011	Poster	cohort IDUs	Log of mean of year's VLs	Poisson regression; closed community	11 yr trend: CVL, % ART, HIV incid, and % IDU; modeled IRRs x 3 intervals; covariates: risk
Trends in HIV viral load among adults in clinical care in the U.S. and Canada, 1997–07	K Althoff (Hopkins)	CROI 2011	Abstract	HIV(+) in care	Median log VL, % VL suppressed	Floor: ≤500 (2.7log); Kruskal-Wallis; Clinical multisite study	11 yr trend: annual VL, % VL suppressed by ART, race, risk group
Use of community viral load as population-based biomarker of HIV—Washington DC, 2004–08	A Castel (DC/GWU)	CROI 2011	Poster	PLWHA dx 2004–08	Mean + total most recent VL over 5 yrs	52% missing VL	Trend mean and total CVL and new dx, Q6 mo x 5yr; mean CVL by risk; mean and total CVL by district
Factors associated with persistent high viremia in HIV-infected New Yorkers, 2006–07	A Terzian (NYC)	CROI 2011	Poster	PLWHA ≥12 yo & 2 VLs ≥2 wks	Persistent high VL (>100K x 2 cons VLs)	GEE; floor: ≤400	Modeled persistent high VL; covariates: demographics, clin course/stage, geography; suppressed vs. persistent VL
Disparities in community viral load among HIV-infected persons in NYC	F Laraque (NYC)	CROI 2011	Poster	PLWHA ≥13 yo 2007& 1VL '08	Mean VL of detectable VL, % VL suppressed	K Wallis, Jonckheere-Terpstra; 36% missing VL, floor ≤400	Mean detectable and % VL suppressed by risk; 3 yr trend % supp; geogr % supp, mean det VL, etc.
Success of Test & Treat in San Francisco: reduced time to virologic suppression, decreased CVL and fewer new HIV infections, 2004–09	M Das (SF/UCSF)	CROI 2011	Poster	PLWHA dx 2004–09	Yearly mean recent, min and max VL; log mean recent	Poisson regression	Time to ART, % VL suppressed by dx yr; % supp @ 6 and 12 mo by dx yr; modeled new dx; covariates: min, max, recent VL, year

Venue: Journal names are underlined; scientific meetings include CROI (Conference on Retroviruses and Opportunistic Infections), IDSA (Infectious Disease Society of America), APHA (American Public Health Association).

Source: Article refers to a scientific publication; PP is an oral presentation at a scientific meeting; abstract is a short description of study and findings submitted to a meeting; poster is a more detailed paper presentation at a scientific meeting.

* As of May 2011

Appendix B. Surveillance

Public Health Surveillance

Surveillance is the foundation of public health. It involves the ongoing, systematic collection, analysis, interpretation, and dissemination of data used by public health to reduce morbidity and mortality and to improve health [1]. Each surveillance system has a number of attributes that contributes to its overall effectiveness. These attributes include: simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, completeness, timeliness, and stability. To ensure ongoing improvement in data quality, efficiency, and usefulness, each surveillance system should be periodically evaluated.

All CDC data originate locally. These data represent a commitment and collaboration between states or jurisdictions and CDC to collect data deemed to be the most vital in fulfilling local and national public health missions. CDC works with local reporting jurisdictions and the Council of State and Territorial Epidemiologists (CSTE) to establish model language and uniformity in state reporting regulations and standardization of data collected for surveillance. CDC works with state and local public health counterparts to decide on national data quality standards, policies, and procedures that can be used to meet surveillance data quality standards.

HIV Surveillance

HIV surveillance includes 65 reporting jurisdictions that represent the 50 states, District of Columbia, 6 cities and 8 U.S. dependent areas. Collectively, these 65 jurisdictions comprise national HIV surveillance data that allows for the enumeration and description of reported new diagnoses of HIV-infected persons, known or prevalent HIV-infected persons, and deaths among HIV-infected persons since the beginning of the U.S. epidemic in the early 1980s. National HIV case surveillance data includes all persons diagnosed with HIV and can be used as a sampling frame by other programs to establish representative samples for study or surveillance.

State and local surveillance staff identify most HIV-infected persons by codified regulations that require healthcare providers (e.g., physicians, hospitals, clinics) and laboratories to report persons with lab test results diagnostic of HIV infection. HIV surveillance data are collected and entered into a standard database. The current HIV surveillance data system, eHARS, is a complex, relational database that collects sentinel HIV disease information through a document-based process. Cases are reported to CDC without identifying information.

As HIV disease and its treatment have evolved, so has HIV surveillance. HIV antiretroviral medications have greatly extended the lifespan of HIV-infected persons, transforming an acute, life-limiting disease into a more manageable chronic disease. Correspondingly, the role of public health surveillance data has evolved from describing persons diagnosed with HIV to assessing the course of the disease throughout their life, and their crucial linkage to and retention in care following diagnosis (see Figure B1).

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[1] CDC. Updated guidelines for evaluating public health surveillance systems: recommendations from the guidelines working group. *MMWR* 2001;50(RR-13):1–36.

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Figure B1. HIV Surveillance Perspective of HIV-infected Persons and Viral Load

- No lab results reported to HIV Surveillance
** CD4+T-lymphocyte or other lab data reported but no viral load results
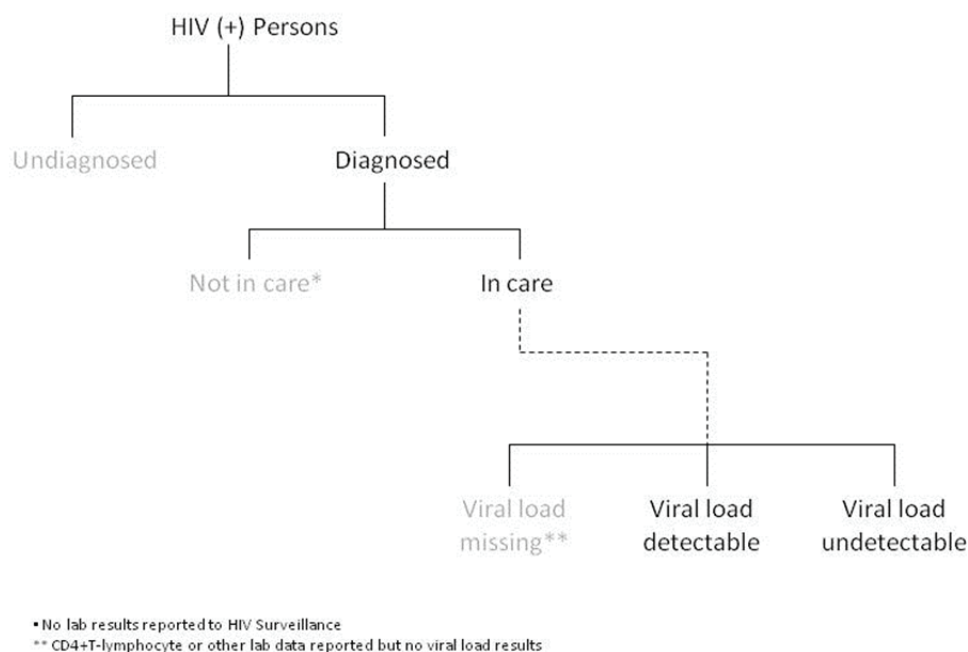
U.S. HIV Treatment Guidelines [2] recommends periodic laboratory testing of HIV-infected persons that are in care. From the surveillance system perspective, serial, periodic laboratory test results are a marker of ongoing utilization of, and access to, healthcare among HIV-infected persons. Recognizing the importance of lab data, states have bolstered their ability to collect these data by means of legislation requiring the reporting of CD4+ T-lymphocyte counts and plasma HIV viral load test results [3].

Because resources for HIV care and prevention are often determined by the person's place of residence at the time of HIV and AIDS diagnosis, address is collected for these sentinel events and maintained by the local jurisdiction. As HIV-infected persons live longer, however, persons may move from one jurisdiction to another. Locally, information from lab reports can be used to update current patient address and identify in-migration of persons with HIV. To help account for in- and out-migration of HIV-infected persons and maintain accurate case counts, jurisdictions and states participate in CDC's intra- and interstate deduplication processes. Cases with the same Soundex and selected demographic factors are referred back to the reporting areas to work out case "ownership" and surveillance responsibility. The reconciliation of such cases helps avoid overcounting and ensures accuracy of local and national estimates. Similarly, HIV-infected persons may die out of state, so jurisdictions are provided the resources and encouraged to match their case registry not only against their state or local vital statistics registry data but

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2 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. January 10, 2011;1–166.

3 CDC. Reported CD4+ T-lymphocyte and viral load results for adults and adolescents with HIV infection—37 states, 2005–2007. *HIV Surveillance Supplemental Report* 2010;16(1). Table 8. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/index.htm#supplemental. Published March 2011. Accessed April 27, 2011.

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also against at least one national death registry [4] to ensure an accurate count of the number of people living with HIV disease in their jurisdiction.

While accurate case counts are important to understand disease burden and where HIV-infected persons seek medical care is important for resource allocation, it is equally important to understand where and how new cases arise for targeted prevention efforts. Jurisdictional boundaries and residency do not predict where healthcare is sought or risk-seeking behaviors occur. For example, persons may cross into an adjacent state to receive health services or engage in high-risk behaviors in a neighboring jurisdiction. Some states have developed lab reporting regulations based on the patient's residence and patient's place of care to accurately describe care patterns. As part of understanding HIV transmission, surveillance areas with residents that cross state lines to engage in high-risk HIV behaviors should take this into consideration when conducting any assessment of HIV transmission potential for their residents.

Assessing those in care

In general, HIV surveillance relies on reported lab test (i.e., CD4+ T-lymphocyte count or viral load) results as a marker of persons receiving health care and thus being "in care." While it may be possible to identify HIV-infected persons who are receiving care but lacking lab test results, such as persons identified from linking to Ryan White Care AIDS Drug Assistance Program databases, such cases can be followed-up to address the reasons for missing lab results. To determine whether someone was linked to and retained in ongoing HIV healthcare, serial lab results over an extended period would need to be observed in surveillance data.

A limited number of HIV jurisdictions are able to conduct ongoing medical chart review of HIV-infected persons that reside in their jurisdiction. Those jurisdictions have collected supplemental data that are not routinely collected as part of HIV surveillance, such as engagement in care, insurance, and use and type of antiretroviral medications. Other jurisdictions have been funded to participate in special surveillance/prevention activities and, as such, may also be conducting ongoing medical chart reviews and collecting similar type of supplemental data.

States annually estimate the proportion of HIV-infected persons living in their state that are in and out of care. Some HIV reporting jurisdictions may report for their jurisdictional cases, not residential cases, because they are more likely to have complete information for their jurisdictional cases [5].

Viral load test results

To ensure that all (detectable and undetectable) viral load results are received by HIV surveillance, jurisdictions must expend great time and resources. As a first step, state public health reporting laws or regulations provide the authority for State Health Departments to receive such information from laboratories. It may be necessary to include language that specifies that all (detectable and undetectable) HIV viral load results are reportable. This type of policy lays the foundation for receiving viral load results but cannot account for the personal interaction needed

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[4]   The National Death and Social Security Death Indexes are both national death registries. The Social Security Death Index requires about one year for death data to be complete; the National Death Index's lag time is about two years. An out-of-state death may provide the first piece of evidence that a person moved out of state. Although matching to a national death registry may help identify whether a person has died out of state, it does not help with HIV-infected persons who may return to their country of birth and then subsequently die. The magnitude of this problem is not known. This miscounting may contribute to an overestimation of some racial/ethnic groups that are considered not in care and an underestimate of some race/ethnicity-specific HIV-mortality rates.

[5]   See the HRSA section that follows for explanation of jurisdictional versus residential case.

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in establishing relationships with laboratories for reporting and then ongoing work to ensure continued reporting. The magnitude of this can be appreciated by the fact that some jurisdictions have over 80 laboratories that report viral load results [6].

The volume of viral load reporting is large and is likely to increase. U.S. HIV Treatment Guidelines recommend periodic assessments among persons that are on antiretroviral therapy or among persons whose HIV disease is being monitored, and the number of persons living with HIV is increasing. It is not uncommon for a laboratory to cease VL reporting for a short period as new laboratory staff are hired or veteran laboratory staff take vacations. To identify such lapses in reporting, HIV surveillance jurisdictions monitor laboratories for their volume of reporting over time.

The complete absence of any lab test result (CD4+ T-lymphocyte count or viral load) may suggest the person is not in care, moved away, is receiving care out of jurisdiction, or died, or there is a significant reporting issue (see Table B1). There are some instances, however, where an HIV-infected person resides and receives care within an HIV reporting jurisdiction but no medical care information is shared with HIV surveillance. There are a limited number of federal and private facilities that do not share or allow HIV surveillance staff to have access to medical records of persons being cared for by the facility. Efforts to address these barriers are underway with some facilities.

As technology has advanced, laboratories are moving toward reporting lab results electronically, but many laboratories still do not have this capability. Some HIV reporting jurisdictions have a backlog of paper lab results, and some jurisdictions with early electronic lab reporting have maintained electronic HIV lab reports in a separate database apart from eHARS. Viral load results reported on paper that have not been entered into eHARS are not available for analysis. Separately stored electronic lab files that have not been entered into eHARS may also not be accessible for analytic purposes.

The extent of missing lab results is best described from a recent survey of selected HIV reporting jurisdictions. Of the 15 jurisdictions that responded, *26–89% of persons living with HIV and reported to surveillance were missing a viral load result* [6]. The large range of missing viral load results may be attributable to many factors as described in Table B1.

The issue of jurisdictional versus residential case status has some implications for missing lab results. Persons diagnosed in one jurisdiction, by convention, remain in the database as a case in that jurisdiction even if the person moves across the country and receives care in their new home state. The recommended procedure for each HIV reporting area is to enter all lab results into their HIV database, regardless of jurisdictional or residential case status. After all jurisdictions upload their data to CDC, it may be possible to link lab results to jurisdictional cases that have moved; at this time, there is no mechanism that allows for sharing this information with local jurisdictions by CDC or between local jurisdictions directly. Early in the epidemic, when HIV diagnosis was often shortly followed by death, describing jurisdictional cases was reasonable. Today, with effective antiretroviral treatment available and the impetus to look more closely at transmission and prevention of new HIV infections, residential cases may also be an important population to surveil.

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6   Community Viral Load Workgroup Survey, conducted January–February 2011 among the 26 participating Workgroup jurisdictions.

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Table B1. Circumstances of missing viral load (VL) results and strategies for addressing

Issue	Strategy
• State laws/regulations are not in place for laboratories to report **all** VL results	Amend state regulations (see Appendix C, state-specific status of reporting laws for all VL results).
▪ Detectable VL results may be used for a subset of VL analyses (see Figure 4b)	Although jurisdiction may be able to conduct limited analyses, they should strive to collect all VL results, using strategy listed above.
• Not all laboratories that should be reporting VL results are reporting	Get to know your local laboratories and establish relationship for reporting.
▪ May be limited to a period, such as during holiday season when staff coverage changes	Monitor the reporting by laboratory each month to ensure ongoing reporting.
• Private or federal hospital/clinic labs do not report HIV lab results to state or allow surveillance staff access to medical records (varies by state or jurisdiction)	Establish working relationship with local institutions; this may require federal assistance.
• Neighboring HIV jurisdiction not sharing lab results with the jurisdiction in which the case resides (e.g., resident of State A receives HIV care in State B, State B receives all lab results from clinic in State B, but State B does not share those lab results with State A)	Option 1: State A changes language of its lab reporting regulations to facilitate receiving its residents' lab results. Option 2: Develop mechanism for data sharing.
• There is evidence that HIV-infected persons are in care but VL results are missing (e.g., CD4 results but no VLs)	Some investigation needed to determine reason for missing VLs; e.g., lab not sending VLs, etc.
• HIV-infected person may have died	Jurisdictions should conduct annual data linkage to registries with death information, such as their state vital statistics database, and at least one national registry, such as the Social Security Death Index or National Death Index.
• HIV-infected person may have moved out of jurisdiction	Participate in CDC's intra-and interstate case deduplication processes.
• Not all VL results have made it into the surveillance data system (e.g., results reside on paper or in a supplementary database)	Obtain resources to enter backlog of paper lab reports and continue with real-time entry; increase electronic reporting from labs; request CDC assistance to implement import into eHARS.
• HIV-infected person is not engaged in ongoing care for his/her HIV disease (may be by choice or influenced by other social/mental health issues; other reasons, see Strategy)	Partner with other public health colleagues and community-based organizations to determine reasons for not being engaged in care and, if possible, link to ongoing care.

HRSA

The Health Resources and Services Administration [7], HRSA, is one of several agencies, including CDC and NIH, under the leadership of U.S. Department of Health and Human Services. HRSA is responsible for improving access to health care services for people who are uninsured, isolated, or medically vulnerable.

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[7] HRSA web pages accessed on 29 April 2011 include: http://www.hrsa.gov/about/index.html, http://hab.hrsa.gov/tools/needs/NAGSecII.htm, http://hab.hrsa.gov/tools/HIVoutreach/HIVoutreach2.htm.

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Since the early 1990s, the Ryan White HIV/AIDS Program has provided an array of HIV-related and health care services to help vulnerable HIV-infected persons manage their disease. Based on the numbers of persons infected with HIV, service needs among these persons, local resources available, and an assessment of unmet need and service gaps, HRSA provides states with funding to bridge these gaps. Medical care and antiretroviral medications (through the AIDS Drug Assistance Program) are just two services that HRSA funds through and in partnership with states.

Each year, jurisdictions provide an epidemiologic description of HIV-infected persons to HRSA's HIV/AIDS Bureau. Most of the data used to describe the epidemic in a jurisdiction originates from HIV surveillance, so it is important to try to harmonize terms and processes that meet both HRSA and CDC needs.

Definitions and terms

- Persons living with HIV (with and without AIDS) in a jurisdiction.

  - HIV surveillance would refer to these individuals as resident cases, which is distinct from jurisdictional cases. HIV surveillance case "ownership" is limited to jurisdictional cases that are residents at diagnosis.

- Persons with unmet need are diagnosed with HIV infection but not in care for a defined 12-month period [8].

  - HIV surveillance uses lab test results (CD4+ T-lymphocyte count or viral load) as a marker for being in care. Those persons without a lab result for 12 months or greater would be considered not in care (or out of care). HRSA includes lab results and receipt of antiretroviral medications within a 12-month period as markers of being in care.

- Persons "in care" are receiving primary healthcare for their HIV disease. This care should be consistent with the U.S. HIV Treatment Guidelines [2].

  - HIV surveillance uses lab test results as a marker for being in-care. While ongoing evidence of laboratory testing is strongly suggestive of ongoing encounters with the healthcare system, the quality and appropriateness of these medical encounters cannot be fully assessed with routine HIV surveillance data. For most surveillance jurisdictions, with geographically dispersed cases and varying health facility-specific rules and policies, costs are prohibitive to collect detailed medical care information. Collecting this type of medical encounter information is possible for circumscribed populations of HIV-infected persons and is part of the CDC's Medical Monitoring Project (MMP), which includes a representative sample of HIV-infected persons who are engaged in HIV care.

- HIV-infected persons are retained in care as assessed by at least two clinical visits in a year that are at least 60 days apart [9].

  - HIV surveillance uses lab results as a marker for being in-care. Based on the temporal distribution of the collection date for each lab test, it is possible to assess whether two medical encounters occurred within a calendar year, spaced at least 60 days apart. It would be difficult, however, for surveillance data to determine with certainty if the lab tests were part of the same continuous care

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8   Douglas Morgan and Emily McKay. Estimating and assessing unmet needs; presented July 14 and 15, 2009 at CDC's HIV Surveillance Workshop, Atlanta, Georgia.

9   Horberg MA, Aberg JA, Cheever LW, Renner P, Kaleba EO, Asch SM. Development of national and multiagency HIV care quality measures. *Clin Infect Dis* 2010;51:732–738.

or might represent fragmented care as, for example, one test may be ordered by an HIV healthcare provider and another test ordered by an emergency department physician.

- Persons in care that begin antiretroviral treatment achieve virologic suppression after 6 month [9]

    - HIV surveillance can provide a rough proxy assessment of reporting the proportion of persons in care that have viral load results ≤200 copies/mL for a calendar year. Because antiretroviral medication use and initiation is not collected by HIV case surveillance, this type of clinical measure is best addressed by MMP.

Appendix C. Viral Load Reporting

Viral load reporting by HIV surveillance reporting area as of April 2011—
50 states, funded cities, District of Columbia, and U.S. dependent areas

| State/Area | Viral load | | |
	Reporting required	Reportable level[a]	When all VLs became available[b]
Alabama	No	—	—
Alaska	Yes	All results	Feb 1999
American Samoa	No	—	—
Arizona	Yes	Detectable	—
Arkansas	Yes	All results	Jan 2005
California	Yes	All results	Apr 2006
Chicago	Yes	All results	Jan 2006
Colorado	Yes	All results	Apr 2010
Connecticut	Yes	All results	Jan 2006
Delaware	Yes	All results	July 2001
District of Columbia	Yes	All results	June 2007
Florida	Yes	All results	Nov 2006
Georgia	Yes	All results	Dec 2003
Guam	Yes	All results	May 2009
Hawaii	Yes	All results	Mar 2008
Houston	Yes	All results	Jan 2010
Idaho	Yes	Detectable	—
Illinois	Yes	All results	Jan 2006
Indiana	Yes	All results	Sep 2000
Iowa	Yes	All results	Jan 2005
Kansas	Yes	Detectable	—
Kentucky	Yes	Detectable	—
Los Angeles	Yes	All results	Apr 2006
Louisiana	Yes	All results	Feb 1999
Maine	Yes	All results	Apr 2008
Maryland	Yes	All results	Apr 2007
Marshall Islands	No	—	—
Massachusetts	No	—	—
Michigan	Yes	All results	Apr 2005
Micronesia	No	—	—
Minnesota	Yes	Detectable	—
Mississippi	Yes	All results	Jan 1996
Missouri	Yes	All results	June 2000
Montana	Yes	Detectable	—
Nebraska	Yes	All results	Jan 2001
Nevada	Yes	Detectable	—
New Hampshire	Yes	All results	June 2008
New Jersey	Yes	All results	Jan 2000
New Mexico	Yes	All results	Jan 1998
New York City	Yes	All results	June 2005
New York	Yes	All results	June 2005
North Carolina	Yes	Detectable	—
North Dakota	Yes	All results	Aug 2002
Ohio	Yes	Detectable	—
Oklahoma	Yes	All results	June 2007

Appendix C. Viral Load Reporting

State/Area	Viral load		
	Reporting required	Reportable level[a]	When all VLs became available[b]
Oregon	Yes	All results	Aug 2006
Palau	No	—	—
Pennsylvania	Yes	Detectable	—
Philadelphia	Yes	Detectable	—
Puerto Rico	Yes	All results	Jan 2003
Rhode Island	Yes	Detectable	—
San Francisco	Yes	All results	Apr 2006
South Carolina	Yes	All results	Jan 2004
South Dakota	No	—	—
Tennessee	Yes	Detectable	—
Texas	Yes	All results	Jan 2010
Utah	Yes	All results	Sep 1999
Vermont	Yes	All results	Oct 2005
Virgin Islands, U.S.	Yes	Detectable	—
Virginia	Yes	All results	May 2007
Washington	Yes	All results	Sep 2006
West Virginia	Yes	All results	July 1999
Wisconsin	Yes	All results	Jan 2011
Wyoming	Yes	All results	Jan 2000

[a] Level at which viral load reporting is required by state laws, regulations or statutes. All results include undetectable and detectable viral load test results.

[b] For some states this is the time when the statute took effect; for other states, because of the breadth and lack of specificity of their reporting regulation, this is the period when they started to receive all VL results

Appendix D

U.S. HIV Treatment Guidelines

The most recent update of ***Guidelines for the Use of Antiviral Agents in HIV-1–Infected Adults and Adolescents*** was released January 2011 [2] (hereafter referred to as the U.S. HIV Treatment Guidelines). The U.S. HIV Treatment Guidelines describe in detail the recommended clinical management of persons infected with HIV and from this and other work, HIV quality of care measures have been developed [8]. The focus of this section is on laboratory monitoring that is part of clinical management because lab data are actively pursued as part of HIV surveillance.

As part of monitoring HIV disease progression and response to antiretroviral medications, monitoring of CD4+ T-lymphocyte counts and plasma HIV RNA concentration (viral load) have been recommended. Both tests should be ordered when an HIV-infected person enters care, at antiretroviral treatment initiation, every 3–6 months until clinically stable, and when clinically indicated. Because viral load is the most important indicator of antiretroviral treatment response, more frequent viral load monitoring may be performed when a treatment regimen is changed. At a minimum, one would expect at least 1–2 viral load measurements over the course of a year in which a person is engaged in HIV care.

Tests that measure viral load have become more sensitive over time. Older viral load tests' lower limit of detection was 1000 copies/mL, but some tests today can detect and quantitate as few as 20 copies/mL. A viral load of 250 copies/mL may have been interpreted as undetectable using the older test but detectable using the most sensitive test available today. Across a jurisdiction, different viral load tests with varying levels of test sensitivity may be in use at the same time. Also, because there is some variability in viral load results at low levels, the U.S. HIV Treatment Guidelines adopted "**viral load >200 copies/mL as indicative of virologic failure**" [2]. For an individual, the minimal change in viral load that is considered significant is a 3-fold or a 0.5 $\log_{10}$ copies/mL change.

Antiretroviral treatment initiation, for the most part, is guided by CD4+ T-lymphocyte counts. One instance, however, in which viral load levels are used for treatment is when "**rapid initiation of treatment is recommended when viral load is high, i.e., >100,000 copies/mL**" [2].

Appendix E

National HIV/AIDS Strategy

In July 2010, the White House released the National HIV/AIDS Strategy [10]. The document included three primary goals: 1) reducing the number of people who become infected with HIV; 2) increasing access to care and improving health outcomes for people living with HIV; and 3) reducing HIV-related health disparities.

The Strategy defines in its "Reducing HIV-Related Disparities and Health Inequities" chapter the following actions related to community viral load:

- Step 1.1 Ensure that high-risk groups have access to regular viral load and CD4 tests.
- Step 2.2 Ensure that all high prevalence localities are able to collect data necessary to calculate community viral load, measure the viral load in specific communities, and reduce the viral load in those communities where HIV incidence is high.

The Federal Implementation Plan [11], a companion document to the National HIV/AIDS Strategy, lists in the "Reducing HIV-Related Health Disparities" chapter that:

By the end of 2011, CDC will:

- Conduct consultation with HRSA to develop recommendations for gathering and reporting data to calculate CVL.
- In consultation with States, provide technical assistance to localities, particularly those with a heavy disease burden, to collect necessary data to calculate community viral load.

Furthermore, the National HIV/AIDS Strategy establishes national targets—by end of 2015:

- Increase the proportion of HIV-diagnosed gay and bisexual men with undetectable viral load by 20 percent.
- Increase the proportion of HIV-diagnosed blacks with undetectable viral load by 20 percent.
- Increase the proportion of HIV-diagnosed Latinos with undetectable viral load by 20 percent.

On March 9–10, 2011, a consultation on "Monitoring and Use of Laboratory Data Reported to HIV Surveillance" was hosted by CDC and HRSA. The recommendations from that consultation will become available in 2011.

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[10] National HIV/AIDS strategy for the United States. http://www.whitehouse.gov/ONAP. Published July 2010. Accessed August 25, 2011.

[11] National HIV/AIDS strategy for the United States. Federal implementation plan. http://www.whitehouse.gov/files/documents/nhas-implementation.pdf. Published July 2010. Accessed August 25, 2011.

Appendix F. List of Test and Treat Clinical Trials

Today there are several trials evaluating the use of ARV-based prevention in people with HIV. The goal of these "treatment as prevention" strategies is to reduce viral load and thereby reduce individuals' infectiousness. Data gathered from serodiscordant couples enrolled in a trial of HSV-2 treatment for HIV prevention showed that effective ARV treatment reduced HIV transmission by approximately 92 percent. These data were not from a randomized controlled trial and ongoing trials—many listed below—will provide additional information. Not included in this table are the many ecological studies of ART impact on HIV prevalence in different settings.

ARV-Based Prevention in HIV-Positive Individuals: Relevant studies *(April 2011)*					
Study	**Location**	**Funder**	**Population / Mode of exposure**	**Hypothesis/Study Aim**	**Status / Results expected**
HIV VCT and Linkage to Care in Uganda	Uganda	National Institutes of Health (NIH)	3,314 men and women	Tests the hypothesis that enhanced counseling and testing for HIV among hospitalized adults is more efficacious than traditional counseling and testing in reducing HIV risk behavior. Tests if an enhanced linkage to HIV-specific medical care is more effective than usual referral in receipt of OI prophylaxis, ART and reducing mortality.	Ongoing / Q4 2011
SEARCH: Sustainable East African Research for Community Health	Uganda, Kenya, Tanzania	NIH	Rural populations	Is a streamlined health care delivery approach that combines HIV/AIDS, TB, malaria treatment and community-health screening feasible and does it reduce incidence of HIV, TB and malaria in a community randomized trial?	Ongoing / 2011–12
TLC-Plus (HPTN 065): Evaluating Methods to Increase HIV Testing, Access to HIV Care and HIV Prevention Strategies	US (Bronx, NY, and Washington, DC)	NIH	22,000 men and women	Is it feasible to implement a community-level test, link to care plus treat strategy in the US? What is the effectiveness of a financial incentive intervention versus standard of care in enhancing linkage to care and viral suppression? Does a computer-delivered intervention enhance standard of care for prevention with positives?	Ongoing / 2013
Methods for Prevention Packages Program (MP3): An HIV Prevention Package for Mochudi	Botswana	NIH	14,000 men and women	What is the feasibility and acceptability of a package of interventions including education for behavior modification, circumcision of adult males and the use of antiretroviral drugs to decrease transmission at the community level? Data to be gathered include incidence, prevalence and behavioral risk factors; uptake of services; and acceptance of ART among HIV-positive individuals with acute infection and/or VL > 100,000 who do not otherwise qualify for treatment based on national guidelines, AIDS-defining illness or CD4 < 250.	Ongoing / 2013
PopART: Population Effects of Antiretroviral Therapy to Reduce HIV Transmission	Uganda (pilot study in Wakiso District), Malawi, Tanzania, Zambia	UK Medical Research Council	15,000 men and women	Is it feasible and acceptable to undertake a study of universal VCT, followed by immediate ART for all testing positive for HIV, to reduce population-level transmission?	Start Q3 2011 / 2014
START: Strategic Timing of Antiretroviral Treatment	Africa, the Americas, Asia, Australia, Europe (30 countries)	NIH	4,000 ARV-naïve men and women with CD4 counts above 500	How does early treatment initiation affect clinical outcomes including progression to AIDS, serious non-AIDS diagnoses and mortality?	Ongoing / 2015
Preventing Sexual Transmission of HIV with Anti-HIV Drugs (HPTN 052)	Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, Zimbabwe	NIH	3,500 sero-discordant couples (opposite and same sex)	Does early initiation of treatment for the HIV-positive partner reduce risk of transmission in serodiscordant couples?	Ongoing / 2015
Treatment as Prevention (TasP or Ukuphila kwami, ukuphila kwethu)	South Africa (Kwazulu Natal)	Agence nationale de recherches sur le sida et les hépatites virales (French AIDS Research Agency)	40,000 men and women	After feasibility is established: Does early treatment initiation reduce incidence in a cluster-randomized design?	Start Q3 2011 / 2015
MP3: Acute HIV Infection in Heterosexuals	Malawi	NIH	115 men and women with acute HIV infection	The specific aims of the study are to: 1) Develop a novel program to prevent HIV transmission by identifying and informing persons with acute HIV infection (AHI); 2) Evaluate a short-term, combined behavioral and ART intervention to prevent HIV transmission among persons with AHI, 3) Determine the potential individual and combined impact of each intervention.	Start Q3 2011 / 2015
MP3: Enhanced Prevention in Couples (EPIC)	Lesotho	NIH	1,770 serodiscordant couples	The EPIC study aims to decrease the risk of HIV acquisition in HIV-negative partners within serodiscordant couples in Lesotho through implementation of an Enhanced Prevention Package, elements of which will be evaluated in feasibility studies. These interventions include male circumcision, couples counseling for HIV testing, ART adherence and risk reduction, and could also incorporate new interventions such as PrEP and microbicides identified in ongoing trials.	Start 2011 / To be determined

Appendix G. Mathematical Formula for Sample Size

Sample size required to detect the difference of GM between two subpopulation groups

April 21, 2011

Suppose that we would like to have a power of W (say 80% chance) to detect a difference that one group has a GM at least as k fold high as the GM of the other group.

Null hypothesis: $GM_1 = GM_2$ or $GM_{max}/GM_{min} = 1$

where $GM_{max} = \max(GM_1, GM_2)$ and $GM_{min} = \min(GM_1, GM_2)$

Alternative hypothesis: $GM_1 \neq GM_2$ or $GM_{max} / GM_{min} > 1$

Test statistic:

$$z = \frac{1}{SE} log10 \; (\widehat{GM}_{max}/\widehat{GM}_{min})$$

where SE is the pooled standard error estimate given by

$$SE = \sqrt{S_1^2/n_1 + S_2^2/n_2}$$

The p-value for this test is given by $p = Prob(Z > z) = 1 - \varphi^{-1}(z)$ where $Z \sim$ Normal $(0,1)$ and $\varphi^{-1}(z)$ is the inverse function of the standard normal distribution

Given the type I error rate α (e.g., 0.05) and the difference desired to detect: $GM_{max} / GM_{min} = k$, the power or the probability to detect this difference can be calculated as

$$W = Prob\left(Z > \varphi^{-1}(1 - \alpha) - log_{10}(k)/(S\sqrt{1/n_1 + 1/n_2})\right)$$

where S is the expected standard deviation of $log_{10}(VL)$ in the population of interest.

When $n_1 = n_2 = n$, we have

$$W = Prob\left(Z > \varphi^{-1}(1 - \alpha) - log_{10}(k)/(S\sqrt{2/n})\right)$$

Given the type I error rate (α), the relative difference to detect (k), the expected standard deviation of $log_{10}(VL)$ (S), and the desired power (W), the required sample size is

$$n = 2[(\varphi^{-1}(1 - \alpha) - \varphi^{-1}(1 - W))S/log_{10}(k)]^2$$

The required sample sizes are listed in Table 1a for $W = 0.8$ and Table 1b for $W = 0.9$ with $\alpha = 0.05$ and various S and k.

Appendix H. Community Viral Load Workgroup

History

On March 16, 2010, staff from the HIV Incidence and Case Surveillance Branch of CDC initiated a Community Viral Load Workgroup composed of HIV surveillance coordinators experienced and/or interested in estimating community viral load in their area. The purpose of the Workgroup was to develop recommendations for estimating community viral load at the local, state, and national level. The Workgroup had 10 calls between March 16, 2010 and April 27, 2011.

During these calls, participants reviewed current methods being used for calculating community viral load, definitions, estimation assumptions, strengths and weaknesses of estimates, and representativeness of the data used to produce the estimates. Participation in the Workgroup grew from 8 city and state health department staff (Chicago, District of Columbia, Los Angeles, Maryland, Minnesota, New York City, San Francisco, and Washington) on the first call to 26 city/state health departments on the last calls (California, Colorado, Connecticut, Florida, Georgia, Houston, Kentucky, Louisiana, New York State, North Carolina, Oregon, Pennsylvania, Philadelphia, South Carolina, Tennessee, Texas, Virginia, and Wisconsin).

A sub-working group was formed to discuss the details for the final recommendations. There were four sub-working group calls and its active members included: California, Chicago, District of Columbia, Houston, Los Angeles, New York City, New York State, Oregon, and San Francisco.

Glossary

ART: antiretroviral treatment or therapy.

ARV: antiretroviral; usually used in association with treatment or medication use.

Categorical VL measures: categories of VL measurement that are useful indicators. Standardized categorical measures include: percentage suppressed/not suppressed, percentage undetectable, and percentage high VLs.

Component VL measures: boxed groups described in Figure 2. They include: A. In care and with undetectable VL; B. In care with detectable VL; C. In care, no VL; D. Diagnosed but not in care; and E. Undiagnosed.

CVL: community viral load.

eHARS: standardized HIV surveillance database used by all jurisdictions. It is a relational database that is document-based.

Jurisdictional case: person diagnosed with HIV or AIDS while a resident of the jurisdiction

Lag time: delay between the occurrence of an event and when the event is known or reported; e.g., deaths in 2009 may not be recorded until 2010 because there is an 18-month lag time for $\geq 90\%$ of deaths in 2009 to be recognized and captured in a database.

Log$_{10}$=log base 10: the logarithm for base 10 is the exponent; e.g., the logarithm of 1000 to base 10 is 3. The log$_{10}$ transformation of a viral load of 1000 copies/mL is 3.

MMP: Medical Monitoring Project (MMP) is a nationally representative surveillance system administered by CDC among HIV-infected persons that are receiving medical care for their HIV disease.

Multiple imputation: analytic process in which missing data are populated with values based on existing data through multiple rounds of data simulations.

NDI: National Death Index. See Vital Statistics for an explanation.

Resident case: HIV-infected person currently residing in a jurisdiction. Not all residential cases are jurisdictional cases (see definition above) as persons may be diagnosed in one jurisdiction but move to another.

SAS: software in wide use for statistical analyses of HIV surveillance data.

Soundex: 4-character alphanumeric "code" that is based on the sound or pronunciation of an individual's last name. Soundex is used instead of name to identify a case along with demographic information.

SSDI: Social Security Death Index is based on the national Social Security Death Master File, which includes death information (name, social security number, date of death, possibly residence at time of death) for most persons that have a Social Security number. The SSDI is updated quarterly.

Viral load (VL): measure of the concentration of viral particles per volume of blood. The unit of measurement for HIV viral load is copies per milliliter or copies/mL.

Viremia: presence of virus in the blood.

Vital statistics: collection of birth, death, and marriage information; local jurisdictions collect or receive this information. For this document, death data are the focus. Death certificates, which include cause of death information, are collected by local Vital Statistics departments. States aggregate local death information and then provide this data to CDC's National Center for Health Statistics, where a national death dataset is created and cause of death information are recoded to provide uniformity across states. The national dataset is called the National Death Index or NDI.