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The prevalence of HIV-infected patients with virological suppression but a CD4+ T-cell count of ≤ 200 cells/mm^3 after highly active antiretroviral therapy initiation: A meta-analysis

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Abstract

Highly active antiretroviral therapy (HAART) strongly inhibits HIV replication. However, many patients show suboptimal immune recovery (SIR), as defined by virological suppression (i.e. low viral load) with a CD4+ T-cell count of ≤ 200 cells/mm^3, after HAART initiation. Here, we performed a systematic evaluation of the SIR prevalence among HIV-infected patients in cohort studies. We searched PubMed, Cochrane Library, Embase, CNKI, Wanfang database, and Chinese Biomedicine Database for cohort studies about HIV-infected participants whose CD4+ T-cell count was ≤ 200 cells/mm^3 but still had virological suppression after HAART initiation. The SIR prevalence from each of those cohort studies was pooled into a random-effect meta-analysis. We obtained two kinds of pooled post-HARRT initiation SIR prevalence: one among participants with virological suppression (11 cohort studies involving 18,672 participants), and the other among all HIV-infected participants (seven cohort studies involving 12,063 participants). The pooled SIR prevalence among HIV-infected patients with virological suppression after HAART initiation was 43% (95% confidence interval [CI], 34-51%) at 6 months post-HAART initiation and 10% (95% CI, 5-18%) at 36 months post-HAART initiation; among all HIV-infected patients after HAART initiation, it was 17% (95% CI, 0-55%) and 5% (95% CI, 2-10%) at 6 and 36 months post-HAART initiation, respectively. The SIR prevalence among HIV-infected patients is high at 6 months post-HAART initiation, but its prevalence gradually reduces over time under continuous HAART. Thus, it is important to follow-up on variations in the CD4+ T-cell count and viral load.

Keywords

Highly active antiretroviral therapy. HIV. Suboptimal immune recovery. Cohort study. Meta-analysis.

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Introduction

The HIV epidemic remains a worldwide public health problem. At the end of 2019, the Joint United Nations Program on HIV/AIDS (UNAID)[1] reported that there are 38 million people living with HIV worldwide. HIV mainly invades the host CD4+ T lymphocytes, causing a decreased CD4+ T-cell count. All-cause mortality is the highest when people living with HIV have a CD4+ T-cell count of ≤ 200 cells/mm^3 [2]. The introduction of highly active antiretroviral therapy (HAART) has significantly decreased morbidity and mortality[3] by suppressing viral replication and recovering the CD4+ T-cell count[4-9]. However, many individuals exhibit a failed or incomplete recovery of CD4+ T-cell counts despite virologic suppression (i.e. low viral load) after continuous HAART. This phenomenon is known as suboptimal immune recovery (SIR) or poor immune reconstitution (PIR)[10-12].

Not surprisingly, HIV-infected patients with SIR have worse outcomes compared with those with a complete response, such as increased risk of cardiovascular diseases[13], AIDS-related complications[14], and HIV-related neurocognitive diseases[15,16] along with increased risk of associated mortality. However, the prevalence rate of SIR varies greatly among locations as well as between time points post-HAART initiation. At 6 months post-HAART initiation, the SIR prevalence was 19%[17] in Brazil and 26.7%[10] in France. At 12 months post-HAART initiation[18], the SIR prevalence was 43.9% in Canada; at 18 months post-HAART initiation, the SIR prevalence was 33.1%[19] in France; and at 24 months post-HAART initiation, the SIR prevalence was 32%[20] in Spain.

At present, there is no widely accepted criterion for defining HIV SIR. For example, Gaifer Ali et al.[21] defined SIR as a plasma HIV viral load of < 50 copies/ml and a CD4+ T-cell count of < 350 cells/μl after least 2 years of HAART; Muzah et al.[22] defined SIR as an increase in the CD4+ T-cell count of < 50 cells/mm^3 within 3-6 months of HAART initiation with virologic suppression; Casotti et al.[17] defined SIR as a CD4+ T-cell count of < 350 cells/mm^3 in patients with virological suppression after > 1 year of HAART; and Darraj et al.[23] defined SIR as a CD4+ T-cell increase from baseline of < 100 CD4+ T cells/mm^3 or a lack of increase to > 200 cells/mm^3 within 1 year of virological suppression.

A CD4+ T-cell count of ≤ 200 cells/mm^3 in HIV-infected patients with virological suppression after HAART initiation is representative of the diagnostic criteria that have been applied for SIR. Here, our main objective was to determine the pooled prevalence rates of patients whose CD4+ T-cell count was ≤ 200 cells/mm^3 but had virological suppression at different lengths of time post-HAART initiation.

Methods

Search strategy and data extraction

We conducted a literature search utilizing the PubMed, Cochrane Library, Embase, and Chinese language databases (i.e. CNKI, Wanfang database, and Chinese Biomedicine Database). In our search, conducted on December 29, 2020, we used the following terms: (*Acquired immunodeficiency syndrome* OR *AIDS OR HIV OR human immunodeficiency virus*) AND (*immune reconstitution failure* OR *immunological treatment failure* OR *immunological discordance* OR *immune discordant* OR *immune discordance* OR *discordant immune response* OR *suboptimal immune reconstitution* OR *suboptimal immune response* OR PIR OR *poor immunologic reconstitution* OR *less immune reconstitution* OR *incomplete immune reconstitution* OR *incomplete immune restoration* OR *incomplete immune recovery* OR *immunological non-response* OR *non-immunological response*). Articles published in English or Chinese were considered for inclusion in this analysis.

Two independent reviewers (W. Z. and Y. C.) screened articles for eligibility, with a third reviewer (G.H. or J. Y.) making the final decision for articles on which the two main reviewers had differing opinions. The full texts that met the inclusion criteria were included in the study.

The general inclusion criteria were as follows: (1) the study participants had HIV and were antiretroviral-naive; (2) the study participants were aged ≥ 18 years old; (3) a defined method of SIR diagnosis was applied; (4) the number of participants with a CD4+ T-cell count of ≤ 200 cells/mm^3 and virologic suppression after HAART initiation was listed; (5) the total number of participants with virologic suppression or the total number of all participants was provided; and (6) the study was a cohort study. The general exclusion criteria were as follows: (1) the study was a review or meta-analysis; (2) the study was a duplicate article or study; or (3) the study was missing data.

Two reviewers (W.Z. and Y. C.) independently extracted the cohort study data, including the first author name, publication time, study location, baseline CD4+ T-cell count,

treatment regimen, study period, criterion used for virological suppression, and number of HIV-infected patients whose CD4+ T-cell count was ≤ 200 cells/mm^3 and had virological suppression after HAART initiation, total number of HIV-infected patients with virological suppression after HAART initiation, total number of study participants, and number of study participants lost to follow-up for analysis.

Statistical analysis

The purpose of this study was to assess the pooled prevalence of HIV-infected patients with virological suppression but a CD4+ T-cell count of ≤ 200 cells/mm^3 after HAART initiation. Follow-up data were available, and the pooled prevalence of SIR was estimated for different lengths of time post-HAART initiation by determining common milestones used by all the included cohort studies. Cumulative SIR prevalence estimates were calculated at 6, 12, 24, and 36 months post-HAART initiation.

We obtained two kinds of pooled prevalence: the prevalence of HIV-infected patients with virological suppression but a CD4+ T-cell count of ≤ 200 cells/mm^3 after HAART initiation (numerator) among all participants with virologic suppression (denominator), and the prevalence of these individuals (numerator) among all participants regardless of virologic suppression (denominator). Patients who were lost to follow-up at any point were excluded from the meta-analysis.

Heterogeneity in this study was analyzed by the I^2 statistic; if $I^2 < 50\%$ and $p < 0.05$, we used a fixed-effects model, but if $I^2 > 50$ and $p < 0.05$, indicating a high heterogeneity, then a random-effects model was used to aggregate assessments. The source of heterogeneity was analyzed by subgroup analysis or sensitivity analysis when possible. If the sample size of the study under consideration was not large enough to conduct a subgroup analysis, other sources that could cause high inter-study heterogeneity were assessed by analyzing the study characteristics and referring to its data. All statistical analyses were conducted using R software.

Results

Study selection and basic characteristics

Our searches initially yielded a total of 10,389 articles (2280 in PubMed, 502 in Cochrane Library, 3345 in Embase, 2923 in CNKI, 1257 in Wanfang, and 82 in the Chinese Biomedical Literature Database). After removing duplicate articles and meta-analyses of reviews and applying our inclusion criteria, a total of 217 full-text articles remained to be analyzed. Ultimately, 15 articles[24-38] were included in our study (Fig. 1).

We applied two different approaches for examining the pooled prevalence of SIR (defined as having virological suppression but a CD4+ T-cell count of ≤ 200 cells/mm^3) after HAART at key points. In one, we used the number of HIV-infected patients with virological suppression after HAART initiation as the denominator; this analysis was conducted with 11 cohort studies that included a total of 18,672 participants. In the other, we used the number of all HIV-infected participants after HAART initiation as denominator; this analysis was conducted with seven cohort studies that included a total of 12,063 participants. Most of participants in the included studies each had a baseline CD4+ T-cell count of ≤ 200 cells/mm^3. Most of the research sites were in China[31,33,35-37] and Africa[24,29,30]. These articles were mainly published between 2010 and 2020 (Table 1). A total of 36 months of SIR prevalence are provided in the present cohort study.

Prevalence of SIR

By conducting a meta-analysis of the selected cohort studies, we obtained two kinds of pooled estimate of the cumulative prevalence of SIR. For the first type, the number of participants with virological suppression was used as the denominator; this yielded a pooled SIR prevalence of 43% (95% confidence interval [CI], 33-46%) at 6 months post-HAART initiation and of 10% (95% CI, 6-10%) at 36 months post-HAART initiation (Fig. 2). For the second type, the total number of HIV-infected participants after HAART initiation was used as the denominator. This yielded a pooled SIR prevalence of 17% (95% CI, 6-10%) at 6 months post-HAART initiation and of 5% (95% CI, 2-4%) at 36 months post-HAART initiation (Fig. 3).

Discussion

In this meta-analysis of 15 cohort studies, we determined the prevalence of SIR in two different ways. In the first method, we used the number of participants with virological suppression after HAART initiation as the denominator (11 cohort studies), and in the other method, we used the total number of HIV-infected participants who underwent HAART as the denominator (seven cohort studies). The first method produced a pooled prevalence of post-HAART SIR of 43% at 6 months, 30% at 12 months, 19% at 24 months, and 10% at 36 months, whereas the second method pro-

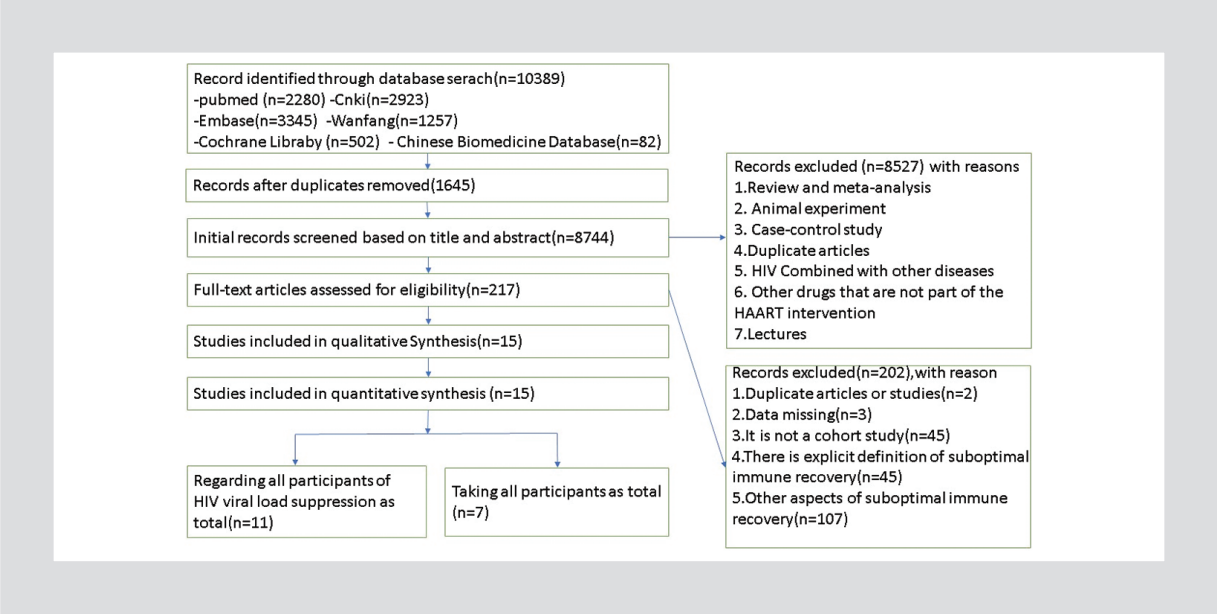

Figure 1. *Flow chart of the study selection process.*

duced a pooled prevalence of post-HAART SIR of 17% at 6 months, 20% at 12 months, 15% at 24 months, and 5% at 36 months. Because of the difference in denominator used for the calculations, the pooled prevalence determined by the first method is higher than that determined by the second method. Some previous studies reported a range of SIR prevalence of approximately 10-40%[39-41], which is generally consistent with our results, except for the pooled SIR prevalence at 6 months post-HAART initiation.

Regardless of the method applied for calculating the pooled prevalence of SIR, it was found to decrease progressively over longer durations of HAART, but with a gradual decrease in the magnitude of the reduction. These findings highlight the importance of early HAART initiation and support the assertion by Moore et al.[42] that longer periods of time with an undetectable HIV viral load reduce the prevalence of SIR. However, one measure of the pooled prevalence of SIR indicated that it was 14% at 60 months post-HAART initiation; such a high prevalence of SIR requires attention. Alternatively, this value may simply reflect the limitations of a cohort study, which represent the prevalence in one place. Notably, we found an unexpected increase in the pooled prevalence of SIR at 12 months from that at 6 months when the second method was applied. This finding may reflect a difference in the antiviral therapy regimens applied in various different countries or poor adherence. Both meta-analysis methods revealed the highest pooled prevalence of SIR at 6 months, which could be the reason why most AIDS-related events or deaths occur in the first 6 months following HAART initiation[30]. This finding supports the importance of early HAART initiation.

There are many different associated factors with SIR, including therapy regimen. For example, participants who initiated therapy with zidovudine were 3.6 times more likely to develop SIR compared with participants receiving therapy with a d4T-containing regimen, presumably owing to the myelosuppressive effects of zidovudine[43]. Another study found that a protease inhibitor-based regimen is protective against SIR[44,45]. Barreiro et al.[46,47] reported that the increase in $CD4^+$ T-cell counts was more pronounced in therapy using a protease inhibitor compared with that using an Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), especially in subjects with the lower initial $CD4^+$ T-cell counts. Other authors demonstrated[48] that using integrase strand transfer inhibitor-, non-nucleoside reverse transcriptase-, or boosted protease inhibitor-based regimens can lead to immune recovery in antiretroviral-naive HIV-infected patients. Unfortunately, our meta-analysis could not analyze the contribution of different antiviral compounds (e.g. zidovudine, stavudine, and didanosine, PI-based) to the prevalence of SIR. In addition, a low baseline $CD4^+$ T-cell count is a predictor for SIR. Patients with a baseline $CD4^+$ T-cell count of 0-19 cells/μl are more likely to develop SIR compared with those with a baseline $CD4^+$ T-cell count of 0-49 cells/μl at 6 months and 12 months[30], and some studies found that baseline $CD4^+$ T-cell counts can predict the likelihood of SIR[37]. Furthermore, other factors, such as older age, poor HAART adherence, base-

Table 1. Study characteristics

Author (Year)	Location	Baseline of CD4	Therapy Regime	Study period (months)[a]	Undetectable viral load[b]	Positive number[c]	Viral load suppressors No[d]	Enrolled No[e]	Lost-to follow-up
Nakanjako et al., 2008[24]	Africa	NA	NNRTI+NRTI	24	≤ 400	58	309	559	93
Loutfty et al., 2010[25]	Canada	< 200	NNRTI/SinglePI/Boosted PI/INSTI	24	< 50	404	2028	3316	NA
Engsig et al., 2010[26]	Danish	≤ 200	NA	36	< 50	55	705	1666	NA
Zoufaly et al., 2011[27]	Germany	< 200	PI/NNRTI/NRTI	24	< 500	233	1062	NA	NA
Merlini et al., 2011[28]	Italy	< 200	NNTI+PI/NRTI+NNRTI	12	< 60	15	44	NA	NA
Retshabile, et al., 2013[29]	Africa	NA	NA	12	NA	51	249	NA	NA
Takuva et al., 2014[30]	Africa	≤ 200	NNRTI+NRTI	24	< 400	1829	4473	NA	344
Tian et al., 2014[31]	China	NA	AZT-based/No AZT-based	24	< 50	76	503	NA	NA
Lapadula et al., 2015[32]	Italy	< 200	NNRTI/SinglePI/Boosted PI	12	< 50	319	1221	1869	171
Zhang et al., 2015[33]	China	< 200	NNRTI+NRTI	36	< 50	18	123	NA	NA
Premchand et al., 2017[34]	UK	< 200	NA	24	< 50	10	NA	207	NA
Hu et al., 2017[35]	China	< 200	NNRTI+NRTI/NNRTI+PI	60	< 50	16	116	NA	NA
Wang et al., 2018[36]	China	NA	TDF-based or No TDF	24	<50	29	NA	104	17
Yu et al., 2020[37]	China	< 200	PI-based or No PI	24	< 50	28	90	NA	NA
Han et al., 2020[38]	Thailand	< 200	NNRTI-based/PI-based	36	< 400	29	NA	375	NA

[a]Length of follow-up time after HAART initiation.
[b]The criterion used for assessing virological suppression.
[c]The number of HIV-infected patients with virological suppression but a CD4+ T-cell count of ≤ 200 cells/mm3 after HAART initiation.
[d]The number of HIV-infected patients with virological suppression after HAART initiation.
[e]The number of HIV-infected patients who underwent HAART.

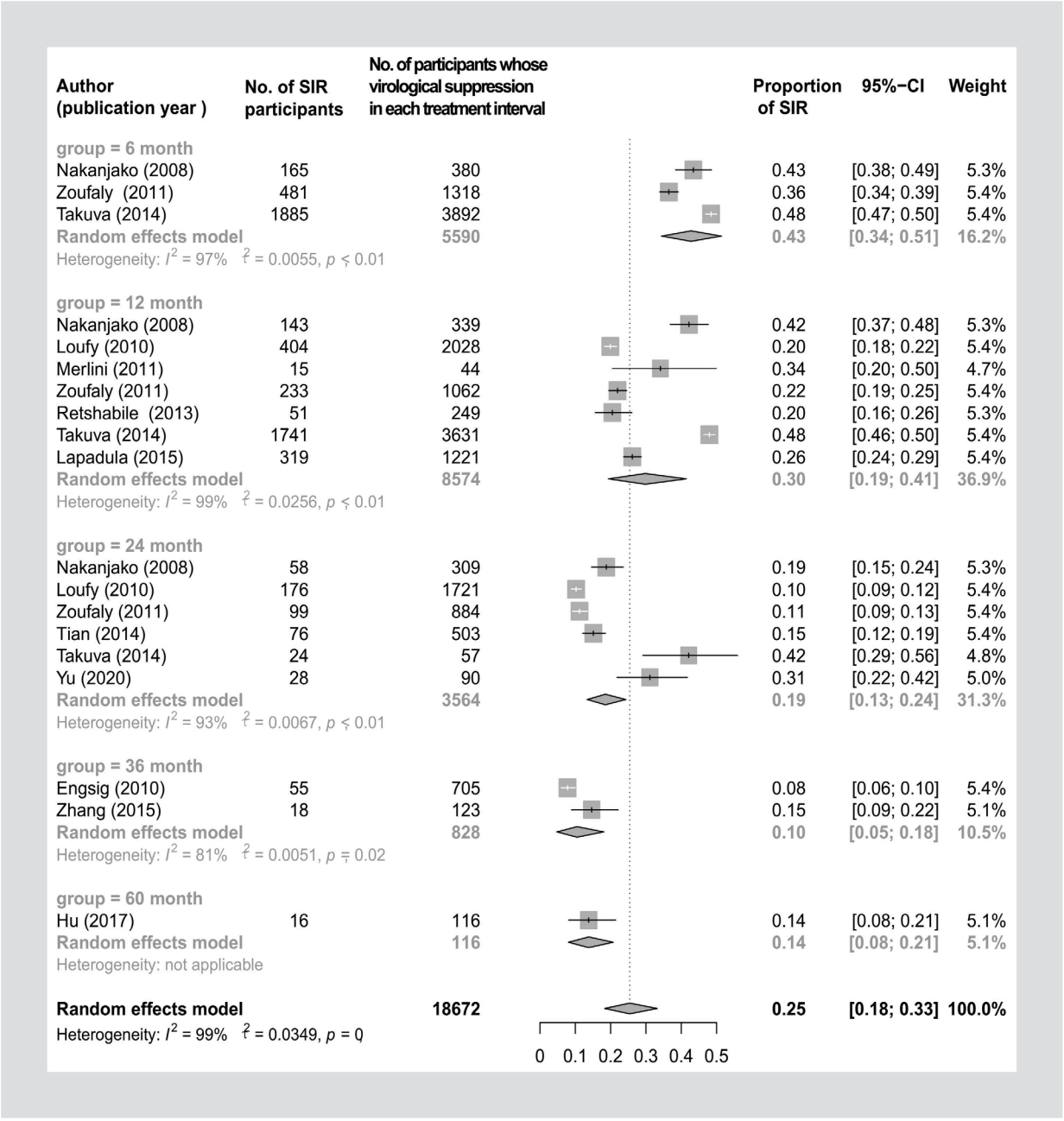

Figure 2. *Pooled prevalence of SIR among all HIV-infected patients after HAART initiation in 11 cohort studies. SIR is defined as having virological suppression but a CD4⁺ T-cell count of ≤ 200 cells/mm³.*

line viral load levels, HIV transmission category[14], and comorbidities[22], can all affect the prevalence of SIR.

There are some limitations to our study. First, the criterion applied for defining virological suppression differed among the included studies, for example, some defined it as an undetectable HIV viral load of < 50 copies/ml[25,26,31-37], while others defined it as an undetectable HIV viral load of < 60 copies/ml[28] or < 400 copies/ml[24,30,38], or < 500 copies/ml[27]. However, these varying definitions had a minimal effect on the outcome because most of the patients categorized as having virological suppression had fewer than 50 copies/ml. Second, the limited locations of the included cohort studies, mainly in China and Africa, constrict the generalizability of our results. Third, due to continuous HAART, all participants could be lost to follow-up or death, and some cohort studies did not explicitly clarify these issues. Fourth, given the limitations of our study,

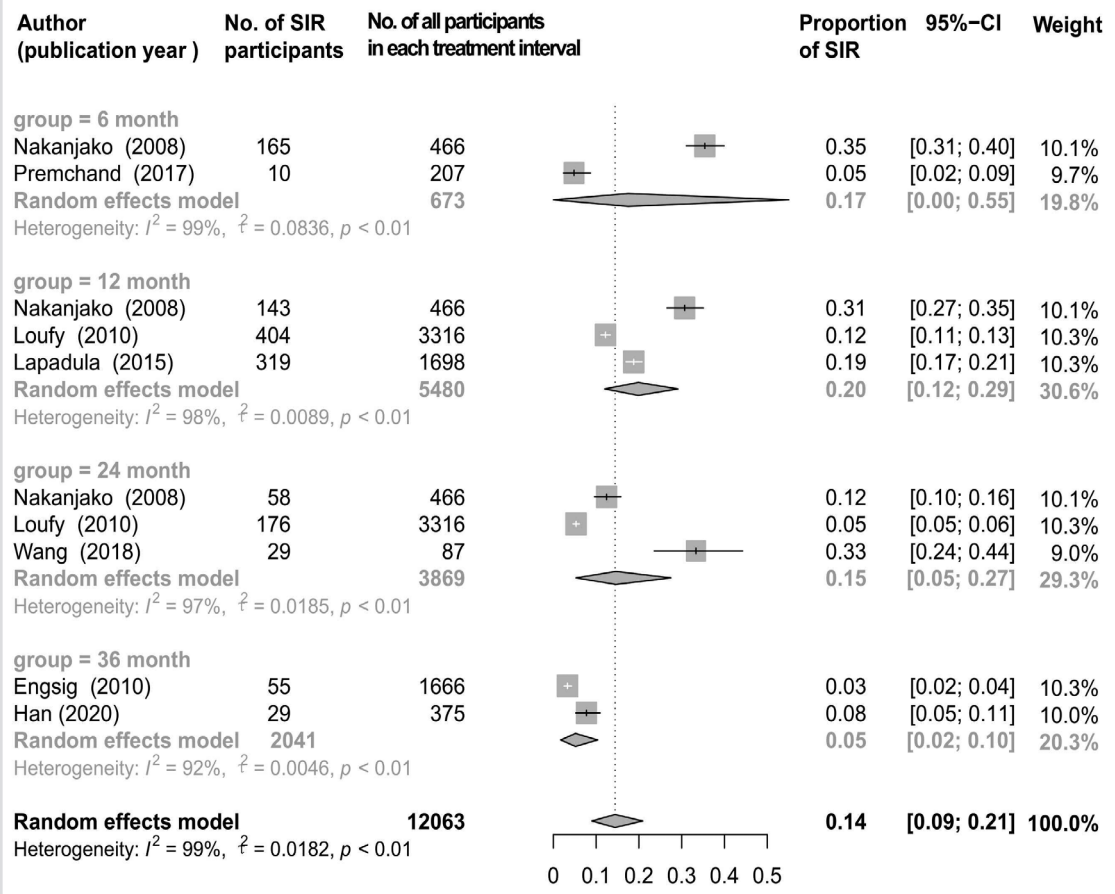

Figure 3. *Pooled prevalence of SIR among all HIV-infected patients after HAART initiation in seven cohort studies. SIR is defined as having virological suppression but a CD4⁺ T-cell count of ≤ 200 cells/mm³.*

we could not conduct stratified analyses on the correlations between SIR prevalence and different HAART regimens or other potential factors (e.g. lower baseline CD4⁺ T-cell count and older age).

In summary, the prevalence of SIR is high (43% among cases with virologic suppression at 6 months post-HAART initiation). Our study demonstrates that the prevalence of SIR decreases gradually the longer a patient remains on continuous HAART. Therefore, during the stages of antiviral therapy, clinicians should monitor not only whether the viral load is suppressed but also whether the CD4⁺ T-cell count is increased.

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