**How recent findings on the pharmacokinetics and pharmacodynamics of integrase inhibitors can inform clinical use**

Emilie Elliot1,2, Mimie Chirwa1, Marta Boffito1,3

1 SSAT, Chelsea and Westminster Hospital, London, UK

2 University of Liverpool, Liverpool, UK

3 Imperial College, London, UK

**CORRESPONDING AUTHOR:**

Dr Marta Boffito

St. Stephen’s Centre – Chelsea and Westminster Hospital

369 Fulham Road

London SW10 9NH

Tel: +44(0)20 33156506

Fax: +44(0)20 33155628

Email: marta.boffito@chelwest.nhs.uk

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**Abstract**

**Purpose of review**: This review of recent published literature and data presented at scientific meetings on integrase stand transfer inhibitors (InSTIs) examines how these findings may impact on their future clinical use.

**Recent findings**: Elvitegravir (EVG), raltegravir (RAL) and dolutegravir (DTG) are InSTIs recommended as first line options for treatment naïve patients by EACS, BHIVA, IAS-USA and DHHS. InSTIs have gained a leading role in management of HIV-1 because of increased viral suppression and maintaining undetectability with fewer side effects.

RAL 1200mg QD has been shown to be non-inferior to 400mg BD and the European Medicines Agency (EMA) has approved QD RAL for review. RAL and DTG are not metabolized via cytochrome P450 (CYP) resulting in fewer drug interactions and less toxicity risk in patients receiving direct acting antivirals (DAAs) and other co-administered medications.

EVG is currently available as a single tablet regimen and requires cobisistat (COBI), a pharmacokinetic booster and CYP3A inhibitor to allow QD dosing. EVG will soon be available in combination with tenofovir alfenamide (TAF) which is as efficacious as tenofovir disoproxil fumarate (TDF), but offers better renal and bone outcomes.

DTG has a high genetic barrier to resistance and has been the subject of a number of simplification and treatment failure trials and shown promise. There are some emerging reports of neuropsychiatric and gastrointestinal side-effects associated with DTG which were not reported in clinical trials emphasizing the importance of real life data.

Carbotegravir, a long acting InSTI is currently in the pipeline of development.

**Summary**: All three InSTIs have impressive data on efficacy, tolerability and safety. The unique differences of each InSTI’s pharmacokinetics and pharmacodynamics lend themselves to various clinical scenarios, enabling us as clinicians to provide better patient-centered care.

**Introduction**

The landscape of HIV therapy has changed significantly with the advent of integrase stand transfer inhibitors (InSTIs; introduced in 2007 with raltegravir, RAL). They are equivalent or superior to existing treatments in efficacy and display high potency and favorable pharmacokinetics (PK), safety and tolerability. Most also benefit from paucity of drug-drug interactions (DDI), no cross-resistance to other drug classes, rapid HIV-RNA reduction and availability in single tablet regimens. InSTIs are now approved for first-line treatment in all guidelines and have become very popular, even credited for a marked overall increase seen in viral suppression and maintenance of undetectability. (1-3)

There are three InSTIs licensed for HIV therapy in treatment naïve and experienced patients, these are RAL, elvitegravir (EVG) and dolutegravir (DTG).

Adding to the existing abundance of registration data, much needed real life evidence is emerging with rapid expanded use, including data in novel strategies and specific clinical settings (e.g. pregnancy, renal replacement therapy, hepatitis co-infection, etc). Interestingly, recent post-marketing data show that InSTI associated drug reactions may be observed more frequently than expected (especially for EVG and DTG) (4) and that, although the prevalence of InSTI resistance remains low compared to reverse transcriptase and protease inhibitors, it is emerging with increased use of this drug class. (5)

In this article, we aim to select the latest and most relevant PK and pharmacodynamic (PD) findings in recent published literature and from 2015/2016 scientific meeting proceedings to provide an expert opinion on their clinical impact.

**Raltegravir**

The first in class InSTI, twice-daily (BID) RAL has a long track record, excellent safety and tolerability, and limited DDI. (3). Research in the last year has focused on the new once-daily (QD) formulation/dose, use in pregnancy and DDI with the new directly acting antivirals (DAA) for hepatitis C.

*RAL PK exhibits considerable intra- and inter individual variability and this has complicated the elaboration of a PK model for RAL and the understanding of the drug PK/PD relationship. The latter may also be masked by the robust efficacy of RAL 400 BID containing regimens, which deliver concentrations well above RAL IC50 (inhibitory concentration). (6)*

Furthermore, data on RAL impact on body composition, showing no difference in fat accumulation after initiating RAL- versus protease inhibitor-containing treatment have been presented. (7)

Once daily administration

The 2011 QDMRK trial had failed to show non-inferiority of 800mg RAL QD to 400mg BID in treatment-naive patients, (8) probably related to RAL’s high inter and intra-patient PK variability (coefficient of variation, CV, up to 200%), unclear PK/PD relationship and response dependence on trough concentrations (Ctrough)remainingabove the protein binding–adjusted (PA) >IC95. (3, 8)

However, Cahn et al. recently presented promising findings from the ongoing **ONCEMRK** trial, in which reformulated RAL 1200mg QD (two 600mg tablets) was non-inferior to 400mg BID in treatment-naïve subjects at 48 weeks (combined with tenofovir disoproxil fumarate/emtracitabine [TDF/FTC]). This new formulation of QD RAL brings the exposure-response curve closer to BID dosing. (9) Rizk et al have investigated the PK of the new RAL 1200mg QD formulations and demonstrated that although the geometric mean Ctrough achieved with the reformulated RAL administered QD is still lower than the oral compressed tablet (OCT) administered 400mg BID (81 vs 132 nM with CV ranging from 56 to 71%), it is higher than the Ctrough achieved by the OCT at 800mg QD (40 nM, CV >55%, associated to virological failure in QDMRK in a sub-group of patients). Notably, there is less significant food effect on the PK of reformulated RAL. (6, 10, 11)

Although data on the use of the unlicensed dose of RAL 800mg QD in individuals with undetectable viral loads exist, (12) the ONCEMRK data will change the drug license and simplify the management of individuals who are struggling with adherence to BID dosing of RAL. Studies in treatment experienced patients and special populations are however needed.

Pregnancy

A recent PK study of 22 HIV-infected pregnant women demonstrated that RAL area under the curve (AUC) and Ctrough were on average 29% and 36% lower, respectively, in the 3rd trimester compared with postpartum, with wide inter individual variability. The median cord/maternal blood RAL concentration ratio was 1.21, showing excellent cross-placental transfer, with no HIV vertical transmission. (13) InSTIs have also been associated to a lower median time to 1-log RNA reduction (8 days) compared to non-InSTI regimens (35 days) started in pregnancy. (14)

In fact, on the basis of accumulating clinical and PK data, RAL was upgraded to preferred agent for ARV-naive, pregnant women in the 2015 US perinatal HIV guideline update. (3, 15, 16) Nevertheless, large randomized controlled studies with long-term follow up of infants are not yet available.

Drug-drug Interactions

RAL is mainly metabolized by glucuronidation involving UGT1A1, and very few DDIs have been reported unless very potent drug-metabolizing inducers (e.g. rifampin) or UGT1A1 inhibitors (e.g. atazanavir) are co-administered.(17)

Recent data report no interaction between RAL and most DAAs (18) except for a 134% increase in RAL AUC with the 3D regimen (paritaprevir/ritonavir, ombitasvir, dasabuvir), which is not clinically significant. (19)

Interestingly, a case report by Cattaneo et al described an unexpected 3-fold increase in RAL exposure following 3D treatment in a man post-liver transplant for hepatocellular carcinoma, with Genotype 1 HCV reactivation on ciclosporin, with no side effects.(20)

Table 1 summarizes recent important studies on raltegravir.

**Elvitegravir**

EVG requires pharmacological boosting by cobicistat (COBI, a potent CYP3A4 inhibitor) to allow therapeutic and QD dosing and it is characterized by a lower inter individual variability than RAL (Ctrough CV = 32%). (21, 22) EVG/COBI are available co-formulated with FTC plus TDF in Stribild and tenonofvir alfenamide (TAF) in Genvoya. Data in the last year have focused on TAF efficacy and safety and the use of E/C/F/TDF in special populations (women and hepatitis co-infection).

EVG/COBI/FTC combined with TAF:

Clinical efficacy and safety

In both ARV naïve and stable patients on treatment, the recent **GS104/111 and GS 109** studies showed that E/C/F/TAF was non-inferior to E/C/F/TDF up to 96 weeks (23, 24) and led to viral load suppression with significantly less renal and bone toxicity.(25)

Importantly, however, in naïve patients, higher total cholesterol, HDL, LDL and TG increases were seen in the TAF group, with no statistical difference in TC:HDL. The potential loss of TDF-mediated lipid protection needs to be taken into consideration, albeit many patients over 50 with HIV will be on lipid lowering therapy. Virological failure with resistance was uncommon.

Another key study, **GS112** investigated the safety and efficacy of switching to E/C/F/TAF in patients with eGFR 30-69mL/min and demonstrated improvements in proteinuria, albuminuria, and BMD. Benefits were greatest in patients switching from a TDF containing regimen. (26)

Finally, virologically suppressed patients with ≥2 ART class resistance, including ≤3 TAMs and K65R but no integrase or darunavir resistance, were randomised to switch immediately to E/C/F/TAF plus DRV or defer. 94% of patients who switched were undetectable at week 48 in comparison with 76% who remained on their current regimen, suggesting that in carefully selected patients, this may be an option, (27) despite the change in DRV and EVG concentrations during co-administration.

Hepatitis B co-infection

The first study on efficacy and safety of E/C/F/TAF in HIV/HBV co-infected subjects recently showed that 91% of patients who switched to E/C/F/TAF from other regimens achieved or maintained HIV and HBV viral suppression at 48 weeks with comparable rates of sAg and eAg seroconversion to HBV mono-infected patients (n=72). (28)

Therefore, while waiting for real life data, individualized use of E/C/F/TAF in HIV/HEP B co-infected individuals may be of value.

EVG/COBI/FTC combined with TDF:

Women

The **WAVES** study showed that E/C/F/TDF was superior to ATV/r plus TDF/FTC at week 48 (87% vs 81% respectively), regardless of baseline viral load (VL) and CD4 count in HIV infected ARV naïve women, with no background resistance. More discontinuations and grade 3/4 AEs were seen in the ATV/r arm. (29)

There was only one case report of successful use of Stribild in pregnancy this year.(30)

Drug Interactions with DAAs

The TDF and COBI components of Stribild are most concerning when it comes to drug interactions with the DAAs. Phase 1 studies have shown increases in tenofovir (TFV) concentrations with ledipasvir/sofosbuvir, (31) not reflected in significant changes in baseline creatinine in a phase III study. (32) COBI also increases TFV levels, so arguably the combination of the two interactions with Stribild may increase the risk of renal toxicity. Using TAF would negate the clinical impact but data are required.

Co-administration of EVG/COBI with daclatasvir and simepravir has not been studied, but would anticipate increased levels of anti-HCV drug due to CYPA3A4 inhibition by COBI. (33) Ritonavir containing HCV regimens (3D) should not be co-administered with COBI due to the risks of co-administering two strong CYP3A4 inhibitors together. (33)

Recent data on elvitegravir are summarized in table 2.

**Dolutegravir**

DTG is the newest InSTI and the first to be dosed QD without boosting, with a limited inter individual variability (Ctrough CV = 24%) (22). Importantly, in vitro experiments aimed at identifying resistance mutations by passaging virus in cell culture in the presence of drug suggest that InSTIs bind to the HIV integrase with a two-step mechanism and mutations alter the second step, leading to fast InSTI dissociation kinetics integrase resistance development. Furthermore, DTG demonstrated a dissociative half-life of 71 hours (versus 8.8 for RAL and 2.7 for EVG); demonstrating an off-rate 5–40 times slower than RAL and EVG. (34) The slow dissociation of DTG from the integrase enzyme could contribute to DTG’s high barrier to resistance. The latter is also due to the high inhibitory quotient of DTG, which is determined by the remarkable distance of DTG IC50 and the DTG Ctrough achieved following a 50mg QD dose. (3) Compounded with a high genetic barrier, excellent safety and tolerability profiles in clinical trials, it stands relatively ahead of other ARVs. (3, 35).

Data in the last year have concentrated on the PK tail of DTG, treatment simplification, special populations, real life tolerability and DDI not previously signalled in Phase II/III trials.

Pharmacokinetic forgiveness

To understand the management of late and missed doses, Elliot et al. evaluated the PK of DTG and EVG/COBI in HIV-negative volunteers up to 10 days after drug cessation. DTG concentrations remained above the IC90 for wild type virusfor 72 hours post-drug cessation, showing robust PK forgiveness associated to DTG. (22) DTG C48hours CV was also quite limited (35%) and concentrations were 427 ng/mL (48 hours post-dose), 131 ng/mL (72 hours post-dose, with still 16/17 of the studied subjects with levels above the PA-IC90). (22)

EVG terminal elimination half-life was lower than its half-life within the dosing interval of 24 hours: 10.8 hours (9.7-13.0) versus 5.5 hours (4.7-6.1); and concentrations were above the PA-IC95 (45 ng/mL) in 100% of subjects at 24 hours, 65% at 36 hours but 0% after 48 hours. (22)

Treatment simplification

*Dual therapy: DTG + lamivudine (3TC) or DTG + rilpivirine (RPV)*

ARV-naïve patients: In the **PADDLE** study, 20 ARV-naïve patients initiated Dolutegravir/Lamivudine QD, 18 achieved HIV-1 RNA < 50 c/mL at week 48 (1 committed suicide, unrelated to study drugs) and 1 experienced protocol defined virological failure (PDVF) at week 36 but re-suppressed without ART change. (36) A phase III non-inferiority study with planned enrollment of 700 patients is now recruiting ([www.clinicaltrials.gov](http://www.clinicaltrials.gove); NCT02831673).

With caution applied to hepatitis B screening to prevent suboptimal hepatitis B therapy in co-infection, this strategy, if proven successful, may reduce toxicity, DDI and cost compared to triple therapy. (37)

Pre-treated patients: In the last 18 months, cohort studies, based in clinical practice have reported promising outcomes of DTG-based dual therapy in pre-treated patients. Diaz and colleagues reported that switching virologically suppressed HIV-infected patients with multiple previous treatment failures to standard dose DTG/RPV QD was safe and effective through to 48 weeks, with improved safety profiles. (38)

Results are promising; however, widespread recommendation changes cannot be made until long-term RCT data become available. Whilst well-powered studies are underway, switches to DTG-based dual therapy are not currently recommended in guidelines and, if considered, must only be done in very carefully selected patients.

*Monotherapy*

Different small non-randomized studies have investigated the use of DTG monotherapy in selected ARV-naïve and experienced patients with conflicting results but with a positive response in some individuals. (39-42) This strategy is currently not recommended and requires further study before use.

Real life tolerability

DTG was well tolerated in registration trials with relatively lower risks of adverse events (AEs) than other agents. (35, 43) Data from clinical practice, however, are starting to emerge, showing unexpectedly high rates of DTG intolerance, with up to 14.5% of patients in cohort studies switching because DTG toxicity (insomnia, neuropsychiatric and gastrointestinal side effects), compared to <2% reported in clinical trials. (44)

Of note, the impact of dolutegravir on sleep in HIV infected individuals over the age of 60 years is being investigated ([www.clinicaltrials.gov](http://www.clinicaltrials.gov); NCT02509195).

Special populations

*Women and pregnancy*

**ARIA** is a phase IIIb randomised, open-label, multi-centre study that showed superior activity and a favourable safety profile of the fixed-dose DTG/ABC/3TC (Triumeq) compared with atazanavir boosted with ritonavir (ATV/r) plus TDF/FTC in treatment-naïve adult women over 48 weeks.(45)

Although DTG has been classified by the FDA as category B, UK and US perinatal guidelines state that there are insufficient data to make recommendations on its use in pregnancy.(16) The first PK evaluation of standard dose DTG in 21 pregnant women (IMPAACT P1026) showed DTG AUC0-24 was 30% lower and Cmax 40% lower during pregnancy than postpartum. The differences were not significant. Maternal viral loads remained undetectable with good placental transfer shown; all infants so far are HIV negative. (46) Case reports have also been published (47, 48)

*Renal Impairment*

DTG is highly protein bound with low water solubility. There is no effect on exposure in mild to moderate renal impairment but unexpected lower DTG exposures were reported in HIV-seronegative subjects with severe renal impairment (AUC0–oo 40% lower) and caution should be applied, especially in the context of InSTI resistance. (49, 50) With regards to renal replacement therapy, Molto at al, newly demonstrated minimal DTG removal by hemodialysis (extraction ratio 7%) suggesting no specific dosage adjustments required in this setting.(49, 51)

Drug Interactions

DTG is metabolized by UGT1A1 and, to a lesser extent by CYP3A4 (10-15%)(52), without being an inducer or inhibitor of metabolic pathways; it is therefore characterized by a low potential for DDI.

However, co-administration of DTG and metformin significantly increased metformin plasma expo­sure in a dose dependent manner. This is explained by DTG-mediated renal Organic Cation Transporter 2 (OCT2) inhibition. Although metformin has a wide therapeutic index and alone is not associated with hypoglycemia, dose adjustments and monitoring for lactic acidosis is recom­mended in those at risk.(53)

Recent relevant dolutegravir studies are summarised in table 3.

**Pipeline**

Long acting (LA) ARVs, facilitating adherence, are the next step on the horizon. Cabotegravir (CAB) is a potent HIV integrase inhibitor in clinical development as an oral and a long-acting IM injectable. The **LATTE-2** study showed non-inferiority of 4-weekly and 8-weekly IM CAB/RPV compared with PO CAB/RPV QD in the 32wks FDA snapshot analysis (following a 20-week oral induction period). Virological success ranged between 91 and 95%. The commonest AE was injection site reaction (ISR), grade 1 or 2, resolving within a week. Participant satisfaction was high. (54)

The placebo-controlled **ÉCLAIR** study showed high safety and tolerability of cabotegravir as a potential candidate for PrEP in healthy male volunteers. PK measurements, however, showed suboptimal Ctrough levels with 12 weekly injections and 8 weekly scheduling will likely be taken to phase 3 (table 4). (55) Exposure and tolerability in women needs investigation.

Recent studies have also shown no changes in cardiac repolarization with cabotegravir at high doses and low likelihood of DDI except for co-administration with OAT1 or OAT3 substrates or strong metabolic inducers like rifampicin. (56-58)

Finally, bictegravir (GS-9883) is an unboosted integrase inhibitor co-formulated with TAF/FTC, which is also currently under development. It does not require COBI, which will offer fewer DDIs; multiple phase III studies are ongoing.

**Conclusion**

Over the past few years InSTIs have become the preferred third agents recommended by International HIV treatment guidelines. This recommendation is based on clinical trial data where InSTI demonstrated superiority compared with older guideline preferred regimens containing efavirenz.

Although there are differences within the InSTI class, when considered as a whole, the favourable efficacy and tolerability profiles of InSTI, the absence of cross-resistance with other

ARV classes, the favorable PK profiles for QD dosing, (which today can be said for RAL too in view of the new successful data on the QD 1200mg dose) it is easy to understand why they have become important components of effective cART regimens in individuals living with HIV/AIDS.

Importantly, however, real life data are emerging suggesting at times surprises on InSTI tolerability and side-effect profiles. This has been true for all available ARVs. While following all the new data presentation in this context, it is interesting to reflect on the role of this class in view of new ARV agents being studied, such as injectables, entry inhibitors and attachment inhibitors.

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Although there are differences within the InSTI class, when considering as a whole the favourable efficacy and tolerability profiles of InSTIs, the absence of cross-resistance with other ARV classes and the favourable PK profiles for QD dosing, (which today can be said for RAL too in view of the new successful data on the QD 1200mg dose), it is easy to understand why they have become important components of effective cART regimens in individuals living with HIV/AIDS.

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**KEYPOINTS**

* Integrase Strand Transfer Inhibitors are now recommended as first line therapy in all treatment guidelines and have gained a leading role in management of HIV-1.
* RAL 1200mg QD has recently been shown to be non-inferior to 400mg BD and the EMA has approved QD RAL for review.
* EVG combined with TAF has shown very convincing efficacy results whilst offering significantly improved tolerability and safety compared with TDF.
* DTG stands relatively ahead of other ARVs and studies this year have looked at its use in simplified regimen, showing promising results.
* Real life data on these new drugs are however emerging, with some reports of higher rates of side effects with DTG than seen in clinical trials.

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