Original Investigation

Human Immunodeficiency Virus Transmission at Each Step of the Care Continuum in the United States

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IMPORTANCE Human immunodeficiency virus (HIV) transmission risk is primarily dependent on behavior (sexual and injection drug use) and HIV viral load. National goals emphasize maximizing coverage along the HIV care continuum, but the effect on HIV prevention is unknown.

OBJECTIVES To estimate the rate and number of HIV transmissions attributable to persons at each of the following 5 HIV care continuum steps: HIV infected but undiagnosed, HIV diagnosed but not retained in medical care, retained in care but not prescribed antiretroviral therapy, prescribed antiretroviral therapy but not virally suppressed, and virally suppressed.

DESIGN, SETTING, AND PARTICIPANTS A multistep, static, deterministic model that combined population denominator data from the National HIV Surveillance System with detailed clinical and behavioral data from the National HIV Behavioral Surveillance System and the Medical Monitoring Project to estimate the rate and number of transmissions along the care continuum. This analysis was conducted January 2013 to June 2014. The findings reflect the HIV-infected population in the United States in 2009.

MAIN OUTCOMES AND MEASURES Estimated rate and number of HIV transmissions.

RESULTS Of the estimated 1 148 200 persons living with HIV in 2009, there were 207 600 (18.1%) who were undiagnosed, 519 414 (45.2%) were aware of their infection but not retained in care, 47 453 (4.1%) were retained in care but not prescribed ART, 82 809 (7.2%) were prescribed ART but not virally suppressed, and 290 924 (25.3%) were virally suppressed. Persons who are HIV infected but undiagnosed (18.1% of the total HIV-infected population) and persons who are HIV diagnosed but not retained in medical care (45.2% of the population) were responsible for 91.5% (30.2% and 61.3%, respectively) of the estimated 45 000 HIV transmissions in 2009. Compared with persons who are HIV infected but undiagnosed (6.6 transmissions per 100 person-years), persons who were HIV diagnosed and not retained in medical care were 19.0% (5.3 transmissions per 100 person-years) less likely to transmit HIV, and persons who were virally suppressed were 94.0% (0.4 transmissions per 100 person-years) less likely to transmit HIV. Men, those who acquired HIV via male-to-male sexual contact, and persons 35 to 44 years old were responsible for the most HIV transmissions by sex, HIV acquisition risk category, and age group, respectively.

CONCLUSIONS AND RELEVANCE Sequential steps along the HIV care continuum were associated with reduced HIV transmission rates. Improvements in HIV diagnosis and retention in care, as well as reductions in sexual and drug use risk behavior, primarily for persons undiagnosed and not receiving antiretroviral therapy, would have a substantial effect on HIV transmission in the United States.

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Preventing new human immunodeficiency virus (HIV) infections is essential to reducing future morbidity and mortality due to HIV infection in the United States. In 2009, an estimated 45 000 persons were newly infected with HIV.[1] Transmission of HIV from HIV-infected persons is primarily a function of risk behavior (eg, unprotected anal or vaginal sex with an HIV-uninfected partner) and HIV viral load. Interventions at each step of the HIV care continuum[2-4] (diagnosis, retention in medical care, prescription of antiretroviral therapy [ART], and viral suppression) have the potential to reduce HIV transmission. Persons aware of their HIV infection have lower transmission risk behavior than those infected but unaware of their infection.[5,6] Regular engagement in medical care is necessary to access ART and achieve viral suppression, which is strongly associated with reduced HIV transmission.[7-9] In addition, persons engaged in regular medical care are more likely to receive counseling interventions[10] and screening and treatment for sexually transmitted infections that might reduce HIV transmission.[8]

Although increasing the number of persons who attain each step in the HIV care continuum is part of the national strategy to reduce HIV transmission in the United States,[11,12] previous analyses of the HIV care continuum have focused on its clinical implications for morbidity and mortality rather than the potential ramifications for HIV prevention.[2-4] Estimates of the number of HIV transmissions arising at each step of the HIV care continuum are essential for policy makers and programs seeking to allocate HIV prevention resources in ways that maximize their epidemiological returns on investment. Such estimates provide a basis for understanding the number of transmissions that could be averted by directing additional resources toward particular continuum steps (eg, earlier diagnosis through increased testing or better retention in care through case management support).

To quantify the potential population-level prevention effect of deploying interventions at different points along the care continuum, we constructed a model to estimate the rate and number of HIV transmissions from HIV-infected persons in the United States by HIV care continuum step and stratified by sex, HIV acquisition risk category, and age group. We used data on HIV transmission risk behavior and viral load from 3 national surveillance systems.

Methods

Data Sources

In accordance with the federal human participants protection regulations, the National HIV Surveillance System (NHSS) and the Medical Monitoring Project (MMP) were determined to be nonresearch, public health surveillance activities used for disease control program or policy purposes. As such, the NHSS and the MMP are not subject to federal institutional review board review. If required locally to conduct MMP, participating states or territories and facilities obtained local institutional review board approval. The National HIV Behavioral Surveillance System (NHBS) was approved by local institutional review boards in each of the participating cities. All participants in the NHBS were explicitly assured during the recruitment process of the anonymous nature of the survey and the HIV testing. For NHBS, no personal identifiers were collected during enrollment, interview, or testing and all participants provided verbal informed consent to take part in the interview and to be tested for HIV. No authors had access to any information that would directly identify individual persons on whom data were collected.

We estimated the number of HIV transmissions in 2009 that were attributable to individuals at each of the following 5 steps of the HIV care continuum: (1) HIV infected but undiagnosed, (2) HIV diagnosed but not retained in medical care, (3) retained in care but not prescribed ART, (4) prescribed ART but not virally suppressed, and (5) virally suppressed. Data from the NHSS were used to estimate the number of HIV-infected undiagnosed persons.[4] Data from the MMP,[13,14] a nationally representative surveillance system of persons receiving HIV care, were used to estimate the number of HIV-diagnosed persons who were retained in care, were prescribed ART, and achieved viral suppression.[4] Data on transmission risk behaviors were obtained from the NHBS 2006-2011 cycles for persons unaware of their HIV infection and those who were HIV-diagnosed but not retained in care (steps 1-2), and the MMP 2009 cycle for persons who were retained in care, prescribed ART, and virally suppressed (steps 3-5).

Model Description

We used a multistep, static, deterministic model that incorporated the primary data in the NHBS and MMP to estimate the rate and number of HIV transmissions along the care continuum. First, we computed the expected number of HIV transmissions in the previous year for each MMP and HIV-infected NHBS respondent by aggregating transmission probabilities across acts with reported sex or drug use partners (**Box** and **Figure 1**). These calculations incorporated information on the numbers and types of sex and injection drug partners, types of sex acts, and condom use reported by respondents in the previous year, as well as viral load measures abstracted from the MMP respondents' medical records in the previous year. For persons with multiple viral load measures, the area under the curve approximating the mean daily viral load was calculated.[15] Further model assumptions, such as per-act transmission probability and the number of sex acts, were based on a literature review (eAppendix in the Supplement).

Second, respondent-level transmissions were combined to estimate the mean annual per-person transmissions (ie, transmission rate) at each continuum step overall and by respondent sex, HIV acquisition risk category, and age group. Because the MMP is a probability survey, weighted means for the 3 in-care steps could be directly computed using sampling weights. By contrast, transmission rate estimates for the first 2 continuum steps, which relied on the NHBS data, required an additional standardization step. The mean numbers of transmissions were first computed for all combinations of continuum step, sex, HIV acquisition risk category, and age group strata and then weighted by the representation of each stratum using the NHSS-based and MMP-based population size estimates.

Third, the transmission rates were multiplied by the NHSS-based and MMP-based population size estimates to calculate

the number of HIV transmissions attributable to individuals at each continuum step. All rates and numbers of transmissions were then proportionally calibrated to fit the 2009 estimate of 45 000 US HIV transmissions (calibration factor, 0.587).[1] Therefore, the final results include HIV transmission rates and numbers of transmissions at each continuum step, as well as the percentage reductions in transmission associated with each subsequent step of the care continuum.

To assess whether transmission varies among population subgroups, results were stratified by sex, HIV acquisition risk category, and age group. Finally, to explore whether variation in transmission rates across the HIV care continuum was related to differences in HIV risk behaviors reported in the previous year, we also quantified the total number of sex partners, any unprotected sex with an HIV-discordant or unknown status partner, and any injection drug use and needle sharing using standardized descriptive measures for the first 2 steps and weighted measures for the final 3 steps of the care continuum.

Bias Analysis

We conducted a probabilistic bias analysis to understand the sensitivity of the estimated rates, numbers of transmissions, and reductions in transmission to misspecification of model inputs and random error in the estimation of population denominators.[16] In a Monte Carlo simulation (1000 runs), we jointly sampled from probability distributions placed around behavioral and clinical inputs and estimated 95% simulation intervals (95% SIs) for all model transmission rates and rate reductions. These results were combined with 95% CIs for population size denominators to produce 95% SIs for the estimated number of transmissions.

Box. Estimated Number of Human Immunodeficiency Virus Transmissions per Each Respondent in the Previous 12 Months

Equation 1. Full model

$$\left(\sum_{j=1}^{J}\sum_{k=1}^{2}\sum_{t=1}^{T_{j,k}}\left[\sum_{\ell=1}^{2}p(S_{j,k,\ell,m=1}\cap tx) + \left(1-\sum_{\ell=1}^{2}p(S_{j,k,\ell,m=1}\cap tx)\right)\sum_{\ell=1}^{2}p(S_{j,k,\ell,m=2}\cap tx)\right]\right) + \sum_{u=1}^{U}p(I_u\cap tx)$$

Equation 2. Probabilities of sexual transmission

$$p(S_{j,k,\ell,m}\cap tx) = p(S_{j,k,\ell,m})\times p(D_{j,k,\ell}) \times\left(1-\left[1-\left(p(tx)\times RR_{S_{j,m}}\right)(1-[\ell-1]c)\right]^{A_{j,k,m}}\right)$$

Equation 3. Probability of IDU transmission

$$p(I_u\cap tx) = p(D_u)\times(1-[1-(p(tx)\times RR_I)]^F)$$

Equation 4. Per-act transmission risk, vaginal sex (by Hughes et al[8])

$$p(tx) = 0.0000173\times 2.89^{log_{10}(VL)}$$

$A_{j,k,m}$ Indicates annual per-partner number of episodes for sex act or role; c, proportion of transmissions averted by condom use (condom effectiveness); $D_{j,k,l}$, sex partner serodiscordance; D_u, drug partner serodiscordance; F, annual per-partner episodes of IDU distributive sharing; I_u, injection drug use (IDU); j, partner sex (1 if male, 2 if female); J, maximum number of partner sex types (1 if partner is female, 2 if male); k, partner main or casual type; l protected or unprotected sex partner (1 if unprotected, 2 if protected); m, insertive or receptive sex role; RR_I, per-act relative risk of needle sharing compared with vaginal sex; $RR_{S\,j,\,m}$, per-act relative risk of act and role compared with vaginal sex; $S_{j,k,l,m}$, vaginal or anal act or role with partner; $T_{j,\,k}$, total partners of sex j and type k; tx, transmission; and U, total IDU-sharing partners.

Results

Of the estimated 1 148 200 persons living with HIV in 2009, there were 207 600 (18.1%) who were undiagnosed, 519 414 (45.2%) were aware of their infection but not retained in care, 47 453 (4.1%) were retained in care but not prescribed ART, 82 809 (7.2%) were prescribed ART but not virally suppressed, and 290 924 (25.3%) were virally suppressed (**Table 1**). Of the estimated 45 000 HIV transmissions that occurred in 2009, HIV-infected but undiagnosed persons and persons diagnosed as having HIV but not retained in care accounted for 91.5% (95% SI, 84.8%-98.2%) (30.2% and 61.3%, respectively), while persons retained in care, including those who were prescribed ART or achieved viral suppression, contributed 8.5% (95% SI, 7.3%-9.7%) (**Figure 2**A). Compared with the estimated HIV transmission rate from HIV-infected but undiagnosed persons (6.6 transmissions per 100 person-years [/100PY]), the transmission rate from persons who were HIV diagnosed and not retained in care (5.3 transmissions/100PY), retained in care but not prescribed ART (2.6 transmissions/100PY), prescribed ART but not suppressed (1.8 transmissions /100PY), and virally suppressed (0.4 transmissions/100PY) were 19.0%, 61.0%, 72.8%, and 94.0% lower, respectively (Table 1). These findings were robust to uncertainty related to model input parameters, including viral load assumptions, behavioral assumptions, and base population denominator estimates. The corresponding 95% SIs based on Monte Carlo simulations are listed in Table 1 (further details are described in the eAppendix in the Supplement).

We estimated the total number of HIV transmissions by sex, HIV acquisition risk category, and age group (**Table 2**, Figure 2B-D, and eTable in the Supplement). Men accounted for most transmissions (86.5%). When sex and HIV acquisition risk category were considered simultaneously, men who acquired HIV via male-to-male sexual contact accounted for the most transmissions (26 269 [58.0%]), and women who acquired HIV via injection drug use accounted for the fewest transmissions (2861 [6.3%]). Men who acquired HIV via male-to-male sexual contact and injection drug use had the highest transmission rate (7.1 transmissions/100PY), and women who acquired HIV via heterosexual contact had the lowest transmission rate (1.6 transmissions/100PY). Stratified by age group, persons 35 to 44 years old accounted for the most HIV transmissions (12 728 [31.8%]), while persons 25 to 34 years old had the highest transmission rate (6.2 transmissions/100PY).

Each of the 3 HIV transmission risk behavioral factors we examined (mean total number of sex partners, any unprotected sex with HIV-discordant or unknown status partner, and

Figure 1. Simplified Schematic for Estimating Number of Human Immunodeficiency Virus Transmissions per Each Respondent in the Previous 12 Months

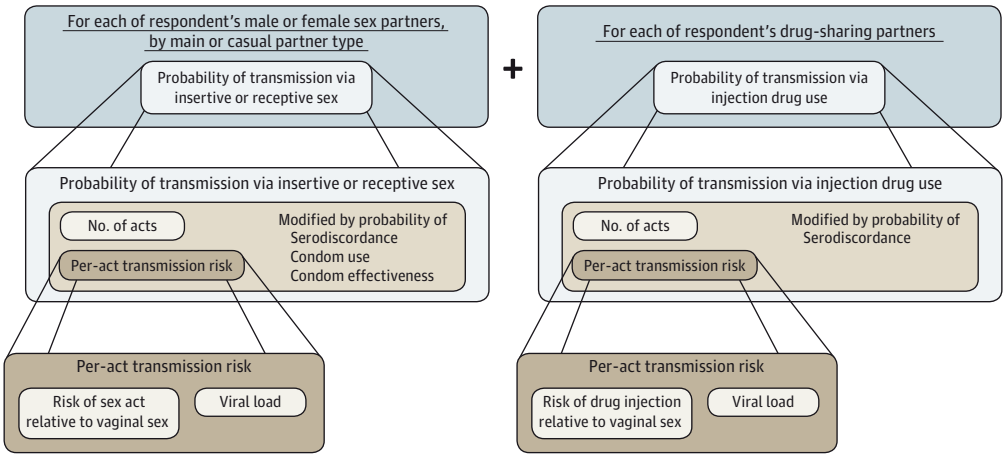


Table 1. Estimated Number and Percentage of Transmissions Along the HIV Care Continuum, United States, 2009

Variable	Population Denominator (95% CI)	Population, %	% (95% SI)			No. (95% SI) of Transmissions	Total No. of Transmissions, % (95% SI)
			Transmission Rate (95% SI) per 100 Person-years	Cumulative Reduction in Transmission Rate Compared With HIV Infected But Undiagnosed	Reduction in Transmission Rate Compared With Previous Step		
Total	1 148 200 (1 117 800-1 178 600)	100	3.9	NA	NA	45 000	NA
HIV infected but undiagnosed	207 600 (196 500-218 700)	18.1	6.6 (6.3-7.0)	0	0	13 603 (12 592-14 642)	30.2 (28.0-32.5)
HIV diagnosed but not retained in medical care	519 414 (468 144-570684)	45.2	5.3 (5.1-5.5)	19.0 (12.8-27.0)	19.0 (12.8-27.0)	27 570 (24 696-30 485)	61.3 (54.9-67.7)
Retained in care but not prescribed ART[a]	47 453 (38 284-56 622)	4.1	2.6 (2.4-2.9)	61.0 (57.2-63.8)	51.8 (43.4-56.8)	1213 (954-1487)	2.7 (2.1-3.3)
Prescribed ART but not virally suppressed	82 809 (71 551-94 067)	7.2	1.8 (1.6-2.0)	72.8 (70.5-75.1)	30.3 (27.4-33.8)	1476 (1241-1722)	3.3 (2.8-3.8)
Virally suppressed[b]	290 924 (256 250-325 598)	25.3	0.4 (0.4-0.4)	94.0 (93.4-94.4)	78.0 (76.5-79.1)	1139 (958-1332)	2.5 (2.1-3.0)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; NA, not applicable; SI, simulation interval.

[a] Retained in care is defined as attending at least 1 visit with a medical care provider from January to April 2009.

[b] Viral suppression is defined as the most recent viral load documented as undetectable or 200 copies/mL or less.

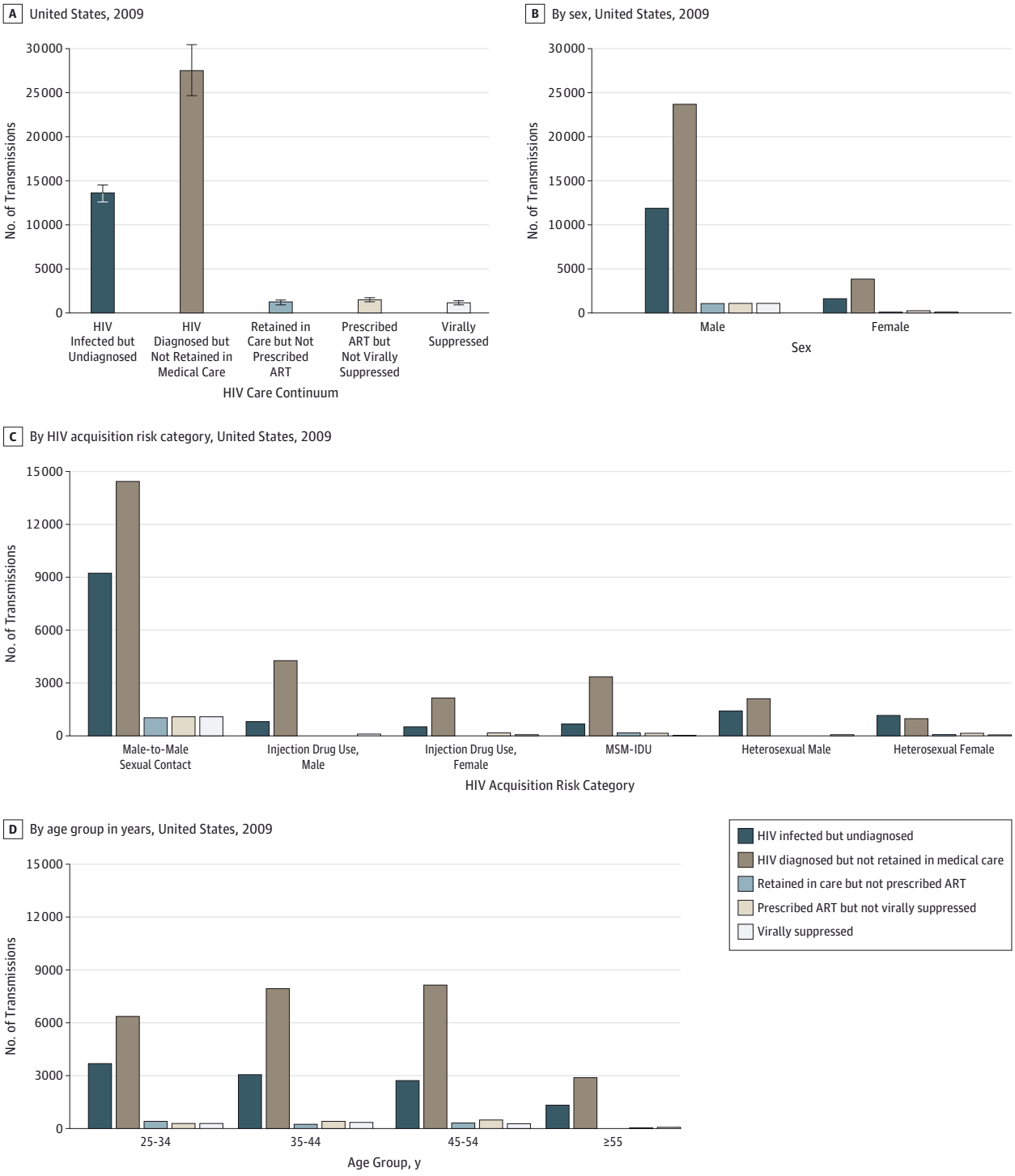
any injection drug use and needle sharing) declined across the HIV care continuum with 2 exceptions. Persons diagnosed but not retained in care reported a higher mean total number of sex partners and injection drug use and needle sharing than HIV-infected undiagnosed persons (**Table 3**).

Discussion

Persons who are HIV infected but undiagnosed and persons diagnosed as having HIV but not retained in care accounted for 91.5% of the HIV transmissions estimated to have occurred in the United States in 2009. By contrast, as a consequence of the effectiveness of current ART regimens, those who were retained in care, were prescribed ART, and achieved viral suppression (ie, those who reached the final step in the continuum) accounted for 2.5% of transmissions and were 94.0% less likely to transmit HIV than HIV-infected undiagnosed persons. Focusing national HIV prevention efforts on increasing the percentage of HIV-infected persons who are diagnosed and retained in medical care that leads to immediate prescription of ART will contribute substantially to reducing HIV transmission in the United States.

Persons who are HIV infected but undiagnosed accounted for almost one-third of transmissions (30.2%) and had the highest transmission rate. The modest transmission rate

Figure 2. Estimated Number of Human Immunodeficiency Virus (HIV) Transmissions Along the HIV Care Continuum



ART indicates antiretroviral therapy; MSM-IDU, male-to-male sexual contact and injection drug use. Retained in care is defined as attending at least 1 visit with a medical care provider from January to April 2009. Viral suppression is defined as the most recent viral load documented as undetectable or 200 copies/mL or less. In A, error bars represent 95% simulation intervals. In D, estimates for persons 13 to 24 years old were not calculated because the Medical Monitoring Project and the National HIV Behavioral Surveillance System collect data only on persons 18 years or older, and the base population size estimated from the National HIV Surveillance System prevalence could not be determined by smaller age strata owing to sample size limitations.

reduction (−19.0%) between HIV-infected undiagnosed persons and those diagnosed and not retained in care was primarily due to a decrease in HIV-discordant unprotected sex among the latter group. The modest decrease in risk behav-

Table 2. Estimated Number and Percentage of Transmissions Along the HIV Care Continuum by Selected Characteristics, United States, 2009[a]

Variable	Population Denominator, No. (%)	Transmission Rate (95% SI) per 100 Person-years	No. of Transmissions		No. of Transmissions by HIV Care Continuum, No. (%)				
			No. (95% SI)	% (95% SI)	HIV Infected but Undiagnosed	HIV Diagnosed but Not Retained in Medical Care	Retained in Care but Not Prescribed ART[b]	Prescribed ART but Not Virally Suppressed	Virally Suppressed[c]
Total	1 148 200 (100)	3.9	45 000	100	13603 (100)	27570 (100)	1213 (100)	1476 (100)	1139 (100)
Sex									
Male	869 000 (75.7)	4.5 (4.3-4.7)	38957 (37 210-40 732)	86.5 (82.6-90.5)	11926 (87.7)	23725 (86.0)	1091 (90.3)	1144 (77.6)	1071 (92.8)
Female	279 100 (24.3)	2.2 (1.6-2.6)	6071 (4721-7449)	13.5 (10.5-16.5)	1675 (12.3)	3866 (14.0)	117 (9.7)	330 (22.4)	83 (7.2)
HIV acquisition risk category									
Male-to-male sexual contact	592 100 (51.8)	4.4 (3.9-5.1)	26269 (22 735-29 847)	58.0 (50.2-65.9)	9055 (66.6)	14162 (51.4)	995 (80.0)	1027 (62.4)	1030 (82.6)
Injection drug use, male	113 200 (9.9)	4.5 (2.6-5.8)	5072 (3225-6982)	11.2 (7.1-15.4)	781 (5.7)	4151 (15.1)	7 (0.6)	53 (3.2)	80 (6.4)
Injection drug use, female	70 200 (6.1)	4.1 (2.2-5.4)	2861 (1723-4062)	6.3 (3.8-9.0)	509 (3.7)	2108 (7.7)	23 (1.9)	194 (11.8)	27 (2.2)
MSM-IDU	60 200 (5.3)	7.1 (6.7-7.4)	4297 (3718-4886)	9.5 (8.2-10.8)	679 (5.0)	3272 (11.9)	155 (12.5)	156 (9.5)	35 (2.8)
Heterosexual male[d]	100 600 (8.8)	3.5 (3.2-3.9)	3543 (3084-4025)	7.8 (6.8-8.9)	1404 (10.3)	2067 (7.5)	6 (0.5)	34 (2.1)	32 (2.6)
Heterosexual female[e]	207 100 (18.1)	1.6 (1.3-1.9)	3218 (2604-3852)	7.1 (5.8-8.5)	1161 (8.5)	1776 (6.4)	57 (4.6)	181 (11.0)	43 (3.4)
Age group, y									
13-24[f]	76 400 (6.7)	NA	NA	NA	NA	NA	NA	NA	NA
25-34	175 000 (15.2)	6.2 (6.2-6.3)	10900 (10 210-11 591)	27.3 (25.5-29.0)	3619 (34.1)	6226 (24.1)	432 (36.7)	315 (23.9)	308 (28.5)
35-44	319 900 (27.9)	4.0 (3.9-4.0)	12728 (12 050-13 411)	31.8 (30.1-33.5)	3017 (28.4)	8616 (33.4)	283 (24.1)	429 (32.5)	383 (35.4)
45-54	380 900 (33.2)	3.1 (3.1-3.2)	11957 (11 361-12 556)	29.9 (28.4-31.4)	2676 (25.2)	8043 (31.2)	434 (36.9)	515 (39.1)	289 (26.7)
≥55	196 000 (17.1)	2.2 (2.2-2.2)	4400 (4097-4707)	11.0 (10.2-11.8)	1316 (12.4)	2896 (11.2)	27 (2.3)	59 (4.5)	102 (9.4)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; MSM-IDU, male-to-male sexual contact and injection drug use; NA, not applicable; SI, simulation interval.

[a] The numbers of transmissions have been estimated and may not sum to heading totals.

[b] Retained in care is defined as attending at least 1 visit with a medical care provider from January to April 2009.

[c] Viral suppression is defined as the most recent viral load documented as undetectable or 200 copies/mL or less.

[d] Man who ever had heterosexual contact with a person known to have or be at high risk for HIV infection.

[e] Woman who ever had heterosexual contact with a person known to have or be at high risk for HIV infection.

[f] Estimates for persons 13 to 24 years old were not calculated because the Medical Monitoring Project and the National HIV Behavioral Surveillance System collect data only on persons 18 years or older, and the base population size estimated from the National HIV Surveillance System prevalence could not be determined by smaller age strata owing to sample size limitations. Therefore, percentages for the number of transmissions by age group are calculated with the exclusion of those 13 to 24 years old from the denominator.

iors associated with diagnosis alone is lower than other estimates.[17] However, previous studies[5,6] have grouped those diagnosed and not retained in care with those who are retained in care to form a single category of HIV-diagnosed individuals. Our findings indicate substantial heterogeneity in risk behaviors among those diagnosed as having HIV infection and suggest that the reduction in risk behavior may be more strongly associated with being engaged in HIV care rather

Table 3. HIV Transmission Risk Behaviors in the Previous 12 Months Along the HIV Care Continuum, United States, 2009

Variable	Mean No. of Total Sex Partners	%	
		Unprotected Sex With HIV-Discordant or Unknown Status Partners	Injection Drug Use and Needle Sharing[a]
Total	6.2	38.7	6.9
HIV infected but undiagnosed	8.0	62.3	6.3
HIV diagnosed but not retained in medical care	8.8	51.2	12.2
Retained in care but not prescribed ART[b]	3.1	15.7	0.9
Prescribed ART but not virally suppressed	2.1	12.1	0.9
Virally suppressed[c]	1.8	10.5	0.5

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

[a] Needle sharing was defined as receptive needle sharing in the National HIV Behavioral Surveillance System data and as distributive sharing in the Medical Monitoring Project data.

[b] Retained in care is defined as attending at least 1 visit with a medical care provider from January to April 2009.

[c] Viral suppression is defined as the most recent viral load documented as undetectable or 200 copies/mL or less.

than HIV diagnosis alone. Early diagnosis of HIV infection remains central to comprehensive HIV prevention strategies. Diagnosis is a necessary, although in many cases insufficient, step to eliminate transmission. Therefore, HIV prevention efforts should continue to support early diagnosis by promoting implementation of existing recommendations for routine, universal HIV screening in health care settings[18,19] and targeted testing for persons at high risk of HIV infection, such as men who have male-to-male sexual contact and those who inject drugs.[20]

Persons diagnosed as having HIV and not retained in care accounted for the most transmissions (61.3%). In part, this finding reflects their proportionate representation among persons living with HIV (45.2%). However, persons diagnosed as having HIV but not retained in care were more likely to transmit HIV than were persons who were retained in care, even among those who had not been prescribed ART. As recommended by guidelines,[20-22] comprehensive HIV care should include interventions aimed at reducing HIV transmission such as HIV care provider counseling on risk reduction, screening and treatment for sexually transmitted infections, treatment for mental health and substance use disorders, and other prevention services. Although the relative contribution of these services to transmission risk reduction was not directly assessed in this model, the decrease in transmission rates evident between persons retained and not retained in care suggests that the receipt of HIV care, even in the absence of ART prescription and subsequent viral suppression, might be associated with reduced HIV transmission. Such an association underscores the importance of linkage to and retention in care not only for the individual living with HIV but also for his or her current and future partners and the community at large. Evidence-based interventions to improve linkage to and retention in care need to be more widely implemented,[23-26] and HIV care providers should continue to provide risk reduction services as recommended by guidelines.[20-22] Moreover, emerging best practices with respect to the use of HIV case surveillance data to identify and relink persons not retained in care,[27] as well as connecting with HIV-infected persons through media campaigns, offer new opportunities to support HIV-infected persons' engagement in and progress along the care continuum.

The benefits of ART as a tool to reduce HIV transmission have been documented in observational investigations,[9] randomized clinical trials,[7] mathematical models,[28] and program evaluations.[29] In our model, persons who achieved viral suppression had a 94.0% lower HIV transmission rate than HIV-infected undiagnosed persons. Therefore, the 25.3% of HIV-infected persons with viral suppression accounted for only 2.5% of HIV transmissions. Persons who were prescribed ART but did not achieve viral suppression were 30.3% less likely to transmit HIV than persons retained in care but not prescribed ART, a finding that underscores the importance of current national treatment guidelines recommending that all persons retained in medical care should be offered ART.[30,31] Nonetheless, persons prescribed ART and virally suppressed were 78.0% less likely to transmit HIV than persons prescribed ART but not virally suppressed, a finding that highlights the importance of adherence counseling, vigilance and treatment for drug resistance, and other interventions to evaluate and treat virologic failure for reducing HIV transmission.[30,31]

Two-thirds of transmissions were from men who acquired HIV via male-to-male sexual contact or male-to-male sexual contact and injection drug use, and most of the transmissions in this subgroup were attributed to those who were HIV infected but undiagnosed or HIV diagnosed but not retained in care. Targeted HIV prevention efforts are needed to increase HIV diagnosis and linkage to and retention in care among men who have male-to-male sexual contact. Among all persons, the transmission rate decreased with age (eg, 6.2 transmissions/100PY for persons 25-34 years old vs 3.1 transmissions/100PY for persons 45-54 years old). However, the absolute number of transmissions was similar for persons 25 to 34 years old, 35 to 44 years old, and 45 to 54 years old (range, 10 090-12 728 transmissions) due to more persons in older age groups. To reduce the overall number of transmissions, our prevention efforts need to reach persons of all age groups.

While the best available data from the NHSS, the MMP, the NHBS, and the literature were used to construct population size and transmission rate estimates, this analysis has some limitations. First, not all factors that are associated with HIV transmission risk (eg, acute HIV infection, presence of concurrent sexually transmitted infections, and potential nonindependence of injection drug use and sexual partners) were accounted for in our estimates. Second, although reference period dates for 2 of the systems used to produce our estimates were closely matched (ie, 2009 for the MMP and the NHSS), the NHBS data were collected between 2006 and 2011. Third, this analysis might overestimate the number of persons who were HIV diagnosed but not retained in medical care based on the MMP definition of retention (1 visit to an HIV care provider in the first 4 months of the year); persons who had medi-

cal visits only in the last 8 months of the year would not have been considered to be retained in care. Fourth, the NHBS data on men who have sex with men are limited to those who attend venues frequented by men who have sex with men; persons who attend such venues might have increased risk behaviors. Fifth, the MMP and NHBS data on self-reported sex and drug use behavior are subject to social desirability and recall bias. Sixth, the HIV care continuum is presented as a static representation at the population level; however, it does not capture the dynamic nature of care because individuals can cycle in and out of care or on and off ART. Seventh, we are limited by the observational nature of these data. For example, the observed reductions in HIV transmission rate might be due to the unmeasured characteristics of persons who are more likely to be retained in care rather than any aspect of care. As such, these results can help guide population-level investment in HIV prevention programs but should not be applied to estimate individual-level risk of HIV transmission.

Conclusions

In the United States, persons living with HIV who are retained in care and have achieved viral suppression are 94.0% less likely to transmit HIV than HIV-infected undiagnosed persons. Unfortunately, too few persons living with HIV have achieved viral suppression. These estimates of the relative number of transmissions from persons along the HIV care continuum highlight the community-wide prevention benefits of expanding HIV diagnosis and treatment in the United States. Improvements are needed at each step of the continuum to reduce HIV transmission. Through stronger coordination of efforts among individuals, HIV care providers, health departments, and government agencies, the United States can realize meaningful gains in the number of persons living with HIV who are aware of their status, linked to and retained in care, receiving ART, and adherent to treatment.

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Invited Commentary

The HIV Treatment Cascade—A New Tool in HIV Prevention

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The human immunodeficiency virus (HIV) treatment cascade provides a snapshot of the effectiveness of the health care system in diagnosing and treating the estimated 1.2 million persons living with HIV infection in the United States.[1] Like many concepts in health care, the cascade developed and evolved over time.

In 2005, my colleagues and I published an estimate of the population effectiveness of HIV care in the United States, which noted that for HIV care to be effective for an infected population, the following "steps in care" needed to occur: persons with HIV infection need to be diagnosed, enter care, receive antiretroviral therapy, and adhere to antiretroviral therapy and visits.[2] Based on the published literature at that time, we estimated that 26% of persons in the United States with HIV infection had viral suppression. Simultaneously, the HIV/AIDS Bureau in the Health Resources and Services Administration developed a continuum of engagement in care model that highlighted the fact that engagement in care was not a permanent state for many persons.[3] In 2009, Greenberg et al[4] published an HIV cascade that estimated that less than 20% of HIV-infected persons had achieved viral suppression in the Washington, DC area. In 2011, Gardner et al[5] published their national estimate of the HIV treatment cascade, estimating from a literature review that only 19% of persons living with HIV in the United States had viral suppression. Subsequent work by the Centers for Disease Control and Prevention (CDC)[1] estimated that 26% of persons with HIV infection in the United States were virally suppressed in 2009, and their most recent estimate is that 30% were virally suppressed in 2011.

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The article by Skarbinski et al[6] published in this issue of *JAMA Internal Medicine* is the next step in the evolution of the cascade. The authors elegantly model the HIV viral load and transmission risk behaviors of persons at each step of the cascade to estimate new HIV infections caused by the population in each step. This exercise turns the treatment cascade into an HIV prevention tool. The results confirm what is apparent from a careful consideration of the cascade: as the cascade proceeds from undiagnosed HIV to viral suppression, the average viral load decreases, and there is a glut of persons lost in the cascade between diagnosis and retention in care. Not surprisingly then, the study demonstrates that the steps of the cascade that propel HIV transmission in the United States are delayed diagnosis and inadequate retention in care. However, what is surprising is the magnitude of the effect of those steps: the authors estimate that more than 90% of transmissions in the United States can be attributed to undiagnosed HIV and poor retention in care.

There are important limitations to the study as acknowledged by the authors. Foremost is that in this analysis (and in analyses by the CDC[1] of the cascade for 2009 and 2011), "retention" is estimated from data from the Medical Monitoring Project, which defines retention as having completed at least 1 visit with an HIV care provider during a single 4-month period in 1 calendar year. This definition is necessary given the Medical Monitoring Project study protocol, but it is overly narrow. No doubt some persons were miscategorized as not in care. In addition, some persons not in care by that definition (and most definitions) will have viral suppression, which is not accounted for in the model by Skarbinski et al.[6] Viral suppression among persons poorly retained in care is not common, and visits in 2009 for patients with viral suppression were not frequently at 6-month visit intervals. Therefore, the magnitude of these limitations is likely small. The Medical Monitoring Project has revised its protocol to address this limitation moving forward. The study by Skarbinski et al[6] also does not consider