Le Infezioni in Medicina, n. 3, 268-278, 2025
doi: 10.53854/liim-3303-3

Extending follow-up visits in people with HIV (PWH) receiving bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) therapy: an expert opinion

Giovanni Di Perri, Stefano Bonora
Dept of Medical Sciences, University of Torino Medical School, Torino, Italy.

Article received 20 June 2025 and accepted 22 July 2025

SUMMARY

Our confidence on the efficacy of antiretroviral therapy has steadily increased in the last decade thanks to the continuous improvement of drugs, strategies and the ability to cope with the increase in life expectancy of people with HIV (PWH). Nevertheless antiretroviral therapy keeps on being a lifelong commitment and the current clinical research on anti-HIV treatment also points on the possibility to mitigate a series of remaining difficulties like patients' adherence, stigma and the logistic burden associated to periodical monitoring and drug refills. The newly developed long-acting injectables drugs made it possible to reduce the frequency of administration and improved adherence, but at present the recipients of these new solutions are asked to join the outpatient HIV services at least every two months to receive their injections and undergo immunovirological monitoring. This also because these newly developed options consist of two (2DR) instead of three drugs and such close monitoring might be necessary due to the lesser genetic barrier and forgiveness. The patients who instead are under stable oral antiretroviral therapy with persistent virologic suppression may benefit from extension of the time between consecutive controls. This particularly applies when 2nd generation integrase inhibitors (INSTIs)-based three-drug regimens (3DR) are considered. Properties like intrinsic potency, genetic barrier, forgiveness, tolerability and safety make such regimens well suitable for less frequent immunovirological monitoring. The case of the single-tablet regimen consisting of Bictegravir/Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) is unique, as in a single pill with a total net weight of 275 mg we actually find all the necessary ingredients to ensure the success of such initiative. Such powerful option looks as the most promising treatment to successfully increase the time between consultations and monitoring up to 9 or 12 months and thus providing the resulting advantages.

Keywords: Patients Living with HIV (PLHIV), Immunovirological monitoring, Two-drug regimens (2DR), Three-drug regimens (3DR), HIV-RNA, HIV-DNA, Bictegravir/Emtricitabine/Tenofovir Alfenamide (BIC/FTC/TAF), Dolutegravir (DTG), Long-Acting Injectables.

INTRODUCTION

The pathway to make antiretroviral therapy a stable immunovirological success has been long and several obstacles had to be overcome before the full reliance on anti-HIV medications we have today was reached [1]. In the therapeutic management of patients with HIV infection many challenges had to be faced before a successful balance was achieved, depending upon the individual history and attitude and the availability of antiretrovirals [2]. However, thanks to the uninterrupted development of new drugs and particularly new drug classes, the main difficulties in obtaining a stable virologic suppression are mostly over and in almost every patient we can

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

expect to achieve a full and persistent virologic suppression. The fundamental step in this process was the development of integrase strand-transfer inhibitors (INSTIs), whose properties in terms of intrinsic antiretroviral potency, genetic barrier, forgiveness, tolerability and safety are truly unprecedented [3]. One of the proofs of such consistent improvement in the overall strength of antiretroviral therapy is the approval of regimens made by two instead of three drugs [4]. In appropriate individual conditions an INSTI-based two-drug (2DR) option may actually fulfil the immunovirologic targets, as far as the conventional monitoring parameters are concerned. In the pipeline of the pharmaceutical industry no new 3DRs are under scrutiny today, and most forthcoming options consist of 2DR long-acting injectable regimens [5]. But in the current situation the need for conservative 3DR solutions is still substantial, as more than 50% of newly diagnosed patients had already a CD4+ T-cell decrease below the value of 350/μL at presentation, with the majority of them having values below 200/μL [6]. Furthermore there is a sizeable proportion of chronic patients whose history includes several treatment failures with selection of resistance-associated mutations (RAMs) [7]. Thus the therapeutic scenario is dichotomised; on one side the patients who still require a conventional 3DR to reverse an unfavourable immunovirologic profile or to avoid further therapeutic failures and on the other side the offer of alternative lighter regimens to patients whose condition is such that even a 2DR might provide the desired immunovirologic results. The one of 2DRs is a long story, as the first attempts were made decades ago [8], although in no cases registration clinical trials were made and no approval of 2DRs was asked before DTG/RPV and DTG/3TC were licensed for clinical use in 2017 and 2019 respectively [9-10]. This happened, however, when some of the reasons for developing 2DRs were no longer relevant, such the intention to reduce drug toxicity or the number of pills to be taken daily. The introduction of TAF for replacing TDF and the progressive decreasing use of ABC made it possible to avoid the TDF-associated proximal renal tubule toxicity and bone mineral density reductions as well as the still disputed cardiovascular risk associated to ABC [11, 12]. In a more remote past the same applied to thymidine analogs and the associated risk of mitochondrial toxicity [13]. Beyond the wish of avoiding side effects and toxicity, several variables concerning treatment convenience are no longer in place as testified by issues like the frequency of intake, the number of pills to be taken daily and the size of the pills. BIC/FTC/TAF is a single tablet regimen that combines the integrase strand transfer inhibitor (INSTI) bictegravir with the nucleotide reverse transcriptase inhibitors (NRTIs) emtricitabine and tenofovir alafenamide. It has demonstrated high efficacy and a favorable safety profile in clinical trials and real-world settings.

Basic pharmacologic parameters of the individual components of the single tablet combination of BIC/FTC/TAF of particular clinical relevance are represented in Tables 1 and 2. As an example, DTG/3TC consists of a single pill whose size is

Table 1 - Pharmacologic parameters of the three drugs co-formulated in the single tablet BIC/FTC/TAF [32].

	Bictegravir	*Emtricitabine*	*Tenofovir Alafenamide*
T/2 (h)	17.3	10.0 plasma, 54.5 IC	32.37 plasma, 69.6 IC
VD (L)	15.56	1.4+/-0.3 L/Kg	>100
Absorption	Fat meal increases AUC and Cmax by 24 and 13%	Food irrelevant	Fat meal increases AUC by 65%
Protein binding	>99%	4%	TAF 80%, tenofovir 0.7%
Clearance	35% renal (glucuronide)	86% renal (13% as metabolites - (excreted by glomerular filtration and tubular secretion)	Cleared by glomerular filtration (2/3) and tubular secretion (1/3)
Metabolism	CYP3A and UGT1A1 Inhibitor of OCT2 and MATE	Limited	Carboxylesterase-1, cathepsin A, CYP3A (minimal), substrate of P-gp, BCRP, OATP1B1, OATP1B3

Note: T/2: elimination half-life; IC: intracellular, AUC: area under the curve.

Table 2 - Dissociation half-lives of INSTIs from integrase-DNA complex [32].

INSTI	*Dissociation Time (h) WT*	*Dissociation Time (h) G140S + Q148H*
Bictegravir	163±31	5.7±0.4
Dolutegravir	96±29	1.9±0.2
Raltegravir	10±2	nd
Elvitegravir	3.3±0.9	nd

the same of BIC/FTC/TAF and, paradoxically, if we look at the net treatment weight the former is 350 mg while the single-tablet triple regimen here concerned is 275 mg. As a consequence a 2DR today may be less appealing than 10 years ago and new advantages to opt for a 2DR should be searched. The tendency to develop long-acting injectable regimens can be thus interpreted today as a new advantage a 2DR can provide, such as an unprecedented reduction of the frequency of administration, a property more difficult to be achieved by oral medications. So the question is while a 2DR injectable long-acting regimen may actually be a game changer in simplifying the everyday life of patients by decreasing the frequency of drug intake [14], is there any advantage that can be associated to the administration of a 3DR? In other words, can we take advantage of the higher antiretroviral coverage provided by a 3DR as compared to 2DR in order to also simplify the life of 3DR intakers? A possible and seemingly plausible answer lies in the possibility to prolong the time intervals between sequential clinical and laboratory controls HIV-infected patients undergo on a regular basis.

HOW FREQUENTLY PATIENTS WITH HIV INFECTION SHOULD UNDERGO CONTROL VISITS?

The never ending improvement of the overall performance of antiretrovirals have gradually transformed the perception of HIV treatment from an almost dramatic life-saving procedure into a simple, effective and safe practice. The life expectancy of HIV-infected patients under regular and effective antiretroviral therapy increased to such an extent that in western countries in most patients the major difficulty today is to cope with the risk of age-related diseases rather than selecting the most appropriate antiretrovirals [15]. The appraisal of such advances had already spontaneously determined the extension of the time between consecutive control visits with a proportional decrease of burden both for patients and providers. There is some evidence that programmes aimed at reducing the frequency of control visits are appreciated by patients with no negative clinical outcomes [16]. The World Health Organization (WHO) currently recommends 6-month intervals between consecutive clinical visits but has recently encouraged to check whether less frequent controls have any negative impact on clinical outcomes [17]. The European AIDS Clinical Society (EACS) guidelines have moved towards extending monitoring intervals for PWH, particularly for those who are stable on ART with sustained viral suppression. CD4 T-cell count and HIV viral load should be monitored every 3 to 12 months. This reiterates the flexibility and extended intervals for stable patients compared to previous, more frequent recommendations. The general principle is to reduce unnecessary burden while ensuring continued excellent care for people living with HIV who are well-controlled on ART. This reiterates the flexibility and extended intervals for stable patients compared to previous, more frequent recommendations. The general principle is to reduce unnecessary burden while ensuring continued excellent care for people living with HIV who are well-controlled on ART [18].

Here the intention is to decrease the workload associated to patients whose viral load is persistently suppressed in order to dedicate more attention to unstable patients. The time has thus come to reconsider on an individual basis which is the most appropriate time interval for an effective monitoring of patients receiving antiretroviral therapy.

PROs and CONs - To pursue the intention of reducing the frequency of control visits there are many factors and potential threats to consider in order to achieve and maintain the essential bio-medical improvements that antiretroviral treatment is able to provide to people with HIV (PWH). A first point is retention in care, which does not exactly mean virologic suppression, but it actually is an indispensable pre-requisite for it [19]. Two are the sides of the coin, such as the wish of maintaining a more frequent contact with doctors, that could work like a periodical reassuring procedure for those patients who actually

desire it, or the opposite, once the individual perception of a steadily controlled infection has been obtained, the extension of time between consecutive visits might be taken by the patient as a confirmation of the good health status, with fringe benefits resulting from time saving and reduced costs for transportation. For this reason we should thus also consider how PWH might be in logistic trouble when they have to travel long distances in order to join their HIV care provider and, as a consequence, an extended period between consecutive controls may actually favourably impact on this aspect. While in most western countries, and particularly around some major urban areas, the geographic density of providers may be such that travelling to the HIV medical centre is not going to be problematic for most patients, there are however less privileged areas in which this issue is still substantial [20].

The vast majority of clinical studies aimed at exploring the effect of longer intervals between consecutive control visits and drug delivery have been carried out in low- or middle-income countries, and as a consequence the results might not fully apply to western standards. In a meta-analysis of clinical studies in which this issue was addressed it was found that there were no significant differences in retention in care by comparing consultation intervals of 3 months with 6-12 months periods or drug refill made at 3 or 6 months, while no firm conclusions could be made regarding viral suppression and death [21]. Inconsistency in data availability and reporting as well as differences in the HIV-RNA cutoff for defining viral suppression may actually account for such uncomplete answer. In a large retrospective study carried out in South Africa during the COVID-19 pandemic, 54.7% of 27.148 recently suppressed PWH (<50 HIV-RNA copies/mL) were seen once in a 12-month period, while the rest had two consultations in the same time interval [22]. Retention in care was found to be of 94.6% in the 12 months group and 91.8% in the 6 months group, while virologic suppression was 92.4 and 92.0% respectively. Prior exposure to antiretrovirals, age (median 39 years) and sex were similar across groups, with the only relevant difference being the intake of Dolutegravir (DTG), that was 60.0% in the 12 months group and 46.3% in the 6 months group. Although this study had a retrospective design with several potential biases and a short follow-up period, the data gathered suggest that longer time intervals may actually be a fruitful option with no apparent negative downstream consequences in terms of both retention in care and maintenance of virologic suppression.

In dealing with this subject we must also distinguish between medical controls and drug refill [23]. While the former mostly depends upon bio-medical variables, the frequency of the latter could impact on the economic and administrative convenience. With the chronic deficiency of financial resources of national health systems, the purchase of smaller amount of drugs to be delivered more frequently is often adopted as a strategy to postpone part of the expenditure and improve the end-of-year balance sheet. This will thus require the involvement of pharmacists and administrators in order to carefully planning the extension of time between sequential visits for those who are in the suitable medical conditions [24]. The grim perspective of a worse short-term financial balance should be weighted against the reduction of the workload and the resulting advantages [25]. The variables here challenged are thus the retention in care of antiretrovirals recipients while maintaining, or even improving, their adherence to this lifelong commitment, and to make such changes feasible and affordable for providers. Beyond the potential advantages for PWH, the intention to reduce the frequency of control visits for recipients of oral regimens comes also from the recent introduction of long-acting injectables antiretrovirals, whose supervised administration is associated to an increased workload for the HIV outpatient services [26]. This increased workload stems from various factors, including the need for more frequent clinic visits for injections, potential staffing shortages, and the need for additional training and resources. As compared to the conventional delivery of oral drugs by pharmacists, the procedure requires some additional steps like drug thawing at room temperature and a carefully performed injection in order to ensure the appropriate intramuscular delivery [27]. To our best knowledge in the vast majority of italian HIV outpatient services such additional work is being faced by the same staff that was on service in the pre-injectable era and the impression is that these services could guarantee the administration of long-acting injectables to a limited number of patients only. Thus the issue of extending the time

intervals between consecutive visits might allow to save time and resources to increase the capacity to make the injectable long-acting treatment accessible to greater number of patients. While this currently applies to the three available injectable drugs, such as Cabotegravir and Rilpivirine for maintenance therapy and Lenacapavir for the treatment of patients with limited options, looking at the future the demand for injectable antiretrovirals is bound to increase, as also testified by the recent approval of both Cabotegravir and Lenacapavir as agents to be administered in the setting of pre-exposure prophylaxis (PrEP) [28, 29].

Individual Factors to Consider - Many are the factors to consider when selecting patients who are suitable for control visits to be made at longer intervals. Technically speaking, the issue of longer intervals between consecutive consultations might be critical for those patients whose risk of virologic failure is recognized and need to be checked more frequently in order to detect the increase of the viral load as soon as possible, so that the required countermeasures can be adopted before an excessive viral growth under suboptimal treatment leads to selection of RAMs [30]. In these cases longer intervals might actually increase the possibility to miss the virologic failure at its first onset. PWH with prior history of poor adherence and virologic failures as well as recipients of complex regimens with limited or no residual options should not be considered as candidates for less frequent controls [17]. Depending on patients' history and the establishment of a solid relationship between patients and doctors, a major variable is by all means the real adherence of the patient and how it is perceived by the doctor. The fear of poor adherence justified by prior virologic failures and/or by a specific patient attitude (e.g. risky lifestyle, poor knowledge of what HIV infection is and what it implies in terms of consistent commitment to treatment intake) works against the opportunity to check the patient profile at longer intervals [31]. Thus adherence is the first factor to consider before delaying the next control visit and setting a less frequent agenda. The value of adherence in selecting possible candidates for less frequent controls is pivotal, although with comparable estimations of adherence the intake of a more potent three-drug regimen (3DR) based on 2nd generation strand-transfer inhibitors (INSTIs) might guarantee greater genetic barrier and forgiveness and allow for a longer between sequential medical controls [32]. One of the most beneficial achievements resulting from the development of INSTIs is the reduction of the minimal adherence level required to maintain virologic control. While the need for adherence was estimated to be around 95% in the first years of triple antiretroviral therapy, with the inclusion of an INSTI in the regimen the cutoff value for virologic control was estimated to be less than 70% [33]. This is to say that with minimal uncertainties concerning the patient' adherence, if the latter is receiving a triple regimen based on a 2nd generation INSTI, she/he could still be controlled at longer time intervals with no major fear of virologic failure. Furthermore, such a regimen, even in case of failure, has a very negligeable risk of generating RAMs. Single tablet regimens like Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) are associated to persistent virologic suppression even if RAMs related to NRTIs/NtRTIs are present at baseline [34]. In any case, regardless the regimen being taken by the patient, if there is a long story of persistent virologic suppression with no major additional factors threatening the viral control, a longer interval between controls can be considered. Beyond the medical variables to be periodically checked in PWH, a further question to take into consideration concerns the influence of longer intervals for drug refill on the adherence of patients. Is there any reason for envisaging a lower adherence in case of extending the time between two consecutive drug refills? Does a longer interval in drug delivery interfere with the individual patient perception about the unchanged need of a consistent adherence to treatment? This seems actually unlikely, although a careful explanation of the advantages of such modified procedure might be relevant for some, in order to ensure that nothing has changed in terms of adherence requirements to maintain a full virologic suppression [35]. For no reasons patients should interpret such an initiative as a lesser commitment of doctors and providers toward their health priorities.

Among the factors to be included in evaluating a patient's profile in order to increase the time between controls, the duration of ongoing viral suppression might also be a crucial factor [36]. A long history of persistent virologic suppression does testify at least two elements, such as that the antiretroviral regimen being taken is effective and,

again, that the patient is sufficiently adherent to it. What might cast additional doubts before switching the control intervals to longer duration? If the patient has been long receiving an INSTI-based 3DR and had a consistently suppressed viral load, with no INSTI RAMs in her/his background the way is smooth, with no contraindications in delaying the periodical controls unless significant behavioural factors are present [34]. The things might not be the same if the patient is receiving a dual regimen (2DR), as by definition there is no a 3rd drug to contribute to the genetic barrier and forgiveness [37]. Dual regimens are mostly based on DTG or CAB in association to a NRTI or NNRTI inhibitor. These 2DRs can only be prescribed when both drugs are deemed to be fully active. Failures of DTG-based dual regimen with RAMs selection have been described in the presence of 3TC- and/or in case of NRTI-associated RAMs [38], while failures to injectable CAB/RPV 2DR were found to occur when two of three specific technical items were present, such as viral subtypes A1/A6, baseline RPV RAMs and a body mass index higher than 30 [39]. The latter suggests that in some circumstances a suboptimal drug exposure may be responsible or co-responsible for virologic failure and a proportion of patients exceeding 30% was found in several clinical studies to actually have a pharmacokinetic exposure of CAB or RPV or both below the currently indicated cutoff values [40, 41]. This proportion of patients with suboptimal Pk exposure, however, is much higher than the low rate of virologic failure recorded both in clinical studies and real world practice, thus suggesting that variables other than the suboptimal Pk exposure should also be in place in patients undergoing virologic failure [42]. Although not formally indicated in the drug leaflet, in order to better predict the risk of virologic failure the consideration of some baseline parameters might be of value, and could also influence the decision regarding the extension of time intervals between controls. In these cases, when available, the evidence of a very long period of uneventful persistent virologic suppression could be reassuring and allow for longer intervals between visits [36]. The issue here is, however, delicate, as the risk of loosing the activity of 2nd generation INSTIs is higher with 2DRs, especially if the injectables are considered. While the latter met the criteria for non-inferiority when compared to 3DRs, it is also true that the proportion of virologic failures resulting in the selection of RAMs was well higher than what is normally measured with other regimens, and even higher when compared to the unlicensed use of DTG monotherapy [43, 44]. The use of DTG monotherapy has never been recommended for the unacceptable rate of virologic failures, but some findings from its experimental clinical use might provide additional keys to better understand the individual factors that influence the chance of virologic failure [45]. In the DOMONO study 8 out of 95 patients receiving maintenance DTG monotherapy underwent virologic failure [46]. Among the individual baseline variables explored, three were found to be associated to the risk of virologic failure. The value of nadir CD4+ T-cell count (the lowest value recorded in the course of HIV infection), the median total peripheral mononuclear cell HIV-DNA copy number and the time spent with untreated HIV infection before receiving the first antiretroviral regimen did correlate with the risk of virologic failure. Although these findings resulted from an extreme and never approved therapeutic setting, nevertheless they may actually suggest that these additional parameters, whose bio-clinical intrinsic nature make sense as complementary items, could be investigated in order to better estimate the individual risk of virologic failure even in case of more robust conventional regimens when prior failures have occurred. Uncertainties might arise when a patient is being considered for a 2DR instead of a conventional 3DR regimen and/ or when longer time intervals between consecutive consultations are proposed. Although the role of these parameters in such decision-making process is far from being validated, whenever the conventional variables are not conclusive, the supplementary information possibly deriving from these parameters might help in driving the choice of treatment and/or of the frequency of consultations in the right direction.

Clinical and Pharmacologic Issues - All such reasoning about the risk of virologic failure and the resulting cautiousness in making the routine therapeutic practice less demanding in case of weaker regimens (2DRs) are reminiscent of the old days when INSTIs were not available and avoidance of therapeutic failure and RAMs selection was a more frequent and difficult issue to face [47]. That was the time when we became accustomed

to estimate the inhibitory quotient (IQ) of single drugs or regimens, by integrating parameters like Pk exposure and the presence of RAMs, with the awareness that in many cases the treatment we were giving was barely above the minimal requirements. The need to reconsider a series of immunovirologic parameters related to the risk of failure does not come from a new crisis resulting from the resurgence of drug resistance, but rather from the wish of pursuing the same therapeutic targets by using two instead of three drugs. There are no doubts that with two instead of three drugs the overall regimen potency is reduced and that sort of straightforward confidence we gradually acquired overtime with 2nd gen INSTIs-based 3DRs has to be re-tailored at lower levels. But this should not make us to forget that the 1st line 3DRs are instead devoid of most of the described potential pitfalls and are much easier to be managed at longer intervals [32, 37]. Then, back to the original question, the overall scenario points on the appraisal of the technical guarantees achieved in the last 30 years of antiretroviral therapeutics and how to take advantage of the properties of the currently available regimens in order to decrease the efforts being made by patients, doctors, nurses and pharmacists to keep ongoing this worldwide adopted effective therapeutic outpatient practice. It is clear how a conventional 1st line INSTI-based 3DR regimen provides the strongest barrier against virologic failure and drug resistance, and therefore it represents the best starting point for reducing the frequency of periodical controls. In this perspective, it may be reassuring to quickly review the major properties of these regimens that make it easily feasible to reduce the frequency of periodical consultations. Some characteristics of the clinical pharmacology profile of these regimens are helpful in understanding how and why these regimen actually provide the safest opportunity to extend the control intervals.

As anticipated, a crucial characteristic here is made by a combination of intrinsic potency, genetic barrier and forgiveness, whose functional reciprocal synergy represents the net result of the combination of three top-class antiretrovirals. The case of BIC/FTC/TAF is actually exemplary, as it combines in a single tablet three drugs, each representing the point of arrival of the evolution in their own categories [32]. Intrinsic potency first; this mainly refers to BIC, that shares with DTG the label of 2nd generation INSTIs. What is unprecedented for these drugs is the very fast viral decrease they determine upon introduction in treatment-naïve patients [48]. Further to the nice graphical effect showing how these INSTIs are much quicker than any other antiretroviral in lowering the viral load in treatment-naïve patients, we should consider which is the main advantage resulting from such fast removal of circulating virions. Since the duration of exposure to drugs of any viral biomass is proportional to the possibility to select out resistant mutants, such fast removal of the virus from the central compartment dramatically shortens the time virions are exposed to drugs thus proportionally reducing the likelihood of RAMs selection [32]. This phenomenon led to revise the way genetic barrier is defined for INSTIs [49]. When no INSTIs were available and the so-called 3rd drugs were protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), the strength of the genetic barrier was measured in terms of number of RAMs required to make the drug inactive [50]. While for boosted-PIs multiple sequentially acquired mutations were necessary, with NNRTIs even a single mutation was enough to make these drugs no longer effective [51]. If the same criterion is applied to INSTIs, the latter would appear equal to NNRTIs, such as with a low genetic barrier, since with one-two mutations only even the 2nd generation INSTIs would loose their antiretroviral effect. However, when challenged in clinics this does not occur and the likelihood of selecting RAMs against 2nd generation INSTIs was found to be barely anecdotical both in clinical trials and normal practice [52]. The impressive initial "debulking" of the viral load leaves no enough time for the selection of RAMs and the elimination half-life (T/2) of 2nd generation INSTIs (both around 15-16 hrs) also cooperate in decreasing the risk of selecting RAMs in case of treatment discontinuation [32]. Once a patient does not take the drug any longer the drug disappear from the circulation in a rather short time thus leaving the ensuing viral regrowth unexposed to INSTIs. An additional characteristic of 2nd generation INSTIs is represented by their remarkably long persistence bound to the target, such as for a time well longer than their plasma T/2 [3]. Although the contribution of this property to the drug action and genetic barrier is unknown, it appears likely that a

prolonged action on its target may actually results from its long persistence at the site of action inspite of the decrease of plasma concentrations. To support some possible role of the long dissociation time of 2nd gen INSTIs there is a recent small phase II clinical study in which recipients of daily BIC/FTC/TAF who were permanently suppressed were randomly assigned to continue their ongoing regimen (controls) or to switch to the same regimen to be taken thrice, twice or once weekly [53]. Thirty-three patients were evaluable at 48 weeks and the 3 cases of virologic failure occurred in 2 patients taking BIC/FTC/TAF once weekly and in a patient receiving the regimen thrice weekly. No resistance was detected in these participants and all resuppressed to undetectable after switching back to daily dosing. Although lower than in case of standard dosing, the Pk levels of BIC were reported to be still above the cutoff concentration for efficacy (but cutoff levels were not reported), and it is noteworthy that no differences in terms of ultrasensitive measurement of HIV-RNA were recorded across the study arms. Regardless the unlikely application of these results into the clinical scenario (at least for the once weekly dosing), it is impressive how doses of BIC/FTC/TAF well lower than those recommended were able to maintain the virologic suppression in the majority of patients. While similar results were also obtained, although with a less extreme study design (intermittent triple therapy four or five days per week) in a prior study with various 3rd drugs [54], these findings provide new and strong support to the relevant antiretroviral properties of BIC/FTC/TAF. Beyond the hypothesis of a role by the long dissociation time, we must also consider the pharmacodynamic/pharmacokinetic characteristics of the other two components of the regimen [32]. TAF is the second prodrug of Tenofovir (TFV), a drug requiring to be complexed with a salt in order to be absorbed by the intestine. In the case of Tenofovir disoproxil fumarate (TDF), the first prodrug of TFV, the dissociation from the salt occurs soon after absorption, and the drug freely diffuses into the systemic circulation. In the case of TAF most of TFV remains bound to alafenamide after the absorption and this drives a selective uptake by cells that are rich in carboxy-esterase. This corresponds to an ideal selective distribution of the active mojety (TFV) into lymphocytes that leads on one side to higher intracellular concentrations of TFV into the target cells and on the other side to a much lower plasma Pk exposure. The latter is responsible for the significant decrease in toxicity for the renal proximal tubule with additional favourable downstream advantages in terms of decreased tubular phosphate loss and very limited reduction in bone mineral density. What is relevant in this setting is the higher (up to 6-7 times) concentration in target cells, a finding plausibly associated to a stronger genetic barrier and greater forgiveness. Looking back at the phase II study that investigated the performance of BIC/FTC/TAF given at lower frequency [53], it seems thus likely that the presence of TAF, with its long T/2 and high intracellular concentrations, might have significantly contributed to maintain undetectable viral loads in most patients inspite of the experimental sub-standard intake of the regimen. The 3rd component is FTC, a cytidine analog developed after Lamivudine (3TC) and able to show stronger antiretroviral properties than 3TC when challenged in a short head to head monotherapy study [55]. FTC has higher intracellular concentrations and a longer intracellular T/2, both findings suggesting an additional contribution to the antiretroviral strength of the regimen.

Clinical Stability in Virologically Suppressed PWH Receiving BIC/FTC/TAF in the long term - PWH receiving BIC/FTC/TAF who have achieved and maintained undetectable viral loads are considered clinically stable. Clinical trials and real-world studies have demonstrated the high efficacy of BIC/FTC/TAF in sustaining virological suppression over the long term. A recent systematic review and meta-analysis including over 7,500 PWH confirmed the clinical stability of individuals receiving BIC/FTC/TAF, particularly those already virologically suppressed. At 48 weeks, pooled suppression rates were 95% in treatment-experienced (TE) and 97% in treatment-naïve (TN) participants, with no signal of diminished efficacy in routine clinical settings [56]. Notably, high suppression rates were maintained even in TE subgroups with archived resistance mutations such as M184V/I, reinforcing the regimen's robustness in complex virological profiles. Among individuals who were already virologically suppressed at baseline, a key focus of long-term ART management, the rate of discontinuation for any reason was low (3%), and interruptions due to toxicity

Table 3 - Pooled Outcomes at Week 48 [56].

Population	*Virologic Suppression at 48 Weeks*	*Discontinuation Rate (Any Reason)*	*Discontinuation for Toxicity*
Treatment-Naïve (TN)	97% (89-100)	5% (0-15)	2% (0-7)
Treatment-Experienced (TE)	95% (94-96)	3% (2-5)	1% (0-2)
TE with M184V/I mutation	95% (88-100)	Not Reported	Not Reported

were rare (1%). The Table 3 summarizes the key pooled outcomes reported in the meta-analysis [56] stratified by treatment experience and resistance profile.

Key Considerations - All these pharmacologic properties combined in a single pill well describe the excess margin of power this single-tablet regimen exerts in clinical practice. Such characteristics unambiguously suggest that this single-tablet regimen STR of BIC/FTC/TAF well fits with the proposal of extending the time intervals between consecutive visits up to 12 months, unless a standard frequency remains necessary to manage ongoing comorbidities and/or specific individual medical risks other than HIV infection. It thus seems that now more than ever before we have the opportunity to make it easier the long-term management of HIV infection, and several therapeutic weapons today available look more than suitable for this aim. While the most relevant factor here is adherence, the intention to pursue the reduction of the frequency of consultations looks more feasible with a conventional 3DR regimen like BIC/FTC/TAF, whose forgiveness and genetic barrier provide a strong limit to the risk of both virologic failure and RAMs selection. By increasing the consultation intervals to 9 or even 12 months we have an unique opportunity to re-organize the outpatient management of HIV chemotherapy in a way more compatible with the evolution that antiretroviral therapy is having in these years. Furthermore, should we manage in gradually increasing the time between consultation intervals we would also achieve a reduction in the expenditure associated to immunovirological examinations [57], an advantage that could trigger the right attention this intention deserves.

Conflicts of interest

The authors, Giovanni Di Perri and Stefano Bonora, in the last two years served as advisors and/or speakers for the following pharmaceutical companies: MSD, ViiV, Gilead, Janssen, Pfizer, Astra Zeneca, Roche, Atea.

Funding

The article here concerned does not report any original research carried out by the Authors and it consists of an expert opinion for which no funding was provided.

REFERENCES

[1] Vella S, Schwartländer B, Sow SP, et al. The history of antiretroviral therapy and of its implementation in resource-limited areas of the world. *AIDS*. 2012; 26(10): 1231-1241.

[2] Trickey A, Sabin CA, Burkholder G, et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. *Lancet HIV*. 2023; 10: e295-e307.

[3] Di Perri G, Calcagno A, Trentalange A, Bonora S. The clinical pharmacology of integrase inhibitors. *Expert Rev Clin Pharmacol*. 2019; 12(1): 31-44.

[4] Gibas KM, Kelly SG, Arribas JR, et al. Two-drug regimens for HIV treatment. *Lancet HIV*. 2022; 9(12): e868-e883.

[5] Li Y, Choudhary M, Mellors JW. The Current Pipeline of Antiretroviral Therapy: Expanding Options and Filling Gaps. *Infect Dis Clin North Am*. 2024; 38(3): 395-408.

[6] Mondi A, Cozzi-Lepri A, Tavelli A, et al. Persistent poor clinical outcomes of people living with HIV presenting with AIDS and late HIV diagnosis - results from the ICONA cohort in Italy, 2009-2022. *Int J Infect Dis*. 2024; 142: 1-10.

[7] World health Organization. HIV drug resistance – brief report 2024 https://www.who.int/publications/i/item/9789240086319.

[8] Burgos J, Crespo M, Falcó V, et al. Dual therapy based on a ritonavir-boosted protease inhibitor as a novel salvage strategy for HIV-1-infected patients on a failing antiretroviral regimen, Journal of Antimicrobial *Chemotherapy*. 2012; 67: 1453-1458.

[9] Properzi M, Magro P, Castelli F, Quiros-Roldan E. Dolutegravir-rilpivirine: first 2-drug regimen for

HIV-positive adults. *Expert Rev Anti Infect Ther*. 2018; 16(12): 877-887.
[10] Cahn P, Madero JS, Arribas JR, et al; GEMINI study team. 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*. 2019; 393(10167): 143-155.
[11] De Clercq E. Tenofovir alafenamide (TAF) as the successor of tenofovir disoproxil fumarate (TDF). *Biochemical Pharmacology*. 2016; 119: 1-7.
[12] Alvarez A, Orden S, Andújar I, et al. Cardiovascular toxicity of abacavir: a clinical controversy in need of a pharmacological explanation. *AIDS*. 2017; 31(13): 1781-1795.
[13] Hunt M, Phillips R, Hardy Y, et al. Renal mitochondrial toxicity: effects of thymidine analogues and tenofovir disoproxil fumarate in African people with HIV. *AIDS*. 2022; 36(7): 1049-1051.
[14] Nachega JB, Scarsi KK, Gandhi M, et al. Long-acting antiretrovirals and HIV treatment adherence. *Lancet HIV*. 2023; 10(5): e332-e342.
[15] de Camargo Vicioli LB, de Souza ELDR. Brief communication: comorbidities and aging in people living with HIV. *AIDS Res Ther*. 2024; 21(1): 77.
[16] Ahn JY, Boettiger D, Law M, et al. TREAT Asia HIV Observational Databases (TAHOD). Implementation and Operational Research: Effects of CD4 Monitoring Frequency on Clinical End Points in Clinically Stable HIV-Infected Patients With Viral Suppression. *J Acquir Immune Defic Syndr*. 2015; 69(3): e85-e92.
[17] World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. July 16, 2021. https://www.who.int/publications/i/item/9789240031593.
[18] EACS Guidelines version 12.1 November 2024.
[19] Hendricks L, Eshun-Wilson I, Rohwer A. A mega-aggregation framework synthesis of the barriers and facilitators to linkage, adherence to ART and retention in care among people living with HIV. *Syst Rev*. 2021; 10(1): 54.
[20] Cook PA, Downing J, Wheater CP, et al. Influence of socio-demographic factors on distances travelled to access HIV services: enhanced surveillance of HIV patients inorth west England. *BMC Public Health*. 2009; 9: 78.
[21] Le Tourneau N, Germann A, Thompson RR, et al. Evaluation of HIV treatment outcomes with reduced frequency of clinical encounters and antiretroviral treatment refills: A systematic review and meta-analysis. *PLoS Med*. 2022; 19(3): e1003959.
[22] Lewis L, Sookrajh Y, van der Molen J, et al. Clinical outcomes after extended 12-month antiretroviral therapy prescriptions in a community-based differentiated HIV service delivery programme in South Africa: a retrospective cohort study. *J Int AIDS Soc*. 2023; 26(9): e26164.
[23] Cassidy T, Grimsrud A, Keene C, et al. Twenty-four-month outcomes from a cluster-randomized controlled trial of extending antiretroviral therapy refills in ART adherence clubs. *J Int AIDS Soc*. 2020; 23(12): e25649.
[24] Sokpa D, Lyden E, Fadul N, et al. Antiretroviral Refill Histories as a Predictor of Future Human Immunodeficiency Virus Viremia. *Open Forum Infectious Diseases*. 2022; ofac024.
[25] Keene CM, Zokufa N, Venables EC, et al. Only twice a year': a qualitative exploration of 6-month antiretroviral treatment refills in adherence clubs for people living with HIV in Khayelitsha, South Africa. *BMJ Open*. 2020; 10: e037545.
[26] Koshy L, Payne E, Barakat L, et al. Real-world Rollout of Injectable Antiretrovirals for HIV Prevention and Treatment: Correlates of Early Adoption. *Open Forum Infectious Diseases*. 2025; 12: ofaf029.
[27] Cocohoba J, Cuca Y, Sherman E,et al. Preparing for pharmacy-based delivery of long-acting injectable antiretrovirals: a pre-implementation study. *BMC Health Serv Res*. 2025; 25(1): 808.
[28] Taki E, Soleimani F, Asadi A, et al. Cabotegravir/Rilpivirine: the last FDA-approved drug to treat HIV. *Expert Rev Anti Infect Ther*. 2022 Aug; 20 (8): 1135-1147.
[29] Hitchcock AM, Kufel WD, Dwyer KAM, Sidman EF. Lenacapavir: A novel injectable HIV-1 capsid inhibitor. *Int J Antimicrob Agents*. 2024; 63(1): 107009.
[30] Gunn JKL, Patterson W, Anderson BJ, Swain CA. Understanding the Risk of Human Immunodeficiency Virus (HIV) Virologic Failure in the Era of Undetectable Equals Untransmittable. *AIDS Behav*. 2021; 25(7): 2259-2265.
[31] Penn AW, Azman H, Horvath H, et al. Supportive interventions to improve retention on ART in people with HIV in low- and middle-income countries: A systematic review. *PLoS One*. 2018; 13(12): e0208814.
[32] Di Perri G. Clinical pharmacology of the SingleTablet Regimen (STR) Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF). *Infez Med*. 2023; 31(3): 283-289.
[33] Stover S, Milloy MJ, Grant C, et al. Estimating the minimum antiretroviral adherence required for plasma HIV-1 RNA viral load suppression among people living with HIV who use unregulated drugs. *AIDS*. 2022; 36(9): 1233-1243.
[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 Feb 10; 22 (1): 33.

[35] Mutasa-Apollo T, Ford N, Wiens M, et al. Effect of frequency of clinic visits and medication pick-up on antiretroviral treatment outcomes: a systematic literature review and meta-analysis. *J Int AIDS Soc*. 2017 Jul 21; 20 (Suppl. 4): 21647.
[36] Rosenblum M, Deeks SG, van der Laan M, Bangsberg DR. The Risk of Virologic Failure Decreases with Duration of HIV Suppression, at Greater than 50% Adherence to Antiretroviral Therapy. *PLoS ONE*. 2009; 4 (9): e7196.
[37] Pisaturo M, Onorato L, Russo A, et al. Risk of failure in dual therapy versus triple therapy in naïve HIV patients: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021; 27(1): 28-35.
[38] McCluskey SM, Gandhi M. Predictors of treatment-emergent resistance to dolutegravir. *Lancet HIV*. 2025; S2352-3018(25)00127-4.
[39] 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.
[40] Ehret R, Krudewagen B, Obermeier M. Cabotegravir/rilpivirine based long acting therapy with insufficient drug levels in routine drug monitoring. EACS 2023, October 18-21, 2023, Warsaw. Abstract eP.B1.037.
[41] Thoueille P, Saldanha SA, Shaller F, et al. Real-world trough concentrations and effectiveness of long-acting cabotegravir and rilpivirine: a muticenter prospective observational study in Switzerland. *Lancet Regional Health*. 2024; 36: 100793.
[42] Cutrell AG, Schapiro JM, Perno CF, et al. Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis. *AIDS*. 2021; 35(9): 1333-1342.
[43] Perez Navarro A, Nutt CT, Siedner MJ, et al. Virologic failure and emergent integrase strand transfer inhibitor drug resistance with long acting cabotegravir for HIV treatment: A meta-analysis. *Clin Infect Dis*. 2024; ciae631.
[44] Perez Navarro A, Siedner Mj, McCluskey SM, et al. Increased incidence of emergent integrase drug resistance with cabotegravir versus dolutegravir in randomised switching trials. IAS 25th International Aids Conference, July 2024 Munich. Abstr. n. LB17.
[45] Blanco JL, Marcelin AG, Katlama C, Martinez E. Dolutegravir resistance mutations: lessons from monotherapy studies. *Curr Opin Infect Dis*. 2018; 31(3): 237-245.
[46] Wijting I, Rutsaert SL, Rokx C, et al. Predictors of virological failure in HIV-1-infected patients switching to dolutegravir maintenance monotherapy. *HIV Med*. 2019; 20 (1): 63-68.
[47] Beyrer C, Pozniak A. HIV Drug Resistance - An Emerging Threat to Epidemic Control. *N Engl J Med*. 2017; 377(17): 1605-1607.
[48] Jacobson K, Ogbuagu O. Integrase inhibitor-based regimens result in more rapid virologic suppression rates among treatment-naïve human immunodeficiency virus-infected patients compared to non-nucleoside and protease inhibitor-based regimens in a real-world clinical setting: A retrospective cohort study. *Medicine (Baltimore)*. 2018; 97(43): e13016.
[49] Blanco JL, Varghese V, Rhee SY, et al. HIV-1 integrase inhibitor resistance and its clinical implications. *J Infect Dis*. 2011; 203(9): 1204-1214.
[50] Maïga AI, Malet I, Soulie C, et al. Genetic barriers for integrase inhibitor drug resistance in HIV type-1 B and CRF02_AG subtypes. *Antivir Ther*. 2009; 14(1): 123-129.
[51] Clutter DS, Jordan MR, Bertagnolio S, Shafer RW. HIV-1 drug resistance and resistance testing. *Infect Genet Evol*. 2016; 46: 292-307.
[52] Zhao AV, Crutchley RD, Guduru RC, et al. A clinical review of HIV integrase strand transfer inhibitors (INSTIs) for the prevention and treatment of HIV-1 infection. *Retrovirology*. 2022; 19(1): 22.
[53] Chivite I, Elisa De Lazzari, Abiu Sempere, et al for the BETAF-RED Study Team. Safety, Tolerability, and Efficacy of a BIC/FTC/TAF Dose Reduction Strategy. CROI 2025. Poster abstract 659.
[54] 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. *The Lancet HIV*. 2022; 9(2): e79-e90.
[55] Rousseau FS, 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*. 2003; 188(11): 1652-1658.
[56] Chivite I, Berrocal L, de Lazzari E, Navadeh S, Lluis-Ganella C, 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. *Journal of Antimicrobial Chemotherapy*. 2024; 79: 1775-1783.
[57] Vyas S, Songo J, Guinness L, et al. Assessing the costs and efficiency of HIV testing and treatment services in rural Malawi: implications for future "test and start" strategies. *BMC Health Serv Res*. 2020; 20: 740.