Le Infezioni in Medicina, n. 4, 365-373, 2019

Clinical pharmacology of the single tablet regimen bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF)

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SUMMARY

The fourth HIV strand-transfer integrase inhibitor (INSTI) has been released into the market as part of a single-tablet-regimen (STR) consisting of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF). The newest component is thus BIC, a booster-free INSTI with pharmacological characteristics similar to those of dolutegravir (DTG), including high intrinsic antiretroviral potency. The BIC-containing STR underwent clinical development in both treatment-naïve and virologically suppressed patients and was found non-inferior to DTG-based comparator arms. In the currently evolving therapeutic scenario, the BIC/FTC/TAF STR regimen represents the smartest response on the side of triple conventional regimens, while new 2-drug regimens have received regulatory approval and nowadays epitomize the search for simpler and lighter antiretroviral regimens. The overall characteristics of BIC/FTC/TAF, however, make this therapeutic option quite comparable in terms of simplicity to the newly approved dual regimens, and the main reasons (*e.g.*, toxicity) accounting in the past for the search of regimens consisting of less than three drugs are no longer in place.

Keywords: HIV, single tablet regimen, integrase inhibitors

INTRODUCTION

The growing list of Strand-Transfer Integrase Inhibitors (INSTIs) now includes also bictegravir (BIC), the last member of this drug-class, whose only available pharmaceutical form is in co-formulation with emtricitabine (FTC) and tenofovir alafenamide (TAF) in a single-tablet regimen (STR). This STR contains 50 mg of BIC, 200 mg of FTC and 25 mg of TAF, and represents the final result of a stepwise evolution eventually leading to an INSTI-based STR with no booster and the substitution of tenofovir disoproxil fumarate (TDF) by the safer TAF [1]. Based on pre-clinical and phase I studies results, the clinical development of BIC in phase III was almost entirely designed to prove its non-inferiority vs dolutegravir (DTG), as the latter had been found to be superior (in non-inferiority head-to-head trials) to both efavirenz (EFV) and darunavir/ritonavir (DRV/r)-based regimens, and the superiority of DTG was also demonstrated beyond the 48 weeks when compared to the 1st generation INSTI raltegravir (RAL) [2-5]. As a simple consequence, by proving its non-inferiority vs DTG, BIC actually deserved to be included in the treatment guidelines in the same position as DTG [6]. Further to its DTG-oriented development, BIC actually seems to share with its competitor a series of characteristics, such as intrinsic antiviral potency, activity against HIV resistant to 1st generation INSTIs, metabolism and

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pharmacokinetics (Pk). In this fast-evolving era of antiretroviral therapy, with the impending emergence of various forms of dual therapy, the STR BIC/FTC/TAF looks as a sort of "conservative" therapeutic resource for those patients who might not be compatible with the newly developed 2-drug regimens [7]. In this perspective, the clinical/pharmacological features of this BIC-based regimen make it a preferred conventional choice along with triple DTG-based options.

PHARMACOLOGICAL FEATURES

Basic characteristics

In Tables 1 and 2 several basic pharmacologic parameters of INSTIs are represented [8]. It is apparent from these figures how BIC is similar to DTG. Alike DTG BIC has two main metabolic pathways, such as it is a substrate of both CYP3A and UGT1A1, it undergoes transportation by the glycoprotein P (Pgp) and the breast cancer resistant protein (BCRP), it has a protein binding approaching 100% and an elimination half-life (T/2) slightly longer than DTG [9, 10]. Alike DTG, BIC inhibits the organic cation transporter-2 (OCT2), which in the clinics corresponds to slight harmless increases of serum creatinine. Absorption of BIC is rather fast, with peak concentrations being achieved in 2.0-2.4 hrs. As compared to fasting conditions, the intake of moderate or high-fat meal is associated to a 24% increase in AUC, and no food-related restrictions apply for BIC. From the comparative tables 1 & 2 it is apparent that BIC maintains the characteristics of 2nd generation INSTIs, including (further to a longer T/2) a reduced food effect and a smaller Pk coefficient of variation, which makes BIC Pk exposure more predictable across different individuals. The pharmacokinetics of BIC was studied with different multiple daily doses (5, 25, 50 and 100 mg) and was found to be dose-proportional. In case of moderate hepatic impairment or severe renal failure (eGFR 15-29 ml/min) no effects on BIC Pk were measured [9, 10].

Clinical pharmacodynamics

The cleanest test to evaluate the potency of an antiretroviral drug in the clinics is to measure the effect on circulating HIV-RNA when the drug is administered alone in treatment-naïve patients. Bictegravir has been studied in a 10-day monotherapy, phase 1b, placebo-controlled trial [11]. In treatment-naive subjects with HIV-1 infection BIC was administered at doses of 5, 25, 50 or 100 mg once daily, with dose-dependent $\log_{10}$ HIV-RNA reductions of -1.45, -2.06, -2.08 and -2.43, respectively measured. It is noteworthy that 3 out of 20 participants (on BIC 50 or 100 mg) achieved undetectability (<50 copies HIV-RNA/mL) by the end of the study. These findings well compare to those of a similar study carried out with DTG and actually testify about the in vivo potency of BIC, which was subsequently confirmed in clinical studies in treatment-naïve patients [12]. The protein-adjusted 95% inhibitory quotient (IQ)of BIC at the selected daily dose of 50 mg (based on the drug concentration at the end of the dosing interval and the in vitro protein-adjusted 95% concentration for wild-type HIV-1, such as 162 ng/mL) is 13.4 [13].

In the pharmacodynamic (PD) studies of INSTIs, attention has always been paid to the time of residence of the drug on its target, a parameter termed dissociation time. The possible relevance of the dissociation time lies in the hypothesis that INSTIs exert their inhibitory activity during just a fraction of the integration window (the time during which proviral DNA is integrated into human genome). According to this hypothesis, in order to be successful, the INSTI should have a residence time on the integrase/DNA complex not inferior to the half-life of the pre-integration complex that proviral DNA forms to be integrated into host-cell DNA [14, 15]. Such hypothesis would actually lessen the relevance of the drug concentration at the end of the dosing interval as the parameter driving the PK/PD relationship of INSTIs. In table 3 the dissociation times of the four available INSTIs is represented. Although the values attributed to the dissociation time of each drug here considered might vary across different studies, it is nevertheless apparent that 2nd generation INSTIs actually have a dissociation time longer than their 1st generation ancestors. In this specific PD setting BIC was found to have the longest dissociation time among INSTIs, and this also applies in case of common INSTI resistance-associated mutations (RAMs), although here the dissociation time is expectedly shorter [16, 17].

Activity in the presence of INSTIs RAMS

Although no clinical studies have been carried out with BIC in case of patients with prior virological

failure with INSTIs-based regimens, some data is available on phenotypic susceptibility of HIV-1 carrying INSTIs RAMs. BIC activity was assayed against 20 clinical HIV-1 isolates with single substitutions and 44 with 2 or more substitutions. BIC full activity, as established by the less than 2.5-fold reduced susceptibility cut-off, was proven in all isolates with single mutations and in double mutants lacking the Q148H/K/R substitutions, as well as in 10 out of 24 isolates with Q148H/K/R and additional substitutions. Reduced fold susceptibility ≥2.5 was recorded in 14 out of 24 isolates with both G140A/C/S and Q148H/K/R; 9 of these 14 resistant isolates also had mutations at L74M, T97A or E138A/K. It must be noted that one patient enrolled in a treatment-naïve registration trial, in spite of the presence of pre-existing INSTIs RAMs Q148H and G140S, achieved and maintained virologic suppression at week 96, and the same occurred in 6 patients who had T97A at baseline [9-18].
It is also worth noting that no BIC-treated patients recruited in clinical trials had evidence of newly selected INSTI RAMs in case of virologic failure.

Drug-drug interactions
As based on its metabolic profile, BIC is expected not be a perpetrator of drug-drug interactions, but possibly a victim, when drugs interfering with CYP3A and/or UGT1A1 are co-administered. Data from phase 2 and phase 3 studies (48 weeks treatment), have shown a good safety profile with up to a 2.4-fold increase in bictegravir AUC, and as a consequence the risk of BIC being victim of a clinically significant drug-drug interactions is more on the side of underexposure [9, 10]. This is the case when potent inducers of CYP3A and UGT1A1 are co-administered; rifampicin (AUC of BIC: -75%) and St. John' wort are contraindicated for this reason. Although the effect of rifabutin on BIC would not be enough to significantly decrease BIC activity, its co-administration is not recommended as the plasma concentrations of the co-formulated TAF might be significantly decreased by rifabutin (which is also a Pgp inducer) [9, 10]. It must be noted, however, that co-administration of TAF with the more potent Pgp inducer rifampicin led to intracellular TAF active concentrations still higher than those measured in case of rifampicin co-administration with Tenofovir disoproxil fumarate (TDF) [19]. Since the latter co-administration has no restrictions, it seems likely that rifabutin might be concurrently taken with BIC and TAF. More data are needed as this issue is relevant considering the frequent overlap of HIV and TB in some countries. Other CYP3A, UGT1A1 and Pgp inducers are the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital and phenytoin, which are not recommended in co-administration with BIC, although no clinical data is available. Among the inhibitors of CYP3A, UGT1A1 and/or Pgp, the co-administration of the antiretroviral protease (PI) atazanavir is not recommended due to the significant increase in BIC Pk exposure (AUC: +306-315%), while in case of the other PI darunvair/cobicistat (CYP3A and Pgp inhibitor) the increase of BIC AUC (+74%) is not considered to be clinically relevant [9, 10]. No restrictions apply when the antifungals voriconazole (CYP3A inhibitor, BIC AUC: +61%), itraconazole and psaconazole (Pgp and BCRP inhibitors) are co-administered with BIC. Antibiotics belonging to the class of macrolides (azithromycin, clarithromycin) are Pgp inhibitors, and their co-administration with BIC might increase the Pk exposure of the INSTI. No clinical data is available, but caution is advised in case of concurrent intake of BIC with macrolides. The same applies to cyclosporin, which also inhibits Pgp.
A common feature among INSTIs is to undergo reduced intestinal absorption in case of co-administration with antacids, due to chelation with polyvalent cations. BIC is no exception (AUC: -79% with magnesium/aluminium antacid suspension) and the recommendation here is to take BIC at least 2 hours before the antacid or with food at least 2 hours following the antacid. On the side of proton-pump inhibitors or H2-antagonists no impact is expected on BIC Pk, as studies have shown no evidence that bictegravir solubility is impacted by changes in pH [9, 10].
A specific feature of both DTG and BIC is the inhibition of the influx transporter OCT2, which is responsible of the uptake of creatinine by the proximal tubule (to be secreted into urine) as well as of the oral antidiabetic drug metformin. In case of co-administration of metformin with BIC, the AUC of the former is increased by 39%, but no special recommendation is indicated unless the patient has a moderate renal failure, as in such a case there is an increased risk of lactic acidosis and dose adjustment of metformin is therefore

advised. For the same reason (inhibition of OCT2) the association of BIC and dofetilide is contraindicated. Based on the metabolism of dofetilide, which undergoes renal clearance (both glomerular filtration and tubular secretion), the inhibition of OCT2 by BIC is thought to reduce dofetilide uptake by OCT2 transporters on proximal tubule epithelial cells and consequently its secretion into urine. Although no data is available, the association is contraindicated for the risk of arrhythmias due to higher dofetilide Pk exposure [9, 10].

CLINICAL STUDIES

Treatment-naive patients

Two phase III registration clinical trials have been carried out in the development of BIC. The first (GS-US-380-1489) compared the STR BIC/FTC/TAF with DTG/3TC/ABV with 314 and 315 patients per arm, respectively [20]. In the 2nd study (GS-US-380-1490) BIC/FTC/TAF was compared to DTG+FTC/TAF with 320 and 325 patients per arm, respectively [21]. The baseline characteristics of the patients recruited into the two studies were rather similar, with the usual prevalence of male patients (89%), a mean CD4+ T-cell count of 460 and a mean plasma HIV-RNA of 4.4 $\log_{10}$/mL. The proportion of patients with less than 200 CD4+ T-cells/uL at baseline was 11% and that of patients with HIV-RNA >100.000/mL was 18%. Virological non-inferiority of the study regimen (BIC/FTC/TAF) was proven at both 48 weeks and 96 weeks time points, as testified by the pooled data for BIC/FTC/TAF compared to the control arms of the two studies. The pooled proportion of patients who achieved virologic suppression (<50 copies HIV-RNA/mL) with BIC/FTC/TAF was 91% and 86% at week 48 and 96, respectively, while the suppression rates for DTG/3TC/ABV recipients were 93% and 90%, and those achieved by DTG + FTC/TAF intakers were 93% and 86%. Suppression below 20 copies HIV-RNA/mL at week 48 and 96 was 85%-80% for BIC/FTC/TAF, 87%-85% for DTG/3TC/ABV, and 87%-80% for DTG + FTC/TAF, respectively. Virologic suppression rates at week 48 and 96 in patients who had <200 CD4+ T-cells/uL at baseline were 90% - 83% in the BIC/FTC/TAF pooled arms, 81% at both time points in the DTG/3TC/ABV arm and 100% - 94% in the DTG + FTC/TAF arm. Patients with >100.000 HIV-RNA copies/mL at baseline achieved virologic suppression at 48 and 96 weeks in 87% and 82% of cases in the pooled BIC/FTC/TAF arm, 90% and 84% in the DTG/3TC/ABV arm and 94% and 87% in the DTG + /FTC/TAF arm.

The discontinuation rate attributable to side effects or death at 96 weeks was 1% in the pooled BIC/FTC/TAF arms and 2% in the two DTG-based comparator arms [20, 21].

Virologic suppressed patients (Switch studies)

Two registration studies with patients who achieved virologic suppression with their previous regimens were performed in the phase III development of BIC/FTC/TAF. In the first study (GS-US-380-1844), the study regimen BIC/FTC/TAF was compared to DTG/3TC/ABV (or DTG + 3TC/ABV) according to a switch design in patients (n=563) who were virologically suppressed (<50 HIV-RNA copies/mL) for at least 3 months while receiving the DTG-based regimen and were randomized to BIC/FTC/TAF or to continue with the DTG-based regimen [22]. Virologic suppression at 48 weeks was 94% in the BIC/FTC/TAF arm and 95% in the DTG-based arm.

The 2nd study (GS-US-380-1878) had the same design, but with the control arm consisting in patients receiving either FTC/TDF or 3TC/ABV in association to darunavir (DRV) or atazanavir (ATV) boosted with cobicistat (COBI) or ritonavir (RTV) [23]. The number of patients randomized to BIC/FTC/TAF were 290, while 287 patients were randomized to continue their prior PI-based regimen. Virologic suppression at 48 weeks was 92% in the BIC/FTC/TAF arm and 89% in the control arm. The discontinuation rate due to side effects or death at week 48 was 2% in the BIC/FTC/TAF arm and 1% in the DTG/3TC/ABV arm in the study GS-US-380-1844 and 1% in both arms in the study GS-US-380-1878.

In a third double-blind, active controlled, phase III non-inferiority clinical trial, also designed as switch study (GS-380-4030), patients receiving DTG+ FTC/TAF and being virologically suppressed for ≥3 months were randomized to BIC/FTC/TAF (n=284) or to continue DTG + FTC/TAF. Patients were stratified according known/suspected NRTI resistance at BL (K65R or ≥3 TAMs vs other NRTI RAMs vs none). At 48 weeks the non-inferiority of the study regimen was found to be non-inferior to the comparator, as at

the snapshot analysis suppression below 50 HIV-RNA copies/mL was 93% in the BIC/FTC/TAF arm and 91% in the DTG + FTC/TAF arm. No patient with pre-existing RAMs had HIV-RNA copies >50/mL and in no cases new RAMs were detected in patients undergoing virologic failure. Side effects leading to treatment discontinuation occurred in 6 cases (2.1%) per each arm (Acosta R, Willkom M, Andreatta K, et al. Keeping the pressure on archived NRTI resistance: Switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) triple therapy in study 4030. International AIDS Society 2019, Abstract MOPEB241).

Side effects

Along the development of BIC/FTC/TAF the occurrence of side effects was recorded as common, when the frequency was in between 1/100 and 1/10, and uncommon when the rate was ≥1/1000 and <1/100. The untoward effects classified as common included depression, abnormal dreams, headache, dizziness, diarrhea, nausea and fatigue, while the list of uncommon side effects comprised anaemia, suicidal intentions, anxiety, sleep disorders, vomiting, abdominal pain, dyspepsia, flatulence, hyperbilrubinemia, angioedema, rash, pruritus, urticaria and arthralgia. No signature toxicities emerged for this STR. A common occurrence in BIC/FTC/TAF was a slight increase in creatininemia, with a median value of 0.09 mg/dL. In the DTG-based arms serum creatinine values rose by a median of 0.09 in case of DTG/3TC/ABV and 0.11 with DTG + FTC/TAF. The inhibition of OCT2 by both BIC and DTG accounts for these creatinine increases [9, 10].

DISCUSSION

Among the recommended first-line options for treatment-naïve patients in the current guidelines for antiretroviral therapy we find several INSTIs-based regimens, including BIC/FTC/TAF, which is the last entry. These 1st line regimens are detailed in Table 3, according to two characteristics, such as the n. of pills to be taken daily (all such regimens are now QD) and the total dose of the regimen (i.e. the sum in mg of each drug included in the regimen). The progress achieved by the development of BIC/FTC/TAF appears quite clear when compared to the other INSTI-based options, both in terms of n. of pills and the total dose to be taken on a daily basis. Two are the regimens here considered which are co-formulated in a STR. The STR consisting of BIC/FTC/TAF contains a total of 275 mg of drugs, the least amount of medication across all the recommended INSTI-based regimens, while the other STR available (DTG/3TC/ABV) has a total weight in active substances of 950 mg. The only other regimen which equals the total dose of BIC/FTC/TAF is the one

Table 1a - Basic Pharmacological features of Strand-Transfer Integrase Inhibitors (INSTIs).

	MW	*T/2 (h)*	*Protein binding*	*Substrate*	*Inhibitor*	*Inducer*
RAL	482.51	9	83%	UGT1A1	–	–
ELV/COBI	447.9	12.9	98-99%	CYP3A, UGT1A1-3, OATP1B1-3	OATP1B3	CYP2C9 (+), UGT
DTG	441.36	14	98.9%	UGT1A1-3-9, CYP3A, Pgp, BCRP	OCT2	–
BIC	471.4	17.3	> 99%	CYP3A, UGT1A1, Pgp, BCRP	OCT2, MATE1	–

RAL: raltegravir; ELV/COBI: elvitegravir/cobicistat; DTG: dolutegravir; BIC: bictegravir. MW: molecular weight; T/2: elimination half-life; UGT: glucuronosyltransferase; CYP: isoenzymes of the cytochhrome P450 mixed function oxydase; OATP: organic anion transporter; Pgp: glycoprotein P; BCRP: breast cancer resistant protein; OCT: organic cation transporter.

Table 1b - Basic Pharmacological features of Strand-Transfer Integrase Inhibitors (INSTIs).

	Food Effect Low-Fat	*Food Effect High-Fat*	*Pk CV (%)*	*Urinary Clearance*
RAL	+ 13%	+ 200%	122 - 212	32%
ELV/COBI	+ 36%	+ 91%	25.5	6.7%
DTG	+ 33%	+ 66%	20 - 40	31%
BIC	+ 24%	+ 24%	22.9 – 35.2	35%

RAL: raltegravir; ELV/COBI: elvitegravir/cobicistat; DTG: dolutegravir; BIC: bictegravir. Pk CV: pharmacokinetic coefficient of variation.

combining DTG and FTC/TAF (also 275 mg), but two pills are required. By looking at table 1, where the molecular weights (mw) of the four available INSTIs are shown, we can appreciate how these values are quite similar, but the daily doses to be taken vary from 50 to 1200 mg. The simple fact that much less drug is required by 2nd generation INSTIs to achieve the desired antiretroviral effect testifies that INSTIs like DTG and BIC are actually intrinsically more potent than their predecessors. By following this line, we see how this also applies to citidine analogues (FTC vs 3TC) [24] and to tenofovir prodrugs (TAF vs TDF) [25]. In all such cases, the newer drug was at least equally effective than the older one but at lower doses.

The competition among different antiretroviral regimens is moving now toward the new scenario of dual vs triple regimens, as newly approved 2-drug combinations have been actually found to be effective in a patient denominator which is larger than previously thought [26]. Based on the overall characteristics of the available oral regimens, we can foresee how the hardest competition in treatment-naïve patients will be between the newly released STR dual regimen consisting of DTG coformulated with 3TC and BIC/FTC/TAF. Based on current knowledge, two important drivers will be the CD4+ T-cell count and HIV-RNA at baseline, but individual behavioural factors (to be thoroughly evaluated by doctors) will also play an important role, as well as the cost of each regimen. The attraction of a regimen able to do the job with a lesser number of drugs is "ecologically" intuitive, especially considering patients' aging and the additional therapeutic burden brought by concomitant medications. If, however, instead of considering the n. of drugs included in the regimen, we rank these therapeutic options according to the total daily dose, we find how the STR consisting of BIC/FTC/TAF is actually made up of a lower total amount of drug (275 mg) as compared to the dual DTG/3TC (350 mg). This view would not be complete without considering the other recently released 2-drug combination, such as DTG/RPV, which was approved as switching option in virologically suppressed patients [27]. The latter is by far the "lightest" regimen so far approved in antiretroviral therapy, as its total daily dose is just 75 mg. Whatever the attention we deem to pay to these parameters (the n. of drugs and/or the total dose), the real current issue in the clinics is the impact of a triple vs dual regimen when the additional drug is TAF. TAF represents the innovative evolution of a very successful adenosine analogue, TDF, which has been efficaciously administered for more than 15 years [28]. As compared to TDF, TAF is being administered at a 10-fold lower dosage, and it has been pharmaceutically devised to target specific cells rather than having a much wider tissue distribution, and this translates into much higher intracellular concentration of the active moiety in target cells [29]. One of the most relevant advantages of TAF consists in its significantly lesser impact on both proximal renal tubular function and bone mineral density [30, 31], the two being pathophysiologically linked by the increased renal loss of phosphates. Although the frequency of major severe TDF-associated toxicity has been rather low in almost two decades of widespread TDF use (with the exceptions of some recently emerged cohort data), the patient population being treated nowadays is actually significantly more aged than the

Table 2 - Dissociation Time of Strand-Transfer Integrase Inhibitors (INSTIs) in case of Wild-Type (WT) HIV-1 and in presence of specific INSTIs resistance-associated mutations (RAMs).

	WT	*G140S + Q148H + other INSTIs RAMs*
RAL	5.2	nm
EVG/COBI	1.5	nm
DTG	16	0.65
BIC	38	2.5

RAL: raltegravir; ELV/COBI: elvitegravir/cobicistat; DTG: dolutegravir; BIC: bictegravir.nm: unmeasureable.

Table 3 - First-line recommended options represented according to the number of pills to be taken daily (all regimens are QD) and the total daily dose (in mg).

	n. of pills/ daily	*Regimen total weight (mg)*
BIC/FTC/TAF	1	275 (50 + 200 + 25)
DTG/3TC/ABV	1	950 (50 + 300 + 600)
DTG + FTC/TDF	2	495 (50 + 200 + 245)
DTG + FTC/TAF	2	275 (50 + 200 + 25)
RAL + FTC/TDF	2	1645 (1200 + 200 + 245)
RAL + FTC/TAF	2	1425 (1200 + 200 + 25)

RAL: raltegravir; DTG: dolutegravir; BIC: bictegravir, 3TC: lamivudine; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; ABV: abacavir.

one that was exposed to TDF, and reliance on a safer drug seems to be therefore advisable [32]. As compared to the recent past, in order to have a "TDF-sparing regimen" today we can thus also rely upon TAF, further to a 2-drug option or to an ABV-based regimen (with the still unsolved issue of a possible increased cardiovascular risk). Based on the available knowledge on long-term TAF intake, the overall impression is that the impact of additional TAF is minimal [33]. The recently emerged issue of a possible excess weight gain in women associated to TAF intake requires further investigation and possibly diet-controlled clinical trials [34, 35]. A further potential issue of having one more drug in the regimen concerns a higher likelihood of such additional drug being victim or perpetrator of drug-drug interactions. A common feature of N/NtRTIs is the lack of any interaction with the cytochrome P 450 mixed function oxidase system, which otherwise involves to a different extent all other antiretroviral categories. With few rare exceptions, the presence of TAF in any regimen is virtually devoid of significant drug-drug interactions. As a consequence, the choice between a TAF-free dual regimen or a TAF-containing triple regimen like BIC/FTC/TAF will be mainly based on the immunovirological patient's profile, on the history of prior treatment failures and on her/his attitude to consistently adhere to the regular intake of antiretrovirals. The issue of adherence will be inevitably revived by the successful development of dual regimens, as, easy to say, three drugs are conceptually more protective than two whenever suboptimal intake and, consequently, suboptimal Pk exposure will occur. As an example, in the development of injectable cabotegravir and RPV, suboptimal exposure of RPV in virological suppressed patients (under supervised treatment intake) led to several virological blips and (rare) failures [36]. In the ATLAS and FLAIR trials, several virological failures occurred in patients with pre-existing RPV RAMs, a therapeutic situation in which only one drug (cabotegravir) was active [37, 38]. Although these occurrences were rare and did not compromise our perception of the validity of dual regimens in appropriately selected patients, nevertheless these episodes made us understand that if we choose two drugs only for treating our patients, both drugs should have an adequate Pk exposure and be fully active against the virus.

A new era has just started in antiretroviral therapy, and the new flow of innovation is providing significant advances in both conventional and newly identified 2-drug options. The new alternatives in the growing area of dual antiretroviral regimens claim for a re-consideration of patients' adherence whose importance was partially downgraded by the development of INSTIs in conventional triple combinations. The good news here are that even on the side of conservative 3-drug-based regimens the innovation has brought substantial improvements to make the daily intake of antiretroviral much easier than in the recent past.

REFERENCES

[1] Atta M.G., De Seigneux S., Lucas G.M. Clinical pharmacology in HIV therapy. *CJASN* 14, 435-444, 2019.
[2] Neogi U., Singh K., Aralaguppe S.G., et al. Ex-vivo antiretroviral potency of newer integrase strand transfer inhibitors cabotegravir and bictegravir in HIV type 1 non-B subtypes. *AIDS* 32, 469-476, 2018.
[3] Walmsley S.L., Antela A., Clumeck N., et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N. Engl. J. Med.* 369, 1807-1818, 2013.
[4] Clotet B., Feinberg J., van Lunzen J., et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48-week results from the randomised open-label phase 3b study. *Lancet* 28, 2222-2231, 2014.
[5] Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96-week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect. Dis.* 13, 927-935, 2013.
[6] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services, 2019. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. [Accessed 30th Oct 2019].
[7] Corado K.C., Caplan M.R., Daar E.S. Two-drug regimens for treatment of naïve HIV-1 infection and as maintenance therapy. *Drug Des. Devel. Ther*. 12, 3731-3740, 2018.
[8] Di Perri G., Calcagno A., Trentalange A., Bonora S. The clinical pharmacology of integrase inhibitors. *Expert Rev. Clin. Pharmacol*. 12, 31-44, 2019.
[9] Gilead Sciences. Biktarvy 50 mg/200 mg/25 mg flm-coated tablets: EU summary of product characteristics. 2018. Available at: http://www. ema.europa.eu/. [Accessed 30th Oct 2019].
[10] Gilead Sciences. Biktarvy® (bictegravir, emtricitabine, and tenofovir alafenamide): US prescribing in-

formation. 2018. Available at: https://www. accessdata.fda.gov/ [Accessed 30th Oct 2019].
[11] Gallant J.E., Thompson M., DeJesus E., et al. Antiviral activity, safety, and pharmacokinetics of bictegravir as 10-day monotherapy in HIV-1-infected adults. *J. Acquir. Immune Defic. Syndr*. 75, 61-66, 2017.
[12] Min S., Sloan L., DeJesus E., et al. Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. *AIDS* 25, 1737-1745, 2011.
[13] Neogi U., Singh K., Aralaguppe S.G., et al. Ex-vivo antiretrovi- ral potency of newer integrase strand transfer inhibitors cabo- tegravir and bictegravir in HIV type 1 non-B subtypes. *AIDS* 32, 469-476, 2018.
[14] Grobler J.A., McKenna P.M., Ly S., et al. Functionally irreversible inhibition of integration by slowly dissociating strand transfer inhibitors. 10th International Workshop on Clinical Pharmacology of HIV Therapy. April 15-17, 2009, Amsterdam. Abstract. O-10.
[15] Wenning L., Nguyen B., Teppler H., et al. Pharmacokinetic/pharmacodynamic analyses for raltegravir in phase II and III studies in treatment experienced HIV-infected patients. 9th International Workshop on Clinical Pharmacology of HIV Therapy. April 7-9, 2008. New Orleans. Abstract O-21.
[16] White K.L., Niedziela-Majka A., Nikolai Novikov N., et al. Bictegravir dissociation half-life from HIV-1 G140S + Q148H integrase/DNA complexes. 24th Conference on Retroviruses and Opportunistic Infections. Seattle, Feb 13-17, 2017. Abstr. n. 497.
[17] Hightower K.E., Wang R., Felix DeAnda F., et al Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 Integrase-DNA Complexes. *Antimicrob. Agents Chemoter.* 55, 4552-4559, 2011.
[18] Tsiang M., Jones G.S., Goldsmith J, et al. Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. *Antimicrob. Agents Chemother.* 60, 7086-7097, 2016.
[19] Cerrone M., Alfarisi O., Neary M., et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. *J. Antimicrob. Chemother.* 74, 1670-1678, 2019.
[20] 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* 390, 2063-2072, 2017.
[21] Sax P.E., Pozniak A., Montes M.L., et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 390, 2073-2082, 2017.
[22] Molina J-M., Ward D., Brar I., et al. Switching to fixed-dose bicte- gravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV* 5, e357-365, 2018.
[23] Daar E.S., De Jesus E., Ruane P., et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV.* 5, e347-356. 2018.
[24] Rousseau F.S., Wakeford C., Mommeja-Marin H., et al. Prospective randomized trial of emtricitabine versus lamivudine short-term monotherapy in human immunodeficiency virus-infected patients. *J. Infect. Dis.* 11, 1652-1658, 2003.
[25] Ruane P.J., DeJesus E., Berger D., et al. Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J. Acquir. Immune Defic. Syndr.* 63, 449-455, 2013.
[26] Cahn P., Sierra Madero J., Arribas J.R., et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet* 393, 143-155, 2019.
[27] Aboud M., Orkin C., Podzamczer D., et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. *Lancet HIV* 6, 576-587, 2019.
[28] Ustianowski A., Arends J.E. Tenofovir: what we have learnt after 7.5 million person-years of use. *Infect. Dis. Ther*. 4, 145-157, 2015.
[29] Podany A.T., Bares S.H., Havens J., et al. Plasma and intracellular pharmacokinetics of tenofovir in patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. *AIDS* 32, 761-765, 2018.
[30] Gupta S.K., Post F.A., Arribas J.R., et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate. A pooled analysis of 26 clinical trials. *AIDS* 33. 1455-1465, 2019.
[31] Seto W.K., Asahina Y., Brown T.T., et al. Improved bone safety of tenofovir alafenamide compared to tenofovir disoproxil fumarate over 2 years in patients with chronic HBV infection. *Clin. Gastroenterol. Hepatol.* 3565, 30633-30635, 2018.
[32] Borges A.H., Hoy J., Florence E., et al. Antiretrovi-

rals, fractures, and osteonecrosis in a large international HIV cohort. *Clin. Infect. Dis.* 64, 1413-1421, 2017.
[33] Raffi F., Orkin C., Clarke A., et al. Long-term (96-week) efficacy and safety after switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) in HIV-infected, virologically suppressed adults. International Congress of Drug Therapy in HIV Infection. October 2016. Glasgow, UK. Abstract O125.
[34] Norwood J., Turner M., Bofill C., et al. Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir. Immune Defic. Syndr.* 76, 527-531, 2017.
[35] Bakal D.R., Coelho L.E., Luz P.M., et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. *J. Antimicrob. Chemother*. 73, 2177-2185, 2018.
[36] Margolis D.A., 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. *The Lancet* 390, 1499-1510, 2017.
[37] Swindells S., Andrade-Villanueva J.F., Richmond G.J. et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: atlas week 48 results. CROI 4-7 March 2019, Seattle. Oral abstract 139.
[38] Orkin C., Arastéh K., Hernández-Mora M.G., et al. Long-acting cabotegravir + rilpivirine for HIV maintenance: FLAIR week 48 Results. CROI 4-7 March 2019, Seattle. Late breaker oral abstract 140LB.