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A systematic review and meta-analysis to estimate the time from HIV infection to diagnosis for people with HIV

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Abstract

Timely HIV diagnosis is critical to minimizing transmission events. We sought to estimate the meantime from HIV infection to diagnosis and its temporal trend among people with HIV. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a search of MEDLINE, Embase, and Google Scholar, supplemented by a hand search of bibliographies of articles, was conducted. Study information and outcome measures of time from HIV infection to diagnosis were synthesized. Random-effects meta-analyses were performed. The search identified 12 articles from 4541 unduplicated citations. Studies were conducted in the UK (k = 3), US (k = 3), France (k = 2), Australia (k = 1), Switzerland (k = 1), Netherlands (k = 1), and China (k = 1). The pooled meantime from HIV infection to diagnosis was 3.00 years (95% confidence interval: 2.16-3.84). From 1996 to 2002, meantime reduced from 4.68 to 2.66 years. Subsequently, it increased to 3.20 years in 2003 and remained relatively stable until 2015. In sub-group meta-analyses, men who have sex with men (MSM) had a meantime of 2.62 years (1.91-3.34), while for heterosexuals and people who inject drugs, it was 5.00 (4.15-5.86) and 4.98 (3.97-5.98) years, respectively. In the high- and upper-middle-income countries included in this study, persons live with undiagnosed HIV for about 3 years before being diagnosed. This period is shorter for MSM relative to people with infections attributable to other risk factors.

Keywords

HIV diagnosis. HIV testing. HIV screening. Delayed diagnosis. Systematic review. Meta-analysis.

Introduction

Significant improvements in HIV care services in the highly active antiretroviral therapy (HAART) era have been closely associated with better health outcomes for persons who are aware of their HIV infection and receive early treatment[1,2]. The first critical entry point to accessing care is receiving timely HIV testing and early HIV diagnosis; however, not all people with HIV (PWH) have benefitted from this intervention. During 2017 in developed countries, about 21-45% of HIV diagnoses were made at a late stage of HIV infection (CD4+ cell count of < 350 cells/μL or having an AIDS-defining event)[3-6]. Delayed diagnoses result in missed opportunities for early receipt of HAART and thus

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impaired immune function, lack of HIV viral load suppression[7], and increased health expenditures[8]. Further, transmissions from undiagnosed PWH are estimated to cause about 30-40% of new HIV infections[9,10]. A study of routinely collected HIV surveillance data estimated that eight transmissions are probably avoidable for every 100 persons newly diagnosed with HIV[11]. As such, early and frequent HIV testing geared toward early detection of HIV infection must remain a primary goal of HIV prevention efforts.

The time interval between HIV infection to diagnosis represents a crucial period for PWH to forestall disease progression[2] and adopt risk reduction strategies to prevent onward HIV transmission[12]. Time from HIV infection to diagnosis provides information on whether HIV testing initiatives capture early or late HIV diagnosis of PWH. As it is typically impossible to ascertain the exact time that an individual is infected with the virus, particularly in persons who engage in high-risk behavior, the duration of HIV infection at the time of HIV diagnosis is not readily measured.

Early in the epidemic – in the pre-HAART era, researchers used incubation period distribution to model estimates of time from HIV infection to AIDS diagnosis to track the course of the epidemic and obtain future projections[13,14]. The advent of HAART has lengthened the incubation period between HIV infection and the emergence of AIDS symptoms[15], thereby resulting in a decline in the proportion of PWH with AIDS-related comorbidities[16]. Thus, it has become increasingly difficult to use this approach as a measure of the effectiveness of the public health response to the HIV epidemic. Recent modeling studies[17-19] have incorporated information such as observed CD4 count levels at diagnosis to provide more precise estimates of time from HIV infection to diagnosis. Therefore, this review is focused on the duration of HIV infection at the time of diagnosis, which is as an important indicator of HIV disease stage.

To the best of our knowledge, no systematic review of this topic has been conducted. Thus, the objective of this study was to conduct a systematic review and meta-analysis of the meantime from HIV infection to diagnosis and its temporal trend for PWH in the HAART era.

Methods

This review was registered in the PROSPERO International Prospective Register of systematic reviews, registration number CRD42020160319[20]. We followed the guidelines outlined in the Cochrane Group Handbook for Systematic Reviews of Intervention[21] and recommendations for reporting by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[22].

Search strategy and identification of studies

We included all peer-reviewed studies reporting any measure of time from HIV infection to diagnosis in the HAART era. We excluded case studies, abstracts, and articles not published in English. We searched MEDLINE and Embase for studies published from the earliest time available in these databases up until April 11, 2019. Two authors (RJ and SOG) jointly conducted the search using extensive keywords and Medical Subject Heading terms. The search terms included: "HIV" AND ("back-calculation" OR "stratified extrapolation" OR "CD4 depletion") (Supplementary Table 1 for full search strategy). A librarian with extensive experience in search methodologies was consulted to refine the search strategy. We also conducted a manual search of bibliographies of included studies and Google Scholar. All citations were imported into Covidence[23] and duplicates were removed. Two authors (RD and SOG) independently screened titles and abstracts to identify relevant studies for full-text review. Articles that did not have sufficient information in the title and abstract were moved to full-text review. Further, the authors independently examined the articles assigned for full-text review to identify those that met our inclusion criteria and were relevant to our research topic. Discordant findings were resolved by discussion and consensus. The reviewing pair, RJ and SOG, independently abstracted information under the following headings: study information (first author, publication year, study design and country, study year, data source, sample population), subjects' demographic information (sex, transmission risk category), modeling technique used, and outcome measures reported. We resolved all discrepancies by consensus.

Data analysis

We extracted the summary statistical measures, including the mean and 95% confidence interval (CI), standard deviation (SD) or standard error (SE), or the median and interquartile range (IQR) of time from HIV infection to diagnosis, stratified by study year. For studies that reported only the medians and IQR, we converted these estimates to means and SD using the formula proposed by Luo et al. [4] and Wan et al. [5],

respectively, and computed the SE by multiplying the SD by the square root of the sample population. In some studies that did not report the sample population, we obtained these numbers by contacting study authors. In addition, for studies that reported only the mean and CI values, we computed the SE using the method proposed in the Cochrane Handbook[21]. Only studies that had meantimes from HIV infection to diagnosis and SE values (reported or computed) were included in the meta-analyses. By aggregating all the studies with complete data, we estimated a summary parameter (meantime from HIV infection to diagnosis in years) using the random-effects meta-analysis given the differences in characteristics across studies. Heterogeneity of the studies was assessed using Cochran's Q (Chi-square) and Moran's I^2 (Inconsistency)[21]. To determine whether a study had undue influence on the summary parameter, we performed a leave-one-out sensitivity analysis by iteratively omitting one study at a time and recomputing the summary parameter. Additionally, sub-analyses were done by sex, country, modeling technique, and transmission risk category. We also assessed the temporal trend of the meantime from HIV infection to diagnosis from the year 1996 to 2015 using a cumulative meta-analysis[26]. In this analysis, for studies that reported meantime from HIV infection to diagnosis for a group or separate groups of years, we took a conservative approach by allowing this summary measure to represent the last year for that group. All data were analyzed using STATA Version 15 (College Station, Texas).

Quality assessment

Two authors (RJ and SOG) appraised the methodological quality of included studies using seven out of the 8-item Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies[27]. This tool assesses different domains such as selection, measurement and confounding bias, and data analysis. Each item uses a scale with options "Yes," "No," "Unclear," or "Not applicable." A score of 1 was given if the item was checked as "Yes" and 0 for the others. A total score was calculated as a sum of all items. A score of 6-7 indicated good quality, 4-5 indicated moderate quality, and < 4 indicated poor quality.

Results

The search identified 6194 citations for the title and abstract screening (Fig. 1). After de-duplication, 4541 citations remained. Of these, 149 were eligible for full-text review; 140 articles were excluded as these articles were reviews, did not contain the relevant outcome, or did not report quantitative data or statistics that allowed calculation of the parameter. Nine articles remained and we identified three additional articles from the manual search. A final sample of 12 articles was included in the narrative synthesis; seven of the articles had complete information for inclusion in the meta-analysis.

Description of included studies

All studies were published between 2008 and 2018: four[28-31] of the 12 studies were published in 2008 and 2012, while the majority[17-19,32-36] were published between 2013 and 2018. The study period ranged from 1996 to 2015. Most studies[17-19,29-33,36] were ecological studies (k = 9), while only three[28,34,35] were cross-sectional studies as shown in supplemental table 1. Based on The World Bank[37] classification of countries by income level, except for China (k = 1) which is an upper-middle-income country, all of the other studies were conducted in high-income countries: England and Wales/ United Kingdom (UK) (k = 3)[17,31,35], US (k = 3)[18,32,36], France (k = 2)[30,33], Australia (k = 1)[29], Switzerland (k = 1)[28], and the Netherlands (k = 1)[19]. While most of the earlier studies[17,19,28-31,33,35,36] utilized the back-calculation method (n = 9) or its modification as the preferred modeling technique, more recent studies[18,32,34] used the CD4-depletion model (k = 3). One study further analyzed data with Bayesian and biomarker models[35]. Nine out of the 12 studies reported data on the total PWH included in their models (n = 89,613). Of the 12 studies, six[17,19,29,31,34,36] included men who have sex with men (MSM) only, five[18,30,32-34] evaluated differences in HIV transmission risk category (one study[34] analyzed male-to-male sexual contact and heterosexual contact as one group), and one study[28] did not report estimates by any group. Only five studies[18,30,32-34] analyzed sex differences out of the 12 included studies. The duration of time from HIV infection to diagnosis ranged from 0.72 years in 2007 among MSM, reported by a study[29] using back-calculation modeling from Australia to 7 years in 2003 among all newly diagnosed HIV cases, reported by a study[18] using the CD4-depletion model from the US.

Meta-analysis

Of the seven studies[18,19,29,30,32-34] included in the meta-analysis, four studies[18,29,30,32] reported an estimate for each study year under consideration, and three

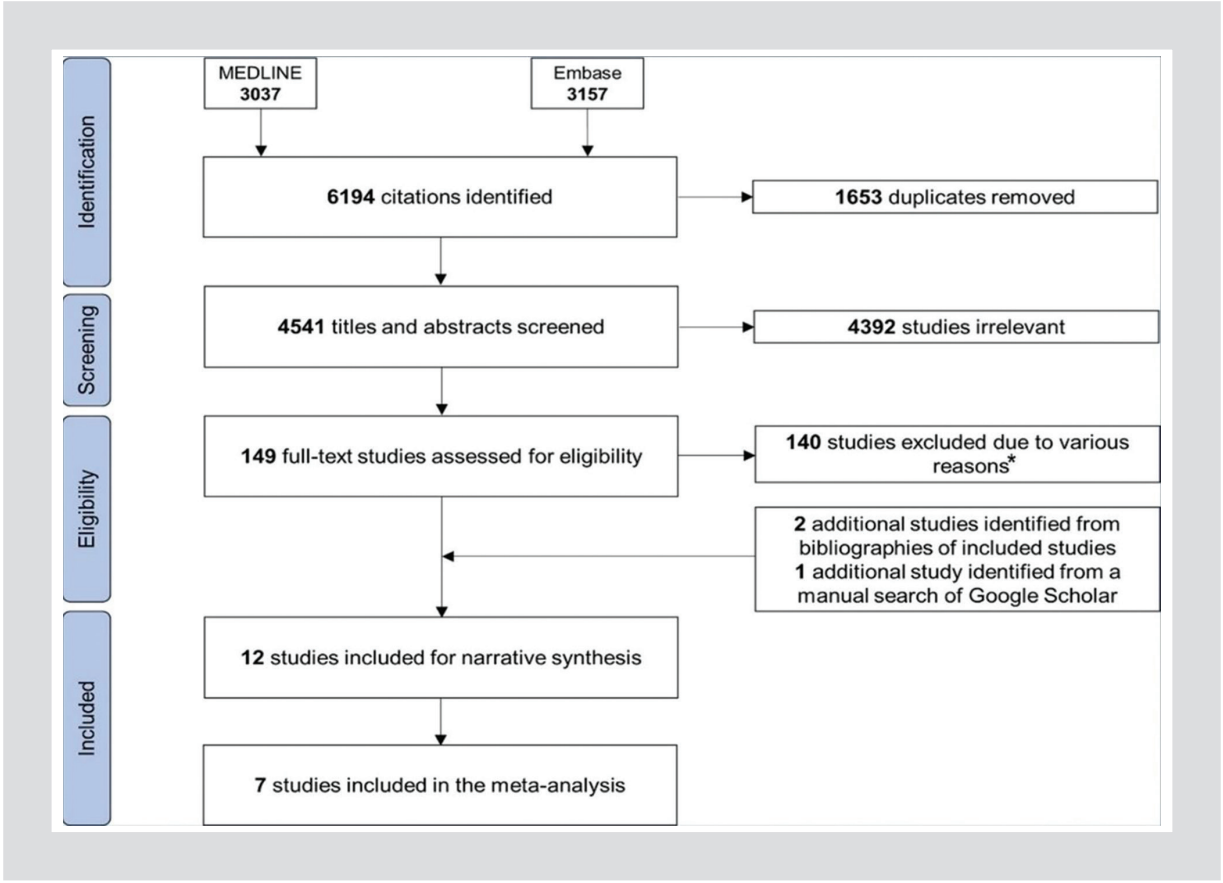

Figure 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for the search strategy and inclusion of studies reporting time from HIV infection to diagnosis conducted from 1996 to 2015. *Reasons for exclusion: (i) review articles, (ii) studies without the relevant outcome, or (iii) studies with incomplete quantitative data or statistics to calculate the effect size.*

studies[19,33,34] reported summary estimates for multiple years. Overall, the meta-analysis aggregated summary measures (n = 20) for single-year and multiple-year data for which the meantime was reported or computed. Two studies[18,19] did not report the total PWH used for their analyses; therefore, we obtained these numbers from correspondence with study authors. Including these, the total number of PWH represented in the meta-analysis was 166 620. Four studies were excluded since we were unable to estimate the measure of dispersion. Two of these studies[17,35] reported only credible intervals for the mean, one study[28] reported the mean and IQR without the median, and one study[31] did not provide any information to calculate the measure of dispersion.

Overall meantime from HIV infection to diagnosis

The summary parameter for the meantime from HIV infection to diagnosis was 3.00 years (95% CI: 2.16, 3.84). The heterogeneity among the seven studies was high (I^2 = 99.99%; Q = 104102.06; $P <$ 0.0001) (Fig. 2). In evaluating the robustness of the pooled mean, the leave-one-out sensitivity analysis performed had little or no effect on the magnitude of the summary parameter. An assessment of the temporal trend in the meantime using the cumulative meta-analysis revealed changes in the magnitude of the summary effects in earlier years. Significant reductions in the meantime were observed from 4.68 years (95% CI: 4.65, 4.71) in 1996 to 2.66 years (95% CI: 1.62, 3.70) in 2002. However, from 2002 to 2003, the meantime increased to 3.20 years and remained relatively stable over subsequent years.

Exploratory subgroup analyses

The summary parameter for the meantime from HIV infection to diagnosis for MSM was 2.62 years (95% CI: 1.91, 3.34), while individuals who acquired HIV through heterosexual contact and injection drugs were

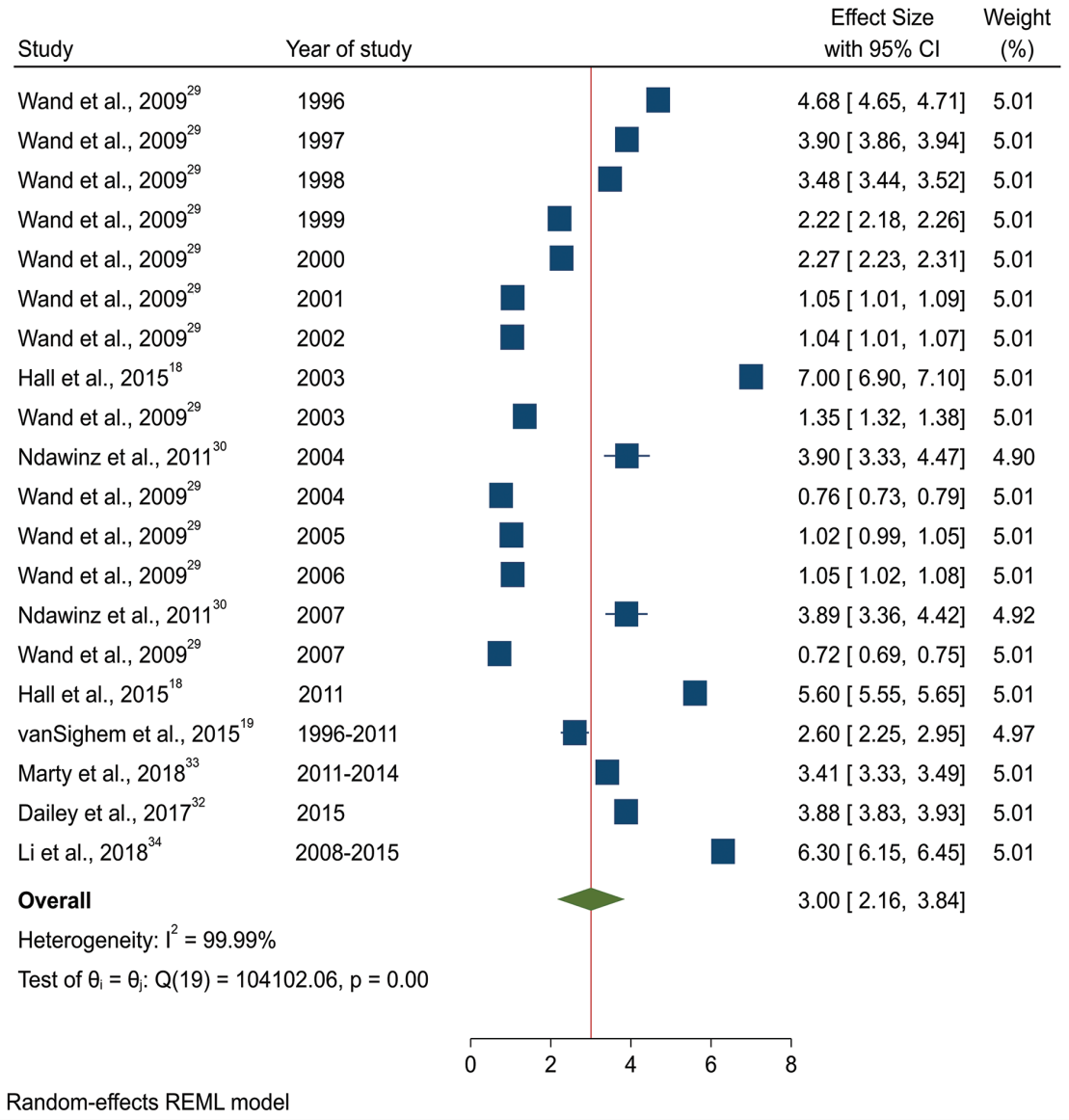

Figure 2. *Forest plot of individual study and pooled mean and 95% confidence intervals (CI) of time from HIV infection to diagnosis, k = 7.*

5.00 years (95% CI: 4.15, 5.86) and 4.98 years (95% CI: 3.97, 5.98), respectively (Fig. 3A-C).

The summary parameter for the meantime from HIV infection to diagnosis for men was 2.99 years (95% CI: 2.16, 3.83) compared to a summary parameter of 4.96 years (95% CI: 3.69, 6.24) for women.

Sub-group analysis by modeling technique revealed a meantime from HIV infection to diagnosis of 2.32 years (95% CI: 1.66, 3.00) and 5.70 years (95% CI: 4.38, 7.00) for studies that used the back-calculation method and CD4-depletion model, respectively.

Only the US and France had ≥ two studies conducted in these countries with complete information for a meta-analysis. The summary parameter for the meantime from HIV infection to diagnosis in the US was 5.49 years (95% CI; 3.72, 7.26) while France was 3.85 years (95% CI; 3.55, 4.16).

Using the JBI tool, the quality assessment showed that six studies had good quality, and six had moderate quality. The moderate quality in the six studies was primarily due to inadequate description of confounding.

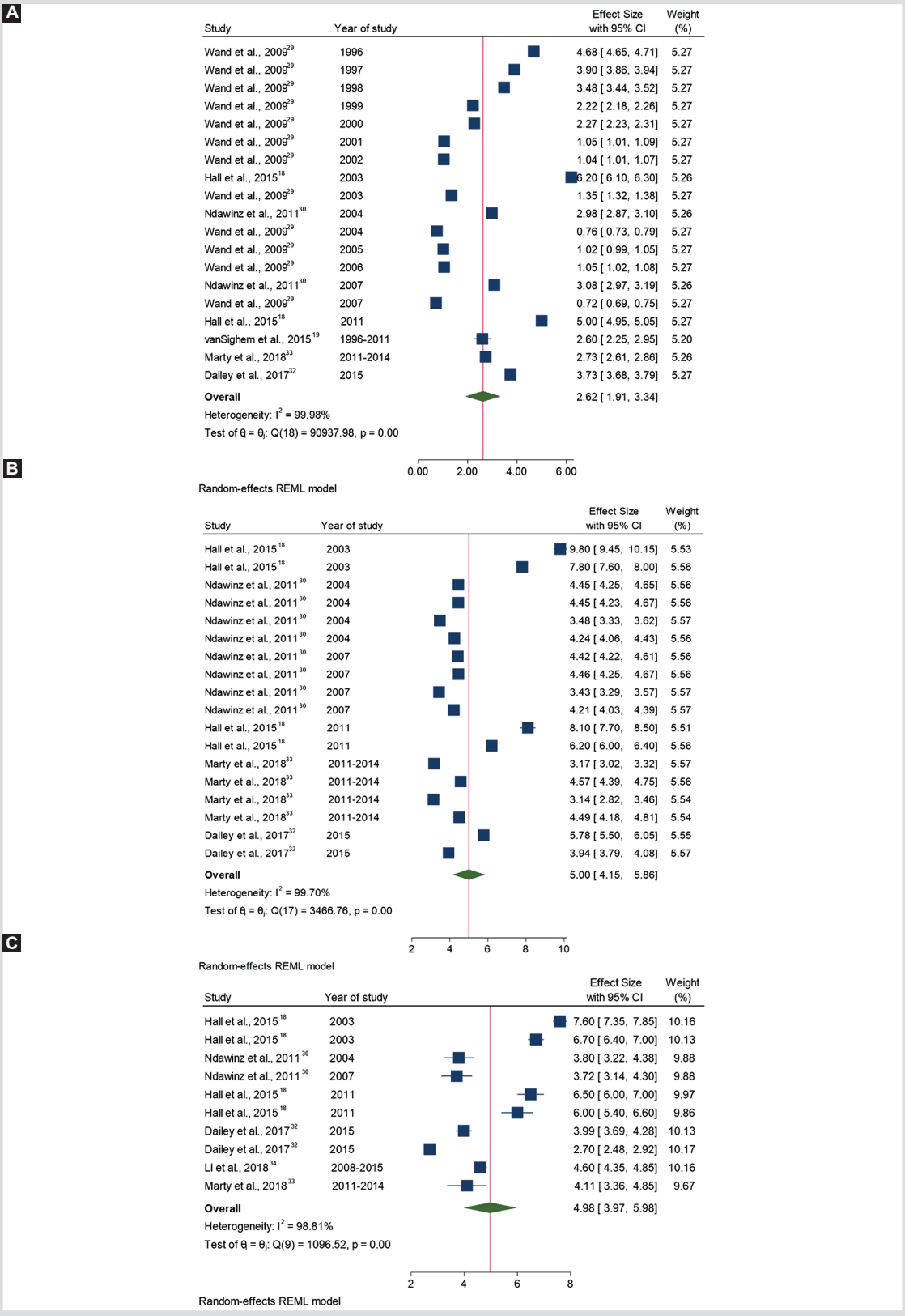

Figure 3. *Forest plot of individual study and pooled mean and 95% confidence intervals (CI) of time from HIV infection to diagnosis among individuals with infection attributed to (A) male-to-male sexual contact only, k = 6 (B) heterosexual contact only, k = 4 (C) injection drug use only, k = 5.*

Discussion

Our findings indicate that in high- and upper-middle-income countries included in this study, PWH had been infected for 3 years on average before their HIV diagnosis during the period 1996-2015. From 1996 to 2002, coinciding with the start of the HAART era, we observed an initial decline in the overall duration of infection at the time of diagnosis as the years progressed but remained stable at roughly 3 years in the following 12 years. This may be attributable to decreases in undiagnosed HIV infection[6,38] as a result of increased testing efforts, especially in groups at high risk of HIV acquisition. We also observed that men, particularly MSM, experienced a shorter length of time from HIV infection to diagnosis relative to women or compared to other PWH who acquired the infection by heterosexual contact or injection drug use.

On average, it takes an estimated 7-8 years from primary HIV infection to developing AIDS without treatment[39]. Notably, there is a lack of consensus on how to adequately assess late diagnosis. Several studies[40,41] used a time-based approach from HIV diagnosis to the occurrence of AIDS at initial diagnosis or within a study defined period as a surrogate measure for late diagnosis. Other studies, commonly in Europe, use CD4+ count levels at initial diagnosis to measure late diagnosis[5,42], although this may be subject to bias due to incomplete reporting of laboratory results. Using the time from HIV diagnosis to AIDS to identify late diagnoses misclassifies individuals, as one study[43] found that up to 13% of newly infected patients may develop AIDS within a year of HIV infection. In addition, current measures of delayed diagnosis which use time from HIV diagnosis to AIDS may be inaccurate, as they are likely to classify many people as "not delayed" (given the absence of an AIDS diagnosis) despite spending on average 3 years with undiagnosed HIV.

The inverse relationship between HIV testing efforts and late diagnoses has been observed across national HIV surveillance reports[3-6]. This may be attributable to the success of sustained policies and strategies to improve HIV-related service provisions, especially routine testing policies that have led to an increased awareness of HIV and testing coverage. Using national surveys of HIV diagnosis data in the US from 2013 to 2016, a study found that a five-point percentage increase in HIV testing in the preceding 12 months was associated with a three-point percentage decrease in late-stage diagnoses among individuals aged 25-45 years[41]. Despite these declines, the proportion of individuals with late diagnoses in developed countries is still high[3-6], suggesting gaps in HIV testing remain. These gaps are likely due to HIV testing barriers such as low-risk perception, fear of testing positive, and HIV-related stigma[32,44]. Current efforts must shift focus toward adopting innovative strategies that are tailored and targeted at populations with a considerable need to improve early detection of HIV infection.

In high-income countries, the HIV burden is concentrated mainly among MSM[16]. It also appears that MSM may contribute about half of HIV acquisitions in heterosexuals[10]. For these reasons, there have been intensified efforts aimed at reaching more MSM with HIV care services. This may partly explain our findings that MSM experience a shorter length of time from HIV infection to diagnosis relative to infections attributable to heterosexual contact and injection drug use. In the US, the CDC's Testing Makes Us Stronger[45] and MSM Testing Initiative[46] promoted HIV testing in 11 cities and expanded testing and linkage-to-care services from 2011 to 2015 to racial/ethnic minority MSM, respectively. A systematic review of outreach HIV testing in resource-rich countries found that the most common group targeted for testing was MSM[47].

Another explanation for these differences in time to diagnosis in transmission risk categories could be the role of health care providers in practicing risk-based testing over opt-out testing[48]. From 2015 to 2017, among individuals who received an HIV diagnosis at sexual health centers in the Netherlands, the majority were MSM (90%), while other men and women accounted for 6% and 4%, respectively[6,49]. Similarly, in the UK in 2017, sexual health services were more likely to test MSM (89%) compared to heterosexual men (78%) and women (59%)[5]. It is also likely that health care providers perceived high-risk heterosexual persons as having lower risks for HIV infection than MSM, resulting in fewer opportunities to offer the former HIV testing[50].

The differential estimates of time from HIV infection to diagnosis observed in the analysis by modeling technique may partly be explained by some factors. The back-calculation method requires the specification of the AIDS incubation distribution, which is largely influenced by HIV detection and testing of infected individuals that have improved over the years[3-6,51]. Thus, it may have led to an underestimation of the estimate for this method. The CD4 depletion model relies on laboratory testing and individual-level data of CD4 count, which are sometimes incomplete or underreported. Moreover, a rapid CD4 decline at the early

stage of HIV disease occurs, which subsequently rebounds temporarily to a steady-state during the asymptomatic phase[52]. There is a possibility of capturing CD4 profiles during the early stage and misclassifying them as long-standing infections. This can lead to an overestimation of the distribution of the time from HIV infection to diagnosis.

Our study is not without limitations. First, it was unclear how some studies defined the distribution of their target population, whether among those infected in a given year or those diagnosed in a given year. The two distributions (and their mean values) could be very different unless the diagnosis delay patterns have been stabilized. While one study[19] reported estimates for both groups, we limited our analysis to the distribution represented by diagnosis year. In another study[29], we computed the meantime by subtracting the mean age at infection from mean age at diagnosis. The differences in methodological approaches, especially modeling parameters and underlying assumptions of the models used in the studies, may have provided estimates that are not directly comparable; hence, our findings should be interpreted with caution. Second, five of the 12 eligible studies were excluded from the meta-analysis as a result of incomplete information, which may have inadvertently led to the high heterogeneity observed among the studies. Although for some of the excluded studies, it is likely that the primary focus of those studies was not to measure the duration of HIV infection at the time of diagnosis; therefore, basic descriptive statistics were not reported. Finally, our search did not identify any studies that have been conducted in low- and middle-income countries; therefore, our findings may not be generalizable to their populations. Given the dynamics of the HIV epidemic in these countries, this is an area for future research.

Conclusion

In summary, this systematic review and meta-analysis shows that, on average, people live with undiagnosed HIV infection for 3 years before being diagnosed in high- and upper-middle-income countries. Undiagnosed infections cause delays in treatment and preclude interventions for behavioral risk reductions that may avert HIV transmissions. MSM experience a shorter length of time from HIV infection to diagnosis relative to infections attributable to heterosexual contact and injection drug use. These findings have important implications for public health monitoring and targeted initiatives to increase routine HIV testing.

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Supplementary data

Supplementary data are available at AIDS Reviews online (10.24875/AIDSRev.21000007). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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