Addis Ababa University
College of Health Sciences

Efficacy and Safety Profile of Integrase Strand Transfer Inhibitors (InSTIs) for treatment of HIV in Pregnant Women: Systematic Review and Meta-Analysis

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Table of Contents

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ABBREVIATION/ACRONYMS

ADIS	Acquired immunodeficiency syndrome
ART	Antiretroviral Therapy
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
DTG	Dolutegravir
EVG	Elvitegravir
FDC	Fixed Dose Combination
HIV	Human Immunodeficiency Virus
InSTI	integrase strand transfer inhibitor
RAL	reltagravir
MeSH	medical subject headings
NTD	Neural Tube Defects
PD	pharmacodynamics
PK	pharmacokinetic
RCT	Randomized Controlled Trials
RR	relative risk
WHO	World Health Organization

ABSTRACT

Background: Integrase strand transfer inhibitors (InSTIs) are the most recent class of drugs approved on the basis of their efficacy and safety profiles (16). Dolutegravir and elvitegravir are considered US Food and Drug Administration pregnancy category B; while raltegravir belongs to category C.

Objective: To assess the efficacy and safety profile of Integrase Strand Transfer Inhibitors drugs for treatment of HIV in Pregnant Women

Method: Literature search strategies were done using medical subject headings (MeSH) and text words related to InSTIs drugs and pregnancy. Pubmed, EMBASE, Web of Science, Science Direct, Henari, and the Cochrane Central Register of Controlled Trials and other databases were searched. The estimated effect (Relative Risks) and associated 95% confidence intervals for the reduction of HIV RNA viral load were meta-analyzed using a DerSimonian– Laird random-effects model (25). Statistical analysis was performed using RevMan 5.3 software.

Result: Based on our systematic review and meta-analyses data, treatment with InSTIs based ART regimens showed to be more beneficial for HIV positive pregnant women compared to other currently used treatment strategies. Both preterm delivery and proportion of infants with Small for Gestational Age didn't show statistically significant association with the use of InSTIs (risk ratio 0.82, 95% CI 0.60–1.13, I^2=0%) and (risk ratio 0.90, 95% CI 0.58–1.40, I^2=0%) respectively. DTG based ART showed a lowered maternal serious adverse event compared to current treatment regimen (risk ratio 1.94, 95% CI 1.13–3.32, I^2=0%).

Conclusion: We suggest use of DTG based ART regimen to be preferred first line choice for HIV positive pregnant women, if the pregnancy is confirmed already past 8 weeks of gestation. Although further investigation is necessary about safety data, we suggest InSTI drugs, especially RAL, can be safely used during pregnancy particularly in late presenter pregnant women or as an intensification strategy. Because of the short and long-term consequences of adverse events seen in infants, particularly preterm birth and SGA, future studies need to assess the safety profile of DTG for infants and explore potential mechanisms of adverse outcomes.

Key words: InSTIs, pregnant women, viral load, efficacy and safety

BACKGROUND

1.1 INTRODUCTION

The human immunodeficiency virus (HIV) is one of the most serious health crises the world faces today (1). The epidemiologic characteristics of HIV infection differ according to geographic region and depend upon the mode of transmission, governmental prevention efforts and resources. The annual number of deaths from Acquired immunodeficiency syndrome (AIDS) related illness globally has fallen from a peak of 1.7 million in 2004 to 770 000 in 2018. Since 2010, AIDS related mortality has declined by 33% (2). Ethiopia is one of the sub-Saharan African countries with high burden of HIV; according to the Ethiopian Demographic and Health Survey done in 2016, the national HIV prevalence was 0.9% and the urban prevalence was 2.9%, which is more than seven times higher than that of the rural (0.4%) (3,4).

CD4 T lymphocyte (CD4) cell count to assess immune function, and plasma HIV RNA (viral load) to assess level of HIV viremia are the two surrogate markers are routinely used to monitor patients with HIV. Measurement of CD4 count is particularly useful before initiation of Antiretroviral Therapy (ART). Thus, the most important use of determining the viral load is to monitor the effectiveness of therapy after initiation of ART (5).

The treatment of HIV infection is complex and changes rapidly as advances are made in basic science and clinical experience. Because the science of HIV evolves rapidly, various events in the HIV life cycle plus host factors have been identified as potential targets for antiretroviral therapy (5,6). And on the other hand management of patients with HIV has changed substantially with the availability of newer, more potent, and less toxic antiretroviral agents. Without ART, most individuals with HIV will eventually develop progressive immunodeficiency marked by CD4 cell depletion leading to AIDS-defining illnesses and premature death. The key goal of ART is to achieve and maintain durable viral suppression (7).

Antiretroviral therapy for pregnant women is proven to be the most efficient intervention by reducing the rate of mother-to-child transmission (MTCT) to lower than 2% and decreasing maternal and child mortality (8). Ethiopia started universal HIV screening of pregnant women in 2007 (3). Pregnant women experience unique physiological changes that may result in clinically significant alterations in drug pharmacokinetic and pharmacodynamics.

These changes begin early in gestation and include:

- ✓ GI transit time that can alter the rate and extent of drug absorption
- ✓ Large changes in total body water and fat, increasing drug distribution volume
- ✓ Albumin and increased alpha-1 acid glycoprotein concentrations that may cause changes in drug protein binding
- ✓ Cardiac output, ventilation, and hepatic and renal blood flow which may impact drug metabolism and elimination
- ✓ Concentrations of endogenous glucocorticoids that may affect the activity of hepatic enzyme systems that regulate drug metabolism

The mechanism for HIV vertical transmission is not known exactly, but during the intrauterine life, in the peripartum period and through breastfeeding are the three believed main forms of transmission. It is estimated that 25% of transmission cases occur during the gestational period, 75% during the peripartum period (9). A study that assessed the risk of perinatal transmission showed that higher plasma viral load values were associated with a significant risk of transmitting HIV-1 from mother to infant (10). It is estimated that around 1000 children acquire HIV through vertical transmission daily (9).

Today, combination ART is recommended to treat HIV-infected pregnant women. Treating HIV during pregnancy can be challenging as it is essential to (1) determine the optimal combination of ART to treat maternal HIV infection; (2) determine the optimal combination of ART to prevent perinatal transmission; (3) determine if physiological changes during pregnancy or underdeveloped processes in the neonate alter drug absorption and disposition; and (4) weigh the benefits of ART against the risks of adverse events to the woman, fetus and newborn (11). A lot of recent studies present conflicting evidence of a link between preterm deliveries and exposure to ART during pregnancy (12).

According to many national guidelines, HIV-infected pregnant women have to receive ART preferably as a combination of three drugs from at least two different classes; regardless of viral load, immunologic status or clinical manifestations (9). The WHO Option B+ recommends the use of ART to all pregnant and lactating women infected with HIV irrespective of CD4 count or

the disease status. It recommends continuing its use after birth to control maternal disease and to prevent MTCT and sexual transmission of HIV. Ethiopian national protocol follows the same guidelines to prevent MTCT of HIV (13).

Physiological changes during pregnancy that can significantly alter drug absorption, distribution and elimination occur as early as the first trimester and peak during the third trimester. The most practical problem of decreasing drug absorption during pregnancy is nausea and vomiting leading to non-adherence of ART (11,14). During pregnancy, the apparent volume of distribution increases with subsequent decreases in peak plasma concentrations; and alterations in drug elimination clearance during pregnancy can affect steady-state concentrations (15).

Drugs which cross placental barrier could bring about teratogenicity leading to harm and/or malformation when administered in the first trimester of pregnancy. Furthermore, transplacental transfer of drugs increases during the third trimester producing physiological defects to the fetus due to increased maternal and placental blood flow, and decreased thickness and increased surface area of the placenta (11,14). Nevertheless, the increased use of combined ART during pregnancy can cause adverse effects in pregnant women and their newborns. (8).

1.2 INTEGRASE STRAND TRANSFER INHIBITORS (InSTIs)

HIV genomes that fail to integrate cannot command the production of new infectious viral particles. Thus, inhibiting this step prevents proliferation of the viral infection (11). InSTIs are the most recent class of drugs approved on the basis of their efficacy and safety profiles. raltegravir (RAL), elvitegravir (EVG) and Dolutegravir (DTG) are now part of preferred first-line regimens in DHHS guidelines(16). The InSTI class of medication could play a significant role not only in resource-rich settings, but also in low-resource settings where women may only access prenatal care in the third trimester or not start ART until close to delivery (17).

1.2.1 USE OF InSTIs IN PREGNANT WOMEN

Development of efficacious and safe antiretroviral interventions for the prevention of mother to child transmission of HIV has been a major achievement in the fight against HIV/AIDS (11). The first study to demonstrate the efficacy of antepartum, intrapartum and newborn antiretroviral prophylaxis, specifically zidovudine monotherapy in reducing perinatal HIV transmission was done in 1994 (11,18). DTG and EVG are considered US Food and Drug Administration

pregnancy category B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women); while RAL belongs to category C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). One of the major benefits of DTG and EVG is their once-daily dosing schedule (17).

The World Health Organization (WHO) supports the expansion of DTG-based first-line regimens in low and middle-income countries, such as in southern and eastern Africa where pretreatment drug resistance to nonnucleoside reverse transcriptase inhibitors is of concern (19).

InSTIs are generally well tolerated with few discontinuations due to adverse reactions. The most common drug-related adverse reactions reported with RAL were nausea, headache and diarrhea (20). Previous studies demonstrated that there was an increase in the plasma level of transaminases during RAL based ART which recommended frequent check-ups of transaminases levels and discontinuing the ART if necessary (9). Raltegravir was observed to have good tolerance and efficacy profile in pregnancy without producing any adverse effects in the newborns (21). Recommendations for the use of Raltgravir based ART during pregnancy are increasing due to its safety and fast drop of the viral load during delivery reducing the risk of vertical transmission.

For women who become pregnant while taking EVG/c, switching to a more effective, recommended regimen should be considered. No data are available on placental transfer of Bictegravir and there is insufficient data to assess teratogenicity in humans. There is no evidence of teratogenicity in rats or rabbits for Bictegravir (22).

1.3 SIGNIFICANCE OF THE REVIEW

Development of new ARV drug with higher viral suppression rate, reduced drug resistance and lower cost is important in HIV therapy program and cART with higher prevention of MTCT is also crucial. While developing a new drug its safety and efficacy could be a concern for its use in pregnant women. The purpose of this review is to analyze studies done on InSTIs drugs on their effectiveness and safety in HIV positive pregnant women.

OBJECTIVE

To assess the Efficacy and Safety profile of Integrase Strand Transfer Inhibitor drugs in HIV infected Pregnant Women

METHODS

This systematic review is conducted in accordance with a pre-specified protocol. Findings are reported in order to comply with both the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statement and MOOSE (Meta-Analyses and Systematic Reviews of Observational Studies) reporting guidelines (23).

3.1 Eligibility criteria

Study characteristics used as criteria for eligibility for the review were the following:

3.1.1 Inclusion criteria:

- Clinical trials or Cohort studies
- Studies which examined HIV positive pregnant women
- Studies which involved InSTI drugs, as Single dose and Fixed Dose Combination (FDC)
- Studies which involved Standard Care as a comparator and single arm studies
- Studies conducted on any setting
- Articles reported in English

3.1.2 Exclusion Criteria

- Studies done on non-pregnant women
- Studies that did not report virological endpoints
- Studies that report only safety endpoint
- case studies

3.2 outcomes

Primary outcome

- Virologic outcome: rates of patients with viral load (VL) below 50 copies/ml during delivery

Secondary outcome

- Any Adverse Events on the Mother or infant

3.3 Search Methods for Identification of Studies

3.3.1 Electronic Searches

Literature search strategies were done using medical subject headings (MeSH) and text words related to InSTIs drugs and pregnancy. Pubmed, EMBASE, Web of Science, Science Direct, Henari, and the Cochrane Central Register of Controlled Trials (CENTRAL) and other databases were searched. Other databases including Clinical- Trials.gov (http://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/) were also searched for ongoing trials.

PubMed searches were performed using the following search terms: 'Raltegravir OR Isentress' OR 'Elvitegravir OR Cobicistat OR GS-9137 OR GS-9350 OR Stribild OR Genvoya' OR 'Dolutegravir OR Tivicay OR Triumeq OR GSK1349572' OR 'Cabotegravir OR GSK1265744' OR 'Bictegravir OR GS-9883' AND pregnancy OR pregnant women.

The literature searches were limited to the English language and human subjects. Grey literature sources, such as conference proceedings, as well as reference lists of identified studies and in existing systematic reviews and meta-analyses were also searched for additional studies.

3.3.2 Studies Selection Process

The titles and abstracts yielded by the search against the inclusion criteria were independently screened by two reviewers (Hiwot Getachew and Tilahun Temeche). The initial selection criteria were broad to ensure that as many studies as possible were assessed as to their relevance to the review. Articles that were obviously unsuitable were excluded in the early stages. For all titles that appear to meet the inclusion criteria, full reports were obtained. Then the reviewers paired to screen the full text reports and decide whether these meet the inclusion criteria. Any disagreements were resolved through discussion.

3.3.3 Data Extraction and Management

The two reviewers (HG and TT) independently performed literature searching, evaluation of literature quality, information extraction, and cross checking. In case of disagreement, the

reviewers discussed the issue until a consensus opinion was obtained. Data extraction was done using a customized data extraction form (Annex I), which was piloted before the main data extraction. Any disagreements were noted and resolved by consensus among reviewers or by arbitration by the advisors (Yimtubezinash Woldeamanuel and Eyasu Makonnen).

3.4 Risk of Bias Assessment

The Cochrane collaborations risk of bias tool was used to assess heterogeneity and quality for the included RCTs studies. All six domains in the risk of bias tool were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each domain was graded as (a) low bias, (b) unclear bias or (c) high bias(23).

The Newcastle-Ottawa Quality Assessment Scale, which consists of a 'star-rating system' in which a study is judged on three broad domains: the selection of the study groups, the comparability of the groups and the ascertainment of outcome of cohort studies, was used to assess the methodological quality of cohort studies included in the review (24).

All study assessments were carried out independently by two reviewers and checked for agreement. Differences were resolved through consensus or in consultation with the advisors.

3.5 Data Synthesis

The following data were collected: (a) basic study characteristics including study design, study phase, single center or multicenter; (b) population characteristics including population size, antiretroviral treatment, InSTIs naïve or experienced and exclusion criteria; (c) intervention characteristics including the drugs used, drug dosage, duration of treatment, and follow-up; (d) outcome parameters including viral load and CD4 count, clinical and laboratory adverse events (AEs)

3.6 Data Analysis

The estimated effect (Risk Ratio) and associated 95% confidence intervals, as all outcomes were dichotomous, for the reduction of HIV RNA viral load and adverse event were meta-analyzed using a DerSimonian– Laird random-effects model (25). A random effect model was used because of the likelihood of heterogeneity among the included studies. Statistical heterogeneity was assessed using the I^2 statistic, with results ranging from 0 to 100% and values of 25, 50 and 75% representing low, moderate and high levels of heterogeneity, respectively and source of

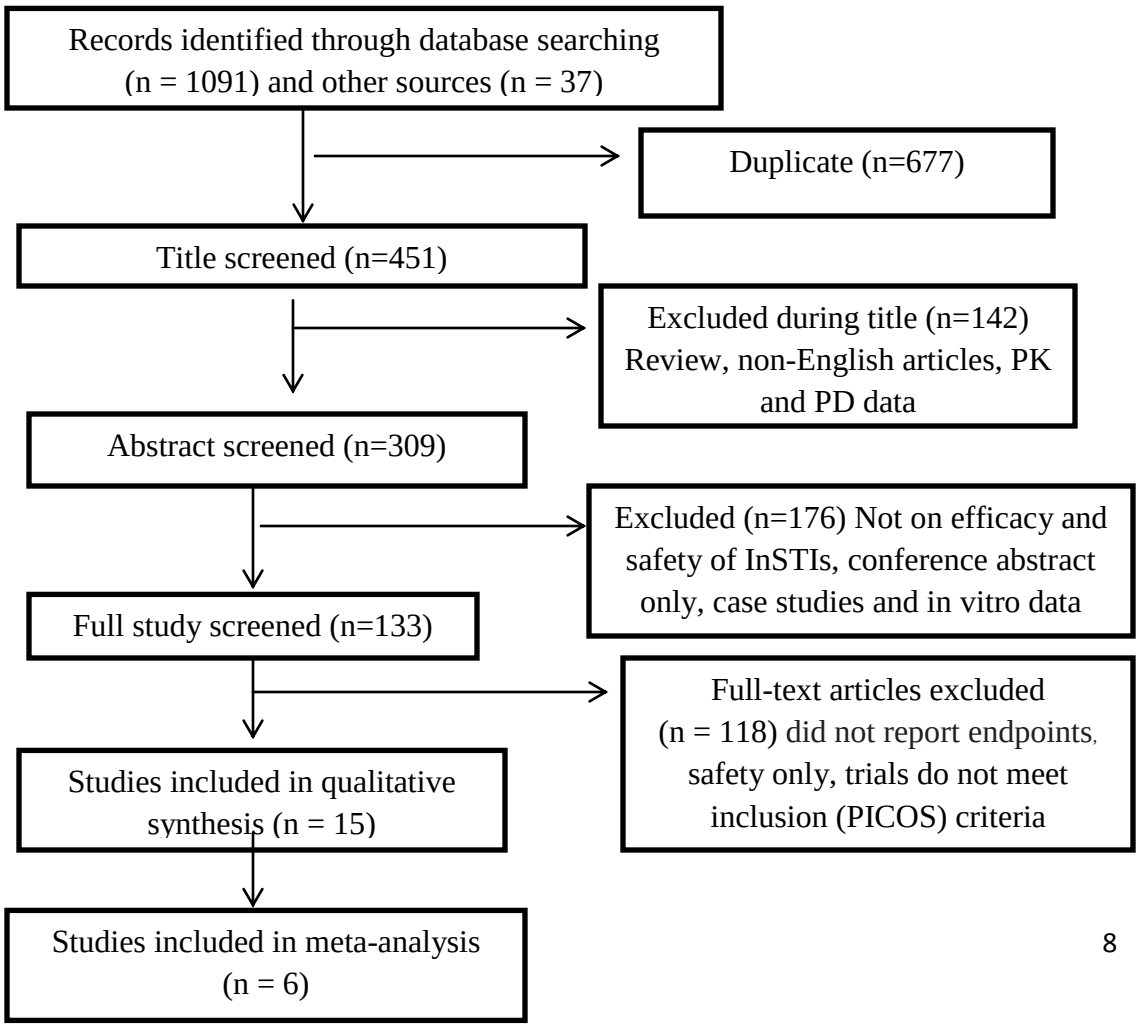
heterogeneity was explained by subgroup analysis. Statistical analysis was performed using RevMan 5.3 software, according to the statistical guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions (26). Results were pooled from the selected studies, as well as according to study design. Studies were pooled separately as randomized controlled trials and cohort studies.

RESULTS

4.1 Basic study characteristics

The detailed search steps are summarized in the PRISMA flow diagram. From the search of databases and other sources 1128 articles were identified initially. After reading titles and abstracts, we selected133 potential articles for full-text view and after reading the texts we excluded, articles that did not report endpoints, safety only articles, case studies and trials that do not meet inclusion (PICOS) criteria. A total of 15 articles were selected for qualitative synthesis, six clinical trials (15,27–31), and nine cohort studies (17,32–39). Finally, four RCT studies and two cohort articles (27,28,30,31,34) were selected for quantitative synthesis (meta-analysis). One prospective cohort study, national program on surveillance on antiretroviral treatment in pregnancy, is used twice in the meta-analysis for comparison of InSTI with two different ART regimens (34).

PRISMA Flow Diagram



Among the clinical trials, two of them were uncontrolled interventional trial having DTG and RAL based ART as intervention. The rest four were RCTs with DTG and RAL based ART as intervention and EFV and PI as control group. Among the cohort studies most of the studies had DTG as intervention followed by RAL. The median gestational age (GA) for clinical trials was 32 and the median age of the participant was 29.7 and 29 for cohort and clinical trials, respectively. Duration of patient follow-up in the clinical trials studies ranged from 24 weeks to 48 weeks and from 22 months to 120months for cohort studies.

The characteristics of participants across the studies were summarized in table 1 and 2. For clinical trial studies, population size ranged from twenty two individuals in the smallest (15) to three hundred seven in the largest (27). Cohort study sizes ranged from thirteen participants in the smallest to five hundred eighty individuals in the largest cohort study (34,39). All four RCTs had 1:1 randomization between the intervention and control groups and all clinical trials were open label (Table 1). From total participants in the cohort studies 364 (67.1%) were naive and 179(32.9%) were experienced to InSTIs. For cohort studies 110(20.3%) and 433(79.7%) participants had baseline viral load of less than 50 copies/ml and greater than 50 copies/ml respectively (Table 2).

Table 1: Basic characteristics for clinical trial articles included in the review

Author, Year	Study Design	Type	ITT/PP	Total S.Z	Intervention (E/C)	Sample Size (E/C)	Age (years, median) (E/C)	Median GA (E/C)	Setting	Randomization and Masking
Catriona Waitt, 2019	RCT	Open label, multicenter	ITT and PP	60	DTG/EFV	29/31	27 (19–42)/25 (19–35)	31 (27–35)/30 (27–36)	Uganda and South Africa	1:1,
Carlos Brites, 2018	RCT	Open label, single center	ITT	33	RAL/lopinavir/ ritonavir	17/16	26.7/26.7	32.5/32.7	Brazil	1:1, NO
Esau C Joao, 2020	RCT	Open-label, multi center		307	RAL/EFV	153/154	27 (23-32)/25(22-31)	28 (22-31)/27(23-31)	Argentina, Brazil, S.A, Tanzania, Thailand, and USA	permuted block allocation with stratification : NO
Kenneth Kintu, 2020	RCT	Open-label, multi center	ITT	268	DTG/EFV	135/133	28/27.4	31(29-34)/31(29-33)	Uganda and South Africa	1:1, NO
Nikki Mulligan, 2018	UCT	open-label, parallel-group, multi-center phase-IV	ITT	29	DTG	29	32 (21–42)	32 (21 – 42)	USA	NO, NO
Maren I. Blonk, 2015	UCT	open-label multicenter, phase IV	PP	22	RAL	22	33 (29–36)	33 (32–35)	Europe	NO, NO

UCT-uncontrolled clinical trial, RCT-randomized controlled trial, PP-perprotocol, ITT-intention to treat, E-experimental, C-control, GA-gestational age, NR-not reported

Table 2: Basic characteristics for articles with cohort study design which are included in the review

Author, Year	Study Design	Study Duration (Months)	Total S.Z	Group S.Z	Experimental Drug	Age (Years, Median)	Naïve to InSTI n(%)	Experienced to InSTI n(%)	Setting
Riikka Bornhede, 2018	Retrospective Cohort	44	36	36	DTG	34 (19-43)	22 (61.1%)	14 (38.9%)	Sweden
Clara Grayhack, 2018	Retrospective Cohort	41	66	66	DTG	28	38(57.6%)	28 (42.4%)	USA
Bassam H. Rimawi, 2017	Prospective Cohort	15	13	13	InSTI(3DTG, 10EVG)	29 (18–34)	13 (100%)	0 (0%)	Atlanta, GA
Lisa Rahangdale, 2016	Retrospective Cohort	72	101	39	InSTI	27 (23-32)	20 (51%)	19 (48.7%)	USA
Monique L. Mounce, 2017	Retrospective Cohort	100	21	7/14	InSTI (4RAL,2DTG,1 EVG)/PI	30 (25–33)	4 (57.1%)	3 (42.9%)	USA
Pierre Gantner, 2019	Retrospective Cohort	60	94	94	RAL	33 (20–45)	61 (64.9%)	33 (35.1%)	France
Thanyawee Puthanakit, 2018	Prospective Cohort	22	154	154	RAL	23 (19–29)	154 (100%)	0 (0%)	Thailand
Martina L. Badell, 2019	Retrospective Cohort	39	134	134	EVG	28 (15–44)	52 (38.8%)	82 (61.2%)	USA
Marco Floridia, 2020a	Prospective Cohort	120	145	43/101	INSTI/NNRTI	30 (26–37)/ 32 (27–36)	NR	NR	Italy
Marco Floridia, 2020b	Prospective Cohort	120	580	43/537	INSTI/PI	30 (26–37)/ 34 (30–37)	NR	NR	Italy

4.2 Maternal Viral Load Suppression

The inclusion of pregnant women in clinical trials involves complex risk-benefit assessments that vary depending on the seriousness of the disease, the trial design, the availability of other treatments and it also have complex ethical issues. Our search result showed that most researches done on HIV positive pregnant women are cohort studies with single arm treatment. Since the single arm cohort studies that are included in the review showed significant and valuable input for the review, they are narrated and discussed with supporting findings which are done in worldwide setting and with other systematic reviews.

Table 3: Viral Load value at delivery, Adverse Drug Events and Serious Adverse Events values for the included studies

Author, year	Study Design	Intervention (E/C)	Sample Size (E/C)	VL at Delivery <50 Copies/ml (E/C)	Any ADE (E/C)	SAE (E/C)
Catriona Waitt, 2019	RCT	DTG/EFV	29/31	20(69%)/21(67.7)	55/107 ADE	2 (6.9%)/1 (3.2%)
Carlos Brites, 2018	RCT	RAL/ lopinavir/ritonavir	17/16	13(76.5%)/4(25%)	4 /10 patient	0/0
Kenneth Kintu, 2020	RCT	DTG/EFV	120/117	89(74.2%)/50(42.7%)	NR	30/137(22%)/14/131(11%)
Esau C Joao, 2020	RCT	RAL/EFV	153/154	131(85.6%)/90(58.4%)	NR	59/197(30%)/61/206(30%)
Maren I. Blonk, 2015	UCT	RAL	22	20(90.9%)	10 ADE	NR
Nikki Mulligan, 2018	UCT	DTG	29	27(93.1%)	8 patient	8 (27.6%)
Monique L. Mounce, 2017	Retrospective Cohort	InSTI/PI	7/14	5(71.4%)/13(92.8%)	6/19 patient	NR
Marco Floridia, 2020a	Prospective Cohort	InSTI/NNTI	43/101	36(83.7%)/98(97%)	28/56 patient	NR
Marco Floridia, 2020b	Prospective Cohort	InSTI/PI	43/537	36(83.7%)/432(80.4%)	28/237 patient	NR
Riikka Bornhede, 2018	Retrospective Cohort	DTG	36	27(75%)	NR	NR
Clara Grayhack, 2018	Retrospective Cohort	DTG	66	49(74.2%)	NR	NR
Bassam H. Rimawi, 2017	Prospective Cohort	InSTI (DTG 3, EVG 10)	13	12(92.3%)	NR	NR
Lisa Rahangdale, 2016	Retrospective Cohort	InSTI	39	35(89.7%)	NR	NR
Pierre Gantner, 2019	Retrospective Cohort	RAL	94	66(70.2%)	NR	NR
Thanyawee Puthanakit, 2018	Prospective Cohort	RAL	154	67(43.5%)	NR	NR
Martina L. Badell, 2019	Retrospective Cohort	EVG	134	109(81.3%)	NR	NR

UCT-uncontrolled clinical trial, RCT-randomized controlled trial, ADE-adverse drug event, SAE-serious adverse event, E-experimental, C-control, GA-gestational age, NR-not reported, VL- viral load

Six studies were selected for meta-analysis, with 330 subjects in the intervention group and 708 subjects in the control group. The analyses for viral load suppression rate for included studies are reported in Fig. 1 and Table 3. The pooled estimated effect for viral load suppression in the analyses of all studies didn't show significant treatment difference between the two therapeutic arms as observed in the forest plot (risk ratio 1.15, 95% CI 0.90–1.46, I^2=89%). Most studies are pointing towards the overall effect size and contribute equivalent weight for the overall effect. Funnel plots were not performed because when the number of studies is small (<10) the plot may not detect publication bias (26) (Fig 1).

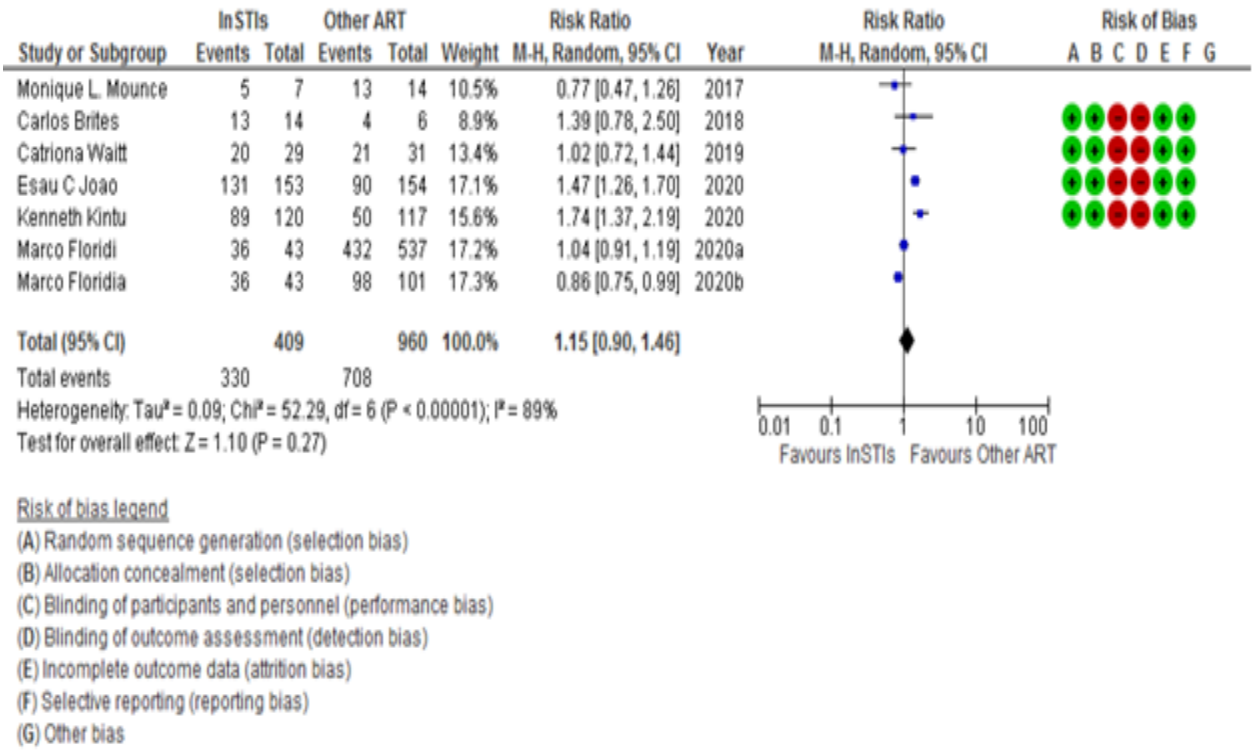


Fig.1: Forest plot for viral load suppression rate (green=low risk of bias, red=high risk of bias)

To explore possible source of heterogeneity subgroup analysis based on drugs in InSTIs class and sample size was determined. RAL based ART showed a lowered viral load suppression compared to the controls (risk ratio 1.46, 95% CI 1.27-1.69, I^2=0%) while DTG based ART (risk ratio 1.35, 95% CI 0.79-2.29, I^2=89%) and InSTIs whole class (risk ratio 0.93, 95% CI 0.79-1.09, I^2=53%) showed a favorable but non-significant risk ratio compared to controls. There was a high observed evidence of heterogeneity among the subgroups (I^2 = 88.3%) and statistically significant difference between these subgroups (p=0.0002).

The test for subgroup differences based on sample size indicates that there is no statistically significant subgroup effect (p = 0.37), suggesting that sample size does not modify the effect of InSTIs in comparison to other ART regimen. However, there is substantial unexplained heterogeneity between the trials within each of these subgroups (small sample size: I^2 = 15%; large sample size: I^2 = 94%) (Fig 2).

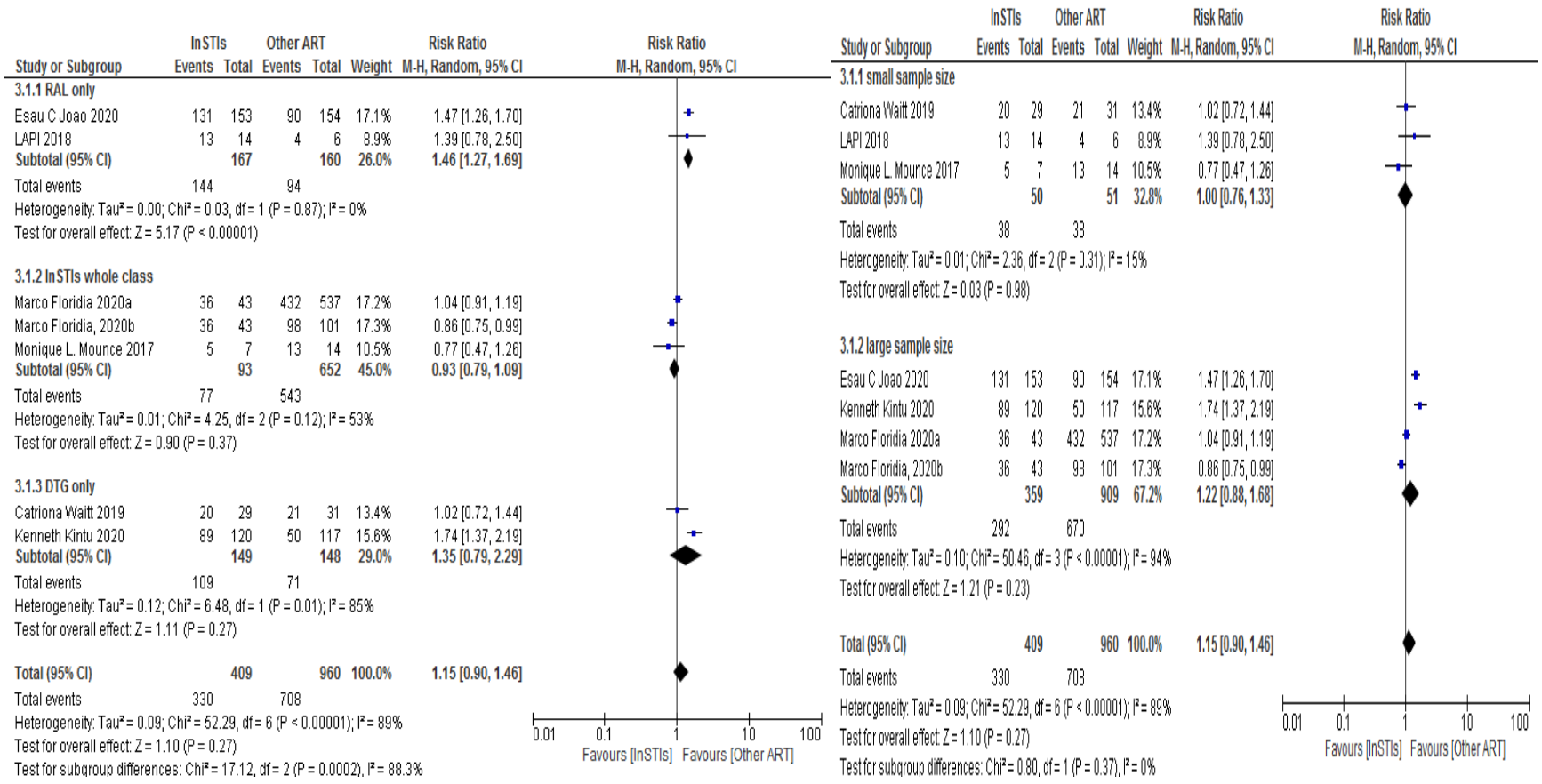


Fig. 2: Forest plot for Viral load rate based on drugs in the class and sample size subgroups

All articles included in the review showed that InSTIs would help achieve and maintain undetectable viral load at delivery. A retrospective cohort analysis of 92 HIV positive pregnant women showed more rapid viral suppression with an integrase inhibitor-containing regimen compared to women on non-integrase inhibitor based ART (17). A study which is included on the meta-analysis, compare InSTI (n=7) with PI (n=14), showed that out of the total pregnant women on InSTI 71.4% had undetectable VL at delivery (37); a study done by Grayhack *et al* also supported these findings with achievement of 74.2% undetectable VL at delivery (36). However there were no statistically significant differences between treatment groups with respect to the proportion of patients achieving VL suppression prior to delivery (71.4% vs. 92.9% for InSTI and PI, respectively, p = 0.247) (37).

Virologic outcome of DTG 50 mg once daily dosing was assessed in a retrospective cohort study of HIV positive pregnant women and children exposed to DTG at any stage of the pregnancy. Although 63.8% of the participants already had undetectable VL at the first sampling during pregnancy, of which 14/36 were on DTG based cART regimen before pregnancy and 22/36 were introduced to DTG at the indexed pregnancy, having DTG in their treatment regimen made 90% (27/30) of the women achieve and maintain undetectable VL at delivery (33). Out of the total HIV positive pregnant women who received DTG (n=10) and EVG (n=3) based ART during their gestational period, 92.3% achieved VL less than 40 copies /ml at delivery and 46.2% had CD4 count greater than 500 cells/mm^3 (39).

A study that enrolled twenty-nine pregnant women taking DTG 50mg once-daily, multicenter nonrandomized phase IV prospective study, the viral load was undetectable in 93% of the women during delivery (29). Moreover, an RCT study showed that the viral load was significantly lower in the DTG-ART arm compared with EFV-ART (p = 0.007), with analyses of log10 HIV RNA at 2 week post-partum (30).

Amongst the studies with raltegravir; a study that compare RAL 400 mg BID or ritonavir-boosted lopinavir as a standard drug in HIV-infected late-presenting pregnant women, which could not be incorporated in the meta-analysis, yields important additional information. With intention-to-treat analysis, the proportion of patients reaching virologic suppression at delivery was 76% and 25% in raltegravir group and lopinavir/ritonavir group respectively (RR = 3.1; 95%

CI: 1.3–7.4, p = 0.002) (31). Another non-randomized open label phase 4 multicenter study, conducted in 22 HIV infected pregnant women to determine safety and efficacy of raltegravir 400mg twice daily dosing, showed RAL in combination with other antiretroviral agents was effective in preventing MTCT by reducing and/or maintaining the HIV RNA load at an undetectable (<50 copies/mL) level in more than 86% of the participants (15).

Reltagravir initiation before pregnancy was associated with significantly higher rates of virologic control compared to initiations during the third trimester of pregnancy. The cohort analysis showed that plasma viral load was < 50 copies/mL at delivery in 82%, 55% and 56% of women when RAL was started before pregnancy, during the second trimester and during the third trimester, respectively (35). A significantly higher proportion of virologic suppression rate was seen with RAL based ART than with lopinavir/ritonavir based ART at weeks 2, 4, and 6; with all patients in RAL group compared with only 20% of lopinavir/ritonavir group achieving virologic suppression at week 6 (26).

A retrospective multicenter study of pregnant women living with HIV showed the earlier the EVG based ART regimen started during pregnancy, the higher the rate of viral suppression achieved (88.2%, 87.5%, 84.6% and 37.5% before pregnancy, first trimester, second trimester and third trimester, respectively) (32). HIV RNA at delivery was <50 copies/mL in 76% of women (40).

Three studies evaluated the ART duration for viral load reduction prior to delivery. A study done by Rahangdale *et al* showed that pregnant women on InSTI based ART had a shorter ART duration prior to delivery compared to those on non-InSTI based ART (35 (8-59) days for InSTI Vs 71 (47-86) days for non-InSTI based ART) (17). A cohort analysis by Monique L. *et al* also showed a trend of faster virologic suppression with InSTI based ART compared to the PI based ART (9.5 weeks for InSTI Vs 15.5 weeks for PI) (37).

4.3 Maternal Safety Outcome

Four RCT studies were selected for meta-analysis which reported maternal serious adverse event, consisting 95 subjects and 80 subjects in intervention and control group respectively. The result included DTG and RAL based ART comparing with other current standard care (risk ratio 1.30, 95% CI 0.84–2.02, I^2=32%). Furthermore we have conducted a subgroup analysis based on the class of drugs. DTG based ART showed a lowered maternal serious adverse event compared to control (risk ratio 1.94, 95% CI 1.13–3.32, I^2=0%). There was a high observed evidence of heterogeneity among the subgroups (I^2 = 76.7%) and statistically significant difference between these subgroups (p=0.04) (Fig 3).

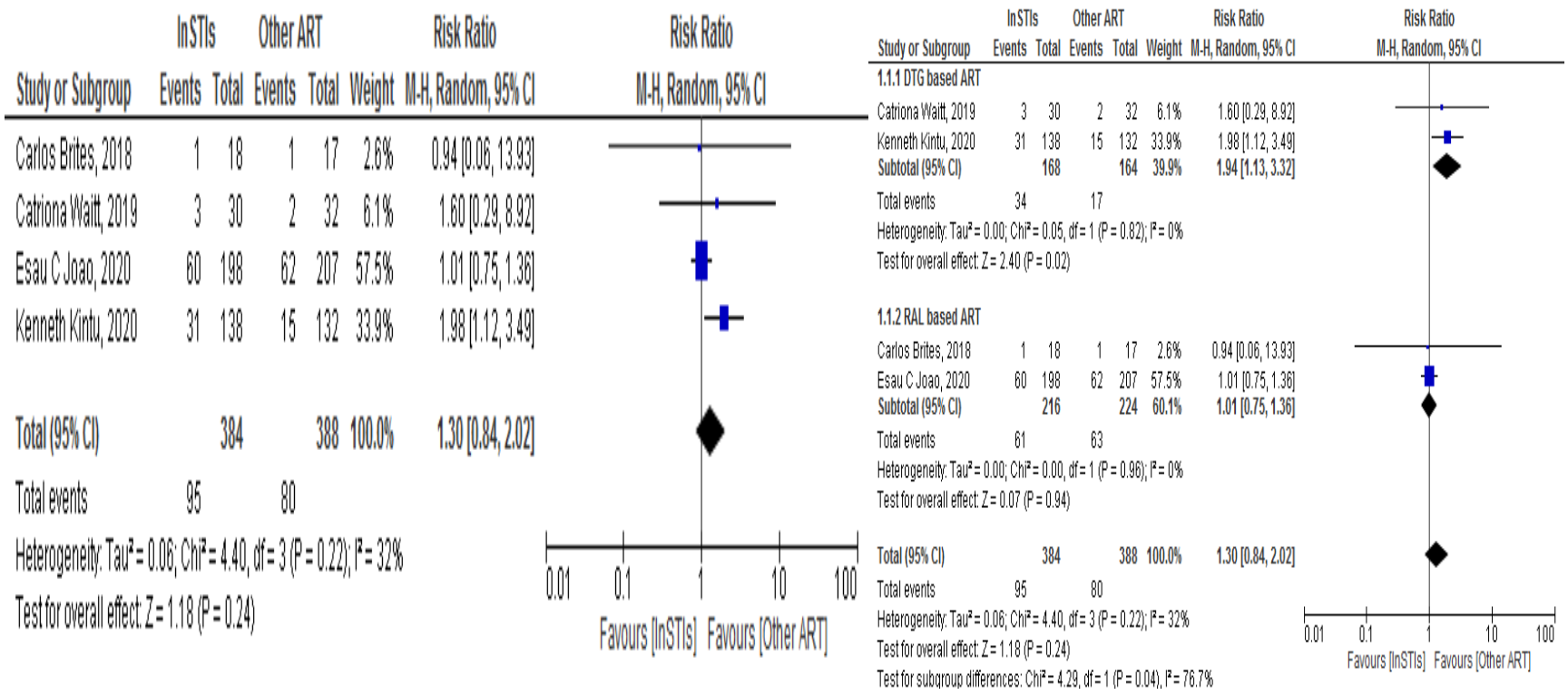


Fig. 3: Forest plot for maternal serious adverse event and subgroup analysis based on drug class

Majority of the pregnancies were completed without major complications. Common early pregnancy symptoms were reported for EVG and DTG based ART regimens with 10.3% and 3.4% of the participants, respectively (29,32). Adverse drug effects associated with EVG that were reported in more than 1 patient were upper extremity numbness (n = 3) and difficulty in swallowing the pill (n = 2). Among all included articles, one article reported hyperemesis gravidarum in 27 out of 36 women and a total of 4 cases of preeclampsia were diagnosed in late pregnancy for DTG 50 mg once daily dosing (29,33).

Except mild elevations of liver enzymes observed in seven cases of DTG based ART (33), there were no reported liver enzymes abnormalities in the single arm cohort study analysis (17,36,37). In a retrospective cohort study that matched 21 patients (7 InSTI and 14 PI), there was no significant difference with respect to ALT, AST and total bilirubin from baseline to delivery (37). In a trial that compared RAL with Lopinavir/ritonavir in late presenting pregnant women, the proportion of patients with grade 3 or 4 laboratory abnormalities was similar between the two arms, and did not require treatment modification (31).

A maternal outcome from mother–infant pairs using DTG for HIV treatment during pregnancy showed there was no new resistance developed while on DTG, and there were no documented side effects from DTG during pregnancy (36).

4.4 Infant Safety Outcome

Among the included studies for the meta-analysis, both preterm delivery and proportion of infants with Small for Gestational Age didn't show statistically significant association with the use of InSTIs and there were no evidence of heterogeneity between the included studies (risk ratio 0.82, 95% CI 0.60–1.13, I^2=0%) and (risk ratio 0.90, 95% CI 0.58–1.40, I^2=0%) respectively (Fig 4).

From included studies, higher preterm delivery (31.6%) is reported in cohort study that analyzes effect of DTG based ART (36). Around 20% and 19% of preterm delivery is also reported in cohort studies with EVG and RAL based ART respectively (32,35). One infant was delivered prematurely at GW 34 due to maternal preeclampsia and myelitis, from a mother who was on DTG based ART (33).

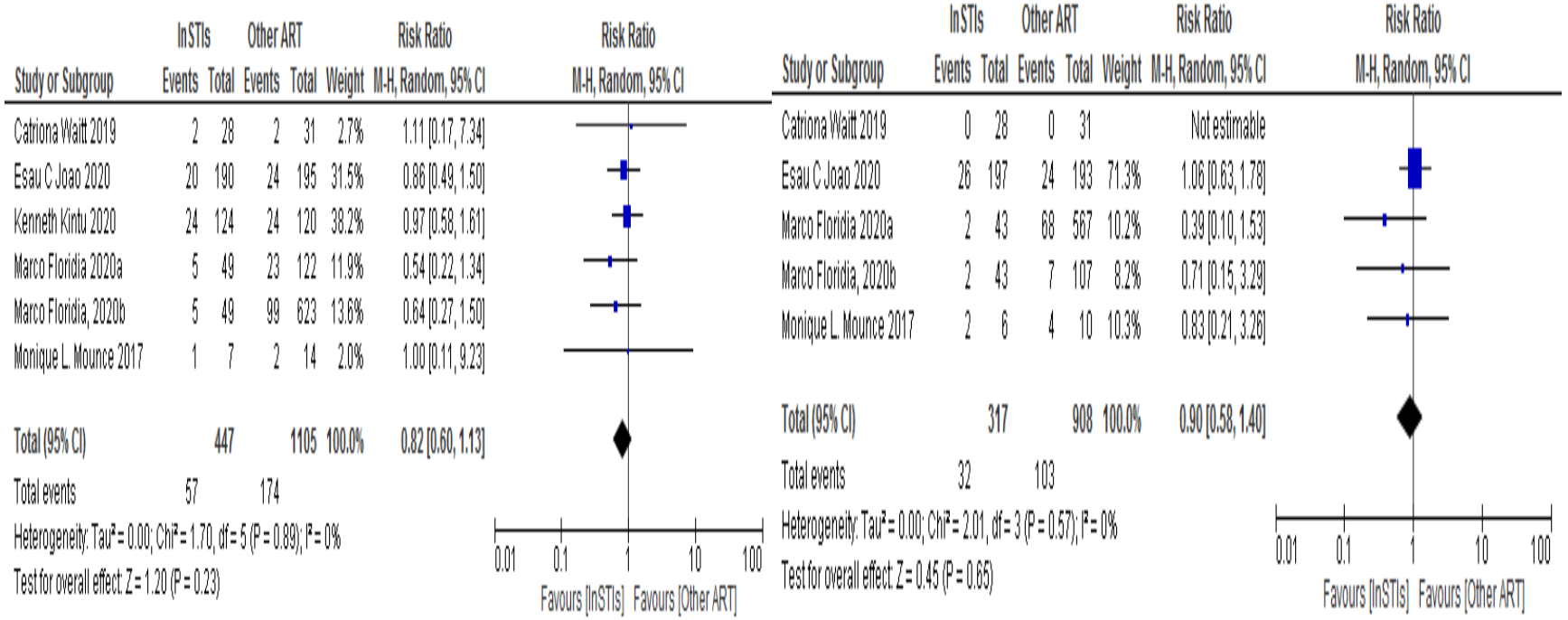


Fig.4: Forest plot for preterm delivered infants and infants with Small for Gestational Age

A maximum of 15.8% (n=9) and a minimum of 3.3% (n=1) infants with small for gestational age (SGA) was reported in the cohort studies, occurring form DTG based ART predominately. Mullign *et al* and Maren I *et al* RCT studies showed 31% (n=9) and 14% (n=3) SGA side effect in infants from mothers who were taking DTG and RAL, respectively (15,29), which was higher than the rate observed in the United States for children born from HIV-infected women (7.3%) (41).

Except one cohort study, evaluate mother-infant pair using DTG for HIV treatment during pregnancy reported 0% of NTD, all included study didn't report about NTD at all.

Among six studies (5 cohorts and 1 RCT) that assessed vertical transmission rate, three cohort studies reported 0.8%, 3.3% (DTG) and 3.9% (RAL) of HIV positive infants (32,33,38). The other three studies showed all infants tested negative for HIV (15,35,36). From five cohort studies that assessed birth defect (congenital anomalies) from InSTIs by prenatal ultrasound and physical examination, four infants had a birth defect: nonimmune hydrops fetalis, congenital heart abnormality, trisomy 21 and gastroschisis (36,38).

From the total studies included in this analysis three studies reported deaths of infants (one cohort and two RCT). The cohort study reported two deaths, one in utero and one in the neonatal period (38). From RCT studies two deaths from RAL vs EFV based ART study, one death from each group, and six deaths from DTG vs EFV based ART study, two (2%) from EFV and four (3%) from DTG based ART, was reported.

Renal abnormalities diagnosed by ultrasound in two infants were possibly related to dolutegravir exposure. One infant had an isolated renal cyst in the left kidney and another infant had a multi-cystic dysplastic right kidney, also diagnosed with cystic fibrosis and experienced numerous adverse events over the first months of life (29).

DISCUSSION

This is the first systematic review done on efficacy and safety of InSTIs in HIV positive pregnant women. We performed a systematic review on all published efficacy and safety data concerning integrase inhibitors in HIV positive women and meta-analyzed those studies with controlled arms based on the virologic outcome, maternal and infant safety outcomes. The endpoint of the included studies was the proportion of participants in each treatment group that achieved a viral load lower than 50 copies/mL during delivery, which was established by the US Food and Drug Administration, to define the time to loss of virological response (TLOVR) algorithm (42).

In pregnant women with advanced gestational age, time to reach undetectable viral load could be a concern as this may be the main risk determinant for HIV MTCT. Decreasing plasma viral load prior to delivery may modify the risk not only of infant HIV infection, but also of adverse maternal outcomes by decreasing the need for elective cesarean delivery (17,31).

It is critical that providers caring for HIV-infected pregnant women are aware of InSTIs use as a potential strategy for rapid virologic suppression in pregnancy, which are ideal at any gestational age to prevent both antepartum and intrapartum infections. Additionally, the potential role of InSTIs-containing regimens to rapidly reduce viral load in settings where maternal complications, preterm labor, or premature rupture of membranes may shorten pregnancy unexpectedly is appealing.

Based on the systematic review and meta-analyses data, treatment with InSTIs based ART regimens showed to be more beneficial for HIV positive pregnant women compared to other currently used treatment strategies. Although efavirenz plus two NRTIs as a backbone remains a safe and efficacious regimen for pregnant women, our review found that InSTIs effectiveness during pregnancy in terms of viral load suppression at delivery was superior, ranging from 43.5% to 93%, and this might mostly depended on baseline VL, the timing of InSTIs initiation and adherence. From data on 240 HIV infected women starting HAART during pregnancy, most pregnant women (73%) initiating HAART antenatally delivered with an undetectable viral load, and the remaining women delivered with a detectable but generally very low viral load (43).

Late ART initiation in pregnancy is a major concern as it is associated with a 7-fold higher risk of MTCT compared to women who initiated ART prior to 28 weeks of gestation (44). Two

cohort studies from the review showed that the earlier RAL or EVG based ART regimens started the higher the viral suppression rate is achieved during delivery, ranging from 88.2% to 37.5% when started before pregnancy and at third trimester respectively (29,32). However from the review most studies showed InSTI drugs, particularly RAL, have better viral load reduction for late presenter pregnant women. The British HIV Association (BHIVA) guidelines for the management of HIV-1 infection in pregnant women recommend use of a RAL based ART regimen for women who presented late after 28 weeks of pregnancy with an unknown VL or with a VL >100,000 copies/mL (45).

From our review evidences suggests that reltagravir and dolutegravir is superior to other ART combination regimens with respect to viral suppression, adverse effect and rates of discontinuation. With regard to achievement and maintenance of virologic suppression during delivery, there are differences among the InSTIs: dolutegravir being the most effective followed by raltegravir and elvitegravir. These findings were supported by systematic review and network meta-analysis which assessed comparative efficacy and safety of first line ARVs for treatment of HIV in adults and adolescents (46). A worldwide non-inferiority phase 3b RCT study on non-pregnant women showed 82% of participants in the DTG group compared with 71% in the atazanavir group had viral loads of less than 50 copies/mL at week 48 (mean difference 10.5%, 95% CI 3.1–17.8, p=0.005) (47).

Antiretroviral guideline for adult and adolescents 2019 panel, 2019 WHO recommendation on ART use and BHIVA 2018 guideline recommend, if women identify pregnancy after the first trimester or if the pregnancy is confirmed already past 8 weeks' gestation, it is not recommend switching from DTG rather it should be initiated or continued for the duration of the pregnancy (16,22,45). According to Ethiopian national guideline, DTG is excluded for childbearing women (<50 years) including pregnant and breastfeeding women because of potential risk to the fetus (13). The present review on studies that assessed efficacy and safety of DTG 400 mg suggests that it could be an important candidate for a first-line ART regimen for HIV positive pregnant women after first trimester. However, beside cohort studies, evidence for this finding is restricted to DoIPHIN 1 and DoIPHIN 2 RCT studies (28,30).

The pooled estimated effect for viral load suppression in the analyses of all studies didn't show statistically significant treatment difference between the two therapeutic arms. Although the pooled estimated effect for viral load suppression from the forest plot indicated a favorable effect for the control group, with high evidence for heterogeneity (I^2 = 89%, p <0.0001) among the studies, it should not be ignored the fact that most single arm cohort studies proves effectiveness of InSTIs for HIV positive pregnant women.

Even if the included studies in the review didn't report any neural-tube defects for the use of InSTIs during pregnancy, the TSEPAMO study done in Botwana reported 5 NTD (0.30% of deliveries) from1683 deliveries in which the mother was taking DTG at conception (48). Since development of neural tube occurs early during organogenesis, exposure window of interest for neural tube defects is narrow and theoretically before the end of the fourth week of gestation (49).

Although the etiology of NTDs is not clear yet several factors such as genetics, nutrition, folate deficiency, co-medications and environmental factors have been suggested. A study on the safety profile of InSTIs indicated that almost half of the women who conceived while they were on DTG were either not using folic acid or had no available data on its use, which seems like a significant gap in prevention of NTDs (20). All women on dolutegravir wishing to conceive, in whom a switch off dolutegravir is declined or is likely to result in treatment failure, should be started on folic acid 5 mg od based on the original Medical Research Council data on prevention of neural tube defects in the general population (45).

After the panel members weighed the updated data about DTG-associated risk of infant neural tube defects (NTDs) from Botswana, 2019 updated WHO recommendation list DTG as a preferred ARV drug throughout pregnancy and an alternative ARV drug for women who are trying to conceive. The members also state the important lack of comparable data about the risk of NTDs when using DTG in other settings, and what is known about the risk of NTDs and other adverse pregnancy outcomes, such as preterm birth, when using other preferred and alternative ARV drugs and drug combinations as reason for the use of DTG in pregnancy (22).

With a reason appear to be linked to the degree of immunosuppression, pregnant women with HIV-infection are at high risk of preterm birth (PTB <37 weeks), with 2–4-fold the risk of uninfected women (50). Most studies that have examined the relationship between the timing of cART initiation and preterm delivery have found that the risk increased in those either conceiving while on cART or taking it in the first trimester (45). Our review also revealed occurrence of preterm delivery and SGA for DTG and RAL based ART regimens. Since etiology of preterm remains imperfectly understood beside having InSTIs based ART regimen, socio-demographic characteristics, nutritional, medical, obstetric, and environmental factors may increase the risk of spontaneous preterm birth (41).

Even if some early reports have indicated that dolutegravir might have negative effects on liver function and the levels of liver enzymes (51) except one study, all included studies in the review couldn't able to confirm this. The observed variations in liver enzyme values are probably due to normal fluctuations in pregnancy (52).

The strength of the current systematic review is that it address timely and relevant clinical question, mainly the virologic efficacy of InSTIs ART regimens in pregnant women. We found high quality evidence related to the higher virologic efficacy of InSTI-containing ART compared to other non-InSTI containing ART in HIV positive pregnant women. For other outcomes such as occurrence of adverse events the available evidence is not conclusive. All the included clinical trial studies were open label, so the risk of detection or observer bias could be high. Most articles included in the review have small sample size which makes it difficult to detect rare events like NTD, preterm delivery and SGA. The other limitation was studies included in the review use different undetectable viral load cut of point and our review might have several limitations inherent to included retrospective cohort studies.

CONCLUSION AND RECOMMENDATIONS

There are several reasons outside of efficacy and safety for standard-dose efavirenz and protease inhibitor-based ART to continue being the favored first-line drug for HIV positive pregnant women worldwide; however, the reported benefits of integrase strand inhibitors, RAL and DTG mainly, signal the possibility for future change.

Although InSTI drugs have favorable safety profiles and rapid antiviral activity that make them preferable 1st line drug during pregnancy; clinical experience, safety data in pregnancy and regulatory approvals are required. We suggest use of DTG based ART regimen to be preferred first line choice for HIV positive pregnant women, if the pregnancy is confirmed already past 8 weeks of gestation (after development of neural tube). Although further investigation is necessary about safety data we suggest InSTI drugs, especially RAL, can be safely used during pregnancy particularly in late presenter pregnant women or as an intensification strategy.

Because of the short and long-term consequences of adverse events seen in infants, particularly preterm birth and SGA, future studies need to assess the safety profile of DTG for infants, and explore potential mechanisms of adverse outcomes.

Declarations of Interest

There is no conflict of interests

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ANNEX

I- Data Extraction Form

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Report title *(title of paper/ abstract/ report that data are extracted from)*	
Report author contact details	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Eligibility

Study Characteristics	**Review Inclusion Criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Yes/ No / Unclear**	**Location in text** *(pg & ¶/fig/table)*
Type of study	Randomised trial	...	
	Non-randomised trial	...	
	Controlled before-after study • Contemporaneous data collection • At least 2 intervention and 2 control clusters	...	
	Interrupted time series OR Repeated measures study • At least 3 timepoints before and	... ...	

Study Characteristics	**Review Inclusion Criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Yes/ No / Unclear**	**Location in text** *(pg & ¶/fig/table)*
	3 after the intervention • Clearly defined intervention point		
	Other design (specify):	...	
Participants		...	
Types of intervention		...	
Types of outcome measures		...	
Decision:	...		
Reason for exclusion			
Notes:			

Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶/fig/table)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶/fig/table)*
Notes:		

Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Aim of study		
Design *(e.g. parallel, crossover, non-RCT)*		
Unit of allocation *(by individuals, cluster/ groups or body parts)*		
Duration of participation *(from recruitment to last follow-up)*		
Notes:		

Participants

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomised *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Severity of illness		
Co-morbidities		
Other treatment received *(additional to study intervention)*		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

Intervention groups

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Description *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		
Resource requirements to replicate intervention *(e.g. staff numbers, cold chain, equipment)*		

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Notes:		

Outcomes.

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Outcome name		
Time points measured *(specify whether from start or end of intervention)*		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)*		
Person measuring/ reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
Notes:		

Results

	Description as stated in report/paper				Location in text *(pg & ¶/fig/table)*
Comparison					
Outcome					
Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results *Note whether:* **...** *post-intervention OR* **...** *change from baseline And whether* **...** *Adjusted OR* **...***Unadjusted*	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
Baseline data	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					

	Description as stated in report/paper		Location in text *(pg & ¶/fig/table)*
Unit of analysis *(e.g. by individuals, health professional, practice, hospital, community)*			
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*			
Reanalysis required? *(if yes, specify why, e.g. correlation adjustment)*	... *Yes/No/Unclear*		
Reanalysis possible?	... *Yes/No/Unclear*		
Reanalysed results			
Notes:			

Applicability

Have important populations been excluded from the study? *(consider disadvantaged populations, and possible differences in the intervention effect)*	... *Yes/No/Unclear*	
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	... *Yes/No/Unclear*	
Does the study directly	...	

address the review question? *(any issues of partial or indirect applicability)*	*Yes/No/Unclear*	
Notes:		

Other information

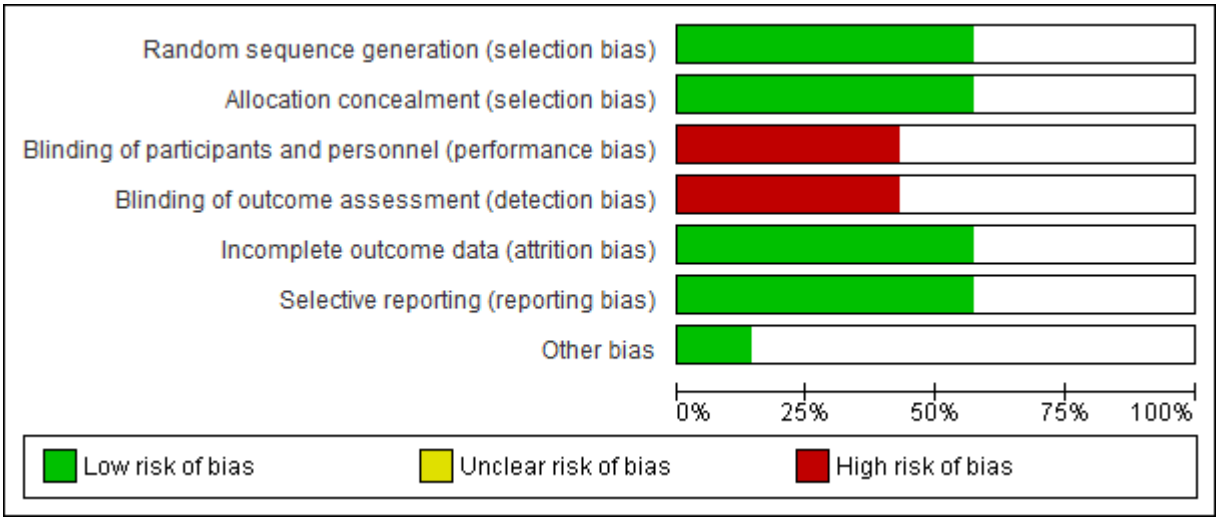
	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(what and from whom)*		
Further study information requested *(from whom, what and when)*		
Correspondence received *(from whom, what and when)*		
Notes:		

II Risk of Bias Assesssment Tool

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Selection bias Random sequence generation	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Random sequence generation method should produce comparable groups	Not described in sufficient detail	High Low Unclear	
Selection bias Allocation concealment	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	Intervention allocations likely could not have been foreseen in before or during enrollment	Not described in sufficient detail	High Low Unclear	
Reporting bias Selective reporting	Stated how the possibility of selective outcome reporting was examined by the authors and what was found	Reporting bias due to selective outcome reporting	Selective outcome reporting bias not detected	Insufficient information to permit judgment††	High Low Unclear	
Other bias Other sources of bias	Any important concerns about bias not addressed above*	Bias due to problems not covered elsewhere in the table	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias	High Low Unclear	

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Performance bias ***Blinding (participants and personnel)***	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Detection bias ***Blinding (outcome assessment)***	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Attrition bias ***Incomplete outcome data***	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment (e.g., number randomized not stated, no reasons for missing data provided)	**High** **Low** **Unclear**	

III Risk of bias graph for RCT studies



IV Study quality grade for cohort studies

Author, Year	**Study quality**
Riikka Bornhede, 2018	Selection 1a 2c 3a 4a Compatibility 1- Outcome 1b 2a 3b Score: 7
Clara Grayhack, 2018	Selection 1a 2a

	3a 4a Compatibility 1- Outcome 1b 2a 3b Score: 7
Bassam H. Rimawi, 2017	Selection 1b 2a 3a 4a Compatibility 1- Outcome 1a 2a 3a Score: 7
Lisa Rahangdale, 2016	Selection 1a 2a 3a 4a Compatibility 1-

	Outcome 1b 2a 3a Score: 7
Monique L. Mounce, 2017	Selection 1a 2a 3a 4a Compatibility 1a b Outcome 1b 2a 3a Score: 9
Pierre Gantner, 2019	Selection 1a 2a 3a 4a Compatibility 1- Outcome 1b 2a 3a Score: 7

Thanyawee Puthanakit, 2018	Selection 1a 2a 3a 4a Compatibility 1- Outcome 1b 2a 3a Score: 7
Martina L. Badell, 2019	Selection 1a 2a 3a 4a Compatibility 1- Outcome 1b 2a 3a Score: 7
Author, Year	**Study quality**
Riikka Bornhede, 2018	Selection 1a 2a 3a

	4a Compatibility 1a b Outcome 1b 2a 3b Score: 9
Clara Grayhack, 2018	Selection 1a 2a 3a 4a Compatibility 1a b Outcome 1b 2a 3b Score: 9
Bassam H. Rimawi, 2017	Selection 1b 2a 3a 4a Compatibility 1a b Outcome 1a

	2a 3a Score: 9
Lisa Rahangdale, 2016	Selection 1a 2a 3a 4a Compatibility 1a b Outcome 1b 2a 3a Score: 9
Monique L. Mounce, 2017	Selection 1a 2a 3a 4a Compatibility 1a b Outcome 1b 2a 3a Score: 9
Pierre Gantner,	Selection 1a

2019	2a 3a 4a Compatibility 1a b Outcome 1b 2a 3a Score: 9
Thanyawee Puthanakit, 2018	Selection 1a 2a 3a 4a Compatibility 1a b Outcome 1b 2a 3a Score: 9
Martina L. Badell, 2019	Selection 1a 2a 3a 4a Compatibility 1a

	b Outcome 1b 2a 3a Score: 9

This is to testify that the thesis paper prepared by Hiwot Getachew which is entitled with *"Efficacy and Safety Profile of Integrase Strand Transfer Inhibitors (INSTI) for treatment of HIV in Pregnant Women: Systematic Review and Meta-Analysis*" and submitted in partial fulfillment of the requirements for the degree of Master of Science in Clinical Trial complies with the regulations of the university and meets the accepted standards with respect to originality and quality.

Name: Hiwot Getachew Mekuria

Signature

Date of submission July 2020

Approved by

Advisors

1. Dr. Yimtubezinash Woldeamanuel Signature---------- Date July 2020
2. Prof. Eyasu Makonnen Signature----------Date July 2020

Examiners

1. Dr. Medhin Signature---------- Date July 2020
2. Dr. Getnet Yimer Signature---------- Date July 2020