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THERAPY IN PRACTICE

# Modifying Antiretroviral Therapy in Virologically Suppressed HIV-1-Infected Patients

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**Abstract** HIV-1-infected patients with suppressed plasma viral loads often require changes to their antiretroviral (ARV) therapy to manage drug toxicity and intolerance, to improve adherence, and to avoid drug interactions. In patients who have never experienced virologic failure while receiving ARV therapy and who have no evidence of drug resistance, switching to any of the acceptable US Department of Health and Human Services first-line therapies is expected to maintain virologic suppression. However, in virologically suppressed patients with a history of virologic failure or drug resistance, it can be more challenging to change therapy while still maintaining virologic suppression. In these patients, it may be difficult to know whether the discontinuation of one of the ARVs in a suppressive regimen constitutes the removal of a key regimen component that will not be adequately supplanted by one or more substituted ARVs. In this article, we review many of the clinical scenarios requiring ARV therapy modification in patients with stable virologic suppression and outline the strategies for modifying therapy while maintaining long-term virologic suppression.

## Key Points

In patients who have never experienced virologic failure while receiving ART and have no evidence of drug resistance, switching from stable suppressive therapy to any of the acceptable DHHS first-line regimens is expected to maintain virologic suppression.

ART modifications in patients with known drug resistance or prior virologic failure requires knowledge of past regimens, past episodes of failure, and past genotypic resistance tests when switching and it is usually necessary to select a regimen with a high genetic barrier to resistance.

Several reduced intensity regimens may provide treatment modification options for carefully selected patients with medication intolerance or co-morbidities, but typically carry an increased risk of virologic failure and require excellent medication adherence and close follow-up.

## 1 Introduction

Advances in antiretroviral (ARV) therapy (ART) have made it possible to achieve and maintain virologic suppression in nearly all HIV-1-infected patients. However, even patients with sustained virologic suppression require ART changes to manage acute toxicities, limit long-term adverse effects, improve adherence, and avoid drug–drug interactions [1, 2]. Indeed, ART is modified more commonly for these indications than for virologic failure (VF) [3–6]. ART modification in patients with stable virologic

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suppression has been reported in more than one-third of patients on first-line ART over a 7-year period in a large Canadian cohort and between 8 and 43 % annually in a variety of other clinical cohorts [3–5, 7–10].

Although modifying a suppressive ART regimen may be beneficial or even required for many patients, it carries a risk of VF and the development of resistance to one or more of the ARVs in a patient's modified regimen [9]. This risk is heightened in patients with a history of VF because potentially not all ARVs in such patients' regimens will be fully active. Therefore, modifying or switching therapy in such patients requires a review of past and current ARV regimens.

As new ARVs with improved toxicity profiles have been developed, there have been an increasing number of clinical trials of ART modification in virologically suppressed patients, and many of these studies have been summarized in an excellent review by Van den Eynde and Podzamczer [11]. Together, these trials provide guidance for several specific clinical scenarios and outline important principles necessary to maintain virologic suppression while changing therapy. However, many clinical scenarios and ART modification strategies have not been evaluated in randomized clinical trials and are instead supported primarily by non-randomized trials, observational cohort studies, and expert opinion. Here we review many of the clinical scenarios requiring ART modification in patients with stable virologic suppression and the accompanying strategies for modifying therapy while maintaining long-term virologic suppression.

## 2 Indications for Antiretroviral Therapy (ART) Modification

In the earliest years of ART, several studies attempted to limit the potential toxicity of ART by reducing the number of ARVs prescribed to virologically suppressed patients [12–14]. The VF rates in these early studies were unacceptably high, in part because virologic suppression was defined by insensitive virus load assays with lower limits of detection of 400–500 copies/ml and in part because the ARVs used to attain virologic suppression were less efficacious than the ARVs used now. As a result of these early failures and the improved tolerability of current ARVs, the strategy of simply removing an ARV from the regimen of a patient with stable virologic suppression is now studied primarily in patients receiving medications with a high genetic barrier to resistance, most commonly pharmacologically boosted protease inhibitors (PIs).

There have also been several intensification studies in which an ARV is added to the regimen of a patient with stable virologic suppression. The goal of these studies was to eliminate or reduce the residual levels of viremia that can often be detected with highly sensitive single-copy HIV-1 assays [15]. The rationale for these studies was based on the hypothesis that even very low levels of virus (fewer than 50 copies/ml) may be associated with damaging systemic inflammation and replenishment of the HIV-1 proviral DNA reservoir. Intensification studies, however, generally demonstrated no clinical benefit or effect on low-level residual viremia using highly sensitive single-copy/ml assays [15–18]. As a result, the addition of an ARV to the regimen of a patient with stably suppressed viremia is not recommended.

Table 1 is a comprehensive list of the main indications for switching ARVs in patients with stable virologic suppression. Among the most common chronic toxicities and forms of intolerance leading to ARV switches are gastrointestinal intolerance, lipid or other metabolic abnormalities, coronary artery disease, neuropsychiatric symptoms, renal dysfunction, and jaundice caused by unconjugated hyperbilirubinemia. Mitochondrial toxicity and injection site reactions are currently uncommon causes of treatment switches because there has been a marked decrease in the use of the mitochondrial toxic nucleoside reverse transcriptase inhibitors (NRTIs)—stavudine (d4T), didanosine (ddI), and zidovudine (AZT)—and of the parenteral fusion inhibitor enfuvirtide (ENF).

Co-morbid conditions typically necessitate ARV regimen changes when they exacerbate a pre-existing ARV-associated toxicity or require the use of a medication that has undesired or unpredictable pharmacologic interactions with an ARV in a patient's regimen. For example, switching ARVs to avoid interaction with rifamycins during tuberculosis (TB) therapy is common in areas in which TB is endemic. Switching ARVs to limit pharmacologic interactions with direct-acting antivirals for hepatitis C treatment or to improve absorption in patients receiving proton-pump inhibitors is common in upper-income regions (Table 1).

There are also numerous drug–drug interactions between ARVs and other commonly prescribed drugs. Although the effects of many of these interactions on drug absorption and metabolism have been well characterized, other empirically observed interactions are poorly understood. As a result, there is no substitute for reviewing the potential interactions of a new ARV with each medication a patient is receiving. The US Department of Health and Human Services (DHHS) guidelines document contains an extensive highly accessible series of tables containing the most common interactions associated with each ARV. There are also several up-to-date authoritative websites containing even more extensive information on drug–drug interactions such as the one maintained by the University of Liverpool: http://www.hiv-druginteractions.org.

**Table 1** Indications for modifying antiretroviral therapy in virologically suppressed patients

| Type of indication | Specific indication | Main implicated ARVs | Comments and key references |
|---|---|---|---|
| Chronic toxicity | Lipoatrophy | d4T >AZT | Lipoatrophy is an NRTI-induced mitochondrial toxicity strongly associated with d4T and to a lesser extent AZT. Patients who discontinue one of these NRTIs—including those who switch to ABC or TDF—prevent a worsening of their condition and may experience clinical improvement [19, 20] |
| | Lipid abnormalities and coronary artery disease | LPV/r | LPV/r and several less frequently used PI/r's increase triglyceride and total cholesterol levels often increasing a patient's predicted risk of coronary artery disease and requiring the use of lipid lowering drugs [21]. ATV/r, ATV/c, DRV/r, and DRV/c have much more modest effects than LPV/r on lipid levels [22, 23] |
| | | ABC | Several observational studies including one recent study [24] have suggested there is a 1.5- to 2.0-fold increased risk of myocardial infarction associated with cumulative ABC use. But this risk has not been observed in all studies and no plausible mechanism for a risk has been identified [25]. Nonetheless, the DHHS guidelines suggest ABC be used with caution in patients with high cardiovascular risk [1]. Compared with TDF, ABC is associated with slightly higher levels of LDL but no change in the total/HDL cholesterol ratio |
| | Renal dysfunction | TDF | TDF can be associated with a slow progressive reduction in GFR and renal tubular dysfunction that typically improves upon TDF discontinuation [26–28]. It is also necessary to discontinue TDF or adjust its dose in patients with an eGFR <60 ml/min regardless of the cause of renal insufficiency [1]. TAF is associated with reduced markers of renal tubular dysfunction. Long-term effects of TAF on eGFR as well as guidelines on its dosing with impaired renal function are not yet available [29, 30] |
| | Osteopenia | TDF | TDF is associated with slightly reduced bone density in a large proportion of patients and requires discontinuation in patients with moderate or severe osteopenia [31]. TAF is associated with less short-term loss of bone mineral density compared to TDF but long-term data are not available [29, 30] |
| Intolerance | Gastrointestinal | LPV/r | Diarrhea and nausea are among the most common clinical adverse reactions associated with LPV/r and several older PIs. These symptoms are much less severe with ATV/r, ATV/c, DRV/r, and DRV/c [32] |
| | Neuropsychiatric | EFV | Headache, confusion, impaired concentration, amnesia, and sleep abnormalities occur commonly during the first few days of treatment and lead to discontinuation in 5–10 % of patients [33]. In most patients, these CNS symptoms decline to baseline levels within weeks with continued therapy [33, 34]. In an analysis of four ACTG studies of 3,241 EFV-recipients and 2,091 comparators, EFV use carried a hazard ratio of 2.6 for attempted or completed suicide (17 events vs. five events) [35]. A subsequent larger meta-analysis, however, did not demonstrate this association [34]. In combination with TDF/FTC, 400 mg has been shown to be as effective as 600 mg of EFV and to be associated with fewer treatment discontinuations and may be an option where such formulations are available [36] |
| | Jaundice | ATV or ATV/r | ATV causes indirect hyperbilirubinemia in some patients related to its inhibition of the UGT1A1 enzyme [37]. In some studies, this has been a major reason for changing therapy [38] |
| Acute toxicity | Hypersensitivity reactions | ABC | Screening for HLA-B[a]5701 should prevent nearly all cases of ABC hypersensitivity [39, 40] |
| | | NVP | NVP is associated with an increased risk of severe rash-associated liver toxicity especially in women with elevated baseline transaminase levels or CD4 counts greater than 250 [1, 19, 41] |
| | | Other ARVs | Hypersensitivity reactions occur in <1 % of patients receiving ARVs other than ABC and NVP. The DHHS guidelines specifically cite DTG as being associated with a hypersensitivity reaction in less than 1 % of patients during registration trials and an uncommon MVC-associated hypersensitivity reaction associated with transaminase elevations. Mild rashes have been reported in about 5 % of patients receiving DRV/r. These can be managed by close follow-up because they often resolve spontaneously [1, 19] |

**Table 1** continued

| Type of indication | Specific indication | Main implicated ARVs | Comments and key references |
|---|---|---|---|
| Parenteral administration | Injection site reactions | ENF | Shortly after its approval, ENF became a key component of successful salvage therapy for patients with few other options. However, with the subsequent approval of RAL, DRV, and ETR, it became possible to create an equally suppressive ART regimen in a high proportion of patients receiving ENF |
| Drug dosing | Twice daily | LPV/r, RAL, ETR, DRV/r | Twice-daily LPV/r dosing is recommended for patients with ≥3 LPV-resistance mutations, pregnant women, or patients receiving EFV, NVP, or any drug that reduces LPV levels [1]. RAL and ETR are approved and recommended for twice-daily dosing. DRV/r and DRV/c can be administered once daily in patients without DRV-resistance |
| | Food requirement | RPV | RPV absorption has a greater dependency on being taken with food than other ARVs [42] |
| | Risk of non-adherence | Complicated ARV combinations | Fixed-dose combinations (FDCs) improve adherence but reduce dosing flexibility when adjustments are required. Five FDCs suitable both for first-line therapy and maintenance scenarios have been approved: TDF/FTC/EFV, TDF/FTC/EVG/c, TDF/FTC/RPV, ABC/3TC/DTG, and TAF/FTC/EVG/c. Two additional FDCs containing TAF in place of TDF are nearing FDA approval |
| Pregnancy | Fetal issues | EFV | There are conflicting data on whether EFV is associated with an increased risk of neural tube defects [43]. The DHHS panel recommends that EFV not be initiated during the first 8 weeks of pregnancy [44]. The WHO makes no such recommendation as pregnancy is rarely recognized during its first 8 weeks [45] |
| | Maternal issues | NVP | NVP hepatotoxicity and rash are more common during pregnancy particularly in patients with pre-existing liver disease or CD4 count >250 cells/mm$^3$ [46] |
| | | PI/r | PK changes may lead to lower plasma levels of PIs [44]. LPV/r and DRV/r should be administered twice daily. Unboosted ATV is not recommended |
| Co-infections | Tuberculosis | NNRTIs | Standard EFV dose is acceptable. RPV and ETV are not recommended in patients receiving rifampin due to CYP3A induction of NNRTI metabolism [1] |
| | | PI | Not recommended in patients receiving rifampin due to CYP3A induction of PI metabolism by rifampin. May be used with close monitoring in patients receiving rifabutin [1] |
| | | INSTI | Twice the standard RAL dose (800 mg twice daily) is recommended but has not been evaluated in clinical studies. DTG must be used twice daily in patients receiving rifampin. In patients with documented or suspected INSTI resistance, DTG should be used with rifabutin [1] |
| | HCV[a] | Ledipasvir | Ledipasvir increases TDF levels, which is enhanced further with ritonavir or cobicistat-boosted PIs or EVG/c [47]. Patients receiving ledipasvir should therefore be monitored for TDF toxicity. TPV is contraindicated in patients receiving ledipasvir |
| | | Sofosbuvir | TPV co-administration is not recommended because it may lower sofosbuvir concentration by inducing P-glycoprotein |
| | | Simeprevir | PIs, EFV, NVP, ETR, and EVG/c not recommended. Expert consultation is recommended |
| | | Ombitasvir/paritaprevir/dasabuvir/ ritonavir | PIs other than ATV, NNRTIs, and EVG/c are contraindicated. Expert consultation is recommended |

**Table 1** continued

| Type of indication | Specific indication | Main implicated ARVs | Comments and key references |
|---|---|---|---|
| Additional drug–drug interactions | Drug absorption | Acid reducing agents<br>Polyvalent cations<br>p-glycoprotein effects | There are many interactions between ARVs and between ARVs and other drugs commonly used in HIV-1-infected patients. The DHHS guidelines and several websites contain comprehensive tables and expert recommendations on which drug combinations are contraindicated and which require dosage modifications of the ARV or interacting drug [1] |
| | Hepatic induction and inhibition | CYP450 enzymes<br>UGT enzyme | |

*ABC* abacavir, *ACTG* AIDS Clinical Trials Group, *ART* antiretroviral therapy, *ARV* antiretroviral, *ATV* atazanavir, *AZT* zidovudine, *c* cobicistat, *d4T* stavudine, *ddI* didanosine, *DHHS* US Department of Health and Human Services, *DTG* dolutegravir, *EFV* efavirenz, *ENF* enfuvirtide, *eGFR* estimated glomerular filtration rate in ml/min, *ETR* etravirine, *EVG* elvitegravir, *FDA* US Food and Drug Administration, *FDC* fixed-dose combination, *FTC* emtricitabine, *HCV* hepatitis C virus, *HDL* high-density lipoprotein, *INSTI* integrase strand transfer inhibitor, *LDL* low-density lipoprotein cholesterol, *LPV* lopinavir, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleos(t)ide reverse transcriptase inhibitor, *NVP* nevirapine, *PI* protease inhibitor, *PI/r* ritonavir-boosted protease inhibitor, *PK* pharmacokinetic, *r* low-dose ritonavir, *RAL* raltegravir, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate, *TPV* tipranavir, *WHO* World Health Organization

<sup>a</sup> Available HCV medications and data on interactions are rapidly emerging. Up-to-date detailed drug interactions can be found at: http://www.hep-druginteractions.org/

Pre-conception counseling coupled with prospective ART modification for women likely to become pregnant will reduce the likelihood that ART will need to be changed during pregnancy. The DHHS preferred regimens for treatment-naïve pregnant patients include ritonavir-boosted atazanavir (ATV/r), darunavir (DRV/r), or raltegravir (RAL) in combination with one of the following NRTI backbones: abacavir (ABC)/lamivudine (3TC), tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), TDF/3TC, or AZT/3TC [44]. The initiation of efavirenz (EFV) is not recommended during the first 8 weeks after conception in treatment-naïve patients. However, as pregnancy is frequently not detected until several weeks after conception, this recommendation is relevant primarily for the choice of therapy in women planning to conceive.

Pharmacokinetic changes may lower PI plasma levels during the third trimester of pregnancy [44]. Therefore ritonavir-boosted lopinavir (LPV/r) and DRV/r should be administered twice daily and unboosted ATV is not recommended. Although there are fewer data on the safety to the fetus of both the most recently approved ARVs such as elvitegravir (EVG), dolutegravir (DTG), cobicistat, and tenofovir alafenamide (TAF) and the more rarely used ARVs such as tipranavir (TPV), maraviroc (MVC), and ENF, no ARVs, other than the combined use of d4T and ddI, are specifically contraindicated [44]. ARV switches during pregnancy may also be associated with a greater risk of VF compared with continued unchanged therapy, supporting the recommendation that pregnant patients be managed in consultation with specialists experienced in treating HIV in pregnancy [48].

Adherence to ART is essential for both attaining and sustaining virologic suppression. Adherence can be influenced by several factors under the control of a health-care provider including the selection of a well tolerated ART regimen with an uncomplicated dosing schedule. Fixed-dose combinations (FDCs) improve adherence and reduce the risk of drug resistance by preventing patients from accidentally or intentionally not taking all of their prescribed drugs. Five single-tablet FDCs suitable for both first-line therapy and, many maintenance therapy scenarios, have been approved by the US Food and Drug Administration (FDA).

Patients who are responsible for a significant proportion of the cost of an ART regimen either through cost-sharing or individual drug co-payments are at higher risk of non-adherence. It is not possible to provide specific recommendations on which regimens are associated with the lowest cost to a patient because these are typically driven by market forces and negotiations among pharmaceutical companies, treatment programs, and third-party payers. Nonetheless, health-care providers should be aware of the direct patient costs when choosing therapy.

## 3 Clinical Trials of ART Modification

ART modification trials can be divided into those enrolling patients with no history of VF who are receiving an initial or early ART regimen and those enrolling patients who may have a history of VF with documented or suspected drug resistance. In patients with stable virologic suppression and no history of VF, many ART regimens are likely to be effective options when a change in therapy is necessary. Indeed, each of the regimens classified by the DHHS into Recommended, Alternative, or Other options for first-line therapy (Table 2) appear to be acceptable options for patients with stable virologic suppression and no history of VF. For example, TDF/FTC/rilpivirine (RPV) is categorized as an Alternative option for first-line therapy because it is not recommended for patients with plasma HIV-1 RNA levels above 5.0 log copies/ml. However, it has been shown to be highly effective in patients with stable virologic suppression regardless of their pre-therapy plasma HIV-1 RNA level [49].

It is more challenging to modify therapy in virologically suppressed patients with a history of VF. In such patients it is difficult to know whether the discontinuation of one of the ARVs in a suppressive regimen constitutes the removal of a key regimen component that will not be adequately supplanted by a substituted ARV. In such patients it is necessary to consider past drug resistance test results and past ARVs to which drug resistance may have developed but may not have been documented by resistance testing [50, 51].

Table 3 summarizes the design and main findings of most of the randomized controlled trials of ART modification in virologically suppressed patients. The trials are grouped according to the ARV classes substituting for one another. In most trials, virologic suppression was defined as a VL below 50–75 copies/ml for 12–24 weeks. Histories of VF or drug resistance were exclusion criteria for many of the studies.

The primary endpoint in most trials was the proportion of patients with VF by week 48, where VF was defined as the development of HIV RNA levels above a particular threshold ranging from 50 to 400 copies/ml. HIV RNA levels were assessed at either a single time point as in the FDA Snapshot analysis [77] or had to be confirmed with a repeat test. To preserve the principles of intention-to-treat, several studies distinguished primary VF from treatment failure, which included primary VF, treatment discontinuation because of intolerance or drug toxicity, and losses to follow-up. The difference among treatment groups was often assessed using a non-inferiority analysis in which the lower bound of the confidence interval for the difference in proportions of successfully treated patients was compared using a pre-specified margin of difference usually between 10 and 20 %.

**Table 2** Recommended, alternative and other ART regimen options (US Department of Health and Human Services Guidelines) [1][a]

| Class | Base[b] | NRTI backbone[c] | |
|---|---|---|---|
| | | TDF/FTC | ABC/3TC |
| INSTI | RAL | Recommended | Other |
| | EVG/c | Recommended | Not recommended |
| | DTG | Recommended | Recommended |
| PI | DRV/r or DRV/c | Recommended | Alternative |
| | ATV/r or ATV/c | Alternative | Alternative |
| | LPV/r | Other | Other |
| NNRTI | EFV | Alternative | Other |
| | RPV | Alternative | Not recommended |

*3TC* lamivudine, *ABC* abacavir, *ART* antiretroviral therapy, *ATV* atazanavir, *c* cobicistat, *EFV* efavirenz, *EVG* elvitegravir, *FTC* emtricitabine, *INSTI* integrase strand transfer inhibitor, *LPV* lopinavir, *NNRTI* non-nucleoside reverse transcriptse inhibitor, *NRTI* nucleos(-t)ide reverse transcriptase inhibitor, *PI* protease inhibitor, *r* low-dose ritonavir, *RAL* raltegravir, *TDF* tenofovir disoproxil fumarate

[a] Additional other regimens include DRV/r + RAL, LPV/r + 3TC, and DRV/r + 3TC

[b] RPV should be used as initial therapy only in patients with HIV RNA below 100,000 c/ml and a CD4 count greater than 200 cells/m$^3$. Cobicistat is not recommended for use in patients with creatinine clearance <70 ml/min

[c] Patients receiving ABC should be HLA-B*5701 negative. Patients with creatinine clearance below 50 ml/min should have the TDF dosing interval adjusted in accordance with the product label. EFV plus 3TC/ABC and ATV/c or ATV/r plus 3TC/ABC should be used in patients with HIV RNA below 100,000 copies/ml

## 4 ART Modification Strategies

The following sections organize ART modifications in patients with stably suppressed virus according to the ARV class of a drug that requires discontinuation and the ARV class of its replacement drug. Three sections address ART modifications that involve discontinuing NRTIs, PIs, and NNRTIs regardless of whether discontinuation is required to manage toxicity, address drug–drug interactions, or improve adherence. Additional sections address the potential roles for boosted PI monotherapy, boosted PIs plus lamivudine, and boosted PIs plus an integrase strand transfer inhibitor (INSTI), several unorthodox ART modification approaches, and the discontinuation of ENF.

### 4.1 Discontinuation of a Nucleoside Reverse Transcriptase Inhibitor (NRTI)

d4T, ddI, and to a lesser extent AZT are associated with a wide range of toxicities as a result of their off-target inhibition of human mitochondrial gamma polymerase [19,

**Table 3** Clinical trials of ART modification in virologically suppressed patients

| Classes | Study | Study design | Key inclusion criteria | Findings |
|---|---|---|---|---|
| Within NRTI | BICOMBO [52] | • 2 NRTIs → ABC/3TC (n = 190) vs. TDF/FTC (n = 290)<br>• 48 W | • VL <200 × 24 W<br>• Cr <2 mg/ml | • Trend towards increased TF[a] by ITT with ABC (19 %) vs. TDF (13 %; p = 0.06)<br>• 4 patients on ABC vs. 0 on TDF developed VF (p = 0.04)<br>• Median CD4 increase was greater with ABC (44 cells/mm³) vs. TDF (−3 cells/mm³) |
| | STEAL [53] | • ≥2 NRTIs → ABC/3TC (n = 180) vs. TDF/FTC (n = 180)<br>• 96 W | • VL <50 × 12 W<br>• eGFR ≥70 | • Similar rates of VF (confirmed VL >400) for ABC/3TC (5.6 %) vs. TDF/FTC (3.9 %)<br>• ↑ Cardiac events with ABC/3TC (2.2/100 patient years) vs. TDF/FTC (0.3/100 patient years; p = 0.05)<br>• ↓ Bone mineral density (hip T-score) with TDF/FTC |
| | SWIFT [54] | • ABC/3TC + PI/r → TDF/FTC + PI/r (n = 155) vs. no change (n = 156)<br>• 96 W | • VL <200 × 12 W<br>• No resistance to TDF/FTC or PI/r<br>• eGFR ≥50 | • ↑ VF (confirmed VL >200) with ABC/3TC (11/156; 7.1 %) than TDF/FTC (3/155; 1.9 %, p = 0.03)<br>• ↓ Cholesterol, triglycerides and Framingham risk with TDF/FTC<br>• ↓ Bone mineral density (hip T-score) with TDF/FTC<br>• ↓ eGFR (8.3 vs. 4.5 ml/min) with TDF/FTC |
| | Behrens et al. [55] | • ABC/3TC + LPV/r → TDF/FTC + LPV/r (n = 43) vs. no change (n = 42)<br>• 12 W | • VL <50 × 12 W<br>• Total cholesterol ≥200 mg/dl | • ↓ Total cholesterol (26 mg/dl, p < 0.001) and LDL cholesterol (15 mg/dl, p = 0.005) with TDF/FTC. ↓ HDL cholesterol with TDF/FTC (4 mg/dl) compared to control (1 mg/dl, p = 0.026) |
| | ASSURE [56] | • TDF/FTC + ATV/r → ABC/3TC + ATV (n = 199) vs. no change (n = 97)<br>• 24 W | • VL <75 × 2 tests<br>• No prior VF | • 87 % of patients in both arms had VL <50 at week 24<br>• Adverse reactions were low in both arms |
| | ROCKET [57] | • ABC/3TC + EFV → TDF/FTC + EFV (n = 78) vs. no change (n = 79)<br>• 12 W | • VL <50 × 12 W<br>• Hyperlipidemia<br>• eGFR ≥60 | • ↓ LDL cholesterol with TDF/FTC (22 mg/dl). ↓ HDL cholesterol with TDF/FTC (5 mg/dlL) |
| | SWAP [58, 59] | AZT/3TC → ABC/3TC (n = 20) vs. TDF/FTC (n = 20) | VL <40 × 12 W | • ↓ Bone mineral density by 2 % at 24 and 48 W with TDF/FTC |

**Table 3** continued

| Classes | Study | Study design | Key inclusion criteria | Findings |
|---|---|---|---|---|
| Within PI | SWAN [60] | • PI or PI/r-regimen → ATV (n = 278) (ATV/r if on TDF, n = 26) vs. no change (n = 141)<br>• 48 W | • Stable PI ≥12 W<br>• VL <50 × ≥12 W<br>• No prior VF on a PI-containing regimen | • ↓ VF for those on ATV or ATV/r (19/278; 7 %) vs. control (22/141; 16 %, $p = 0.004$)<br>• ↓ Total cholesterol, non-HDL cholesterol, and fasting TG for those on ATV or ATV/r |
| | ATAZIP [61] | • LPV/r + NRTIs → ATV/r + NRTIs (n = 121) vs. no change (n = 127)<br>• 48 W | • VL <200 × 24 W<br>• ≤2 episodes of VF on a PI-regimen<br>• ≤5 PI-DRMs | • Similar rates of TF with ATV/r (21/121; 17 %) vs. LPV/r (25/127; 20 %)<br>• Similar rates of VF (confirmed VL >200) with ATV/r (6/121; 5 %) vs. LPV/r (9/127; 7 %) |
| | ARIES [62] | • ATV/r + ABC/3TC induction × 36 W → ATV + ABC/3TC (n = 210) vs. no change (n = 209)<br>• 48 W | • ART-naïve<br>• VL <50 × 36 W<br>• HLA-B*5701− | • Similar rates of overall TF (14 vs. 19 % by TLOVR[b]) and VF (1/210; 0.5 % vs. 7/209; 3.5 %) with ATV vs. ATV/r, respectively |
| | InduMa [63] | • ATV/r + 2 NRTIs induction × 24 W → ATV + 2 NRTIs not including TDF (n = 87) vs. no change (n = 85)<br>• 48 W | • ART-naïve<br>• VL <50 × 24 W | • Similar rates of TF with ATV/r (21/85; 25 %) vs. ATV (19/87; 22 %)<br>• ↓ TG with ATV but no differences in LDL or HDL levels<br>• ↓ hyperbilirubinemia (26 % vs. 15 %) with ATV |
| | ASSURE [56] | • TDF/FTC + ATV/r → ABC/3TC + ATV (n = 199) vs. no change (n = 97)<br>• 24 W | • VL <75 × 2 tests<br>• No prior VF | • 87 % of patients in both arms had VL <50 at week 24<br>• Adverse reactions were low in both arms |
| | SLOAT [64] | • LPV/r-containing regimen → ATV (n = 102) (ATV/r if TDF used n = 53) vs. no change (n = 87)<br>• 48 W | • VL <50 × 24 W | • Similar rates of VF with ATV (5/49; 10 %), ATV/r (7/53; 13 %), and LPV/r (9/87; 10 %). Of patients with VF, 5/12 on ATV or ATV/r vs 1/9 on LPV/r failed with PI resistance<br>• ↓ TG (−80mg/dl) and total cholesterol (−19mg/dl; $p < 0.001$) in the ATV group |
| PIs to INSTI | SWITCHMRK [65] | • LPV/r + ARVs → RAL + ARVs (n = 350) vs. no change (n = 352)<br>• 24 W | • VL <50–75 × ≥12 W<br>• No CAD, DM, lipid-lowering drugs | • ↑ TF with RAL (16 %) vs. control (9 %; $p < 0.05$)<br>• ↓ 13 % reduction in total cholesterol and 42 % reduction in TG with RAL |
| | SPIRAL [66] | • PI/r + ARVs → RAL + ARVs (n = 134) vs. no change (n = 139)<br>• 48 W | • VL <50 × 24 W | • Similar proportion with TF for RAL (15/139; 11 %) vs. control (18/134; 13 %). 4 patients in RAL arm vs 6 in control arm with VF |
| | STRATEGY-PI [67] | • PI/r + TDF/FTC → EVG/c + TDF/FTC (n = 293) vs. no change (n = 140)<br>• 48 W | • No prior VF<br>• No pre-ART TDF or FTC resistance | • ↓ TF with TDF/FTC/EVG/c (6 %) vs. control (13 %; $p = 0.025$) driven by non-VF discontinuations in control arm |

**Table 3** continued

| Classes | Study | Study design | Key inclusion criteria | Findings |
|---|---|---|---|---|
| PI to NNRTI | NEFA [68] | • PI or PI/r-regimen to 2NRTIs + NVP (n = 155), EFV (n = 156), or ABC (n = 149)<br>• 48 W | • NNRTI and ABC-naïve<br>• VL <200 × 24 W | • Kaplan–Meier estimates of death, AIDS progression, or VL >200 were 6, 10, and 13 % for EFV, NVP, and ABC, respectively. Both EFV and NVP were superior to ABC. No significant difference between EFV and NVP<br>• 23 of 29 with VF had prior suboptimal ART regimen |
| | AI266073 [69] | • PI, PI/r, NNRTI-regimen to TDF/FTC/EFV (n = 203) vs. no change (n = 97)<br>• 48 W | • VL <200 × 12 W<br>• No prior VF | • Similar proportion with TF (confirmed VL >200) for TDF/FTC/EFV (11 %) vs. unchanged therapy (12 %)<br>• Similar results when stratified by baseline PI, PI/r, or NNRTI-regimen |
| | SPIRIT [49] | • PI/r + 2NRTIs → TDF/FTC/RPV (n = 317) vs. no change (n = 159)<br>• 24 W | • VL <50 × 24 W<br>• No prior VF<br>• No NRTI or RPV-resistance | • Similar proportion with TF for TDF/FTC/RPV (6 %) vs. PI/r therapy (10 %; p = 0.15)<br>• VF in 3/317 (0.9 %) on TDF/FTC/RPV and 8/159 (5 %) in the PI/r arm<br>• None of 18 with a pre-ART K103N developed VF on TDF/FTC/RPV |
| Within NNRTI | Waters et al [70] | • 2 NRTIs + EFV → 2NRTIs + ETR 400 mg OD (intermediate vs. delayed switch)<br>• n = 38<br>• 12 W | • VL <50<br>• Ongoing CNS symptoms after 12 W | • ↓ CNS symptoms with ETR vs. continued EFV by 12 W (90 % vs. 60 %; p = 0.04) |
| | SWITCH-EE [71] | • EFV + 2 NRTIs → EFV vs. ETR + 2 NRTIs × 12 W (double-blind crossover)<br>• ETR administered 400 mg OD<br>• n = 58 | • VL <50 × 12 W | • Median time on EFV was 3.9 years, few reported adverse CNS effects at baseline<br>• No significant differences in CNS symptoms on EFV vs. ETR |
| | Mills et al [72] | • TDF/FTC/EFV → TDF/FTC/RPV<br>• n = 49<br>• 48 W | • VL <50 × 12 W<br>• EFV intolerance<br>• No prior ART or RPV resistance | • EFV remained therapeutic for 2–4 W post switch. RPV was therapeutic by 1–2 W post switch, because of EFV CYP450 3A4 induction<br>• VF without drug resistance in 2/49 patients by 48 W |
| NNRTIs to INSTIs | SWITCH-ER [73] | • EFV + 2NRTIs → RAL + 2NRTIs vs. no change × 4 W (double-blind crossover)<br>• n = 57 | • VL <50 × 12 W | • Patient preference for RAL in 41 %, EFV in 23 %, and neither in 36 % based on CNS symptomatology |
| | STRATEGY-NNRTI [74] | • NVP or EFV + TDF/FTC → EVG/c + TDF/FTC (n = 292) vs. no change (n = 147)<br>• 48 W | • VL <50 × 24 W<br>• No prior VF<br>• No TDF or FTC resistance<br>• eGFR ≥70 | • Approximately 75 % were on TDF/FTC/EFV at entry<br>• Similar proportion with TF, TDF/FTC/EVG/c (7 %) vs. no change (12 %; p = 0.07). VF in 1 % in each arm, none failed with drug resistance |
| Multiple regimens to INSTIs | STRIIVING [75] | • PI, PI/r, NNRTI, or INSTI (RAL or EVG)-regimen → ABC/3TC/DTG (n = 274) vs. no change (n = 277)<br>• 24 W | • VL <50 × 2 tests<br>• Stable ART × 24 W<br>• No prior VF | • Virologic non-inferior, 85 vs. 88 % had VL <50<br>• More discontinuations due to adverse events in switch arm 10/275 (4 %) vs. 0/277 in the continuation arm |

**Table 3** continued

| Classes | Study | Study design | Key inclusion criteria | Findings |
|---|---|---|---|---|
| | GS Study 109[76] | • EFV, EVG/c, ATV/r or ATV/c + TDF/FTC → TAF/FTC/EVG/c (n = 959) vs. no change (n = 477)<br>• 48 W | • VL <50 × 24 W<br>• eGFR ≥50<br>• Successful completion of prior clinical study for ARV initiation | • Switch superior, 97 vs. 93 % had VL < 50 at 48 W (p < 0.001).<br>• VF 1 % in both arms<br>• Small improvement in bone density and markers of renal tubular dysfunction (measured as % change) in the switch arm |

*3TC* lamivudine, *ABC* abacavir, *ART* antiretroviral therapy, *ARV* antiretroviral, *ATV* atazanavir, *AZT* zidovudine, *c* cobicistat, *CNS* central nervous system, *Cr* serum creatinine, *d4T* stavudine, *ddI* didanosine, *EFV* efavirenz, *eGFR* estimated glomerular filtration rate in ml/min, *ETR* etravirine, *EVG* elvitegravir, *FDA* US Food and Drug Administration, *FTC* emtricitabine, *HDL* high-density lipoprotein, *INSTI* integrase strand transfer inhibitor, *ITT* intention-to-treat, *LDL* low-density lipoprotein cholesterol, *LPV* lopinavir, *N* number in overall study, *n* number in study subgroup, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleos(t)ide reverse transcriptase inhibitor, *NFV* nelfinavir, *NVP* nevirapine, *PI* protease inhibitor, *PI/r* ritonavir-boosted protease inhibitor, *r* low-dose ritonavir, *RAL* raltegravir, *TDF* tenofovir disoproxil fumarate, *TF* treatment failure, *TG* triglycerides, *TLOVR* time to loss of virologic response, *VF* virologic failure, *VL* plasma viral load, *vs.* versus, *W* week

[a] Treatment failure (TF) definitions differ slightly between studies. TF typically encompasses virologic breakthrough, confirmed virologic failure, and medication switches due to intolerance. In ITT analyses participants lost to follow-up are considered TFs. Individual study differences are noted in the table

[b] TLOVR analysis is a time-dependent method of assessing antiviral treatment efficacy in study subjects with virologic suppression. Subjects with two consecutive viral load measurements over the threshold (typically 50 copies/ml) are considered failures. The FDA Snapshot algorithm has now become the preferred method of assessment because it gives similar results but is easier to calculate and interpret. Details can be found at the FDA's website [77]

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20] (Table 1). Although d4T and ddI are no longer recommended and although AZT is indicated solely for the treatment of certain drug-resistant HIV strains [1, 2, 45], one still occasionally encounters patients on these older NRTIs.

Table 3 summarizes seven studies in which the NRTI backbones ABC/3TC and TDF/FTC were compared as ART modification options. Three studies enrolled patients receiving older NRTIs randomized to receive ABC/3TC or TDF/FTC. These studies confirmed that stably suppressed patients can be switched from AZT or d4T to TDF or ABC without an increased risk of VF [52, 53, 58]. Two studies enrolled patients receiving ABC/3TC plus a ritonavir-boosted PI [54, 55], one enrolled patients receiving ABC/3TC/EFV [57], and one enrolled patients receiving TDF/FTC plus a a ritonavir-boosted PI [56]. Taken as a whole, these studies demonstrated borderline increases in VF with ABC/3TC and small reductions in renal function and bone density with TDF/FTC. In three studies, a change from ABC/3TC to TDF/FTC was associated with modest reductions in LDL cholesterol but not in the total/HDL cholesterol ratio. In one study, there was an increased risk of cardiac events with ABC/3TC (2.2 per 100 patient-years) compared with TDF/FTC (0.3 per 100 patient-years; $p = 0.05$) [53].

Although TDF and ABC are equally potent inhibitors of HIV-1 replication [54, 56, 78], TDF has a more favorable cross-resistance profile primarily because the most common NRTI-resistance mutations M184V/I cause low-level reduction in ABC susceptibility but increased TDF susceptibility [79, 80]. Therefore, in patients with possible pre-therapy resistance, a switch from TDF to ABC carries an inherently higher risk of emerging drug resistance than a switch from ABC to TDF. Additionally, before discontinuing TDF it is also necessary to know whether a patient is HBsAg positive because such patients would require an additional anti-HBV agent such as entecavir to prevent HBV rebound, hepatitis flare, and the development of HBV resistance to 3TC and FTC [1].

When there are relative or absolute contraindications to both ABC and TDF, it is possible to switch virologically suppressed patients without PI resistance to DRV/r or LPV/r monotherapy or DRV/r, LPV/r or ATV/r in combination with 3TC (Table 4). The pro and cons of this strategy and the supporting clinical trials are described in a Sect. 4.4. NRTI discontinuation has also been proposed for ARV-experienced patients in whom levels of NRTI resistance are so high that their predicted benefit does not appear to outweigh their toxicity and cost. However, unless the aforementioned boosted PIs are fully active, one or more ARVs from an additional class will also be needed to bolster the regimen's genetic barrier to resistance.

## 4.2 Discontinuation of a Protease Inhibitor (PI)

Ritonavir-boosted PIs are among the most common ARVs requiring substitution because they are more likely than NNRTIs and INSTIs to be associated with gastrointestinal intolerance, elevated lipids, and drug–drug interactions [21]. Although each of the most commonly used PI/r's— DRV/r, ATV/r, and LPV/r—can have these side effects, they are usually more severe with LPV/r. This is due in part to LPV's uniform requirement for 200 mg rather than 100 mg of ritonavir for boosting.

It is not yet known whether adverse effects associated with DRV/cobicistat (DRV/c) and ATV/cobicistat (ATV/c) are less frequent than those associated with DRV/r and ATV/r, but initial data suggest that these new formulations have a similar side-effect profile [91]. Jaundice from unconjugated hyperbilirubinemia is the most common side effect of pharmacologically boosted ATV and it often requires a treatment change in patients who find the condition disturbing [38]. ATV/r is also associated with an increased risk of nephrolithiasis [92]. There are three main approaches to modifying therapy in virologically suppressed patients with PI-associated toxicity including changing therapy to a different boosted PI or unboosted ATV (at an increased dose of 400 mg daily), changing therapy to an INSTI, or changing therapy to an NNRTI.

### 4.2.1 Switching Among PIs

Table 3 summarizes six clinical trials that studied the effect of changing PI therapy in virologically suppressed patients. In three trials, previously treated patients receiving LPV/r or an older PI were randomized to either continued therapy or to a change from LPV/r to ATV/r or ATV while continuing the other ARVs in their regimen [60, 61, 64]. In one trial, previously treated patients on ATV/r were randomized to either continued ATV/r or a change to ATV [56]. In two trials, previously ART-naïve patients received an induction regimen of ATV/r plus two NRTIs and were then randomized to continued therapy or change to unboosted ATV [62, 63]. Previous VF on a PI-containing regimen was an exclusion criterion in all but one trial. Because TDF reduces ATV levels, studies of unboosted ATV did not include patients with stable virologic suppression on a TDF-containing regimen.

The SWAN trial compared a switch to ATV/r or ATV with continued therapy with one of the older, generally less well tolerated PIs. It demonstrated that a change to ATV/r or ATV was associated with a lower risk of VF than continued therapy (7 vs. 16 %; $p = 0.004$) [60]. One-third of the patients in the SWAN study were initially receiving LPV/r and two-thirds were receiving PIs that are now rarely used, including nelfinavir (NFV), indinavir (IND),

and saquinavir (SQV). Two of the five trials reported an improved lipid profile associated with a switch to ATV/r or ATV, and one reported a modest reduction in hyper-bilirubinemia in patients switching from ATV/r to ATV [63].

LPV/r and DRV/r have a strong track record for salvage therapy in patients with high-level NRTI resistance [93, 94]. Two lines of evidence suggest LPV/r and DRV/r have a higher genetic barrier to resistance than boosted ATV. First, these boosted PIs usually require three or more drug-resistance mutations (DRMs) in the protease before most of their inhibitor activity is lost [95, 96]. In contrast, a single protease DRM is often sufficient for the loss of ATV/r activity. Second, LPV/r and DRV/r have significantly higher clinical phenotypic cut-offs compared with ATV/r [97]. Despite the favorable outcome of a change to ATV/r or ATV in these trials, they do not provide evidence supporting the switch from LPV/r or DRV/r to ATV/r in stably suppressed patients with a history of previous VF [98, 99]. However, changes from ATV or ATV/r to either LPV/r or DRV/r would be expected to maintain virologic suppression, regardless of a patient's past treatment history.

### 4.2.2 Switching from PIs to Integrase Strand Transfer Inhibitors (INSTIs)

There are five randomized clinical trials in which stably suppressed patients have switched therapy from a PI/r to an INSTI (Table 3). The STRATEGY-PI, STRIIVING, and GS Study 109 trials enrolled patients without a history of VF or resistance to TDF or FTC [67, 75, 76]. The SWITCHMRK and SPIRAL studies included patients with a history of VF [65, 66].

In the STRATEGY-PI study, there were significantly more treatment failures in patients continuing an LPV/r, ATV/r, or DRV/r-containing regimen than those switching to TDF/FTC/elvitegravir/cobicistat (EVG/c) (13 vs. 6 %; $p = 0.025$), the difference driven by discontinuations for non-virologic reasons. Preliminary results from the GS Study 109, which randomized 1,436 suppressed participants on TDF/FTC plus either EVG/c (32 %), EFV (26 %), ATV/r, or ATV/c (42 %) to a FDC of TAF/FTC/EVG/c or continued therapy was superior at 48 weeks with 97 versus 93 % suppressed ($p < 0.001$) [76]. Small improvements were seen in short-term measures of bone density and renal function in participants in the switch arm.

The STRIIVING study also switched virologically suppressed patients without a history of VF who were HLA*B-5701 negative from a variety of first-line regimens to the FDC of ABC/3TC/DTG and compared them to those who continued their current treatment. This switch was non-inferior to continued therapy at 24 weeks with 85 versus 88 % maintaining virologic suppression [75].

**Table 4** Phase II/III trials of boosted protease inhibitor mono- and dual therapy

| PI | Study | Study design | Key inclusion criteria | Findings |
|---|---|---|---|---|
| LPV/r | OKO4 [81, 82] | • LPV/r + 2 NRTIs → LPV/r (n = 100) monotherapy vs. no change (n = 98)<br>• 96 W | • VL <50 × 24 W<br>• No prior VF on a PI-containing regimen | • LPV/r was non-inferior to LPV/r + 2 NRTIs according to the primary TF analysis which allowed for the readdition of NRTIs. The rates of maintaining HIV VL <50 in the more strict intention to treat analysis were also similar among the two arms (77 vs. 78 %)<br>• Discontinuation due to adverse events less common with LPV/r (0 vs. 8 %; p = 0.003) |
| | OLE [83] | • LPV/r + 2 NRTIs → LPV/r + 3TC (n = 123) vs. no change (n = 127)<br>• 48 W | • VL <50 × 24 W<br>• No resistance to LPV/r or 3TC | • TF[a] defined as confirmed VL >50, clinical progression, or discontinuation occurred in 3 % of each arm |
| DRV/r | MONOI-ANRS [84] | • DRV/r + 2NRTIs induction × 8 W followed by DRV/r (n = 112) vs. continued DRV/r + 2NRTIs (n = 113)<br>• 48 W | • VL <400 × 72 W and <50 × 12 W<br>• No history of VF on a PI-containing regimen | • Rates of TF for DRV/r were not non-inferior to DRV/r +2 NRTIs in either the per-protocol (6 vs. 1 %) or ITT analysis (12.5 vs. 8 %) |
| | MONEt [85, 86] | • Stable ART → DRV/r (n = 127) vs. DRV/r + 2 NRTIs (n = 129)<br>• 96 W | • VL <50 × 24 W<br>• No prior VF | • TF occurred in a similar proportion receiving DRV/r (25 %) vs. DRV/r +2 NRTIs (19 %) but the non-inferiority criterion was not met<br>• In analysis that permitted re-addition of NRTIs, TF was similar for DRV/r (7 %) vs. DRV/r + 2 NRTIs (8 %) |
| | PROTEA [87] | • Stable ART → DRV/r + 2NRTIs induction × 4 W → DRV/r (n = 137) vs. DRV/r + 2 NRTIs (n = 136)<br>• 48 W | • VL <50 × 24 W<br>• No prior VF<br>• No PI resistance | • An increased proportion of DRV/r monotherapy patients had TF (VL >50 or ARV switch) 14 vs. 5 %<br>• Difference driven by patients with nadir CD4 <200<br>• No emergent PI resistance |
| ATV/r | MODAt [88, 89] | • ATV/r + 2NRTIs → ATV/r (n = 51) vs. no change (n = 52)<br>• 48 W | • VL <50 × 24 W<br>• No prior VF | • ↑ VF (confirmed VL >50) with ATV/r (11 patients) vs. ATV/r + 2 NRTIs (2 patients)<br>• VF without ATV-resistance mutations. Re-addition of NRTIs was successful in all patients |
| | SALT [90] | • ART × 48 W → ATV/r + 3TC (n = 143) vs. ATV/r + 2 NRTI (n = 143)<br>• 48 W | • VL <50 × 24 W<br>• No prior VF<br>• No resistance to ATV/r or 3TC | • TF occurred in a similar proportion of patients in the ATV/r + 3TC (21/133; 17 %) vs. ATV/r + 2 NRTI (30/135; 22 %). Non-inferiority criterion met<br>• VF (2 consecutive VL >50) occurred in similar proportions in the dual vs triple therapy arms (6/143; 4 % and 4/143; 3 %) |

3TC lamivudine, ART antiretroviral therapy, ATV atazanavir, ATV/r ritonavir-boosted atazanavir, ITT intention to treat, LDL low-density lipoprotein cholesterol, LPV/r ritonavir-boosted lopinavir, n number in study subgroup, NRTI nucleos(t)ide reverse transcriptase inhibitor, PI protease inhibitor, TF treatment failure, TLOVR time to loss of virologic response, VF virologic failure, vs. versus, W week

[a] Treatment failure (TF) definitions differ slightly between studies. TF typically encompasses virologic breakthrough, confirmed virologic failure, and medication switches due to intolerance. In ITT analyses participants lost to follow-up are considered TFs. Individual study differences, including clinical progression of disease, are noted in the table

Analysis of adverse events noted that ten participants randomized to ABC/3TC/DTG (4 % of the total) but 0 participants who did not change therapy stopped ARVs due to various forms of intolerance.

In the SWITCHMRK trials (SWITCHMRK 1 and SWITCHMRK 2), 702 patients stably suppressed on LPV/r plus two NRTIs for 12 weeks were randomized to either continued therapy or a switch to RAL + 2 NRTIs [65]. Approximately 60 % of patients in the trials had received one or more previous ART regimens and approximately 30 % of patients had a history of VF on an earlier regimen. Despite having screening plasma HIV-1 RNA levels below 50 copies/ml, 5 % had detectable viremia (median RNA level: 101 copies/ml; IQR: 63–193) immediately prior to starting study drugs.

Within 12 weeks, patients who had switched to RAL experienced reductions in their non-HDL cholesterol and triglyceride levels of 15 and 42 %, respectively. However, the trial was terminated prematurely because, by 24 weeks, VF was significantly more likely in patients who had switched to RAL than in those who had continued their previous regimen (15.6 vs. 9.4 %). Among those patients with VF who underwent genotypic resistance testing, most had developed RAL resistance. Of the 32 RAL recipients with VF, 27 (84 %) reported that the LPV/r regimen at study entry was not their first ART regimen, and 18 of these 27 had a history of previous VF. Of the 17 RAL recipients with a baseline RNA level above the 50 copies/ml threshold of detection, seven developed VF.

The SPIRAL trial enrolled 273 patients most of whom were stably suppressed for 24 weeks on LPV/r (44 %), ATV/r (35 %), or FPV/r (12 %), then randomized them to either continue therapy or to switch to RAL [66]. Nearly 90 % of these patients had received one or more previous ART regimens and nearly 40 % had a history of VF. At 48 weeks, treatment failure had occurred in 11 % of patients receiving RAL and in 13 % of those remaining on PI/r's. Possible reasons for the discordant results between SWITCHMRK and SPIRAL may be the longer period of virologic suppression prior to randomization in SPIRAL or genotypic resistance to the NRTI backbone, which was detected in half of SWITCHMRK participants who failed RAL but not in SPIRAL.

The significant increase in VF in patients switching to RAL in the SWITCHMRK studies underscores the importance of an uncompromised NRTI backbone in patients receiving RAL. Although RAL and EVG/c may be as potent antiviral inhibitors as the currently used PI/r's, they have lower genetic barriers to resistance. Just one or two drug resistance mutations may be sufficient to cause high-level RAL and EVG resistance [100], whereas four or more drug resistance mutations are usually required for high-level LPV/r or DRV/r resistance [95, 96]. Three or more drug-resistance mutations in the integrase gene region are usually required for DTG resistance [101–103], and DTG has been shown to be more effective than RAL at treating ARV-experienced patients with VF [104]. An ongoing study of ABC/3TC/DTG for second-line therapy in patients with NRTI-resistant viruses will provide insight into the ability of DTG-containing regimens to maintain virologic suppression in PI/r-treated patients with underlying NRTI resistance [105].

### 4.2.3 Switching from PIs to Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

There have been two studies in which stably suppressed patients without a history of VF switched therapy from a PI/r to an NNRTI. The first of these studies, AI266073, enrolled patients receiving a wide range of PI- and NNRTI-containing regimens and randomized them to either continued therapy or a switch to TDF/FTC/EFV [69]. Over a period of 48 weeks, 89 % of patients receiving TDF/FTC/EFV and 88 % whose therapy was unchanged maintained virologic suppression.

The second study, SPIRIT, enrolled patients receiving mainly ATV/r, LPV/r, and DRV/r who had no history of VF or prior ART and no evidence for NRTI or RPV resistance. These patients were randomized to switch to TDF/FTC/RPV or to continue their current therapy [49]. After 24 weeks, there was no difference in VF between the two groups (6 % of those who had switched to TDF/FTC/RPV and 10 % of those who did not change therapy experienced VF; $p = 0.15$). Of note, none of the 18 patients with a pre-ART genotype containing K103N, the commonly transmitted nevirapine (NVP) and EFV-resistance mutation, developed VF on TDF/FTC/RPV. Plasma HIV-1 RNA levels prior to the start of their initial PI/r containing regimen did not predict VF, suggesting that once virus loads are stably suppressed the risk of VF may not be greater in patients with pre-therapy RNA levels that exceed 5.0 log10 copies/ml.

One of the earliest ART modification studies substituted EFV, NVP, or ABC for a PI in patients with plasma HIV-1 RNA levels below 200 copies/ml for 24 weeks. Approximately 90 % of these patients were receiving IDV or NFV, and approximately 50 % had a history of mono or dual NRTI therapy prior to attaining virologic suppression [68]. At 12 months, the Kaplan–Meier estimates of VF or disease progression were 6 % in the EFV group, 10 % in the NFV group, and 13 % in the ABC group. A history of suboptimal therapy prior to attaining virologic suppression was a strong risk factor for VF with 23 of 29 patients with VF having a history of mono- or dual NRTI therapy.

## 4.3 Discontinuation of an NNRTI

NVP is no longer recommended as a preferred medication by the WHO, DHHS, or EACS for any specific indication and is now used infrequently in middle- and upper-income countries [1, 2, 45]. NVP is associated with severe hypersensitivity including rash and hepatitis in about 2 % of patients and less severe abnormalities in up to 10 % [19, 41, 46]. EFV is a key component of most WHO-recommended ART regimens. It was recently removed from the list of DHHS-Recommended ART regimens, but the FDC of TDF/FTC/EFV remains in wide use as a DHHS-Alternative regimen. Central nervous system symptoms are the main side effects of EFV [33–35]. The dose-dependency of these symptoms and the frequency with which they persist to cause non-adherence or serious morbidity is now being studied as newer FDCs have become available for comparison [34–36].

The newer NNRTIs etravirine (ETR) and RPV have fewer safety and tolerability concerns than NVP and EFV. Although ETR and RPV have similar cross-resistance profiles, ETR is considerably more potent and has a higher genetic barrier to resistance because the recommended 400-mg daily dosage of ETR is 16-fold higher than the recommended 25-mg daily dosage of RPV. The lower daily dosage of RPV is due to the fact that healthy, non-infected human volunteers experienced QT prolongations at doses of 75 mg or higher [106]. However, the high potency and lack of co-formulation of ETR mean it is primarily used as a salvage therapy option.

### 4.3.1 Switching Among NNRTIs

There have been two randomized, blinded studies in which a small number of patients receiving an EFV-containing regimen were randomized to either switch to ETR 400 mg once daily or to continue EFV, and one non-randomized study in which a small number of patients receiving TDF/FTC/EFV were switched to TDF/FTC/RPV (Table 3). These studies suggest that despite the inductive effects of EFV on CYP450 3A4, such a switch can occur without jeopardizing virologic suppression because EFV levels remain therapeutic while RPV (and presumably also ETR) levels increase [72, 107]. These studies also suggest that those patients with persistent central nervous system symptoms on EFV will experience a reduction of these symptoms with ETR (and presumably also RPV) [70]. Because TDF/FTC/RPV has been associated with a greater risk of emergent drug resistance compared with TDF/FTC/EFV [108–110], switching from TDF/FTC/EFV to TDF/FTC/RPV should only be done in patients without a history of VF or evidence of resistance to TDF, FTC, or RPV.

### 4.3.2 Switching from NNRTIs to an INSTI

A randomized, double-blind, crossover study of a small number of patients switching from EFV to RAL demonstrated a significant reduction in anxiety while patients were on RAL [73]. The much larger STRATEGY-NNRTI demonstrated the non-inferiority of a switch from an NNRTI plus two NRTIs to the FDC of TDF/FTC/EVG/c and also noted a reduction in sleep disturbances in patients switching to EVG/c [74, 111]. The aforementioned GS Study 109 and STRIVIING studies both enrolled substantial proportions of participants on NNRTI-based therapy (31 and 26 %) and switched them to INSTI-based therapy, supporting the efficacy of this modification strategy [75, 76].

### 4.3.3 Switching from NNRTIs to PIs

Pharmacologically-boosted PIs have higher genetic barriers to resistance than NNRTIs and switches from NNRTIs to boosted PIs are commonly made in patients failing NNRTI-based therapy. Changing the NNRTI component of a virologically suppressive regimen to pharmacologically boosted DRV or ATV—the most well tolerated of the DHHS Acceptable first-line PIs—is likely to be highly effective in most virologically suppressed patients. This type of switch, however, has not been studied in virologically suppressed patients because boosted PIs have been highly effective substitutes for an NNRTI even in patients with VF [37, 93, 112].

## 4.4 Boosted PI Mono or Dual Therapy

A large number of randomized clinical trials suggest that LPV/r and DRV/r monotherapy are effective options for stably suppressed patients without a history of PI resistance (Table 4) (reviewed in Arribas et al. [113, 114]). Although LPV/r and DRV/r monotherapy are associated with an increased risk of virologic rebound compared with triple ART, this viral rebound is rarely associated with emergent drug resistance. The re-administration of NRTIs in these patients nearly always leads to re-suppression of virus levels to below 50 copies/ml [81, 82, 84–87, 115]. The risk of VF in patients receiving PI/r monotherapy is strongly associated with a patient's nadir CD4 count and may be confined to patients with nadir CD4 counts below 200 cells/mm$^3$ [87, 116].

Several small studies suggest that ATV/r monotherapy is associated with a higher risk of VF than LPV/r and DRV/r monotherapy [88, 89, 117–119]. One large observational study suggests that DRV/r is also more effective than LPV/r [120]. Although patients receiving PI/r monotherapy have an elevated risk of detectable CSF virus

when compared with those receiving triple therapy, they do not appear to have an increased risk of central nervous system symptoms [116, 121–124].

Several recent and ongoing trials have shown that LPV/r, ATV/r, and DRV/r in combination with 3TC are not associated with an increased risk of virologic rebound compared with PI/r's plus two NRTIs provided there is no baseline 3TC resistance [83, 90, 125]. Supporting this concept the GARDEL trial showed that a regimen of LPV/r plus 3TC is as effective as LPV/r plus two 2 NRTIs as initial therapy in ARV-naïve patients [126].

### 4.5 Boosted PIs Plus INSTIs

There have been several clinical trials in which LPV/r, DRV/r, and ATV/r have been used in combination with RAL for first- and second-line therapy or for maintenance therapy in virologically suppressed patients [22, 92–94, 127–129]. These trials have shown the following: (1) DRV/r plus RAL was comparable to DRV/r plus TDF/FTC for first-line therapy except in patients with high VL or low CD4 counts where DRV/r plus RAL was less effective in subgroup analyses [127]; (2) LPV/r plus RAL was virologically comparable to but no better than LPV/r plus two NRTIs in patients with previous VF on a first-line NRTI plus NNRTI-containing regimen [93, 94]; (3) LPV/r plus RAL and DRV/r plus RAL were comparable to LPV/r and DRV/r plus two NRTIs in virologically suppressed patients [22, 92]; and (4) ATV/r plus RAL was associated with a higher risk of virologic rebound (7/72; 10 %) compared with ATV/r plus TDF/FTC (1/37; 3 %) in patients with stable virologic suppression [128].

Regardless of the clinical scenario and boosted PI, many patients with VF developed RAL-resistance mutations that would limit future treatment options. Even under the most favorable circumstances—the use of DRV/r plus RAL for first-line therapy in closely monitored patients [127]—a drug-resistance sub-study showed that 4 % of 805 patients developed RAL resistance by week 80 [130]. A likely explanation for this finding is that the prevention of RAL resistance may require a consistently high level of boosted PI adherence that is often not achieved outside of a clinical trial. Therefore switching stably suppressed patients to a boosted PI plus INSTI-containing regimen should be restricted to the use of boosted DRV—because of its combination of tolerability and high genetic barrier to resistance—plus RAL or DTG and should be done primarily for the management of NRTI toxicity in highly adherent patients without a history of PI resistance.

### 4.6 Discontinuation of Enfuvirtide (ENF)

The demonstration that virologically suppressed patients receiving ENF could switch to RAL without risking virologic rebound [131–134] paved the way for many of the ART modification studies that followed. As several additional, highly potent and novel ARVs were approved (including DRV, ETR, and RAL), the number of patients receiving ENF has decreased dramatically. The few patients currently receiving ENF are likely to have failed many ARV regimens and to have extensive resistance to the more commonly used drug classes. ENF discontinuation in these patients requires expert consultation to choose an individually tailored replacement ART regimen with sufficient antiviral potency and a genetic barrier high enough to replace ENF.

### 4.7 Miscellaneous Other Regimens

#### 4.7.1 Maraviroc-Containing Regimens

In patients for whom MVC is being considered it is necessary to exclude the presence of CXCR4 tropic variants, which would render MVC inactive. In virologically suppressed patients, however, it is not possible to test plasma virus for CXCR4 tropism. Therefore several commercial laboratories have developed proviral DNA tropism assays. The "Appendix" summarizes the rationale for proviral drug resistance and tropism assays in virologically suppressed patients [50, 51, 135–140].

One small trial assessed the possible role of maraviroc (MVC) in virologically suppressed patients on a three-drug PI/r- or NNRTI-containing regimens by randomizing 30 such patients to either switch to MVC plus two NRTIs or to continue their therapy [141]. Additional inclusion criteria included a negative proviral DNA genotypic test for CXCR4-tropic viruses and no history of NRTI resistance. Although only one of the 15 patients randomized to MVC developed VF—a patient subsequently found to have CXCR4-tropic virus missed by the screening tropism assay—this strategy cannot be recommended until further studies are performed [1].

#### 4.7.2 Triple NRTIs

There have been two meta-analyses of randomized controlled trials published between 2001 and 2013 in which stably suppressed patients on two NRTIs plus an NNRTI or a PI were placed on a three-drug ABC-containing regimen—usually AZT/3TC/ABC—to simplify therapy and reduce lipid levels [142, 143]. These meta-analyses concluded that AZT/3TC/ABC appeared to be as effective as

continued two-class therapy but cautioned that the ARVs used in those studies were often inferior to those currently used. However, as a result of the established inferiority of AZT/3TC/ABC for first-line therapy [144], this regimen is generally not considered a suitable option for maintenance therapy in virologically suppressed patients.

### 4.7.3 Non-NRTI-, Non-PI-Containing Regimens

There have been several pilot studies of combinations of ARVs including RAL plus MVC [145], RAL plus ETR [146], and the long-acting investigational INSTI cabotegravir in combination with RPV [147]. The RAL plus MVC trial was discontinued prematurely because it was associated with a high rate of virologic failure. VF occurred in only one of 25 patients receiving RAL plus ETR at 48 weeks, two others discontinued because of intolerance.

### 4.7.4 Long-Acting Parenteral Therapy

Long-acting injectable ARVs may soon provide novel treatment strategies in HIV-infected patients who cannot take oral pills for medical reasons (surgery or transplant), for whom adherence to daily oral medications is poor or for prevention of HIV in uninfected patients. For example, the phase IIb LATTE study used an oral induction phase with cabotegravir (an INSTI) plus two NRTIs; participants who were suppressed after 24 weeks were switched to a maintenance regimen of dual therapy cabotegravir plus RPV. At week 96, virologic suppression for the experimental regimen was similar to EFV plus two NRTIs [147]. Both cabotegravir and RPV have the potential to be administered as long-acting injectable formulations. A study evaluating a similar switch strategy from standard ART to dual therapy oral DTG plus RPV is also underway [148].

## 5 Conclusions and Future Directions

In patients who have never experienced VF while receiving ART and have no evidence of drug resistance, switching to any of the acceptable DHHS first-line regimens is expected to maintain virologic suppression. An increasing number of clinical trials of once daily FDC combinations offer convenience for patients and have now been shown to be both highly effective for maintaining virologic suppression in this population. Even in these patients with little risk of virologic failure, changes can expose them to medication intolerance or adverse effects, so the indications for switching therapy should be carefully considered.

In virologically suppressed patients with a history of VF or drug resistance, it is more challenging to change therapy while still maintaining virologic suppression. In these patients, it is necessary to consider all past ARV regimens, episodes of VF, and past genotypic resistance tests. Additionally, it is usually necessary to select a regimen with a high genetic barrier to resistance and occasionally necessary to select a regimen containing ARVs from more than two drug classes.

A growing number of studies have included switches to INSTI-based regimens. The pivotal SWITCHMRK trial showed that the substitution of RAL for LPV/r carries a risk of VF and emergent INSTI resistance in patients harboring NRTI-resistant viruses. As a result of this finding, clinical trials of switches to newer INSTIs (EVG/c and DTG) have been performed almost exclusively in patients without a history of past VF or evidence of drug resistance mutations. In contrast, DTG – which has a higher genetic barrier to resistance than RAL or EVG/c and is currently being studied as an option for second-line therapy in patients who have failed a first-line NNRTI-based regimen [105] – may eventually prove to be a switch option in stably suppressed patients with prior VF. Results of a study that switched patients with prior VF who are now suppressed on a complex regimen to the FDC TAF/FTC/EVG/c plus DRV are expected in the near future [149].

Increasing data show that LPV/r or DRV/r, either alone or in combination with 3TC, are effective maintenance regimens in patients without previous PI or 3TC resistance. These regimens are likely to be useful in patients with NRTI toxicity. However, in patients without such toxicity they may be complicated to administer because they require closer follow-up for VF. LPV/r or boosted DRV plus an INSTI have also been effective maintenance regimens, and are useful options for patients with NRTI toxicity. Patients receiving such regimens must be particularly adherent to the boosted PI component of the regimen because non-adherence poses a high risk of emergent INSTI resistance and loss of future options.

Genotypic resistance and co-receptor tropism testing from peripheral blood mononuclear cells are commercially available but not frequently used. They assess the proviral DNA that is integrated into resting memory CD4+ T cells forming an "archive" of resistance mutants that can be sequenced when no virus is detected in the blood. These tests are likely to be reliable when they detect resistance mutations or CXCR4 tropism but the validity of negative assays requires further study.

## 6 Case Vignettes

### 6.1 Case 1

A 46-year-old woman with a 15-year history of ART initially with SQV/r/D4T/3TC then with EFV/TDF/FTC

presented with progressive renal dysfunction and a partial Fanconi syndrome. She had no known history of VF or drug resistance. Her CD4 count was 1,056 cells/mm$^3$ and her viral load was consistently below 50 copies/ml. She also has a history of migraine headaches often requiring intravenous dihydroergotamine infusions.

Her progressive renal dysfunction and tubular dysfunction made it urgent to discontinue TDF. An HLA*B5701 test, which was performed to ensure that ABC was a viable option, was negative. Given her preference for a once-daily single-table regimen, she was changed to ABC/3TC/DTG. Her renal function has since improved and she has remained virologically suppressed. Simply substituting ABC for TDF was considered to be an inferior option because of the possibility that during her long past period of treatment she may have developed some degree of latent NRTI or NNRTI resistance that might reactivate due to the lower activity of ABC compared with TDF in the face of resistance. A boosted PI regimen was not used because of the established drug–drug interaction between boosted PIs and dihydroergotamine.

## 6.2 Case 2

A 42-year-old man with a history of hypertension had been treated initially with TDF/3TC/EFV and then TDF/FTC/EFV for a total of 9 years. He had no known history of VF and had a nadir CD4 count of 262 cells/mm$^3$. During the past year, he has developed progressively increasing anxiety and depression requiring visits to a psychiatrist who is inquiring about the possibility of discontinuing EFV before starting an antidepressant.

Although it is unusual for EFV-associated neuropsychiatric symptoms to develop so late into therapy, it is possible that EFV could be exacerbating these symptoms even if it is not their primary cause. Considering the absence of any history of VF or drug resistance, the patient has many treatment options including each of the three DHHS-recommended single tablet regimens: TDF/FTC/RPV, TDF/FTC/EVG/c, and ABC/3TC/DTG. The newly available TAF/FTC/EVG/c FDC is also supported by evidence but not yet incorporated into treatment recommendations. In this patient, we chose to use TDF/FTC/RPV. The patient's depression and anxiety improved dramatically within several weeks and his virus load remained undetectable.

## 6.3 Case 3

A 72-year-old man with a more than 20-year history of ART has been stably suppressed on TDF/FTC/ATV/r for 8 years. He began therapy in the early 1990s with a series of mono- and dual-NRTI regimens. He has a history of

EFV and LPV/r intolerance. His nadir CD4 count was 70 cells/mm$^3$ and his last genotypic resistance test prior to starting TDF/FTC/ATV/r contained multiple thymidine analog resistance mutations, M184V, and several NNRTI-resistance mutations. A recently ordered HLA-B*5701 test was negative. Although he has no history of coronary artery disease, he has inquired about the possibility of switching ATV/r to an INSTI to reduce that risk. Interestingly, a genotypic resistance test of proviral DNA detected the presence of three TAMs, M184V, and two NNRTI-resistance mutations that closely matched the pattern of resistance observed on his last test prior to starting his current regimen.

At the time the patient first made this inquiry DTG had not yet been approved and it was decided that a switch to RAL or to TDF/FTC/EVG/c would entail an increased risk of VF because of the partially compromised NRTI backbone. Since then DTG has been approved and, due to its higher genetic barrier to resistance, is likely to be associated with a lower risk of VF and emergent INSTI resistance than RAL or EVG/c. However, considering the relatively weak association of ATV/r with an atherogenic lipid profile and the fact that clinical trials of DTG in this scenario have not yet been completed, it was decided to continue the patient's current therapy.

## Appendix: Proviral DNA Testing for HIV-1 Drug Resistance and Co-Receptor Tropism in Patients with Virological Suppression

During its replication cycle, proviral HIV-1 DNA integrates into host chromosomal DNA and is then usually expressed leading to productive infection and cell killing. In resting memory CD4+ T cells, however, integrated proviral DNA may persist for many years forming a stable reservoir of latently infected cells [135]. As a result, proviral DNA levels in peripheral blood mononuclear cells (PBMCs) remain detectable even in patients receiving ART who have undetectable plasma HIV-1 RNA levels [136, 7].

There is a strong but imperfect correlation between the drug-resistance mutations (DRMs) in PBMC proviral DNA and plasma HIV-1 RNA from the same blood samples [50, 137]. Indeed, in patients with suppressed plasma HIV-1 RNA levels, the DRMs present in PBMCs are consistent with a patient's past ART history and previous genotypic tests [51, 138, 139]. However, PBMC sequencing does not necessarily detect all of the DRMs that were previously present in samples from patients who had past genotypic resistance tests [51, 139, 150]. Therefore, PBMC genotypic resistance should be used in conjunction with past genotypic test results and should be interpreted in light of drug resistance likely to have emerged during past episodes of virological failure.

Most studies suggest that little HIV-1 evolution occurs during ART-mediated virological suppression—particularly with most current regimens [15]. Therefore, if co-receptor tropism was determined shortly before virological suppression, it is unlikely to have changed during therapy [140]. However, if tropism was not determined previously and if a switch to maraviroc is being considered, genotypic or phenotypic PBMC tropism tests are considered reasonable but have not been validated for predicting maraviroc activity [1].

# References

1. US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2015. http://aidsinfo.nih.gov/guidelines. Accessed 12 Nov 2015.
2. EACS. European AIDS Clinical Society Guidelines Version 8.0—October 2015. European AIDS Clinical Society (EACS). 2015. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed 30 Oct 2015.
3. Davidson I, Beardsell H, Smith B, Mandalia S, Bower M, Gazzard B, et al. The frequency and reasons for antiretroviral switching with specific antiretroviral associations: the SWITCH study. Antivir Res. 2010;86(2):227–9. doi:10.1016/j.antiviral.2010.03.001.
4. Vo TT, Ledergerber B, Keiser O, Hirschel B, Furrer H, Battegay M, et al. Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. J Infect Dis. 2008;197(12):1685–94. doi:10.1086/588141.
5. Tsuchiya N, Pathipvanich P, Wichukchinda N, Rojanawiwat A, Auwanit W, Ariyoshi K, et al. Incidence and predictors of regimen-modification from first-line antiretroviral therapy in Thailand: a cohort study. BMC Infect Dis. 2014;14:565. doi:10.1186/s12879-014-0565-5.
6. Keiser O, Fellay J, Opravil M, Hirsch HH, Hirschel B, Bernasconi E, et al. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: effect on mortality and treatment modification. Antivir Ther. 2007;12(8):1157–64.
7. Cesar C, Shepherd BE, Krolewiecki AJ, Fink VI, Schechter M, Tuboi SH, et al. Rates and reasons for early change of first HAART in HIV-1-infected patients in 7 sites throughout the Caribbean and Latin America. PLoS One. 2010;5(6):e10490. doi:10.1371/journal.pone.0010490.
8. Boyle A, Sonecha S, Mandalia S, Nelson M. An investigation into frequency and reasons why patients switch antiretroviral therapy and which antiretrovirals are commonly implicated in toxicity. J Int AIDS Soc. 2012;15(Suppl 4):18121. doi:10.7448/IAS.15.6.18121
9. Hull M, Cescon A, Raboud J, Klein MB, Walmsley S, Ding E et al., editors. Switching from first antiretroviral therapy regimen while virologically suppressed is associated with increased risk of subsequent virologic failure. 20th International AIDS Conference; 2014 July 20–25; Melbourne, Australia.
10. Dieleman JP, Jambroes M, Gyssens IC, Sturkenboom MC, Stricker BH, Mulder WM, et al. Determinants of recurrent toxicity-driven switches of highly active antiretroviral therapy. The ATHENA cohort. AIDS. 2002;16(5):737–45.
11. Van den Eynde E, Podzamczer D. Switch strategies in antiretroviral therapy regimens. Expert Rev Anti Infect Ther. 2014;12(9):1055–74. doi:10.1586/14787210.2014.944506.
12. Havlir DV, Marschner IC, Hirsch MS, Collier AC, Tebas P, Bassett RL, et al. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. N Engl J Med. 1998;339(18):1261–8. doi:10.1056/NEJM199810293391801.
13. Pialoux G, Raffi F, Brun-Vezinet F, Meiffredy V, Flandre P, Gastaut JA, et al. A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team. N Engl J Med. 1998;339(18):1269–76. doi:10.1056/NEJM199810293391802.
14. Reijers MH, Weverling GJ, Jurriaans S, Wit FW, Weigel HM, Ten Kate RW, et al. Maintenance therapy after quadruple induction therapy in HIV-1 infected individuals: Amsterdam Duration of Antiretroviral Medication (ADAM) study. Lancet. 1998;352(9123):185–90. doi:10.1016/S0140-6736(98)06193-5 (pii:S0140673698061935).
15. Siliciano JD, Siliciano RF. Recent trends in HIV-1 drug resistance. Curr Opin Virol. 2013;3(5):487–94. doi:10.1016/j.coviro.2013.08.007.
16. Dinoso JB, Kim SY, Wiegand AM, Palmer SE, Gange SJ, Cranmer L, et al. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. Proc Natl Acad Sci USA. 2009;106(23):9403–8. doi:10.1073/pnas.0903107106.
17. Gandhi RT, Zheng L, Bosch RJ, Chan ES, Margolis DM, Read S, et al. The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. PLoS Med. 2010;7(8). doi:10.1371/journal.pmed.1000321.
18. McMahon D, Jones J, Wiegand A, Gange SJ, Kearney M, Palmer S, et al. Short-course raltegravir intensification does not reduce persistent low-level viremia in patients with HIV-1 suppression during receipt of combination antiretroviral therapy. Clin Infect Dis. 2010;50(6):912–9. doi:10.1086/650749.
19. Calmy A, Hirschel B, Cooper DA, Carr A. A new era of antiretroviral drug toxicity. Antivir Ther. 2009;14(2):165–79.
20. de Waal R, Cohen K, Maartens G. Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction. PLoS One. 2013;8(5):e63623. doi:10.1371/journal.pone.0063623.
21. da Cunha J, Maselli LM, Stern AC, Spada C, Bydlowski SP. Impact of antiretroviral therapy on lipid metabolism of human

immunodeficiency virus-infected patients: old and new drugs. World J Virol. 2015;4(2):56–77. doi:10.5501/wjv.v4.i2.56.

22. Ofotokun I, Sheth AN, Sanford SE, Easley KA, Shenvi N, White K, et al. A switch in therapy to a reverse transcriptase inhibitor sparing combination of lopinavir/ritonavir and raltegravir in virologically suppressed HIV-infected patients: a pilot randomized trial to assess efficacy and safety profile: the KITE study. AIDS Res Hum Retroviruses. 2012;28(10):1196–206. doi:10.1089/AID.2011.0336.

23. Martinez E, Gonzalez-Cordon A, Ferrer E, Domingo P, Negredo E, Gutierrez F, et al. Early lipid changes with atazanavir/ritonavir or darunavir/ritonavir. HIV Med. 2014;15(6):330–8. doi:10.1111/hiv.12121.

24. Young J, Xiao Y, Moodie EE, Abrahamowicz M, Klein MB, Bernasconi E, et al. The effect of cumulating exposure to abacavir on the risk of cardiovascular disease events in patients from the Swiss HIV Cohort Study. J Acquir Immune Defic Syndr. 2015. doi:10.1097/QAI.0000000000000662.

25. Costagliola D, Lang S, Mary-Krause M, Boccara F. Abacavir and cardiovascular risk: reviewing the evidence. Curr HIV/AIDS Rep. 2010;7(3):127–33. doi:10.1007/s11904-010-0047-3.

26. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 2010;51(5):496–505. doi:10.1086/655681.

27. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A: D study. J Infect Dis. 2013;207(9):1359–69. doi:10.1093/infdis/jit043.

28. Young J, Wang Q, Fux CA, Bernasconi E, Furrer H, Vernazza P, et al. The rate of recovery in renal function when patients with HIV infection discontinue treatment with tenofovir. HIV Med. 2014;15(8):505–10. doi:10.1111/hiv.12149.

29. Mills A, Crofoot G Jr, McDonald C, Shalit P, Flamm JA, Gathe J Jr, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 Therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr. 2015;69(4):439–45. doi:10.1097/QAI.0000000000000618.

30. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606–15. doi:10.1016/S0140-6736(15)60616-X.

31. Walker Harris V, Brown TT. Bone loss in the HIV-infected patient: evidence, clinical implications, and treatment strategies. J Infect Dis. 2012;205(Suppl 3):S391–8. doi:10.1093/infdis/jis199.

32. Croxtall JD, Perry CM. Lopinavir/ritonavir: a review of its use in the management of HIV-1 infection. Drugs. 2010;70(14):1885–915. doi:10.2165/11204950-000000000-00000.

33. Maggiolo F. Efavirenz: a decade of clinical experience in the treatment of HIV. J Antimicrob Chemother. 2009;64(5):910–28. doi:10.1093/jac/dkp334.

34. Ford N, Shubber Z, Pozniak A, Vitoria M, Doherty M, Kirby C, et al. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: a systematic review and meta-analysis of randomized trials. J Acquir Immune Defic Syndr. 2015. doi:10.1097/QAI.0000000000000606.

35. Mollan KR, Smurzynski M, Eron JJ, Daar ES, Campbell TB, Sax PE, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014;161(1):1–10. doi:10.7326/M14-0293.

36. Encore Study Group, Puls R, Amin J, Losso M, Phanuphak P, Nwizu C, et al. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2014;383(9927):1474–82. doi:10.1016/S0140-6736(13)62187-X.

37. Croom KF, Dhillon S, Keam SJ. Atazanavir: a review of its use in the management of HIV-1 infection. Drugs. 2009;69(8):1107–40. doi:10.2165/00003495-200969080-00009.

38. Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotokun I, Na LH, Godfrey C, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. Ann Intern Med. 2014;161(7):461–71. doi:10.7326/M14-1084.

39. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358(6):568–79. doi:10.1056/NEJMoa0706135.

40. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis. 2008;46(7):1111–8. doi:10.1086/529382.

41. Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Thery F, Shaffer N, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. AIDS. 2013;27(9):1403–12. doi:10.1097/QAD.0b013e32835f1db0.

42. Schafer JJ, Short WR. Rilpivirine, a novel non-nucleoside reverse transcriptase inhibitor for the management of HIV-1 infection: a systematic review. Antivir Ther. 2012;17(8):1495–502. doi:10.3851/IMP2254.

43. Ford N, Mofenson L, Kranzer K, Medu L, Frigati L, Mills EJ, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS. 2010;24(10):1461–70. doi:10.1097/QAD.0b013e32833a2a14.

44. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2015. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed 14 Oct 2015.

45. World Health Organization HIV/AIDS Programme. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: WHO; 2013.

46. Ford N, Calmy A, Andrieux-Meyer I, Hargreaves S, Mills EJ, Shubber Z. Adverse events associated with nevirapine use in pregnancy: a systematic review and meta-analysis. AIDS. 2013;27(7):1135–43. doi:10.1097/QAD.0b013e32835e0752.

47. El-Sherif O, Back D. Drug interactions of hepatitis C direct-acting antivirals in the HIV-infected person. Curr HIV/AIDS Rep. 2015. doi:10.1007/s11904-015-0277-5.

48. Floridia M, Ravizza M, Pinnetti C, Tibaldi C, Bucceri A, Anzidei G, et al. Treatment change in pregnancy is a significant risk factor for detectable HIV-1 RNA in plasma at end of pregnancy. HIV Clin Trials. 2010;11(6):303–11. doi:10.1310/hct1106-303.

49. Palella FJ Jr, Fisher M, Tebas P, Gazzard B, Ruane P, Van Lunzen J, 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):335–44. doi:10.1097/QAD.0000000000000087.

50. Devereux HL, Loveday C, Youle M, Sabin CA, Burke A, Johnson M. Substantial correlation between HIV type 1 drug-associated resistance mutations in plasma and peripheral blood mononuclear cells in treatment-experienced patients. AIDS Res Hum Retrovir. 2000;16(11):1025–30. doi:10.1089/08892220050075273.

51. Delaugerre C, Braun J, Charreau I, Delarue S, Nere ML, de Castro N, et al. Comparison of resistance mutation patterns in historical plasma HIV RNA genotypes with those in current proviral HIV DNA genotypes among extensively treated patients with suppressed replication. HIV Med. 2012;13(9):517–25. doi:10.1111/j.1468-1293.2012.01002.x.

52. Martinez E, Arranz JA, Podzamczer D, Lonca M, Sanz J, Barragan P, et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. J Acquir Immune Defic Syndr. 2009;51(3):290–7. doi:10.1097/QAI.0b013e3181aa12d5.

53. Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. Clin Infect Dis. 2009;49(10):1591–601. doi:10.1086/644769.

54. Campo R, DeJesus E, Bredeek UF, Henry K, Khanlou H, Logue K, et al. SWIFT: prospective 48-week study to evaluate efficacy and safety of switching to emtricitabine/tenofovir from lamivudine/abacavir in virologically suppressed HIV-1 infected patients on a boosted protease inhibitor containing antiretroviral regimen. Clin Infect Dis. 2013;56(11):1637–45. doi:10.1093/cid/cis1203.

55. Behrens G, Maserati R, Rieger A, Domingo P, Abel F, Wang H, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol: effect on lipid profiles. Antivir Ther. 2012;17(6):1011–20. doi:10.3851/IMP2305.

56. Wohl DA, Bhatti L, Small CB, Edelstein H, Zhao HH, Margolis DA, et al. Simplification to abacavir/lamivudine + atazanavir maintains viral suppression and improves bone and renal biomarkers in ASSURE, a randomized, open label, non-inferiority trial. PLoS One. 2014;9(5):e96187. doi:10.1371/journal.pone.0096187.

57. Moyle GJ, Orkin C, Fisher M, Dhar J, Anderson J, Wilkins E, et al. A randomized comparative trial of continued abacavir/lamivudine plus efavirenz or replacement with efavirenz/emtricitabine/tenofovir DF in hypercholesterolemic HIV-1 infected individuals. PLoS One. 2015;10(2):e0116297. doi:10.1371/journal.pone.0116297.

58. Rasmussen TA, Jensen D, Tolstrup M, Nielsen US, Erlandsen EJ, Birn H, et al. Comparison of bone and renal effects in HIV-infected adults switching to abacavir or tenofovir based therapy in a randomized trial. PLoS One. 2012;7(3):e32445. doi:10.1371/journal.pone.0032445.

59. Rasmussen TA, Tolstrup M, Melchjorsen J, Frederiksen CA, Nielsen US, Langdahl BL, et al. Evaluation of cardiovascular biomarkers in HIV-infected patients switching to abacavir or tenofovir based therapy. BMC Infect Dis. 2011;11:267. doi:10.1186/1471-2334-11-267.

60. Gatell J, Salmon-Ceron D, Lazzarin A, Van Wijngaerden E, Antunes F, Leen C, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. Clin Infect Dis. 2007;44(11):1484–92. doi:10.1086/517497.

61. Mallolas J, Podzamczer D, Milinkovic A, Domingo P, Clotet B, Ribera E, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. J Acquir Immune Defic Syndr. 2009;51(1):29–36. doi:10.1097/QAI.0b013e31819a226f.

62. Squires KE, Young B, Dejesus E, Bellos N, Murphy D, Zhao HH, et al. Similar efficacy and tolerability of atazanavir compared with atazanavir/ritonavir, each with abacavir/lamivudine after initial suppression with abacavir/lamivudine plus ritonavir-boosted atazanavir in HIV-infected patients. AIDS. 2010;24(13):2019–27. doi:10.1097/QAD.0b013e32833bee1b.

63. Ghosn J, Carosi G, Moreno S, Pokrovsky V, Lazzarin A, Pialoux G, 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. doi:10.3851/IMP1666.

64. Soriano V, Garcia-Gasco P, Vispo E, Ruiz-Sancho A, Blanco F, Martin-Carbonero L, et al. Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. J Antimicrob Chemother. 2008;61(1):200–5. doi:10.1093/jac/dkm413.

65. Eron JJ, Young B, Cooper DA, Youle M, Dejesus E, Andrade-Villanueva J, 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. doi:10.1016/S0140-6736(09)62041-9.

66. Martinez E, Larrousse M, Llibre JM, Gutierrez F, Saumoy M, Antela A, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. AIDS. 2010;24(11):1697–707. doi:10.1097/QAD.0b013e32833a608a.

67. Arribas JR, Pialoux G, Gathe J, Di Perri G, Reynes J, Tebas P, 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):581–9. doi:10.1016/S1473-3099(14)70782-0.

68. Martinez E, Arnaiz JA, Podzamczer D, Dalmau D, Ribera E, Domingo P, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. N Engl J Med. 2003;349(11):1036–46. doi:10.1056/NEJMoa021589.

69. Dejesus E, Young B, Morales-Ramirez JO, Sloan L, Ward DJ, Flaherty JF, et al. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate versus unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. J Acquir Immune Defic Syndr. 2009;51(2):163–74. doi:10.1097/QAI.0b013e3181a572cf.

70. Waters L, Fisher M, Winston A, Higgs C, Hadley W, Garvey L, et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. AIDS. 2011;25(1):65–71. doi:10.1097/QAD.0b013e328341685b.

71. Nguyen A, Calmy A, Delhumeau C, Mercier IK, Cavassini M, Fayet-Mello A, et al. A randomized crossover study to compare efavirenz and etravirine treatment. AIDS. 2011;25(1):57–63. doi:10.1097/QAD.0b013e32833f9f63.

72. Mills AM, Cohen C, Dejesus E, Brinson C, Williams S, Yale KL, 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):216–23. doi:10.1310/hct1405-216.

73. Nguyen A, Calmy A, Delhumeau C, Mercier I, Cavassini M, Mello AF, et al. A randomized cross-over study to compare raltegravir and efavirenz (SWITCH-ER study). AIDS. 2011;25(12):1481–7. doi:10.1097/QAD.0b013e328348dab0.

74. Pozniak A, Markowitz M, Mills A, Stellbrink HJ, Antela A, Domingo P, 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):590–9. doi:10.1016/S1473-3099(14)70796-0.

75. Trottier B, Lake J, Logue K, Brinson C, Santiago L, Brennan C et al. Switching to abacavir/dolutegravir/lamivudine fixed dose combination (ABC/DTG/3TC FDC) from a PI, INI or NNRTI based regimen maintains HIV suppression. ICAAC 2015, 55th interscience conference on antimicrobial agents and chemotherapy; San Diego, CA; 2015.

76. Mills T, Andrade J, DiPerri G, Van Lunzen J, Koenig E, Elion R et al. Switching from a tenofovir disoproxil fumarate (TDF)-based regimen to a tenofovir alafenamide (TAF)-based regimen: data in virologically suppressed adults through 48 weeks of treatment. In: 8th IAS conference on HIV pathogenesis, treatment and prevention; July 19–25, 2015; Vancouver, Canada; 2015.

77. U. S. Food and Drug Administration. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment guidance for industry: U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2015. Revision 1. Available from: http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM355128.pdf. Updated Nov 2015; cited 23 Nov 2015.

78. Smith KY, Patel P, Fine D, Bellos N, Sloan L, Lackey P, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS. 2009;23(12):1547–56. doi:10.1097/QAD.0b013e32832cbcc2.

79. Whitcomb JM, Parkin NT, Chappey C, Hellmann NS, Petropoulos CJ. Broad nucleoside reverse-transcriptase inhibitor cross-resistance in human immunodeficiency virus type 1 clinical isolates. J Infect Dis. 2003;188(7):992–1000. doi:10.1086/378281.

80. Melikian GL, Rhee SY, Taylor J, Fessel WJ, Kaufman D, Towner W, et al. Standardized comparison of the relative impacts of HIV-1 reverse transcriptase (RT) mutations on nucleoside RT inhibitor susceptibility. Antimicrob Agents Chemother. 2012;56(5):2305–13. doi:10.1128/AAC.05487-11.

81. Arribas JR, Delgado R, Arranz A, Munoz R, Portilla J, Pasquau J, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. J Acquir Immune Defic Syndr. 2009;51(2):147–52. doi:10.1097/QAI.0b013e3181a56de5.

82. Pulido F, Perez-Valero I, Delgado R, Arranz A, Pasquau J, Portilla J, et al. Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression. Antivir Ther. 2009;14(2):195–201.

83. Arribas JR, Girard PM, Landman R, Pich J, Mallolas J, Martinez-Rebollar M, 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):785–92. doi:10.1016/S1473-3099(15)00096-1.

84. Katlama C, Valantin MA, Algarte-Genin M, Duvivier C, Lambert-Niclot S, Girard PM, 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):2365–74. doi:10.1097/QAD.0b013e32833dec20.

85. Arribas JR, Horban A, Gerstoft J, Fatkenheuer G, Nelson M, Clumeck N, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. AIDS. 2010;24(2):223–30. doi:10.1097/QAD.0b013e3283348944.

86. Clumeck N, Rieger A, Banhegyi D, Schmidt W, Hill A, Van Delft Y, et al. 96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/ml at baseline. J Antimicrob Chemother. 2011;66(8):1878–85. doi:10.1093/jac/dkr199.

87. Antinori A, Arribas J, Fehr J, Girard PM, Horban A, Hill A, et al. The PROTEA trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV-1 RNA below 50 copies/ml. J Int AIDS Soc. 2014;17(4 Suppl 3):19525. doi:10.7448/IAS.17.4.19525.

88. Castagna A, Spagnuolo V, Galli L, Vinci C, Nozza S, Carini E, et al. Simplification to atazanavir/ritonavir monotherapy for HIV-1 treated individuals on virological suppression: 48-week efficacy and safety results. AIDS. 2014;28(15):2269–79. doi:10.1097/QAD.0000000000000407.

89. Spagnuolo V, Galli L, Bigoloni A, Nozza S, Monforte A, Antinori A, et al. Atazanavir/ritonavir monotherapy as maintenance strategy in HIV-1 treated subjects with viral suppression: 96-week analysis results of the MODAT study. J Int AIDS Soc. 2014;17(4 Suppl 3):19806. doi:10.7448/IAS.17.4.19806.

90. Perez-Molina JA, Rubio R, Rivero A, Pasquau J, Suarez-Lozano I, Riera M, 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):775–84. doi:10.1016/S1473-3099(15)00097-3.

91. Gallant JE, Koenig E, Andrade-Villanueva J, Chetchotisakd P, DeJesus E, Antunes F, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. J Infect Dis. 2013;208(1):32–9. doi:10.1093/infdis/jit122.

92. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Endo T, Horiba M, et al. Switching tenofovir/emtricitabine plus lopinavir/r to raltegravir plus Darunavir/r in patients with suppressed viral load did not result in improvement of renal function but could sustain viral suppression: a randomized multicenter trial. PLoS One. 2013;8(8):e73639. doi:10.1371/journal.pone.0073639.

93. Paton NI, Kityo C, Hoppe A, Reid A, Kambugu A, Lugemwa A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. N Engl J Med. 2014;371(3):234–47. doi:10.1056/NEJMoa1311274.

94. Boyd MA, Kumarasamy N, Moore CL, Nwizu C, Losso MH, Mohapi L, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label,

non-inferiority study. Lancet. 2013;381(9883):2091–9. doi:10.1016/S0140-6736(13)61164-2.

95. de Meyer S, Vangeneugden T, van Baelen B, de Paepe E, van Marck H, Picchio G, et al. Resistance profile of darunavir: combined 24-week results from the POWER trials. AIDS Res Hum Retroviruses. 2008;24(3):379–88. doi:10.1089/aid.2007.0173.

96. King MS, Rode R, Cohen-Codar I, Calvez V, Marcelin AG, Hanna GJ, et al. Predictive genotypic algorithm for virologic response to lopinavir-ritonavir in protease inhibitor-experienced patients. Antimicrob Agents Chemother. 2007;51(9):3067–74. doi:10.1128/AAC.00388-07.

97. Monogram Biosciences PhenoSense HIV Drug Resistance Assay. 2015. http://www.monogrambio.com/hiv-tests/phenotype-assays/phenosense. Accessed 14 Oct 2015.

98. Baril J, Conway B, Giguere P, Ferko N, Hollmann S, Angel JB. A meta-analysis of the efficacy and safety of unboosted atazanavir compared with ritonavir-boosted protease inhibitor maintenance therapy in HIV-infected adults with established virological suppression after induction. HIV Med. 2014;15(5):301–10. doi:10.1111/hiv.12118.

99. Foca E, Ripamonti D, Motta D, Torti C. Unboosted atazanavir for treatment of HIV infection: rationale and recommendations for use. Drugs. 2012;72(9):1161–73. doi:10.2165/11631070-000000000-00000.

100. Blanco JL, Varghese V, Rhee SY, Gatell JM, Shafer RW. HIV-1 integrase inhibitor resistance and its clinical implications. J Infect Dis. 2011;203(9):1204–14. doi:10.1093/infdis/jir025.

101. Seki T, Suyama-Kagitani A, Kawauchi-Miki S, Miki S, Wakasa-Morimoto C, Akihisa E, et al. Effects of raltegravir or elvitegravir resistance signature mutations on the barrier to dolutegravir resistance in vitro. Antimicrob Agents Chemother. 2015;59(5):2596–606. doi:10.1128/AAC.04844-14.

102. Kobayashi M, Yoshinaga T, Seki T, Wakasa-Morimoto C, Brown KW, Ferris R, et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother. 2011;55(2):813–21. doi:10.1128/AAC.01209-10.

103. Eron JJ, Clotet B, Durant J, Katlama C, Kumar P, Lazzarin A, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis. 2013;207(5):740–8. doi:10.1093/infdis/jis750.

104. Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382(9893):700–8. doi:10.1016/S0140-6736(13)61221-0.

105. ClinicalTrials.gov. Comparative efficacy and safety study of dolutegravir and lopinavir/ritonavir in second-line treatment. ClinicalTrials.gov Identifier: NCT02227238. 2015. https://clinicaltrials.gov. Accessed 19 Oct 2015.

106. Edurant [package insert]. Titusville, NJ: Janssen Products, LP; 2011. Available from: http://www.edurant.com/shared/product/Edurant/EDURANT-PI.pdf. Updated August 2015; cited 23 Nov 2015.

107. Rokx C, Blonk M, Verbon A, Burger D, Rijnders BJ. The efficacy, pharmacokinetics, and safety of a nevirapine to rilpivirine switch in virologically suppressed HIV-1-infected patients. J Acquir Immune Defic Syndr. 2015;68(1):36–9. doi:10.1097/QAI.0000000000000363.

108. Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet. 2011;378(9787):238–46. doi:10.1016/S0140-6736(11)60936-7.

109. Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet. 2011;378(9787):229–37. doi:10.1016/S0140-6736(11)60983-5.

110. Rimsky L, Vingerhoets J, Van Eygen V, Eron J, Clotet B, Hoogstoel A, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. J Acquir Immune Defic Syndr. 2012;59(1):39–46. doi:10.1097/QAI.0b013e31823df4da.

111. Stellbrink HJ, Antinori A, Pozniak A, Flamm J, Bredeek F, Patel K, et al. Switch to Stribild versus continuation of NVP or RPV with FTC and TDF in virologically suppressed HIV adults: a STRATEGY-NNRTI subgroup analysis. J Int AIDS Soc. 2014;17(4 Suppl 3):19793. doi:10.7448/IAS.17.4.19793.

112. Deeks ED. Darunavir: a review of its use in the management of HIV-1 infection. Drugs. 2014;74(1):99–125. doi:10.1007/s40265-013-0159-3.

113. Arribas J, Girard PM, Paton N, Winston A, Marcelin AG, Elbirt D, et al. Efficacy of PI monotherapy versus triple therapy for 1964 patients in 10 randomised trials. J Int AIDS Soc. 2014;17(4 Suppl 3):19788. doi:10.7448/IAS.17.4.19788.

114. Arribas JR, Doroana M, Turner D, Vandekerckhove L, Streinu-Cercel A. Boosted protease inhibitor monotherapy in HIV-infected adults: outputs from a pan-European expert panel meeting. AIDS Res Ther. 2013;10(1):3. doi:10.1186/1742-6405-10-3.

115. Paton N, Wolfgang S, Arenas-Pinto A, Dunn D, Group PT, editors. Randomised controlled trial of a PI monotherapy switch strategy for long-term HIV management [abstract]. Conference on retroviruses and opportunistic infections; 2014 March 3–6; Boston, MA.

116. Gutmann C, Cusini A, Gunthard HF, Fux C, Hirschel B, Decosterd LA, et al. Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. AIDS. 2010;24(15):2347–54. doi:10.1097/QAD.0b013e32833db9a1.

117. Wilkin TJ, McKinnon JE, DiRienzo AG, Mollan K, Fletcher CV, Margolis DM, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy: final 48-week clinical and virologic outcomes. J Infect Dis. 2009;199(6):866–71. doi:10.1086/597119.

118. 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):417–22. doi:10.1097/QAI.0b013e31802e2940.

119. Guiguet M, Ghosn J, Duvivier C, Meynard JL, Gras G, Partisani M, et al. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. AIDS. 2012;26(18):2345–50. doi:10.1097/QAD.0b013e32835646e0.

120. Curran A, Monteiro P, Domingo P, Villar J, Imaz A, Martinez E, et al. Effectiveness of ritonavir-boosted protease inhibitor monotherapy in the clinical setting: same results as in clinical trials? The PIMOCS Study Group. J Antimicrob Chemother. 2014;69(5):1390–6. doi:10.1093/jac/dkt517.

121. Cusini A, Vernazza PL, Yerly S, Decosterd LA, Ledergerber B, Fux CA, et al. Higher CNS penetration-effectiveness of long-term combination antiretroviral therapy is associated with better HIV-1 viral suppression in cerebrospinal fluid. J Acquir Immune Defic Syndr. 2013;62(1):28–35. doi:10.1097/QAI.0b013e318274e2b0.

122. Perez-Valero I, Gonzalez-Baeza A, Estebanez M, Monge S, Montes-Ramirez ML, Bayon C, et al. A prospective cohort study of neurocognitive function in aviremic HIV-infected patients treated with 1 or 3 antiretrovirals. Clin Infect Dis. 2014;59(11): 1627–34. doi:10.1093/cid/ciu640.

123. Perez Valero I, Gonzalez-Baeza A, Montes Ramirez ML. Central nervous system penetration and effectiveness of darunavir/ritonavir monotherapy. AIDS Rev. 2014;16(2):101–8.

124. Perez-Valero I, Gonzalez-Baeza A, Estebanez M, Montes-Ramirez ML, Bayon C, Pulido F, et al. Neurocognitive impairment in patients treated with protease inhibitor monotherapy or triple drug antiretroviral therapy. PLoS One. 2013;8(7):e69493. doi:10.1371/journal.pone.0069493.

125. Borghetti A, Mondi A, Piccoli B, Gagliardini R, Lamonica S, Ciccarelli N, et al. Switching to lamivudine plus darunavir/r dual therapy in a cohort of treatment-experienced HIV-positive patients: the experience of an Italian centre. J Int AIDS Soc. 2014;17(4 Suppl 3):19817. doi:10.7448/IAS.17.4.19817.

126. Cahn P, Andrade-Villanueva J, Arribas JR, Gatell JM, Lama JR, Norton M, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. Lancet Infect Dis. 2014;14(7):572–80. doi:10.1016/S1473-3099(14)70736-4.

127. Raffi F, Babiker AG, Richert L, Molina JM, George EC, Antinori A, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. Lancet. 2014;384(9958):1942–51. doi:10.1016/S0140-6736(14)61170-3.

128. Van Lunzen J, Pozniak A, Gatell J, Antinori A, Klauck I, Serrano O, et al., editors. HARNESS study: ritonavir-boosted atazanavir (ATV/r)+raltegravir (RAL) switch study in virologically suppressed, HIV-1-infected patients. International AIDS Conference; 2014 July 20–25; Melbourne, Australia.

129. Reynes J, Trinh R, Pulido F, Soto-Malave R, Gathe J, Qaqish R, et al. Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study. AIDS Res Hum Retroviruses. 2013;29(2):256–65. doi:10.1089/AID.2011.0275.

130. Lambert-Niclot S, Flandre P, Valantin MA, Peytavin G, Duvivier C, Haim-Boukobza S, et al. Factors associated with virological failure in HIV-1-infected patients receiving darunavir/ritonavir monotherapy. J Infect Dis. 2011;204(8):1211–6. doi:10.1093/infdis/jir518.

131. De Castro N, Braun J, Charreau I, Pialoux G, Cotte L, Katlama C, et al. Switch from enfuvirtide to raltegravir in virologically suppressed multidrug-resistant HIV-1-infected patients: a randomized open-label trial. Clin Infect Dis. 2009;49(8):1259–67. doi:10.1086/605674.

132. Grant PM, Palmer S, Bendavid E, Talbot A, Slamowitz DC, Cain P, et al. Switch from enfuvirtide to raltegravir in virologically suppressed HIV-1 infected patients: effects on level of residual viremia and quality of life. J Clin Virol. 2009;46(4):305–8. doi:10.1016/j.jcv.2009.09.025.

133. Talbot A, Machouf N, Thomas R, Marcotte S, Therrien R, Lessard B, et al. Switch from enfuvirtide to raltegravir in patients with undetectable viral load: efficacy and safety at 24 weeks in a Montreal cohort. J Acquir Immune Defic Syndr. 2009;51(3):362–4. doi:10.1097/QAI.0b013e3181aa1398.

134. Sayana S, Prosser P, Ricaurte JC, Sanchez S, Hamwi G, Hershey-Weber J, et al. Analysis of a switch from enfuvirtide to raltegravir in patients with undetectable viral load: efficacy and quality of life at 24 weeks. J Int Assoc Physicians AIDS Care (Chic). 2009;8(2):85–6. doi:10.1177/1545109709331473.

135. Siliciano JD, Kajdas J, Finzi D, Quinn TC, Chadwick K, Margolick JB, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. Nat Med. 2003;9(6):727–8. doi:10.1038/nm880.

136. Koelsch KK, Liu L, Haubrich R, May S, Havlir D, Gunthard HF, et al. Dynamics of total, linear nonintegrated, and integrated HIV-1 DNA in vivo and in vitro. J Infect Dis. 2008;197(3):411–9. doi:10.1086/525283.

137. Verhofstede C, Noe A, Demecheleer E, De Cabooter N, Van Wanzeele F, Van Der Gucht B, et al. Drug-resistant variants that evolve during nonsuppressive therapy persist in HIV-1-infected peripheral blood mononuclear cells after long-term highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2004;35(5):473–83. doi:10.1097/00126334-200404150-00005.

138. Diallo K, Murillo WE, de Rivera IL, Albert J, Zhou Z, Nkengasong J, et al. Comparison of HIV-1 resistance profiles in plasma RNA versus PBMC DNA in heavily treated patients in Honduras, a resource-limited country. Int J Mol Epidemiol Genet. 2012;3(1):56–65.

139. Wirden M, Soulie C, Valantin MA, Fourati S, Simon A, Lambert-Niclot S, et al. Historical HIV-RNA resistance test results are more informative than proviral DNA genotyping in cases of suppressed or residual viraemia. J Antimicrob Chemother. 2011;66(4):709–12. doi:10.1093/jac/dkq544.

140. Lee GQ, Dong W, Mo T, Knapp DJ, Brumme CJ, Woods CK, et al. Limited evolution of inferred HIV-1 tropism while viremia is undetectable during standard HAART therapy. PLoS One. 2014;9(6):e99000. doi:10.1371/journal.pone.0099000.

141. Bonjoch A, Pou C, Perez-Alvarez N, Bellido R, Casadella M, Puig J, 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):1382–7. doi:10.1093/jac/dks539.

142. Cruciani M, Mengoli C, Serpelloni G, Parisi SG, Malena M, Bosco O. Abacavir-based triple nucleoside regimens for maintenance therapy in patients with HIV. Cochrane Database Syst Rev. 2013;6:CD008270. doi:10.1002/14651858.CD008270.pub2.

143. Sprenger HG, Bierman WF, van der Werf TS, Gisolf EH, Richter C. A systematic review of a single-class maintenance strategy with nucleoside/nucleotide reverse transcriptase inhibitors in HIV/AIDS. Antivir Ther. 2014;19(7):625–36. doi:10.3851/IMP2726.

144. Gulick RM, Ribaudo HJ, Shikuma CM, Lustgarten S, Squires KE, Meyer WA 3rd, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med. 2004;350(18):1850–61. doi:10.1056/NEJMoa031772.

145. Katlama C, Assoumou L, Valantin MA, Soulie C, Duvivier C, Chablais L, 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):1648–52. doi:10.1093/jac/dkt536.

146. Monteiro P, Perez I, Laguno M, Martinez-Rebollar M, Gonzalez-Cordon A, Lonca M, et al. Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study. J Antimicrob Chemother. 2014;69(3):742–8. doi:10.1093/jac/dkt406.

147. Margolis D, Griffith S, St. Clair M, Spreen W, Brinson C, Smith G et al., editors. Cabotegravir and Rilpivirine As 2-Drug Oral Maintenance Therapy: LATTE W96 Results. Conference on retroviruses and opportunistic infections; 2015 February 23–26; Seattle, Washington.

148. ClinicalTrials.gov. Regimen switch to dolutegravir + rilpivirine from current antiretroviral regimen in human immunodeficiency virus type 1 infected and virologically suppressed adults (SWORD-1). ClinicalTrials.gov Identifier: NCT02429791. 2015. https://clinicaltrials.gov. Accessed 16 Oct 2015.

149. ClinicalTrials.gov. Phase 3 open-label study to evaluate switching from optimized stable antiretroviral regimens containing darunavir to elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) plus darunavir (DRV) in treatment experienced HIV-1 positive adults. ClinicalTrials.gov Identifier: NCT01968551. 2015. https://clinicaltrials.gov. Accessed 12 Nov 2015.

150. Hart E, Curtis H, Wilkins E, Johnson M. National review of first treatment change after starting highly active antiretroviral therapy in antiretroviral-naive patients. HIV Med. 2007;8(3): 186–91. doi:10.1111/j.1468-1293.2007.00451.x.