Optimizing Antiretroviral Therapy in the Setting of Viral Suppression <mark>(Last updated December 18, 2019; last reviewed December 18, 2019)</mark>

Key Considerations and Panel's Recommendations

- Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance make it possible to consider switching a person with HIV from an effective regimen to an alternative regimen in some situations.

- The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options.

- Adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt a regimen switch.

- It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results, before selecting a new antiretroviral therapy regimen **(AI)**.

- Monotherapy with either a boosted protease inhibitor or an integrase strand transfer inhibitor has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switch strategy **is not recommended (AI)**.

- When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV infection should be continued **(AII)**. <mark>Using 3TC or FTC as the only drug in a regimen with HBV activity **is not recommended (AII)**, as HBV resistance to these drugs can emerge.</mark> Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage.

- Consultation with an HIV specialist is recommended when planning a regimen switch for a patient with a history of resistance to one or more drug classes **(AIII)**.

- Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

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With currently available antiretroviral therapy (ART), most persons with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in antiretroviral (ARV) treatment and a better understanding of drug resistance make it possible to consider switching a person with HIV from one effective regimen to another in some situations (see below). When considering such a switch, clinicians must keep several key principles in mind to maintain viral suppression while addressing the concerns with the current regimen.

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 (see Adverse Effects of Antiretroviral Agents and Table 18 for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug-drug interactions (see Drug-Drug Interactions)
- To eliminate food or fluid requirements
- To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur (see the Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Optimization

Maintain Viral Suppression

The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with the emergence of new resistance

mutations, the patient may require more complex and/or expensive regimens.

Careful Review of Antiretroviral Treatment and Drug Resistance History Before Optimization

The review of a patient's full ARV history—including virologic responses and past ARV-associated intolerances, toxicities, and adverse reactions—is critical before any treatment switch **(AI)**.

If a patient with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can safely assume that no new drug resistance mutation emerged while the patient was on the suppressive regimen. In patients with a history of virologic failure or pre-treatment drug resistance, review of cumulative resistance test results and clinical response to prior regimens is essential when designing a new regimen. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype, 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 is likely to re-emerge under the appropriate selective drug pressure. When resistance data are not available, resistance can often 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 inhibitor (NNRTI), elvitegravir (EVG), raltegravir (RAL), lamivudine (3TC), or emtricitabine (FTC), one should assume that there is resistance to these drugs. If there is uncertainty about prior resistance, it is generally not advisable to switch 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), dolutegravir (DTG), or bictegravir (BIC), to one with a lower barrier to resistance.[1] The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends that clinicians consult an HIV specialist when contemplating a regimen switch for a patient with a history of resistance to one or more drug classes **(AIII)**.

If regimen switching is considered in patients with suppressed viral loads who do not have prior drug resistance data, proviral DNA genotypic resistance testing can be considered. For patients who have no prior virologic failures and who are on their first or second regimen, or for those who have genotypic test results from prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide valuable information. In individuals with a history of multiple prior failures or multiple prior ARV regimens, the use of proviral DNA genotypic testing may be useful. 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 ART regimen. In addition, these assays may identify mutations that appear to be inconsistent with a patient's response to treatment, making the clinical relevance of the assay results questionable. Overall, the clinical utility of these assays remains an area of active investigation (see Drug-Resistance Testing).

Optimization in a Person with Hepatitis B Virus Coinfection

When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) should be continued as part of the new regimen, unless these drugs are contraindicated. Both TDF and TAF are active against HBV.[2] Discontinuation of these drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage. In persons with HIV/HBV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity **is not recommended (AII)**, as HBV resistance to these drugs can emerge. If TDF or TAF cannot be used as part of the ARV regimen, refer to Hepatitis B Virus/HIV Coinfection for recommendations.

Assess for Potential Drug Interactions

Before switching a regimen, it is important to review the ARV drugs in the new regimen and concomitant

medications to assess whether there are any potential drug-drug interactions. For example, rilpivirine (RPV) may interact with acid-lowering agents, and TAF and BIC may interact with rifamycins (see Drug-Drug Interactions). In addition to new drug interactions, the discontinuation of some ARV drugs may also 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 previously been managed with dose adjustments will need to be re-evaluated in the context of the new ART regimen.

Assess for Potential for Pregnancy and Use of INSTI in Persons of Childbearing Potential

Persons of childbearing potential should have a pregnancy test before switching ART. If a person with HIV is found to be pregnant, clinicians should refer to the Perinatal Guidelines for recommendations on the safety and efficacy of ARV use in pregnancy.

Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen. Preliminary data from a study conducted in Botswana suggested that there is an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[3,4] Follow-up data, however, showed that the prevalence of infant NTDs in association with maternal DTG exposure at conception is lower (0.3%), but still higher than in infants exposed to non-DTG containing ARV regimens (0.1%).[5,6] There are insufficient safety data on the use of BIC around the time of conception and during pregnancy to determine whether it is safe. An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**.

Monitoring after Switch

Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch (see below).

Specific Regimen Optimization Considerations

As with ART-naive patients, the use of a two-drug (as discussed below) or three-drug combination regimen is generally recommended when switching patients with suppressed viral loads **(AI)**. Patients who have no resistance mutations or history of virologic failure can likely switch to any regimen that has been shown to be highly effective in ART-naive patients. Patients with prior drug resistance can be switched to a new regimen based on their ARV history and resistance testing results. Monotherapy with either a boosted PI or an INSTI has been explored in several trials or cohort studies. Monotherapy has been associated with a higher rate of virologic failure than combination regimens and has been associated with the development of resistance, especially INSTI monotherapy; therefore, **monotherapy as an optimization strategy is not recommended (AI)**.

Optimization Strategies with Good Supporting Evidence for Persons with No History of Drug Resistance

Many clinical trials have enrolled participants with stably suppressed viral loads without underlying drug resistance and switched them to another regimen, typically including at least two fully active drugs. Most of these studies demonstrated maintenance of viral suppression; some of these studies are referenced below. The SWITCHMRK 1 and 2 studies illustrated the importance of considering the possibility of underlying drug resistance before switching therapy in those with virologic suppression.[1] This is particularly important when the new regimen may not include three fully active agents. In the two SWITCHMRK studies, those with viral suppression on two NRTIs plus lopinavir/ritonavir (LPV/r) were switched to two NRTIs plus RAL. The studies showed that individuals with a history of previous virologic failure had an increased risk of virologic failure when switching to the RAL-based regimen. A possible explanation for this finding is that,

when only one of the accompanying NRTIs is fully active, viral suppression can be maintained by drugs with relatively high barriers to resistance, such as boosted PIs, DTG, and BIC, but not by those with lower barriers to resistance such as EVG, RAL, and NNRTIs. The strategies listed below support these observations and principles of optimizing therapy.

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, 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. Some examples of within-class switch strategies that have been studied in individuals without underlying drug resistance include switching from:

- TDF[7,8] or abacavir (ABC)[9] to TAF
- RAL to DTG
- DTG,[10,11] EVG/c,[12] or RAL to BIC
- Efavirenz (EFV) to RPV,[8,13] or to doravirine (DOR)[14]
- Boosted atazanavir (ATV/c or ATV/r) to unboosted ATV (when used with ABC/3TC)[15-17]

Between-Class Switches

Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the regimen. In general, such switches should be avoided if there is any doubt 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,[18] BIC,[19] or EVG[20,21])
- Replacing a boosted PI with RPV[22] or DOR[14]
- Replacing an NNRTI with an INSTI[23,24]
- Replacing a boosted PI with maraviroc (MVC).[25] When switching to MVC, co-receptor usage in patients with virologic suppression can be determined from proviral DNA (see Co-receptor Tropism Assays).[25-27]

Two-Drug Regimens

There is growing evidence that some two-drug regimens are effective in maintaining virologic control in patients who initiated therapy and achieved virologic suppression with three-drug regimens, provided their HIV is susceptible to both ARV drugs in the new regimen. However, since none of the two-drug regimens discussed below has adequate anti-HBV activity, these regimens are not recommended for individuals with HBV coinfection (AIII). Below are examples of successful strategies for switching from three- to two-drug regimens in persons with suppressed HIV.

Dolutegravir plus Rilpivirine

Two Phase 3 trials enrolled 1,024 participants with viral suppression for ≥1 year (defined by no HIV RNA >50 copies/mL in the past 6 months, and no more than one instance of HIV RNA 50–200 copies/mL in the 6–12 months before enrollment) who were on their first or second regimen and had no history of virologic failure and no documented evidence of any major drug-resistance mutations.[28] Participants were randomized to remain on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV (early-switch arm). Viral suppression was maintained in 95% to 96% of the participants in both arms at 48 weeks. At 52 weeks, those who were randomized to remain on their current regimens were allowed to switch to DTG plus RPV (late-switch arm). At 100 weeks, 89% of participants in the early-switch arm and 93% of those in the late-switch arm maintained HIV RNA <50 copies/mL.[29] DTG plus RPV is available as a

coformulated single-tablet regimen. It is a reasonable option when the use of nucleoside reverse transcriptase inhibitors (NRTIs) is not desirable. DTG plus RPV should only be given to patients who do not have chronic HBV infection, have no evidence of resistance to either DTG or RPV, and have no significant drug-drug interaction that might reduce the concentration of either drug **(AI)**.

Dolutegravir plus Lamivudine

A switch from three-drug regimens to DTG plus 3TC as maintenance strategy in patients with virologic suppression has been examined in a large randomized clinical trial (TANGO),[30] in two small clinical trials,[31,32] and in observational studies[33,34] with good success. The result of the TANGO trial is discussed below.

The Phase 3 TANGO study enrolled participants who were on their first ARV regimen with HIV RNA <50 copies/mL for ≥6 months. Participants were randomized to switch to open label DTG plus 3TC (n = 369) or to continue their TAF-based triple therapy (n = 372). The participants had no history of virologic failure or evidence of resistance to DTG or 3TC and did not have HBV coinfection. At week 48, switching to DTG plus 3TC was non-inferior to continuing on the current regimen, with 93% of participants in both arms maintaining HIV RNA <50 copies/mL. No unexpected adverse events were identified as related to DTG or 3TC.[30] Switching to a DTG plus 3TC regimen can be a good option for individuals who have no evidence of resistance to either drug and do not have HBV coinfection **(AI)**.

Ritonavir-Boosted Protease Inhibitor plus Lamivudine

A ritonavir-boosted protease inhibitor (PI/r) plus 3TC may be a reasonable option when the continued use of TDF, TAF, or ABC is contraindicated or not desirable. There is growing evidence that a PI/r-based regimen plus 3TC can maintain viral suppression in patients who initiated triple-drug therapy, who achieved sustained viral suppression for ≥1 year, and who have no evidence of, or risk for drug resistance to, either the PI/r or 3TC. Examples of boosted PI plus 3TC regimens that have been studied in clinical trials include the following:

- ATV/r plus 3TC **(CI)**,[35,36]
- Darunavir/ritonavir (DRV/r) plus 3TC **(BI)**,[37]
- LPV/r plus 3TC **(CI)**.[38]

Boosted Darunavir plus Dolutegravir

An open-label, Phase 3b, non-inferiority clinical trial randomized 263 participants who were on boosted DRV plus two NRTIs to continue on the same regimen or switch to boosted DRV plus DTG (study recruitment was stopped prematurely due to slow recruitment). At 48 weeks, the study demonstrated that switching to DTG plus boosted DRV was non-inferior to continuing triple therapy. In both arms, approximately 87% of participants maintained viral suppression at HIV RNA <50 copies/mL, and both groups had comparable rates of adverse events.[39] Because of the small sample size of this study, the regimen of boosted DRV plus dolutegravir is only recommended if there are no other alternative options **(CI)**. Similar results were observed in two small observational studies (13 participants and 56 participants).[40,41]

Optimization Strategies for Persons with Viral Suppression and a History of Limited Drug Resistance

There are some data demonstrating the safety and efficacy of within-class switches for individuals with underlying drug resistance who are on a stable ARV regimen with suppressed HIV RNA. However, there are limited data regarding between-class switches in this population, and support for such a switch generally depends on findings extrapolated from other studies, as discussed below.

Within-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from DTG to BIC [BI])
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. After 48

weeks, the groups had similar rates of sustained suppression.[42] 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.[43]

Between-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from a Boosted PI to a BIC- or DTG-Containing Regimen with At Least One Fully Active NRTI)
The GS 4030 study provides theoretical support for replacing a boosted PI-regimen with a BIC- or DTG-containing regimen, if at least one of the NRTIs in the regimen is fully active.[42,43] Although there are no switch studies testing this strategy, based on the GEMINI studies in treatment-naive patients, a DTG plus 3TC regimen (**when both ARVs are fully active**) is highly effective. In addition, the TANGO study (described above), demonstrated that in the setting of no underlying drug resistance, DTG plus 3TC, as the active NRTI, was a very effective switch strategy. In the DAWNING study,[44] in the setting of virologic failure with underlying NRTI resistance, DTG plus one fully active NRTI was more effective than LPV/r plus one fully active NRTI. Based upon standard optimization principles, if DTG plus two NRTIs, one of which is fully active, was effective in those with virologic failure, it should also be effective in those already virologically suppressed **(BIII)**.

Optimization Strategies for Persons with Viral Suppression and a History of Complex Underlying Resistance

Before optimization of the ARV regimen of a person with viral suppression who has a history of treatment failure and drug resistance, a careful review of the individual's ARV history and cumulative drug resistance profile should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended **(AIII)**.

One randomized controlled trial conducted in this patient population is described below.

Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir
Switching to the combination of EVG/c/TAF/FTC plus DRV has been shown to be a potential optimization strategy in patients on complicated salvage regimens.[45] A randomized controlled trial enrolled 135 patients with virologic suppression who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Participants had up to three thymidine analog resistance mutations and/or the K65R mutation, but no history of either the Q151M mutation or T69 insertion. The participants were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their current regimen. At 48 weeks, optimization to EVG/c/TAF/FTC plus DRV was superior to continuation on a current regimen with 94.4% of participants in the switch arm and 76.1% in the continuation arm maintaining viral suppression. With regimen simplification, the pill burden was reduced from an average of five tablets per day to two tablets per day. EVG/c/TAF/FTC plus DRV would be an appropriate option for individuals who have treatment and drug resistance histories similar to those of participants included in this study **(AI)**.

Optimization Strategies Not Recommended

Boosted Protease Inhibitor Monotherapy
The strategy of switching patients with virologic suppression without PI resistance from one ART regimen to PI/r monotherapy has been evaluated in several studies. The rationale for this strategy is to avoid NRTI toxicities and decrease costs while taking advantage of the high barrier to resistance of PIs. PI/r monotherapy maintains virologic suppression in most patients, but at lower rates than regimens that include one or two NRTIs.[46-48] Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy than with regimens that include one or two NRTIs. In most studies, resuming NRTIs in patients who are experiencing low-level viral rebound has led to re-suppression.[49-52] No clinical trials have evaluated the use of coformulated PI/c regimens as monotherapy or compared different PI/r monotherapy regimens. Based on the results from these studies, boosted-PI monotherapy **is not recommended (AI)**.

Dolutegravir Monotherapy

The strategy of switching patients with virologic suppression to DTG monotherapy has been evaluated in cohort studies and in clinical practice[53,54] and in a randomized controlled trial.[55] This strategy has been associated with an unacceptable rate of virologic failure and subsequent development of INSTI resistance; therefore, a switch to DTG monotherapy **is not recommended (AI)**.

Boosted Atazanavir plus Raltegravir

In a randomized study, patients with virologic suppression switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. The ATV/r plus RAL regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the switch to ATV/r plus TDF/FTC.[56] A regimen consisting of ATV/r plus RAL **cannot currently be recommended (AI)**.

Maraviroc plus Boosted Protease Inhibitor

In a randomized controlled trial, patients with virologic suppression who were on a regimen of two NRTIs plus a boosted PI and who had only CCR5-tropic HIV (as detected by proviral DNA testing) were randomized to continue their current regimen or to switch to MVC plus two NRTIs or to MVC plus a boosted PI. The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC **cannot be recommended (AI)**.[57]

Maraviroc plus Raltegravir

In a nonrandomized pilot study, patients with virologic suppression were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in five out of 44 patients.[58] Based on these study results, use of MVC plus RAL **is not recommended (AII)**.

Monitoring after Treatment Changes

After a treatment switch, patients should be evaluated closely for 3 months (e.g., a clinic visit or phone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 8 weeks after the switch) **(AIII)**. The purpose of this close monitoring is to assess medication tolerance and to conduct targeted laboratory testing if the patient had pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormality is a reason for the ARV change or is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. 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 (see Laboratory Testing for Initial Assessment and Monitoring).

References

1. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet.* 2010;375(9712):396-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20074791.

2. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology.* 2018;67(4):1560-1599. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29405329.

3. Zash R, Holmes L, Makhema J, et al. Surveillance for neural tube defects following antiretroviral exposure from conception. Presented at: 22nd International AIDS Conference. 2018. Amsterdam.

4. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. *N Engl J Med.* 2018;379(10):979-981. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30037297.

5.   Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329379.

6.   Raesima MM, Ogbuabo CM, Thomas V, et al. Dolutegravir use at conception - additional surveillance data from Botswana. *N Engl J Med*. 2019;381(9):885-887. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329378.

7.   Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV*. 2016;3(4):e158-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27036991.

8.   Hagins D, Orkin C, Daar ES, et al. Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials. *HIV Med*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30101539.

9.   Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. *Lancet HIV*. 2018;5(4):e162-e171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29475804.

10.   Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(7):e357-e365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29925489.

11.   Bictegravir/emtricitabine/tenofovor alafenamine (Biktarvy) [package insert]. Food and Drug administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210251s006lbl.pdf.

12.   Kityo C, Hagins D, Koenig E, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) in virologically suppressed HIV-1 infected women: a randomized, open-label, multicenter, active-controlled, phase 3, noninferiority trial. *J Acquir Immune Defic Syndr*. 2019;82(3):321-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31609930.

13.   Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. *HIV Clin Trials*. 2013;14(5):216-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24144898.

14.   Johnson M, Kumar P, Molina JM, et al. Switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) maintains HIV-1 virologic suppression through 48 weeks: results of the DRIVE-SHIFT trial. *J Acquir Immune Defic Syndr*. 2019;81(4):463-472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30985556.

15.   Squires KE, Young B, DeJesus E, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. *HIV Clin Trials*. 2012;13(5):233-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23134624.

16.   Ghosn J, Carosi G, Moreno S, et al. Unboosted atazanavir-based therapy maintains control of HIV type-1 replication as effectively as a ritonavir-boosted regimen. *Antivir Ther*. 2010;15(7):993-1002. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21041914.

17.   Wohl DA, Bhatti L, Small CB, et al. The ASSURE study: HIV-1 suppression is maintained with bone and renal biomarker improvement 48 weeks after ritonavir discontinuation and randomized switch to abacavir/lamivudine + atazanavir. *HIV Med*. 2016;17(2):106-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26176344.

18.   Gatell JM, Assoumou L, Moyle G, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. *AIDS*. 2017;31(18):2503-2514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29112070.

19.   Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(7):e347-e356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29925490.

20.   Arribas JR, DeJesus E, van Lunzen J, et al. Simplification to single-tablet regimen of elvitegravir, cobicistat, emtricitabine, tenofovir DF from multi-tablet ritonavir-boosted protease inhibitor plus coformulated emtricitabine and tenofovir DF regimens: week 96 results of STRATEGY-PI. *HIV Clin Trials*. 2017;18(3):118-125. Available at: https://www.ncbi.nlm.

nih.gov/pubmed/28555519.

21. Hodder S, Squires K, Kityo C, et al. Brief Report: Efficacy and safety of switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) in virologically suppressed women. *J Acquir Immune Defic Syndr*. 2018;78(2):209-213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29481486.

22. Palella FJ Jr, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS*. 2014;28(3):335-344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24670520.

23. Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis.* 2014;14(7):590-599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24908550.

24. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis*. 2014;14(7):581-589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24908551.

25. Pett SL, Amin J, Horban A, et al. Week 96 results of the randomized, multicentre Maraviroc Switch (MARCH) study. *HIV Med.* 2018;19(1):65-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28703491.

26. Vitiello P, Brudney D, MacCartney M, et al. Responses to switching to maraviroc-based antiretroviral therapy in treated patients with suppressed plasma HIV-1-RNA load. *Intervirology.* 2012;55(2):172-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22286889.

27. Bonjoch A, Pou C, Perez-Alvarez N, et al. Switching the third drug of antiretroviral therapy to maraviroc in aviraemic subjects: a pilot, prospective, randomized clinical trial. *J Antimicrob Chemother*. 2013;68(6):1382-1387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23354282.

28. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet.* 2018;391(10123):839-849. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29310899.

29. Aboud M, Orkin C, Podzamczer D, et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. *Lancet HIV*. 2019;6(9):e576-e587. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31307948.

30. van Wyk J, Ajana F, Bisshop F, et al. Switching to DTG+3TC fixed dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) in maintaining virologic suppression through 24 weeks (TANGO Study). Presented at: IAS Conference on HIV Science. 2019. Mexico City, Mexico.

31. Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through Week 48 in a pilot randomized trial. *Clin Infect Dis*. 2018;66(11):1794-1797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29293895.

32. Joly V, Burdet C, Landman R, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob Chemother*. 2019;74(3):739-745. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30476165.

33. Maggiolo F, Gulminetti R, Pagnucco L, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. *BMC Infect Dis*. 2017;17(1):215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28302065.

34. Borghetti A, Baldin G, Lombardi F, et al. Efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicentre cohort of patients with suppressed HIV-1 replication. *HIV Med.* 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29573320.

35. Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. 2015;15(7):775-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26062881.

36. Fabbiani M, Gagliardini R, Ciccarelli N, et al. Atazanavir/ritonavir with lamivudine as maintenance therapy in virologically

suppressed HIV-infected patients: 96 week outcomes of a randomized trial. *J Antimicrob Chemother*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29668978.

37. Pulido F, Ribera E, Lagarde M, et al. Dual therapy with darunavir and ritonavir plus lamivudine versus triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of HIV-1 viral suppression: randomised, open label, non-inferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis*. 2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29020293.

38. Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. 2015;15(7):785-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26062880.

39. Spinner C, Kümmerle T, Schneider J, et al. A switch to dolutegravir in combination with boosted darunavir is safe and effective in suppressed patients with HIV—a subanalysis of the dualis study. Presented at: IAS Conference on HIV Science. 2019. Mexico City, Mexico.

40. Capetti AF, Cossu MV, Orofino G, et al. A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. *BMC Infect Dis*. 2017;17(1):658. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28964268.

41. Wheeler J, Chan S, Harrigan PR, Becker M, Kasper K, Keynan Y. Dolutegravir with boosted darunavir treatment simplification for the transmitted HIV thymidine analog resistance in Manitoba, Canada. *Int J STD AIDS*. 2018;29(5):520-522. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29513131.

42. Sax PE, Rockstroh J, Luetkemeyer A, et al. Switching to a single-tablet regimen bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) from dolutegravir (DTG) plus emtricitabine and either tenofovir alafenamide or tenofovir disoproxil fumarate (F/TAF or F/TDF). Presented at: International AIDS Society. 2019. Mexico City, Mexico.

43. Acosta R, Willkom M, Andreatta K, et al. Keeping the pressure on archived NRTI resistance: Switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) triple therapy in study 4030. Presented at: International AIDS Society. 2019.F Mexico City, Mexico.

44. Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. *Lancet Infect Dis*. 2019;19(3):253-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30732940.

45. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;74(2):193-200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27753684.

46. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS*. 2009;23(3):279-291. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114854.

47. Arribas JR, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/mL at baseline. *HIV Med*. 2012;13(7):398-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22413874.

48. Ciaffi L, Koulla-Shiro S, Sawadogo AB, et al. Boosted protease inhibitor monotherapy versus boosted protease inhibitor plus lamivudine dual therapy as second-line maintenance treatment for HIV-1-infected patients in sub-Saharan Africa (ANRS12 286/MOBIDIP): a multicentre, randomised, parallel, open-label, superiority trial. *Lancet HIV*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28566227.

49. Guiguet M, Ghosn J, Duvivier C, et al. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS*. 2012;26(18):2345-2350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22695301.

50. Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. *J Acquir Immune Defic Syndr*. 2007;44(4):417-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17159658.

51. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*. 2010;24(15):2365-2374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20802297.

52. Vernazza P, Daneel S, Schiffer V, et al. The role of compartment penetration in PI-monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial. *AIDS*. 2007;21(10):1309-1315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17545707.

53. Blanco JL, Rojas J, Paredes R, et al. Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24 week analysis of the DOLAM randomized clinical trial. *J Antimicrob Chemother*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29608685.

54. Oldenbuettel C, Wolf E, Ritter A, et al. Dolutegravir monotherapy as treatment de-escalation in HIV-infected adults with virological control: DoluMono cohort results. *Antivir Ther*. 2017;22(2):169-172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27588613.

55. Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. *Lancet HIV*. 2017;4(12):e547-e554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29107562.

56. van Lunzen J, Pozniak A, Gatell JM, et al. Brief report: switch to ritonavir-boosted atazanavir plus raltegravir in virologically suppressed patients with HIV-1 infection: a randomized pilot study. *J Acquir Immune Defic Syndr*. 2016;71(5):538-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26605505.

57. Pett SL, Amin J, Horban A, et al. Maraviroc, as a switch option, in HIV-1-infected individuals with stable, well-controlled HIV replication and R5-tropic virus on their first nucleoside/nucleotide reverse transcriptase inhibitor plus ritonavir-boosted protease inhibitor regimen: Week 48 results of the randomized, multicenter MARCH Study. *Clin Infect Dis*. 2016;63(1):122-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27048747.

58. Katlama C, Assoumou L, Valantin MA, et al. Maraviroc plus raltegravir failed to maintain virological suppression in HIV-infected patients with lipohypertrophy: results from the ROCnRAL ANRS 157 study. *J Antimicrob Chemother*. 2014;69(6):1648-1652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24535278.

Discontinuation or Interruption of Antiretroviral Therapy (Last updated April 8, 2015; last reviewed April 8, 2015)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression.[1-5] Thus, planned interruptions of ART are not generally recommended. However, unplanned interruption of ART may occur under certain circumstances as discussed below.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or interrupted access to drugs. Stopping ART for a short time (i.e., less than 1 to 2 days) because of a medical/surgical procedure can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Short-Term Therapy Interruption

When a Patient Experiences a Severe or Life-Threatening Toxicity or Unexpected Inability to Take Oral Medications:

• All components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short-Term Therapy Interruption (Up to 2 Weeks)

When All Regimen Components Have Similar Half-Lives and Do Not Require Food for Proper Absorption:

• All drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously. All discontinued regimen components should be restarted simultaneously.

When All Regimen Components Have Similar Half-Lives and Require Food for Adequate Absorption, and the Patient Cannot Take Anything by Mouth for a Short Time:

• Temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.

When the Antiretroviral Regimen Contains Drugs with Different Half-Lives:

• Stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically a non-nucleoside reverse transcriptase inhibitor [NNRTI]), which may increase the risk of selection of NNRTI-resistant mutations. Some experts recommend stopping the NNRTI first and the other antiretroviral drugs 2 to 4 weeks later. Alternatively, the NNRTI may be replaced with a ritonavir- or cobicistat-boosted protease inhibitor (PI/r or PI/c) for 4 weeks. The optimal time sequence for staggered discontinuation of regimen components, or replacement of the NNRTI with a PI/r or PI/c, has not been determined.

Planned Long-Term Therapy Interruptions

Planned long-term therapy interruptions are **<u>not recommended</u>** outside of controlled clinical trials **(AI)**. Several research studies are evaluating approaches to a functional (virological control in the absence of therapy) or sterilizing (virus eradication) cure of HIV infection. Currently, the only way to reliably test the effectiveness of these strategies may be to interrupt ART and closely monitor viral rebound over time in the setting of a clinical trial.

If therapy must be discontinued, patients should be aware of and understand the risks of viral rebound, acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations such as oral thrush or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), development of drug resistance, and the need for

chemoprophylaxis against opportunistic infections as a result of CD4 decline. Patients should be counseled about the need for close clinical and laboratory monitoring during therapy interruptions.

References

1. Holkmann Olsen C, Mocroft A, Kirk O, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. *HIV Med*. 2007;8(2):96-104. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17352766.

2. Kousignian I, Abgrall S, Grabar S, et al. Maintaining antiretroviral therapy reduces the risk of AIDS-defining events in patients with uncontrolled viral replication and profound immunodeficiency. *Clin Infect Dis*. 2008;46(2):296-304. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18171266.

3. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet*. 2006;367(9527):1981-1989. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16782488&itool=iconabstr&query_hl=147&itool=pubmed_docsum.

4. DART Trial Team DTT. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/microl. *AIDS*. 2008;22(2):237-247. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18097226.

5. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17135583.