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REVIEW

Optimizing Antiretroviral Therapy with Bictegravir/Emtricitabine/Tenofovir Alafenamide in virologically suppressed PLWH

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SUMMARY

The pillar of treatment success, defined as viral suppression and immune restoration, should be integrated into a modern vision of therapeutic success with pharmacological attributes of ART, such as potency, forgiveness, and genetic barrier of single drugs and regimens, as well as their longterm tolerability and safety. Moreover, the longterm success of lifelong treatment cannot be separated from the opinions and preferences of PLWH.

Regimen Optimization in the setting of HIV suppression may reduce pill burden, and/or dosing frequency, enhance tolerability and/or decrease toxicity, prevent or mitigate DDIs, eliminate food/fluid requirements, relieve pill fatigue, decrease stigma or concerns associated with taking oral med, allow pregnancy, reduce costs (DHHS 2023).

Regimen Optimization should be tailored by a person-centered perspective, based on the individual therapeutic history, past toxicities and comorbidities. The treatment strategy should be based on the perceived tolerability and quality of life, considering the preferences of people on treatment along with the virological and pharmacological factors.

The health care system should facilitate universal and rapid access to personalized, robust, and effective therapies. The BIC/FTC/TAF association ensures all these characteristics and therefore represents a valid strategy for optimizing treatment in PLWH virologically suppressed.

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With currently available antiretroviral therapy (ART), most people with HIV can achieve and maintain HIV viral suppression. In an Italian Cohort of Antiretroviral Naïve Patients (ICONA), that consists of more than 20,000 HIV-positive individuals enrolled between 1997 and 2023 by the 50 Centers operating throughout Italy, after one year of treatment almost 90% of subjects have undetectable plasma viraemia.

The pillar of treatment success, defined as viral suppression and immune restoration, should be integrated into a modern vision of therapeutic success with pharmacological attributes of ART, such as potency, forgiveness, and genetic barrier of single drugs and regimens, as well as their long-term tolerability and safety. Moreover, the long-term success of lifelong treatment cannot be separated from the opinions and preferences of people living with HIV (PLWH) who must be informed, aware, and involved in the choice of treatment to maximize the quality of life, satisfaction, and adherence to ART.

Switching or simplifying antiretroviral therapy (ART), or in other words making a Regimen Optimization as reported by the DHHS Guidelines, in the setting of HIV suppression may improve pill burden, dosing frequency, safety, tolerability, and/or food requirements. The reasons to consider regimen optimization in the setting of viral suppression are presented in *Table 1*.

Table 1 - *Reasons to consider regimen optimization in the setting of viral suppression.*

To simplify a regimen by reducing pill burden and/or dosing frequency
To enhance tolerability and/or decrease short- or long-term toxicity
To prevent or mitigate drug–drug interactions
To eliminate food or fluid requirements
To switch to a long-acting injectable regimen to relieve pill fatigue or to decrease potential stigma or disclosure concerns associated with taking daily oral medications
To allow optimal use of ARV during pregnancy or when pregnancy is desired or may occur
To reduce costs

Key words:
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At times, ART Optimization is elective, such as consolidating a multiple-tablet to a single-tablet regimen (STR). Other times, it is necessary to eliminate drug-drug interactions (DDIs) and/or minimize active or potential treatment-associated adverse events (AEs), as well as due to costs of therapy, barriers to access, and/or financial constraints.

The fundamental principle of regimen optimization is to preserve virologic suppression without jeopardizing future ART options. Prior to ART modification a full review of patient's ART and resistance history should be conducted including virologic responses, toxicities, and intolerances. Additionally, insurance restrictions, readiness to switch, DDIs, and supporting evidence should be assessed.

The first point to be met in a strategy for maintaining virological suppression is the personalization of ART. This requires a shared decision-making process between the patient and physician, considering patient preferences, pill burden, potential adverse effects and cost. The personalized approach involves selecting the optimal treatment regimen based on patient-specific factors, including age, comorbidities, concomitant medications, adherence difficulties, and patient preferences.

The dramatic change in the natural history of HIV infection since the advent of ART has redefined long-term ART success according to five main concepts: efficacy, safety, rapid initiation, simplicity, and quality of life (Toutain *et al*., 2004). In addition to being the core of adherence to treatment, safety and tolerability are the most important properties of any drug. Once doses have been established by safety assessments, the efficacy of ART relies on the activity of the individual antiretrovirals in the regimen, that is the potency of the regimen, and on the number of genotypic resistance mutations required for the development of resistance to each drug, otherwise called the genetic barrier to resistance (Parienti *et al*., 2021). At least one drug with a high genetic barrier should be included in ART regimens. Moreover, the ideal regimen should include molecules with similar profiles, preferably with a high volume of distribution, to reach the sanctuaries of viral replication and by a long terminal half-life (Eliot *et al*., 2016) to obtain a persistent inhibitory efficacy even in the case of missed doses (Nachega *et al*., 2011, Grdner *et al*., 2009). Potency, genetic barriers, and forgiveness of the regimen are the three main pharmacological determinants of long-term success, however, the role of each can be different in the different stages of the therapeutic history of the person initiating ART.

Suboptimal adherence to drugs is relatively common and can increase over time, therefore forgiveness, defined as the ability to maintain an antiviral effect even after the dosing interval, is a crucial issue (Maggiolo *et al*., 2022, Sung *et al*, 2021, Taramasso *et al*., 2018). Regimen forgiveness is a function of plasmatic and intracellular half-lives of different compounds (Sung *et al*, 2021, Taramasso *et al*., 2018). The use of a backbone based on two drugs supports forgiveness, as in the case of tenofovir disoproxil fumarate (TDF) / tenofovir alafenamide (TAF) and emtricitabine (FTC), the two antiretroviral drugs with long intracellular half-lives. In the clinical setting, for example, Bictegravir (BIC)/FTC/TAF was shown to have more prolonged forgiveness than the dual regimen lamivudine (3TC) / dolutegravir DTG): the minimum requested adherence to maintain virological efficacy was 90% for 3TC/DTG and 70% for BIC/FTC/TAF (Maggiolo *et al*., 2022).

If a regimen switch results in virologic failure with the emergence of new resistance mutations, to obtain a new virological suppression may require more complex and/or less tolerated regimen. In patients with a history of virologic failure or pre-treatment drug resistance, a review of cumulative resistance test results and clinical and virologic response to prior regimens is essential when designing a new regimen (Virden *et al*., 2011). Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype (if available), phenotype, and tropism assays that can be used to guide the selection of a new regimen. Once selected, a drug-resistance mutation, even when it is not detected in the patient's most recent drug-resistance test, can be archived in the HIV reservoir and reemerge under the appropriate selective drug pressure. In the setting of absence nucleoside reverse transcriptase inhibitor (NRTI) resistance, two NRTIs (TAF or TDF plus FTC or 3TC) should be included in the regimen with a fully active, high resistance barrier drug, such as DTG, boosted-darunavir or BIC. Resistance often can be inferred from a patient's ARV history: for patients with documented failure on a regimen that includes drugs with relatively low barriers to resistance (such as a non-nucleoside reverse transcriptase inhibitors (NNRTIs), raltegravir (RAL), 3TC or FTC a clinician should assume that there is resistance to these drugs, so-called inferred resistance. When uncertain about prior resistance, it is generally not advisable to switch from a suppressive ARV regimen, unless the new regimen is likely to be at least as active against potential resistant virus as the current suppressive regimen. This principle is particularly applicable when switching ARV-experienced individuals from a regimen with a relatively high barrier to resistance such as those that include pharmacologically-boosted protease inhibitors (PIs), DTG or BIC to one with a lower barrier to resistance.

People with HIV who have no history of drug-resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in ARV-naïve patients. If optimization is considered in patients with suppressed viral loads who

do not have prior drug resistance data with experience of several treatments, proviral DNA genotypic resistance testing can be considered. However, whenever proviral DNA genotypic testing is used, the results must be interpreted with caution because these assays may not detect all of a patient's drug-resistance mutations, especially those that were selected by a previous ARV regimen (Virden *et al.*, 2011). In addition, these assays may identify mutations that appear inconsistent with a patient's response to treatment, making the clinical relevance of the assay results questionable.

After a treatment switch, patients should be evaluated closely for 3 months. The purpose of this close monitoring is to assess medication tolerance and to conduct targeted laboratory testing if the patient has preexisting laboratory abnormalities or if there are potential concerns with the new regimen. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis. As with ART-naive patients, the use of a two- or three-drug combination regimen is generally recommended when switching patients with suppressed viral loads. Patients who have no history of resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in ART-naive patients.

OPTIMIZATION IN A PERSON WITH ACTIVE HEPATITIS B VIRUS COINFECTION

When switching an ARV regimen in a patient with active hepatitis B virus (HBV)/HIV coinfection (HBsAg positive), TDF or TAF should be continued as part of the new regimen, unless another first-line HBV antiviral (e.g., entecavir) is initiated. Both TDF and TAF are active against HBV and can be used as HBV monotherapy Tarrault *et al.*, 2018). Discontinuation of HBV antivirals may lead to reactivation of HBV, which can result in serious hepatocellular damage. In people with HBV/HIV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity is not recommended, because HBV resistance to these drugs is likely to emerge. In the ALLIANCE study, a double-blind randomized study that enrolled 243 adults HBV/HIV co-infected and HBV treatment naïve, showed that BIC/FTC/TAF was noninferior to DTG+FTC/TDF at achieving HIV plasma viremia suppression at 48 weeks. Moreover, significantly more participants on B/F/TAF had HBV-DNA<29 IU/mL, normal ALT and HBeAg seroconversion than patients in DTG+FTC/TDF (Avihingsanon *et al.*, 2023). Baseline predictors of HBV-DNA suppression were BIC/FTC/TAF treatment, HBeAg-negative status, HBV-DNA <8 $\log_{10}$ and ALT > upper limit normal. These results seem to demonstrate a greater efficacy on HBV infection of TAF versus TDF in HIV/HBV co-infected patients.

ASSESSMENT FOR POTENTIAL DRUG INTERACTIONS

Before switching a regimen, it is important to review each ARV drug in the new regimen and concomitant medications to assess whether any potential drug-drug interaction exists. For example, oral rilpivirine (RPV) and atazanavir interact with acid-lowering agents, and many ARV drugs may interact with rifamycin antibiotics. In addition to new drug interactions, the discontinuation of some ARV drugs also may necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may reduce the concentrations of some concomitant medications. Concomitant medications, which may have been previously managed with dose adjustments, will need to be reevaluated in the context of the new ARV regimen.

THREE-DRUG REGIMENS

Within-Class Switches

Within-class switches may be prompted by adverse events or the availability of ARVs in the same class that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, or lower pill burden or do not require PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. Examples of within-class switch strategies that have been studied in individuals without underlying drug resistance include the following:

From TDF (Alleance CROI, 2023, Gallant *et al.*, 2016) or ABC (Hagins *et al.*, 2018) to TAF.

From DTG (Winston *et al.*, 2018, Molina *et al.*, 2018, Gilead Siences, 2018) or RAL to BIC (Sax *et al.*, 2020).

From efavirenz to RPV (Gallant *et al.*, 2016, Kityo *et al.*, 2019) or doravirine (DOR) (Mills *et al.*, 2013).

Within-Class Switch from Dolutegravir to Bictegravir

The GS 4030 study enrolled 565 individuals who were stably suppressed on DTG plus two NRTIs. The participants were randomized to either remain on their current regimen or switch to BIC/FTC/TAF. This is a switch from a high-barrier drug, DTG, to another high-barrier drug, BIC. After 48 weeks, the groups had similar rates of sustained suppression. The rates of viral suppression were similar for those with a documented history of NRTI resistance (approximately 25% of participants) and those without a history of NRTI resistance (Jonson *et al.*, 2019). Results from this trial lend theoretical support to other opti-

mization strategies that include a switch from one high-barrier drug to another in the setting of a similar NRTI backbone.

Other Switches to Bictegravir in the Setting of Limited Drug Resistance

The BRAAVE study was an open-label, optimization study for Black people with HIV and viral suppression for ≥12 months on a standard regimen of two NRTIs plus a third agent (INSTI, NNRTI, or PI). Individuals were randomized to switch to BIC/FTC/TAF or to remain on current therapy (although individuals on TDF were switched to TAF). Switching to BIC-based therapy was noninferior for maintaining viral suppression compared with continuing current oral therapy. Baseline regimens included 61% INSTI, 31% NNRTI, and 9% PI. Baseline resistance did not affect the outcomes of therapy. In particular, NRTI resistance was present in 14% of participants, and 10% harbored the M184V/I mutation (Acosta *et al*., 2020).

Between-Class Switches

Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the new regimen. In general, such switches should be avoided if any doubt exists about the activity of the other agents in the regimen. As noted earlier, prior resistance test results will be very informative in guiding this switch. The following are between-class switches that have been studied:

Replacing a boosted PI with an INSTI e.g., DTG, (Hagins *et al*., 2021) or BIC (Gatell *et al*., 2017).

Replacing a boosted PI with RPV (Daar *et al*., 2018) or DOR (Mills *et al*., 2013).

Replacing an NNRTI with an INSTI (Palella *et al*., 2014, Pozniak *et al*., 2014).

CONCLUSIONS

Today the attributes of antiretroviral therapy for long-term success are a high genetic barrier to resistance, long-term efficacy, optimal long-term safety and tolerability profile, simplicity and ability to ensure good quality of life. This should be tailored by a person-centered perspective, based on the individual therapeutic history, past toxicities and comorbidities. The treatment strategy should be based on the perceived tolerability and quality of life, considering the preferences of people on treatment along with the virological and pharmacological factors. The health care system should facilitate universal and rapid access to personalized, robust, and effective therapies. The BIC/FTC/TAF association ensures all these characteristics and therefore represents a valid strategy for optimizing treatment in PLWH virologically suppressed patients.

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