# MAJOR ARTICLE







# What Will It Take to Reduce HIV Incidence in the United States: A Mathematical Modeling Analysis

Allison Perry, Parastu Kasaie, David W. Dowdy, and Maunank Shah<sup>2</sup>

<sup>1</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; <sup>2</sup>Johns Hopkins University School of Medicine, Baltimore, Maryland

*Background.* The National HIV/AIDS Strategy has set ambitious goals to improve the epidemic in the United States. However, there is a paucity of usable program-level benchmarks tied to population-level epidemiologic goals. Our objective was to define tangible benchmarks for annual rates along the care continuum that are likely to translate to meaningful reductions in incidence.

*Methods.* We used a validated mathematical model of HIV transmission and care engagement to characterize care continuum parameters that would translate into 50% reductions in incidence by 2025, compared with a base case scenario of the current US care continuum. We generated a large pool of simulations in which rates of screening, linkage, and retention in care were varied across wide ranges to evaluate permutations that halved incidence by 2025.

**Results.** Among all simulations, 7% achieved a halving of incidence. It was impossible for our simulations to achieve this target if the annual rate of disengagement from care exceeded 20% per year, even at high rates of care reengagement. When retention in care was 95% per year and people living with HIV (PLWH) out of care reengaged within 1.5 years (on average), the probability of halving incidence by 2025 was approximately 90%.

*Conclusions.* HIV programs should aim to retain at least 95% of PLWH in care annually and reengage people living with HIV into care within an average of 1.5 years to achieve the goal of halving HIV incidence by 2025.

Keywords. HIV care-continuum; HIV/AIDS; linkage to care; retention in care; mathematical model; economics.

Since the beginning of the epidemic, more than 1.2 million people in the United States have received an AIDS diagnosis, and more than 700 000 people have died [1, 2]. There are currently an estimated 1.1 million persons aged 13 years and older living with HIV (PLWH) in the United States, with some estimates suggesting that less than 50% are retained in care [2–4]. Despite improvements in antiretroviral therapy (ART) and evidence for treatment as prevention with guidance for early ART initiation, incidence of HIV has declined at a slow rate and remains between 36 000 and 39 000 new HIV infections per year [4–7]. Among the challenges is an imperfect HIV care continuum, in which current national estimates suggest that suboptimal numbers of PLWH are virologically suppressed, representing missed opportunities for averting ongoing HIV transmission [8].

Each step along the HIV care cascade, from diagnosis to engagement in HIV care and long-term ART adherence, must be strengthened [9]. There has been widespread focus on testing and initiation of treatment, with efforts to scale-up HIV testing

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for high-risk groups [9]. Nevertheless, research suggests that sustained engagement of PLWH in care is a critical factor for both improved individual health and prevention of further HIV transmission [9–12].

In response to the ongoing HIV epidemic, the National HIV/AIDS Strategy (NHAS) was recently updated in 2015 [13]. Among the key components was enumeration of crosssectional population-level targets for care engagement and improvements in incidence [13]. Our group has previously utilized a mathematical modeling approach to evaluate whether achievement of these NHAS care continuum targets was likely to achieve sustained reductions in transmission. The studies found that failure to improve engagement in HIV care leads to excess infections, treatment costs, and deaths, and that interventions must improve not just HIV screening but also retention in care to optimize epidemiologic impact and cost-effectiveness [9, 11]. Nonetheless, care continuum targets (ie, increasing the percentage of persons with diagnosed HIV infection who are retained in HIV medical care to at least 90%) have not been quantitatively linked to stated epidemiological goals, and many continue to remain aspirational. Moreover, such cross-sectional goals are not easily translated into objective metrics that HIV program managers can utilize to assess success in their own programs on an ongoing basis [9, 11].

In this study, we aimed to define the standards of care engagement along the full spectrum of the HIV care continuum that would be necessary to "bend the curve" of the HIV epidemic in the United States. We sought to determine the annual rates

of screening, retention, and reengagement in care, and the percentage of PLWH linking to care that are needed to achieve an ambitious goal of 50% reduction in HIV incidence by 2025. Our aim was to define tangible metrics for care continuum engagement that are tied to population-level epidemiologic goals and can be used by program managers and public health officials.

## **METHODS**

The Johns Hopkins HIV economic-epidemic model (JHEEM) is a compartmental model of the US HIV epidemic that incorporates transmission, disease progression, and health system engagement (Supplementary Figure 1) [9, 11]. Briefly, this model partitions the adult population (age 18-78 years) of the United States based on sex, age, HIV infection, and transmission category (heterosexuals, men who have sex with men [MSM], and people who inject drugs [PWID]). Lower-risk groups were defined as older heterosexuals, and higher-risk groups were defined to include younger individuals (age 18-28 years), young and old MSM, and PWID. HIV infection, transition through the care continuum, and demographic changes were modeled dynamically as a system of ordinary differential equations [9, 11]. PLWH were further characterized by CD4 strata and stage of HIV care continuum, through which subpopulations can transition: unaware of HIV status, aware but out of care, in care but not on ART, on ART but not virologically suppressed, and virologically suppressed. Those who are in care are initiated per current guidelines (at any CD4 count) on suppressive ART regimens. We modeled retention in care as having sustained access to clinical care and eligibility for ART. Suboptimal adherence was modeled in terms of risks for virologic failure (but still retained in care); for those retained in care, the model assumed timely detection of viremia and initiation of alternative regimens capable of achieving virologic suppression. It also assumed that those lost to follow-up or not retained in care experienced viremia (and not on ART), but were eligible for care reengagement and initiation of suppressive ART regimens at a later point in time. Total health system costs are calculated based on time spent per individual in each compartment and during transitions between compartments, based on HIV status and place in the HIV care continuum (Supplementary Section "Model Costs"). Future costs were discounted 3%. In this study, we modeled outcomes over a 10-year period, from 2016 to 2025. The model output of interest was relative reduction in incident cases of HIV, or the percentage point change in HIV incidence—with a primary target of 50% reduction by 2025, compared with the projected 2025 incidence assuming continuation of the current care continuum. We evaluated a 50% reduction by 2025 as a further extension of epidemiologic goals on the path to elimination, building on current NHAS goals of reducing new diagnoses by 25% by 2020. We additionally evaluated more modest (25% reduction) and more ambitious (75% reduction) reductions in incidence in secondary analyses. We modeled a continuation of the current care continuum (Figure S4) to serve as the baseline comparator to estimate the projected percentage point change in incidence under alternative care continuum scenarios (Table 1; Supplementary Figures 2 and 3) [9, 11]. We used JHEEM to sample ~100 000 simulations in which we simultaneously varied, within wide ranges using a uniform distribution (ie, where all values within the range are equally likely), the care continuum parameters of interest: (1) annual high-risk screening rates, (2) annual lowrisk screening rates, (3) percentages of PLWH linking to care within 1 month of initial diagnosis, (4) annual rates of disengagement from care for those in care, and (5) annual rates of reengagement into care for those aware of their diagnosis and out of care, while holding all other parameters within the model constant (Table 1; Supplementary Figure 1, Supplementary Table 1). We did not incorporate specific care continuum intervention costs to achieve specific rates of screening, linkage, and retention. However, each model simulation incorporated unit costs per HIV test, linkage to care costs per individual linking and establishing care (baseline genotype, viral load, CD4 count, clinic visit), and incorporated an annual cost per individual retained on a yearly basis (Supplementary Data); as such, we projected the incremental total health system costs of improving the care continuum in each simulation, compared with the

Table 1. Key Model Parameters

| Model Parameters                                  | Baseline Value <sup>a</sup> | Simulation Range <sup>b</sup><br>[min., max.] | References <sup>a</sup> |
|---|-----------------------------|---|-------------------------|
| Annual rate of retention in care, %/y             | 86–89                       | [50, 99]                                      | 9,11                    |
| Annual rate of reengagement into care, %/y        | 20                          | [1, 100]                                      | 9,11                    |
| Annual screening rate among high-risk group, %/yc | 7.5–25                      | [1, 100]                                      | 9,11                    |
| Annual screening rate among low-risk groups, %/yc | 12.5–17.5                   | [1, 100]                                      | 9,11                    |
| Percentage of PLWH linking to care <sup>d</sup>   | 55–75                       | [1, 100]                                      | 9,11                    |

Abbreviation: PLWH, people living with HIV.

<sup>&</sup>lt;sup>a</sup> Base-case values (stratified by risk group) were based on literature estimates and model calibration to current estimates of the care continuum (see the supplementary section on Additional Model Details, Supplementary Table 1 [3].

<sup>&</sup>lt;sup>b</sup> Ranges represent ranges across which we varied the parameters for our simulation experiments

<sup>&</sup>lt;sup>c</sup> High-risk groups include heterosexual youths, people who inject drugs, men who have sex with men

d Percentage of PLWH linking to care represents percent linking to care within 1 month; PLWH not linked to care can still engage in care at a later point in time.

base-case scenario of continuation of current rates of care continuum engagement.

To assess the relationships between the care continuum parameters and the dichotomous outcome of halving incidence by 2025 (yes/no), scatterplots with Locally Weighted Scatterplot Smoothing (Lowess) were created and evaluated for linearity. A linear regression model with a robust estimate of variance was run to explore the additive association between a 10% increase in each of the care continuum parameters, treated as continuous variables, and the projected probability of halving incidence by 2025.

Next, to explore the interaction between retention (ie, complement of disengagement from care) and reengagement in care, a 10-by-10 color-coded grid was created, with each cell in the grid corresponding to the estimated probability of halving incidence by 2025 for different combinations of retention and reengagement strata.

Finally, to explore potential interactions among all model parameters, we conducted a probabilistic sensitivity analysis where we ran ~100 000 simulations in which all model parameters were varied simultaneously within their plausible ranges and repeated statistical analyses similar to the above (Supplementary Section 3).

Data were analyzed using R, version 3.0.1 (R Foundation for Statistical Computing), and Stata, version 14.1.

#### **RESULTS**

If current rates of engagement in the HIV care continuum continue (and without other behavioral or pharmacologic interventions), our model projects 374 000 (95% UR 152 000-606 000) new HIV infections and 225 000 deaths among PLWH (95% UR 66 000-464 000) between 2016 and 2025[11]. Of the approximately 100 000 experimental simulations in this analysis, 26% achieved at least a 25% projected reduction in incidence, 7% achieved at least a 50% reduction in incidence, and no simulations achieved at least a 75% reduction in incidence by 2025, as compared with projections with continuation of the current care continuum. Compared with a baseline estimate of total health system costs of \$251 billion, we projected median incremental costs of \$77 billion (31% increase; IQR, \$62 billion-\$91 billion) associated with achieving a 25% reduction and \$93 billion (37% increase; IQR, \$79 billion-\$106 billion) to achieve a 50% reduction in incidence by 2025, attributable to increased health care engagement (eg, increased antiretroviral drug (ARV) utilization among simulations with higher rates of retention in care).

The projected probability of halving incidence is most closely associated with retention and reengagement in care (Figure 1). With a baseline probability of disengagement from care greater than 20%, there was a projected 0% probability of halving incidence within the next 10 years (Figure 1A; Supplementary Table 2, ie, sixth to tenth strata). Each absolute 10% increase in annual rates of care reengagement (eg, reengagement of individuals out

of care from 50% per year to 60% per year) increased the estimated probability of halving HIV incidence by 2025 by an average of approximately 2% (Figure 1B; Supplementary Table 2).

Using multivariable linear regression, all 5 elements of the care cascade were associated with the projected probability of halving incidence by 2025, but the strength of the association varied by care continuum element (Table 2). For every 10% absolute improvement in the rate of retention above 80% (eg, from 85% to 95% per year), the estimated probability of halving incidence by 2025 increased by approximately 25% (95% confidence interval [CI], 24.8%-25.6%), and for each 10% absolute increase in the rate of reengagement (eg, from 40% per year [average 2.5-year duration of disengagement] to 50% per year [average 2.0-year duration]), the projected probability increased by 2.0% (95% CI, 1.96%-2.05%). Annual screening rates among high-risk groups and the percentage of PLWH linking to care had significant, but weaker, associations with the estimated probability of halving incidence—and annual screening rates among low-risk groups had very little association (Table 2).

Figure 2 displays the projected probability of halving incidence by 2025 among different strata of rates of retention and reengagement and suggests that improved rates of both retention and reengagement are needed to maximize the estimated probability of halving incidence within the next 10 years. At poor rates of annual retention in care (ie, less than 95%), notably higher rates of yearly reengagement into care (ie, median 71%) are needed to maintain a reasonable projected probability of achieving this target (Figure 2, Table 2; Supplementary Table 3). When retention rates are at least 95% and more than 70% of people living with HIV out of care reengage into care annually, there is nearly a 90% projected probability of halving incidence by 2025 (Figure 2).

We evaluated the estimated probability of halving incidence by 2025 according to level of suppression at the population level as the final step in the care continuum. Current NHAS targets suggest increasing the percentage of diagnosed individuals to 80% (with a goal of at least 90% awareness). We estimated a probability of halving incidence of only 9% if population-level suppression among all PLWH is less than or equal to 80%, and a 62% probability if this target were increased to 80%–85% viral suppression among all PLWH. By contrast, the estimated probability of achieving a halving of incidence was 98% if more than 85% of all PLWH can be virally suppressed by 2025 (Supplementary Figure 5).

We conducted extensive sensitivity analyses to explore the impact and interactions with other non-care continuum parameters. Varying all model parameters simultaneously did not impact our findings or inferences (Supplementary Section 3).

## **DISCUSSION**

We found that high rates of both annual retention (for those in care) and reengagement (for those out of care) are critical to

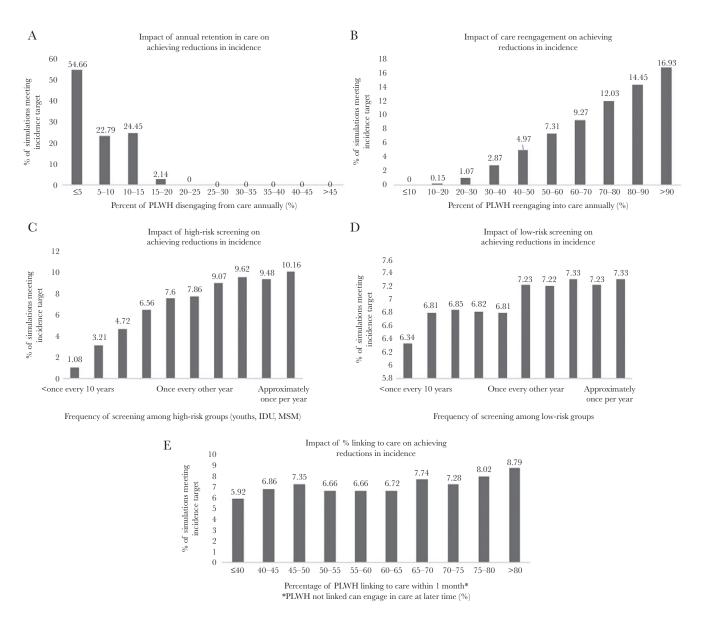


Figure 1. Projected probability of halving US HIV incidence by 2025 by rates of each care continuum parameter. Each care continuum parameter is divided into 10 even strata. Bars represent the percentage of simulations that achieved a 50% reduction in incidence by 2025, according to each stratum. Shown are the percentage of people living with HIV (PLWH) disengaging from care annually (A), percentage of PLWH reengaging into care annually (B), frequency of screening among high-risk groups (ie, youths, people who inject drugs, men who have sex with men) (C), frequency of screening among low-risk groups (D), and percentage of PLWH linking to care within 1 month (E). Abbreviations: IUD, injection drug users; MSM, men who have sex with men; PLWH, people living with HIV.

| Table 2. Impact of 10% Change in Annual Rates of Screening, Lin | kage, Retention, and Reengagement on Achieving Reductions in HIV Incidence <sup>a</sup>        |
|---|--|
| Care Continuum Parameter  | Change in Projected Probability of Achieving Incidence Target<br>Mean (95% CI), <sup>b</sup> % |
| Annual rate of retention above 80%                              | 25.17 (24.77–25.57)  |
| Annual rate of reengagement                                     | 2.00 (1.96–2.05)   |
| Annual rate of high-risk screening <sup>c</sup>                 | 0.96 (0.92–1.01)   |
| Annual rate of low-risk screening                               | 0.11 (0.06–0.15)   |
| Percentage of PLWH linking to care annually <sup>d</sup>        | 0.37 (0.32–0.41)   |

Abbreviations: CI, confidence interval; PLWH, people living with HIV.

a Multivariable linear regression with robust estimate of variance of achieving 50% reduction in incidence by 2025 on care continuum parameters

<sup>&</sup>lt;sup>b</sup> 50% reduction in incidence (95% CI) per 10% absolute increase in each care continuum parameter.

<sup>&</sup>lt;sup>c</sup> High-risk groups include heterosexual youths, people who inject drugs, men who have sex with men.

d Percentage of PLWH linking to care represents percentage of PLWH linking to care within 1 month; those who are not linked to care can still engage in care at a later point in time.

| % of PLWH        |      |                  |                    |                    |                    |                    |                     |                     |                     |                     |
|------------------|------|------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|---------------------|---------------------|
| retained in care |      |                  |                    |                    |                    |                    |                     |                     |                     |                     |
| per year:        |      |                  |                    |                    |                    |                    |                     |                     |                     |                     |
| <55%             | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0                   | 0                   | 0                   |
| 55-60%           | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0                   | 0                   | 0                   |
| 60-65%           | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0                   | 0                   | 0                   |
| 65-70%           | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0                   | 0                   | 0                   |
| 70-75%           | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0                   | 0                   | 0                   |
| 75-80%           | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0                   | 0                   | 0                   |
| 80-85%           | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0                   | 0                   | 0                   |
| 85-90%           | 0    | 0                | 0                  | 0                  | 0                  | 0                  | 0                   | 0.55<br>(6/1098)    | 4.86<br>(49/1009)   | 15.46<br>(164/1061) |
| 90-95%           | 0    | 0                | 0                  | 0                  | 2.89<br>(30/1037)  | 11.72<br>(115/981) | 25.97<br>(274/1055) | 46.10<br>(490/1063) | 61.55<br>(626/1017) | 73.83<br>(776/1051) |
| >95%             | 0    | 2.01<br>(16/795) | 12.46<br>(107/859) | 34.16<br>(289/846) | 56.51<br>(469/830) | 74.44<br>(626/841) | 83.59<br>(652/780)  | 88.67<br>(712/803)  | 93.26<br>(803/861)  | 94.66<br>(798/843)  |
| Reengagement:    | <10% | 10-20%           | 20-30%             | 30-40%             | 40-50%             | 50-60%             | 60-70%              | 70-80%              | 80-90%              | >90%                |
|                  |      |                  |                    | % of PLWH out      | of care returning  | g to care per year |                     |                     |                     |                     |

1-20 20-50 50-70 70-90 >90

Figure 2. Projected probability of halving US HIV incidence by 2025 by annual rates of retention and reengagement in care. Chart displaying percentages of simulations achieving 50% reduction in incidence, in  $2 \times 2$  fashion, by annual rates of retention and reengagement in care. The values in each box represent the total percentage (and fraction) of scenarios within each combination of annual rates of retention and reengagement in care that achieved a 50% reduction in incidence by 2025. Cells with 0s represent permutations where no simulations met this target; these cells represent 25742 simulations of the approximately  $100\,000$  total simulations. Abbreviation: PLWH, people living with HIV.

reducing HIV incidence. In our model, when rates of retention are less than 80% per year, it is essentially impossible, without other non–care continuum interventions, to achieve a 50% reduction in HIV incidence in the United States by 2025. Our modeling results suggest that, to maximize the projected probability of halving HIV incidence within the next decade, annual rates of retention in care should be at least 90%, and preferably greater than 95%, coupled with annual rates of care reengagement (for those aware of their HIV serostatus but not in care) of at least 70% (ie, reengaging diagnosed PLWH into care within an average of 1.5 years). When retention in care was more than 95% per year and PLWH who were lost to care reengaged within approximately 1.5 years (on average), the estimated probability of halving incidence by 2025 was approximately 90%.

Our proposed quality metric for HIV programs of retaining at least 95% of individuals in care on an annual basis will require dedicated effort in the United States. Current estimates of annual rates of retention in HIV care in the United States are heterogeneous and sparse, and defining retention in care has been difficult, with no consensus definition [12, 14–16]. Current literature reviews estimate that current rates of retention in care range from 45% to 70% per year, although retention has mostly been evaluated in cross-sectional analyses and has not yet been fully studied longitudinally [3, 12, 14, 17–20]. Most existing research, however, suggests that retaining 95% of individuals in care per year will require new interventions [21]. Potential opportunities for intervention strategies to improve retention in HIV care include using community-based organizations to emphasize the importance of regular care, involving patients'

social networks in retention-focused interventions, and incorporating clinical staff with expertise to serve high-risk populations [22, 23]. Furthermore, integration of services, provider notification systems, and, to a lesser extent, case management, technology, and clinic-based interventions may be potentially efficacious strategies [14].

Coupled with high rates of retention in care, our modeling suggests a need for relatively high rates of reengaging people out of care back into care within an average of 1.5 years, to shorten the potential time of viremia and excess HIV transmissions. Given the challenges of achieving such high rates of retention and re-engagement, realistic approaches to achieving a 50% reduction in incidence by 2025 will need to be comprehensive in nature—including not only retention and reengagement in care, but also preventive strategies (eg, pre-exposure prophylaxis, behavioral interventions, and condom promotion) and improved treatment options. Ultimately, we must prioritize patient-centered approaches that consider the diverse needs of PLWH and seek to meet those needs in a holistic fashion [11].

Not surprisingly, we found that in addition to retention and reengagement, annual screening and the percentage of PLWH linking to care were also associated with simulations achieving high reductions in HIV incidence, highlighting the fact that screening and diagnosis are essential entry steps toward care engagement and ART usage. Our findings support current recommendations focusing on high-risk populations, which recommend screening groups at very high risk for new HIV infection at least annually, whereas we found that screening rates in low-risk groups have very little association with

the estimated probability of halving the incidence within the next 10 years [10, 22]. Nevertheless, the absolute incremental improvements associated with more frequent screening and percentage of PLWH linked to care within 1 month of diagnoses were modest as compared with achieving high rates of retention and reengagement in care, suggesting that improving screening rates and linkage to care alone will not impact incidence. A focus on other care continuum parameters, notably retention and reengagement in care, is necessary.

Our findings are consistent with prior studies, which have found that continuous retention in care is critical and must be of high priority to achieve ambitious reductions in incidence [11, 12]. Research describes adverse impacts of poor retention in care on patient outcomes, including decreased likelihood of receiving ART, higher rates of ART failure, increased risky behaviors that promote HIV transmission, increased rates of hospitalization, and decreased survival [24, 25]. Identifying evidence-based interventions is critical to improving long-term retention and closing the current gap in the HIV care continuum [24, 26, 27]. Currently, most HIV care outcomes that are reported are limited by their cross-sectional nature and short time period for follow-up. However, given the temporally dynamic nature of the care continuum, it is important to report longitudinal measures of outcomes per unit time to allow for a more comprehensive understanding of intervention efficacy [14]. This study is among the first to quantify rates of care continuum engagement that are needed to maximize the projected probability of achieving population-level reductions in incidence. Our findings have significant value for policy makers, HIV clinics, and HIV care programs by quantifying programmatic benchmarks that correlate with population levels of reduced incidence. Moreover, our model provides interpretable probabilities of halving incidence within the next 10 years at different levels of annual retention and reengagement.

Our study is limited in that the model is calibrated to national-level epidemiology; to the extent that there are regional variations in HIV care engagement, our results may over- or underestimate the relative impact of improvements in local care continua [11, 19]. Furthermore, given the relative paucity of evidence-based data, our model did not evaluate feasibility, nor did it evaluate specific interventions that would likely be needed to achieve such recommendations [14]. Nonetheless, independent of specific intervention costs, we present the estimated overall incremental increases in total health system costs associated with increased care engagement along the HIV care continuum required to achieve epidemiologic goals. Needed increases in screening, linkage, and retention in care (ie, with increased sustained ART usage) were estimated to result in more than 30% higher total health system expenditures compared with continuing at current levels of care engagement. Our results suggest that efforts to improve testing,

linkage, and adherence or care engagement will likely require a combination of health system, policy, and clinical innovations, along with sustained financial commitments to providing comprehensive HIV care and ARV therapy [11]. Our model of the HIV care continuum does not address the potential effects of scale-up of pre-exposure prophylaxis (PrEP) or other preventive interventions; thus, to the extent that these interventions are effective at the population level and scaled up over time, our care continuum targets may be overly ambitious. Our results should therefore be interpreted as the levels of retention and reengagement that should be achieved in order to maximize the estimated probability of halving incidence by 2025, in the absence of large scale-up of additional preventive interventions. The high levels of retention and reengagement necessary speak to the importance of scaling up prevention (in addition to strengthening the care continuum) in order to achieve NHAS goals.

In conclusion, our model suggests that sustained improvements in retention and reengagement in care, retaining at least 95% of PLWH in care annually and reengaging PLWH out of care back into care within an average of 1.5 years, should be prioritized if we are to halve HIV incidence in the United States by 2025. Our results offer quantitative guidance to inform policy recommendations and help programs evaluate success in care by focusing on dynamic rates. These goals for retention and reengagement rates are ambitious, and future research should focus on their feasibility (ie, specific intervention efficacy and costs) and identifying evidence-based effective strategies to achieve such targets, while also emphasizing the need for a comprehensive approach including scale-up of prevention (eg, PrEP) and accounting for potential changes in transmission over the next decade. As HIV care programs move forward, our model suggests that efforts, resources, and priorities must be focused on retaining almost all PLWH in care and frequently reengaging those out of care to reduce HIV incidence in the United States over the next decade.

# **Supplementary Data**

Supplementary materials are available at *Open Forum 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.

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