How Can Progress Toward Ending the Human Immunodeficiency Virus Epidemic in the United States Be Monitored?

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The plan for Ending the HIV (human immunodeficiency virus) Epidemic (EHE) in the United States aims to reduce new infections by 75% by 2025 and by 90% by 2030. For EHE to be successful, it is important to accurately measure changes in numbers of new HIV infections after 5 and 10 years (to determine whether the EHE goals have been achieved) but also over shorter timescales (to monitor progress and intensify prevention efforts if required). In this viewpoint, we aim to demonstrate why the method used to monitor progress toward the EHE goals must be carefully considered. We briefly describe and discuss different methods to estimate numbers of new HIV infections based on longitudinal cohort studies, cross-sectional incidence surveys, and routine surveillance data. We particularly focus on identifying conditions under which unadjusted and adjusted estimates based on routine surveillance data can be used to estimate changes in new HIV infections.

Keywords. HIV; infections; estimates; incidence surveys; surveillance data.

MONITORING THE US HIV EPIDEMIC

In the midst of the coronavirus disease 2019 (COVID-19) pandemic, it is important that the United States does not lose sight of its goal of Ending the HIV (human immunodeficiency virus) Epidemic (EHE) in the United States within 10 years. In 2019, goals were set to reduce the number of new US HIV infections by 75% by 2025 and by 90% by 2030 [1]. Efforts are focused on 4 key strategies: diagnosing people living with HIV as quickly as possible to increase awareness of living with HIV and engage them in care; treating people living with HIV rapidly and effectively to ensure persistent viral suppression and reduce infectiousness; scaling up prevention interventions including preexposure prophylaxis (PrEP) and syringe services programs to prevent new transmissions; and responding to potential HIV outbreaks to prevent onward transmission [2]. Given the geographical heterogeneity of the US HIV epidemic, with varying HIV transmission risks and variable HIV intervention coverage, the EHE initiative aimed to initially focus (in phase 1) on the 50 counties that accounted for more than 50% of new HIV diagnoses in 2016–2017 and 7 states with a high rural HIV burden [1]. Expansions to increase the likelihood of reaching EHE goals have been proposed [3]. However, these efforts may be slowed or reversed by disruptions to health services during the COVID-19 pandemic [4, 5], making it vital that progress toward EHE is carefully monitored.

Monitoring progress toward the EHE goals will require accurate measurements of changes in numbers of new HIV infections at the national level after 5 and 10 years in order to determine whether the intermediate and final EHE goals have been achieved and at the county level (in the 50 phase 1 counties) over shorter timescales to monitor progress and intensify prevention efforts if required. However, to date, no details have been provided about how changes in the numbers of new HIV infections will be measured. Here, we aim to demonstrate why the method used to monitor progress toward the EHE goals needs to be carefully considered.

In this viewpoint, we briefly describe, discuss, and analyze methods often used to estimate numbers of new HIV infections, typically based on longitudinal cohort studies, cross-sectional incidence surveys, or routine surveillance data, to highlight why monitoring progress toward the EHE goals could be challenging and will require careful consideration and planning (Table 1). Given their extensive use, we particularly focus

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Table 1. Potential Measures to Monitor Progress Toward Achieving the Ending the Human Immunodeficiency Virus Epidemic Goals

Measure	Definition	Data Source	Advantages	Disadvantages
Cohort and cross-sectional studies				
HIV incidence (directly measured)	New HIV infections per person-year	Longitudinal cohort studies	• Directly measures incidence • Not influenced by changes in HIV testing	• Large sample size required when incidence is low • Difficult to obtain a representative cohort of most at-risk populations in concentrated epidemic settings • Expensive and intensive • Need to conduct a baseline survey before EHE efforts begin • Behavior change in cohort may mean it underestimates true population incidence
Cross-sectional incidence (recency testing)	HIV incidence estimated from recency testing algorithm	Cross-sectional studies	• Simple and rapid recency assays are available • Standardized methods and tools have been developed • Not influenced by changes in HIV testing	• Large sample size required when incidence is low • Difficult to obtain representative sample of most at-risk population in concentrated epidemic settings • Expensive • Need to conduct a baseline survey before EHE efforts begin • False recency rate may change over time and be affected by changes in antiretroviral therapy coverage, reducing accuracy of estimates of changes in new HIV infections
Surveillance data				
New HIV diagnoses, unadjusted	Number of new HIV diagnoses per year	Surveillance data on diagnoses	• Data already collected through surveillance • Pre-EHE data available • Reliable estimate after 10 years if HIV testing stabilizes after first year	• Strongly affected by changes in testing • Affected by a >12-month reporting delay at the onset • Even without reporting delays, underestimates incidence reduction in the short to medium term (≤5 years) if testing increases during EHE efforts with substantial variability • Overestimates incidence reduction if testing decreases during EHE efforts
New HIV diagnoses of recent infection	Number of new diagnoses per year with recent infection	Surveillance data on diagnoses and recency assays	• Data already collected through surveillance • Pre-EHE estimates available • Only recent infections included	• Strongly affected by changes in testing • Affected by a >12-month reporting delay at the onset • Even without reporting delays, underestimates incidence reduction in both the short and long term (≤10 years), with substantial variability if testing increases during EHE efforts • Limited number of diagnoses with recent infection reduces precision of estimates
New HIV diagnoses, adjusted for time since infection	New diagnoses per year corrected for time since infection based on first CD4 + cell count after diagnosis	Surveillance data on diagnoses and CD4 + cell counts with a CD4 decay model	• Data already collected through surveillance • Pre-EHE estimates available • Accounts for time elapsed between infection and diagnosis • Reliable estimates after 5 and 10 years if HIV testing stabilizes after first year	• Strongly affected by changes in testing • Affected by a >12-month reporting delay at the onset • Even without reporting delays, underestimates incidence reductions in the short term (≤2 years), with substantial variability if testing increases during EHE efforts
New HIV diagnoses, adjusted for testing volume	Number of new diagnoses per year divided by number of tests conducted per year	Surveillance data on diagnoses and testing data	• Diagnosis data and some testing data already collected through surveillance • Only slightly biased (but uncertain) short-term (2 year) estimates	• Affected by a >12-month reporting delay at the onset • Variability in estimates of incidence reduction in both the short and long term • Overestimates reductions in incidence after long time periods (5, 10 years) as adjusting for number of tests overcompensates for reduced difference between numbers of new infections and diagnoses • Data on all tests conducted not available in the United States
Viral nonsuppression	Proportion of those diagnosed whose most recent viral load level in past 12 months was above 200 copies/mL	Surveillance data on viral load testing	• Data already collected through surveillance • Pre-EHE estimates available • Unbiased (but uncertain) short-term (2 year) estimates	• Affected by a >12-month reporting delay at the onset • Variability in estimates of incidence reduction in both the short and long term • Underestimates reductions in incidence over the long term (after 5 and 10 years) • Does not capture impact of expanded testing or preexposure prophylaxis on incidence • Viral load testing not done for everyone; changes in the completeness of viral load testing data could affect this measure
Recommendations				
Triangulate data from multiple sources for estimating reductions in new HIV infections, subject to validity: • Cross-sectional incidence estimates (where available). • Surveillance data on new diagnoses adjusted for time since infection using CD4 + cell count data (valid if data indicate that rates of HIV testing or time to diagnosis have remained stable in recent years). • Surveillance data on the proportion of those diagnosed who are not virally suppressed and/or on diagnoses adjusted for testing volume (where testing volume data available); these measures are only recommended for use when time-adjusted diagnoses are not valid, but note uncertainty in them.				

Abbreviations: EHE, Ending the HIV Epidemic HIV, human immunodeficiency virus.

(using mathematical modeling analysis) on identifying conditions under which unadjusted and adjusted estimates based on routinely collected data on new HIV diagnoses can be used to infer changes in new HIV infections, both when EHE efforts are successfully implemented and when they are disrupted, for example, due to COVID-19.

LONGITUDINAL COHORT STUDIES

Ideally, HIV incidence rates would be estimated from longitudinal cohort studies, with regular monitoring of progress toward EHE goals [6]. However, these studies are time-consuming and expensive since they would require enrolling and repeatedly

testing cohorts of people not living with HIV over the course of the initiative. Cohorts would need a fairly large sample size, around 1800 followed up for 1 year to detect a 90% reduction and 7800 to detect a 50% reduction from a baseline HIV incidence of 1.5% (80% power; see Supplementary Table 1 for illustrative sample size calculations). Another issue with longitudinal cohort studies is representativeness. Given that the United States has a concentrated HIV epidemic, these cohorts would need to enroll individuals in the most at-risk populations [7] (eg, men who have sex with men [MSM]), who are often hard to reach, and to sample representatively. Such cohorts could be recruited online or using venue-based or respondent-driven sampling methods [8, 9]. Cohort participation may also lead to behavior change among participants and compromise the representativeness of the cohort [10]. Furthermore, at the county level (for the 50 counties in phase 1), small numbers of infections may limit the precision of cohort-based incidence estimates.

Cohort studies would need to have been conducted prior to implementation of EHE strategies to have a baseline against which 5- and 10-year incidence estimates could be compared.

CROSS-SECTIONAL SURVEYS

Cross-sectional surveys that test for the "recency" of HIV infection have been successfully used in large-scale population-based surveys in sub-Saharan Africa to estimate HIV incidence [11, 12]. These surveys involve testing a representative sample of the population for HIV infection and then using a testing algorithm to detect recent HIV infection among those with HIV [13]. HIV incidence is calculated from the number of recent infections detected and the average length of time after infection for which the recency testing algorithm gives a positive result. Although these surveys avoid some of the problems associated with longitudinal cohort incidence measures (eg, loss to follow-up, behavior change), misclassification due to the false recency rate can be of concern (ie, the probability that someone with a long-standing HIV infection is classified as having recently acquired HIV) [14]. This rate can vary over time and across populations if, for example, antiretroviral therapy (ART) coverage or average time to ART initiation changes, which would complicate interpretation of estimates [14, 15]. Alternatively, phylogenetic approaches to measure viral diversity have recently been used in the United States to identify recent infections [16, 17], although they may not be more accurate than other recency testing algorithms [16], and these approaches may not work among those who have already started ART [17]. Importantly, in the context of the US EHE initiative, relatively low baseline incidence and lack of a clear sampling frame for the most at-risk populations also make cross-sectional surveys logistically difficult, with a large sample size required to estimate change in incidence over time, exceeding 6000 participants to detect a 90% reduction from a baseline HIV incidence of 1.5% (80% power; Supplementary Table 1).

As for cohort studies, achieving a representative sample of most at-risk populations is challenging. As with cohort studies, cross-sectional incidence surveys would need to have been conducted prior to the initiation of EHE efforts to have a baseline estimate of incidence.

SURVEILLANCE DATA

Given the challenges of estimating HIV incidence from cohort and cross-sectional studies, routine surveillance data are more often used to estimate HIV incidence in the United States [18–20]. In the United States, surveillance data on annual new HIV diagnoses and levels of viral suppression among those with diagnosed HIV infection are required to be reported. Note that an HIV diagnosis reflects a first positive HIV test, which often occurs long after HIV infection. Note also that not everyone receives a viral load test every year, meaning viral suppression data may be incomplete. Surveillance data are available at the national, state, and county levels and could be used to calculate baseline estimates of numbers of new HIV infections prior to the start of EHE activities as well as estimates during EHE efforts. However, surveillance data are typically reported with at least a 12-month delay [21], which would hamper real-time progress monitoring and delay confirmation that the 5- and 10-year goals have been achieved.

We argue that even without these delays, using changes in annual new HIV diagnoses to monitor EHE progress, as previously used to estimate national incidence declines in the United States [19], may over- or underestimate real changes in annual HIV infections under different intervention conditions, compromising our ability to accurately determine whether the EHE goals have been reached.

PERFORMANCE OF SURVEILLANCE MEASURES

To evaluate how well changes in surveillance measures reflect changes in numbers of new HIV infections, we use a mathematical model of HIV transmission among MSM in the United States to simulate the HIV epidemic, the EHE initiative, and collection of surveillance data over 2020–2030 (see Box 1, Supplementary Material, Supplementary Figures 1–3, and Supplementary Tables 2 and 3 for modeling methods).

Our results show that if the first EHE strategy of increasing testing to achieve early diagnosis is successfully implemented, the number of new diagnoses may increase even if the actual number of new infections declines (Figure 1A). As a result, the measure of change in new diagnoses can greatly underestimate change in new infections in the short term (Figure 1B). The bias is more substantial if a larger proportion of people living with HIV become aware of their HIV status during EHE efforts, as more new diagnoses are made (Figure 1B). If, after an initial increase, testing rates remain high but stable, reductions in

Box 1. Mathematical Modeling Approach

To evaluate the performance of surveillance measures for estimating changes in numbers of new HIV infections, we used a deterministic, compartmental model of sexual HIV transmission among MSM in the United States [22]. The modeled MSM population is stratified by age, race, infection stage, and engagement with HIV care and PrEP use. In the model, diagnosis occurs when an undiagnosed individual living with HIV gets tested, either through routine testing or upon seeking treatment for symptoms. The model was parameterized using data from MSM surveillance, US cohort data, other MSM cohort studies, clinical trials, and systematic reviews. The model was fitted to MSM-specific demography, HIV prevalence, PrEP use, and care continuum data in a Bayesian framework [22, 23].

Different potential EHE initiative scenarios were modeled by running the model many times with different levels of improvements to linkage to care, ART and PrEP coverage and retention, alongside different levels of changes in HIV testing rates, starting in 2020, with a 1-year scale-up period. In the model, the reduction in new HIV infections was estimated from the number of new HIV infections occurring in 2025 or 2030 compared with the number in 2019. Estimated changes in new infections based on surveillance data were similarly estimated in the model from comparisons of total/adjusted HIV diagnoses made (or the proportion of diagnosed MSM who were not virally suppressed) in 2025/2030 vs 2019.

See the Supplementary Material for further details.

diagnoses are expected to reflect reductions in new infections more closely after 5 years and even more closely after 10 years (Figure 1B). Conversely, decreased HIV testing rates during EHE efforts, as may occur during the COVID-19 pandemic, can lead to changes in diagnoses overestimating true reductions in new HIV infections over time (Figures 1C, D).

We consider the following 3 refinements that may detect reductions in new infections more accurately: using only data on diagnoses with evidence of recent infection (eg, using past HIV testing results [24], recency testing algorithms [25, 26], serological diagnostic assays [27], or measures of viral diversity [17]; we assess diagnoses within approximately 4 months of infection; see Supplementary Material for details); adjusting all diagnoses for time since infection (using data on CD4 + cell count at diagnosis, as currently used by the US Centers for Disease Control to estimate national and state-level incidence [18]); and adjusting diagnoses for the number of tests performed (to take into account changes in testing rates [28]; Figure 2, Table 1). We focus on situations where testing rates increase early on during EHE efforts.

Surprisingly, using data on diagnoses with evidence of recent infection can lead to even more substantial and variable underestimation of short- and long-term reductions in new infections than estimates based on total diagnoses (Figure 2). This may be attributed to improved testing that can lead to a larger increase in the proportion of infections being diagnosed early, rather than in later stages. Using diagnoses with recent infection also results in less precise estimates of declines in new HIV infections as only a subset of infections is detected at this stage.

Adjusting diagnoses for time since infection also leads to substantial and variable underestimation of reductions in new infections after 2 years. However, it eventually reflects infection reductions well, and slightly better than unadjusted total diagnoses, after 5 and 10 years (Figure 2). The poor short-term performance of time-adjusted diagnoses arises because this method assumes that the diagnosis delay distribution has remained stable over the preceding 8 years, an assumption that is violated if testing rates increase [20]. Note that alternative methods for adjusting diagnoses for time since infection using recency testing (eg, recency testing algorithms or serological diagnostic assays [27]) together with HIV testing history [26, 29] also assume that testing behavior has remained constant for several years and are also expected to perform poorly if HIV testing rates increase [29].

Interestingly, adjusting diagnoses for total number of HIV tests performed (when known) [28] produces, on average, less biased (but still variable) estimates of true short-term changes in new infections than total or time-adjusted diagnoses but more biased and variable estimates than total and time-adjusted diagnoses after 5 and 10 years (Figure 2). In contrast with the other diagnoses-based metrics, when testing rates increase, diagnoses adjusted for numbers of tests tends to overestimate infection reductions, particularly in the longer term. This occurs because higher testing rates lead to numbers of new diagnoses becoming more similar to the real numbers of new infections (Figure 1A), and the adjustment for the larger numbers of tests performed overcompensates for the diminishing gap between diagnoses and infections. The utility of this measure may be limited if data on total numbers of HIV tests performed are not available.

Given the association reported between increased HIV treatment coverage and decreased HIV incidence [30], we also assessed whether changes in viral suppression could be used to estimate changes in new HIV infections over time. Importantly, our results suggest that in the short term, reductions in the proportion of diagnosed people living with HIV who are not virally suppressed performs better than any of the diagnoses-based surveillance measures explored. This measure gives unbiased but variable estimates after 2 years; however, it tends

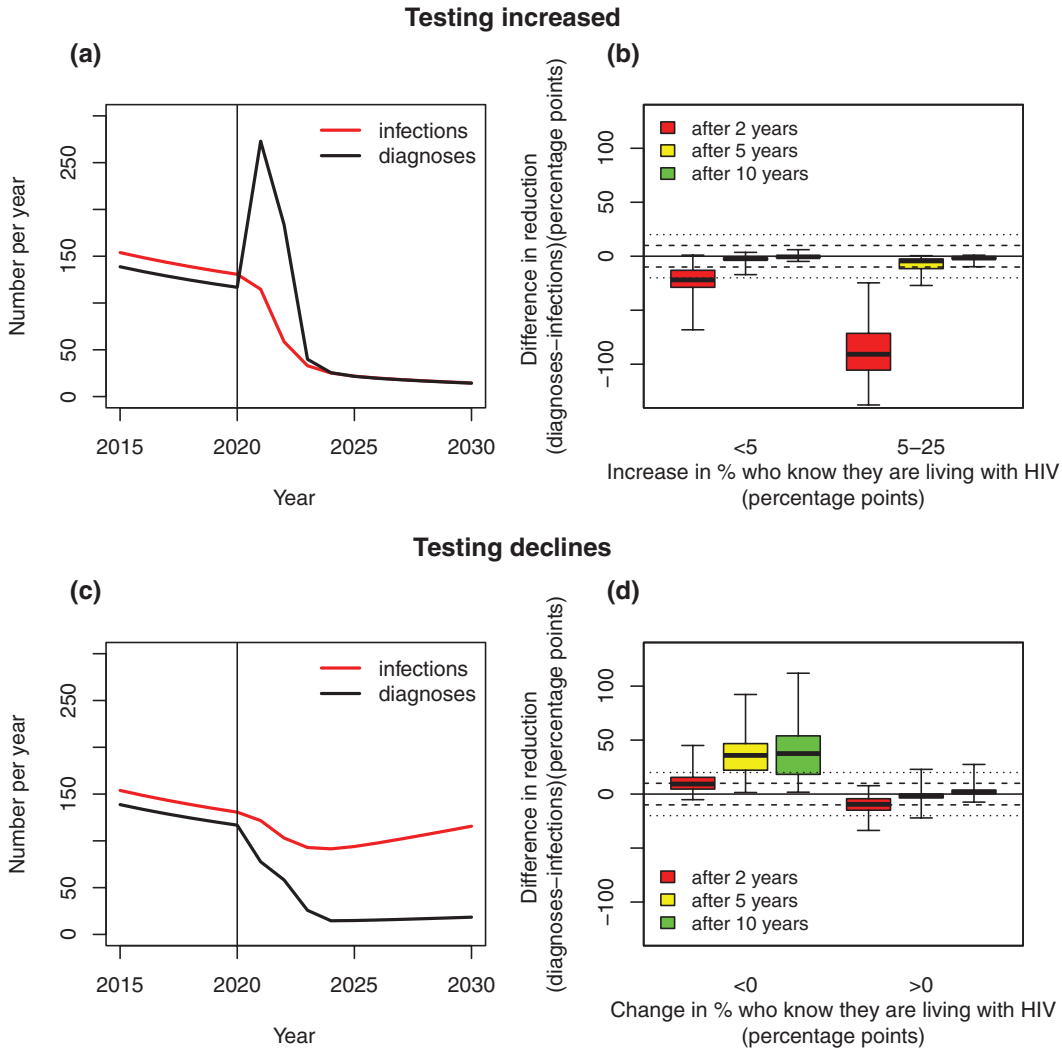

Figure 1. Modeling results showing performance of unadjusted diagnoses for estimating incidence reductions over time compared with baseline. *A, C,* Model-based trends over time in new infections (red lines) and new HIV diagnoses (thick black lines) before and following the introduction of the combination prevention intervention for a single set of fit parameters. *B, D,* Absolute difference between reductions in cumulative diagnoses and reductions in cumulative infections by change in levels of awareness of living with HIV since 2020, for an intervention program scaling up antiretroviral therapy and preexposure prophylaxis over 1 year starting in 2020, with *(A, B)* concomitant increases in HIV testing or *(C, D)* concomitant declines in HIV testing. Modeling results are shown after 2, 5, and 10 years. Numbers are for a modeled population of 7000 men who have sex with men. Middle and line box and whisker represent median, 25th, and 75th percentiles and minimum and maximum values, respectively. Dashed and dotted lines are at ±10 percentage points and ±20 percentage points from the true reduction in new infections, respectively. Abbreviation: HIV, human immunodeficiency virus.

to underestimate reductions in infections over 5 and 10 years (Figure 2), partly because it does not capture the effects of increased levels of awareness of living with HIV or increased PrEP use. Changes in the completeness of viral load measurements could also affect the performance of this measure.

IMPLICATIONS FOR MONITORING EHE

We argue that accurately monitoring the impact of the EHE response will be challenging and needs to be carefully planned since all incidence estimation methods have limitations, especially in a context such as the United States with a concentrated HIV epidemic and with low and very heterogeneous HIV incidence and levels of intervention across counties. The performance comparison across data methods and over time suggests that multiple measures will be needed to determine when the EHE has been achieved nationally, as well as to monitor its progress in the earlier years.

Since successful EHE efforts will likely increase levels of awareness of living with HIV initially, early reductions in new HIV infections are likely to be underestimated, or even not detected, if estimated by changes in total or time-adjusted diagnoses. These measures will become more reliable in the longer term when testing rates have stabilized. In contrast, using new diagnoses adjusted for number of tests (provided that accurate information on the number of tests is available) and/or changes in levels of viral suppression could provide reasonable estimates of changes in new HIV infections initially, but their performance

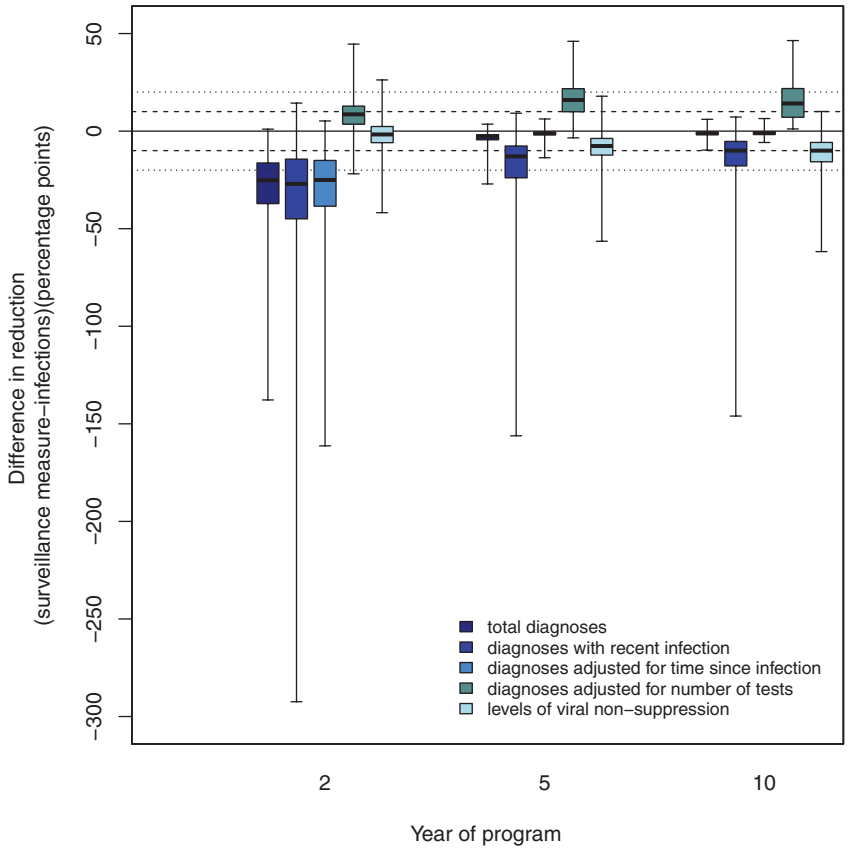

Figure 2. Modeling results showing performance of adjusted diagnoses and other surveillance markers for estimating incidence reductions. Absolute difference between reductions in diagnoses with evidence of recent infection, diagnoses adjusted for time since infection, diagnoses adjusted for number of tests performed, or the proportion of diagnosed men who are not virally suppressed, and reductions in cumulative infections, across all intervention runs, after 2, 5, or 10 years of a program expanding antiretroviral therapy, preexposure prophylaxis and testing together, with a 1-year scale-up period, starting in 2020. Middle line and box and whisker represent median, 25th, and 75th percentiles and minimum and maximum values, respectively. Dashed and dotted lines are at ±10 pp and ±20 pp from the true reduction in new infections, respectively.

deteriorates over time. We have shown that estimates of changes in infections based on new diagnoses with recent infection are not reliable following increases in levels of awareness of living with HIV. Our analysis of the reliability of surveillance data used an MSM model that did not include other populations. We would expect to see similar biases in surveillance measures when considering the whole US HIV epidemic, as MSM account for a large proportion (69%) of new HIV diagnoses in the United States and overall levels of awareness of HIV status are similar to those seen among MSM [31].

With current reporting delays in the national US surveillance system, the feasibility and cost of using cross-sectional recency-based estimates at a few key time points should be investigated. This approach may provide a more accurate assessment of the impact of EHE efforts following changes in levels of awareness when diagnoses-based indicators are more biased. Efforts should also be made to improve the timely release of surveillance data to increase its usefulness for regular monitoring of EHE progress.

When using changes in total and time-adjusted HIV diagnoses to infer early changes in HIV incidence, larger underestimation is expected to occur in settings with substantial increases in levels of awareness of living with HIV early in EHE efforts. This is particularly problematic when assessing and comparing progress across heterogeneous counties to guide allocation of resources. Counties with existing high levels of awareness of living with HIV may see more rapid declines in diagnoses compared with those with lower initial levels of awareness who rapidly expand their HIV testing, leading to temporary observations of increases in numbers of diagnoses despite similar impacts on incidence. This could potentially result in misallocation of resources, if resources are focused in counties that are achieving substantial reductions in new infections but not yet seeing a reduction in diagnoses or if successful interventions are not deemed to be effective and therefore stopped or not replicated in other locations.

In conclusion, among the surveillance measures considered here, surveillance data on new diagnoses adjusted for time since infection (estimated from CD4 + cell count) performed poorly following rapid changes in levels of awareness of HIV status due to expansion of HIV testing programs [18] but could be used to evaluate the EHE goals once HIV testing rates have stabilized.

Changes in diagnoses adjusted for testing volume or changes in levels of viral suppression perform better than time-adjusted diagnoses for estimating short-term changes in numbers of infections early in EHE efforts but have limited precision. Reducing reporting delays will be important if surveillance data are to be used to monitor early progress toward EHE. If feasible, conducting cross-sectional surveys with recency testing may provide complementary and more accurate estimates of changes in new HIV infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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