Update on Adverse Effects of HIV Integrase Inhibitors

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Abstract
Purpose of review The goal of this paper is to provide an up-to-date review of adverse events related to the class of integrase strand transfer inhibitors (INSTIs), which became the class of choice in few years. We sought answers specifically to issues pertaining to neuropsychiatric adverse events, as well as weight gain, which were the two most important categories of adverse events raised in recent studies based on real-life experience. The primary focus of this paper is on adults with a brief summary on pregnant women and children/adolescents.
Recent findings Dolutegravir (DTG) bears the heaviest burden of neuropsychiatric side effects. Weight gain was reported with all INSTIs, although there are methodological caveats in the analyses and the findings need to be interpreted with caution. Moreover, due to recent findings on neural tube defects in infants exposed to dolutegravir during their peri-conception period, its use is not recommended for women of childbearing age without proper birth control method, while raltegravir remains the only drug which may be prescribed without caution. Given the importance of cognitive and metabolic co-morbidities in people living with HIV in regard to their quality of life, future research needs to focus on long-term effects of INSTIs in relation to these adverse events. Pharmacogenetics seems to be a promising tool. Safety during pregnancy is also another important issue to further clarify.
Summary INSTIs are a generally well-tolerated class of antiretrovirals (ARV), and has a

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higher antiviral potency compared to other classes of ARV. Clinicians and patients need however to be aware of some red flags when starting with and monitoring patients on INSTIs. All INSTIs can lead to mild increases in creatinine levels, usually without clinical significance, but caution is needed in patients with low eGFR (<30ml/min), when using other nephrotoxic drugs, such as as tenofovir disoproxil. Neuro-psychiatric (NP) effects are to be monitored with INSTIs, especially with DTG (though reports are at times contradictory); clinicians might want to avoid DTG for patients with history of severe NP symptoms, until clarity is provided. Weight gain was reported with all INSTIs, especially with DTG, with possible differential effects according to sex and ethnicity (female and non-white patients being at increased risk). This is worrying since patients from African descent are at higher risk of cardiovascular events and increased body mass index (BMI) can cause further increase metabolic risk. There is possibly an additional effect of tenofovir alafenamide (TAF) on weight increase.

Discrepancies between clinical trials – with low rates of adverse events – and reports from real-life settings might be due partly to under-representation of some groups of patients in clinical trials, and/or the short duration of follow-up, since some adverse effects may only occur after prolonged exposure.

Preliminary data on safety of bictegravir (BIC), from clinical trials and non-trial settings, are very reassuring and seem to show lower rates of adverse events compared to DTG. Elvitegravir/cobicistat (EVG/cobi) need to be used with caution in patients with other comorbidities given potential for polypharmacy, as it is the case for aging patients, because of the high potential of drug-drug interactions due to effects of the cobicistat booster. We are awaiting the release of cabotegravir (CAB), which could represent a good option for patients struggling with adherence, despite injection site reactions. Pharmacogenetics is a promising way to explore adverse effects occurrence in the INSTI class.

### Introduction

Over the past 40 years, remarkable advance in antiretroviral therapy (ART) has enabled people living with HIV (PLWH) to enjoy longer life expectancy and improved quality of life. Increasing options in drugs constituting the ART regimen allow a more personalized approach to choice of treatments, taking into account tolerability and risk of adverse events. Integrase strand transfer inhibitors (INSTIs), which block the integration of the viral genome into the host genome, are presently one of the most popular drugs used in first-line combination therapy, due to their high potency, good tolerability, low toxicity, and high genetic barrier to resistance, particularly the second-generation INSTIs [1–3].

Raltegravir (RAL) and elvitegravir (EVG) were the first INSTIs to be approved in 2007 and 2012, respectively [4, 5]. However, the emergence of resistance to RAL and EVG (thereby cross-resistance to each other) has been a challenge [1, 6], and subsequently second-generation INSTIs were developed: dolutegravir (DTG) was approved in 2013; bictegravir (BIC), formerly GS-9883, approved in the USA in February 2018; and cabotegravir (CAB), also known as GSK744, now in phase III of clinical development with an anticipated release in 2019 [7–9]. CAB, a structural analog of DTG, displays unique physicochemical and pharmacokinetic properties allowing the formulation to be used as a single oral tablet for daily dosing or as a long-acting nanosuspension for monthly to quarterly intramuscular injection.
INSTIs are generally well tolerated during real-world clinical use. Toxicity profiles for this class of drugs have included neurological, weight gain, and gastrointestinal symptoms [2, 8–10], and in the long-acting CAB, injection-site reactions [10]. Studies have reported INSTIs’ any adverse effect rates (proportions) as 5.7–7.6/100 person-years (3.6–5.8%) for RAL, 3.8–13.9/100 person-years (2.5–13.7%) for DTG [2, 11–13], and 4.4–10.3/100 person-years (3.4–12.3%) for EVG [2, 11–13]. Understanding the differences in adverse drug reaction profile between INSTIs can better inform personalized ART selection (Fig. 1).

Neuropsychiatric symptoms

Neuropsychiatric (NP) symptoms have been reported with all INSTIs, and their onset is usually described during the first few weeks after introduction. Symptoms include headaches, reduced concentration, anxiety, irritability, dizziness, insomnia, altered dreams, depression, unexplained pain, and more recently, mood changes (see Table 1).

In clinical trials, there were low and comparable rates of NP symptoms among patients receiving RAL, EVG-COBI, and DTG. However in real-life settings, findings about NP effects have been variable and at times contradictory, although several authors have reported higher rates of NP symptoms than in clinical trials (early or longer term symptoms, leading to discontinuations at times), especially among patients on DTG [21–25]. Reasons for these differences are likely two-tiered. Firstly, assessment of NP symptoms is often difficult, subject to inter-observer variations, and possibly observer bias depending on their awareness of NP effects. Secondly, many scales for the assessment of NP exist, rendering comparisons between studies or between clinical trials and real-life settings challenging especially since the numbers of subjects evaluated in trials are relatively small compared to studies in routine care settings once a drug is approved. The most salient issue for patients is to detect and minimize NP symptoms.
Insomnia is one of the most commonly reported neurologic symptoms associated with INSTI, although studies did not find significant differences between INSTI drugs. Murrell et al. [15••] and Wohl et al. [19] reported quite high occurrences of abnormal dreams, whereas these were rare during clinical trials.

Murrell et al. [15••] did not find any significant difference in rates of anxiety between drugs, but the observed rates were much higher (29.5%) than in clinical trials where they did not exceed 10%.

Headaches are often reported at the beginning of all antiretroviral (ARV) therapies, and they usually gradually disappear.

|                      | RAL % | EVG % | DTG % | Reference |
|----------------------|-------|-------|-------|-----------|
| Insomnia             | -     | -     | 8     | [14]      |
|                      | 30.4  | 8.7   | 19    | [15••]    |
|                      | 8.5   | 8.6   | 7.7   | [16]      |
|                      | -     | -     | 4     | [17]      |
|                      | 5     | -     | 6     | [18]      |
|                      | -     | 3.4   | -     | [19]      |
| Abnormal dreams      | 30.4  | 4.3   | 9.5   | [18]      |
|                      | -     | 4.6   | -     | [19]      |
| Anxiety              | -     | -     | 5     | [14]      |
|                      | 34.8  | 17.4  | 33.3  | [15••]    |
|                      | 10.2  | 6.8   | 6.6   | [16]      |
|                      | -     | -     | 2     | [17]      |
|                      | 6     | -     | 4     | [18]      |
| Headache             | -     | -     | 17    | [14]      |
|                      | 17.4  | 8.7   | 33.3  | [15••]    |
|                      | 13    |       | 14    | [18]      |
|                      | -     | 5.1   | -     | [19]      |
|                      | -     | -     | 3     | [17]      |
| Depression           | -     | -     | 6     | [14]      |
|                      | 14.1  | 9.5   | 10.1  | [16]      |
|                      | 2     | -     | 3     | [20]      |
|                      | -     | -     | 2     | [17]      |
|                      | 5     | -     | 7     | [18]      |
|                      | -     | 4.3   | -     | [19]      |
| Suicidality          | -     | -     | 2     | [14]      |
|                      | 0.2   | 0.2   | 0.1   | [16]      |
|                      | 1     | -     | < 1   | [18]      |
| NP side effects of any kind | 1.7   | 1.3   | 2.7   | [21]      |
The proportion reporting headache was substantially higher in Murrell’s study at one-third of patients (33%) on DTG, while other studies reported much lower estimates of 3% [17].

Moreover, some authors found risk factors associated with NP side effects with DTG, with higher risk among women, those aged 60 years and more and those who started abacavir (ABC) at the same time as DTG vs those who did not [11, 23, 26]. Some data on therapeutic drug monitoring suggest that morning dosing or reducing dosage of DTG could reduce the NP effects [26, 27].

Lastly, in a randomized clinical trial (RCT) led by Wohl et al. [28], patients reported more dizziness (6% vs 4%) and more sleep disorders (3% vs 1%) with DTG than with BIC respectively, without information on statistical significance.

Effects of INSTIs on the central nervous system are still being investigated, and new forms of assessments, such as brain integrity measurement, have started to appear [29]. This cross-sectional study showed a reduction of brain volume in patients taking INSTIs, as well as decreased performance in memory and learning, compared to patients not taking INSTIs [29]. Recently, pharmacogenetics analysis showed several single nucleotide polymorphisms associated with some adverse events with INSTIs, paving the way for future research on precision medicine [15]. Indeed, high inter-individual variations in drug concentrations (and thus risk of adverse events) could be related to inter-individual difference in pharmacokinetics.

Weight gain

PLWH are at higher risk of cardiovascular disease when compared with the HIV-uninfected population [14, 24]. There is no direct correlation between higher body mass index (BMI) and risk of myocardial infarction in PLWH, but higher BMI is a recognized risk factor for diabetes mellitus, which is a known risk factor for myocardial infarction in the general population and in PLWH [16, 18]. Weight gain and BMI increase are central issues in PLWH, who need to reduce the risk of metabolic disease.

Some reports have highlighted a possible role of DTG in weight gain [20] and of RAL in body fat composition changes [30]. This leads to question the potential class effect of INSTIs in fat gain.

Two RCTs comparing BIC to DTG [28, 31] both reported an increase in body weight ranging from 2.4 to 3.9 kg, for BIC or DTG, at week 96. Information collected through the SCOLTA cohort [24] revealed a significant 1-year BMI increase in patients treated with DTG ($p = 0.004$), RAL ($p = 0.0004$), and EVG ($p = 0.004$). At 1 year, patients in Centers for Disease Control (CDC) stages A and B experienced a mean BMI increase of 0.13 ($\pm$ 0.06), significantly associated with low baseline BMI ($p = 0.002$) and older age ($p = 0.0007$) at start of treatment. As compared with DRV, RAL patients had a significantly lower BMI modification ($p = 0.038$). Focusing instead on patients in CDC stage C, the mean BMI increase at 1 year was 0.46 ($\pm$ 0.08) and was associated with lower BMI ($p = 0.005$) and lower CD4+ T cell count ($p = 0.007$) at enrollment. Previous study demonstrated that the greatest increase in BMI occurred during the first year of ARV therapy [32], while SCOLTA cohort demonstrated a significant increase in BMI even in patients who had already been treated for more than 3 years before switching to INSTI-including regimen.
These findings need to be interpreted against the general population data, in which a BMI increase over time was found more likely in people with normal BMI or overweight [33]. In contrast, among PLWH, a higher BMI gain was found in those who had lower baseline BMI values [24]. One of the hypotheses could be that PLWH with lower CD4 count at baseline might have lost weight as a result of various inflammatory marker effects on metabolism before starting the ART (effect of “return to healthy status”).

Studies reporting BMI changes after enrollment of treatment-naïve patients need to consider their baseline weight before disease progression, even if these self-reported data are more subjective. Alternatively, studies on weight gain in treatment experience patients switching to INSTI-based regimens could be easier to interpret.

Norwood et al. looked at BMI changes when patients switched from efavirenz to an INSTI-containing regimen [20]. In their retrospective observational study, the authors found a significant increase in BMI after switching to any INSTI, with the greatest change in DTG-containing regimens. Hill et al. pooled data from 4 observational studies (France, Brazil, and 2 in the USA) and reported a significant increase in body weight for patients initiating on or switching to INSTIs. This increase was particularly evident in women (especially non-white) and among patients on an ABC-containing INSTI regimen.

In summary, weight gain seems to be a significant issue for all INSTIs although patients with lipoatrophy could benefit from a switch to INSTIs, as showed in a study by Domingo et al. [35].

### Metabolic disorders

#### Glucose metabolism

Abnormally high fibroblast growth factor 21 (FGF21) levels are considered a marker of disturbed metabolism in non-HIV-infected patients with obesity, diabetes, or congenital lipodystrophy [36–38], whereas betaKlotho (KLB) repression is associated with an impairment of glucose uptake and other health effects mediated by FGF21 [39]. Studies in distinct HIV patient cohorts have consistently reported that elevated FGF21 levels are associated with indicators of insulin resistance, insulinemia, and glycemia [38, 40, 41]. Lifestyle interventions in HIV patients that achieve metabolic improvement are also associated with a decline in FGF21 levels that correlates with indications of improved energy metabolism [40].

EVG induces FGF21 and represses KLB, eliciting ER stress/oxidative stress. Other INSTIs are neutral toward the FGF21/KLB system [42*].

Norwood et al. [20] also found a non-significant increase in Hb A1c level when switching from EFV to an INSTI regimen. In contrast, Calza et al. [43] reported reassuring data with over 10-year follow-up, with a significant decrease in homeostasis model assessment (HOMA) of insulin resistance index after a switch from PI/r to INSTIs.

#### Lipid metabolism

The SPIRAL study [44], which switched patients from PI/r to RAL-based regimens, reported better lipid profile at 48 weeks and significant improvements in
several cardiovascular biomarkers associated with inflammation, insulin resistance, and hypercoagulability resulting in reduction of risk for coronary heart disease. In 2 RCTs comparing BIC vs DTG (with similar or same backbone nucleoside reverse transcriptase inhibitors (NRTIs)), at week 96, larger increases from baseline in total and low-density lipoprotein cholesterol rates were reported for patients on BIC compared to DTG, but the introduction of lipid-modifying drugs was very low (< 5%) [31], and not different between BIC and DTG [28, 31].

Hepatic outcome

Neither alkaline phosphatase (ALP) nor alanine aminotransferase (ALT) level outside the normal range was reported among patients on INSTIs, which suggests that this class of drugs may not significantly modify transaminases unless other factors are involved [45]. In a study by Tebas et al., DTG, when co-administered with ABC and lamivudine, was shown to increase ALP by 50% from baseline at 144 weeks [46]. Additionally, when switching from an efavirenz to a RAL-based regimen, serum ALP significantly decreased in the RAL group compared to the efavirenz group at 24 weeks [47]. Similarly, none of the grade 3 and 4 liver abnormalities were related to study drugs BIC and DTG, in 2 RCTs [28, 31].

Renal outcome

All INSTIs have been associated with an increase in creatinine levels. In vitro data have shown DTG to inhibit organic cation transporter 2 (OCT2) on the basolateral side of proximal tubular cells [48]. Therefore, DTG can block tubular uptake of creatinine from the blood, leading to increased serum creatinine and decreased eGFR or CrCl, without changing effective GFR [49]. In the SPRING-2 trial, during the first 2 and 3 weeks of treatment, the mean estimated CrCl decreased by 16.5 mL/min in the DTG group compared with 5.4 mL/min in the RAL group at the end of weeks 4 and 5, without proteinuria (ratio proteinuria to creatinuria) in both groups [5]. This change was non-progressive. The VIKING trial [50], which assessed the effectiveness of additional DTG in patients who failed to suppress HIV replication, reported a non-progressive creatinine increase (12.38 mmol/L for both cohorts, 50 mg of DTG once-daily dose and twice-daily regimen), plateauing at 4 weeks after initiation of therapy. The SPRING-2 study showed a small increase in the mean serum creatinine of 8.2 mmol (with a decrease in mean creatinine clearance (CrCl) of 9.3 mL/min) but no evidence of any proteinuria in RAL-treated patients after 48 weeks of therapy [5]. The SAILING study [51] exhibited similar small increases in creatinine at week 2, approximately 4 and 10 mmol/L in the RAL and DTG treatment arms, respectively, that remained stable for the duration of the 48-week trial.

It has been suggested, given the similarities, that RAL may have an effect on tubular function similar to that of DTG. However, in a study of Gupta et al. [48], 30 individuals who switched from EFV to RAL presented an increased serum creatinine and cystatin C, as well as a decrease in GFR (measured by cystatin C clearance) by 8.50 mL/min/1.73 m² in the switch group. This finding might
suggest a possible genuine reduction in renal function rather than an effect on creatinine by renal tubular cells. Furthermore, unlike DTG, RAL has no effect on OCT2.

There is no difference in renal function between EVG boosted with ritonavir and RAL with a median decrease in eGFR from baseline to 96 weeks of 10.8 mL/min/1.73 m² in the EVG arm compared to 11.7 mL/min/1.73 m² for RAL, and with no documented formal renal adverse effects [52]. As for cobicistat (COBI), it inhibits the tubular secretion of creatinine and a rise in serum creatinine is expected, with no effect on the actual GFR [53].

BIC and DTG seem to lead to similar decrease in eGFR at week 96 in a RCT comparing BIC/FTC/TAF vs DTG/FTC/TAF [31].

In summary, clinicians should monitor closely the renal function for abnormal decrease in eGFR, as compared to an expected decrease of approximately 10 mL/min/1.73 m². Unfortunately, there is currently no alternative way of routinely assessing renal function that would not be affected by INSTI and COBI.

Rhabdomyolysis

RAL-based therapy is the only INSTI associated with a higher prevalence of symptomatic skeletal muscle toxicity, which does not seem to be concentration or time dependent, nor associated with elevated CK. Proximal myopathy may be an uncommon but authentic side effect of RAL exposure [54].

Gastrointestinal outcome

Diarrhea was reported in 18% of RAL subjects [51], while the STARTMRK study reported 1.0% [55]. Eighteen percent of patients receiving DTG in the FLAMINGO trial [45] and 20% in the SAILING study [51] experienced diarrhea, whereas this rate was only 5% with DTG/ABC/3TC [17]. The occurrence of diarrhea reported for EVG/FTC/TDF was respectively of 25% and 26% at 96 and 144 weeks [19] and in LATTE-2, 20% in the oral group (CAB/ABC/3TC) and 28% in the monthly injectable group (CAB/RPV) [7]. With an overall occurrence of diarrhea in 29.5% of subjects, RAL, EVG, and DTG grouping yielded 30.4%, 26.1%, and 30.9%, respectively, without association with a particular regimen, in Murrell's observational study (p = 0.955) [15].

Nausea has been previously reported in 8% of RAL subjects in SAILING study [51] and 3% in the STARTMRK results [55]. In the FLAMINGO study [45], nausea was present in 17% of subjects receiving DTG and 2% in a DTG/ABC/3TC regimen [17]. EVG/FTC/TDF showed 22% (96 weeks) and 23% (144 weeks) occurrence of nausea [19] and in LATTE-2 in 16% in both oral and intramuscular groups [7]. Murrell et al. [15] reported that nearly one in five subjects (18.2%) experienced nausea. DTG group exhibited slightly higher occurrence at 23.8%, while EVG and RAL tied at 13.0%. No significant difference (p = 0.459) was found between regimen and nausea occurrence.

The trial "1475" was 60 weeks of blind induction with BIC/FTC/TAF or DTG/FTC/TAF, followed by a continuation with/switch to BIC/FTC/TAF, with a total of 91 enrolled persons. At week 72, among 30 participants who switched from DTG to BIC, there was only 1 diarrhea and 1 nausea events (grade 1), related to BIC, without treatment discontinuation [9].
Stellbrink et al. [31] reported fewer gastrointestinal adverse effects in patients receiving BIC, compared to DTG, in their 96-week RCT (9% vs 14%, without statistical significance). Wohl et al. [28] also reported significantly fewer gastrointestinal adverse events with BIC compared to DTG, especially for nausea (6% vs 17%, \( p < 0.0001 \)).

**Aging patients**

Abnormal platelet count is a predictor of mortality in the elderly [56]. In the SPIRAL trial [44], a switch from PI/r to RAL led to a slight reduction of platelet count over time of follow-up (mean values, from 240,936/mm\(^3\) to 200,731/mm\(^3\), \( p = 0.02 \)). The result remained statistically significant when hepatitis B and C co-infected patients were excluded from the analysis (mean values, from 230,300/mm\(^3\) to 197,125/mm\(^3\), \( p = 0.04 \)). Ral-Age study [57] reported that switching to a RAL-containing regimen in PLWH over 60 years old showed a statistically significant reduction of median values of triglycerides (\( p = 0.0001 \)) as well as of cholesterol at 36 months of follow-up (\( p = 0.0023 \)). Significantly increased dosages of DTG were found in patients 60 years [26], potentially explaining reported association between age and DTG NP effects.

**Drug–drug interactions**

RAL is better absorbed in an environment at higher pH. Combined use of omeprazole and RAL in healthy subjects led to a 212% increase of RAL plasma concentrations [51], but it is not expected that concomitant omeprazole use will lead to a lower tolerability of RAL. PLWA often have achlorhydria or hypochlorhydria, and hence the effect of any acid-reducing agent may be less compared to a healthy volunteer.

Dose adjustment is needed only when INSTI is taken with rifampin, where a dose increase of RAL to 800 mg BID is advised, and with unboosted atazanavir, where a dose increase of atazanavir to 600 mg QD or 300 mg BID is recommended [59].

DTG has an excellent profile in terms of drug interactions. Metformin constitutes one of the exceptions, with a significant increase in metformin levels when co-administered with DTG [60]. This should prompt clinicians to closely monitor lactic acidosis symptoms when prescribing both drugs and US Prescribing Information suggests limiting the total daily dose of metformin to 1000 mg.

COBI is a potent inhibitor of cytochrome P450 (CYP) 3A, of which its role is the elimination of several drugs [61], therefore taking pharmokinetic advantage as a booster, to decrease EVG administration. As such, EVG/COBI has important restrictions in terms of co-medications, albeit with lower potency of inhibition than ritonavir [61]. Examples of contraindicated drugs are simvastatin and risks of rhabdomyolysis and the need for dose adjustments with direct oral anticoagulants. Interactions need to be checked upon initiation or switch to these drugs, for instance on the Liverpool website (https://www.hiv-druginteractions.org/). This issue is particularly important in aging patients, who usually have co-morbidities. A study by Demessine et al. showed a significantly higher drug–
drug interaction–induced direct and indirect care costs in case of EVG/COBI,
compared to other INSTIs [62].

BIC inhibits 2 transporters implied in renal excretion (OCT2 and MATE1). It
may thus increase concentrations of drugs eliminated by the same transporters,
such as dofetilide, an antiarrhythmic drug. Metformin dosage might also in-
crease with BIC, though of less clinical significance than with DTG [63]. BIC is
not recommended to be co-administered with rifampicin or rifabutin, since BIC
Cthrough might drop significantly [59].

General symptoms

Murrell et al. [15••] reported in an observational study with long-term follow-
up on INSTI, occurrence of fatigue at 33.0% in the whole INSTI group, 34.8% for
RAL, 33.3% for DTG, and 30.4% for EVG (p = 1.000). In other studies,
fatigue was reported in RAL subjects in 1% [55], 7% [51], and 3.9% [45]; in
DTG group 6% [45] and 4% [51]; in EVG/FTC/TDF in 13% and 15% of subjects
at 96 weeks and 144 weeks, respectively [19].

INSTIs and pregnancy

Until recently, only 400 mg of BID RAL and DTG was recommended during
pregnancy and/or for childbearing age women living with HIV, due to their
pharmacokinetic properties and their “clinical relevance.”

The report of increased rate of neural tube defects (NTD) among women
exposed to DTG in the periconception period in Botswana (0.94% [64••];
0.67% Tsepamo Study [65]; vs 0.12% in women not exposed to DTG [64••])
led the World Health Organization (WHO) to recommend avoiding DTG in
potential childbearing aged women wishing to become pregnant [66]. Howev-
er, a modeling study [67] based on data from a randomized trial in Cameroon
[68] concluded that DTG + NRTI regime, due to its strong genetic barrier and
good tolerability, was the most cost-effective regimen for the prevention of
AIDS-related deaths and for the prevention of mother-to-child HIV transmis-
sion in low- and medium-income countries, even after taking into account the
NTD occurrence [67]. While we wait for updated data from the Botswana
Tsepamo study relating to NTD occurrence, access to/use of DTG among
women of childbearing age varies widely across countries and the public health
policies and guidelines in place.

Given the expected decrease in exposure and/or increased clearance of EVG
during pregnancy especially in the second and third trimesters, this drug is not
recommended in pregnant women living with HIV [69–71].

Long-acting CAB and its potential decreased exposure would limit its use in
pregnant women [69]. BIC Cthrough is likely to be reached during the pregnancy,
and further prospective evaluations are necessary to prove that pregnancy “does
not affect BIC protein binding” [69, ]. Since NTD might be a class effect, caution
is needed also with BIC [63].

Peri-conception exposure to RAL is not associated with NTD and therefore
remains the only INSTI recommended in high-income countries for women
during the peri-conceptional period or during pregnancy (DHHS (USA), the
European AIDS Clinical Society [] and Canadian guidelines [74]). Further trials
on efficacy and tolerability are needed on the use of RAL QD 1200 mg in this population [69].

**INSTIs in children and adolescents**

Data in this group of patients are still scarce, but are expected to increase given the WHO recommendation to position DTG as the preferred first-line regimen for children and adolescents in low- and middle-income countries. IMPACT P1066 is a phase 1/2 open-label, non-randomized multicenter trial, following 122 children living with HIV, aged from 4 weeks to 18 years old for 240 weeks. They all received RAL BID adults' tablets, chewable tablets, or granules for oral suspension according to their age and weight. One patient had a transient liver function enzyme elevation that was possibly related to treatment and resolved without study’s drug discontinuation. Two participants (1%) had a drug-related allergic rash: one of them was grade 3 at day 7, and had to discontinue the study because of an adverse event [75].

No adverse effect was related to DTG at 48 and 144 weeks in IMPACT P1093 trial, which enrolled 22 treatment experienced adolescents living with HIV [76, 77]. ODYSSEY is a large multi-country trial evaluating the safety and efficacy of DTG-based regimen for the first or second ART as compared to standard of care in 700 children and adolescents. While the main trial is ongoing, the nested PK study has reported no grade 3 or 4 adverse effects in 15 children from Uganda and Zimbabwe receiving 50 mg and 30 mg film-coated DTG in lower weight bands (20–25 kg) [78]. In routine care settings, a French multicenter retrospective study of 50 adolescents beginning DTG between January 2014 and December 2015 described two patients (4%) who experienced NP side effects during follow-up: moderate headache and dizziness, without treatment cessation in one case; and one severe case of dizziness (grade 4), sleeping disorders, and anxiety, resolved with DTG discontinuation []. A National Collaborative UK and Ireland ART children and adolescent study (CHIPS) reported, among 406 children who were introduced INSTI, there were low rates of toxicity/discontinuation and no change in BMI/z score on DTG but an increase on RAL [80].

**Injection-site reactions**

Injection-site pain was the most frequently reported adverse event of CAB in the LATTE-2 study [7]. Most injection-site reactions were mild or moderate in intensity, with median symptom duration of 3 days. Although injection-site reactions were common, they did not appear to compromise high levels of patient-reported satisfaction, with very few withdrawals resulting from injection-site reactions, two patients (≤ 1%) through 96 weeks.

**Conclusions**

Taken together, studies affirm that all INSTIs are generally well tolerated, although side-effect profiles differ between drugs. Persons who experience adverse effects with one INSTI may tolerate an alternative drug in this class; however, switching from one INSTI to another may result in new side effects.
Comparisons of older and newer drugs can be confounded by shorter follow-up times for newer agents and changing prescribing patterns over time. NRTIs in the backbone regimen might also constitute a confounding factor in analyzing the adverse events.

Rare adverse events may be related to extended use of INSTIs, and long-term follow-up on INSTI are warranted to capture such events.

Future research including precision medicine (i.e., pharmacogenetics) might help in the future in choosing the best INSI to prescribe for an individual patient.

Compliance with Ethical Standards

Conflict of Interest
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References and Recommended Reading
Papers of particular interest, published recently, have been highlighted as:

1. Anstett K, Brenner B, Mesplede T, Wainberg MA. HIV drug resistance against strand transfer integrase inhibitors. Retrovirology. 2017. https://doi.org/10.1186/s12977-017-0360-7.
2. Elzi L, Erb S, Furrer H, Cavassini M, Calmy A, Vernazza P, et al. Adverse events of raltegravir and dolutegravir. AIDS. 2017;31:1853–8.
3. Brenner BG, Wainberg MA. Clinical benefit of dolutegravir in HIV-1 management related to the high genetic barrier to drug resistance. Virus Res. 2017;239:1–9.
4. Shimura K, Kodama E, Sakagami Y, et al. Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). J Virol. 2008;82:764–74.
5. Grinsztejn B, Nguyen B-Y, Katlama C, Gatell JM, Lazzarin A, Gonzalez CJ, Chen J, Harvey CM, Isaacs RD (2007) Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. 369:9
6. Mesplede T, Quashie PK, Zanichelli V, Wainberg MA. Integrase strand transfer inhibitors in the management of HIV-positive individuals. Ann Med. 2014;46:123–9.
7. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine
in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet. 2017;390:1499–510.

8. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390:2063–72.

9. Sax PE, DeJesus E, Crofoot G, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. Lancet HIV. 2017;4:e154–60.

10. Margolis DA, Brinson CC, Smith GHR, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Infect Dis. 2015;15:1145–55.

11. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink H-J, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017;18:56–63.

12. Peñafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. J Antimicrob Chemother. 2017;72:1752–9.

13. Cid-Silva P, Llibre JM, Fernández-Bargiela N, Margusino-Framiñán L, Balboa-Barreiro V, Pernas-Souto B, et al. Clinical experience with the integrase inhibitors dolutegravir and elvitegravir in HIV-infected patients: efficacy, safety and tolerance. Basic Clin Pharmacol Toxicol. 2017;121:442–6.

14. Armah KA, Chang C-CH, Baker JV, et al. Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans. Clin Infect Dis. 2014;58:121–9.

15. Murrell DE, Cluck DB, Moorman JP, Brown SD, Wang K-S, Duffourc MM, et al. HIV integrase inhibitor pharmacogenetics: an exploratory study. Clin Drug Investig. 2019;39:285–99.

16. Freiberg MS, Chang C-CH, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med. 2013;173:614.

17. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369:1807–18.

18. Womack JA, Chang CH, So-Armah KA, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc. 2014. https://doi.org/10.1161/JAHA.114.001305.

19. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/EMtricitabine/Tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr. 2014;65:e118–20.

20. Norwood J, Turner M, Bofill C, et al (2018) Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. 10

21. Cuzin L, Pugliese P, Katlama C, et al. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. J Antimicrob Chemother. 2019;74:754–60.

22. de Boer MGJ, van den Berk GEL, van Holten N, Orszucyn JE, Doraima W, Moha DA, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS. 2016;30:2831–4.

23. Cailhul J, Rouver C, Alloui C, Jeantils V. Dolutegravir and neuropsychiatric adverse events: a continuing debate. AIDS. 2017;31:2023–4.

24. Bonfanti P, Martinelli C, Ricci E, Carradori S, Parruti G, Armignacco O, et al. An Italian approach to postmarketing monitoring: preliminary results from the SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) project on the safety of lopinavir/ritonavir. J Acquir Immune Defic Syndr. 2005;39:317–20.

25. Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. AIDS. 2017;31:1201–3.

26. Elliot ER, Wang X, Singh S, Simmons B, Vera JH, Miller RF, Fitzpatrick C, Moyle G, McClure M, Boffito M. Increased dolutegravir peak concentrations in people living with HIV aged 60 and over and analysis of sleep quality and cognition. n.d. 30

27. Parant F, Mialilhes P, Brunel F, Gagnieu M-C. Dolutegravir-related neurological adverse events: a case report of successful management with therapeutic drug monitoring. Curr Drug Saf. 2018;13:69–71.

28. Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2019. https://doi.org/10.1016/S2352-3018(19)30077-3.

29. O’Halloran JA, Cooley SA, Strain JF, Boerwinkle A, Paul R, Presti RM, et al. Altered neuropsychological performance and reduced brain volumetrics in people living with HIV on integrase strand transfer inhibitors. AIDS. 2019;1:1477–1483.

30. McComsey GA, Moser C, Currier J, Ribaudo HJ, Paczuski P, Dubé MP, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. Clin Infect Dis. 2016;62:853–62.

31. Stellbrink H-J, Arribas JR, Stephens IL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2019. https://doi.org/10.1016/S2352-3018(19)30080-3.

32. Koethe JR, Jenkins CA, Lau B, et al. Rising obesity prevalence and weight gain among adults starting...
antiretroviral therapy in the United States and Canada. AIDS Res Hum Retrovir. 2016;32:50–8.
33. Stenholm S, Vahtera J, Kawachi I, Pentti J, Halonen I, Westerlund H, et al. Patterns of weight gain in middle-aged and older US adults, 1992–2010. Epidemiology. 2015;26:165–8.
34. Hill A, Waters I, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad. 2019 Jan 1;5(1):41–43.
35. Domingo P, del Gutierrez M, Gallego-Escuredo JM, et al. Effects of switching from stavudine to raltegravir on subcutaneous adipose tissue in HIV-infected patients with HIV/HAART-Associated Lipodystrophy Syndrome (HALS). A Clinical and Molecular Study. PLoS One. 2014;9:e89088.
36. Zhang X, Yeung DCY, Karpisek M, et al. Serum FGF21 levels are increased in Obesity and are independently associated with the metabolic syndrome in humans. Diabetes. 2008;57:1246–53.
37. Gallego-Escuredo JM, Gómez-Ambrosi J, Catalan AM, et al. Reciprocal effects of antiretroviral drugs used to treat HIV infection on subcutaneous adipose tissue in HIV-infected patients with HIV-1 infection: A randomized, open-label, phase 3b study. Lancet HIV. 2015;2:e127–36.
38. Miehlke K, Ebert T, Kralisch S, Hoffmann A, Kratzsch J, Schlögl H, et al. Serum concentrations of fibroblast growth factor 21 are elevated in patients with congenital or acquired lipodystrophy. Cytokine. 2016;83:239–44.
39. Díaz-Delfín J, Hondares E, Iglesias R, Giralt M, Caelles E, et al. Improvement in insulin sensitivity and composite alterations in FGF21 and FGF19 levels and expression of JNK1 in the FGF21 pathway. Endocrinology. 2012;153:4238–45.
40. Srinivasa S, Wong K, Fitch KV, Wei J, Petrow E, Cypess AM, et al. Effects of lifestyle modification and metformin on irisin and FGF21 among HIV-infected subjects with the metabolic syndrome. Clin Endocrinol. 2015;82:678–85.
41. Lindegaard B, Hvid T, Grøndahl T, Frosig C, Gerstoft J, Hojman P, et al. Expression of fibroblast growth factor 21 in muscle is associated with lipodystrophy, insulin resistance and lipid disturbances in patients with HIV. PLoS One. 2013;8:e55632.
42. Moure R, Domingo P, Villarroja Y, Gasa L, Gallego-Escuredo JM, Quesada-Lopez T, et al. Reciprocal effects of antiretroviral drugs used to treat HIV infection on the fibroblast growth factor 21/β-Klotho system. Antimicrob Agents Chemother. 2018;62:e00029–18. https://doi.org/10.1128/AAC.00029-18.AAC.
This article provides a thorough description of antiretroviral classes on glucose metabolism.
43. Calza L, Colangeli V, Borderi M, Coladonato S, Tazza B, Bon I, et al. 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. J Antimicrob Chemother. 2019;74:731–8.
44. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. AIDS. 2010;24:1697–707.
45. Molina J-M, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naïve adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV. 2015;2:e127–36.
46. Tebas P, Kumar P, Hicks C, Granier C, Wynne R, Min S, et al. Greater change in bone turnover markers for efavirenz/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naïve adults over 144 weeks. AIDS. 2015;29:2454–64.
47. Gupta SK (2014) Effects of Switching from Efavirenz to Raltegravir on Endothelial Function, Bone Mineral Metabolism, Inflammation, and Renal Function: A Randomized, Controlled Trial. J Acquir Immune Defic Syndr. 2014 Nov 1;64(3):279–83.
48. Maggi P, Montinaro V, Mussini C, et al Novel Antiretroviral Drugs and Renal Function Monitoring of HIV Patients. AIDS Reviews 2014 Jul-Sep;16(3):144–51. Review.
49. Wang Z-J, Yin OQP, Tomlinson B, Chow MSS. OCT2 polymorphisms and in-vivo renal functional consequences of the VIKING study. J Infect Dis. 2013;207:740–8.
50. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382:740–8.
51. Elion R, Molina J-M, López JRA, Cooper D, Maggiolo F, Margot N, et al. Greater change in bone turnover markers for raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING study. J Infect Dis. 2013;207:740–8.
52. German P, Liu HC, Szwarcberg J, Hepner M, Andrews J, Kearney BP, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. J Acquir Immune Defic Syndr. 2013;62:31–40.
53. Lee FJ, Amin J, Bloch M, Pett SL, Marriott D, Carr A. Skeletal muscle toxicity associated with raltegravir-based combination antiretroviral therapy in HIV-infected adults. J Acquir Immune Defic Syndr. 2013;62:525–33.
54. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results from a randomised, open-label, phase 3b study. Lancet. 2010;374:796.
56. Tefferi A, Hanson CA, Inwards DJ. How to interpret and pursue an abnormal complete blood cell count in adults. Mayo Clin Proc. 2005;80:923–36.

57. Pavone P, Giustini N, Fimiani C, et al. Long-term treatment with raltegravir is associated with lower triglycerides and platelets count in the older HIV+ population: results from the Ral-Age Study. Curr HIV Res. 2017. https://doi.org/10.2174/1570162X1566170927124558. This study provides informations on raltegravir’s impact on lipid profile in elderly HIV patients.

58. Burger DM (2009) Drug-drug interactions with Raltegravir. Eur J Med Res. 2009 Nov 24;14 Suppl 3:17–21.

59. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother. 2009;53:2852–6.

60. Masich A, Badovski ME, Liedtke MD, Fulco PP. Evaluation of the concurrent use of dolutegravir and metabolin in human immunodeficiency virus-infected patients. Int J STD AIDS. 2017;28:1229–33.

61. Tseng A, Hughes CA, Wu J, Seet J, Phillips EJ. Cobicistat versus ritonavir: similar pharmacokinetic enhancers but some important differences. Ann Pharmacother. 2017;51:1008–22.

62. Demessine L, Peyro-Saint-Paul L, Gardner EM, Ghosn J, Parent JL. Risk and cost associated with drug–drug interactions among aging HIV patients receiving combined antiretroviral therapy in France. Open Forum Infect Dis. 2019. https://doi.org/10.1093/ofid/ofz051.

63. Demessine L, Peyro-Saint-Paul L, Gardner EM, Ghosn J, Parent JL. Risk and cost associated with drug–drug interactions among aging HIV patients receiving combined antiretroviral therapy in France. Open Forum Infect Dis. 2019. https://doi.org/10.1093/ofid/ofz051.

64. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med. 2018;379:979–91. This paper provides revised data on Dolutegravir safety profile at the time of conception.

65. Dugdale CM, Claranello AL, Bekker L-G, Stern ME, Myer L, Wood R, et al. Risks and benefits of dolutegravir- and efavirenz-based strategies for South African women with HIV of child-bearing potential: a modeling study. Ann Intern Med. 2019;170:614.

66. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society–USA Panel. JAMA. 2018;320:379.

67. Phillips AN, Venter F, Havlir D, et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV. 2019;6:e116–27.

68. Counil A, Kouanfack C, Eymard-Duvernay S et al. Dolutegravir versus efavirenz 400mg-based regimens for the initial treatment of HIV-infected patients in Cameroon: 48 weeks results of the NAMSAL ANRS 12313 trial HIV Glasgow 2018, Scotland; Ot28-31.2018;Abstr O342.

69. van der Galiën R, ter Heine R, Greupink R, Schalkwijk SJ, van Herwaarden AE, Colbers A, et al. Pharmacokinetics of HIV-integrase inhibitors during pregnancy: mechanisms, clinical implications and knowledge gaps. Clin Pharmacokinet. 2019;58:309–23.

70. AIDSim. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States; https://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf Department of Health and Human Services – Recomended maternal nursing Nov 2017 [Consulted 11/05/2019].

71. ANSM. Lettre aux professionnels de santé. Genvoya®. Sribild®. Risque accru d’échec virologique et secondairement de transmission de l’infection VIH de la mère à l’enfant en raison d’une réduction de l’exposition pharmacocinétique à l’elvitégravir et au cobicistat au cours des deuxièmes et troisièmes trimestres de la grossesse. 2019.

72. Shamsuddin H, Raudenbush CL, Sciba BL, Zhou Y-P, Mast TC, Greaves WL, Hanna GJ, Leong R, Strauss W (2019) Evaluation of Neural Tube Defects (NTD) After Exposure to Raltegravir During Pregnancy. J Acquir Immune Defic Syndr Jul 1;81(3):247–250.

73. Nguyen B, Foisy MM, Hughes CA (2019) Pharmacokinetics and Safety of the Integrase Inhibitors Elvitegravir and Dolutegravir in Pregnant Women With HIV. Ann Pharmacother Aug;53(8):833–844.

74. Nguyen B, Foisy MM, Hughes CA. Pharmacokinetics and safety of the integrase inhibitors elvitegravir and dolutegravir in pregnant women with HIV. Ann Pharmacother. 2019;106002801983078.

75. Nachman S, Alvero C, Tepler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a phase 1/2 open label, non-randomised, multicentre trial. Lancet HIV. 2018;5:e715–22.

76. Viani RM, Alvero C, Fenton T, Acosta EP, Hazra R, Townley E, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: forty-eight-week results from IMPAACT P1093. Pediatr Infect Dis J. 2015;34:1207–13.

77. Viani RM, Ruel T, Alvero C, et al. Long-term safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: results of the IMPAACT P1093 study. J Pediatr Infect Dis Soc. 2019. https://doi.org/10.1093/jpids/piy139.

78. Pauline Bollen, Anna Turkova, Hilda Mujuru, Eizabeth Kaudha, Abbas Lenguema, Pauline Amuge, Angela Colbers, Cecilia Moore, Anna Parker, Victor Musiime, James G. Hakim, Deborah Ford, Diana Gibb, David M. Burger adult dolutegravir 50mg tablets in children living with HIV weighing 20 to 25kg. Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts. 2020. Abstract Number: 830.
79. Briand C, Dollfus C, Faye A, et al (2016) Efficacy and tolerance of dolutegravir-based combined ART in perinatally HIV-1-infected adolescents: a French multicentre retrospective study. J Antimicrob Chemother 2017 Mar 1;72(3):837-843

80. Collins IJ, Crichton S, Turkova A, Bamford A, Foster C, Riordan A, Lyall H, A Judd on behalf of the CHIPS Steering Committee. Children and adolescents in the UK/Ireland CHIPS cohort on integrase inhibitors: safety and effectiveness. 11th International Workshop on Pediatric HIV, 2019, Mexico City, Mexico. Poster #42.

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