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Review

Meta-analysis and systematic review of the efficacy and resistance for human immunodeficiency virus type 1 integrase strand transfer inhibitors

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ABSTRACT

Integrase strand transfer inhibitors (INSTIs) are the most recent class of antiretroviral drugs with potent and durable antiviral activity used to treat human immunodeficiency virus type 1 (HIV-1) infection. However, development of drug resistance increases the risk of treatment failure, disease progression and mortality. A better understanding of drug efficacy and resistance against INSTIs is crucial for their efficient use and the development of new antiretrovirals. A meta-analysis of studies reporting efficacy and resistance data on INSTI use in HIV-infected patients was performed. Odds ratios (ORs) of efficacy outcome data favouring INSTI use in different clinical settings demonstrated that INSTIs have higher efficacy compared with drugs of other classes. For combination antiretroviral therapy-naïve patients and virologically-suppressed patients who switched to INSTI-based therapy, the OR was 1.484 (95% CI 1.229–1.790) and 1.341 (95% CI 0.913–1.971), respectively. ORs of resistance data indicated decreased treatment-emergent resistance development to dolutegravir (DTG) upon virological failure than to non-INSTIs (OR = 0.081, 95% CI 0.004–1.849), whereas the opposite was observed for raltegravir (RAL) (OR = 3.137, 95% CI 1.827–5.385) and elvitegravir (EVG) (OR = 1.886, 95% CI 0.569–6.252). Pooled analysis of resistance data indicated that development of resistance to DTG and bictegravir was rare, whereas EVG and RAL had low genetic barriers to resistance and the intensive cross-resistance between them limits INSTI efficiency. Efficient means of monitoring the emergence of resistance to INSTIs and the development of drugs with high genetic barriers are clear paths for future research.

1. Introduction

Human immunodeficiency virus (HIV) is the causative agent of acquired immune deficiency syndrome (AIDS). Integrase strand transfer inhibitors (INSTIs) represent the newest antiretroviral drug class and include four drugs approved by the US Food and Drug Administration (FDA) [1]. Raltegravir (RAL) and elvitegravir (EVG) are first-generation INSTI, whilst dolutegravir (DTG) and bictegravir (BIC) are second-generation INSTIs recently approved by the FDA.

HIV integrase catalyses the irreversible integration of reverse-transcribed HIV viral DNA into the host chromosome, which is essential for infection through two successive reactions, namely 3′ processing and strand transfer [2]. To date, all FDA-approved therapeutic integrase inhibitors specifically target the latter step of the integration process [3–5] by binding to the catalytic core domain of the integrase and competing for binding with host DNA.

INSTI-containing regimens are recommended for the treatment of HIV type 1 (HIV-1) infection in many settings [6,7], however the emergence of strains with resistance to INSTIs is inevitable [5,8]. Treatment-emergent resistance to INSTIs is rare at the population level [9] but upon occurrence can cause treatment failure. A better understanding of INSTI efficacy and drug resistance is crucial for efficient use of INSTIs and for the development of new antiretroviral drugs. In this study, a systematic review and meta-analysis of published clinical trials was performed to evaluate the efficacy profile of INSTIs and the emergent INSTI drug resistance profiles in a resistance analysis population upon virological failure.

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2. Materials and methods

2.1. Data sources and search strategies

This study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [10]. The online databases Web of Science, PubMed and ClinicalTrials.gov were systematically searched for clinical trials and studies from database inception until June 2018. The search terms in the Web of Science and PubMed databases were 'AIDS', 'acquired immunodeficiency syndrome', 'HIV' OR 'human immunodeficiency virus' AND 'integrase inhibitor', 'dolutegravir', 'elvitegravir', 'raltegravir' OR 'bictegravir' AND 'treatment', 'therapy' OR 'clinical'. Using this strategy, published studies reporting on INSTI efficacy and drug resistance profiles were identified.

2.2. Study selection

Initial study selection was performed by two independent investigators. Randomised controlled trials, non-randomised trials and prospective analyses of these trials, or cohort studies on the use of INSTIs in HIV-1-infected patients were included. All titles and abstracts identified by the search were analysed. Discrepancies in the analysis were resolved by consensus or by consulting a third reviewer. Abstracts or full-text articles were assessed and were selected for further analysis if they met the following criteria: (i) patient age ≥18 years and participants INSTI-naïve at baseline; (ii) original research articles and analysis of studies on INSTI used in HIV-1-infected patients; (iii) relative results reported for efficacy outcomes, genotypic resistance assays upon virological failure, and emergent resistance to INSTIs and/or comparable drugs; (iv) number of participants >30; and (v) full-text articles were retrievable.

2.3. Data extraction and synthesis

Two reviewers independently selected articles and assessed the eligibility and methodological quality of the studies, summarising the following data from selected articles: (i) study characteristics, including study name, year of publication, study period and design; (ii) participant characteristics, including whether participants had received prior combination antiretroviral therapy (cART), number of participants and number of participants with confirmed virological failure; (iii) efficacy outcome data, including the proportion of patients with successful virological suppression (all plasma virological suppression assays were considered equivalent with the lowest of multiple thresholds used); and (iv) resistance data, including the resistance analysis population and the number of patients with emergent drug resistance to INSTIs or antiretroviral drugs.

HIV mutants with drug resistance were determined by the International AIDS Society–USA (IAS-USA) drug resistance mutations list [11]. Other information, including protocol-defined criteria of genotype resistance assays in each study and mutations conferring resistance to INSTIs, was identified by reference to articles or supplementary material.

2.4. Data analysis

Statistical analyses were conducted using the META package of STATA software v.12.0 (StataCorp LP, College Station, TX, USA) [12]. Heterogeneity across individual studies was assessed using Cochran's Q statistic and the I^2 statistic, and a P-value of <0.05 determined statistical significance. I^2 values of 25%, 50% and 75% corresponded to low, medium and high levels of heterogeneity, respectively. The estimated odds ratio (OR) of efficacy outcome and drug resistance among the resistance analysis population upon virological failure between comparable treatment arms (INSTI versus non-INSTI control) and the 95% confidence interval (CI) were analysed using data extracted from controlled studies. The primary analysis was conducted to estimate overall ORs and their 95% CIs using a fixed-effects analysis (inverse variance method [13]) if significance of heterogeneity was not found (I^2 < 50% and Q-test P > 0.05), and a random-effects analysis (DerSimonian and Laird method [14]) was used otherwise. An OR of 1 signified no difference between INSTIs and the control. If the 95% CI of the OR did not include the value 1, then the difference was considered significant. In cases with substantial heterogeneity, subgroup analysis was conducted. Publication bias was investigated by funnel plotting [15] the log(OR) against standard error, and regression asymmetry tests (Egger's test [16] and Harbord's modified test [17]) were performed to examine funnel plot asymmetry. Subsequently, the estimated pooled proportions (and 95% CI) of patients with successful viral suppression and the resistance prevalence among the resistance analysis population upon virological failure were reported for treatment groups that received INSTI-based regimens from all selected studies by a random-effects model when the heterogeneity was significant, and by a fixed-effects model otherwise. Spearman's correlation was conducted to assess trends in the proportion of successful virologically-suppressed patients for each INSTI drug following initial treatment.

3. Results

3.1. Study selection

Literature searches of the three databases yielded 2110 citations, of which 450 were duplicates and discarded, resulting in 1660 unique citations. The full-text was obtained for 150 studies and was examined in detail, with 73 articles not meeting the inclusion criteria. Consequently, 77 publications on 54 eligible studies were selected. Six articles were excluded during the data extraction process. Thus, a total of 71 articles from 48 studies were included in this systematic review and meta-analysis (Supplementary Table S1). The PRISMA flow of the review process is shown in Fig. 1.

3.2. Systematic review

Of the 48 studies, 27 (56%) described two comparable treatment arms: INSTI-based therapy and non-INSTI therapy. Twelve studies (25%) described two comparable arms and both used INSTI-based regimens. Eight studies (16.7%) were single armed, whilst one study (2.1%) included three treatment arms. Most of the assessed studies (83%; 40/48) were randomised, and all but four [18–21] were registered with ClinicalTrial.gov. The mean population size was 522 (range 52–1733). The study duration ranged from 24–240 weeks. Overall, 18 225 and 6842 participants were enrolled in INSTI-based and non-INSTI treatment arms, respectively. The included studies spanned the period 2007–2018.

3.3. Efficacy profile of integrase strand transfer inhibitors (INSTIs)

3.3.1. INSTIs are more efficacious than non-INSTIs

Efficacy data for INSTI-based and comparable non-INSTI treatment groups were extracted from 26 controlled studies reporting data at similar timepoints (Supplementary Table S2). Meta-analysis results were visualised using forest plots (Fig. 2). A funnel plot of studies included in the meta-analysis was used to assess publication bias (Supplementary Fig. S1A), indicating that the distribution of log(OR) for the efficacy data was symmetrical. Egger's test (P = 0.730) and Harbord's test (P = 0.648) further demonstrated a lack of publication bias in the meta-analysis.

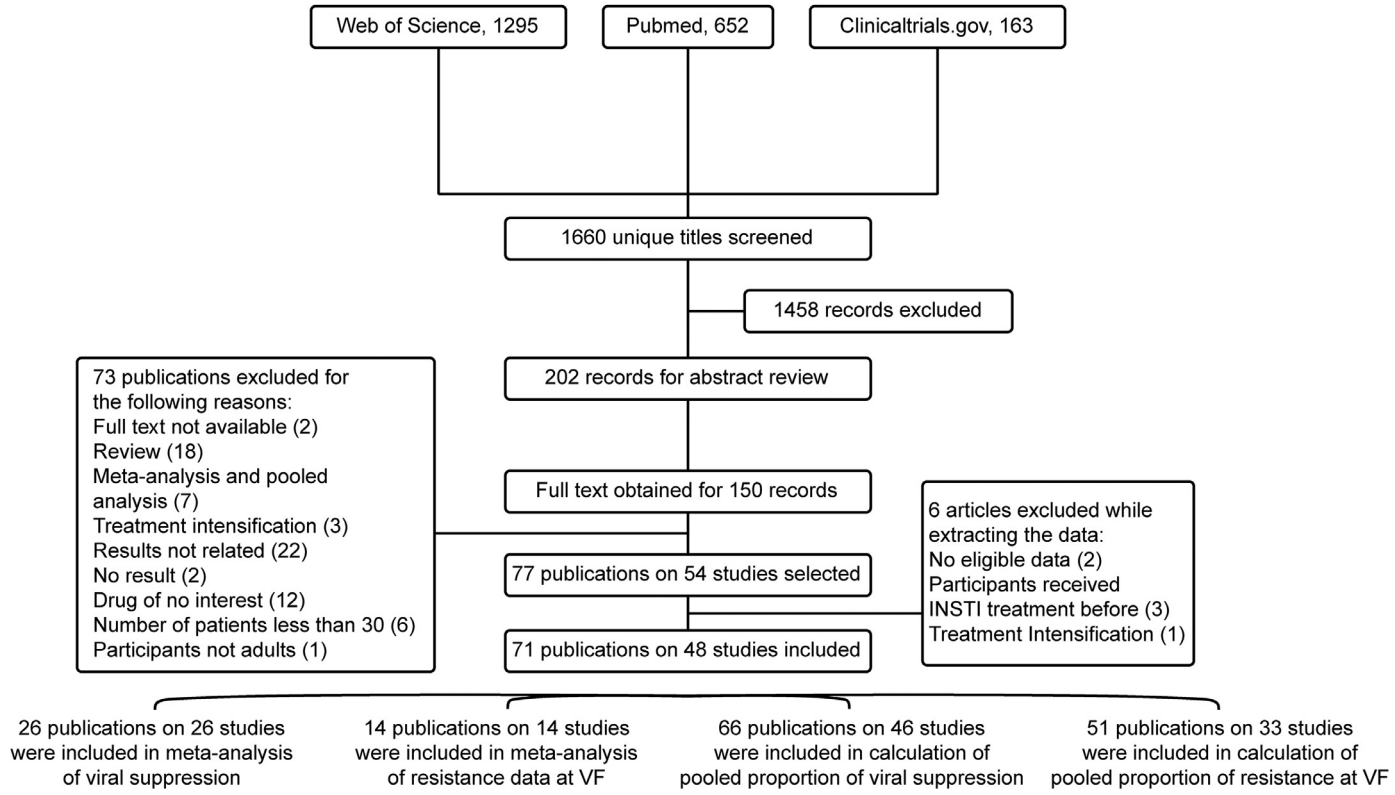

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart. The flow chart illustrates the process starting from literature search to study selection for the systematic review and meta-analysis of efficacy and resistance data for integrase strand transfer inhibitors (INSTIs). VF, virological failure.

A subgroup analysis stratified by participant characteristics was subsequently conducted using three categories: cART-naïve patients (patients who had never received any antiretroviral therapy); cART-experienced patients with virological failure (patients who received antiretroviral therapy and had virological failure); and virologically-suppressed patients (patients displaying suppressed HIV-RNA level who switched to INSTI-based therapy).

Based on pre-defined meta-analysis criteria, 14 studies comparing the use of INSTIs and non-INSTI controls were included in the cART-naïve patient category. A statistically significant OR favouring the use of INSTIs in cART-naïve patients was observed (OR = 1.484, 95% CI 1.229–1.790), indicating that INSTIs were generally more efficient than medicines in other classes (Fig. 2A). Owing to the significant heterogeneity, a subgroup analysis was conducted for DTG, EVG and RAL (Fig. 2A). The ORs of the subgroup study supported the use of INSTIs as an initial therapy for patients with HIV-1 infection [22].

Three controlled studies on RAL versus non-INSTIs regimens used in patients experiencing failure with previous cART were included in the cART-experienced analysis (Supplementary Table S2). Of these trials, two [23,24] described higher efficacy of RAL than placebo. In the third study [25], ritonavir-boosted lopinavir (LPV/r) plus RAL was no less efficacious than the standard regimen of LPV/r. From these trials, RAL showed superior or non-inferior efficacy to non-INSTIs as a salvage therapy in cART-experienced patients.

Subgroup analysis of virologically suppressed patients included nine studies displaying medium heterogeneity ($I^2 = 65.5\%$, Q test $P = 0.003$) (Fig. 2B). The overall OR of 1.341 (95% CI 0.913–1.971) in this subgroup (Fig. 2B) suggested that switching to INSTIs was more efficacious than maintaining the current non-INSTI therapy in virologically-suppressed patients. Due to heterogeneity, all studies included were stratified into four subcategories according to the INSTI drug used (Fig. 2B). The ORs indicated that BIC and EVG are more efficacious than drugs of other classes in this setting and that switching from the current cART to a DTG-based regimen did not alter the regimen's efficacy. However, switching to RAL was less efficacious than continuing with the non-INSTI regimen. This analysis indicates that physicians should exercise caution when switching virologically-suppressed patients from a previously successful regimen to a RAL-based regimen.

3.3.2. INSTIs have high and durable efficacy

The pooled proportion of patients with successful viral suppression was calculated separately for BIC, DTG, EVG and RAL treatment regimens (Table 1). Trends of pooled proportions for DTG, EVG and RAL regimens after initial treatment are presented in Fig. 3. Significantly decreased efficacy outcomes were observed for DTG ($r = -0.5634$, $P = 0.0149$), EVG ($r = -0.7018$, $P = 0.0001$) and RAL ($r = -0.3098$, $P = 0.0487$). The efficacy of INSTIs in the pooled proportion of successful viral suppression was robust at the furthest time points. Long-term efficacy outcomes for DTG, EVG and RAL were 71.5% (95% CI 67.1–75.8%) at 144 weeks, 78.9% (95% CI 75.9–82.0%) at 144 weeks and 69.9% (95% CI 65.6–74.1%) at 240 weeks, respectively (Table 1).

3.4. Resistance profile of integrase strand transfer inhibitors (INSTIs) at virological failure

3.4.1. First-generation INSTIs are more prone to selecting resistance than non-INSTIs at virological failure

Thirteen studies comparing INSTI-based regimens with antiretroviral therapies using other drug classes at similar time points (Supplementary Table S3) were incorporated into the meta-analysis of resistance data upon virological failure. The resistance data meta-analysis funnel plot was symmetrical (Supplementary Fig. S1B). Furthermore, Egger's test ($P = 0.555$) and Harbord's modified test ($P = 0.355$) demonstrated no publication bias in this analysis.

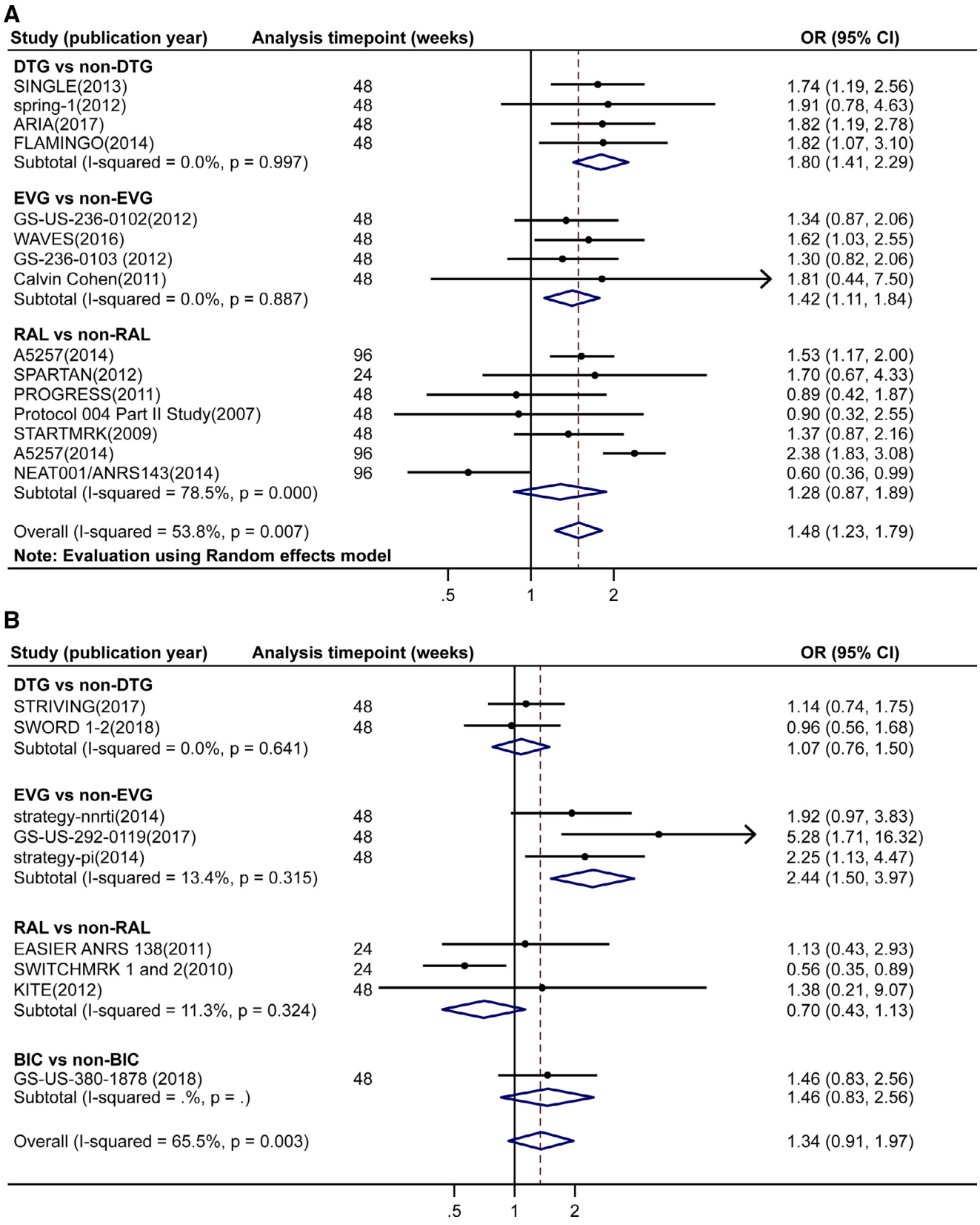

Fig. 2. Forest plots of odds ratios (ORs) of drug efficacy data comparing integrase strand transfer inhibitors (INSTIs) with non-INSTIs. (A) Forest plot of the drug efficacy profile of INSTIs in combination antiretroviral treatment (cART)-naïve patients infected with human immunodeficiency virus type 1 (HIV-1). The solid line indicates OR = 1 and the dotted line indicates overall OR. The blue diamond indicates the pooled OR and 95% confidence interval (CI) for each of the three subgroups based on the INSTI drug class and all studies. Relative to the vertical solid line of OR = 1, an OR on the right signifies that the INSTI had a better efficacy compared with that of the non-INSTI. If the 95% CI of the OR does not include the value 1, then the difference was considered significant. The right column indicates ORs and 95% CI of each individual study. (B) Forest plot of the drug efficacy profile of INSTIs in virologically-suppressed patients who were switched to INSTI regimens. DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir; BIC, bictegravir.

Table 1
Pooled proportions of successful viral suppression by integrase strand transfer inhibitors (INSTIs) stratified by analysis time point.

Time point	No. of studies	Proportion (%) (95% CI)	Heterogeneity[a]	
			I^2 (%)	*P*-value
BIC efficacy outcome data			51.2	0.084
48 weeks	5	92.6 (91.2–94.0)		
DTG efficacy outcome data			93.6	0
24 weeks	1	84.7 (80.5–89.0)	–	–
48 weeks	12	88.2 (84.8–91.7)	91.7	0
96 weeks	4	80.6 (78.4–82.8)	0	0.966
144 weeks	1	71.5 (67.1–75.8)	–	–
EVG efficacy outcome data			96.7	0
24 weeks	1	89.6 (80.9–98.2)	–	–
48 weeks	15	89.3 (86.2–92.5)	94.7	0
96 weeks	6	79.2 (70.9–87.5)	97.4	0
144 weeks	2	78.9 (75.9–82.0)	0	0.407
RAL efficacy outcome data			95.1	0
24 weeks	9	81.9 (75.5–88.4)	91.1	0
48 weeks	17	78.6 (73.5–83.6)	95.2	0
96 weeks	11	74.5 (66.7–82.4)	97.0	0
156 weeks	1	75.4 (70.4–80.5)	–	–
192 weeks	1	76.2 (71.2–81.1)	–	–
240 weeks	2	69.9 (65.6–74.1)	0	0.708

CI, confidence interval; BIC, bictegravir; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.
[a] – indicates that the parameter for the specific variable was not available.

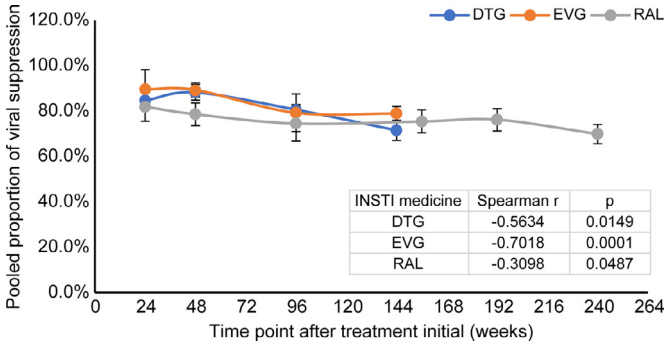

Fig. 3. Efficacy outcome of integrase strand transfer inhibitor (INSTI) regimens over time after initial treatment. Spearman correlations were conducted to assess trends in the proportion of successful virologically-suppressed patients for each INSTI drug over time after initial treatment. Spearman's $r < 0$ represents a decreased trend of efficacy outcome over time, and $P < 0.05$ represents a significant trend. DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.

All studies were stratified into three categories according to the drug used in the INSTI-based groups (Fig. 4). The subgroup of BIC versus non-BIC was not analysed in the meta-analysis because the only study [26] evaluating BIC use versus other drug classes found no emergent resistant mutations in the BIC or control groups.

Based on pre-defined criteria of study inclusion, the resistance data of only one study was included in the subcategory DTG versus non-DTG (Supplementary Table S3) with an OR of 0.081, indicating that fewer DTG treatment group patients developed DTG-associated resistance at virological failure compared with the control group.

In the EVG versus non-EVG subgroup, two studies were included (Supplementary Table S3) and the pooled OR indicated that EVG was more prone to selecting mutations conferring resistance compared with control drugs from other classes (OR = 1.886, 95% CI 0.569–6.252).

Analysis of ten studies comparing resistance data from RAL with non-RAL regimens showed that the mean odds of resistance at virological failure was significantly higher for RAL regimens (OR = 3.137, 95% CI 1.827–5.385).

The ORs of the subgroup analysis indicated that the first-generation INSTIs EVG and RAL were more prone to selecting drug-associated resistance compared with other drug classes. DTG, a second-generation INSTI, was less prone to do so.

3.4.2. Drug resistance is more prevalent at virological failure for first-generation INSTIs than second-generation INSTIs

Resistance profiles at virological failure were assessed by calculating the pooled prevalence of drug resistance at virological failure for each INSTI separately.

The prevalence of resistance against EVG is shown in Fig. 5A. Low heterogeneity was observed ($I^2 = 11.0\%$), therefore a fixed-effects model was used. The prevalence of EVG resistance at virological failure was 29.6% (95% CI 24.4–34.8%), indicating that drug resistance was prevalent in patients suffering virological failure after treatment.

Calculation of drug resistance prevalence of RAL was stratified into subcategories according to patient characteristics, as significant heterogeneity between studies was found. The prevalence of drug resistance at virological failure averaged 33.5% (95% CI 25.5–41.5%) and was ranked from high to low in the following order: virologically-suppressed patients, cART-experienced patients and cART-naïve patients (72.7% vs. 41.3% vs. 21.9%) (Fig. 5B). Subgroup analysis showed that virologically-suppressed patients switched to a RAL regimen and cART-experienced patients prescribed RAL as a salvage regimen were more likely to develop drug resistance. This indicates that when RAL is used as a second-line regimen in cART-experienced patients with viral suppression or virological failure, more attention should be paid to emergent drug resistance.

The prevalence of the primary resistance pathways for EVG and RAL selected in clinical trials are presented in Supplementary Fig. S2. Major resistance mutations to EVG were E92Q (11%), T66I/A/K (9%), Q148R/H (6%) and N155H (6%). Common RAL resistance mutations included Q148H/K/R (19%), N155H (19%) and Y143C/R/H (5%). The prevalence of T97A was 5%, but evidence has shown that T97A is a polymorphic accessory INSTI resistance mutation [27] with minimal effects on RAL susceptibility, but contributing to reduced RAL susceptibility [28] when combined with other INSTI resistance mutations. Both RAL and EVG share the Q148 and N155H major resistance pathways. The emergence of cross-resistance limits the use of alternative INSTIs.

Second-generation INSTIs BIC and DTG resistance profiles were unique. No patients with BIC resistance mutations were observed at virological failure in treatment groups from any clinical trials.

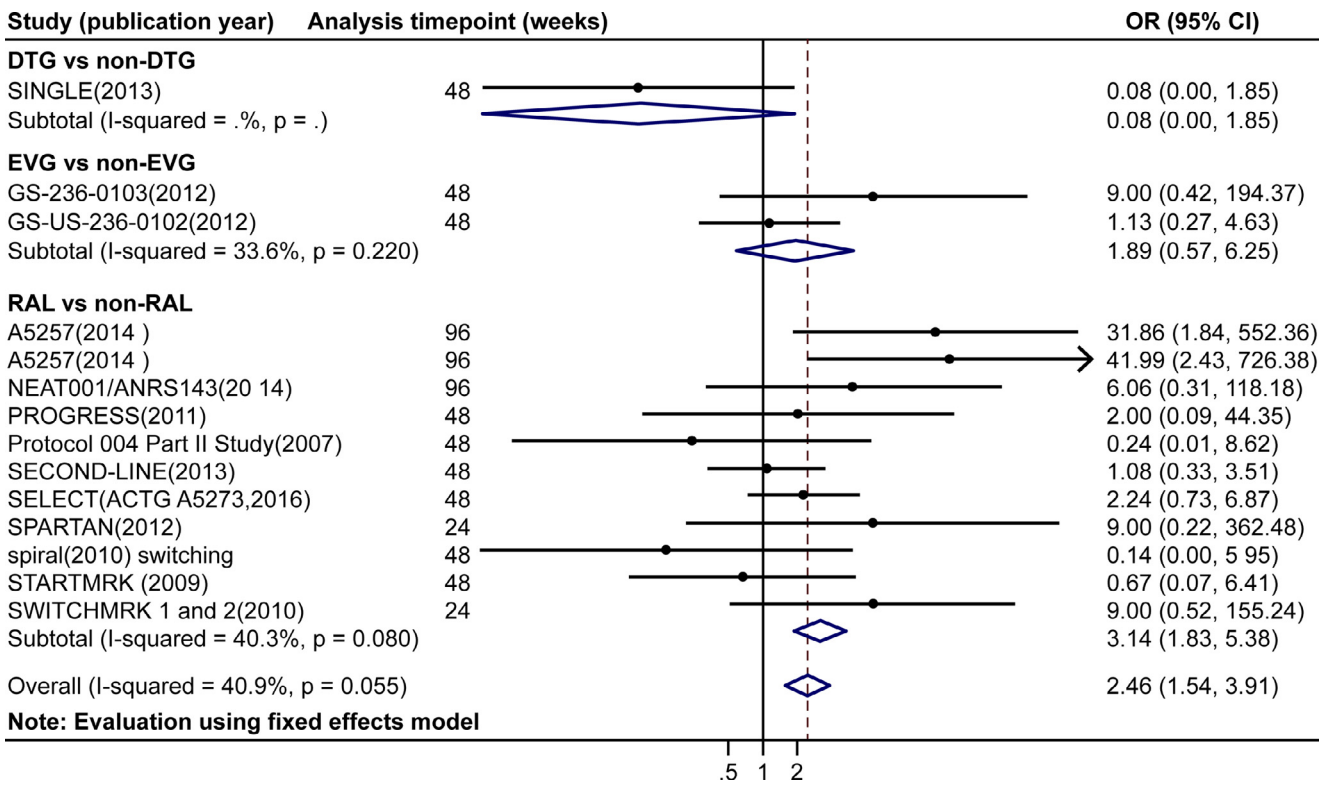

Fig. 4. Forest plot of odds ratios (ORs) of resistance data at virological failure between integrase strand transfer inhibitors (INSTIs) and non-INSTIs. The ORs are organised based on the INSTI drug class used in the study. The solid line indicates OR = 1 and the dotted line indicates overall OR. The blue diamond indicates the pooled OR and 95% confidence interval (CI) for each of the three subgroups based on the INSTI drug class and all studies. Relative to the vertical solid line of OR = 1, an OR on the right signifies a more prevalent drug resistance of the INSTI than of the non-INSTI. If the 95% CI of the OR does not include the value 1, then the difference was considered significant. The right column depicts ORs and 95% CIs from individual studies. DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.

The DTG resistance mutation R263K was observed in only two patients experiencing virological failure [29]. No other DTG-specific resistance mutations were observed.

4. Discussion

A typical cART regimen for HIV-1 infection comprises two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a third drug, either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI) or an INSTI. Wide access to cART has significantly increased the life expectancy and improved the quality of life of HIV-1-infected patients through sustained suppression of HIV-1 replication and immune function restoration. However, the gradual development of HIV drug resistance against these antiretroviral drugs is inevitable and can render existing therapies ineffective, thereby increasing the risk of virological failure, disease progression and mortality. Previous studies have reported the resistance prevalence of NRTIs, NNRTIs and PIs in HIV-1 patients initiating cART during virological failure [30,31]; a systematic review of clinical trials demonstrated that the prevalence of resistance against NRTIs (M184V and K65R mutations in reverse transcriptase) during virological failure in patients who initiated cART was 35% [30]. Resistance to NNRTIs or PIs occurred in 53% and 0.9% of such patients, respectively. However, little information on the comparison between resistance data of INSTIs and those of the other drug classes during virological failure are available. One of the purposes of this meta-analysis was to compare the emergence of resistance against INSTIs with that against drugs of the other classes during virological failure in treated HIV-1 patients. The ORs in the meta-analysis indicated that RAL (OR = 3.137, 95% CI 1.827–5.385) and EVG (OR = 1.886, 95% CI 0.569–6.252) were more prone to selecting drug-associated resistance compared with the other drug classes, whereas DTG (OR = 0.081, 95% CI 0.004–1.849) was less prone.

According to guidelines for the use of antiretroviral agents in adults and adolescents living with HIV, the regimens INSTI + 2 NRTIs including BIC/tenofovir alafenamide/emtricitabine, DTG/abacavir/lamivudine, DTG plus tenofovir/emtricitabine, and RAL plus tenofovir/emtricitabine are strongly recommended as initial regimens for most people living with HIV by the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents [22]. Based on the current meta-analysis, a statistically significant OR indicating better efficacy of INSTIs than that of drugs of the other classes in cART-naïve patients initiating cART was observed (OR = 1.484, 95% CI 1.229–1.790). Furthermore, no resistance mutations were found upon virological failure in clinical trials of cART-naïve patients receiving BIC- or DTG-based cART. The resistance prevalence of RAL upon virological failure in cART-naïve patients after initial RAL-containing cART was 21.9% (95% CI 15.8–28.0%), which was lower than the resistance prevalence of NNRTIs in the same clinical setting. The results of this research provide supporting evidence and rationale for the panel's recommendations.

The characterised resistance profile in the meta-analysis was consistent with previous in vitro and in vivo selection of resistance mutations to RAL and EVG [32–34]. Computational structural studies involving interaction of first-generation INSTIs and integrase provide clues to the mechanisms that control resistance. One study predicted that RAL interacts with integrase protein residues Y143, Q148 and N155 [35], which are involved in the major resistance mutations identified in our study. In a similar study, EVG interacted with residues T66, E92, Q148 and N155 [36]. Disruption of the interaction between RAL/EVG and integrase by these mutations explains, in part, the mechanism of drug resistance.

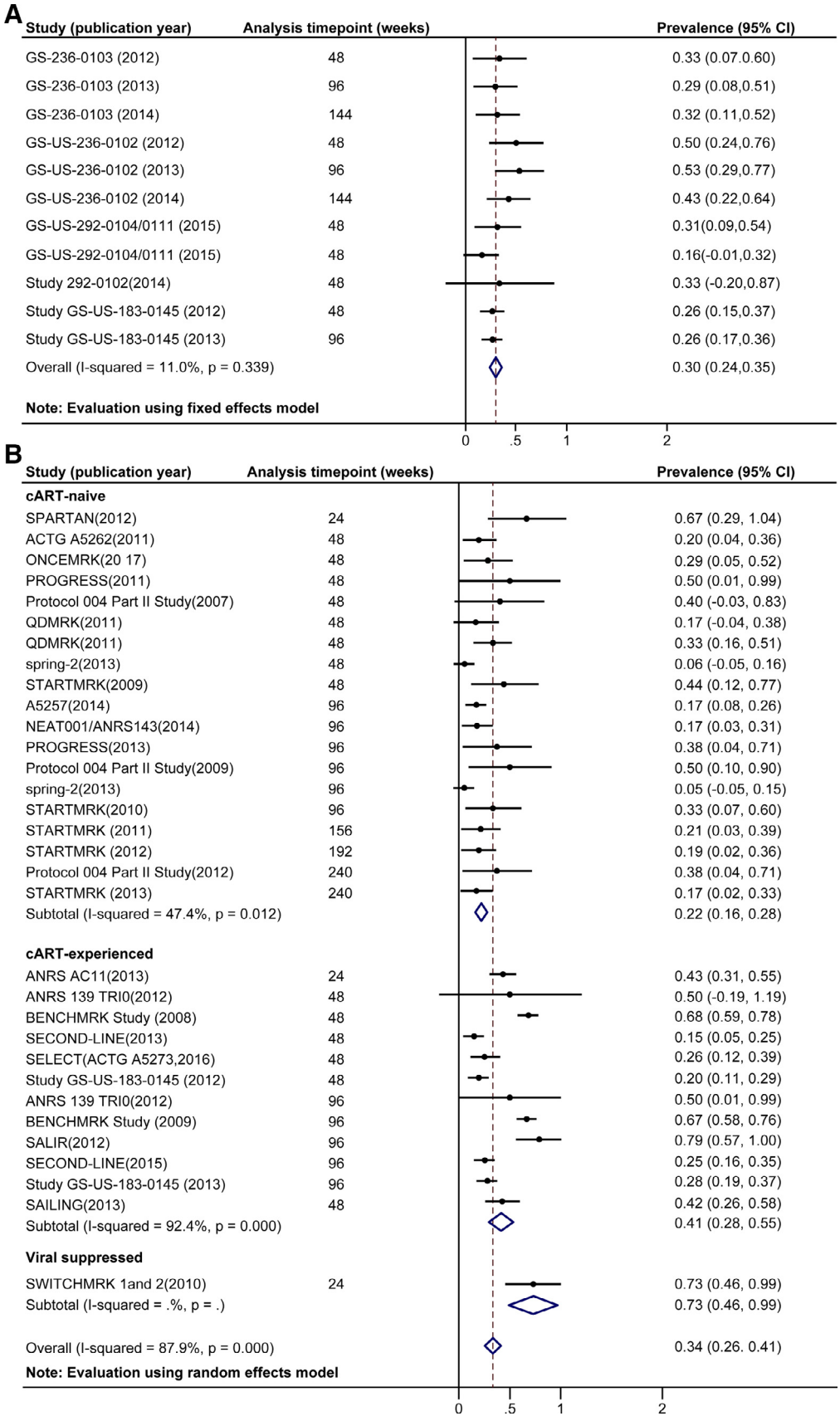

Fig. 5. Forest plots of the prevalence of integrase strand transfer inhibitor (INSTI) drug resistance upon virological failure. Forest plots of the resistance prevalence of (A) elvitegravir and (B) raltegravir stratified by participant characteristics. The solid line indicates prevalence = 0 and the dotted line indicates overall prevalence of all studies. The blue diamond indicates the pooled OR and 95% confidence interval (CI). The right column depicts drug resistance prevalence and 95% CI from individual studies. cART, combination antiretroviral therapy.

Susceptibility of first-generation INSTIs to virological failure through the development of viral resistance mutations as well as a high degree of cross-resistance necessitated the development of the second-generation INSTIs DTG and BIC. As shown in the current meta-analysis, DTG and BIC have unique resistance profiles as we were unable to detect resistant mutations in patients with virological failure in most clinical trials. The distinct structure of DTG and its low dissociation rate from the integrase–DNA complex illuminate the mechanism behind the high genetic barrier of DTG [37,38]. R263K and M50I mutations selected in vitro confer limited resistance to BIC [39]. In addition, resistance-associated mutations against BIC in clinical settings remain undetected. BIC and DTG also maintained antiviral activity against HIV-1 variants resistant to RAL and EVG. The introduction of second-generation INSTIs to the antiretroviral therapy arsenal could help preserve future treatment options for HIV-1 infections.

One limitation in this study is that the meta-analyses cannot explain all efficacy and resistance data on integrase inhibitor use because there is insufficient data available owing to lack of controlled trials on the use of integrase inhibitors. Trials involved in this meta-analysis compared the efficacy of INSTI use with non-INSTIs in cART-experienced patients only from trials that evaluated the use of RAL compared with the use of NRTI or placebo. However, the SAILING [29] and GS-US-183-0145 [40] studies supported the efficacy of DTG and EVG in cART-experienced patients compared with that of RAL. There is a lack of efficacy data for BIC, DTG and EVG use in cART-experienced HIV-1-infected patients, which can be ameliorated by the anticipated arrival of new studies. Another limitation of this report is that high heterogeneity was identified in the efficacy data meta-analysis. Thus, a subgroup meta-analysis was conducted to explore the potential sources of heterogeneity. These subgroup heterogeneities were reduced after the meta-analysis was stratified on the basis of whether participants received cART before the studies began as well as the INSTI that the participants received in the regimens (Fig. 2); these characteristics may explain some of the sources of heterogeneity. Although we tried to eliminate the effect of heterogeneity by using a random-effects model and conducting subgroup analyses, the heterogeneities of some subgroups were still significant. For instance, the heterogeneity of the meta-analysis of efficacy in cART-experienced patients was large and significant ($I^2 = 94.0\%$, Q test $P = 0.00$), which is regarded as a reason to not summarise the pooled OR. Instead, the data of patients with successful viral suppression across the three trials were analysed in the subgroup individually. Owing to the small number of studies included in the subgroup, we did not perform a meta-regression to pursue the sources of heterogeneity. However, we noted that the regimen combinations, masking procedure and $CD4^+$ T-cell count restriction at entry were different (Supplementary Table S2) and may have caused subgroup heterogeneity.

5. Conclusion

Published trials of FDA-approved INSTIs for HIV management in clinical settings were identified. From this analysis, all four INSTIs were found to be highly efficacious at managing HIV status in patients, providing supporting evidence and rationale for using INSTI-based regimens as an initial treatment protocol, salvage therapy or alternative treatment in patients infected with HIV-1. A high drug resistance prevalence in patients with virological failure of RAL and EVG indicates that resistance to INSTIs remains an important factor. BIC and DTG have higher genetic barriers to resistance and have little cross-resistance with RAL and EVG. Further studies characterising the resistance profiles of BIC and DTG and identifying the mechanisms behind the unique resistance profiles will aid the development of antiviral drugs with high genetic barriers. It is also important to monitor the emergence of resistance against INSTIs when choosing RAL and EVG as treatments owing to their low genetic resistance barriers.

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Declaration

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.08.008.

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