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The multifaceted antiretroviral coverage provided by BIC/FTC/TAF: a pharmacokinetic/pharmacodynamic revisitation

Giovanni Di Perri[1], Andrea Calcagno[2,3]

[1]Infectious Diseases Unit, Amedeo di Savoia Hospital, Department of Medical Sciences, University of Torino, Italy;
[2]Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy;
[3]SC Malattie Infettive, AOU "Maggiore della Carità", Novara, Italy

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SUMMARY

The treatment of HIV infection has entered a dichotomous phase, as established oral regimens are now sharing the landscape with long acting injectable combination therapies. By looking at the new antiretrovirals in the pipeline it is apparent that the future of HIV treatment will be largely covered by long-acting regimens, with an increasing shift toward injectable formulations allowing much less frequent administration; in parallel, the development of novel once-daily oral combinations, as well as oral long acting therapies is expected to further expand treatment options. However, the current HIV-infected population still includes a large proportion of patients with a variety of immunovirological conditions whose weaknesses require the currently available strongest option, such as a triple oral regimen including a 2nd generation integrase strand-transfer inhibitor (INSTI) like the co-formulation containing Bictegravir (BIC), Emtricitabine (FTC) and Tenofovir alafenamide (TAF). Further to a proportion of newly diagnosed HIV infections at an advanced disease stage still exceeding 50%, many are the patients whose history may include a late start of treatment, virologic failures and a suboptimal immune recovery. BIC/FTC/TAF is the point of arrival of decades of antiretroviral research and has the pharmacologic characteristics to guarantee the therapeutic success in most patients with difficult-to treat infections. Properties like intrinsic potency, strong genetic barrier and forgiveness of BIC/FTC/TAF are unique among currently available antiretroviral regimens and make this single tablet combination as the gold standard for comparative studies of new therapeutic solutions. The main clinical-pharmacologic features of BIC/FTC/TAF are here analysed with the intention to focus on some key advantages this regimen may offer whenever the individual conditions are less than ideal for other regimens.

Keywords: Bictegravir/Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF), Dolutegravir (DTG), Lamivudine (3TC), Rilpivirine (RPV), Cabotegravir (CAB), Long-Acing Injectables, HIV-RNA, HIV-DNA, CD4+ T-cell, Elimination half-life (T/2), Volume of Distribution (VD), Resistance-Associated Mutation (RAM).

INTRODUCTION

While the antiretroviral horizon is being increasingly populated by novel combinations and most of current pharmaceutical research is oriented toward the development of long-acting injectable formulations, strand-transfer integrase inhibitor (INSTI)-based oral therapy remains a mainstay in antiretroviral treatment guidelines for a variety of reasons [1]. The vast majority of patients currently receiving antiretroviral therapy achieve the suppression of HIV replication below the internationally accepted cut-off of 50 HIV-RNA copies/mL [2]. However, if we look at each individual history, very different substandard pathways to virologic suppression can be described whose impact

Corresponding author
Giovanni Di Perri
E-mail: giovanni.diperri@unito.it

on long-term maintenance of virologic suppression could be substantial if the properties (e.g. potency, forgiveness, genetic barrier) of the current regimen are less ideal than required to ensure persistent suppression of HIV replication. The years spent with uncontrolled viral replication, the degree of immune deterioration as well as of the magnitude of the viral biomass before the treatment was started, are all major variables to consider in evaluating the suitability of patients to receive dual instead of triple antiretroviral regimens [3]. A further major factor to carefully take into consideration is the presence of viral mutations coding for resistance to antiretrovirals. Having been poorly adherent and/or having received suboptimal regimens in the past (e.g. in the era of unboosted protease inhibitors – PIs) put the patients at risk of virologic failure when the new regimen is not potent enough to overcome the weaknesses generated by past history of HIV infection and/or treatment [4]. These are the main reasons why potent combination regimens are still necessary in a sizeable proportion of patients, and beyond the number of drugs there are some specific properties of antiretrovirals that contribute to compensate for several vulnerabilities associated to the individual immune–virologic profile. This is the case of the single-tablet regimen consisting of Bictegravir (BIC), Emtricitabine (FTC) and Tenofovir alafenamide (TAF), whose pharmacologic characteristics, like intrinsic potency, diffusion into compartments, intracellular penetration, elimination half-life (T/2) and dissociation time from target receptors actually account all together for its capacity to overcome most of the difficult to treat situations. Here we review the clinical pharmacologic properties and peculiarities of this combination with an attempt to compare it to other established regimens in order to identify some poorly explored immunovirological parameters that might fruitfully contribute to drive the therapeutic choice.

PHARMACOLOGICAL FEATURES OF BICTEGRAVIR, EMTRICITABINE AND TENOFOVIR ALAFENAMIDE

Table 1 shows the main pharmacological features of BIC, FTC, and TAF as well as of the other most used oral antiretroviral drugs (TDF, 3TC, DTG) [5]. Molecular weight affects all the steps of the absorption, distribution, metabolism and excretion (ADME) process with smaller molecules usually more easily distributed across barriers. Lipophilicity (expressed as LogP, the higher the more lipophile a molecule) affects the ability of a drug to cross barriers and accumulate in fat-rich tissues (such as the brain and adipose tissue). Protein binding represents the amount of total concentration of a given substance bound to plasma proteins (mainly albumin and alpha-1-acid glycoprotein): unbound molecules are available for drug transport and distribution. These features affect

Table 1 - Main pharmacological features of commonly used oral antiretroviral drugs.

	TDF	*TAF*	*3TC*	*FTC*	*DTG*	*BIC*
Molecular weight KDa	519	476	229.3	247.2	441.4	449.4
Lipophilicity LogP	2.1	1.6	-1.4	-0.43	2.2	1.3
Protein binding %	<0.7	80	<36	<4	>98	>99
Bioavailability %	25	82	80-85	93	n.a.	n.a.
Metabolism	Renally, unchanged	Renally, unchanged	Renally, unchanged	Renally, unchanged	UGT1A1 (CYP3A4)	CYP3A4, UGT1A
Volume of distribution L/Kg	0.8	>1.6	1.3	1.4	0.3	0.2
Half-life hours	12-18	17	5-7	10	14	17
*Intracellular half-life** hours	95	87-150	16-19	39	n.a.	n.a.
Dissociation time from integrase hours	n.a.	n.a.	n.a.	n.a.	71-96	163
Cmax ng/mL	326°	6.2°	2000	1800	3670	6150
Ctrough ng/mL	64°	2.3°	40	90	1110	2610

* for NRTIs: tri-phosphorylated or bi-phosphorylated molecules; ° reported pharmacokinetic data rely to tenofovir
Note: "n.a.", not available.

the volume of distribution (Vd), that represent the "virtual" space that a compound may diffuse into: drugs with large Vd have usually high tissue concentrations. Finally terminal half-life represents the time needed for the halving of drug concentrations and is, therefore, a relevant parameter for understanding the persistence of a drug in plasma or in cells and tissues.

Bictegravir

BIC is a potent INSTI that inhibits the HIV integrase enzyme by blocking the strand transfer step of viral DNA integration into the host genome. By chelating divalent metal ions at the integrase active site, it prevents stable insertion of viral DNA, thereby halting viral replication at an early post-entry stage. BIC is orally bioavailable and reaches peak plasma concentrations approximately 2–4 hours after dosing; while food may modestly increase its exposure, these effects are not clinically significant, allowing administration without regard to meals [6, 7]. However, absorption can be reduced by concomitant administration with polyvalent cations (e.g., magnesium, aluminum, calcium), which can chelate the drug in the gastrointestinal tract [8]. BIC is highly protein bound (>99%) and extensively distributed in plasma. Despite high protein binding, the drug distribution is fair with an approximate Vd of 0.2 L/kg. BIC is metabolized primarily by CYP3A4 and UGT1A1-mediated glucuronidation. While it has some susceptibility to enzyme induction or inhibition, it has a favorable drug-drug interaction profile compared with earlier INSTIs. Strong inducers of CYP3A4 or UGT1A1 (e.g., rifampicin) can significantly reduce BIC exposure and are contraindicated unless a double dose is used: conversely, moderate inducers have successfully administered with BIC [9, 10].

Emtricitabine

FTC is a cytidine analogue NRTI that undergoes intracellular phosphorylation to emtricitabine triphosphate. This active metabolite competitively inhibits HIV reverse transcriptase and causes DNA chain termination upon incorporation into the growing viral DNA strand. FTC is active against both HIV-1 and HIV-2 and also exhibits activity against hepatitis B virus. FTC is well absorbed after oral administration, with high bioavailability (>90%). Peak plasma concentrations are typically achieved within 1–2 hours, and absorption is not significantly affected by food. FTC exhibits low plasma protein binding (<4%) and is widely distributed throughout body tissues and fluids. FTC undergoes minimal metabolism and is largely eliminated unchanged via renal excretion through glomerular filtration and active tubular secretion. As a result, FTC has a low potential for metabolic interactions but may require dose adjustment in patients with significant renal impairment [11].

Tenofovir alafenamide

TAF is a prodrug of tenofovir, a nucleotide analogue of adenosine monophosphate. After intracellular activation, tenofovir diphosphate competes with natural deoxyadenosine triphosphate for incorporation into viral DNA by HIV reverse transcriptase. Incorporation results in premature chain termination, inhibiting viral DNA synthesis. Compared with its predecessor TDF, TAF delivers higher intracellular concentrations of the active metabolite with substantially lower plasma tenofovir exposure. TAF is rapidly absorbed following oral administration and exhibits improved plasma stability compared with TDF. It remains largely intact in circulation and is efficiently taken up by target cells, particularly lymphocytes and macrophages. Food has minimal clinically relevant effects on TAF exposure when administered in fixed-dose combination. TAF results in low systemic tenofovir concentrations but achieves high intracellular levels of tenofovir diphosphate within peripheral blood mononuclear cells [12, 13]. Plasma protein binding of TAF is moderate, while tenofovir itself has minimal protein binding. Distribution favors lymphoid tissues, supporting antiviral efficacy while reducing renal and bone toxicity [14]. TAF undergoes intracellular hydrolysis primarily by cathepsin A to release tenofovir, which is subsequently phosphorylated to its active diphosphate form. Minimal metabolism occurs via cytochrome P450 enzymes, reducing the risk of metabolic drug–drug interactions: rifampicin induction, despite lowering TAF exposure, minimally affected intracellular diphosphate concentrations and now the drug can be used in patients treated for tuberculosis [15].

COMPARTMENTAL DISTRIBUTION AND EFFICACY

Beyond systemic viral suppression, long-term therapeutic success depends on adequate drug

exposure in anatomical and cellular compartments that serve as viral reservoirs. These include different cell types, the central nervous system (CNS), the gastrointestinal (GI) tract, and the male and female genital tracts [16]. The pharmacokinetic properties of BIC/FTC/TAF have been extensively characterized and demonstrate differential but complementary penetration across these compartments. The clinical consequences of poor or asymmetric drug exposure in compartments may be residual viral replication, selection of resistance-associated mutations and chronic immune activation. In the CNS this may translate in cerebrospinal fluid (CSF) escape (detectable HIV RNA in the CSF while undetectable in plasma): despite being asymptomatic in the majority of patients it may cause several neurological symptoms [17, 18].

Lymphocytes and Macrophages

HIV primarily infects $CD4^+$ T lymphocytes and monocyte-derived macrophages, both of which contribute to viral persistence. Compared with tenofovir disoproxil fumarate (TDF), TAF results in approximately 4–7-fold higher intracellular TFV-DP concentrations in peripheral blood mononuclear cells (PBMCs) while maintaining ~90% lower plasma tenofovir exposure. This pharmacological profile is particularly advantageous in macrophages, which efficiently convert TAF to TFV-DP and retain the active metabolite for prolonged periods due to slow cellular turnover. BIC achieves high intracellular concentrations and potently inhibits viral integration in both activated and resting lymphocytes, as well as in macrophages, thereby targeting key cellular reservoirs.

The Central Nervous System

The CNS represents a pharmacological sanctuary due to the restrictive nature of the blood–brain barrier and the activity of efflux transporters such as P-glycoprotein and breast cancer resistance protein. Subtherapeutic antiretroviral exposure in the CNS has been associated with ongoing viral replication and HIV-associated neurocognitive disorders. Three studies investigated BIC/FTC/TAF CSF exposure: the PK data as well as CSF HIV RNA are reported in *Table 2* [19-22]. They suggest that CSF drug exposure is low, but the drugs are more unbound than in plasma thus leaving unbound concentrations above inhibitory ones (considering a half-maximal effective concentration or EC50 of 1.1 ng/mL). Specifically, TAF was found to be undetectable in CSF and tenofovir to be low: two published works studied the switch from TDF to TAF in the CSF. They reported the maintenance of virological suppression in plasma and CSF and no effect of biomarkers associated with neuronal damage [22, 23].

The Gastrointestinal Tract

The GI tract, particularly gut-associated lymphoid tissue (GALT), is a major site of early $CD4^+$ T-cell depletion and persistent immune activation. Achieving adequate antiretroviral concentrations in intestinal tissues is therefore critical for reservoir suppression. FTC displays extensive penetration into intestinal mucosa and lymphoid tissue, resulting in high intracellular FTC-TP concentrations in gut-resident immune cells. TAF enhances delivery of TFV-DP to lymphocytes and macrophages within GALT, despite lower luminal exposure compared with TDF (since its bioavailabil-

Table 2 - Bicetgravir/emtricitabine/tenofovir alafenamide cerebrospinal fluid concentrations in published studies.

	Tiraboschi 2020	*Rigo-Bonnin 2020*	*Gelé 2021*
N	15	6	24*
Undetectable plasma HIV RNA %	100	100	67
Undetectable CSF HIV RNA %	100	100	92
Bictegravir ng/mL	6.9	7.1	11.8
Unbound bictegravir ng/mL	2.5	3.7	4.4
Emtricitabine ng/mL	n.r.	n.r.	84.4
Tenofovir ng/mL	n.r	n.r.	1.6

*with CNS opportunistic disorders or cognitive impairment.
Note: "n.r.", not reported.

ity is higher). This targeted intracellular activation reduces off-target toxicity while maintaining antiviral efficacy. BIC exhibits sufficient tissue distribution within the GI tract, with concentrations exceeding the inhibitory threshold for integrase activity despite tissue concentrations in PWH on treatment have not been reported. An interesting study evaluated the dynamics of the decay of HIV RNA and distribution of BIC in the genital tract and rectum in cART naïve adults treated with BIC/FTC/TAF [24]. The time to undetectable HIV-1 RNA was significantly shorter in seminal plasma (SP) and rectal fluid (RF) than in blood plasma (BP). All women achieved undetectable HIV-1 RNA in cervicovaginal fluid (CVF) at Day 14. The median total BIC concentrations in SP, RT, and CVF were 65.5 (20.1–923) ng/mL, 74.1 (6.0–478.5) ng/g, and 61.6 (14.4–1760.2) ng/mL, respectively, representing 2.7%, 2.6%, and 2.8% of the BP concentration; the protein-unbound fractions were 51.1%, 44.6%, and 42.6%, of BP concentrations.

The Male Genital Tract

The male genital tract is relevant for both viral persistence and sexual transmission. FTC penetrates efficiently into seminal plasma, often achieving seminal-to-plasma ratios greater than 1. Intracellular FTC-TP concentrations in seminal leukocytes are sustained and pharmacologically active. Tenofovir exposure in seminal plasma is lower with TAF than with TDF; however, intracellular TFV-DP levels in genital tract immune cells remain within the therapeutic range. Data on BIC indicate moderate seminal penetration, with seminal plasma concentrations generally exceeding the protein-adjusted IC95. These findings support effective suppression of local viral replication and contribute to the reduction of transmission risk in individuals receiving BIC/FTC/TAF [24].

The Female Genital Tract

Drug distribution in the female genital tract is influenced by hormonal fluctuations, tissue compartmentalization, and mucosal immune cell density. FTC demonstrates excellent penetration into cervicovaginal fluids and tissues, with high intracellular FTC-TP levels in $CD4^+$ T cells and macrophages. These properties have been well documented in both treatment and prevention studies. TAF-derived tenofovir shows lower extracellular concentrations in cervicovaginal secretions compared with TDF; however, efficient intracellular conversion ensures adequate TFV-DP exposure in target cells. BIC/FTC/TAF was successfully used as post-exposure prophylaxis in 39 persons (86.4% women) after a sexual assault: no HIV seroconversion was observed [25, 26].

CLINICAL IMPLICATIONS

All these pharmacologic factors and related properties are the result of decades of research in antiretroviral therapy. The rate of virologic suppression today achievable by second-generation INSTI-based regimens like BIC/FTC/TAF is unprecedented, as demonstrated by the therapeutic performance in clinical studies [27, 28]. It is noteworthy how the few virologic failures recorded in clinical trials were not associated to RAMs selection, and how such occurrence is barely anecdotal in clinical practice. To further testify the potency of this regimen is worth noting how in several clinical studies comparable high rates of virological suppression and maintenance overtime were achieved despite the presence of NRTI/NtRTIs RAMs at baseline [29, 30]. The advancements that made it possible to develop these medications were driven by the absolute priority of providing the most potent, tolerable and easy to use drugs. What is available today in terms of triple regimens based on 2nd gen INSTIs is the desired result of years spent in fighting and overcoming problems like drug resistance, poor compliance, side effects, drug-drug interactions as well as the never-ending issue concerning the treatment of very advanced infections.

The key drug class that made it possible these achievements is thus the INSTIs and particularly the properties of 2nd generation drugs, such as Dolutegravir and Bictegravir. While DTG is available alone as well as in triple (DTG/3TC/ABV) and dual fixed combinations (DTG/RPV, DTG/3TC), BIC can only be administered as part of the triple single tablet combination BIC/FTC/TAF. The latter could be seen as a limitation on one side but as a protective factor in another perspective. Since BIC can only be used in combination with FTC and TAF, a reciprocal protection against RAMs selection takes place among the three drugs, and therefore the risk of virologic failure and RAMs selection is markedly limited. The most remarkable pharmacodynamic property of 2nd gen INSTIs

is the very rapid action exerted against HIV replication [31]. The viral fall is very fast and a proportion of patients approaching 80% reaches a viral load level below 50 copies/mL in only 4 weeks in treatment-naïve studies. One might argue that non-INSTI-based regimens take only few weeks more to achieve a comparable result with otherwise similar benefits over the long term. So the question is what is/are the advantage/s, if any, of such quick antiretroviral action? A conceivable answer concerns the genetic barrier of 2nd generation INSTIs. Before INSTIs were released the definition of genetic barrier was made on the basis of the differences between NNRTIs and boosted PIs (PI/b), and the strength of the genetic barrier was thus proportionally defined by the number of RAMs required to make the drug no longer able to inhibit HIV replication. More RAMs were necessary to abolish the activity of PI/b (high genetic barrier) while a single specific RAM was enough to make NNRTIs inactive (low genetic barrier). By applying such definition, we might classify the genetic barrier of 2nd gen INSTIs as barely greater than that of NNRTIs, as one or two mutations might actually compromise the antiretroviral activity of 2nd gen INSTIs, but this is far to be the case in practice. Although slightly lower than the genetic barrier of PI/b, the one of 2nd gen INSTIs is *de facto* well known to be much higher than that of NNRTIs. And here comes the likely contribution of the very rapid viral fall associated to 2nd gen INSTIs. In terms of general chemotherapeutic principles, in anti-infective therapy one of the variables driving the likelihood of resistance selection is the duration of microbial exposure to the selecting factor (the drug in this case). The unique rapid reduction of the viral biomass seen with 2nd gen INSTIs is such that the time available to generate the selection of resistant mutants is actually much shorter than with any other antiretroviral drug. The protection provided by this pharmacodynamic property not only applies to the drugs that generates it (2nd gen INSTIs) but it also encompasses the companion drugs, since the advantage of a very shorter time of exposure also applies to co-administered antiretrovirals. A similar clinically applied example comes from the treatment of *P. falciparum* malaria. By combining the very fast acting artesunate derivatives (with short plasma T/2) with slowly acting antimalarials (with much longer T/2) in the treatment of *P. falciparum* infection it was made possible to achieve a fast reduction (3-4 log units in 48 hours) of parasitaemia driven by artesunates, with only a small amount of residual parasites being subsequently exposed to slower acting 2nd drug [32, 33]. The former, when used alone, was exposed to a progressive loss of activity, due to the long-time persistence of decreasing concentrations in the presence of much more numerous parasites. The association with artesunates not only protected the slowly acting drug from resistance but it even restored in some circumstances the formerly compromised sensitivity of *P. falciparum* to these drugs. Further to these characteristics there are some additional features that might help to interpret why in the vast majority of cases the virologic failure of these regimens is uneventful in terms of RAMs selection. The elimination half-life (T/2) of 2nd gen INSTIs is around 15 hours, and very similar values are also shared by boosted Darunavir (DRV/c) and Doravirine (DOR). Not surprisingly these 3rd drugs are part of most triple regimens currently successfully administered in the western world. We might thus consider that a T/2 value of 15 hours is probably ideal for a conventional triple oral regimen based on two NRTI/NtRTIs. Such T/2 duration is long enough to allow for once daily administration and on the other hand is short enough to make the drug virtually disappear from plasma when viral regrowth takes place following treatment interruption. So the old dilemma between NNRTIs and 2nd gen PIs/b, with long and short T/2 respectively, is today solved by this value in-between the two alternatives. While new drugs are being developed with much longer T/2 with the purpose of providing new long-acting options, as far as we look at conventional triple regimens a T/2 around 15 hours seems thus to be the final desired solution.

A major contribution here also comes from the presence of TAF, as the high Intracellular concentration of the active moiety might even overcome the presence of RAMs that would significantly compromise the activity of the same drug when given as TDF instead of TAF [34]. Although the active moiety is by definition the same, the 6-7 times higher intracellular concentration reached by the intake of TAF might actually compensate for the reduced affinity of the drug for its target. Furthermore, although the intracellular half-life is, again by definition, the same regardless the drug

is taken as TDF or TAF, the decrease of the TAF-determined higher intracellular concentrations of TFV-diphosphate (TFV-PP) below the minimal active value takes a much longer time to reach levels vulnerable to resistance selection, and this also corresponds to a greater forgiveness in case of missed doses. The counterpart of generating much higher intracellular concentrations in target cells is that much lower plasma concentrations are instead present in the in case of TAF intake, with the resulting advantages on the side of the safety of the drug. As opposite to what happens with TDF, such as the quick dissociation between TFV and the disoproxil fumarate salt upon absorption, in the case of TAF the binding between TFV and its alafenamide salt tends to be stable following intestinal absorption and this allows for a selective uptake of the drug by target cells that are rich in carboxylesterase 1 (CES1) and cathepsin A (CatA). Such selective distribution of TFV also implies a much lower TFV plasma concentration (as compared to what happens with TDF), with significant reduction of proximal tubular toxicity and the related downstream consequences in terms of bone structure integrity.

The last component of BIC/FTC/TAF oral regimen is FTC, whose historical comparator is 3TC. Both are very well tolerated and safe cytidine analogues, but as compared to 3TC, FTC is associated to the presence of higher intracellular concentrations of the active moiety as well as to a longer intracellular T/2. Although in a monotherapy study FTC was found to generate a stronger and more durable virologic suppression than 3TC, in treatment-naïve patients no significant differences in efficacy are attributable to the pharmacologic dissimilarities between the two drugs. Nevertheless, the advantages provided by FTC might also contribute to the robustness of the regimen.

BIC/FTC/TAF VS OTHER REGIMENS

Until very recently most of the research done on antiretroviral therapy has been mostly focused on HIV inhibition and immune recovery. In the last decade however other aspects of the long-term drug intake also emerged as priorities. The patients are getting older and conventional age-related comorbidities are on the increase, many co-medications have to be also taken together with antiretrovirals and the need to modify the treatment is increasingly perceived [35, 36] Furthermore, given the quality of the antiretroviral drugs today available, permanent HIV inhibition is now taken for granted. This evolving landscape has led to the development of alternative therapeutic approaches aimed at reducing treatment burden while maintaining immune-virologic efficacy targets. An additional opportunity on this line comes from the long-acting injectable formulations, as an option for those patients who might find this therapeutic modality as an easier way to be treated with less troubles both in terms of compliance and protection from stigma, in spite of more frequent visits. In the light of a lifelong treatment such tendency to develop injectable long-acting regimens appears to be a fruitful option for a sizeable proportion of patients. Several options are currently available as maintenance therapy for virologically suppressed patients, including Dolutegravir/Rilpivirine, Dolutegravir/Lamivudine, and the long-acting injectable combination of Cabotegravir and Rilpivirine. Dolutegravir/Lamivudine is also approved for treatment-naïve patients with a baseline viral load below 500,000 copies/mL. Less frequently prescribed, a darunavir/cobicistat-based regimen is also included among the available options.

However, it remains challenging to directly compare regimens with different pharmacological and clinical characteristics, particularly when their mechanisms supporting efficacy differ from those historically established. These therapeutic approaches represent distinct strategies within the current treatment landscape, developed in different phases of antiretroviral evolution and for different clinical needs, and are characterized by differing profiles in terms of intrinsic potency, genetic barrier, and forgiveness. This makes direct, absolute comparisons inappropriate Nevertheless, comparative clinical studies have been carried out in specific settings defined by individual virologic parameters. The STR combining DTG and 3TC showed non-inferiority when compared to three-drug regimens both as maintenance regimen in virologically suppressed patients and in treatment-naïve patients when compared to TDF/XTC/DTG, in the registration GEMINI trial. In the latter study viral suppression was similar (86% vs. 89.5% at 96 weeks) and no treatment-emergent resistances were observed in either arm [37]. Since some analyses suggested slightly lower response

in participants with CD4 <200 cells/μL a subsequent independent study was performed (DOLCE) in this subgroup of patients with results suggesting a comparable efficacy [38]. Several trials investigated DTG/3TC as a switch therapy in virologically suppressed patients (TANGO, SALSA, ASPIRE, DOLAM): virological suppression rates were similar in both groups and DTG/3TC was found to be non-inferior to triple therapy [39-41]. Data from real-life studies seem to confirm these observations and a recent systematic review and meta-analysis (on more than 10000 participants) concluded that "Overall treatment outcomes in real-world settings confirm the efficacy, tolerability, and high barrier to resistance seen in phase 3 trials across diverse populations, including those naive to ART or with prior ART experience" [42]. However, real-life virological data from a multicentre study in France suggested that a sizable proportion of patients had resistance-associated mutation when failing DTG/RPV (39%), DTG/3TC (18%), DTG/ABC/3TC (8.5%) as compared to B/F/TAF (4%) [43]. The most updated version of the study showed similar results with RAMs observed in 32%, 15% and 3% of patients failing LA_CAB/RPV, DTG/3TC or B/F/TAF respectively [44].

Concerning the comparison between BIC/FTC/TAF and the injectable long-acting association CAB/RPV the task is even mor difficult for pharmacologic reasons. A single-tablet regimen like BIC/FTC/TAF is given daily and every single day a peak concentration exposes the virus for several hours to drug levels well higher than the cutoff C_{trough}, while with long-acting injectables a single peak is achieved after 10-14 days to be followed by decreasing concentration until a new injection is given. The challenge is left in the hand of prescribing doctors who are not in trouble in choosing the regimen when overt conditions are recognizable. An advanced treatment-naïve patient with high viral load and low $CD4^+$ T-cells or an experienced patient with an history of virologic failures requires a cautious and more conservative approach, while at the opposite, a fully virologic suppressed patient with high $CD4^+$ T-cells, intermediate-high baseline immune profile and a rather recently acquired infection allows to select a regimen among a wider choice of possible options, with more room for the patient's preferences. In the middle of these opposite straightforward conditions there is a sort of grey area where several considerations about the individual patient's characteristics are required in order to make a choice with an acceptable chance of providing a successful immune-virologic outcome. While the best chances of a good outcome are by definition associated to a triple 2nd gen INSTI-based regimen, a variable degree of uncertainty might be present when a dual regimen is considered. By respecting several specific limitations, the clinical experience so far gained with oral dual regimens is solid enough to drive a reasonably safe choice in terms of risk of virologic failure and resistance selection. Since all oral 2nd gen INSTIs-based dual regimens are based on DTG it is interesting to consider a recent review on the risk of resistance selection in case of DTG-based regimens virologic failure. Out of a total of 599 viremic patients under treatment with DTG-based regimens, 86 (14.4%) had INSTIs RAMs but only 36 (6%) were found to harbour RAMs associated to DTG resistance [45]. Three were the factors significantly associated with resistance to DTG: monotherapy with DTG, dual therapy with 3TC and NRTIs RAMs at baseline. It is worth noting that the proportion of patients exposed and unexposed to 1st gen INSTIs was similar between those with any INSTIs RAM and those without (33 vs 32%), thus suggesting that prior exposure to 1st gen INSTIs was not a strict pre-requisite for the subsequent selection of INSTIs RAMs. These data highlight the importance of ensuring the absence of relevant NRTI RAMs in the patient's resistance profile when selecting treatment strategies with specific pharmacologic characteristics. Although current selection criteria for DTG/3TC or DTG/RPV generally include the absence of resistance mutations, no active HBV infection, and sustained virologic suppression for at least 6 months, careful patient evaluation remains essential since in some case series other factors also emerged. A similar level of caution and careful patient selection also applies to the injectable long-acting treatment with CAB/RPV, for which the risk of failure (not statistically dissimilar from 2nd gen INSTI-based triple regimens) was found to be associated to three factors, such a viral subtype A1 or A6, baseline RAMs for RPV and a BMI above 30 [46]. While the first two point on virologic variables, the third suggests a possible responsibility of the pharmacokinetic exposure. It must be

stressed that whenever we evaluate the therapeutic performance of long-acting CAB/RPV we should take into account that its administration is fully supervised and no room is left for lack of adherence from patients. This is definitely different from oral regimens, whose virologic failure is often interpreted as possible insufficient adherence. The clinical pharmacology of long-lasting regimens is clearly different from that of daily oral treatments, as a single major peak is followed by slowly decreasing concentrations until the following scheduled injection is given. While the cutoff C_{trough} of RPV was well known from the studies made on the oral formulation and its validity is testified by 15 years of clinical use, the cutoff C_{trough} of the injectable pharmaceutical form of CAB was first established in animal models and subsequently applied in humans. Uninfected animal models (*Macaques Rhesus*) were challenged at different intervals with standardized inocula of a chimeric simian/human virus (Simian/Human Immunodeficiency Virus SHIV 162P3) after exposure to CAB IM injections and the correlates of protection were measured taking the $PAIC_{90}$ (protein-adjusted inhibitory concentration of 90% of the *in vitro* viral growth) as unit of measure. Based on these experiments a pharmacokinetic level of $4xPAIC_{90}$ was found to be fully protective against SHIV infection and the same was adopted for human clinical studies and finally confirmed at drug entry into the market. We might argue that these studies were not done with HIV but on a chimeric simian/human virus, the hosts were not humans but animal models and that the study was not on chronic infection but on prevention against intravaginal and intrarectal infection. Nevertheless, once approved the dual long-acting injectable combination CAB/RPV repeatedly achieved non inferiority both in registration trials and in phase IV comparative studies against 1st line standard oral treatments [47]. The only real and rather consistent difference between this long-acting regimen and standard oral comparators was the rather high rate of virologic resistance recorded in the few patients who had virologic failure with CAB/RPV [48]. To measure and interpret this asymmetric phenomenon we can look back at DTG monotherapy for an indirect comparison. The failure rate of DTG monotherapy was well higher than that of CAB/RPV, such as 18 failures out of 272 patients (6.6%) vs 24 failures out of 2313 CAB/RPV intakers (1.03%) from 5 comparative randomized studies. However, resistance selection among patients with virologic failure was lower in case of DTG monotherapy (7 patients out of 15 in whom resistance testing was possible, 46%), as compared to CAB/RPV (18 out of 24 patients, 75%). This comparison is flawed by several factors, the most relevant being that it was not a comparative properly designed trial but just a comparison between a single non repeatable study (open study of DTG monotherapy vs DTG/ABC/3TC) and the findings taken from 5 clinical comparative studies on injectable CAB/RPV vs oral comparators (LATTE-2, ATLAS, FLAIR, ATLAS-2M and SOLAR). As suggested by the role of BMI as risk factor for virologic failure, pharmacokinetics of CAB/RPV could be an hot point here, as in several reports it was found that in a sizeable proportion of patients the C_{trough} of both CAB and RPV was lower than expected, with cases having barely measurable concentrations at the end of the dosing interval [49]. Thus, an explanation might be the lack of adequate drug levels in some patients. We might envisage how in these cases the slowly descending pharmacokinetic pattern of the drugs makes the concentration fall in the so called "mutant selection window" (MSW) for a time sufficient to determine both virologic failure and selection of RAMs. The MSW identifies a concentration interval within which the drug exposure is still above the sensitivity of most virions but below the level required to inhibit the 1st step mutants, a theoretical framework that was taken into consideration in the past to explain the virologic failure of 1st and 2nd gen NNRTIs intakers (drugs with long T/2). If the time within the MSW is long enough (before the subsequent injection) both virologic failure and RAMs might thus take place. However, such a hypothesis is unlikely to cover the entire story, as the number of patients with borderline or insufficient pharmacokinetic exposure in these studies is disproportionately high as compared to the number of those who undergo virologic failure. Some biologic variables, as the ones found to be associated to DTG monotherapy failure, might contribute to better understand the picture. The low nadir $CD4^+$, the time spent with uncontrolled HIV replication before the first treatment was started and the higher HIV-DNA burden measured in those who failed are proxies of each other, and all three testified an

immunovirological profile for which the use of a single drug, although fully active and intrinsically very potent, might not be sufficient to determine and maintain viral suppression over time [50, 51]. The intimate reasons are almost unknown but the most accredited hypothesis is that the long period of uncontrolled viral replication, with its immunovirological markers, like a low nadir $CD4^+$ T-cell count and an high HIV-DNA reservoir, might still determine a renewal of circulating virus whose magnitude cannot be fully controlled by a single active drug, as it is the case of DTG monotherapy, and possibly in some patients under treatment with CAB/RPV. Several reports that focused on CAB/RPV failures found similar factors to be associated with both virologic failure and RAMs selection and suggest to include some anamnestic items in patient's selection. In a study on 173 recipients of CAB/RPV these variables could be addressed in a setting of Pk with a relatively low frequency of suboptimal exposure. In facts, as compared to other clinical reports, in this study the average Pk exposure of patients was definitely higher, with only a small minority of patients (around 2%) having CAB levels < 4xPA-IC_{90} (664 ng/mL) and none with RPV exposure <4xPAIC_{90} (50 ng/mL). Interestingly, in spite of the better pharmacokinetic profile the failure rate was comparable to other clinical studies (2 patients, 1.15%, both with C_{trough} well above the recognized cutoff value for CAB and RPV). This study, perhaps more than others, shows how virologic failure with CAB/RPV may occur even in the presence of a Pk exposure rated as correct according to the so far recognized cut-offs. The final virologic findings, after a follow-up approaching one year, were stratified according to the values recorded, with 61.3% of patients < 20 HIV-RNA copies/mL, 84.8% <50 copies/mL and 95.9% <200 copies/mL [50]. As compared to patients with <20 copies/mL, those with >20 copies/mL had higher zenith values of pre-treatment viremia, a trend toward lower nadir CD4+ T-cell counts, a higher incidence of viremia episodes in the year preceding the switch to CAB/RPV and a lower likelihood to have <20 copies/mL at the time of switch. We might argue that the threshold of 20 copies/mL is too ambitious and that the conventional cutoff of 50 copies/mL should be taken instead. However, in the same study these variables had similar trends also in case of a cutoff of 50 copies/mL. The Authors suggest that these patients have a large proviral reservoir from which virus production by long-lived infected cells is barely covered by CAB/RPV. In most clinical studies addressing the association between low level viremia and the risk of subsequent virologic failure it was found that some degree of correlation starts with values above 50 copies/mL and it proportionally increases with higher viremias. However, these studies were carried out on patients taking various conventional oral triple regimens and it remains to be established whether minor viremias (<50 copies/mL) detected by ultra-sensitive assays might instead predict virologic failure in case of dual therapies. Whatever is the case, in this study a robust protection against virologic failure or viral blips of any magnitude was provided by switching to CAB/RPV with a viral load <20 copies/mL.

Should these findings be confirmed by similar observations, provided that the approved criteria for CAB/RPV treatment are also met, patients with HIV-RNA <20 copies might be switched to this long-acting option with the least risk of virologic failure.

To provide a further demonstration of the differences in terms of failure rates and RAMs selection across different therapeutic approaches, it is worth considering the results of two studies designed to challenge the standard daily frequency of drug intake. In these two studies B/F/TAF and DTG/3TC respectively were administered less frequently than once a day. In the DUETTO trial participants (214 vs. 291) were randomized to receive DTG/3TC every day or 4 days a week: in the intermittent arm 8 subjects presented virological failure and 4 resistance associated mutations [52]. The BETAF-RED was a smaller (n=40) study in which participants received B/F/TAF every day or 3-2-1 times/week: the three cases of viral failure included two from the once weekly arm and one from the thrice weekly arm [53]. Interestingly no resistance was detected and no significant change was observed in ultrasensitive HIV RNA, HIV reservoir (measured through IPDA) or inflammatory markers (such as intrleukin-6 and high-sensitivity C reactive protein). Although such unusual frequencies of administration are unlikely to be applied with these regimens, what has been observed in these studies does confirm the stronger genetic barrier of B/F/TAF as compared to DTG/3TC.

CONCLUSIONS

The more recent clinical studies concerning the risk of virologic failure and RAMs selection are to some extent reminiscent of older times when we were fighting against drug resistance with a lower number of therapeutic options and with drugs less potent than 2nd gen INSTIs and TAF. The experience gained in trying to overcome and prevent drug resistance by relying upon the knowledge of RAMs, Pk data and past HIV history remains highly relevant in guiding treatment selection for long term success. Although newer drugs have been developed to overcome dug resistance, as it is the case of Fostemsavir and, more recently, Lenacapavir, a major issue today is to preserve 2nd gen INSTIs for future use. However, the most relevant difference between the past experience and what we are facing now in terms of drug resistance prevention is that whenever the individual profile is not reassuring, we can safely opt for a 2nd gen INSTI-based oral therapy with BIC/FTC/TAF. In conclusion, considering both the wide range of suboptimal immune–virological conditions observed in clinical practice and the proportion of patients presenting with advanced HIV infection which remains substantial, a need for a robust and potent therapeutic strategy still persists, particularly for rapid initiation and long term treatment success. In this context, BIC/FTC/TAF, with its high intrinsic potency, strong genetic barrier to resistance, and forgiveness, represents a valuable option both for initial therapy and for treatment optimization in virologically suppressed patients, supporting its role as a reference standard among current antiretroviral regimens.

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Conflicts of interest

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REFERENCES

[1] Ambrosioni J, Levi LI, Alagaratnam J, et al. EACS Governing Board. Major Revision Version 13.0 of the European AIDS Clinical Society Guidelines 2025. *HIV Med.* 2025. https://doi.org/10.1111/hiv.70120.

[2] UNAIDS. Global AIDS Update 2025, 2025. https://www.unaids.org/en/UNAIDS-global-AIDS-update-2025.

[3] Ron R, Martínez-Sanz J, Herrera S, et al. CD4/CD8 Ratio and CD8+ T-Cell Count as Prognostic Markers for Non-AIDS Mortality in People Living with HIV. A Systematic Review and Meta-Analysis. *Front. Immunol.* 2024; 15: 1343124. https://doi.org/10.3389/fimmu.2024.1343124.

[4] Ka'e A C, Bassani F, El Khalili O, et al. Evaluation of HIV-1 Drug Resistance in Newly Diagnosed Individuals in Italy over the Period 2017-2023. *J. Glob. Antimicrob. Resist.* 2026; 46: 38-45. https://doi.org/10.1016/j.jgar.2025.11.003.

[5] Drugbank, 2025. https://go.drugbank.com.

[6] Di Perri, G, Bonora S. Clinical Pharmacology of the Single Tablet Regimen Bictegravir/Emtricitabine/Tenofovir Alafenamide in the Evolving Era of Antiretroviral Therapies. *New Microbiol.* 2024; 47(3): 243-250.

[7] Ekobena P, Briki M, Dao, K, et al. Population Pharmacokinetics of Bictegravir in Real-World People with HIV. *J. Antimicrob. Chemother.* 2025; 80(10); 2782-2789. https://doi.org/10.1093/jac/dkaf297.

[8] Arora P, Hindman JT, West S, et al. The Effect of Antacid and Mineral Supplements on Bictegravir Pharmacokinetics: Results from a Phase 1, Open-Label, Drug-Drug Interaction Study. *Antimicrob. Agents Chemother.* 2026; 70(1); e0078125. https://doi.org/10.1128/aac.00781-25.

[9] Osuala EC, Nkuhairwe IN, Letsoalo MP, et al. Pharmacokinetics of Twice-Daily Tenofovir Alafenamide In Adults with HIV-Associated TB on BIC/FTC/TAF and Rifampicin. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2025; ciaf732. https://doi.org/10.1093/cid/ciaf732.

[10] Arora P, Liu H, Ling J, et al. Clinical Evaluation of Drug-Drug Interactions Between Bictegravir and Strong Inhibitors/Inducers of the CYP3A4, UGT1A1, or P-Gp Pathways. *J. Clin. Pharmacol.* 2025; 65(11): 1420-1432. https://doi.org/10.1002/jcph.70061.

[11] Wonganan P, Limpanasithikul W, Jianmongkol S, et al. Pharmacokinetics of Nucleoside/Nucleotide Reverse Transcriptase Inhibitors for the Treatment and Prevention of HIV Infection. *Expert Opin. Drug Metab. Toxicol.* 2020; 16(7): 551-564. https://doi.org/10.1080/17425255.2020.1772755.

[12] Wassner C, Bradley N, Lee Y. A Review and Clinical Understanding of Tenofovir: Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide. *J. Int. Assoc. Provid. AIDS Care.* 2020; 19: 2325958220919231. https://doi.org/10.1177/2325958220919231.

[13] Yager J, Castillo-Mancilla J, Ibrahim ME , et al. Intracellular Tenofovir-Diphosphate and Emtricitabine-Triphosphate in Dried Blood Spots Following Tenofovir Alafenamide: The TAF-DBS Study. *J. Acquir. Immune Defic. Syndr.* 2020; 84(3): 323-330. https://doi.org/10.1097/QAI.0000000000002354.
[14] De Nicolò A, Palermiti A, Dispinseri S, et al. Plasma, Intracellular and Lymph Node Antiretroviral Concentrations and HIV DNA Change during Primary HIV Infection: Results from the INACTION P25 Study. *Int. J. Antimicrob. Agents* 2024; 64(2): 107200. https://doi.org/10.1016/j.ijantimicag.2024.107200.
[15] Mpofu R, Chandiwana N, Sokhela S, et al. The Effect of Rifampicin on the Plasma and Intracellular Pharmacokinetics of Tenofovir Alafenamide Fumarate in Participants with HIV-Associated Tuberculosis. *J. Acquir. Immune Defic. Syndr.* 2025. https://doi.org/10.1097/QAI.0000000000003810.
[16] Markowitz M, Zolopa A, Squires K, et al. Phase I/II Study of the Pharmacokinetics, Safety and Antiretroviral Activity of Tenofovir Alafenamide, a New Prodrug of the HIV Reverse Transcriptase Inhibitor Tenofovir, in HIV-Infected Adults. *J. Antimicrob. Chemother.* 2014; 69(5): 1362-1369. https://doi.org/10.1093/jac/dkt532.
[17] Chan TYH, De Zan V, Gregg A, et al. The Symptomatology of Cerebrospinal Fluid HIV RNA Escape: A Large Case-Series. *AIDS Lond. Engl.* 2021; 35(14): 2341-2346. https://doi.org/10.1097/QAD.0000000000002992.
[18] Calcagno A, Lipani C, Rizzello B, et al. Full Reservoirs and Poor Adherence: Two Cases of Symptomatic HIV Cerebrospinal Fluid Escape with Tenofovir Alafenamide/Emtricitabine/Bictegravir. *AIDS* 2025; 39(15): 2250-2253. https://doi.org/10.1097/QAD.0000000000004320.
[19] Tiraboschi J, Imaz A, Khoo S, et al. Total and Unbound Bictegravir Concentrations and Viral Suppression in Cerebrospinal Fluid of Human Immunodeficiency Virus-Infected Patients (Spanish HIV/AIDS Research Network, PreEC/RIS 56). *J. Infect. Dis.* 2020; 221(9): 1425-1428. https://doi.org/10.1093/infdis/jiz624.
[20] Rigo-Bonnin R, Tiraboschi JM, Álvarez-Álvarez, M, et al. Measurement of Total and Unbound Bictegravir Concentrations in Plasma and Cerebrospinal Fluid by UHPLC-MS/MS. *J. Pharm. Biomed. Anal.* 2020; 185: 113250. https://doi.org/10.1016/j.jpba.2020.113250.
[21] Gelé T, Chéret A, Castro Gordon A, et al. Cerebrospinal Fluid Exposure to Bictegravir/Emtricitabine/Tenofovir in HIV-1-Infected Patients with CNS Impairment. *J. Antimicrob. Chemother.* 2021; 76(12): 3280-3285. https://doi.org/10.1093/jac/dkab334.
[22] Hermansson L, Yilmaz A, Price RW, et al. Plasma Concentration of Neurofilament Light Chain Protein Decreases after Switching from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide Fumarate. *PloS One.* 2019; 14(12): e0226276. https://doi.org/10.1371/journal.pone.0226276.
[23] Ma Q, Ocque AJ, Morse GD, et al. Switching to Tenofovir Alafenamide in Elvitegravir-Based Regimens: Pharmacokinetics and Antiviral Activity in Cerebrospinal Fluid. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2020; 71(4): 982-988. https://doi.org/10.1093/cid/ciz926.
[24] YilImaz A, Tiraboschi JM, Niubó J, et al. Dynamics of the Decay of Human Immunodeficiency Virus (HIV) RNA and Distribution of Bictegravir in the Genital Tract and Rectum in Antiretroviral-Naive Adults Living With HIV-1 Treated With Bictegravir/Emtricitabine/Tenofovir Alafenamide (Spanish HIV/AIDS Research Network, PreEC/RIS 58). *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2021; 73(7): e1991-e1999. https://doi.org/10.1093/cid/ciaa1416.
[25] Teresita de Jesús CL, Edgar PB, Carlos Ruben NC, et al. Coformulated Bictegravir/Emtricitabine/Tenofovir Alafenamide for Postexposure Prophylaxis After Sexual Assault: A Retrospective Real-World Study. *Open Forum Infect. Dis.* 2024; 11(8): ofae436. https://doi.org/10.1093/ofid/ofae436.
[26] Mayer KH, Gelman M, Holmes J, et al. Safety and Tolerability of Once Daily Coformulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide for Postexposure Prophylaxis After Sexual Exposure. *J. Acquir. Immune Defic. Syndr.* 2022; 90(1): 27-32. https://doi.org/10.1097/QAI.0000000000002912.
[27] Curteis T, Eddowes LA, Chen M, et al. Comparative Safety of B/F/TAF versus Other Antiretroviral Therapy Regimens for Treatment-Naïve People with HIV-1: A Systematic Literature Review and Network Meta-Analysis. *J. Comp. Eff. Res.* 2025; 14(7): e240231. https://doi.org/10.57264/cer-2024-0231.
[28] Ghosn J, Chow J, Gandhi M, et al. Rapid Start with Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) as Initial Treatment in People with Human Immunodeficiency Virus-1 (HIV-1): A Systematic Literature Review of Clinical and Patient-Reported Outcomes. *HIV Med.* 2025; 26(9): 1375-1394. https://doi.org/10.1111/hiv.70065.
[29] Makinson A, Bani-Sadr F, Palich R, et al. Switch to BIC/TAF/FTC or DTG + TDF/FTC in Virologically Suppressed PWH: Outcomes in Real-World Setting with and without Tenofovir Resistance. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2026, ciaf726. https://doi.org/10.1093/cid/ciaf726.
[30] Pezzati L, Conti F, Gennari W, et al. Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide in People with HIV and Prior Resistance Mutations. Data from the Italian ARCA Cohort: The BIC-BARRIER Study. B/F/TAF Switch: Mutations and Outcomes. *J. Antimicrob. Chemother.* 2026; 81(3): dkag035. https://doi.org/10.1093/jac/dkag035.
[31] Ambrosioni J, de Lazzari E, Sánchez-Palomino S, et al. Bictegravir/Emtricitabine/Tenofovir Alafenamide for Primary HIV Infection: Efficacy, Safety and Im-

pact on Viral Reservoir (the BIC-PHI Clinical Trial). *J. Infect.* 2025; 91(5): 106651. https://doi.org/10.1016/j.jinf.2025.106651.
[32] Dondorp AM, Fanello CI, Hendriksen ICE, et al. Artesunate versus Quinine in the Treatment of Severe Falciparum Malaria in African Children (AQUAMAT): An Open-Label, Randomised Trial. *Lancet* 2010; 376(9753): 1647-1657. https://doi.org/10.1016/S0140-6736(10)61924-1.
[33] Zwang, J, Dorsey G, Mårtensson A, et al. Plasmodium Falciparum Clearance in Clinical Studies of Artesunate-Amodiaquine and Comparator Treatments in Sub-Saharan Africa, 1999-2009. *Malar. J.* 2014; 13; 114. https://doi.org/10.1186/1475-2875-13-114.
[34] Iwuji C, Waters L, Milinkovic A, et al. Outcomes of Switching from Protease Inhibitor-Based Antiretroviral Therapy to Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in Virologically Suppressed Adults with Nucleos(t)Ide Analogue Resistance- a Phase IV Randomised, Open-Label Study (PIBIK Study). *Virol. J.* 2025; 22(1): 33. https://doi.org/10.1186/s12985-025-02648-3.
[35] Guaraldi G, Malagoli A, Calcagno A, et al. The Increasing Burden and Complexity of Multi-Morbidity and Polypharmacy in Geriatric HIV Patients: A Cross Sectional Study of People Aged 65 - 74 Years and More than 75 Years. *BMC Geriatr.* 2018; 18(1): 99. https://doi.org/10.1186/s12877-018-0789-0.
[36] Calcagno A, de Nicolò A, Pizzi C, et al. Medication Burden and Clustering in People Living with HIV Undergoing Therapeutic Drug Monitoring. *Br. J. Clin. Pharmacol.* 2021; 87(11): 4432-4438. https://doi.org/10.1111/bcp.14869.
[37] Cahn P, Madero JS, Arribas JR, et al. Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials. *J. Acquir. Immune Defic. Syndr.* 2020; 83(3): 310-318. https://doi.org/10.1097/QAI.0000000000002275.
[38] Figueroa MI, Brites C, Cecchini D, et al. Efficacy and Safety of Dual Therapy With Dolutegravir/Lamivudine in Treatment-Naive Persons With CD4 Counts <200/Mm3: 48-Week Results of the DOLCE Study. *Clin. Infect. Dis.* 2026; 82(1): 122-131. https://doi.org/10.1093/cid/ciaf415.
[39] Rojas J, de Lazzari E, Negredo E, et al. Efficacy and Safety of Switching to Dolutegravir plus Lamivudine versus Continuing Triple Antiretroviral Therapy in Virologically Suppressed Adults with HIV at 48 Weeks (DOLAM): A Randomised Non-Inferiority Trial. *Lancet HIV* 2021; 8(8): e463-e473. https://doi.org/10.1016/S2352-3018(21)00100-4.
[40] Scholten S, Cahn P, Portilla J, et al. Dolutegravir/Lamivudine Efficacy and Safety Outcomes in People With HIV-1 With or Without Historical Resistance Results at Screening: 48-Week Pooled Analysis. *Open Forum Infect. Dis.* 2024; 11(7): ofae365. https://doi.org/10.1093/ofid/ofae365.
[41] Li JZ, Sax PE, Marconi VC, et al. No Significant Changes to Residual Viremia After Switch to Dolutegravir and Lamivudine in a Randomized Trial. *Open Forum Infect. Dis.* 2019; 6(3): ofz056. https://doi.org/10.1093/ofid/ofz056.
[42] Fraysse J, Priest J, Turner M, et al. Real-World Effectiveness and Tolerability of Dolutegravir and Lamivudine 2-Drug Regimen in People Living with HIV: Systematic Literature Review and Meta-Analysis. *Infect. Dis. Ther.* 2025; 14(2): 357-383. https://doi.org/10.1007/s40121-024-01103-0.
[43] Marcelin AG, Soulie C, Wirden M, et al. Emergent Resistance-Associated Mutations at First- or Second-Line HIV-1 Virologic Failure with Second-Generation InSTIs in Two- and Three-Drug Regimens: The Virostar-1 Study. *J. Antimicrob. Chemother.* 2025; 80(1): 95-101. https://doi.org/10.1093/jac/dkae377.
[44] Marcelin AG, Soulie C, Wirden M, et al. Antiretroviral Resistance in at Least Second-Line HIV-1 Treatment Virologic Failure with Common InSTI-Based Regimens. *AIDS* 2025. https://doi.org/10.1097/QAD.0000000000004438.
[45] Loosli T, Bolton Moore C, Buzaalirwa L, et al. Drug Resistance in People With Viremia on Dolutegravir-Based Antiretroviral Therapy in Sub-Saharan Africa: The DTG RESIST Study. *Clin. Infect. Dis.* 2025; 81(4): e128-e131. https://doi.org/10.1093/cid/ciaf204.
[46] Orkin C, Schapiro JM, Perno CF, et al. Expanded Multivariable Models to Assist Patient Selection for Long-Acting Cabotegravir + Rilpivirine Treatment: Clinical Utility of a Combination of Patient, Drug Concentration, and Viral Factors Associated With Virologic Failure. *Clin. Infect. Dis.* 2023; 77(10): 1423-1431. https://doi.org/10.1093/cid/ciad370.
[47] Hedima EW, Ohieku JD, Nasir A, et al. Cabotegravir Plus Rilpivirine Injection for Virally Suppressed Persons with HIV-1 Infection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clin. Ther.* 2025; 47(8): 649-656. https://doi.org/10.1016/j.clinthera.2025.05.015.
[48] Han N, Loosli T, Anderegg N, et al. The Effect of Long-Acting Cabotegravir and Rilpivirine Treatment on Drug Resistance in South Africa: A Modelling Study. *Lancet Glob. Health* 2025; 13(12): e2133-e2143. https://doi.org/10.1016/S2214-109X(25)00350-X.
[49] Thoueille P, Saldanha SA, Schaller F, et al. Population Pharmacokinetics of Cabotegravir Following Oral Administration and Long-Acting Intramuscular Injection in Real-World People with HIV. *Clin. Pharmacol. Ther.* 2024; 115(6): 1450-1459. https://doi.org/10.1002/cpt.3240.
[50] Gutiérrez F, Fernández-González M, Ledesma C, et al. Virological History Predicts Non-Sustained Viral

Suppression With Long-Acting Cabotegravir and Rilpivirine Therapy, Independent of Pharmacokinetic Parameters. *Clin. Infect. Dis.* 2025; 80(4): 842-853. https://doi.org/10.1093/cid/ciae475.
[51] Néant N, Lê MP, Bouchet S, et al. Therapeutic Drug Monitoring of Long-Acting Cabotegravir and Rilpivirine in a National Cohort of People With HIV-1: First Results From the ANRS-MIE CARLAPOP Study. *Clin. Infect. Dis.* 2026; 82(1): 109-118. https://doi.org/10.1093/cid/ciaf385.
[52] Landman R, de Truchis P, Assoumou L, et al. A 4-days-on and 3-days-off maintenance treatment strategy for adults with HIV-1 (ANRS 170 QUATUOR): a randomised, open-label, multicentre, parallel, non-inferiority trial. *Lancet HIV*. 2022; 9(2): e79-e90.
[53) Di Perri Giovanni, Bonora Stefano Extending follow-up visits in people with HIV (PLWH) receiving bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) therapy: an expert opinion. *Infez Med*. 2025; 33(3): 268-278.
[54] Chivite I, Berrocal L, de Lazzari E, et al. Effectiveness, safety and discontinuation rates of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in people with HIV using real-world data: a systematic review and meta-analysis. *J Antimicrobial Chemother*, 2024; 79(8): 1775-1783.