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Using HIV Viral Load From Surveillance to Estimate the Timing of Antiretroviral Therapy Initiation

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Abstract

Introduction—HIV surveillance programs do not typically collect comprehensive data on antiretroviral therapy (ART). We validated a population-based measure of ART initiation that uses HIV viral load (VL) results in the absence of data on ART.

Methods—We used CD4/VL data reported to NYC HIV Surveillance for persons aged ≥13 years and diagnosed with HIV from 2006 to 2012 to validate estimates of ART initiation date based on 3 ART initiation definitions: (1) 1-log decline in copies per milliliter between 2 VLs over 3 months; (2) 2-log decline in copies per milliliter between 2 VLs over 3 months; and (3) the earliest of either a 1-log decline in VL over 3 months, or a change from detectable VL to undetectable VL (<400 copies/mL) over any interval. We plotted median CD4 counts by quarter before and after ART initiation to compare estimated initiation date with nadir of the CD4 trajectory.

Results—A total of 24,348 persons were diagnosed with HIV in NYC from 2006 to 2012. In all, 12,123 persons had probable ART initiation based on 2-log decline, 12,719 based on 1-log decline, and 14,311 based on 1-log decline or detectable–undetectable change. Lowest median CD4 count occurred at the estimated ART initiation date for all 3 definitions. The definition based on a 1-log VL decline or a change from detectable to undetectable VL captured more ART initiations and identified earlier initiation dates.

Conclusions—Serial VL measures are a valid source for estimating ART initiation. A definition that includes a 1-log VL decline or a change from detectable to undetectable VL performed best.

Keywords

HIV; antiretroviral therapy; CD4 count; surveillance; validation

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INTRODUCTION

The HIV care cascade, which depicts prevalence estimates for sequential steps from HIV infection to viral suppression, has become a preferred tool used for monitoring national and local HIV epidemics.^{1–3} HIV case surveillance data are population based, allowing surveillance programs to generate representative cascade estimates using HIV-related laboratory tests [ie, CD4 lymphocyte (CD4) and viral load (VL)] as a proxy measure of HIV care engagement.⁴ Case surveillance data in parallel with comprehensive laboratory reporting allow jurisdictions to quantify the number and proportion of persons with HIV who are diagnosed, linked to care, retained in care, and virally suppressed. Quantifying the HIV cascade at the local level is imperative for monitoring trends, identifying priority areas for prevention and service delivery, and data-driven allocation of resources.

Antiretroviral therapy (ART) prescription and medication adherence data are typically not reported to or collected by surveillance, or otherwise available at the population level. Surveillance programs commonly measure population-level HIV viral suppression by calculating the proportion of persons with HIV (PWH) in their jurisdiction that has undetectable HIV viral loads.³ Viral suppression prevalence is interpreted as a proxy for the extent of effective ART coverage in the population. Although prevalence of viral suppression is an important measure of both the clinical status of PWH and HIV prevention needs in a population, it does not provide information about *initiation* of ART after diagnosis at the population level. Persons who have initiated ART but not yet achieved viral suppression are not counted in measures of the prevalence of viral suppression and are generally not distinguished on surveillance-based HIV care continuums from persons who never initiated ART. Moreover, without information on ART initiation dates, important key population metrics like the level of immunodeficiency at the start of ART cannot be measured.

The development of a valid population-based measure of the time from HIV infection to diagnosis and to ART initiation would allow for more complete characterization of local HIV epidemics. Specifically, quantifying the timing of ART initiation relative to diagnosis would allow for identifying groups for public health intervention (eg, persons not initiating ART in a timely manner after diagnosis) and evaluating the implementation and uptake of national and local treatment guidelines.^{5,6}

ART initiation rapidly induces substantial reductions in HIV RNA.⁷ A typical clinical goal is a 1- to 2-log reduction in viral load within 4–8 weeks after treatment initiation.⁵ Failure to achieve the target level of less than 50 copies per milliliter after 16–24 weeks of treatment should prompt consideration of drug resistance, inadequate drug absorption, or suboptimal medication adherence. Serial HIV viral load measurements reported to HIV surveillance systems could therefore be used to examine and theoretically infer the timing of treatment initiation among individual PWH and ultimately to quantify treatment coverage at the population level.⁸ Given that most jurisdictions have mandatory HIV viral load reporting (44/50 states as of July 2014)⁹ but do not include HIV medication information, the development of such a measure has broad implications and utility in terms of measurement/monitoring the epidemic and progress toward responding to it.

The primary objective of this analysis was to assess the feasibility of using serial HIV viral load results reported to surveillance to infer whether and when a newly diagnosed person initiated ART (probable ART initiation). The secondary objective was to compare different surveillance-based measures of probable ART initiation to identify the definition that (1) is the most inclusive (ie, accurately captures the most individual initiators) and (2) most accurately captures the date of probable ART initiation as based on longitudinal viral load and CD4⁺ count patterns.

METHODS

Data Sources and Study Population

New York State public health law requires named reporting of all HIV/AIDS diagnoses, all HIV-related illness, all CD4 and VL tests, all HIV genotypes, and all positive diagnostic tests to the New York City Department of Health and Mental Hygiene (DOHMH). The HIV Epidemiology and Field Surveillance Program (HEFSP) maintains the population-based HIV Surveillance Registry, which is continuously updated with demographic information on persons meeting the CDC's HIV surveillance case definitions and with results of all CD4 and VL laboratory tests conducted in NYC. Vital status information comes from regular matches of Registry data with DOHMH and national vital statistics databases. All surveillance data used in this analysis were drawn from the Registry as of March 31, 2014.

The source population for this analysis was persons who were newly diagnosed with HIV between 2006 and 2012 in New York City and reported to the HIV Surveillance Registry, and at least 13 years of age at the time of HIV diagnosis. Persons also had at least 2 HIV viral load tests ordered after HIV diagnosis, which were used for measuring ART initiation. Persons included in the ART trajectory analysis had a CD4 count ordered at the time of HIV diagnosis (within 6 months after) and a CD4 count ordered at ART initiation (within 3 months prior); these data enabled examination of CD4 trajectories before and at ART initiation. We included in the CD4 trajectories CD4 counts after estimated ART initiation date for persons who had such a CD4 value.

Measures

Definitions of ART Initiation—We evaluated 3 definitions of probable ART initiation and created analytic cohorts of newly diagnosed persons meeting each definition. The first and second measures of probable ART initiation, which we will refer to as *Log 1* and *Log 2*, were defined as a 1-log decline (ie, base 10 log) in the copies per milliliter between 2 VLs over a 3-month period or a 2-log decline in VL over a 3-month period, respectively. We looked for the decline from the date of diagnosis to the end of the analytic period, including after a person had an undetectable VL. With the exception of a small minority of persons who naturally control their infection,¹⁰ persons with undetectable HIV viral load (ie, viral load levels below the limit of detection on standard HIV viral load testing platforms) can be presumed to be taking ART. Given this, the third measure of ART initiation incorporated a change in viral load levels from detectable to undetectable. The third definition of ART initiation, *Log 1-Plus*, was defined as the first occurrence of either (1) a 1-log decline in VL over a 3-month period or (2) a change from a detectable viral load to an undetectable

viral load (<400 copies/mL) over any interval during the analytic period. For all 3 definitions, the estimated date of ART initiation was calculated as the midpoint of the interval (in days) between the 2 viral loads representing the above 3 definitional scenarios.

ART-Associated CD4 Trajectories—To examine pre- and post-ART initiation CD4 trajectories, we used all CD4 count values reported to the Registry with accompanying CD4 test dates for persons with probable ART initiation. We examined CD4 counts reported in each quarter (91-day intervals) before and after the date of ART initiation, and for each quarter, we took the mean of an individual's CD4 counts. The median CD4 count in a given quarter was calculated as the median of the individual means. Not all persons contributed a CD4 count value to every quarter; however, each person contributed a CD4 at HIV diagnosis and a CD4 at ART initiation to the analysis. For individuals who initiated ART early after diagnosis, these 2 CD4 counts could be the same; in this case, the CD4 would be counted only once in the graph of CD4 count by quarter.

Statistical Methods—To visually assess the validity of the 3 ART definitions, we plotted median CD4 counts before and after ART initiation. The hallmark of HIV infection and disease progression is continuous and progressive depletion of CD4⁺ T cells. After treatment initiation, recovery of CD4⁺ T cells occurs.¹¹ Therefore, we hypothesized that if our definitions of ART initiation were valid, the nadir of the CD4 trajectory would coincide well with the estimated date of ART initiation.¹² Only ART initiation would induce a consistent “V” shaped pattern in the CD4 trajectory, with CD4 falling until ART initiation and rebounding after ART initiation. All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of N = 24,348 persons were diagnosed with HIV in New York City from 2006 to 2012 (Fig. 1). Of these, 73% (N = 17,773) had a CD4 count at HIV diagnosis. There were 14,311 persons who met the *Log 1-Plus* definition, 12,719 who met the *Log 1* definition, and 12,123 who met the *Log 2* definition (Fig. 1). Based on these definitions, 81%, 72%, and 68%, respectively, of persons newly diagnosed with HIV in NYC from 2006 to 2012, who had a CD4 count at diagnosis, initiated ART. To examine CD4 trajectories, the subset of people meeting each ART definition was further restricted to N= 13,014, N= 12,081, and N= 11,607 persons with a CD4 count at the time of initiation of ART based on *Log 1-Plus*, *Log 1*, and *Log 2*, respectively (Fig. 1). Of note, 99.4% (N = 12,938/13,014), 99.3% (N = 11,995/12,081), and 99.3% (N = 11,525/11,607) of people meeting the *Log 1-Plus*, *Log 1*, and *Log 2* definitions, respectively, of ART initiation ever had a CD4 count after ART initiation (Fig. 1). Median time (in days) from ART initiation date to the first CD4 after was 45, 41, and 40 days for people meeting the *Log 1-Plus*, *Log 1*, and *Log 2* definitions, respectively. The lowest median CD4 count occurred at the estimated time of ART initiation for all 3 definitions (Fig. 2). Median CD4 counts declined until ART initiation and rebounded after ART initiation. There was little overall variation between the 3 definitions. Among persons with at least one CD4 reported after ART initiation, the nadir corresponded to the quarter of ART initiation for 67% (N = 8676/12,938), 63% (N = 7560/11,995), and

64% (N = 7358/11,525) of persons meeting the *Log 1-Plus*, *Log 1*, and *Log 2* definitions (Fig. 1).

Comparison of Persons Meeting Log 1 and Log 2 Definitions

More persons met the *Log 1* definition than the *Log 2* definition (12,719 vs. 12,123) (Fig. 1). Among persons meeting the *Log 1* definition, 83% (N = 10,496/12,719) had the same date of ART initiation whether based on the *Log 1* or *Log 2* definition (Table 1). For persons meeting the *Log 1* definition but not the *Log 2* definition and having a CD4 count reported at ART initiation (N = 541), the median CD4 graph appeared to have multiple inflection points; however, the clearest inflection point in median CD4 coincided with the estimated time of ART initiation (Fig. 3A). Among persons who had a *Log 1* date of ART initiation that was earlier than their *Log 2* date of ART initiation and had a CD4 count reported at both dates (N = 1449), the inflection point coincided with the estimated time of ART initiation for both groups (Fig. 3B). As the *Log 1* and *Log 2* estimated dates of ART initiation were the same for 83% of people meeting the *Log 1* definition, the ART dates were a median of 0 days apart from one another, and the 2 groups had similar nadirs (Table 1). Among persons with an earlier *Log 1* date than *Log 2* date of ART, estimated ART initiation dates were a median of 165 days earlier (Table 1). The graph (Fig. 3B) shows that while the inflections occurred close in time to one another, the nadir for *Log 1* is higher because the estimated ART initiation date is earlier for this definition.

Comparison of Log 1 and Log 1-Plus Definitions

More persons met the *Log 1-Plus* definition than *Log 1* (N = 14,311 vs. 12,719) (Fig. 1). Among persons meeting the *Log 1* definition, 73% (N = 11,352/14,311) had the same *Log 1* and *Log 1-Plus* date of ART initiation (Table 1).

Among persons who met the *Log 1-Plus* definition, 21% (N = 2959/14,311) qualified as initiating ART based on a detectable to undetectable viral load (Table 1). The people who qualified through the detectable to undetectable switch either met the *Log 1-Plus* but not the *Log 1* definition (N = 1592) or had a *Log 1-Plus* date of ART that was earlier than *Log 1* (N = 1367) (Table 1). We plotted the CD4 counts for (1) people who qualified as initiating ART based on a detectable to undetectable switch within the *Log 1-Plus* definition and had a CD4 at *Log 1* ART date (N = 2190; Fig. 4A) and (2) the subset of persons who met the *Log 1-Plus* definition but not the *Log 1* definition (ie, these persons *never* had at least a 1-log decline in viral load within 3 months) and had a CD4 count reported at the *Log 1-Plus* ART date (N = 1114) (see Supplemental Digital Content, <http://links.lww.com/QAI/A825>). In both instances, the lowest median CD4 value coincided with the estimated time of ART initiation.

Among persons with a *Log 1-Plus* estimated date of ART initiation that was earlier than the *Log 1* estimated date of ART initiation (ie, persons who had an undetectable viral load reported *earlier* than the 1-log decrease in viral load within 3 months) and a CD4 reported at both dates of ART initiation (N = 993; Table 1), the *Log 1-Plus* date of ART was a median of 333 days earlier than the *Log 1* date of ART. The lowest CD4 point coincided with the estimated ART initiation date based on the *Log 1-Plus* date, whereas based on the *Log 1* date

the lowest CD4 point occurred slightly before the estimated date of ART initiation (N = 993; Fig. 3B).

DISCUSSION

Initiation of antiretroviral therapy is a key stage in the HIV care cascade, but is typically measured indirectly by public health departments or with data from a source other than population-based HIV surveillance data.^{3,13} We validated 3 methods of inferring and estimating the date of ART initiation in a cohort of New York City PWH diagnosed between 2006 and 2012.

The *Log 1-Plus* definition of ART initiation performed best according to our analytic criteria. Based on this definition, 81% of persons newly diagnosed with HIV in NYC from 2006 to 2012, with a CD4 count at diagnosis, initiated ART. In general, the 2 ART initiation definitions that were based on a 1-log decline in viral load (*Log 1* and *Log 1-Plus*) performed better than the definition that used a 2-log decline (*Log 2*). First, these definitions captured more individual PWH as having initiated ART after diagnosis; there were 541 persons who only met the ART initiation definition based on a 1-log decline, whose initiation was not captured by a definition that required a decline of 2 logs. Second, the definitions based on a 1-log decline in viral load were able to identify an earlier estimated date of ART initiation in our study, and thus we assume more accurately capture the timing of ART initiation given the rapid change in HIV viral load induced by ART initiation; for the 1449 persons in the analytic cohort who experienced both a 1-log and 2-log decline in viral load after diagnosis, estimated dates of ART initiation as based on the 1-log decline were earlier. The 541 persons who met the *Log 1* definition but not the *Log 2* definition tended to have higher CD4 counts at ART initiation, which suggests that they initiated earlier in the course of their disease.

The addition of persons who experienced a change from detectable to undetectable viral load to the *Log 1* ART initiation definition—the *Log 1-Plus* definition—resulted in a more inclusive and conceptually stronger measure. Compared with the *Log 1* definition, which considered only persons with a 1-log decline in viral load to have initiated ART, the inflection point of the median CD4 trajectory as based on the *Log 1-Plus* definition corresponded more closely to the estimated date of ART initiation. In addition, more individual PWH were captured as initiating ART based on the *Log 1-Plus* definition than the *Log 1* definition; 1114 persons in the analytic cohort had evidence of a change from detectable to undetectable viral load (and had a CD4 count at ART initiation) but did not experience a 1-log decline in viral load within 3 months and thus were not counted as initiators under the *Log 1* definition. A change in HIV viral load from detectable to undetectable in an individual generally indicates ART initiation; the *Log 1-Plus* definition allows us to include this group of initiators. Finally, our analysis did not require that the change from detectable viral load to undetectable occur within a specified time frame. However, on average the change occurred over a short period of time at the individual level (median: 132 days vs. median 56 days for persons who qualified through an earlier 1-log decrease within 3 months among all persons meeting the *Log 1-Plus* definition, N = 14,311), which supports inclusion of this marker in our selected definition of ART initiation.

Therefore, we propose the *Log 1-Plus* as the most valid and useful definition for estimating the timing ART initiation when ART medication information is not available, and therefore with wide applicability to surveillance-based cascade analyses.

This analysis has several strengths. First, the surveillance data set is population based, with longitudinal data on a large and representative analytic cohort. Second, our results add to the understanding of the extent of ART initiation among newly diagnosed PWH. Measurement of ART initiation using this validated definition could enable jurisdictions to identify gaps between initiation of ART and viral suppression among PWH, both overall and by subgroup, to inform interventions designed to support and improve ART adherence and quality of HIV care.

This analysis also has several limitations. First, ART initiation among persons who are naturally able to control their HIV viral load without treatment (so-called “elite controllers”) may not be captured by any of the evaluated definitions, because they may not experience a substantial enough viral load decline as a result of treatment. However, the population proportion of elite controllers is estimated to be small (<1% of PLWH maintain low to undetectable VL levels without treatment), and thus any effect of including such persons in this analysis likely would not change our estimates substantially.¹⁴ Second, individuals in this analysis may have contributed to the median CD4 count of a given interval in the CD4 trajectories, but not others as they may not have had a CD4 count reported in each quarter.

When ART medication data are not available, we recommend the use of serial VL measures in population-based surveillance data to infer ART initiation and its timing. Specifically, our analyses suggest that the *Log 1-Plus* measure used in our analysis performs well. A population-level measure for ART initiation among PWH has important application for analyses of HIV cascade outcomes, particularly among persons newly diagnosed with HIV.¹⁵ Other jurisdictions without population-based data on ART medication, but with comprehensive reporting of HIV-related laboratory tests, specifically of all HIV viral loads, can apply this definition to improve and deepen measurement of HIV care continuum measures related to ART and viral suppression. Applying a similar approach in other jurisdictions and conducting further validation work using a gold standard ART initiation date from medical records are important next steps.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Eligibility diagram of Log 1-Plus, Log 1, and Log 2 dates of ART initiation.

FIGURE 2. Median CD4 values before and after antiretroviral therapy initiation—Log 1, Log 2, and Log 1-Plus definitions. *ART initiation occurs at time = 0.

FIGURE 3.

Median CD4 values before and after estimated date of antiretroviral therapy initiation—comparison of Log 1 and Log 2 definitions. A, Persons meeting Log 1 definition but not Log 2 (N = 541). B, Persons with an earlier Log 1 date of ART initiation versus Log 2 date of ART initiation (N = 1449). *ART initiation occurs at time = 0.

FIGURE 4.

Median CD4 values before and after antiretroviral therapy initiation—comparison of Log 1 and Log 1-Plus definitions. A, Persons who qualified as initiating ART based on a switch from detectable to undetectable viral load (N = 2190). B, Persons with a Log-1 Plus date of ART initiation that was earlier than the Log-1 date of ART initiation (N = 993). *ART initiation occurs at time = 0.

TABLE 1

Timing of Log 1-Plus, Log 1, and Log 2 Definitions

ART Definition	N (%)	Median No.	CD4 Reported at ART Date	
		Days Different	Number	Figure
Comparison of Log 1 and Log 2 definitions (N = 12,719 met Log 1 definition)				
Met Log 1 and not Log 2	596 (4.96)	NA	541 [*]	Figure 3A
Same Log 1 and Log 2 dates of ART	10,496 (82.52)	0	10,043 [†]	Not shown
Log 1 ART date earlier than Log 2 date	1621 (12.74)	165	1449 [†]	Figure 3B
Log 2 ART date earlier than Log 1 date	6 (0.05)	8	6 [†]	Not shown
Log 1-Plus definition (N = 14,311 met Log 1-Plus definition)				
Earlier switch from detectable to undetectable	2959 (20.67)	NA	2190 [‡]	Figure 4A
Earlier 1-Log decline within 3 mo	11,352 (79.33)	NA	10,248 [‡]	Not shown
Comparison of Log 1 and Log 1-Plus definitions (N = 14,311 met Log 1-Plus definition)				
Met Log 1-Plus and not Log 1 [§]	1592 (11.13)	NA	1114 [‡]	Supp. figure
Log 1-Plus ART date earlier than Log 1 date [§]	1367 (9.55)	333	993	Figure 4B
Same Log 1-Plus and Log 1 dates of ART	11,352 (79.32)	0	10,824	Not shown

^{*} CD4 count reported at Log 1 ART date.

[†] CD4 count reported at Log 1 and Log 2 ART dates.

[‡] CD4 count reported at Log 1-Plus ART date.

[§] Persons who met the Log 1-Plus and not Log 1 (N = 1592) and persons who had an earlier Log 1-Plus date of ART (N = 1367) qualified for the Log 1-Plus definition through a detectable to undetectable VL change.

^{||} CD4 count reported at Log 1-Plus and Log 1 ART dates.