Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: http://www.tandfonline.com/loi/ieds20

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To cite this article: Laia Utrillo, Francesc Vidal, Teresa Puig & Pere Domingo (2016): Switching antiretroviral regimes for the treatment of HIV: safety implications, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2016.1206076

To link to this article: http://dx.doi.org/10.1080/14740338.2016.1206076

Accepted author version posted online: 28 Jun 2016.
Published online: 28 Jun 2016.

Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Safety*

DOI: 10.1080/14740338.2016.1206076

Switching antiretroviral regimes for the treatment of HIV: safety implications

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Article highlights

- Antiretroviral drug switching has been a popular strategy to address antiretroviral drug toxicity
- Keeping viral replication under control is a *sine qua non* condition to design a switch from an otherwise virologically successful therapy
- The driving force for switching strategies has been the availability of newer drugs with improved safety profiles
- The availability of new and better tolerated drugs have modified the spectrum of switching from reactive to proactive
- Integrase inhibitors are currently the most used drugs in switching strategies
- To avoid or prevent drug-drug interactions is an increasingly cause to switch virologically successful drugs

ABSTRACT

Introduction: There are multiple reasons to switch from a virologically successful antiretroviral regimen. Some of them are related to toxicity. Lately, combination antiretroviral treatment (cART) switches have often been related to drug-drug interactions which may also eventually entail safety issues as well.

Areas covered: The purpose of this review is to analyze causes of switching between virologically successful cART regimes related to safety issues. The most relevant papers were selected and summarized.

Expert opinion: Switching cART has been a popular strategy to address safety issues throughout the antiretroviral era. The myriad of switching studies have paralleled the study and release into clinical practice of new antiretroviral drugs with different and often improved safety profiles. Most of them have been successful in improving antiretroviral toxicity while keeping HIV replication under control. However, it should be taken into account that, whenever a new drug is given, there is a possibility of new drug-related toxicity. Notwithstanding that, an increase in cART switching is foreseen, given the fact that we have an wide antiretroviral drug armamentarium and that people living with HIV are ageing and thus more prone to developing age-related co-morbidities whose therapies may entail new interactions and eventually new toxicities.

Keywords; Comibination antiretroviral therapy , Switching , Safety , Toxicity , NNRTI , NRTI , PI , INsTI

1. INTRODUCTION

Why switch a virologically successful cART regimen?

Current combination antiretroviral therapy (cART) regimes are highly effective in controlling viral replication, and their massive implementation has eventually led to an unprecedented decline in morbidity and mortality associated with HIV infection. However, there are still many reasons to change a virologically effective cART regime, namely: intolerance, toxicity, appearance of new comorbidities, drug-drug interactions, simplification issues, dietary needs, pregnancy, and in recent times, cost-effectiveness of the cART regime itself.

1.1 Causes of switching cART regimes

The most important goal to keep in mind when considering switching a virologically successful effective antiretroviral regime is maintenance of virological suppression, while optimization of cART according to the characteristics and preferences of patient should be always be borne in mind [1].

At the beginning of the cART era, back to 1995-96, the main objective was efficacy. However, caregivers soon became aware that efficacy was often limited by toxicity and tolerability issues, causing much discomfort to patients. Notwithstanding that, cART was literally life-saving and, given the scarcity of antiretroviral drugs, there were few switching options and their success was limited. This is exemplified by the continued use of many old nucleoside reverse transcriptase inhibitors (NRTI), despite their known toxicity profile. Later, the emergence of new, more effective drugs, better tolerated and, ultimately, less toxic, improved the quality of life for patients, allowing the old toxic drugs to be changed for others with a better toxicity profile. The change from stavudine or zidovudine to tenofovir to improve lipoatrophy was a paradigm of that situation [2, 3]. Currently, according to a transversal study (undertaken through surveys in routine visits) [4], the most common reason for switching is simplification, even among patients with advanced treatment lines, probably in response to the release of new potent and effective drugs, with a good resistance profile, with less toxic and better adherence (less pills, less dietary restrictions, etc.) profiles, in most cases presented in single tablet regimens. In this setting, the typical

patient to be switched is one with a good immunological reconstitution and with undetectable viral load over a variable period of time.

Safety and toxicity problems that require switching cART rank second in frequency. We must consider that, if a patient has a suppressed viral load, this is because he is able to take the prescribed drugs [1]. Even so, the clinician should not forget that sometimes cART adhesion conveys overexertion by the patient, who is able to cope with adverse effects that he may understand as inevitable or a price to be paid for having cART's beneficial effect. The physician should not assume that a cART regimen is optimal only because viral load is suppressed. Patient overexertion, although never adequately studied, may then be a cause of cART switching and, therefore, the caregiver should assess the effort a patient needs to make to adhere to the prescribed cART regime.

1.2. Safety issues as a cause of switching

Switching an effective cART regime may be proactive or reactive. Proactive switching is forced when solid evidence demonstrates that the patient has an increased risk of a severe, unrecoverable or difficult-to-reverse toxic effect if the current cART is maintained. In general, proactive switches occur before toxicity has developed. A good example is lipoatrophy caused by thymidine analogues, with a switch to tenofovir or abacavir [5]. Reactive change is forced by the appearance of an adverse effect which will eventually disappear after switching. An example would be the central nervous system (CNS) adverse effects caused by efavirenz (EFV), and their improvement after switching to rilpivirine or elvitegravir/cobicistat [6, 7].

There are some situations that deserve a special mention regarding safety issues. One would be pregnant women in whom cART switch is often needed to ensure proper development of pregnancy and reduction of side effects to the foetus while maintaining the effectiveness of cART for mother and foetus. Another example would be patients with HIV/HCV co-infection who need treatment for HCV infection. Current treatment for HCV with direct-acting agents is very effective, but has potential drug-drug interactions with many antiretrovirals (especially PI and first-generation NNRTIs) which may be harmful for the patient. Therefore, it may be necessary to switch cART before starting HCV therapy.

HIV-infected patients are living and ageing due to the effectiveness of current CART regimes. Consequently, HIV infection has become a chronic manageable disease in an increasingly old population [8]. Ageing may be associated with the appearance of new comorbidities which require treatment (and then with the potential for new drug-drug interactions between cART and new drugs) or modification of the cART because of the co-morbid condition. This could be the case in kidney dysfunction whether or not related to the use of tenofovir and/or other antiretroviral drugs [9, 10].

2. SWITCHING BETWEEN PROTEASE INHIBITORS (PI)

2.1 Simplification issues

cART consisting of two nucleoside/nucleotide analogues plus either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) have, been until recently, been among the recommended first-line cART regimes for the treatment of HIV infection [1, 11-13].

The combination of abacavir (ABC)/lamivudine (3TC) plus atazanavir (ATV) boosted with ritonavir (RTV) (ATV/r) is an effective initial protease inhibitor-containing regimen. The addition of low-dose RTV to ATV increases the plasma exposure of ATV yielding an effective cART regimen with rare resistance observed after treatment failure. However, it increases the potential for adverse effects, including lipid disturbances and other metabolic complications [13]. A clinical trial [13] has shown that switching from boosted ATV to non-boosted ATV has similar efficacy and is a somewhat simpler.

Another option to simplify the regime in patients on a PI is to switch from tenofovir/emtricitabine (TDF/FTC) + ATV/r to ABC/3TC + ATV [14]. However, it should be noticed that, because of ATV-TDF interaction, the combination of TDF/FTC plus unboosted ATV is not a viable option [15].

2.2 Toxicity issues

PI present, as their main toxicity problems, a worse lipid profile, eventually leading to an increased cardiovascular risk in the case of lopinavir (LPV) and indinavir (IDV), the appearance of jaundice and hyperbilirubinaemia in the case of ATV, and a greater incidence

of renal dysfunction in patients treated with LPV/r and ATV/r (probably due to interaction with TDF) and diarrhoea secondary to RTV [13, 14].

Switching from ABC/3TC+ATV/r to ABC/3TC+ATV improved the safety profile through improved tolerability, caused a reduction in lipids, and minimized the potential for long-term metabolic adverse events. A clinical trial [13] has shown that this switching is associated with reduced levels of bilirubin, total cholesterol, LDL cholesterol and triglycerides. This change is only possible if ABC/3TC is completely active. This change could also be helpful in patients in whom it is not desirable to continue with RTV because it enhances the toxicity of ATV (hyperbilirubinaemia), due to its own toxicity (dyslipidaemia, diarrhoea) and because of the risk of drug-drug interactions.

Reduction of RTV toxicity can also be achieved by switching from TDF/FTC+ATV/r to ABC/3TC+ATV. A randomized multicentre study [14] has shown that this switch maintained viral suppression, was well-tolerated, and led to improvements in CD4+ cell count, bone biomarkers, renal biomarkers, and HDL cholesterol, without causing increases in other fasting lipid levels or in cardiovascular biomarkers of inflammation and thrombogenesis. This option should be considered in patients who want to avoid the use of TDF as much as that of RTV.

The ATLAS-M trial [16] (a phase IV, multicenter, open-label, randomized study), wanted to demonstrated non-inferiority of treatment simplification to ATV/r + lamivudine (3TC) versus maintaining 3-drugs ATV/r-based cART. Data from 24 weeks suggest that simplification to ATV/r + 3TC is virologically safe. The proportion on treatment failure was 91.7% (in switch arm) vs 85.1% (no switch arm). Clinical and laboratory adverse events occurred at similar rates in the two arms. At week 24, patients in switch arm showed a greater increase in CD4. A greater increase in total cholesterol, HDL and LDL was also observed in switch arm without differences in other lipid parameters. Renal function showed a significant improvement in switch arm. No significant differences in bilirubin levels or other laboratory parameters were observed between the two arms.

A systematic review of the published work on switch to atazanavir-containing regimen [17] demonstrated that the switching from first generation PI to ATV means an improvement in

lipid profile. It were most pronounced for patients switched to unboosted ATV at higher dose (400 mg), but one trial (ATAZIP) [18], included in this systematic review, even demonstrated relevant lipid improvements, when patients on lopinavir-ritonavir switched to atazanavir-ritonavir.

Trials related to switching between PI and their characteristics are summarized in table 1.

Another important aspect is the paper of cobicistat (COBI) as an enhancer of PI. Atazanavir/cobicistat (ATV/c) and darunavir/cobicistat (DRV/c) are newly approved once daily fixed-dose protease inhibitor combinations for the treatment of HIV-1 infection. Studies in healthy volunteers [19] have established bioequivalence between cobicistat and ritonavir as pharmacoenhancers of both atazanavir (ATV) and darunavir (DRV).

A phase II, randomized, partially placebo-controlled, double-blind, multicenter study [20] demonstrated that COBI had sustainable and comparable efficacy and safety to RTV as a pharmacoenhancer of ATV. In this trial, 84% of ATV/c participants and 86% of ATV/r participants suppressed HIV-1 RNA at week 24, and 82 and 86% at week 48, respectively, and mean CD4 cell count increased 203 and 199 cells/ml at week 24 and 208 and 177 cells/ml at week 48, respectively. Study treatment discontinuation due to adverse events occurred in 4% ATV/c and in 3% ATV/r participants through 48 weeks. Treatment-related adverse events occurred in 36% ATV/c and 48% ATV/r participants. Mean estimated glomerular filtration rate (Cockcroft– Gault, ml/min) decrease occurred in both treatment groups and was evident at week 2, and did not progress further through week 48. In addition, a phase III, double-blind and doubledummy study [21] demonstrated that once-daily COBI is a safe and effective pharmacoenhancer of ATV: At week 144, virologic suppression was achieved in 72% (COBI) and 74% (RTV) of patients. Adverse events leading to study drug discontinuation occurred in 11% of patients in each group. Median changes in serum creatinine (mg/dL) were +0.13 (COBI) and +0.07 (RTV) and were unchanged from week 48.

Furthermore, one Phase III, open-label, single-arm, clinical trial [22] reflected virologic and immunologic responses and safety outcomes consistent with prior published data for DRV/r 800/100 mg once daily, supporting the use of DRV/c 800/150 mg once daily for treatment of

treatment-naïve and experienced HIV-1-infected patients with no DRV resistance associated mutations. In this trial, the majority of discontinuations were for adverse events (15/313; 5%). The incidence of treatment-emergent grade 3 or 4 adverse events regardless of causality was 6% through week 24 and 8% through Week 48. Most common adverse events through week 48 were diarrhea (27%) and nausea (23%), which were grade 1 or 2 in severity. Week 48 virologic response rates were 81% overall and 83% in treatment-naïve patients; median increases in CD4+ count at 48 weeks were 167 and 169 cells/mm3, respectively.

In both cases (ATZ/c and DRV/c), low rates of virologic failure secondary to resistance to antiretroviral regimens were present in these clinical studies. Most notable adverse events in the ATV studies were hyperbilirubinemia and in the DRV study rash. Small increases in serum creatinine and minimally reduced estimated glomerular filtration rate Cockcroft–Gault calculation (eGFRCG) were observed in ATV/c and DRV/c clinical studies. These renal parameter changes occurred acutely in the first few weeks and are not necessarily clinically relevant. Cobicistat has numerous advantages compared to ritonavir such as fewer drug–drug interactions, being devoid of anti-HIV-1 activity, as well as it has better solubility affording co-formulation with other antiretrovirals as simplified fixed-dose combinations. Often it considered indifferent use ritonavir or cobicistat as enhancers, but must take into account the differences between them in terms of metabolism to predict potential interactions, especially with other drugs taken by the patient. Therefore, co-medications should be systematically reviewed when switching pharmacokinetic enhancer in order to anticipate potential dosage adjustments [23].

3. SWITCHING BETWEEN NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)

3.1. Simplification issues

Patients taking cART express a preference for and may better adhere to once-daily dosing. Pharmacokinetic ‘‘forgiveness,’’ through prolonged elimination half-lives of certain once-daily agents, may also make dose timing accuracy less critical, improving treatment satisfaction [2].

Switching from stavudine (d4T) or zidovudine (AZT) to TDF or ABC eases the establishment of compact once-daily regimens. Clinical trials have demonstrated these benefits without loss of virological control, with maintenance of CD4 numbers, and facilitate the establishment of compact once-daily regimens, thus improving patient satisfaction [2, 24, 25].

3.2. Toxicity issues

cART has dramatically reduced HIV-associated morbidity and mortality, but may be complicated by adverse effects, including dyslipidaemia and insulin resistance, and clinical adverse events such as limb fat loss and subcutaneous lipoatrophy [2, 26], renal dysfunction, and osteoporosis leading to an increased risk of bone fracture. Adverse events or fear of adverse events remains a key cause of drug interruption or discontinuation.

The morphological changes of lipoatrophy are often stigmatizing and psychologically devastating, thus leading to reduced adherence or treatment discontinuation [2, 24, 27]. Reports from clinical trials of thymidine nucleoside analogue-based (d4T or AZT) regimens indicate that the prevalence of lipoatrophy in persons receiving such therapy for 3 years is 19% or more [24]. Co-administration of a thymidine analogue with some protease inhibitors may further accelerate fat loss [24]. The only approach to its management that has so far demonstrated moderate benefit in randomized controlled trials is switching therapy from a thymidine analogue to ABC [5, 24]. The largest of these trials [5] showed that, in addition to limb fat gains, switching to ABC had no significant effect on HIV-1 RNA, fasting lipids or glucose after 24 weeks. Other randomized studies [24, 28, 29] confirmed these findings and have suggested that switching therapy may also prevent limb fat loss. However, this option is not available to every patient owing to hypersensitivity reactions (only available in patients with negative HLA-B*5701), intolerance or drug resistance. Several randomized

trials demonstrate that these switches are virologically safe and produce a subclinical improvement or stabilization of subcutaneous fat loss [1-3, 24, 25, 30]. There are not significant differences between ABC and TDF in the maintenance of virological suppression [1, 25, 30].

Dyslipidaemia has emerged as an important issue in patients receiving cART and, if not addressed, can represent a significant cardiovascular risk factor [2, 31]. Comparative clinical data indicate that ABC/3TC is associated with greater increases in total cholesterol and other lipid fractions relative to TDF/FTC-based regimens. Switch data indicate that, when replacing a thymidine analogue in persons with lipoatrophy, similar limb fat recovery is observed with ABC or TDF but only TDF leads to declines in lipids [32-35]. In patients with hypercholesterolaemia, switching from ABC/3TC to TDF/FTC maintains virological control and significantly improves key lipid parameters [1, 32, 33]. Exposure to ABC has been associated with an increased rate of cardiovascular events, but this association is highly controversial [1].

Low bone mineral density (BMD) has been reported in studies of HIV-infected individuals [37, 38]. In a meta-analysis, the prevalence of osteoporosis was 3 times higher in HIV-infected patients than HIV-uninfected control subjects [38]. Both virological and immunological factors contribute to decreased BMD in HIV-infected patients [37-39]. Exposure to cART also induces bone demineralization and higher risk of fracture [37]; data suggest a lower BMD among patients receiving PI [37, 40, 41]. However, TDF is currently the antiretroviral drug most associated with BMD loss. [37, 42, 43]. Results from several randomized clinical trials among antiretroviral naive patients have shown that initiation of cART is associated with a decrease in bone mineral density (BMD) of 2%-6% at both the hip and the spine, which occurs within the first year of treatment, with stabilization thereafter [40, 43-49]. Three trials directly compared TDF/FTC with ABC/3TC and found greater decreases in BMD with TDF/FTC-based treatment [40, 43, 48]. Also, in a randomized clinical trial with patients with osteoporosis or osteopaenia, switching from TDF to ABC was followed by an increase of BMD in femur but not in spine [1, 37]. Therefore, guidelines

recommendations [1, 11, 12] suggest that switching from TDF to ABC is an option in patients with osteoporosis or osteopaenia associated with TDF use.

Renal disease is an important contributor to morbidity and mortality in HIV-infected patients [50, 51]. TDF is associated with excellent virological suppression, but some patients develop clinically relevant nephrotoxicity over time, especially individuals with risk factors for renal disease [9]. Although studies suggest that TDF has a low overall toxicity profile and only a modest effect on estimated glomerular filtration rate, numerous case reports have since appeared in the literature describing TDF-associated renal tubular dysfunction, and this is now a significant source of HIV-related referrals to nephrologists. The main target of toxicity appears to be the proximal tubule and, in severe cases, patients can develop Fanconi syndrome [1, 9, 10]. In addition, data from the CHIC cohort suggest that once kidney dysfunction is established, its reversibility may not be complete in the long term [50].

Tenofovir alafenamide (TAF) is a new tenofovir prodrug that reduces tenofovir plasma concentrations by 90% and increases intracellular concentrations by 500% [1, 9]. This is associated with a lower impact on bone mineral density, glomerular filtration and tubular function, thereby decreasing side effects. In two double-blind randomized controlled studies of TAF versus TDF (both added to elvitegravir [EVG], cobicistat [COBI], and emtricitabine [FTC]) for the initial treatment of HIV-1 infection, more than 90% of patients on TAF had virological suppression at week 48, but renal and bone abnormalities were significantly reduced in patients allocated to TAF compared to those allocated to TDF [52]. A randomized clinical [9] trial evaluated switching from TDF/FTC/COBI/EVG, TDF/FTC/EFV or TDF/FTC-ATV/r to TAF/FTC/COBI/EVG in patients with suppressed viral load, demonstrated sensitivity to all regime components, and glomerular filtration > 50 mL/min. At 48 weeks, the switch to TAF resulted in improvements in renal function, including decreases in serum creatinine (in those switching from a boosted regimen), decreases in dipstick proteinuria, decreases in quantitative tests of total urine protein, and total urine albumin, decreases in specific proximal renal tubular proteins, and improvements in tests of proximal renal tubular function. Virological suppression was maintained and the new regime was well tolerated.

Similar results are communicated in a non-randomized clinical trial [50]. Trials related to switching between NRTIs and their characteristics are summarized in table 2.

4. SWITCHING BETWEEN NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)

4.1. Simplification issues

In patients with suppressed viral load who are taking a regime based on 2 NRTIs plus 1 NNRTIs, it is possible to switch to a compact once-daily regimen to increase adherence and treatment satisfaction.

Regimes based on TDF/FTC + nevirapine (NVP) involve taking 3 pills a day, being 2 pills with NVP XR. Nowadays, there are fixed dose co-formulations such as TDF/FTC/EFV or TDF/FTC/rilpivirine (RPV), that allow single-tablet, once-daily treatment.

Switching from TDF/FTC + NVP to EFV/TDF/FTC, in addition to simplifying the treatment, offers less toxicity [53, 54]. Switching from TDF/FTC + NVP to TDF/FTC/RPV is also an option to reduce the number of pills. To switch between these regimes, one must consider that RPV has dietary restrictions (must be taken with at least 390 Kcal), and that it has interactions with proton pump inhibitors [1]. These situations can hinder switching between these regimes in selected patients.

4.2. Toxicity issues

EFV has been associated with neurological and psychological side effects that, in some patients, can lead to discontinuation of therapy [54]. Although it is a generally safe and effective drug, EFV is associated with central nervous system side effects, and prescribing information contains warnings of serious psychiatric side effects, including suicide [47]. In an analysis of four big independent clinical trials, an increased risk was found of developing suicidal ideas or attempted or completed suicides in patients receiving EFV [55], although in two other cohorts this question is not confirmed [1, 56, 57]. EFV use may worsen neurocognitive function or be associated with less improvement in impaired neurocognitive

function than other antiretrovirals [55]. Due to these tolerability issues with EFV, there is another NNRTI option available with a better tolerability profile [54], known as RPV. Switching from TDF/FTC/EFV to TDF/FTC/RPV or TDF/FTC + etravirine (ETR) is a good option for those patients who have unbearable CNS side effects. Two clinical trials [58, 59] suggest that switching from TDF/FTC/EFV to TDF/FTC/RPV is virologically safe and can improve persistent CNS toxicity. There are no data available to recommend a proactive switch in patients who are taking EFV without CNS symptoms [1]. The same is true for switching from TDF/FTC/EFV to TDF/FTC + ETR [60] although this switch means a twice daily administration. A randomized, multicentre, double-blind trial showed that this switch improved the CNS symptoms due to EFV, and that it is virologically safe [61].

EFV also has been associated with the development of glucose metabolism disturbances and dyslipidaemia, specifically increases in total cholesterol: HDL/total cholesterol ratio, LDL cholesterol, and triglycerides [62]. The pathogenesis of these metabolic effects is unclear. Switching from EFV-based therapy to RPV-based regimen improved the lipid profile in fully suppressed HIV-infected patients with dyslipidaemia [63].

In addition to the CNS toxicity and worse lipid profile, EFV can also produce exanthema, but this effect usually occurs during the first few weeks and may disappear thereafter, and thus it is not usually a cause for switching [1,11].

Finally, in women who want to become or are pregnant and are taking EFV, it has long been recommended to switch from EFV due to the increased risk of anencephaly and neural tube defects [1]. Data from primate studies [64] and some human case reports [64, 65] have raised concern regarding an association of first-trimester EFV exposure with central nervous system congenital anomalies. In these cases, the option is switching from EFV-based therapy to RPV-based therapy, which is considered an alternative drug in pregnancy. Other possible switches in this setting may be to PIs or INsTI. However, both WHO and perinatal DHHS guidelines [66] are now recommending EFV as initial therapy, including pregnant women, because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy. Pregnancy is rarely recognized before 5 to 6 weeks, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal

transmission. Trials related to switching between NNRTIs and their characteristics are summarized in table 3.

5. INTERCLASS SWITCHING

5.1. Switching from PI-based to NNRTI-based regime

In an effort to potentially reduce adverse effects, improve adherence, and/or lower pill burden, attention has been focused on changing the protease inhibitor (PI) component in PI-based antiretroviral regimens in virologically suppressed patients to an NNRTI. Several studies have demonstrated that switching from a PI to an NNRTI, while keeping the NRTI backbone unaltered, can be successfully accomplished while maintaining virological suppression after the switch [67-69].

Switching options have classically involved switching from PI to EFV or NVP, and lately to RPV. A prospective, randomized, controlled, open-label, multicentre study [67], demonstrates that switching from PI to EFV is associated with an improvement in the lipid profile (especially in triglycerides and HDL cholesterol), but patients experience more psychiatric symptoms and CNS side effects. However, the study suggests that these effects occur especially at the beginning of treatment and are temporary. On the other hand, in the same clinical trial [67], a significant risk of renal failure in patients with TDF-based regime was not observed. In this study, the patients preferred TDF/FTC/EFV to the previous one (PI-based regime). Adherence and patient satisfaction were better in the experimental group.

A number of non-controlled trials have also shown that NVP can successfully maintain HIV suppression in more than 90% of patients when PIs are replaced with NVP-based regimens [70-71]. It may improve the quality of life of patients by reducing toxic and metabolic side effects of the drugs and by facilitating adherence to antiretroviral regimes [73]. A meta-analysis demonstrates that NVP-based regimens have shown non-inferiority compared with continuation of PI therapy to maintain virological suppression [70]. Overall rates of discontinuation because of adverse events were similar in the two groups. However, NVP-based therapies caused more discontinuations because of liver toxicity than PI-based therapies. At the end of follow-up, there was no statistically significant difference in CD4,

cholesterol, triglyceride and body shape measurements between the two groups. This studies reported greater improvement in quality of life in patients who were switched to NVP.

In patients with diarrhoea, dyslipidaemia, or patients with a desire to reduce the number of daily pills, switching from PI-based regime to fixed-dose TDF/FTC/RPV co-formulated once-daily is a fair option. The SPIRIT study [74], a large randomized clinical trial, demonstrated the safety and efficacy of switching from PI/r + two NRTI to FTC/TDF/RPV over 48 weeks for HIV-1-infected participants who had been virologically suppressed on a PI/r-based regimen for at least 6 months prior to study entry and had no previous antiretroviral treatment failure. Switching to TDF/FTC/RPV resulted in maintenance of HIV-1 suppression and significant improvements in fasting serum lipid profiles (total cholesterol, LDL, TC/HDL ratio, and triglycerides) compared with remaining on PI/r + two NRTIs. This is the first study to evaluate switching from multipill, boosted PI regimens to once-daily TDF/FTC/RPV. The most important trials related to switching from a PI-based regime to an NNRTI-based regime and their characteristics are summarized in Supplemental table 1.

5.2. Switching from a PI-based regime to an INsTI-based regime

PI have been associated with an increased risk of cardiovascular disease due at least in part to their lipid effects. RTV at doses similar to those used for protease inhibitor boosting has been shown to increase plasma lipids [75-79].

The efficacy of RAL-based regimes has been established and to date it has demonstrated a low impact on plasma lipids [75]. Although RAL needs to be taken twice daily, and this schedule may not be as convenient as that of some of the currently available PI that are administered once daily, RAL might be an attractive option to simplify RTV-boosted PI-containing antiretroviral therapy because of potential long-term metabolic concerns [75]. RAL is not metabolized by cytochrome P450 as other antiretrovirals drugs, and this feature implies a lower rate of drug-drug interactions comparing with other drugs. The SPIRAL study [75], a 48-week multicentre, open-label trial, demonstrates that switching from the RTV-boosted PI component to RAL in selected HIV-infected adults, with suppressed viral load

may result in a better lipid profile and non-inferior efficacy. The improvement in lipid profile in patients switching from boosted PI to RAL was also described in SWITCHMRK 1 and 2 studies [76]. These are two multicentre, double-blind, double-dummy, phase 3, randomized controlled trials that compared the efficacy and safety of treatment with RAL vs. continuing with LPV/r. All these trials [75, 76] showed that switching from PI/r to RAL is associated with better levels of total cholesterol, total cholesterol/HDL ratio, and triglycerides. However, in Switchmrk trials, RAL switching failed to demonstrate non-inferiority from a virological point of view compared with maintaining the PI/r-based regime [75, 76].

EVG is a first-generation INsTI. Co-formulated TDF/FTC/COBI/EVG (Stribild™, STB) is safe and effective in HIV-infected, antiretroviral-naive adults, and is a recommended integrase inhibitor-based starting regimen in treatment guidelines [1, 11, 12]. This drug combination is a great alternative for patients who are taking PI/r-based regime, because it helps to simplify the regime (only one pill per day). In terms of safety, switching from PI/r (essentially ATV/r, DRV/r or LPV/r) to TDF/FTC/COBI/EVG has been virologically superior, and some switch patients experienced improvement in the rates of gastrointestinal disturbance. These are results from the STRATEGY-PI study [80], a 96-week, international, multicentre, randomized, open-label, phase 3b trial.

Dolutegravir (DTG) is a second-generation INsTI. Clinical trials using DTG have found that it is effective at suppressing the HIV virus and it is as effective as RAL, and superior to EFV and DRV/r, in antiretroviral naïve patients [81-83]. Potential advantages of DTG include once daily dosing as a single tablet, no need for pharmacological boosting, well-established dose-response characteristics, high genetic barrier and good tolerability [82].

There is one study, NEAT22 [85], which is ongoing, with the purpose of assessing the benefits of switching from a boosted PI to DTG. The aims of this study are to demonstrate whether this switching will improve the cardiovascular health of the patients and also to assess the safety and monitor effectiveness,. The most important trials related to switching from PI-based regimes to INsTI-based regime and their characteristics are summarized in Supplemental table 2.

5.3. Switching from an NNRTI-based regime to an INsTI-based regime

Patients with HIV on an NNRTI-containing regimen might be appropriate candidates for treatment modification to an NNRTI-sparing regimen if they have neuropsychiatric side effects such as anxiety, insomnia, dizziness, and abnormal dreams [7, 54, 55]. Additionally, those who are on a multitablet NNRTI-containing regimen might prefer simplification to a single-tablet regimen.

Co-formulated TDF/FTC/COBI/EVG has proved efficacious, safe and well-tolerated in naïve adult patients with HIV [7]. The STRATEGY-NNRTI study [7] is a 96-week, international, multicentre, randomized, open-label, phase 3b, non-inferiority trial, that included patients with suppressed viral load in two arms: switch to TDF/FTC/COBI/EVG (switch group) or continue the TDF/FTC plus NNRTI regimen or FTC/FTC/EFV (non-switch group). In the NNRTI group there were patients in treatment with EFV (the most common), NVP, RPV or ETR. This trial shows that switching to TDF/FTC/COBI/EVG is non-inferior to continuing an existing NNRTI-based regimen for the treatment of virologically suppressed adult patients with HIV and no history of virological failure. Patients who switched from EFV had an improvement in anxiety, insomnia, dizziness, and abnormal dreams. However, some side effects such as headache, cough, fatigue and nausea were more frequent in TDF/FTC/COBI/EVG group. Proactive switch to this regime in patients without CNS symptoms is not recommended [1]. Another option in patients with suppressed viral load who are taking an EFV-based regimen and have CNS symptoms (including subclinical symptoms) is to switch from EFV to RAL. In the SWITCH-ER study [86], approximately half of patients previously on stable EFV preferred switching to RAL, after double-blind exposure to RAL for 2 weeks. Switching to RAL was associated with a significant improvement in anxiety and stress, as measured by the DRESS scale, and also in lipid profile. The most important trials related to switching from NNRTI-based regime to INSTI-based regime and their characteristics are summarized in Supplemental table 3.

5.4. Switching from NRTI to INsTI

TDF, particularly when given with a ritonavir-boosted PI (PI/r), reduces BMD and increases bone turnover markers, both of which are associated with increased fracture risk [37, 40,

41, 87]. RAL is an INsTI considered as first-line HIV-1 treatment according to the current clinical guidelines [1, 12]. This drug has not been associated with bone loss [87]. In TROP study, an open-label, non-randomized, 48-week study, TDF was switched to RAL while maintaining PI/r in patients who have a reduction of BMD. This trial demonstrates that switching from TDF to RAL (with or without FTC) is virologically safe and is associated with an improvement of BMD in spine and hip and with a reduction in bone turnover markers [87].

SWORD-1 trial [88] is a phase III, randomized, multicenter, parallel-group, non-inferiority study that evaluating the efficacy, safety, and tolerability of switching to DTG plus RPV (once daily) from current antiretroviral regimen (including 2 NRTIs plus a third agent). The study will include a 148-week open-label treatment phase, comprising of an early switch phase (day 1 to week 52) and a late switch phase (week 52 to week 148). This trial is ongoing, but the results could be interesting in terms of simplicity and safety.

Most important trials related to switching from NRTI-based regime to INSTI-based regime and their characteristics are summarized in Supplemental table 4.

Integrase Inhibitors is the drug class in great increase of use. For this reason we would give more emphasis to studies involving this drugs with a table comparing the results in terms of probability of discontinuation and advantages and disadvantages in toxicity (Supplemental table 5).

5.5. Other switching strategies

Switching to ABC/3TC/DTG from a PI, INSTI or NNRTI based regime

When we do not want patients to receive TDF or in those who cannot receive it, and in those who want to simplify the regime, the combination of ABC/3TC/DTG can be used. Currently, it is available in co-formulation as a single pill per day. Triumeq™ is the first single-tablet regimen that contains DTG and is TDF-free. STRIIVING [89] is an open-label clinical trial conducted to evaluate the efficacy, safety, tolerability and treatment satisfaction of switching to ABC/3TC/DTG from a variety of regimes (PI, INsTI or NNRTI based regimes) in stable and virologically suppressed subjects. This study met non-inferiority

endpoints for all population analyses and demonstrates an improvement in patient treatment satisfaction scores. The lipid profile was similar in both groups (switched and not switched patients), whereas small and non-progressive changes in serum creatinine were observed in the ABC/3TC/DTG arm, due to known inhibition of tubular creatinine secretion by DTG. Moreover, since it is a TDF-free regime, it avoids the reduction of BMD due to TDF. A STRIVIING sub-study [90] evaluated the effects of switching to ABC/3TC/DTG on markers of inflammation and immune activation. No worsening of markers associated with cardiovascular disease was observed following switch to ABC/3TC/DTG, when compared with prior antiretroviral therapy. The most important trials related to switching from PI, INsTI or NNRTI based regime to ABC/3TC/DTG and their characteristics are summarized in Supplemental table 6.

Monotherapy with protease inhibitors

Monotherapy with DRV/r (QD) [90] or LPV/r (BID) [92-94] has not demonstrated long-term non-inferiority compared with triple therapy in the intention to treat analysis considering the change of randomized therapy equals failure. PROTEA trial [93] compared switched to DRV/r 800/100 mg once-daily, either as monotherapy or with 2NRTIs. In the primary efficacy analysis, HIV-1 RNA <50 copies/mL by week 48 (intent-to-treat) was 86.1% in the DRV/r monotherapy arm versus 94.9% in the triple therapy arm; DRV/r monotherapy did not show non-inferiority versus triple therapy in the primary analysis. In the multivariate analysis, the main predictor of treatment failure was nadir CD4 count. For patients with nadir CD4 counts <200 cells/mL, HIV-1 RNA suppression rates at week 48 were 66% in the DRV/r monotherapy arm and 97% in the triple therapy arm; for patients with CD4 nadir at least 200 cells/mL, HIV-1 RNA suppression rates were 95% in the DRV/r monotherapy arm and 94%in the triple therapy arm. In the overall population, by a switch included analysis, efficacy was 92% vs 96.3%, showing non-inferiority. In clinical trials of monotherapy with DRV/r or LPV/r with appropriate virological monitoring it has not shown an increased risk of selection of protease MR [93, 94].

Compared with triple ART, monotherapy with DRV/r or LPV/r has not demonstrated long-term benefits besides cost savings. However there is no evidence to justify that if a patient is able to maintain virologic suppression with DRV/r or LPV/r monotherapy is also necessary to use two NRTIs. The factors that predict success of monotherapy are: high adhesion, prolonged and profound viral suppression [94] and nadir level of CD4 + nadir more than 100 cells uL [94].

6. CONCLUSIONS

There are still many reasons to change a virologically effective cART regime, namely: intolerance, toxicity, appearance of new comorbidities, drug-drug interactions, simplification issues, dietary needs, pregnancy, and in recent times, cost-effectiveness of the cART regime itself

However, current cART regimes toxicity ranks among the most important causes of switching, although quite often the cause of switching is mixed, the most frequent being the combination of simplification and toxicity of drug-drug interactions and toxicity.

Switching studies have been very popular since the very beginning of the cART era. Most of them are reactive to the development of toxicity related to the regime which was switched. Lately, there is an increasingly number of proactive switches, especially in the setting of co-morbidity therapy to avoid drug-drug interactions and their eventual toxicity.

Thanks to improvement in the antiretroviral armamentarium, most of the switching studies fulfil the *sine qua non* conditions of this kind of studies, i. e. to maintain virological control while improving the toxicity underlying switching.

In conclusion, development of effective and safer antiretroviral drugs has led to a vast expansion of switching studies, providing the caregiver with successful tools to adequately manage cART- associated toxicity, maintaining or even improving the current high standards of cART efficacy.

7. EXPERT OPINION

cART switching is the change of any component or of the full cART regimen for reasons other than virological failure. Therefore, the concept of switching is changing an otherwise virologically successful cART regime, ruling out virological failure. The reasons leading to a change in a virologically successful cART may be diverse, but among them toxicity and safety issues usually rank among the most important. However, in recent times drug-drug interactions, regime simplification, and even cost containment have been outstanding reasons for cART switching.

From the very beginning of the cART era, it was evident that the most important cause of cART change was not the lack of virological efficacy of antiretroviral regimes, but their associated toxicity. Switching studies and trends to switch in routine clinical practice have paralleled the release of new antiretroviral drugs and formulations with a double objective, to reduce short-term and long-term antiretroviral toxicity and to improve adherence to cART by decreasing the pill burden and the dosing schedule. Therefore, in most trials the switching objectives may not be just a reduction of toxicity but also to make the cART regime simpler and easier to take. The assumed principle that new antiretroviral drugs have a better toxicity profile than the older ones, while being able to maintain virological control, is in general true, with notable exceptions, and extends to the full length of the antiretroviral era. Even now, actual or precluded antiretroviral toxicity remains the main reason for switching cART. Fortunately, the incorporation of INsTI, a family of drugs with a particularly good safety profile, has promoted a number of studies related to switching the classical antiretroviral families.

The caregiver must take into account not only the presumed benefits a cART switch may convey, but also the possible new toxic effects caused by the drug to which the patient switches. Therefore, the benefit of such a switch must be carefully weighed against the possible risks of developing new-onset toxicity, and ideally the benefit should greatly outweigh the risk.

Classically cART switching has been done reactively to the appearance of cART-associated toxicity. However, the availability of new drug classes with an almost ideal toxicity profile, and the increasing number of people living with HIV who are ageing and thus develop age-

related co-morbid conditions, whether or not related to antiretroviral therapy, have changed the pattern of switching. These co-morbidities usually need additional therapy which may increase the potential for drug-drug interactions and eventually toxicity, due to both kinds of drugs. All of this has turned the scenario of cART switching into a proactive one, with the aim of avoiding drug-drug interactions and their associated toll of toxicity. This trend may further increase in the near future since, at present, patients are living and ageing with HIV and our antiretroviral armamentarium enables us to design cART regimes of low toxicity and with low interaction potential. This trend will most probably increase in the future. Therefore, we should think, like Philip Crosby [95] that "Change should be a friend. It should happen by plan, not by accident".

Funding

This work has been partially funded by *Fondo de Investigaciones Sanitarias* (FIS PI13/0796, PI14/0700 and PI14/0063), *Ministerio de Sanidad, Politica Social e Igualdad* (EC11-293), *Programa de Suport als Grups de Recerca AGAUR* (2009 SGR 1061), and *Red de Investigación en SIDA* (RIS RD06/006/0022, RD06/0006/1004, RD012/0017/0014, RD12/0017/0005) and by I *Convocatoria de Proyectos de Investigación en VIH y Hepatitis* 2013, Fellowship Program Gilead (GLD 1300168). Pere Domingo and Francesc Vidal are supported by grants from the *Programa de Intensificación de Investigadores, Instituto de Salud Carlos III* (INT12/383, INT13/232, and INT11/240).

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Table 1. Summary of trials related to switching between PIs

Study (ref)	Switch type		Main outcomes	Follow up
	From	To		
ARIES [13] NCT00440947	ABC/3TC + ATV/r	ABC/3TC + ATV	Simplification Improve side effects related to RTV use: Diarrhea in 3% (ATV) vs. 6% (ATV/r) Hyperbilirubinemia in 4% (ATV) VS. 10% (ATV/r) Lipid Profile improved with ATV TG: 163 mg/dl (ATV) vs 160 mg/dl (ATV/r) at w 36 123 mg/dl (ATV) vs. 153 mg/dl at w 84	84 weeks
ASSURE [14]	TDF/FTC + ATV/r	ABC/3TC + ATV	Hyperbilirubinemia: 30% (TDF/FTC+ATV/r) vs. 13% (ABC/3TC+ATV arm) Lipid levels similar between treatment groups and varied little between baseline and Week 24. HDL increased significantly from baseline (median change +3 mg/dL) in the ABC/3TC+ATV arm Glomerular filtration similar between groups, with a small median increase of 1 mL/min/1.73/m^2 in the ABC/3TC+ATV arm at w 24. B_2-microglobulin/creatinine ratio declined by 58% (ABC/3TC+ATV) while unchanged (TDF/FTC+ATV/r) Improvement in bone biomarkers (ABC/3TC+ATV arm) while unchanged (TDF/FTC+ATV/r arm)	24 weeks

Table 2. Summary of trials related to switching between NRTIs

Study [ref]	Switch		Reason to switch/Main outcomes	Follow up
	From	To		
[23]	d4T or AZT-containing regimes	TDF or ABC	Simplification (compact once-daily regimen) Limb fat mass increase 329 g vs. 483 g in TDF and ABC arms	48 weeks
MITOX [5]	d4T or AZT-containing regimes	ABC	Significant increase in limb fat (ABC) compared with d4T or AZT arms (0.39 vs. 0.08 kg).	24 weeks
[31]	ABC/3TC/EFV	EFV/FTC/TDF	Significant improvements in lipid parameters in TDF/FTC arm: LDL (−0.47 mmol/L, HDL (−0.15 mmol/L, triglycerides (−0.43 mmol/L, and non-HDL (−0.56 mmol/L).	12 weeks
[35]	ABC/3TC + LPV/r	TDF/FTC + LPV/r	Significant improvements lipid parameters in for TDF/FTC arm: median change from baseline -0.73 mmol/l. No change for ABC/3TC. Between groups difference: -0.82 mmol/l.	12 weeks
OsteoTDF Study [36]	TDF	ABC	Increase of BMD in patients with osteopenia or osteoporosis. No difference between groups. Hip BMD: + 2.1% (ABC) vs. 0.7% (TDF). Lumbar spine BMD: -0.7% (ABC) vs. -1.2% (TDF)	48 weeks
[9] GS-US-292-0109	TDF-containing regimes	TAF/EVG/COBI/FTC	Patients on TDF had an increase of creatinine of 1.77 µmol/L. GFR values increased in the TAF arm (median 1.2 mL/min) compared with TDF group (–3.7 mL/min). Hip BMD improved by 1.47% (TAF) while decreased by -0.34% (TDF).	96 weeks
[49] GS-US-292-0112	Any regimen	TAF/EVG/COBI/FTC	Patients with renal failure: TAF-containing regimes are safe (include patients with mild or moderate renal impairment, without dose adjustment)	96 weeks

Table 3. Summary of trials related to switching between NNRTIs

Study (ref)	Switch type		Reason to switch / Main outcomes	Follow up
	From	To		
[58]	EFV/FTC/TDF	RPV/FTC/TDF	Improvement of CNS side effects of EFV in switched patients. Median total CNS score improved from 40 at baseline to 12 at w 4. Median total SQ (sleep questionnaire) improved from 30 at baseline to 19 at w 4 and to 16 at w 12.	24 weeks
[59]	2NRTI/EFV	2NRTI/ETR	Significant reduction in overall CNS adverse events. Proportion of patients with any CNS adverse event (89 to 60%), grade 2-4 insomnia (63 to 37%), abnormal dreams (57 to 20%) and nervousness (29 to 9%)	12 weeks
[60]	EFV	ETR	Improvement in lipid profile. Median plasma cholesterol levels decreased by 0.7 mmol/l. No difference in CNS side effects	12 weeks
[62]	EFV-based therapy	RPV-based therapy	Improved lipid profiles in patients with dyslipidemia. Significant decrease in total cholesterol (-28.06 mg/dL), LDL (-20.96 mg/dL), HDL (-5.11 mg/dL), and triglyceride (-29.79 mg/dL) levels	24 weeks

Supplemental table 1. Summary of trials related to switching from a PI-based regime to an NNRTI-based regime

Study [ref]	Switch type		Main outcomes	Follow up
	From	To		
[66] NCT00365612	PI-based regime	EFV/FTC/TDF	Simplification (compact once-daily regimen) CNS adverse events occurred in 5% (EFV/FTC/TDF) vs. 1% in baseline regime patients. Decrease in fasting triglycerides (EFV/FTC/TDF) vs. baseline regime arm (-2 vs. -3 mg/dL)	48 weeks
[69]	PI-based regime	NVP-based regime	Simplification No significant change in the lipid profile. NVP-based therapies had more discontinuations because of liver toxicity than PI-based therapies (7 vs. 0%)	Meta-analysis. At least 24 weeks
[70]	PI-based regime	NVP-based regime or EFV-based regime	Simplification No significant differences in lipid profile and % of patients with lipoatrophy	48 weeks
LipNEFA study [71]	PI-based regime	NVP-based or EFV-based or ABC-based regime	Simplification Better lipid profile: HDL-c levels increased (EFV, 15%; NVP, 21%) and TC to HDL-c ratios decreased (EFV, 14%; NVP, 19%). Effect not observed in the ABC arm	96 weeks
[72]	PI-based regime	NVP-based regime	Simplification Reduction of the mean cholesterol levels from baseline 24.2% (first year), 25.8% (second year), and 24.5% (third year). Patients who had triglyceride levels > 400 mg/dL, had a 74.8% reduction (1^{st} year), 76.5% (2^{nd} year), and 74.2% (3^{rd} year)	54 months
SPIRIT study [73]	PI/r-based regime	RPV/FTC/TDF	Simplification (compact once-daily regimen) Improvement in lipid profile. Decrease in total cholesterol (-25 mg/dL), LDL (-16mg/dL), triglycerides (-53mg/dL) and HDL (-6mg/dL) There were no signature toxicities or treatment-limiting side effects associated with this switching.	48 weeks

Supplemental table 2. Summary of trials related toswitching from a PI-based regime to an INSTI-based regime

Study [ref]	Switch		Reason to switch/Main outcomes	Follow up
	From	To		
SPIRAL study [74]	PI/r	RAL	TG > 200mg/dL: 14.6% (RAL) vs. 28.9% (PI) Total cholesterol > 240mg/dL: 3.7% (RAL) vs. 17.2% (PI/r)	48 weeks
SWITCHMRK 1 and 2 study [75]	PI/r	RAL	Total cholesterol: –12.6% (RAL) vs. 1% (PI/r) Non-HDL cholesterol: –15% (RAL) vs. 2.6% (PI/r) Triglycerides: –42.2% (RAL) vs. 6.2% (PI/r)	24 weeks
STRATEGY-PI study [79]	IP/r-based regime	TDF/FTC/COBI/EVG	Simplification (compact once-daily regimen) Improvement in lipid profile.	96 weeks
NEAT22 study [84] NCT02098837	PI/r	DTG	Study is ongoing. Aims to evaluate changes in cardiovascular risk	48 weeks

Supplemental table 3. Summary of trials related to switching from an NNRTI-based regime to an INSTI-based regime

Study [ref]	Switch type		Main outcomes	Follow up
	From	To		
STRATEGY-NNRTI study [7]	NNRTI (EFV as commonest drug) + FTC/TDF	EVG/COBI/FTC/TDF	Simplification (compact once-daily regimen) Improvement in CNS symptoms after switching: Anxiety from 49% to 32% at week 4 Dizziness from 37 to 23% at week 48 Vivid dreams from 64 to 35% at week 48 Nightmare from 44 to 20% at week 48 Weird or intense dreams from 61 to 32% at week 48.	96 weeks
SWITCH-ER study [85]	EFV	RAL	Significant decrease in anxiety and stress scores (DASS questionnaire) favoring RAL (median, -2). Cholesterol levels decreased by 0.4 mmol/l, triglycerides by 0.2 mmol/l and low-density lipoprotein by 0.2 mmol/l.	4 weeks

Supplemental table 4. Summary of trials related to switching NRTI to INsTI

Study [ref]	Switch		Main outcomes	Follow up (weeks)
	From	To		
TROP study [86]	TDF/FTC + PI/r	RAL + PI/r ± 3TC	Spine BMD increased by 3.0% and left total hip BMD increased by 2.5%. Markers (N-telopeptide, osteocalcin and bone alkaline phosphatase) all decreased significantly at week 24.	48 weeks

Supplemental table 5. Comparison between studies involving INsTI in terms of probability of discontinuation and advantages and disadvantages in terms of toxicity

Study [ref]	Switch	Treatment discontinuation	Switch advantages	Toxicity
SWITCHMRK 1 study [66]	LPV/r to RAL	• Switch arm 25 (14.1%): • lack of efficacy = 3, • Adverse events 7, • Consent withdrawal/lost follow up = 9 • Other reasons = 6 • Control arm: 17 (9.7%): • Lack of eficacy = 1 • Adverse events = 3 • Consent withdrawal/lost follow up = 10 • Other reasons = 3	Combined switchmrk 1 & 2 Beter lipid profile in RAL group: TC: -12.6% vs. 1% TG: -42% vs. 6.2% LDL and HDL similar in both arms	Combined switchmrk 1 & 2: • Diarrhoea (at least moderate): 10 patients (3%) in LPV/r group and no patients in RAL • Discontinuation because of adverse events in RAL group: 6 patients (1 hyper sensitivity, 1 mild diarrhoea, 1 acute stress disorder, 1 adverse drug reaction, 2 hepatotoxicity • Discontinuation because of adverse events in LPV/r group: 4 patients (1 vomiting, 1 upper abdominal pain, 1 pulmonary tuberculosis, 1 diarrhoea associated with an increaded creatinine). • Grade 3 or 4 laboratory abnormalities were infreqüent and generally balanced between groups
SWITCHMRK 2 study [66]	LPV/r to RAL	• Switch arm: 10 (5.7%): • Lack of efficacy = 4 • Adverse events = 0 • Consent withdrawal/lost follow up = 3 • Other reasons = 3 • Control arm: 6 (3.4%): • Lack of efficacy =2 • Adverse events = 0 • Consent withdrawal/lost follow up = 2 • Other reasons = 2		
SPIRAL study [65]	PI/r to RAL	• Switch arm: 13 patients (9%) • Adverse evenets = 3 • Virological failure = 2 • Lost to follow up = 1 • Consent withdrawal = 5 • Other reasons = 2 • Control arm: 14 patients (10%)	Triglycerides > 200mg/dL: 14.6% (RAL) vs. 28.9% (PI) Total cholesterol > 240mg/dL: 3.7% (RAL) vs. 17.2% (PI/r)	• The incidence of adverse events was similar in RAL (n=78, 55%) and in PI/r groups (n=79, 56%). • Serious adverse events was similar in both groups (n=6, 3 drug-related, 4% in RAL vs. N = 5, 1 drug-related, 4% in PI/r.

		• Adverse evenets = 3 • Virological failure = 2 • Lost to follow up = 4 • Consent withdrawal = 4 • Other reasons = 4		
STRATEGY-NNRTI study [7]	NNRTI (mainlyEFV) + FTC/TDF to EVG/COBI/FTC/TDF	• Switch arm: 22 patients (8.1%) • Consent withdrawal = 9 • Adverse event = 6 • Protocol violation = 6 • Investigator discretion = 2 • Lost to follow up = 1 • Control arm: 18 patients (14.4%): • Consent withdrawal = 13 • Adverse event = 1 • Protocol violation = 1 • Investigator discretion = 1 • Lost to follow up = 2	Improvement in CNS symptoms after EFV discontinuation. Anxiety from 49% to 32% at w 4 Dizziness from 37% to 23% at w 48 Vivid dreams from 64% to 35% at w 48 Nightmare from 44 to 20% at w48 Weird/intense dreams from 61 to 32% at w 48.	• Switch group: 237 patients (81%) with adverse events (grade 3-4 n=19, 7%; serious adverse events n=14, 5%), 1 death (<1%) • Control group: 107 patients (75%) with adverse events (grade 3-4 n=9, 6%; serious adverse events n=6, 4%). • Adverse events that caused drug discontinuation were uncommon in both groups: causes in the switch group were arthralgia, coccydnia, paraesthesia, muscle atrophy, and hypoaesthesia, suicide (1), dysgeusia (1), prurigo (1), acquired Fanconi's syndrome (1), and increased blood creatinine (1); the cause in the no-switch group was altered mood (1)
STRATEGY-PI study [70]	IP/r-based regime to TDF/FTC/COBI/EVG	• Switch arm: 25 patients (8.5%) • Protocol violation = 9 • Consent withdrawal = 6 • Adverse events = 6 • Lost to follow up = 2 • Pregnancy = 2 Control arm: 26 patients (18.5%): • Protocol violation = 4 • Consent withdrawal = 8 • Adverse events = 2 • Lost to follow up = 5 • Pregnancy = 1	Improvement in lipid profile. Triglycerides fell in the switch group (-0.33 mmol/L), whereas they did not change in the control group.	• Switch group: 237 patients (79%) with adverse events (grade 3-4 n=12, 4%; serious adverse events n=17, 6%). • Control group: 104 patients (74%) with adverse events (grade 3-4 n=9, 6%; serious adverse events n=6, 4%); 1 death, <1%). • Adverse events ocurring in at least 5% of participants in either group: nasopharyngitis 12% vs 10%(switch vs no-switch), upper respiratory tract infection 8 vs 4%, diarrhoea 7 vs 8%,

		• Investigator's discretion = 3 • Non-compliance = 3		nàusea 7 vs 3%, headache 6% in both, anxiety 6 vs 4%, back pain 5 vs 1%, cough 5 vs 3% depression 4 vs 6%, insomnia 3 vs 5%.
STRIIVING study [78]	PI, INsTI or NNRTI based regimes to ABC/3TC/DTG	• Switch arm: 35 patients (13%): • Virologic failure = 0 • Adverse event = 10 (4%) • Protocol deviation = 15 (5%) • Lost to follow-up = 3 (1%) • Inventigator discretion = 3 (1%), • Consent withdrawal = 4 (1%) • Control arm: 32 patients (12%) • Virologic failure = 0 • Protocol deviation = 17 (6%), • Lost to follow-up = 3 (1%) • inventigator discretion = 3 (1%) • Consent withdrawal = 9 (3%)	Treatment satisfaction scores increased in both groups, with a statistically significant difference favoring ABC/3TC/FTG	• Switch group: 180 any adverse event (65%), 11 grade 3-4 adverse event (8%), 6 serious adverse event (2%) • Control group: 124 any adverse event (45%), 5 grade 3-4 adverse event (2%), 5 serious adverse event (2%) • Adverse events ocurring in at least 5% of participants in either group: cough 5% vs 3% (switch vs no-switch), diarrhoea 7% vs 1%, fatigue 7% vs 1%, headache 5% vs 1%, nàusea 10% vs 1%, upper respiratory tract infection 7% vs 7%
NCT01815736 [9] GS-US-292-0109	TDF-containing regimes to TAF/EVG/COBI/FTC	• Switch group: 32 patients (3.3%) • Adverse event = 9 • Death = 4 • Lack of efficacy = 1 • Investigator discretion = 2 • Consent withdrawal = 8 • Lost t follow up = 6 • Non-compliance = 2 • Control group: 40 patients (8.3%) • Adverse event = 12 • Consent withdrawal = 16 • Lost t follow up = 7 • Non-compliance = 2 • Investigator's discretion = 3	Patients on TDF had a creatinine increase of 1.77 µmol/L. GFR values increased in the TAF group (median 1.2 mL per min) compared with TDF group (–3.7 mL per min). Hip BMD improved by 1.47% from baseline in TAF group while it was reduced by -0.34% in TDF group.	• Switch group: 828 patients (86%) with adverse events (21% drug-related adverse event; grade 3-4 n=84, 9%; serious adverse events n=65, 7%). • Control group: 399 patients (84%) with adverse events (16% drug-related adverse event; grade 3-4 n=54, 11%; serious adverse events n=35, 7%). • Most common adverse events: upper respiratory tract infection 16 vs 11% (switch vs no switch), diarrhoea 10 vs 9%, nasopharyngitis 9 vs 8%, headache 7 vs 4%, cough 7 vs 5%, insomnia 5 vs 6%, arthralgia 6 vs 5%, bronchitis 6 vs 5%, depression 4 vs 6%, osteopenia 6 vs 5%, back pain 5% in both, nàusea 5 vs 3%, sinusitis 5% in

				both groups.

Supplemental table 6. Summary of related to switching trials from PI, INsTI or NNRTI based regime to ABC/3TC/DTG

Study [ref]	Switch type		Main outcomes	Follow up
	From	To		
STRIIVING study [88]	PI, INsTI or NNRTI based regimes	ABC/3TC/DTG	Simplification Treatment satisfaction scores increased in both groups, with a statistically significant difference favoring ABC/3TC/FTG	24 weeks
STRIIVING sub-study [89]	PI, INsTI or NNRTI based regimes	ABC/3TC/DTG	Simplification Inflammation biomarkers improved after switch: greater declines in I-FABP (-37%) and in sCD14 (-6%). No worsening of markers associated with cardiovascular disease was observed after switch.	24 weeks