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Association between integrase strand transfer inhibitor use with insulin resistance and incident diabetes mellitus in persons living with HIV: a systematic review and meta-analysis

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ABSTRACT

Whether integrase strand transfer inhibitors (INSTIs) are associated with a higher risk of incident type 2 diabetes mellitus (DM) than other antiretroviral therapies (ART) needs to be established.

MEDLINE, Embase, Web of Science, and ClinicalTrials.gov registries were searched for studies published between 1 January 2000 and 15 June 2022. Eligible studies reported incident DM or mean changes in insulin resistance measured by Homeostatic Model for Insulin Resistance (HOMA-IR) in patients on INSTIs compared with other ARTs. We performed random-effects meta-analyses to obtain pooled relative risks (RRs) with 95% CIs.

A total of 16 studies were pooled: 13 studies meta-analyzed for incident diabetes with a patient population of 72 404 and 3 for changes in HOMA-IR. INSTI therapy was associated with a lower risk of incident diabetes in 13 studies (RR 0.80, 95% CI 0.67 to 0.96, I^2=29%), of which 8 randomized controlled trials demonstrated a 22% reduced risk (RR 0.88, 95% CI 0.81 to 0.96, I^2=0%). INSTIs had a lower risk compared with non-nucleoside reverse transcriptase inhibitors (RR 0.75, 95% CI 0.63 to 0.89, I^2=0%) but similar to protease inhibitor-based therapy (RR 0.78, 95% CI 0.61 to 1.01, I^2=27%). The risk was lower in studies with longer follow-up (RR 0.70, 95% CI 0.53 to 0.94, I^2=24%) and among ART-naïve patients (RR 0.78, 95% CI 0.65 to 0.94, I^2=3%) but increased in African populations (RR 2.99, 95% CI 2.53 to 3.54, I^2=0%).

In conclusion, exposure to INSTIs was not associated with increased risk of DM, except in the African population. Stratified analyses suggested reduced risk among ART-naïve patients and studies with longer follow-up.

International Prospective Register of Systematic Reviews (PROSPERO) registration number: CRD42021273040.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ People living with HIV (PLHIV) have a higher prevalence of metabolic perturbations compared with HIV-negative populations, and integrase strand transfer inhibitors (INSTIs) are currently the preferred first-line and second-line antiretroviral therapy (ART).

⇒ Some studies suggested more weight gain among INSTIs users compared with other ART regimens, while others reported accelerated hyperglycemia preceded by weight loss, weeks to a few months after initiating INSTIs.

WHAT THIS STUDY ADDS

⇒ This systematic review and meta-analysis comprising ~75 000 PLHIV on different ART regimens is the first to examine the risk of insulin resistance and type 2 diabetes mellitus (DM) in INSTIs compared to other ART regimens.

⇒ Analyses showed that compared to protease inhibitors and non-nucleoside reverse transcriptase inhibitors, INSTI exposure was not associated with increased risk of insulin resistance and/or DM.

⇒ We also identified in multiple analyses that INSTIs might be associated with a reduced risk of type 2 DM in certain subpopulations of PLHIV.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings contribute to the evidence of metabolic safety of INSTI therapy, which might implicate the choice of therapy for millions of PLHIV.

⇒ We demonstrated that exposure to INSTI therapy did not pose higher risk of insulin resistance and/or DM compared to other ART regimens. Initiating or switching to INSTIs is safe; nevertheless, monitoring is warranted in certain high-risk groups.

INTRODUCTION

Antiretroviral therapy (ART) has revolutionized HIV treatment and significantly reduced AIDS-associated mortality globally, particularly in sub-Saharan Africa.[1] People living with HIV (PLHIV) have more prevalent insulin resistance and diabetes mellitus (DM) than HIV-negative populations due to a combination of demographic and socioeconomic factors, in addition to HIV-related factors.[2 3]

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HIV-associated chronic inflammation and certain forms of ART impair insulin signaling at target organs as well as insulin secretion.[4–6] It remains challenging to distinguish to which extent the increased risk of DM is related to the normal aging process, the HIV infection, ART, or a combination of these factors.[7–12]

In the early ART era, nucleoside reverse transcriptase inhibitors (NRTIs) were coupled in combinations of predominantly stavudine, didanosine, zidovudine, lamivudine and zalcitabine with non-nucleoside reverse transcriptase inhibitors (NNRTIs).[13] These drug combinations were linked to a spectrum of metabolic perturbations, including dyslipidaemia, lipodystrophy, and metabolic syndrome, and hence have largely been phased out of use.[14 15] Since then, ART has conventionally included NNRTIs, protease inhibitors (PIs), and lately, the preferred integrase strand transfer inhibitors (INSTIs) as anchor agents coupled with largely metabolically safe NRTIs.[13 16 17]

In 2018, the WHO recommended the use of INSTIs, particularly dolutegravir (DTG) as first-line ART, and since then, the use of INSTIs has largely overtaken NNRTIs and PIs.[18] This was after multiple countries reported primary resistance to NNRTIs above the recommended threshold of 10%.[19 20] Thereafter, multiple studies demonstrated enhanced efficacy, a higher genetic barrier to resistance, good side effect profiles, and less drug–drug interactions with newer-generation integrase inhibitors.[21–25] Despite their favorable side-effect profiles, INSTIs have consistently been associated with weight gain.[23 26] Whether the weight gain in PLHIV translates to disorders in glucose metabolism in the long term remains to be demonstrated.[27]

Multiple case series on ART-experienced patients presenting with diabetic ketoacidosis with preceding weight loss a few weeks to months after starting INSTIs have been published.[24 25 28 29] However, large population cohort studies have yielded conflicting results about the risk of diabetes among INSTI users.[30]

Given the inconsistent literature and to better quantify the risk, we performed a comprehensive literature review and meta-analyses aiming to summarize the current evidence on the association of INSTI therapy with insulin resistance, hyperglycemia, and incident DM versus PIs and NNRTI-based ART. We also explored the effect of other HIV-related factors and potential confounders on this association.

RESEARCH DESIGN AND METHODS

The protocol for this systematic review is registered on International Prospective Register of Systematic Reviews database (CRD42021273040) and published.[31] This study is being reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[32] The link to the study dataset is listed in the online supplemental material (SD).

Search strategy and selection criteria

We searched PubMed/MEDLINE, Embase, and Web of Science (Clarivate) databases without language or geographical restrictions for randomized controlled trials (RCTs), cohort studies and case–control studies for eligible studies (online supplemental material, Emethods 1). Additionally, we searched Cochrane and clinicaltrials.org registries for eligible RCTs. Our search limit was fixed to the year 2000 to capture phase III clinical trial safety data, given that the first INSTIs, raltegravir, was approved by the Food and Drug Administration in 2007, and the search was last updated on 15 June 2022. We also searched abstracts of HIV conference meetings (International AIDS Society's Conference on Retroviruses and Opportunistic Infections) for the same themes seeking studies that were eventually published. To identify relevant publications, two authors (FM and HK) independently screened all potential abstracts and reference lists in review articles. For published studies with desired outcomes but without data to calculate relative risk (RR) of diabetes, we reached out to authors for raw data. Studies eligible for full review were agreed on through consensus. A senior investigator (NB) was referred to in case of disagreement between the authors.

Studies were eligible if they reported risk of incident diabetes (or reported the required data to calculate incidence) with or without metabolic syndrome and/or insulin resistance, had exposure to INSTIs for ≥12 weeks, and had comparative arms of either NNRTI or PI anchored ART. Studies with cross-sectional design and studies including pregnant or breastfeeding mothers were excluded. Since we aimed to compare INSTIs versus PIs and/or NNRTIs as anchor agents, we also excluded studies where INSTIs were administered with PIs or NNRTIs in the same regimen. For studies with multiple publications, we included the publication with the most extended follow-up.

Data analysis

We evaluated two outcomes: incident hyperglycemia and type 2 DM (new cases) as a discrete outcome or as part of metabolic syndrome (online supplemental table S1). A separate analysis was performed for mean changes in insulin resistance measured by the Homeostatic Model for Insulin Resistance (HOMA-IR) index, a factor of fasting blood glucose and insulin. We extracted variable study and population characteristics into excel forms (online supplemental table S3). Adjusted effect estimates were sought whenever reported; otherwise, raw data were retrieved.

The quality of the studies was assessed using the Newcastle-Ottawa Scale for cohort or case–control studies[33] and the Revised Cochrane Risk-of-Bias tool for randomized trials[34] (online supplemental tables S4 and S5).

Statistical analysis was done using meta-R package V.4.0.5 with R package Metaphor and Stata V.15 to generate forest plots of pooled effects with 95% CIs. We

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performed a random-effects meta-analysis adjusting for in-between-study heterogeneity to pool the risk (new cases/overall population at risk) of DM with or without metabolic syndrome (as discrete outcomes). The populations of interest were HIV patients exposed to INSTIs compared with patients on NNRTI or PI-based ART regimens. We assessed in-between study heterogeneity using the I^2 statistic with DerSimonian and Laird's method, using values <50%, 51%–74%, and ≥75% to represent low, moderate, and high heterogeneity, respectively.[35] We sought evidence for publication bias by applying Egger's test and visually inspecting funnel plots for asymmetry (if ≥10 studies).[36] We also performed several subgroup analyses to explore if the risk of DM was affected by longevity on INSTIs, particular types of INSTIs, geographical region of study participants, and past exposure to ART, as some ART drugs were associated with abnormal glucose metabolism.[14] To further explore sources of heterogeneity, we also carried out subanalyses by study design, type of caring facility, and type of non-INSTIs in the control group to compare pooled effects and heterogeneity. A p value of <0.1 was considered a statistically significant subgroup effect. We considered sensitivity analyses to test the robustness of our findings by including only studies reporting adjusted risk estimates, excluding studies with comorbidities like viral hepatitis B and C, studies where primary outcome was a metabolic endpoint and studies with no apparent conflict of interest. Studies reporting changes in mean HOMA-IR were separately analyzed to pool mean changes (on a continuous scale) of HOMA-IR pre-INSTI and post-INSTIs exposure compared with PIs and/or NNRTIs. Additionally, we performed a univariable metaregression to explore the effect of the following variables on the outcome: the effect of year of publication, follow-up duration, average age, CD4 count, body mass index (BMI) of participants and the proportion of male participants if at least 10 studies reported sufficient data. In this systematic review and meta-analysis, sex was defined as biological sex at birth.

RESULTS

Literature search and study selection

Out of the 124 studies identified for full-text review, 16 studies were deemed eligible for inclusion in the meta-analysis,[27 30 37–50] and 3 studies included in the systematic review could not be pooled in the quantitative synthesis[51–53] (figure 1). Excluded studies and reasons for exclusion are presented in online supplemental table S6.

Study characteristics

The 19 studies included in the systematic review (n=74 827) included 13 RCTs[37–42 45 46 48 49 51–53] and 6 cohort studies[27 30 43 44 47 50] (table 1). In the meta-analysis for incident DM, 13 of these studies, including 8 RCTs[37–42 45 46 48 49 51–53] and 5 cohort studies,[27 30 43 44 47 50] with a patient population of 72 404 were included. To analyze for the effect of INSTIs on insulin resistance, three studies including two RCTs[37–42 45 46 48 49 51–53] and one cohort[27 30 43 44 47 50] study with a patient population of 766 were pooled. Publications spanned from 2010[51] to 2022,[50] with patients' enrolment from 2007 to 2018. Studies included cohorts from North America (six studies),[30 37 41 42 47 50] Europe (five studies),[27 43 44 52 53] Africa (two studies),[46 48] and multinational (six studies).[38–40 45 47 51] No studies originated from Asia.

The majority of studies (n=15)[27 30 38 39 41 42 45–53] involved multiple centers, while four studies were single centers.[37 43 44 50] Eight studies[38–41 45 46 48 49] reported virological primary outcomes, mentioning hyperglycemia among the safety data, while 11 studies had metabolic endpoints.[27 30 37 42–44 47 50–53] In 14 studies,[27 30 38–41 43–49 51] crude numbers of DM were retrieved, while 5 studies[37 42 43 52 53] reported mean changes in HOMA-IR. Four studies[27 30 47 50] provided adjusted estimates for incidence of DM, 4 studies[46–48 50] reported weight changes with INSTI exposure. None of the studies reported DM as part of metabolic syndrome as an outcome.

Overall, the quality of the studies was rated as high (online supplemental table S4 and S5). Common to most RCTs was a lack of blinding in the assessment of the outcome.

Study population characteristics

A total of 74 827 participants were included in the systematic review. The sample size ranged from 30[37] to 22 884[30] patients. Overall, 37.8% (n=28 289) of patients used INSTIs, particularly Elvitegravir (n=10 218), DTG (n=9783) and raltegravir (n=4478).

Non-INSTI users constituted 62.2% (n=46 538) with 21 391 receiving PIs[27 30 39 41 47 51 54] and 17 842 receiving NNRTIs.[27 30 38 40 45 46 48] The mean follow-up duration was 21.2 months, ranging from 5.6[37] to 108.0 months.[44] In INSTI populations, the mean age was 38.7 (IQR 27–54) years, similar to 38.4 (IQR 27.0–54.6) years in non-INSTI populations. Two studies included populations <18 years.[47 48]

In the INSTI group, 82.1% (n=23 231) was male, contrasted to 68.8% (n=32 037) in non-INSTI groups. One study enrolled only female participants.[53]

All studies reported HIV RNA levels at baseline, with 12 studies[27 30 38–43 45 46 48 50] enrolling ART-naïve participants, 5 studies[37 49 51–53] enrolling ART-experienced patients and 2 studies enrolling both ART-naïve and ART-experienced patients.[27 30 39 41 47 51 54]

Risk of incident DM and hyperglycemia with exposure to INSTIs

In the 13 pooled studies[27 30 38–41 43–49] (n=72 404), INSTI exposure carried a lower risk of incident DM as compared with any other ART (n=13, RR 0.80, 95% CI 0.67 to 0.96, I^2=29%; figure 2). Particularly the risk was lower when compared with NNRTIs[27 30 38 40 45 46 48] (n=7, RR 0.75, 95% CI 0.63 to 0.89, I^2=0%) and borderline when compared with PIs[27 30 39 41 43 47] (n=6, RR 0.78,

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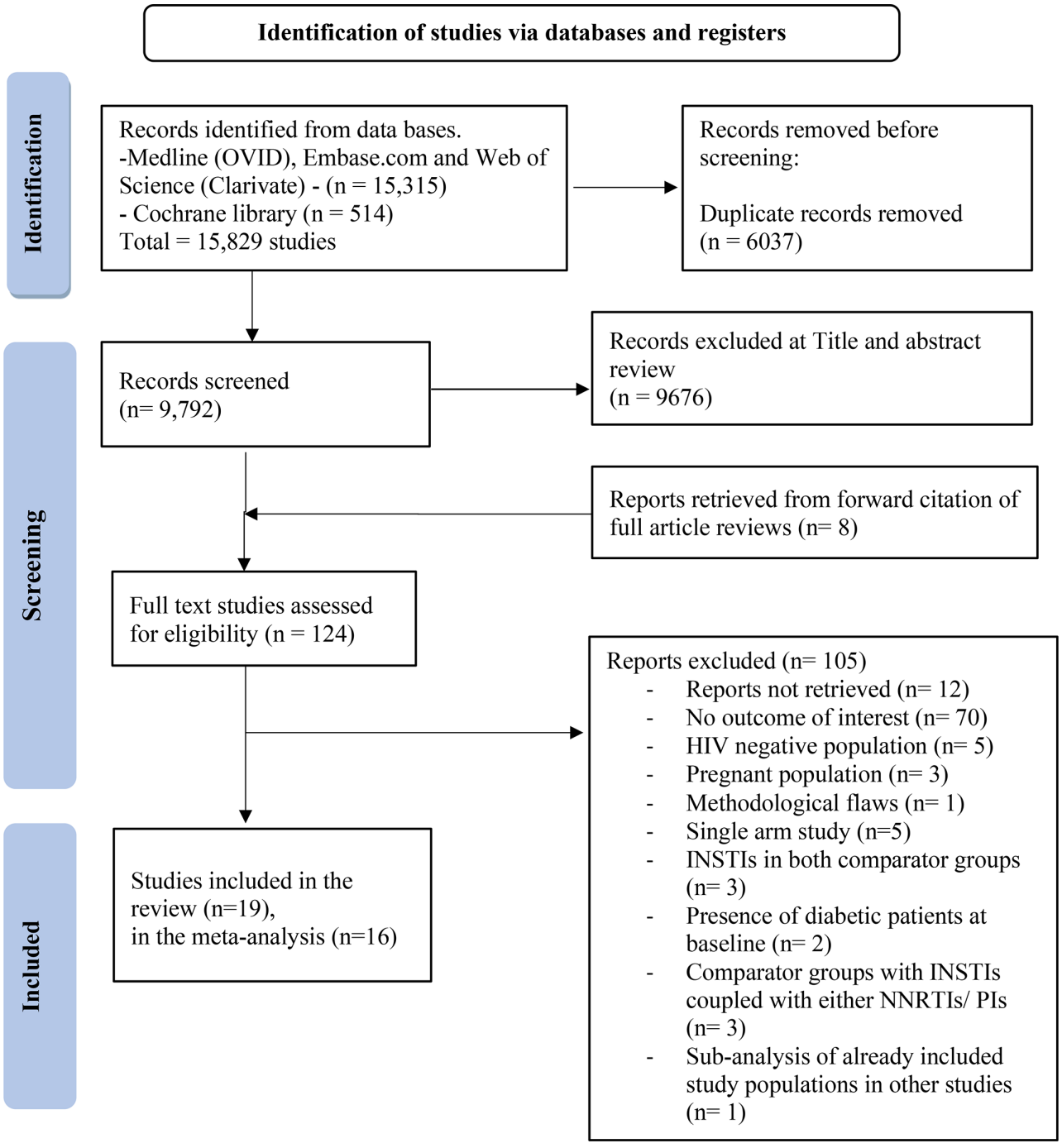

Figure 1 PRISMA flowchart for study selection. INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

95% CI 0.61 to 1.01, I^2=27%). There was minimal heterogeneity in both the aforementioned subanalyses (online supplemental figure S1). The test for subgroup difference indicated no statistically significant subgroup effect (p=0.74), suggesting that use of either PI or NNRTIS did not modify the lower risk in INSTIs group.

Additionally, the risk reduction of diabetes was more evident in studies with a longer follow-up (≥12 months) (n=8, RR 0.70 95% CI 0.53 to 0.94, I^2=24%)[27 30 38 41 43–45 48] (online supplemental figure S2), than studies with less than 1 year follow-up (n=6, RR 0.89 95% CI 0.80 to 0.99, I^2=0). The test for subgroup difference was significant (p=0.07), suggesting that longer follow-up influenced INSTI association with the outcome. The association between INSTIs and lower risk of DM was demonstrated in studies enrolling only adults (RR 0.77, 95% CI 0.65 to 0.91, I^2=26%)[27 30 38–41 43–46 49] and in multicenter studies (RR 0.84, 95% CI 0.77 to 0.93, I^2=0%).[27 30 38–41 45–49] INSTI use in PLHIV of African origin was associated with a threefold increased risk of DM in two studies with minimal heterogeneity (RR 2.99, 95% CI 2.53 to 3.54, I^2=0%),[46 48] and a significant subgroup effect was

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Table 1 Study characteristics of the 13 studies included in the meta-analyses for incident type 2 DM and the three studies for insulin resistance

Study name	First author, journal, year of publication	Study design, setting	Area of origin of study participants (ART status at enrollment)	Outcome measure	On INSTIs (n)*	On non-INSTIs regimen (n)*	Duration of follow-up	Definition of DM	Definition of insulin resistance	Reported potential conflict of interest
STARTMRK trial	Rockstroh *et al*,[38] *J Acquir Immune Defic Syndr*, 2013	RCT, 67 sites in five continents	Europe/Australia, North America, Latin America and South East Asia (ART-naïve)	RR	281	282	240 weeks	≥Grade 2 fasting hyperglycemia*	N/A	Yes
	Gupta *et al*,[37] *J Acquir Immune Defic Syndr*, 2013	RCT, single center	USA (ART-experienced)	Mean changes in HOMA-IR	15	15	48 weeks	N/A	HOMA-IR	Yes
ACTG study A5257	Lennox *et al*,[41] *Ann Intern Med*, 2014	RCT, multicenter	USA, Puerto Rico (ART-naïve)	RR	603	1208	96 weeks	≥Grade 2 fasting hyperglycemia*	N/A	None for the current study
FLAMINGO	Clotet *et al*,[39] *Lancet*, 2014	RCT, 64 research centers	France, Germany, Italy, Puerto Rico, Romania, Russia, Spain, Switzerland and the USA (ART-naïve)	RR	242	242	96 weeks	≥Grade 2 fasting hyperglycemia*	N/A	Yes
SINGLE trial	Walmsley *et al*,[40] *NEJM*, 2015	RCT, multicenter	North America, Europe and Australia (ART-naïve)	RR	414	419	48 weeks	≥Grade 2 fasting hyperglycemia*	N/A	Yes
	Dirajlal-Fargo *et al*,[42] *Open Forum Infect Dis*, 2016	RCT, multicenter	USA (ART-naïve)	Mean changes in HOMA-IR	106	222	96 weeks	N/A	HOMA-IR	Yes
	Spagnuolo *et al*,[44] *BMC Infectious Diseases*, 2017	Cohort, single center	Italy (Mixed population)	RR	772	5423	462 weeks	Two consecutive FPG ≥126 mg/dL or a 2-hour OGTT plasma glucose level ≥200 mg/dL or two consecutive fasting HbA1c levels of ≥48 mmol/mol, or a prescription for any antidiabetic medication	N/A	None for the current study
ANRS 12313 trial	Delaporte *et al*,[46] (NAMSAL study group), *NEJM*, 2019	RCT, multicenter	Cameroon (ART-naïve)	RR	310	303	48 weeks	≥Grade 2 fasting hyperglycemia*	N/A	None for the current study
	Gianotti *et al*,[43] *J Med Vir*, 2019	Cohort, single center	Italy (ART-naïve)	Mean changes in HOMA-IR	218	190 NNRTI, 210 PI/R	48 weeks	N/A	HOMA-IR	Yes

Continued

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Table 1 Continued

Study name	First author, journal, year of publication	Study design, setting	Area of origin of study participants (ART status at enrollment)	Outcome measure	On INSTIs (n)*	On non-INSTIs regimen (n)*	Duration of follow-up	Definition of DM	Definition of insulin resistance	Reported potential conflict of interest
	Ursenbach *et al*,[27] *J Antimicrob Chemother*, 2020	Cohort, multicenter in France and overseas	France (ART-naïve)	RR	3403	16 059	Variable	Documentation of diabetes in medical record, HbA1c >7.5%, being on DM treatment	N/A	None for the current study
	Rebeiro *et al*,[30] *Clin Infect Dis*, 2020	Cohort, multicenter in North America	USA and Canada (ART-naïve)	RR	5183	17 701	Variable	HbA1c ≥6.5%, initiation of diabetes-specific medication or new DM diagnosis	N/A	Yes
ADVANCE trial	Venter *et al*,[48] *Lancet HIV*, 2020	RCT, 11 public health clinics	South Africa (ART-naïve)	RR	690	347	96 weeks	Not stated	N/A	Yes
INSPIRING study	Dooley *et al*,[45] *Clin Infect Dis*, 2020	RCT, multicenter	Argentina, Brazil, Mexico, Peru, Russia, South Africa, and Thailand (ART-naïve)	RR	69	44	52 weeks	≥Grade 2 fasting hyperglycemia*	N/A	Yes
	Hsu *et al*,[47] *AIDS*, 2021	Cohort, 84 multicenter	USA (ART-naïve and experienced)	RR	15 122	2076	Variable	Recorded diagnosis of type 2 DM, antidiabetic medication prescription, lab tests indicative of DM	N/A	Yes
TANGO study	van Wyk *et al*,[49] *J Acquir Immune Defic Syndr*, 2021	RCT, 134 multicenter in 10 countries	USA, Australia, Europe (ART-experienced)	RR	303	290	48 weeks	N/A	N/A	Yes

*The numbers represent patients without DM at baseline enrolled in the metabolic analyses in each study. NB Eron *et al*[51] not included in the metanalyses.
†
ACTG, AIDS Clinical Trials Group; ART, antiretroviral therapy; DM, diabetes mellitus; FPG, Fasting Plasma Glucose; HbA1c, Glycated Hemoglobin; HOMA-IR, Homeostatic model of Insulin Resistance; INSTI, integrase strand transfer inhibitor; N/A, not available; OGTT, Oral Glucose Tolerance Test; RCT, randomized controlled trial; RR, relative risk.

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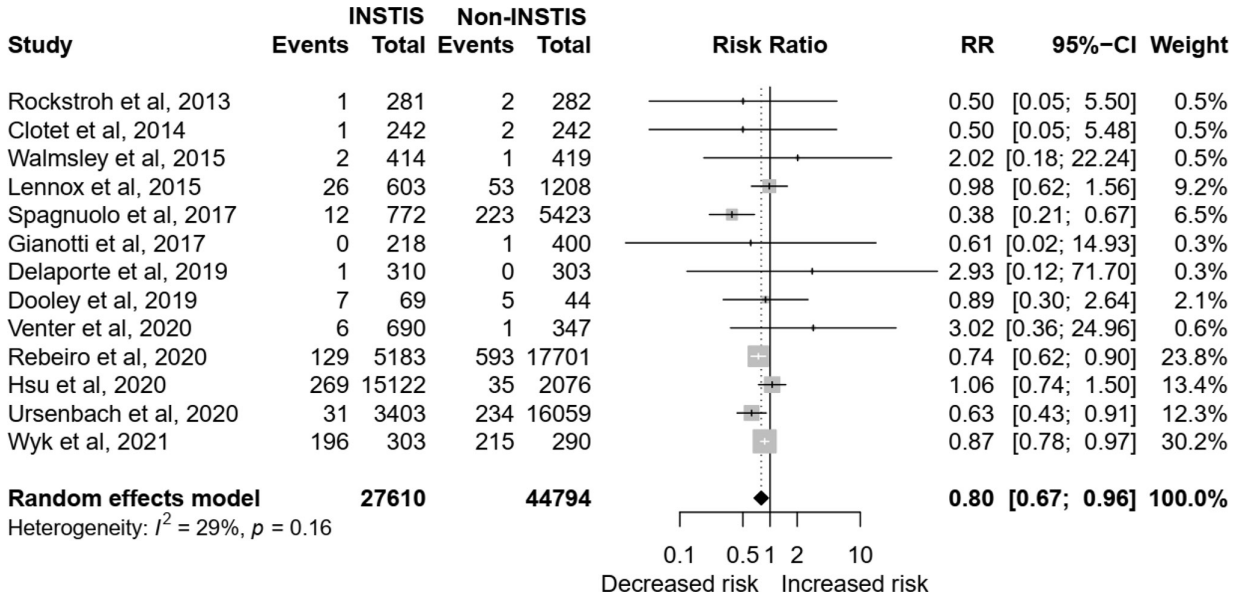

Figure 2 Forest plot of the association of INSTI exposure to incident hyperglycemia and diabetes mellitus compared with other art regimens. The crude numbers of events are based on the longest follow-up reported in the studies. INSTI, integrase strand transfer inhibitor; RR, relative risk.

demonstrated by area of origin (p<0.01). Further interpretation of subgroup analyses is reported in table 2.

Risk of DM and hyperglycemia in treatment naïve or experienced individuals

The risk of DM on exposure to INSTIs was reduced in ART-naïve patients (n=11, RR 0.78, 95% CI 0.65 to 0.94, I^2=3%)[27 30 38–41 43–46 48] but equal to controls in ART-exposed patients (n=2, RR 0.85, 95% CI 0.43 to 1.62, I^2=0%)[47 49] (online supplemental figure S4 and table 2).

No differences in the risk of DM were noted in studies per individual types of INSTIs in ART-naïve patients: DTG (n=7, RR 0.94, 95% CI 0.53 to 1.67, I^2=43%),[30 39 40 45–48] elvitegravir (n=2, RR 0.80, 95% CI 0.01 to 123.82, I^2=78%)[30 47] and raltegravir (n=4, RR 1.23, 95% CI 0.91 to 1.6, I^2=0%).[30 38 41 47]

The risk of DM was lower in five cohort studies providing adjusted estimates, although not statistically significant (n=5, RR 0.83, 95% CI 0.58 to 1.18).[27 30 47 49 50] In RCTs, the risk of developing hyperglycemia and/or DM was lower (n=8, RR 0.88, 95% CI 0.81 to 0.96) with minimal heterogeneity (I^2=0%).[38–41 45 48 49] A trend toward decreased risk was also observed in cohort studies, yet not statistically significant (n=5, RR 0.69, 95% CI 0.44 to 1.10) and with substantial heterogeneity (I^2=60%)[27 30 43 44 47] (online supplemental figure S5).

Effect of weight gain

We sought to analyze the effect of baseline weight, weight gain or changes in BMI on the incidence of diabetes in the study populations. Eleven studies[27 30 38–41 43–49] provided estimates of weight and/ or BMI at baseline, yet changes were not presented per type of ARTs nor stratified per persons who developed diabetes and/or hyperglycemia, making it difficult to analyze.

Effect of exposure to INSTIs on insulin resistance

In the three included studies (n=976), INSTIs were associated with an insignificant increase in mean HOMA-IR from baseline compared with non-INSTIs (0.78, 95% CI −0.15 to 1.70) with substantial heterogeneity (I^2=82.5%).[37 42 43] The same results were noted when comparing INSTIs to PIs (0.90, 95% CI −0.90 to 2.69) and to NNRTIs (0.17, 95% CI −0.44 to 0.79) with substantial heterogeneity in both analyses (online supplemental figure S7).

For studies reporting incident insulin resistance and/or diabetes across different meta-analyses when the number of studies was ≥10, no publication bias or small study effect was detected by funnel plot asymmetry and by Egger's test (online supplemental figure S6).

Metaregression analysis

We further explored the influence of specific study and HIV-related factors on the pooled risk of developing insulin resistance and/or type 2 DM between INSTIs and non-INSTI comparators. Neither the proportions of male, black population, or publication year were associated with the pooled risk in univariable meta-regression analysis. However, studies with longer follow-up duration were significantly associated with lower risk of type 2 DM in INSTIs compared with non-INSTIs (online supplemental table S7 and figure S9).

Influence analysis

We conducted influence analysis by the leave-one-out method to investigate the individual impact of each study (online supplemental figure S10). There was no significant change in the pooled effect estimates. Baujat plot pointed to one study with the most impact on overall

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Table 2 Subanalysis for the risk of diabetes mellitus with exposure to INSTIs in people living with HIV

Analysis	Arms	Studies (n)	References	INSTIs group (n)	Non-INSTIs group (n)	RR (95% CI)	Heterogeneity (I^2), P value	Subgroup analysis: P value, heterogeneity (I^2)	Interpretation of subgroup analysis
All studies	INSTIs versus PI and/or NNRTIs	13	27 30 38–41 43–49	27 610	44 794	**0.80 (0.67 to 0.96)**	29%	–	–
INSTI versus other drug classes	INSTI versus PI	6	27 30 39 41 43 47	24 771	21 049	0.78 (0.61 to 1.01)	27%	0.74, 0%	No subgroup effect, minimal heterogeneity
	INSTI versus NNRTI	7	27 30 38 40 45 46 48	10 350	17 842	**0.75 (0.63 to 0.89)**	0%		
By ART status at baseline	ART-naïve	11	27 30 38–41 43–46 48	17 940	37 972	**0.78 (0.65 to 0.94)**	3%	0.29, 23%	No subgroup effect, minimal heterogeneity
	ART-experienced	2	47 49	8900	1389	0.85 (0.43 to 1.68)	0%		
By presence of conflict of interest	Reported conflict of interest	9	30 38–40 43 45 47–49	22 522	21 801	**0.85 (0.78 to 0.93)**	0%	0.44, 23%	No subgroup effect, minimal heterogeneity
	No reported conflict of interest	4	27 41 44 46	5 088	22 993	0.65 (0.29 to 1.46)	59%		
By age	Participants ≥18 years	11	27 30 38–41 43–46 49	11 798	42 371	**0.77 (0.65 to 0.91)**	26%	0.07, 29%	Statistically significant, qualitative subgroup effect
	Included participants below 18 years	2	47 48	15 812	2423	1.09 (0.13 to 9.29)	0%		
By study setting	Multicenter	11	27 30 38–41 45–49	26 620	38 971	**0.84 (0.77 to 0.93)**	0%	<0.01, 23%	Statistically significant, quantitative subgroup effect
	Single center	2	43 44	990	5823	0.38 (0.13 to 1.11)	0%		
By geographical origin of the study participants	Multinational	5	38–40 45 47	1309	1277	**0.87 (0.81 to 0.94)**	0%	<0.01, 13%	Statistically significant subgroup effect by region of origin, qualitative effect
	African	2	46 48	1000	650	2.99 (2.53 to 3.54)	0%		
	North American	3	30 41 47	20 908	20 985	0.86 (0.53 to 1.42)	45%		
	Europe	3	27 43 44	4393	21 882	0.54 (0.27 to 1.08)	3%		
By study design	RCT	8	38–41 45 48 49	2912	3135	**0.88 (0.81 to 0.96)**	0%	0.27, 12%	No subgroup effect, minimal heterogeneity
	Cohort	5	27 30 43 44 47	24 698	41 659	0.69 (0.44 to 1.10)	60%		
By primary outcome	Virological outcome	8	38–41 45 46 48 49	2912	3135	**0.88 (0.81 to 0.96)**	0%	0.16, 29%	No subgroup effect. Moderate heterogeneity.
	Metabolic outcome	5	27 30 43 44 47	24 698	41 659	0.69 (0.44 to 1.10)	60%		
By follow-up duration	≥12 months	8	27 30 38 41 43–45 48	11 219	41 464	**0.70 (0.53 to 0.94)**	24%	0.07, 29%	No subgroup effect, minimal heterogeneity
	<12 months	6	39 40 45–47 49	16 460	3374	**0.88 (0.79 to 0.99)**	0%		
By type of INSTI in ART-naïve patients	Dolutegravir	7	30 39 40 45–48	5751	17 679	0.94 (0.53 to 1.67)	43%	0.35, 61%	No subgroup effect, moderate heterogeneity
	Elvitegravir	2	30 47	5819	16 324	0.80 (0.01 to 123.82)	78%		
	Raltegravir	4	30 38 41 47	2172	17 814	1.23 (0.91 to 1.66)	0%		

Continued

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Table 2 Continued

Analysis	Arms	Studies (n)	References	INSTIs group (n)	Non-INSTIs group (n)	RR (95% CI)	Heterogeneity (I^2), P value	Subgroup analysis: P value, heterogeneity (I^2)	Interpretation of subgroup analysis
By type of INSTI in ART-experienced patients	Dolutegravir	2	[47 49]	3889	1389	0.92 (0.21 to 3.99)	0%	0.57, 0%	No subgroup effect, minimal heterogeneity
	Elvitegravir	1	[47]	4281	1109	0.75 (0.48 to 1.17)	–		
	Raltegravir	1	[47]	730	1109	1.09 (0.60 to 1.99)	–		
By viral hepatitis comorbidities	Hepatitis B and C included	10	[27 30 38–41 43–49]	26 824	44 041	0.76 (0.58 to 1.00)	67.2%	0.88, 12%	No subgroup effect, minimal heterogeneity
	Only hepatitis C included	3	[27 30 38–41 43–49]	786	753	0.87 (0.78 to 0.98)	32.8%		
By studies providing adjusted risk estimates		5				0.83 (0.58 to 1.18)	100%	–	–

the boldfaced values are Statistically significant.
.ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RCT, randomized controlled trial; RR, relative risk.

study heterogeneity yet with minimal effect on the pooled effect estimates (online supplemental Figure S11).

DISCUSSION

In this comprehensive systematic review and meta-analysis of approximately 75 000 PLHIV exposed to different ART regimens, INSTI use was associated with a lower risk of incident DM and hyperglycemia compared with NNRTI and PI anchored ART. Particularly, ART-naïve PLHIV and prolonged follow-up studies suggested a lower risk of DM among the INSTI group compared with the non-INSTI group. The association was consistent when pooling eight RCTs in the analysis. By contrast, PLHIV of African origin treated with INSTIs had a threefold increased risk of DM compared with their non-INSTI peers. Analysis per individual type of INSTIs showed similar risk compared with peer non-INSTIs, with raltegravir demonstrating a trend toward a higher risk compared with elvitegravir and DTG. Univariable regression analysis suggested that studies with longer follow-up times showed a lower risk.

Multiple cases of accelerated hyperglycemia in patients starting INSTIs have been reported, particularly on DTG and, in a few cases, raltegravir.[25 55] The common presentation was diabetic ketoacidosis preceded by weight loss, weeks to months after initiating therapy, which might represent a typical phenotype of insulin deficiency.[25 29] Some of the postulated mechanisms for the accelerated hyperglycemia included intracellular magnesium chelation induced by INSTIs leading to altered hepatic and skeletal muscle insulin signaling, mitochondrial dysfunction from previous exposure to more toxic NRTIs and possible genetic predisposition (online supplemental file 1, ref. 57).[56] Interestingly, at the population level, INSTIs particularly DTG have been consistently associated with weight gain (online supplemental file 1, ref. 58). A recent systematic review concluded that INSTIs have a higher risk of DM compared with alternative backbone ART regimens.[56] Most of the conclusions in that narrative review were premised on the consistent association of INSTIs with weight gain, a known precursor for metabolic syndrome or DM.[56] We could not conclusively ascertain the effects of weight gain on the incidence of diabetes as data were lacking to perform a subanalysis for BMI changes. In the current analysis, studies with follow-up more than 12 months showed a 30% lower risk of type 2 DM among INSTIs versus non-INSTIs. This reduced risk tended to attenuate when restricted to studies with shorter follow-up. We observed a trend toward more insulin resistance (increase in HOMA-IR) rather than overt type 2 DM among INSTIs compared with non-INSTIs (online supplemental figure S7). It is unclear whether this trend is induced by the increased weight accompanying the 'return-to-health phenomenon' with possible metabolic perturbations in some susceptible individuals or could lead to overt type 2 DM and metabolic syndrome in the long term (online supplemental file 1, ref. 59). Considering the small sample size of this analysis (three studies

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with 766 patients) and the heterogeneity of PLHIV populations, long-term follow-up studies are therefore warranted, particularly accounting for sex, the presence of malnutrition, obesity, and/or metabolic syndrome at treatment initiation.

A threefold increased risk of diabetes in African patients was observed in the subanalysis by geographical origin. These two pooled studies[46 48] were high-quality RCTs involving ART-naïve adults with primarily virological outcomes. They included ART-naïve patients of mean baseline age 32–38 years with unsuppressed viral loads and mean baseline CD4s of 280 and 336 cells/mm^3. The baseline BMI for both studies did not significantly differ from the mean BMI from other meta-analyzed studies with BMI data. Exposure groups had patients on DTG and comparator groups, efavirenz. Estimates of metabolic syndrome prevalence among PLHIV in SSA range from 13% to 58%, with a higher proportion among ART-experienced than among ART-naïve (online supplemental file 1, ref. 60). It is likely that the increased risk of type 2 DM observed is driven by the higher prevalence of metabolic syndrome in this population (online supplemental file 1, ref. 60). On metaregression for age, baseline CD4, and viral load, we found a pattern of an increased risk of diabetes with higher baseline viral loads and low CD4 cell counts (online supplemental file 1, figure S8). This is in tandem with the known literature suggesting that chronically heightened inflammation in patients with high viral loads is a driver of insulin resistance and hence a precursor of type 2 DM (online supplemental file 1, ref. 61). These factors could have been drivers of this risk in this African population with more likely late presentation compared with PLHIV in resource-affluent settings. These results should, however, be interpreted with caution, given there were only two studies meta-analyzed with a small patient population; hence, these findings may not be extrapolated to the general African population. Studies suggested that women living with HIV have higher risk of ART-related weight gain compared with men (online supplemental file 1, ref. 62); moreover, women with HIV have higher odds of type 2 DM compared with women without HIV infection(online supplemental file 1, ref. 63). This might be attributed to higher weight gain, and possibly more prevalent cardiometabolic risk factors in women population with HIV. Whether African women living with HIV have heightened risk for type 2 DM compared with male peers is debated. In a meta-analysis of 20 studies from Africa, the prevalence of type 2 DM was similar in HIV and non-HIV populations regardless of sex, and similar prevalence was noted between treated and untreated PLHIV, though in between-studies heterogeneity was high (online supplemental file 1, ref. 64). In our analysis, sex was not associated with the pooled risk of type 2 DM in metaregression analysis.

INSTI exposure was associated with a low risk of diabetes, noted in ART-naïve populations compared with ART-experienced patients. This is in line with collection of reports on lower prevalence of metabolic syndrome in ART-naïve versus ART-experienced patients (online supplemental file 1, ref. 61). Another potential explanation might be thatbe clinicians tended not to start INSTIs in patients at high risk of diabetes, which could not be applied to ART-exposed patients being switched to INSTIs due to virological failure with less consideration for metabolic risk (online supplemental file 1, ref. 65 and 66).

We encountered certain limitations such as insufficient data on possible factors affecting glucose metabolism, which are potential confounders such as changes in BMI, family history of diabetes, lifestyle, concurrent drugs such as steroids and gender-affirming hormonal therapy in transgender patients. In the ART-experienced populations, we could not adjust for prior exposure to drugs like stavudine, didanosine, and zidovudine, known to cause lipodystrophy, insulin resistance and dyslipidaemia due to lack of patient-level data. There was variation in the criteria used to define diabetes in the different studies, with most retrospective cohort studies using multiple criteria: HBA1C, fasting blood glucose, oral glucose tolerance tests, and prescriptions for diabetes medication, while most RCTs used division of AIDS grading of fasting blood glucose (online supplemental file 1, ref. 67). To partially account for these limitations, we conducted influence and stratified analyses by study design, primary metabolic outcome, and ART status. There was minimal heterogeneity and an absence of publication bias across several subgroups and sensitivity analyses.

CONCLUSION

In conclusion, this meta-analysis demonstrated that INSTI use was not associated with an increased risk of DM compared with PIs and NNRTIs except in African PLHIV. There is a need for long-term follow-up studies with primarily metabolic outcomes to ascertain these results further and delineate the contribution of weight gain in PLHIV exposed to INSTIs on glucose dysmetabolism. Additionally, the increased risk of DM in African PLHIV merits more targeted research as this population in the meta-analysis was largely under-represented.

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takes responsibility for the integrity of the data and the accuracy of the data analysis. FM, HK and NB wrote the protocol, FM and HK performed data extraction. HK and DMB performed the data analysis. Karolinska Institute librarians GK and NH performed the data search. All authors participated in the critical interpretation of the results and revision of the manuscript.

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Association between integrase strand transfer inhibitor use with insulin resistance and incident diabetes mellitus in persons living with HIV: a systematic review and meta-analysis

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Supplementary

SD: Link to the study dataset.

EMethods 1: Documentation of search strategies by Karolinska University Library search consultation group

Tables

- Table S1: Study characteristics of all the studies included in the systematic review and meta-analysis.
- Table S2: Outcome definitions.
- Table S3: Fields of collected data in excel sheet.
- Table S4: Quality assessment of the 12 randomized controlled trials included in the meta-analysis per Revised Cochrane risk-of-bias tool (RoB2)
- Table S5: Quality assessment of the 6 cohort studies included in the meta-analysis per Newcastle-Ottawa scale (NOS)*
- Table S6: Studies excluded upon full text review and reasons for exclusion.
- Table S7: Meta-regression* analysis of study and HIV-related variables on the pooled effect estimate

Figures

- Figure S1: Sub-analysis by non-INSTIs regimen in the control group (protease inhibitors and non-nucleotide reverse transcriptase inhibitors).
- Figure S2: Sub-analysis by follow-up duration
- Figure S3: Sub-analysis geographical origin of the study population.
- Figure S4: Sub-analysis by ART status at baseline.
- Figure S5: Sub-analysis by study design.

Mulindwa F, *et al. BMJ Open Diab Res Care* 2023; 11:e003136. doi: 10.1136/bmjdrc-2022-003136

- Figure S6: Assessment of publication bias by funnel plot asymmetry test for 13 studies meta-analysed
  for incident insulin resistance and/or diabetes in INSTIs compared to non-INSTIs.
- Figure S7. Mean changes in HOMA-IR from baseline in INSTIs group compared to overall non-INSTIs, NNRTIs and PIs groups.
- Figure S8: Bubble plots for univariable meta-regression on (A) Baseline viral load (B) Age (C) Baseline CD4 cell count.
- Figure S9: Bubble plot for univariable meta-regression on follow-up time.
- Figure S10: Influence analysis*by leave one-out-method for 13 studies pooled in the meta-analysis sorted by effect size.
- Figure S11: Baujat plot*showing each study contribution to the overall heterogeneity of the meta-analysis (studies n=13)
- S12; Link to dataset
- Continuation of manuscript references:

SD: https://osf.io/9eh74/?view_only=916713d9739340879e47249c8625b33d

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Date: 15th - June 2022

Topic/research question: Association between integrase strand transfer inhibitor use with insulin resistance and incident diabetes mellitus in persons living with HIV: a systematic review and meta-analysis

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Databases:

1. Medline(OVID)
2. Embase.com
3. Web of Science(Clarivate)

Total number of hits:

- Before deduplication: 15,890
- After deduplication: 9,853

A) Medline

Interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily
Date of Search: 26th of January 2022
Number of hits: 3,930
Comment: In Ovid, two or more words are automatically searched as phrases, i.e. no quotation marks are needed

Field labels
- exp/ = exploded MeSH term
- / = non exploded MeSH term
- .ti,ab,kf. = title, abstract and author keywords
- adjx = within x words, regardless of order
- * = truncation of word for alternate endings

#	Searches	Results
1	exp Anti-Retroviral Agents/	84,542
2	Highly Active Antiretroviral Therapy/	11752
3	((agent* or drug* or inhibitor* or therapy) adj1 (anti-aids or anti-hiv or anti-retroviral or antiretroviral or hiv integrase)).ti,ab,kf.	59278
4	(bictegravir or cabotegravir or dolutegravir or elvitegravir or raltegravir or HAART).ti,ab,kf.	15983
5	or/1-4	115,852
6	Blood Glucose/	177,763
7	exp Diabetes Mellitus/	481,823
8	Glycated Hemoglobin A/	40338
9	Homeostasis/	68,901
10	exp Hyperglycemia/	39650
11	Hyperinsulinism/	8908
12	exp Insulins/	201259
13	exp Insulin Resistance/	94596
14	(diabetes or insulin-dependent or non-insulin dependent or prediabetic).ti,ab,kf.	618990
15	(blood glucose or fasting glucose or glucose intolerance or hemoglobin* or homeosta* or HOMA or hyperglyc?em* or insulin* or hyperinsulin*).ti,ab,kf.	821226
16	((complicat* or syndrome) adj1 (cardiometabolic or cardiovascular or dysmetabolic or metabolic or reaven)).ti,ab,kf.	76848
17	(DM1 or DM2 or IDDM or Hb A1 or HbA1 or Hb A1c or HbA1c or MODY or NIDDM or T1D or T2D).ti,ab,kf.	79840

18	or/6-17	1428922
19	5 and 18	4567
20	exp HIV Infections/	306184
21	(acquired immunodeficiency syndrome or AIDS or HIV).ti,ab,kf.	426783
22	or/20-21	468198
23	5 and 18 and 22	4271
24	limit 23 to yr="2000 -Current"	4034

B) Embase

Interface: embase.com Date of Search: 15th of June 2022 Number of hits: 6,045 Comment: Emtree is the controlled vocabulary in Embase	Field labels • /exp = exploded Emtree term • /de = non exploded Emtree term • ti,ab,kw = title, abstract and author keywords • NEAR/x = within x words, regardless of order • * = truncation of word for alternate endings

#1 'antiretrovirus agent'/exp/mj
#2 'highly active antiretroviral therapy'/mj
#3 ((agent* OR drug* OR inhibitor* OR therapy) NEAR/1 ('anti aids' OR 'anti hiv' OR 'anti retroviral' OR antiretroviral OR 'hiv integrase')):ti,ab,kw
#4 bictegravir:ti,ab,kw OR cabotegravir:ti,ab,kw OR dolutegravir:ti,ab,kw OR elvitegravir:ti,ab,kw OR raltegravir:ti,ab,kw OR haart:ti,ab,kw
#5 #1 OR #2 OR #3 OR #4#6 'glucose blood level'/mj
#7 'diabetes mellitus'/exp/mj
#8 'glycosylated hemoglobin'/exp/mj
#9 'homeostasis'/mj
#10 'hyperglycemia'/mj
#11 'glucose intolerance'/mj
#12 'hyperinsulinism'/mj
#13 'insulin derivative'/exp/mj
#14 'insulin resistance'/mj
#15 'metabolic syndrome x'/mj
#16 diabetes:ti,ab,kw OR 'insulin-dependent':ti,ab,kw OR 'non-insulin dependent':ti,ab,kw OR prediabetic:ti,ab,kw
#17 'blood glucose':ti,ab,kw OR 'fasting glucose':ti,ab,kw OR 'glucose intolerance':ti,ab,kw OR hemoglobin*:ti,ab,kw OR homeosta*:ti,ab,kw OR homa:ti,ab,kw OR hyperglyc$em*:ti,ab,kw OR insulin*:ti,ab,kw OR hyperinsulin*:ti,ab,kw
#18 ((complicat* OR syndrome) NEAR/1 (cardiometabolic OR cardiovascular OR dysmetabolic OR metabolic OR reaven)):ti,ab,kw
#19 'dm1':ti,ab,kw OR 'dm2':ti,ab,kw OR 'iddm':ti,ab,kw OR 'hb a1':ti,ab,kw OR 'hba1':ti,ab,kw OR 'hb a1c':ti,ab,kw OR 'hba1c':ti,ab,kw OR 'mody':ti,ab,kw OR 'niddm':ti,ab,kw OR 't1d':ti,ab,kw OR 't2d':ti,ab,kw
#20 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 #5 AND #20

#22 'human immunodeficiency virus infection'/exp/mj
#23 'acquired immunodeficiency syndrome':ti,ab,kw OR aids:ti,ab,kw OR hiv:ti,ab,kw OR "human immunodeficiency virus $ infection':ti,ab,kw

#24 #22 OR #23

#25 #21 AND #24 AND [2000-2022]/py

C) Web of Science Core Collection

Interface: Clarivate Analytics Date of Search: 15thth of June 2022 Number of hits: 5,755	Field labels • TS/Topic = title, abstract, author keywords and Keywords Plus • NEAR/x = within x words, regardless of order • * = truncation of word for alternate endings Note: sometimes "quotation marks" are needed for single search terms to avoid automatic term mapping (lemmatization).

#1 ((agent* or drug* or inhibitor* or therapy) NEAR/1 ("anti-aids" or "anti-hiv" or anti-retroviral or antiretroviral or "hiv integrase")) OR (bictegravir or cabotegravir or dolutegravir or elvitegravir or raltegravir or HAART)

#2 (diabetes or "insulin-dependent" or "non-insulin dependent" or prediabetic) OR

("blood glucose" or "fasting glucose" or "glucose intolerance" or hemoglobin* or homeosta* or HOMA or hyperglyc$em* or insulin* or hyperinsulin*) OR ((complicat* or syndrome) NEAR/1 (cardiometabolic or cardiovascular or dysmetabolic or metabolic or reaven)) OR

(DM1 or DM2 or IDDM or "Hb A1" or HbA1 or "Hb A1c" or HbA1c or MODY or NIDDM or T1D or T2D)

#3 ("acquired immunodeficiency syndrome" or AIDS or HIV)

#4 #1 AND #2 AND #3 Refined by: PUBLICATION YEARS: 2000- 2022

Table S1: Study characteristics of all the studies included in the systematic review and meta-analysis.

Study name	First author, Journal, year of publication	Study design, setting	Area of origin of study participants, (ART status at enrollment)	Outcome measure	Number on INSTIs*	Number on non-INSTIs regimen*	Duration of follow-up	Definition of diabetes mellitus	Definition of Insulin resistance	Reported potential conflict of interest
	Eron et al[54], The Lancet, 2010	RCT, multicenter	Africa, Asia, Europe, USA, Canada, Australia (ART experienced)	≥ grade 2 fasting hyperglycaemia⁎ (Not meta-analyzable)	350	352	24 weeks	≥ grade 2 fasting hyperglycaemia⁎	N/A	yes
	Saumoy et al[38], Atherosclerosis, 2012	RCT, multicenter	Spain (ART experienced)	Mean changes in HOMA-IR (Not meta-analyzable)	38	37	48 weeks	N/A	HOMA-IR	yes
STARTMRK Trial	Rockstroh et al[40], JAIDS, 2013	RCT, 67 sites in 5 continents	Europe/Australia, North America, Latin America, South East Asia (ART naïve)	RR	281	282	240 weeks	≥ grade 2 fasting hyperglycaemia⁎	N/A	yes
	Gupta et al[39], J Acquir Immune Defic Syndr, 2013	RCT, single center	USA (ART experienced)	Mean changes in HOMA-IR	15	15	48 weeks	N/A	HOMA-IR	yes
ACTG Study A5257	Lennox et al[43], Ann Intern Med., 2014	RCT, multicenter	USA, Puerto Rico (ART naïve)	RR	603	1208	96 weeks	≥ grade 2 fasting hyperglycaemia⁎	N/A	None for the current study
FLAMINGO	Clotet et al[41], Lancet, 2014	RCT, 64 research centers	France, Germany, Italy, Puerto Rico, Romania, Russia, Spain, Switzerland, and the USA (ART naïve)	RR	242	242	96 weeks	≥ grade 2 fasting hyperglycaemia⁎	N/A	yes
SINGLE trial	Walmsley et al[42], NEJM, 2015	RCT, multicenter	North America, Europe, Australia (ART naïve)	RR	414	419	48 weeks	≥ grade 2 fasting hyperglycaemia⁎	N/A	yes
	Fargo et al[44], Open Forum Infect Dis, 2016	RCT, multicenter	USA (ART naïve)	Mean changes in HOMA-IR	106	222	96 weeks	N/A	HOMA-IR	yes
	Spagnuolo et al[46], BMC Infectious Diseases, 2017	Cohort, single center	Italy (Mixed population)	RR	772	5423	462 weeks	Two consecutive FPG ≥126 mg/dl OR a 2-h OGTT plasma glucose	N/A	None for the current study

								level ≥200 mg/dL OR two consecutive fasting HBA1C levels of ≥48 mmol/mol, or a prescription for any antidiabetic medication		
ANRS 12313 trial	Delaporte et al[48], (NAMSAL study group), NEJM, 2019	RCT, multicenter	Cameroon (ART naïve)	RR	310	303	48 weeks	≥ grade 2 fasting hyperglycaemia*	N/A	None for the current study
	Gianotti et al[45], J Med Vir., 2019	Cohort, single center	Italy (ART naïve)	Mean changes in HOMA-IR	218	190 NNRTI, 210 PI/R	48 weeks	N/A	HOMA-IR	yes
	Ursenbach et al[28], Journal of Antimicrobial Chemotherapy, 2020	Cohort, multicenter in France and overseas	France (ART naïve)	RR	3403	16059	Variable	Documentation of diabetes in medical record, HbA1c > 7.5%, being on DM treatment	N/A	None for the current study
	Rebeiro et al[30], Clinical Infectious Diseases, 2020	Cohort, multicenter in North America	USA, Canada (ART naïve)	RR	5183	17701	Variable	HbA1c ≥6.5%, initiation of diabetes-specific medication, or new DM diagnosis	N/A	yes
ADVANCE trial	Venter et al[50], Lancet HIV, 2020	RCT, 11 public health clinics	South Africa (ART naïve)	RR	690	347	96 weeks	Not stated	N/A	yes
INSPIRING study	Dooley et al[47], Clinical Infectious Diseases, 2020	RCT, multicenter	Argentina, Brazil, Mexico, Peru, Russia, South Africa, and Thailand (ART naïve)	RR	69	44	52 weeks	≥ grade 2 fasting hyperglycaemia*	N/A	yes
	Hsu et al[49], AIDS, 2021	Cohort, 84 multicenter	USA (ART naïve and experienced)	RR	15122	2076	Variable	Recorded diagnosis of T2DM, anti-diabetic medication prescription, lab tests indicative of DM.	N/A	yes
TANGO study	Wyk et al[52], JAIDS, 2021	RCT, 134 multicenter in 10 countries	USA, Australia, Europe (ART experienced)	RR	303	290	48 weeks	NA	N/A	yes

	Ibrahim et al[51], HIV med., 2021	RCT, 9 HIV clinics in UK	UK (ART experienced)	Mean changes in HOMA-IR (Not meta-analysable)	34	19	48 weeks	N/A	HOMA-IR	yes
	Asundi et al[53], AIDS Res Hum Retroviruses, 2022	Cohort, Single center	USA (ART naïve)	Adjusted RR	136	1099	18 months	a new prescription for antihyperglycemic medication	N/A	None for the current study

Abbreviations: RCT=randomized controlled trial. ART=antiretroviral therapy. INSTIS=integrase strand transfer inhibitors. HOMA-IR: Homeostatic model of Insulin Resistance. RR= relative risk. N/A= not available. DM=diabetes mellitus. *The numbers represent patients without diabetes mellitus at baseline enrolled in the metabolic analyses in each study. NB Eron et al [(54)] not included in the metanalyses

Table S2. Outcome definitions

Study outcome	Acceptable outcome measures in individual studies included in the meta-analysis
Diabetes mellitus	1- ADA criteria(1): HbA1C ≥6.5% or FPG ≥126 mg/dL (7.0 mmol/L) or 2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT 2- WHO criteria(2): - fasting plasma glucose values of ≥ 7.0 mmol/L (126 mg/dl) OR - 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl) OR - HbA1c ≥ 6.5% (48 mmol/mol) OR - random blood glucose ≥ 11.1 mmol/L (200 mg/ dl) in the presence of signs and symptoms Need for diabetes medication
Metabolic syndrome	1-NCEP ATP III criteria(3): The presence of three or more of the following risk determinants: - increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women); - elevated triglycerides (≥150 mg/dl); - low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); - hypertension (≥130/≥85 mmHg); and - *5*) impaired fasting glucose (≥110 mg/dl) 2-WHO criteria(4): Glucose intolerance, DM2 or insulin-resistance in addition to at least two of the following: - BMI > 30 and HWR > 0.9 (M) and > 0.85 (F) - Serum TG ≥ 150mg/dl - Serum HDL < 35mg/dl (M), <39mg/dl (F) - Blood pressure ≥ 140/90 or on hypertension treatment - Other risk factors: microalbuminuria ≥20mcg/min 3-IDF(5): DM/ Glucose intolerance and two or more criteria - Fasting glucose of 100-125mg/dl Or DM 2 - WC ≥ 94cm (M), 80cm (F) - TG ≥150mg/dl - HDL <40mg/dl or <50mg/dl - On treatment for SAH/ BP ≥130/85mmHG 4-European Group for Study of Insulin Resistance definition(6): Elevated plasma insulin (>75th percentile) plus two other factors from among the following: - Abdominal obesity: waist circumference (WC) ≥94 cm in men and ≥80 cm in women - Hypertension: ≥140/90 mm of Hg or on antihypertensive treatment - Elevated triglycerides (≥150 mg/dl) and/or reduced HDL-C (<39 mg/dl for both men and women) - Elevated plasma glucose: impaired fasting glucose (IFG) or IGT, but no diabetes
Insulin resistance	Homeostatic model for Insulin resistance (HOMA-IR)(7)

Abbreviations: ADA= American Diabetes Association. HbA1C= Glycated Hemoglobin. PG= Plasma Glucose, OGTT= Oral Glucose Tolerance test. WHO= World Health Organization. NCEP ATP III= National Cholesterol Education Program Adult Treatment Panel III. HDL= High Density Lipoproteins. DM2= Diabetes Mellitus type II. BMI= Body Mass Index. TG= triglycerides. IDF=International Diabetes Federation. WC= Waist Circumference. SAH= Systemic Arterial Hypertension. BP= Blood Pressure. IFG= Impaired Fasting Glucose. IGT= Impaired Glucose Tolerance. HOMA-IR=Homeostatic Model for Insulin Resistance.

Table S3: Fields of data collection in excel sheet

Study title	Study ID	Author	Year of publication	Journal	Country	study design	geographical region of the cohort	continent	Setting (nationwide, register based, hospital based)
							Baseline		
Center (primary/ tertiary)	Study period	Recruitment duration	Inclusion criteria	Exclusion criteria	Overall cohort number	Duration of follow up	Number of patients per arm	Number ART naïve pts per arm	Previous exposure to ART duration per arm
Baseline									
number of patients per arm	Number ART naïve pts per arm	Previous exposure to ART duration per arm	ethnicity	at baselinen, % male %	Female n, %	composite age (mean/ median)	Age (mean, SD) or median male	Age (mean, SD) or median female	BMI
Baseline									
BMI women	BMI men	smoking	waist circumference	Presence of lipodystrophy, n, %	Presence of diabetes mellitus or treatment for DM	criteria of DM diagnosis	presence of MS (yes/no)	criteria of diagnsois of MS	Fasting blood glucose (mg/dl)
Baseline									
HbA1C	Insulin resistance	CD4 count (median/mean, SD)	HIV viral load	comorbidities viral hepatitis, n, %	comorbidities tuberculosis, n, %	AIDS			
Outcome									
outcome definition in the study	diagnostic methods of outcome	outcome number, % who developped diabetes per arm	Change in IR	number who developped metabolic syndrome, n%	change in blood sugar level, mean (SD)	change in Hb A1C level, mean (SD)	crude risk/ ?outcome	adjsuted risk /?outcome	Predictors adjusted for in the study
Abbreviations: ART=antiretroviral therapy. BMI=body mass index. MS= metabolic syndrome. HbA1C=glycated hemoglobin subtype 1C. IR=incidence rate.									

Table S4: Quality assessment of the 12 randomized controlled trials included in the meta-analysis

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Other sources of bias	Blinding (participants and personnel) - (performance bias)	Blinding (outcome assessment)- (detection bias)	Incomplete outcome data (attrition bias)
Saumoy et al, 2012							
Rockstroh et al, 2013							
Gupta et al, 2013							
Clotet et al, 2014							
Lennox et al, 2015							
Walmsley et al, 2015							
Fargo et al, 2016							
Delaporte et al, 2019							
Dooley et al, 2019							
Venter et al, 2020							
Wyk et al, 2021							
Ibrahim et al, 2021							

= low risk, = high risk, = unclear

*RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

per Revised Cochrane risk-of-bias tool (RoB2) *

Table S5: Quality assessment of the 6 cohort studies included in the meta-analysis per Newcastle-Ottawa scale (NOS)**

	Selection				Comparability	Outcome			
Study	**1) Representativeness of the exposed cohort**	**2) Selection of the non-exposed cohort**	**3) Ascertainment of exposure**	**4) Demonstration that outcome of interest was not present at start of study**	**1) Comparability of cohorts based on the design or analysis controlled for confounders**	**1) Assessment of outcome**	**2) Was follow-up long enough for outcomes to occur**	**3) Adequacy of follow-up of cohorts**	**Overall score**
Spagnuolo et al, 2017	*	*	*	*	*	*	*	*	8
Gianotti et al, 2017	*	*	*	*	*	*	*	*	8
Ursenbach et al, 2020	*	*	*	*	*	*	*	*	8
Hsu et al, 2020	*	*	*	*	**	*	*	*	9
Rebeiro et al, 2020	*	*	*	*	**	*	*	*	9
Asundi et al, 2022	*	*	*	*	*	*			6

** **Newcastle-Ottawa scale (NOS)** Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
Score ≥7 represents low risk of bias

Table S6: Studies excluded upon full text review and reasons for exclusion

Study title	Year	Journal	Author	Reason for exclusion
1. Simplification from protease inhibitors to once- or twice-daily raltegravir: the ODIS trial	2010	HIV clinical trials	Vispo et al	Single arm study. Additionally, no outcome
2. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study.	2010	AIDS	Martinez et al	No outcome of interest
3. Simplification from protease inhibitors to once- or twice-daily raltegravir: the ODIS trial	2010	HIV Clin Trials	Vispo et al	No outcome of interest
4. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2):	2010	The Lancet	Eron et al	Outcome not studied
5. Durability of a novel salvage therapy in R5 HIV-infected patients: Maraviroc, raltegravir, etravirine	2011	J Acquir Immune Defic Syndr	Nozza et al	No outcome of interest
6. Switching antiretroviral therapy to minimize metabolic complications	2011	HIV Therapy	Lake et al	Narrative systematic review
7. Raltegravir as replacement for PI- or NNRTIbased ART in HIV-infected women with lipohypertrophy: The Women, Integrase, and Fat Accumulation Trial	2011	Antiviral Therapy	Lake et al	No outcome of interest
8. Long-term glucose tolerance in highly experienced HIV-infected patients receiving nucleoside analogue-sparing regimens	2012	AIDS (London, England)	Bigoloni et al	INSTI vs INSTI
9. Elvitegravir/cobicistat /emtricitabine /tenofovir DF (Quad) has noninferior efficacy and favorable safety compared to efavirenz/emtricitabine/tenofovir df in treatment naive HIV-1	2012	Canadian journal of infectious diseases and medical	Sax et al	No outcome of interest
10. A Randomized Trial of Raltegravir Replacement for Protease Inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor in HIV-Infected Women with Lipohypertrophy	2012	Aids patients care and STDs	Lake et al	No outcome of interest
11. Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir	2012	AIDS	Martinez et al	No outcome of interest
12. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil	2012	Lancet	DeJesus et al	Diabetes patients were not excluded at baseline
13. Cardiovascular risk in human immunodeficiency virus-infected patients in Spain. CoRIS cohort	2012	Enferm Infecc Microbiol Clin	Masia et al	No outcome of interest
14. A randomised trial of Raltegravir Replacement for Protease Inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor in HIV Infected Women with Lipohypertrophy	2012	AIDS Patient Care and STDs	Lake et al	Outcome not studied
15. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-	2013	lancet infectious diseases	Raffi et al	Both treatment arms contained INSTIs
16. HIV lipodystrophy in participants randomised to lopinavir/ritonavir (LPV/r) +2-3 nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI) or LPV/r + raltegravir as	2013	PloS one	Martin et al	Protease inhibitors coupled with INSTI in
17. Effects of switching from stavudine to raltegravir on subcutaneous adipose tissue in HIV-infected patients with HIV/HAART-associated lipodystrophy syndrome (HALS). A clinical	2014	PloS one	Domingo et al	Single arm study
18. Dolutegravir: clinical and laboratory safety in integrase inhibitor-naive patients	2014	HIV Clin Trials	Curtis et al	Narrative review

19. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus	2014	J Acquir Immune Defic Syndr	Clumek et al	No outcome of interest
20. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and teno fovir in adults	2014	Lancet Infect Dis	Arribas et al	No outcome of interest
21. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen	2014	J Acquir Immune Defic Syndr	Wohl et al	No outcome of interest
22. The impact of switching from protease-inhibitor to integrase-inhibitor therapy on biomarkers of metabolic and age-associated diseases: A longitudinal matched-cohort study	2014	Antiviral Therapy	Malagoli et al	No outcome of interest
23. Telmisartan to reduce cardiovascular risk in older HIV-infected adults: a pilot study	2015	HIV clinical trials	Lake et al	No outcome of interest
24. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness	2015	AIDS	Stein et al	No outcome of interest
25. Comparative changes of lipid levels in treatment-naive, HIV-1-infected adults treated with dolutegravir vs. efavirenz, raltegravir, and ritonavir-boosted darunavir-based regimens over	2015	Clinical drug investigation	Quercia et al	No outcome of interest
26. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257	2015	Clinical infectious diseases	Ofotokun et al	No outcome of interest
27. Post-prandial lipid effects of raltegravir versus darunavir/ritonavir in HIV-1-infected adults commencing combination ART	2015	J Antimicrob Chemother	Lee et al	No outcome of interest
28. Effects of raltegravir combined with tenofovir/emtricitabine on body shape, bone density, and lipids in African-Americans initiating HIV therapy	2015	HIV clinical trials	Young et al	Single arm study
29. Human immunodeficiency virus (HIV) modulates the associations between insulin resistance and cognition in the current combination antiretroviral therapy (cART) era: a	2015	Journal of neurovirology	Valcour et al	No outcome of interest
30. Rosuvastatin vs. protease inhibitor switching for hypercholesterolaemia: a randomized trial	2016	HIV medicine	Lee et al	No outcome of interest
31. Efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) fixed-dose combination (FDC) compared with ritonavir-boosted atazanavir (ATV/R) plus tenofovir disoproxil	2016	Open Forum Infect Dis	Hagins	No outcome of interest
32. Integrase inhibitor versus protease inhibitor-based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study.	2016	Lancet HIV	Squires et al	No outcome of interest
33. Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Disoproxil Fumarate in Asian Subjects with Human Immunodeficiency Virus 1 Infection: A SubAnalysis of Phase 3	2016	Infect Chemother	Choi et al	Sub-analysis of already included studies
34. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a	2016	Journal of acquired immune deficiency syndromes	Pozniak et al	Single arm study
35. Neither boosted elvitegravir nor darunavir with emtricitabine/tenofovir disoproxil fumarate increase insulin resistance in healthy volunteers: results from the STRIBILD-IR study	2016	Antiviral therapy	Spinner et al	HIV negative study participants
36. Switch to dolutegravir in HIV patients responding to a firstline antiretroviral treatment: 48 weeks results	2016	J Int AIDS Soc	Tau et al	No outcome of interest
37. Changes in liver steatosis after switching efavirenz to raltegravir: The steral study	2017	Clin Infect Dis	Macias et al	No outcome of interest
38. Weight Gain in Persons with HIV Switched from Efavirenz-Based to Integrase Strand Transfer Inhibitor-Based Regimens	2017	JAIDS	Norwood et al	No outcome of interest

39. Phase 3 randomized, controlled trial of switching to fixed-dose bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) from boosted protease inhibitor-	2017	Open Forum Infec Dis	Daar et al	No outcome of interest
40. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk.	2017	AIDS	Gatell et al	Comparator groups had diabetic patients at
41. Switching to the single-tablet regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir DF from non-nucleoside reverse transcriptase inhibitor plus co-formulated emtricitabine and	2017	HIV Clin Trials	Pozniac et al	No outcome of interest
42. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated	2017	Lancet HIV	Orrell et al	No outcome of interest
43. Impact on lipid abnormalities of switching from a ritonavir-boosted protease inhibitor to a raltegravir-based cART regimen	2017	AIDS	Gatell et al	No outcome of interest
44. Body composition and metabolic outcomes after 96 weeks of treatment with ritonavir-boosted lopinavir plus either nucleoside or nucleotide reverse transcriptase inhibitors or	2017	Lancet HIV	Boyd et al	Both comparator groups had patients on INSTIs.
45. Adiponectin and the steatosis marker Chi3L1 decrease following switch to raltegravir compared to continued PI/NNRTI-based antiretroviral therapy	2018	PloS one	Offor et al	No outcome of interest
46. Changes in Waist Circumference in HIV-Infected Individuals Initiating a Raltegravir or Protease Inhibitor Regimen: Effects of Sex and Race	2018	Open forum infectious diseases	Bhagwat et al	No outcome of interest
47. Effects of antiretroviral combination therapies F/TAF, E/C/F/TAF and R/F/TAF on insulin resistance in healthy volunteers: the TAF-IR Study	2018	Antiviral therapy	Spinner et al	Non-HIV population
48. Gestational diabetes in women on dolutegravir- or efavirenz-based ART in Botswana	2018	Topics in Antiviral Medicine	Mmasa et al	Pregnant population
49. Durability and tolerability of first-line combination including two NRTI and RAL or ATV/r or DRV/r in patients enrolled in the ICONA Foundation cohort. HIV Drug Therapy, Glasgow	2018	HIV Clinical Trials	Monforte et al	No outcome of interest
50. Evaluation of the efficacy and safety of integrase inhibitor in the treatment of acute HIV infection.	2018	ChiCtr	Kang et al	Protocol publication. No results posted yet
51. Dolutegravir + lamivudine dual therapy in patients with suppressed HIV-RNA: Long term virological and immunological results of a multicentre cohort	2018	Journal of the International AIDS Society	Maggiolo et al	Single arm, no comparator group
52. Lower pretreatment gut integrity associated with fat gains on antiretrovirals	2018	Topics in Antiviral Medicine	Kamari et al	No outcome of interest
53. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors	2018	The Journal of antimicrobial chemotherapy	Bakal et al	No outcome of interest
54. Diagnostic Accuracy of Noninvasive Markers of Steatosis, NASH, and Liver Fibrosis in HIV-Monoinfected Individuals at Risk of Nonalcoholic Fatty Liver Disease (NAFLD): Results from	2019	Journal of acquired immune deficiency syndromes	Lemoine et al	No outcome of interest
55. Evaluation of Safety and Effectiveness of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Switch Followed by Ledipasvir/Sofosbuvir HCV Therapy in HIV-HCV	2019	Open forum infectious diseases	Doyle et al	No outcome of interest
56. Improvement in liver steatosis after the switch from a ritonavir-boosted protease inhibitor to raltegravir in HIV-infected patients with non-alcoholic fatty liver disease	2019	Infectious diseases (London, England)	Calza et al	No outcome of interest
57. Metabolic, mitochondrial, renal and hepatic safety of enfuvirtide and raltegravir antiretroviral administration: Randomized crossover clinical trial in healthy volunteers	2019	PloS one	Barosso et al	HIV negative population
58. Reduced soluble CD14 levels after switching from a dual regimen with lamivudine plus boosted protease inhibitors to lamivudine plus dolutegravir in virologically suppressed HIV-	2019	HIV Res Clin Pract	Lombardi et al	No outcome of interest

59. Body composition and adipokines changes after initial treatment with darunavir-ritonavir plus either raltegravir or tenofovir disoproxil fumarate-emtricitabine: A substudy of the NEAT001/ANRS143 randomised trial	2019	PloS one	Bernadino et al	One arm had a combination of a protease inhibitor and INSTIs
60. Changes in Lipid Indices in HIV+ Cases on HAART	2019	BioMed research international	Ji et al	No outcome of interest
61. Improvement in insulin sensitivity and serum leptin concentration after the switch from a ritonavir-boosted PI to raltegravir or dolutegravir in non-diabetic HIV-infected patients	2019	The Journal of antimicrobial chemotherapy	Calza et al	Both study arms had INSTIs
62. Incidence of select chronic comorbidities among a population-based cohort of HIV-positive individuals receiving highly active antiretroviral therapy	2019	Current medical research and opinion	Gali et al	No outcome of interest
63. Lipid profile improvement in virologically suppressed HIV-1-infected patients switched to dolutegravir/abacavir/lamivudine: data from the SCOLTA project	2019	Infection and drug resistance	Bagella et al	No outcome of interest
64. Short-term increase in Body Mass Index and systolic blood pressure elevation in treatment naÃ¯ve persons starting INSTI based antiretroviral therapy	2019	HIV Medicine	Galdamez et al	Single arm study (no comparator group)
65. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has	2019	Lancet Infectious Diseases	Aboud et al	Diabetic patients were not excluded at baseline
66. Efficacy and safety of switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) in virologically suppressed women	2019	J Acquir Immune Defic Syndr.	Hodder et al	No outcome of interest
67. Effects of integrase strand-transfer inhibitor use on lipids, glycemic control, and insulin resistance in the women's interagency HIV study (WIHS)	2019	Open Forum Infect Dis	Aldredge et al	No outcome of interest
68. Exploring the Prevalence and Characteristics of Weight Gain and other Metabolic Changes in Patients with HIV Infection Switching to Integrase Inhibitor Containing ART	2019	Open Forum Infect Dis.	Zimmerman et al	No outcome of interest
69. Switching from boosted protease inhibitors (PI/r) to dolutegravir (DTG) in virologically suppressed HIV-infected patients with high cardiovascular risk: 48-week effects on	2020	J Antimicrob Chemother	Gonzalez et al	No outcome of interest
70. Comorbidities, antiretroviral therapy switches, and drug side-effects among HIV-infected patients	2020	Klimik Dergisi	Evlice et al	No outcome of interest
71. Dolutegravir-associated hyperglycaemia in patients with HIV	2020	The lancet. HIV	Mohammed et al	Outcome definition was symptomatic
72. Early scale-up of antiretroviral therapy at diagnosis for reducing economic burden of cardiometabolic disease in HIV-infected population	2020	AIDS	Yang et al	No outcome of interest
73. Factors Associated With Weight Gain in People Treated With Dolutegravir	2020	Open forum infectious diseases	Taramasso et al	No outcome of interest
74. Greater Weight Gain in Treatment-naive Persons Starting Dolutegravir-based Antiretroviral Therapy	2020	Clinical infectious diseases	Bourgi et al	No outcome of interest
75. Metabolic Changes Associated With the Use of Integrase Strand Transfer Inhibitors Among Virally Controlled Women	2020	Journal of acquired immune deficiency syndromes	Summers et al	Both comparator groups had diabetic patients at baseline
76. Real-World Assessment of Weight Change in People with HIV-1 After Initiating Integrase Strand Transfer Inhibitors or Protease Inhibitors	2020	Journal of health economics and outcomes research	Chen et al	No outcome of interest
77. Risk Factors for Weight Gain Following Switch to Integrase Inhibitor-Based Antiretroviral Therapy	2020	Clinical infectious diseases	Lake et al	No outcome of interest

78. The association between HIV tri-therapy with the development of Type-2 Diabetes Mellitus in a rural South African District: A case-control study	2020	PLOS one	Bam et al	Case control design was among exclusion criteria
79. Durable Suppression and Low Rate of Virologic Failure 3 Years After Switch to Dolutegravir + Rilpivirine 2-Drug Regimen: 148-Week Results From the SWORD-1 and SWORD-2	2020	J Acquir Immune Defic Syndr	Jean van Wyk et al	One arm had an INSTI and NNRTI combined
80. Fat gain differs by sex and hormonal status in persons living with suppressed HIV switched to raltegravir/etravirine	2020	AIDS	Assoumou et al	INSTIs and NNRTIs in the same arm
81. Plasma lipidome abnormalities in people with HIV initiating antiretroviral therapy	2020	Translational Medicine Communications	Bowman et al	No outcome of interest
82. Weight gain and dyslipidaemia among virally suppressed HIV-positive patients switching to co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	2020	International journal of infectious diseases	Kuo et al	No outcome of interest
83. Weight Gain Associated With Integrase Stand Transfer Inhibitor Use in Women	2020	Clinical Infectious Diseases	Kerchberger et al	No outcome of interest
84. Weight gain during pregnancy in women with HIV receiving different antiretroviral regimens	2020	Antiviral therapy	Floridia et al	Pregnant study participants
85. Weight gain following antiretroviral therapy (ART) initiation in ART-naive participants in the current treatment era	2020	Pharmacoepidemiology and Drug Safety	Ruderman et al	No outcome of interest
86. Weight gain in persons living with HIV (PLWH) treated with bictegravir compared to other integrase strand transfer inhibitors	2020	Open Forum Infectious Diseases	Fang et al	INSTI vs INSTI study
87. Excess burden of age-associated comorbidities among people living with HIV in British Columbia, Canada: a population-based cohort study	2021	BMJ open	Nanditha et al	Compared HIV patients to HIV negative patients.
88. The burden of non-communicable diseases and mortality in people living with HIV (PLHIV) in the pre-, early- and late-HAART era	2021	HIV medicine	Jespersen et al	Comparative group is a non-HIV population
89. Gestational diabetes in women living with HIV in Botswana: lower rates with dolutegravir- than with efavirenz-based antiretroviral therapy	2021	HIV medicine	Mmasa et al	Pregnant population
90. Weight changes after antiretroviral therapy initiation in CoRIS (Spain): a prospective multicentre cohort study	2021	JIAS	Martinez et al	No outcome of interest
91. Antiretroviral Therapy Initiation Is Associated With Decreased Visceral and Subcutaneous Adipose Tissue Density in People Living With Human Immunodeficiency Virus	2021	Clinical infectious diseases	Debroy et al	No outcome of interest
92. Brief Report: Weight Gain Following ART Initiation in ART-Naive People Living With HIV in the Current Treatment Era	2021	Journal of acquired immune deficiency syndromes	Ruderman et al	No outcome of interest
93. Effect of menopause on weight gain, insulin and waist circumference in women with HIV who switch antiretroviral therapy to abacavir/lamivudine/dolutegravir	2021	AIDS	Hamzah et al	No outcome of interest
94. Implications of weight gain with newer antiretrovirals: 10-year predictions of cardiovascular disease and diabetes	2021	AIDS	McCann et al	No outcome of interest
95. Changes in renal and metabolic indices after switching from tenofovir disoproxil fumarate- to tenofovir alafenamide-containing ART among individuals with HIV in Canada: A	2021	International journal of STD & AIDS	Shokoohi et al	No outcome of interest
96. Antiretroviral Therapy Initiation Is Associated With Decreased Visceral and Subcutaneous Adipose Tissue Density in People Living With Human Immunodeficiency Virus	2021	Clin Infect Dis	Debroy et al	No outcome of interest
97. Insulin resistance in people living with HIV is associated with exposure to thymidine analogues and/or didanosine and prior immunodeficiency	2022	BMC Infectious Diseases	Høgh et al	No outcome of interest

98. Two decade trends in cardiovascular disease risk factor and outcome burden among veterans with HIV	2022	J. Am. Coll. Cardiol.	Haji et al	No outcome of interest
99. Weight changes, metabolic syndrome and all-cause mortality among Asian adults living with HIV	2022	HIV Med.	Han et al	No outcome of interest
100. Longitudinal analysis of new-onset non-AIDS-defining diseases among people living with HIV: A real-world observational study	2022	HIV Med	Duan et al	No outcome of interest
101. Metabolic complications of highly active antiretroviral therapy in adult HIV-infected patients with heart failure: A 7-year prospective cohort study	2022	Metab. Clin. Exp.	Ma et al	Conference abstract
102. Abacavir antiretroviral therapy and indices of subclinical vascular disease in persons with HIV	2022	PLoS ONE	Martinez et al	No INSTI group
103. Adipokines, Weight Gain and Metabolic and Inflammatory Markers After Antiretroviral Therapy Initiation: AIDS Clinical Trials Group (ACTG) A5260s	2022	Clin. Infect. Dis.	Koethe et al	No outcome of interest
104. The risk of hyperglycaemia associated with the use of dolutegravir among adults living with HIV in Kampala, Uganda: a case-control study	2022	Lancet Global Health	Namara et al	Design excluded
105. Estimating atherosclerotic risk in south african youth with perinatally acquired HIV	2022	Top. Antiviral Med.	Mahtab et al	Could not retrieve record
106. Atrial fibrillation risk factors among patients in hiv care in the United States	2022	Top. Antiviral Med.	Nance et al	No outcome of interest
107. Trends in myocardial infarction risk by hiv status in 2 US healthcare systems	2022	Top. Antiviral Med.	Silverberg et al	Poster
108. InSTI-related body composition differences in chronically infected MLWH	2022	Top. Antiviral Med.	Wisch et al	Poster
109. Metabolic Profile of People Living with HIV in a Treatment Hub in Manila, Philippines: A Pre- and Post-Antiretroviral Analysis	2022	J. ASEAN Fed. Endocr. Soc.	Francisco et al	No INSTI arm
110. Metabolic comorbidities and systemic arterial hypertension: the challenge faced by HIV patients on long-term use of antiretroviral therapy	2022	Hosp Pract (1995)	Mendicino et al	Cross sectional study
111. Evaluation of cardiotoxicity and other adverse effects associated with concomitant administration of artemether/lumefantrine and atazanavir/ritonavir-based antiretroviral regimen in patients living with HIV	2022	Saudi Pharm. J.	Usman et al	No outcome of interest
112. Real-World Characterization of the Portuguese Population Living with HIV who Initiated Raltegravir Based-Regimens: The REALITY Study	2022	Acta Med. Port.	SerrÃ£o et al	Single arm, no comparator group
113. Real life use of dolutegravir doravirine dual regimen in experienced elderly PLWH with multiple comorbidities and on polypharmacy A retrospective analysis	2021	Medicine	Mazzitelli et al	Single arm
114. Factors associated with cardiometabolic parameters at 3 years in the TANGO Study, comparing a switch to dolutegravir/ lamivudine versus maintenance of tenofovir alafenamide-based regimens	2021	Antiviral Ther.	Batterhan et al	Poster
115. Integrase strand transfer inhibitors are associated with higher blood pressure and renin-angiotensin-aldosterone system activity	2021	Antiviral Ther.	Siddiqui et al	No outcome of interest
116. Increase in pro-atherogenic apolipoprotein B in people living with HIV (PLWH) following switch from tenofovir disoproxil fumarate to tenofovir alafenamide	2021	Antiviral Ther.	Savinelli et al	No outcome of interest
117. Growth and Metabolic Changes after Antiretroviral Initiation in South African Children	2021	Pediatr. Infect. Dis. J.	Masi-Leon et al	No INSTI arm

118. Contemporary antiretrovirals and body-mass index: a prospective study of the RESPOND cohort consortium	2021	Lancet HIV	Bansi-Matharu et al	No outcome of interest
119. Tenofovir Alafenamide (TAF) is an Independent Risk Factor for Hyperlipidemia in Persons with Human Immunodeficiency Virus (HIV) on Antiretroviral Therapy (ART)	2021	Open Forum Infect. Dis.	Patel et al	Poster
120. Evaluation of the Incidence of Hypertension, Diabetes, and Hyperlipidemia in Patients on Antiretroviral Therapy	2021	Open Forum Infect. Dis.	Idrees et al	Poster
121. Short- and Long-Term Metabolic Changes in Virologically Suppressed Patients Switching from TDF to TAF Containing Antiretroviral Therapy	2021	Open Forum Infect. Dis.	Schafer et al	Poster
122. Incidence of metabolic complications among treatment-naI&Die	2021	Open Forum Infect. Dis.	Daar et al	All arms contain DTG
123. A Real-world Study Assessing the Risk of Lipid Changes and Other Metabolic Effects Associated with Integrase Inhibitor-based Antiretroviral Therapy	2021	Open Forum Infect. Dis.	Gruss et al	Poster
124. Stratifying the risk of NAFLD in patients with HIV under combination antiretroviral therapy (cART)	2021	eClinicalMedicine	Bischoff et al	No outcome of interest
125. Implications of weight gain with newer anti-retrovirals: 10-year predictions of cardiovascular disease and diabetes	2021	AIDS	McCann et al	No outcome of interest
126. Association of HIV-1 Infection and Antiretroviral Therapy With Type 2 Diabetes in the Hispanic Population of the Rio Grande Valley, Texas, USA	2021	Front. Med.	Lopez et al	Cross sectional study
127. Weight and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in people living with HIV: A Cohort Study	2021	Ann. Intern. Med.	Surial et al	No INSTI arm
128. Changes in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) Index in Treated HIV-1 Infected People on Virological Suppression Who Switched to a Different Antiretroviral regimen	2021	J. Acquired Immune Defic. Syndr.	Muccini et al	Cohort already reported on in another study by
130. Lower Cumulative Antiretroviral Exposure in People Living with HIV and Diabetes Mellitus	2020	J. Acquired Immune Defic. Syndr.	Mann et al	No outcome of interest
131. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness	2015	AIDS	Stein et al	No raw data to calculate relative risks
132. Metabolic changes in the patients on second-line highly active antiretroviral therapy (HAART): A prospective cohort study from north India.	2020	Journal of Family Medicine & Primary Care	Meena et al	No INSTI arm
133. Integrase Strand Transfer Inhibitors are associated with incident diabetes mellitus in poeple with HIV	2022	Clinical infectious Diseases	O'Halloran et al	INSTIS arm contains PI and NNRTI

Table S7: Meta-regression* analysis of study and HIV-related variables on the pooled effect estimate

Variable	Number of studies included	Estimate	LCI	UCI	I^2 Residual heterogeneity (%)	R^2 Amount of heterogeneity accounted for (%)
Publication year	13	0.02	-0.08	0.13	51.2	0
Proportion of black population	11	0.002	-0.01	0.01	28.4	0
Male proportion	12	-0.002	-0.02	0.01	24	0
Follow-up duration (per year)	13	-0.11	-0.18	-0.04	0%	100%

*Only when ≥10 studies are included. LCI=lower confidence interval. UCI=upper confidence interval. Only follow-up duration is significantly associated with the pooled effect estimate in 13 studies, every additional year carries an 11% decrease in the pooled risk.

Sub-analysis forest plots for the association of integrase inhibitor use with incident diabetes mellitus with or without metabolic syndrome. In all Forest plots, the black polygon represents the summary measure of the random effects meta-analysis for each subgroup analysis. RR= relative risk, INSTIs= integrase strand transfer inhibitors, PIs=protease inhibitors, NNRTIs=non nucleotide reverse transcriptase inhibitors.

Figure S1: Sub-analysis by non-INSTIs regimen in the control group (protease inhibitors and non-nucleotide reverse transcriptase inhibitors)

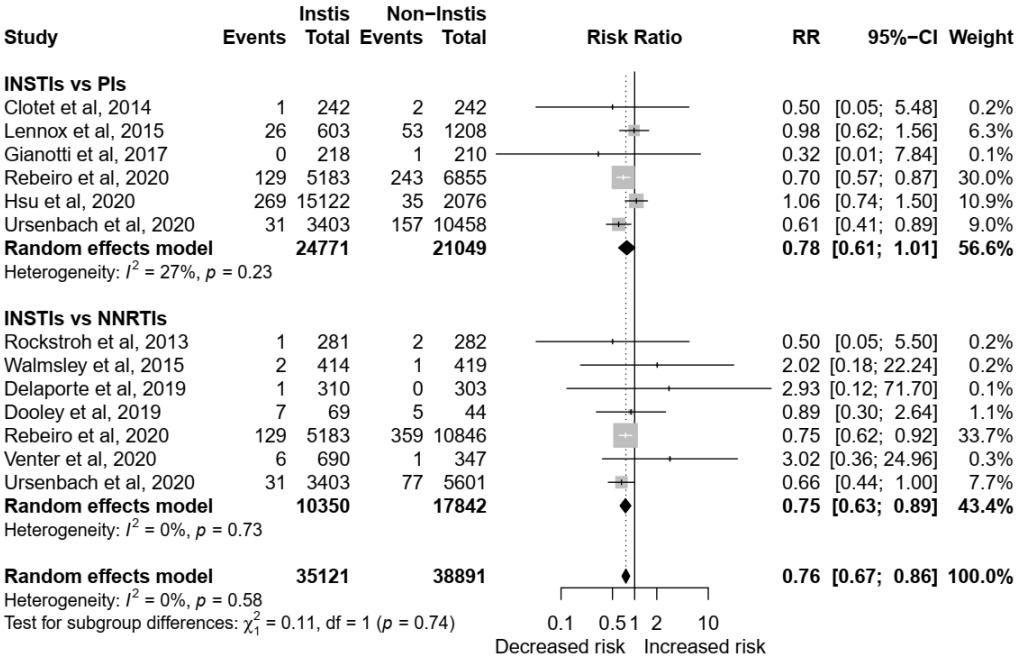
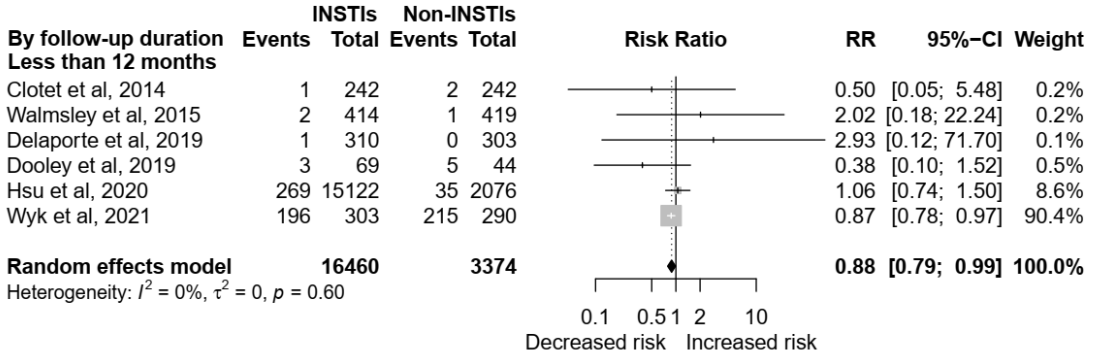


Figure S2: Sub-analysis by follow-up duration



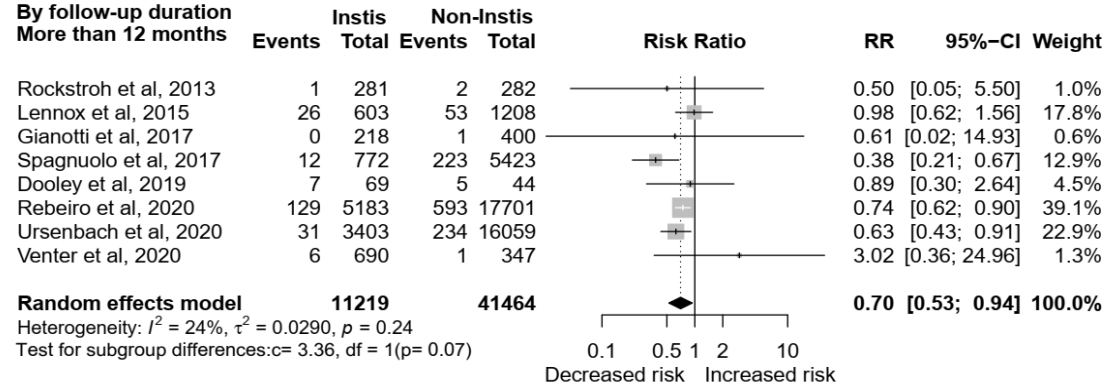


Figure S3: Sub-analysis geographical origin of the study population

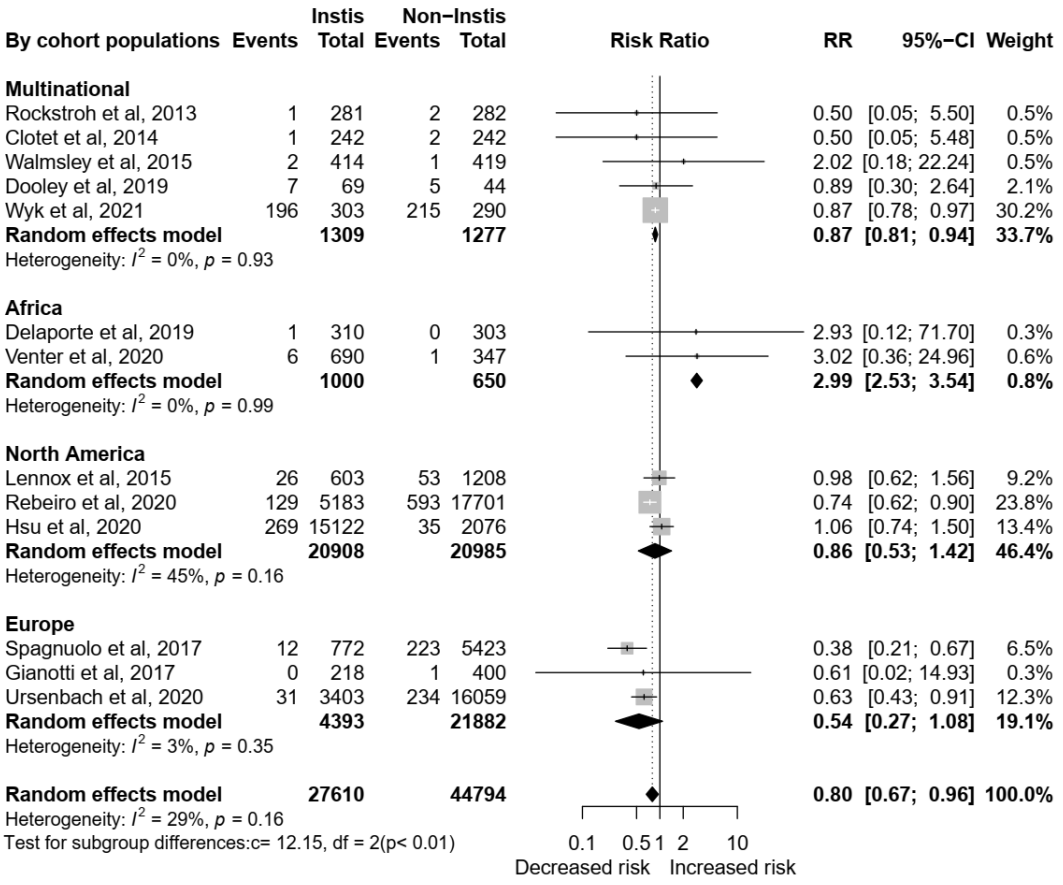


Figure S4: Sub-analysis by ART status at baseline

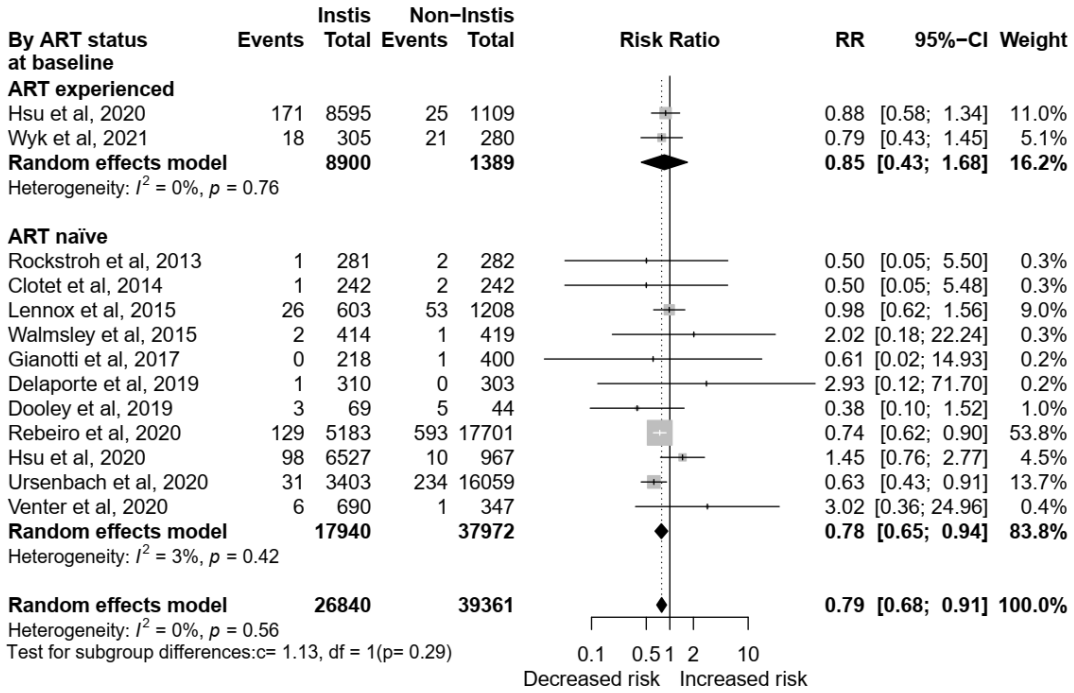


Figure S5: Sub-analysis by study design

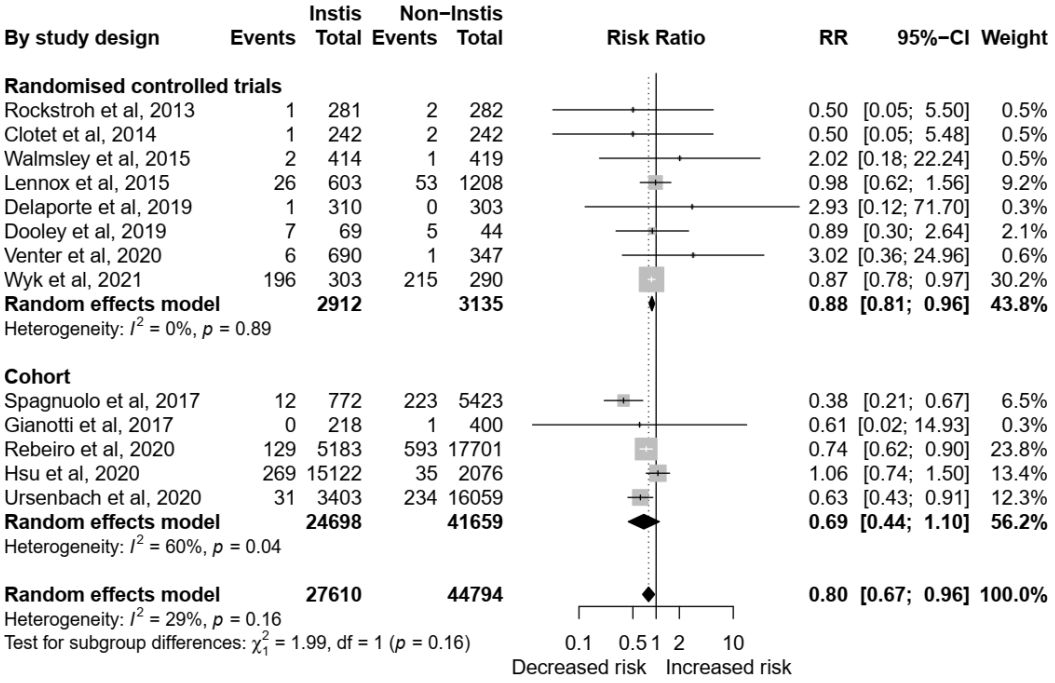
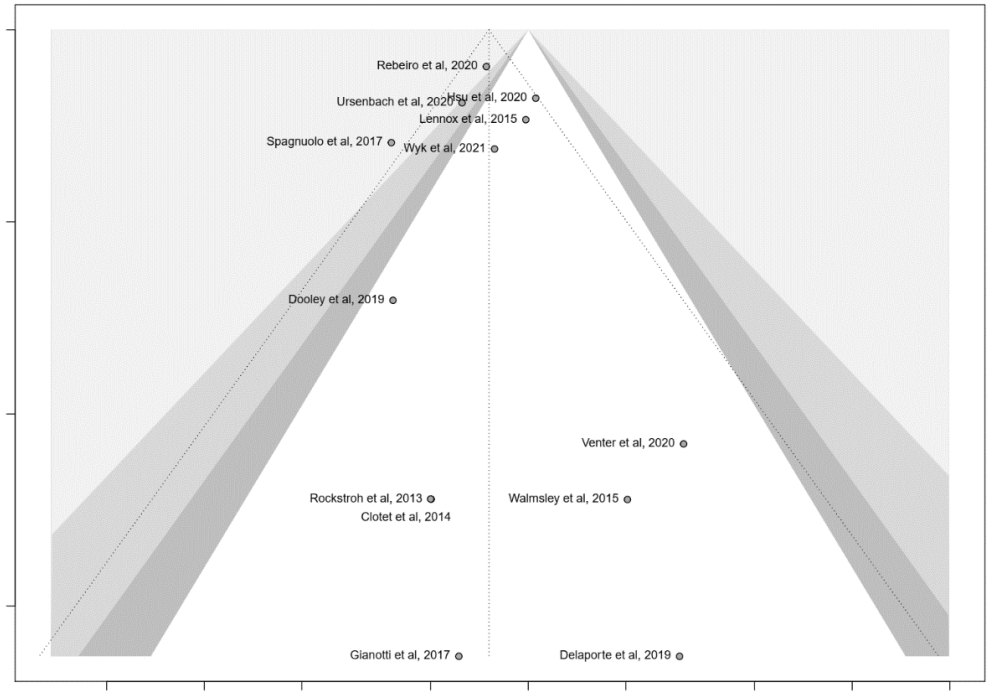


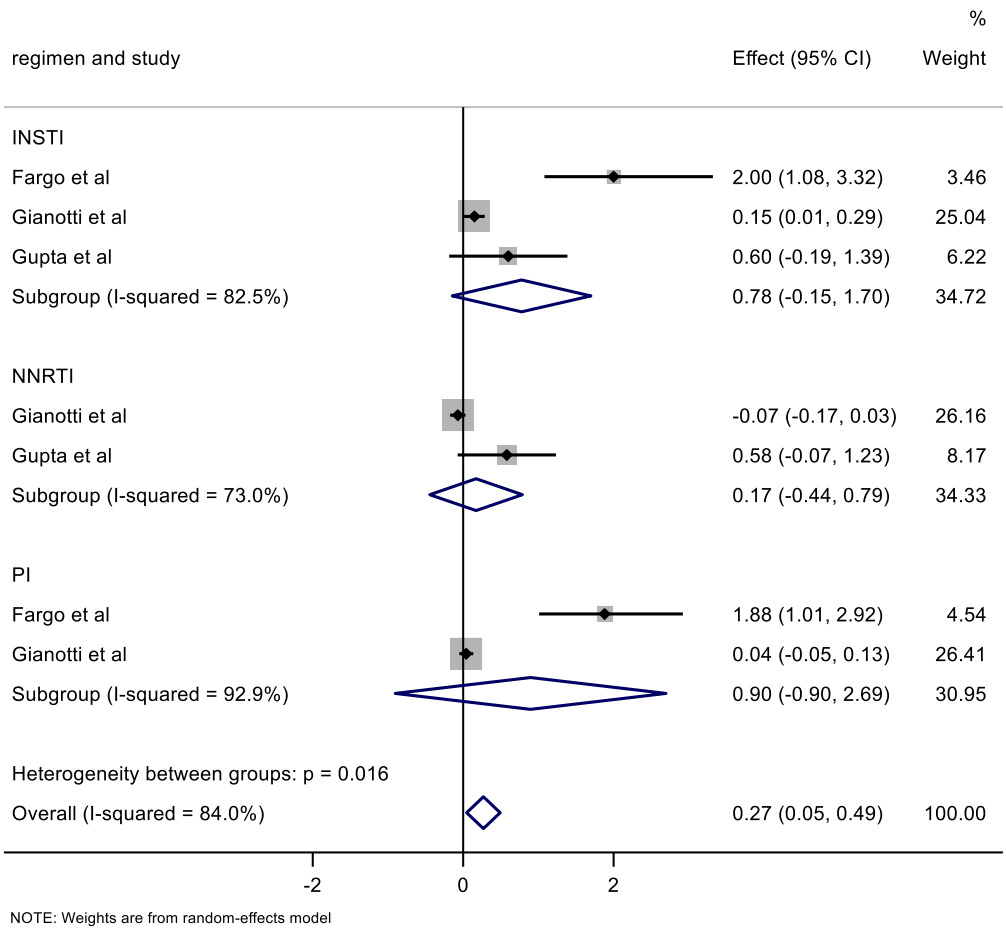
Figure S6. Assessment of publication bias by funnel plot asymmetry test for 13 studies meta-analysed for incident insulin resistance and/or diabetes in INSTIs compared to non-INSTIs.



Egger's test for the intercept:

Intercept = 0.093 (95% CI -0.84 – 1.03, P=0.85)
There is no funnel plot asymmetry by Egger's test.

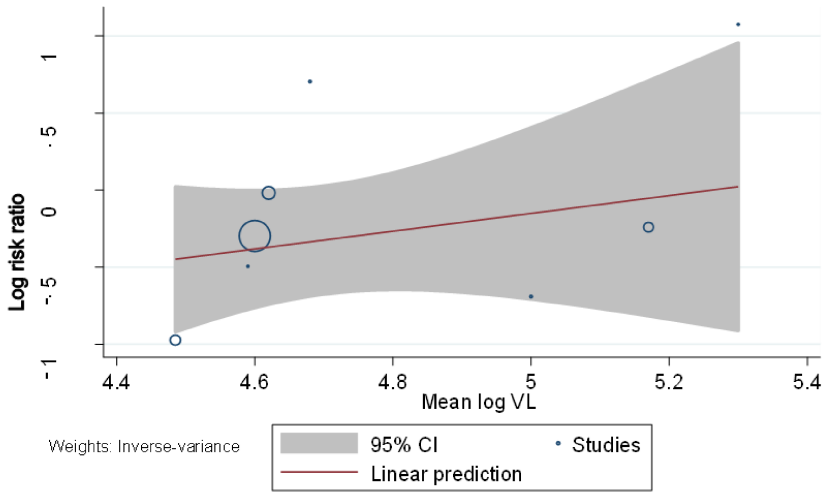
Figure S7. Mean changes in HOMA-IR from baseline in INSTIs group compared to overall non-INSTIs, NNRTIs and PIs groups.



Abbreviations: HOMA IR- Homeostatic model for insulin resistance index. INSTIs=integrase strand transfer inhibitors. NNRTI=non-nucleoside reverse transcriptase inhibitors, PI=protease inhibitors.

Figure S8: Bubble plots for univariable meta-regression on (A) Baseline viral load (B) Age (C) Baseline CD4 cell count

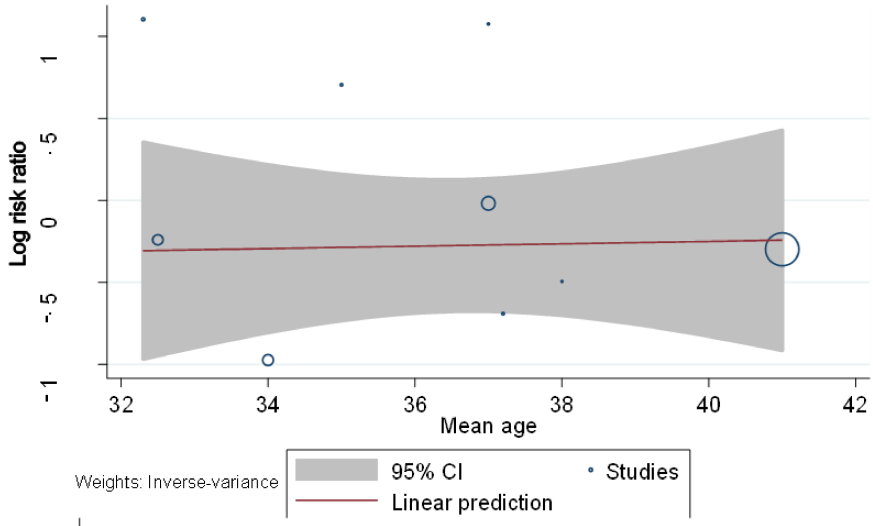
A)



VL- viral load

P= 0·434

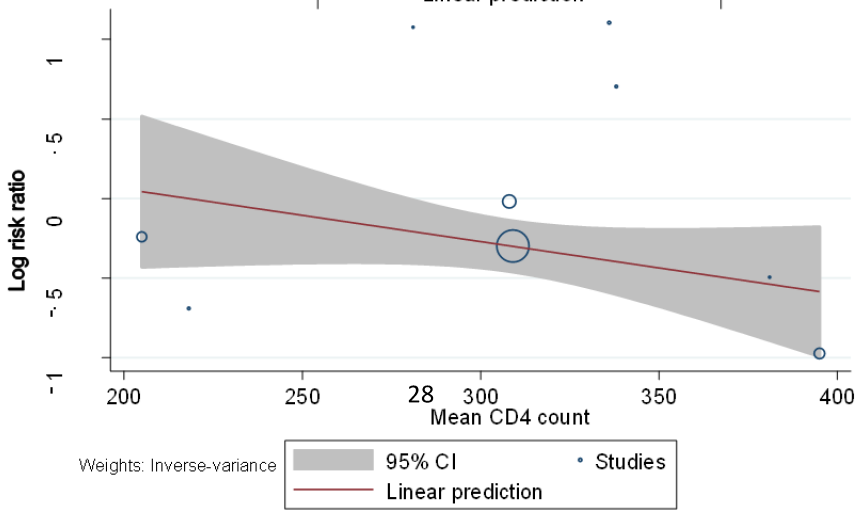
B)



P=

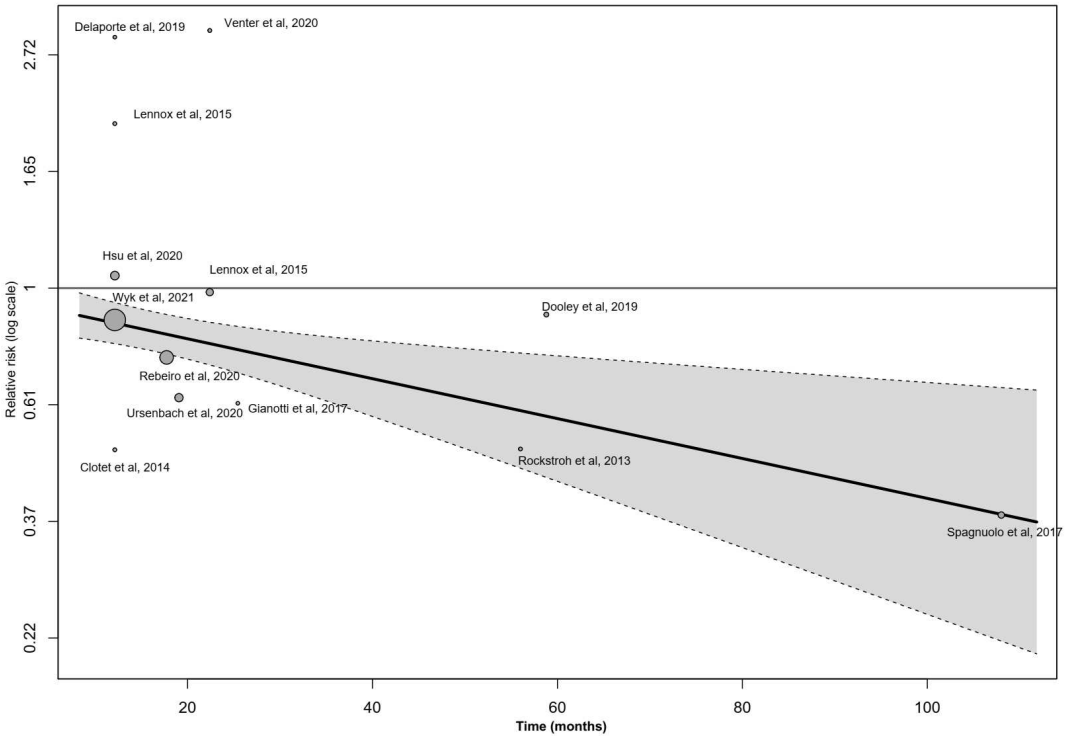
Age 0·907

C)



Visual trends suggest a heightened risk of diabetes with exposure to INSTIs in patients with a high baseline viral load (A) and low $CD4^+$ cell count (C). However, this heightened risk was not statistically significant. There was no trend suggestive of age affecting the association between integrase strand transfer inhibitors and incident diabetes.

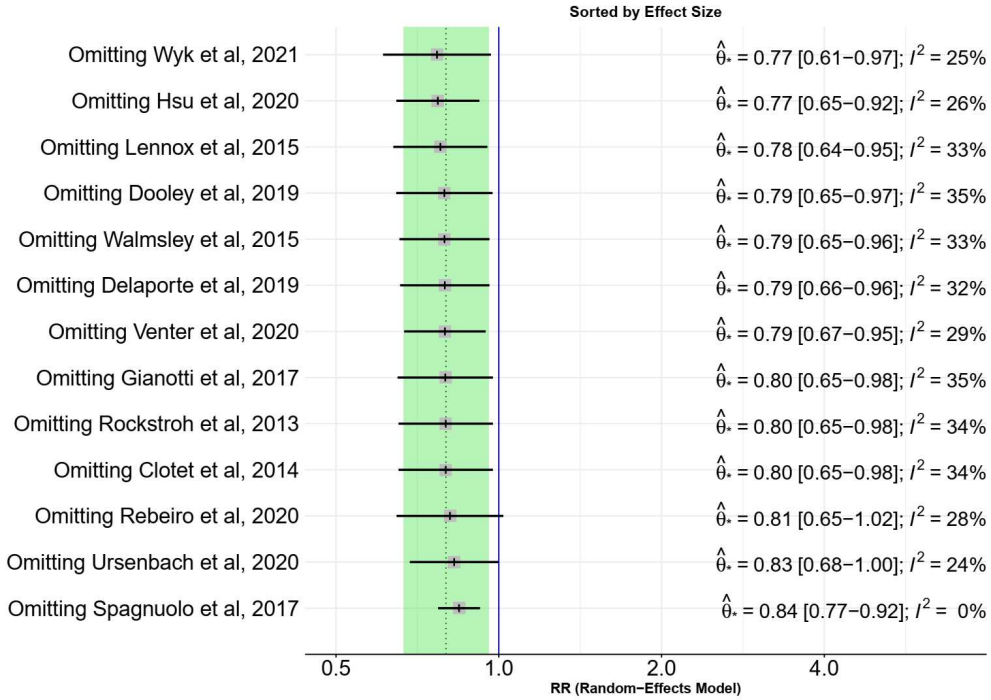
Figure S9: Bubble plot for univariable meta-regression on follow-up time



As demonstrated, the risk of developing diabetes with exposure to INSTIS decreased significantly with longer duration of follow-up.

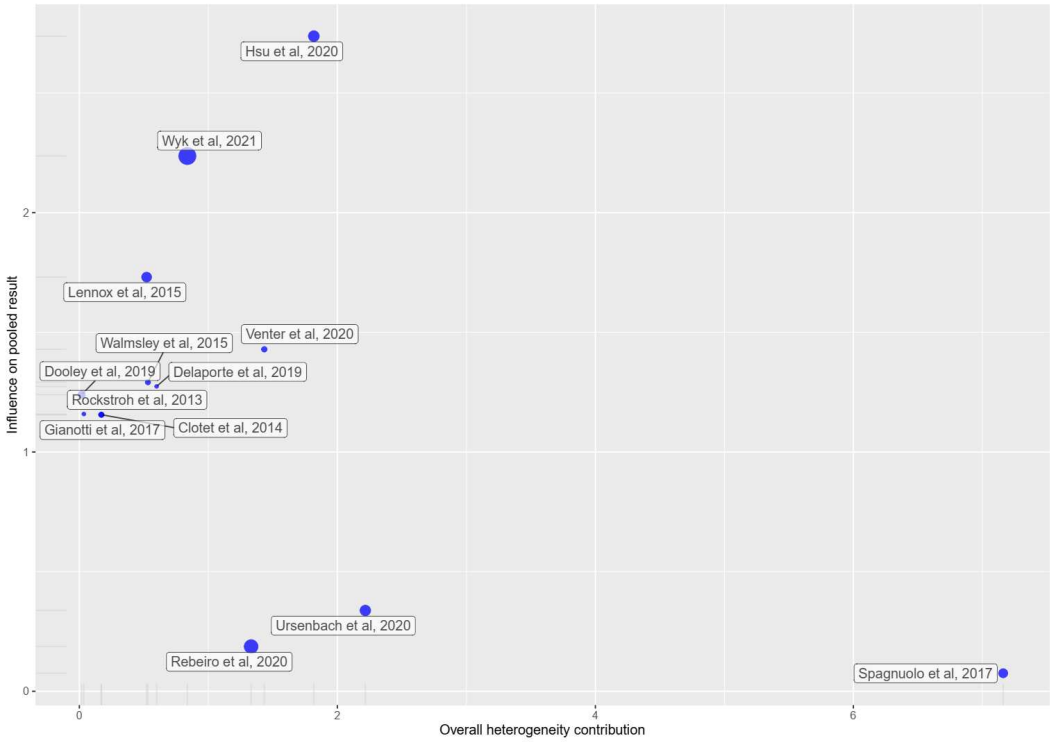
See Figure S2 for the pooled risk by follow-up time (12 months).

Figure S10: Influence analysis*by leave one-out-method for 13 studies pooled in the meta-analysis sorted by effect size.



Abbreviations: θ=effect size; I2=heterogeneity; RR=relative risk. In Influence analysis the pooled effect estimate is calculated while omitting one study at a time to detect the individual impact of each study. For e.g., omitting Spagnuolo et al.2017 will yield a pooled relative risk of the remaining 12 studies= 0.84 with 95% CI (0.77-0.92) with minimal heterogeneity I2=0%.

Figure S11: Baujat plot*showing each study contribution to the overall heterogeneity of the meta-analysis (studies n=13)



The contribution of each study to the overall heterogeneity is plotted on the X axis, and each study influence on the pooled effect estimate is plotted on the Y axis. Study by Spagnuolo et al. added the most to heterogeneity but with minimal impact on the effect size due to its small sample size.

**Baujat B, Mahe C, Pignon JP, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Stat Med.2002 Sep 30;21(18):2641-52. doi:10.1002/sim.1221*

Continuation of manuscript references:

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