A Comprehensive Development Agenda on Tenofovir Alafenamide in Clinical Practice

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Abstract

The introduction of tenofovir (TFV) alafenamide (TAF) into clinical practice will be a further revolution in antiretroviral therapy. Currently available HIV-1 regimens are wide enough to allow diversified usage in different settings. Despite the fact that TAF is not capillary accessible, even in industrialized countries, ultimate International Guidelines have already included TAF in backbone or in single-tablet regimens. Due to a better safety profile, TAF will progressively replace TFV disoproxil fumarate, both in naïve and experienced patients. However, therapeutic innovations have to deal with budget constraints and different global spending-review patterns. The aim of this article is to give a comprehensive agenda of TAF use in naïve and experienced HIV-1 infected patients, providing a full review of the studies present in the literature and contextualizing these findings into daily clinical practice. (AIDS Rev. 2018;20:75-82)

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Key words

Tenofovir alafenamide. Tenofovir disoproxil fumarate. Combination antiretroviral treatment. Antiretroviral strategies.

Introduction

The combination antiretroviral treatment (cART) regimens containing tenofovir (TFV) alafenamide (TAF), the novel pro-drug of the nucleotide reverse transcrip-

tase inhibitor (NRTI) TFV, are recommended for the treatment of naïve and experienced patients by national and international guidelines^{1,2}.

Since its introduction, TAF has demonstrated high efficacy and tolerability in the treatment of people living

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Received in original form: 28/08/2017
Accepted in final form: 19/02/2018
DOI: 10.24875/AIDSRev.M18000017

with HIV (PLWHIV) when used in combination with other antiretroviral agents³⁻⁵. TAF, due to lower circulating levels of TFV, but higher concentrations of its metabolically active form TFV-DP, inside lymphoid cells, ensures a better safety profile compared to TFV disoproxil fumarate (TDF) and may play a key role in reducing bone and renal cART-related toxicity in PLWHIV⁶⁻⁸.

In Europe, in a short-time have been launched on the market two different single-tablet regimen (STR) containing TAF (elvitegravir [EVG]/cobicistat [c]/emtricitabine [FTC] and rilpivirine [RLP]/FTC) and a fixed dose containing FTC/TAF, and other TAF-based combinations will be launched in the near future (Table 1).

In antiretroviral naïve patients and antiretroviral experienced patients already in TDF-based regimen, TAF will replace TDF progressively when patients are linked to care. There are more than 35 million PLWHIV and 15 million are receiving cART⁹; the majority of them is on treatment with TDF in combination with FTC or lamivudine¹⁰, therefore, to avoid excessive costs, to minimize long-term cART related side effects and to guarantee a further treatment option in all patients, it should be suggested to prioritize switching strategies from TDF to TAF. In the near future, even experienced patients currently treated with TDF-free regimen may benefit of switching to TAF.

The aim of this review is to give a comprehensive agenda of TAF use in naïve and experienced HIV-1 infected patients.

What is TAF?

TAF, originally named GS-7340, is a novel NRTI, pro-drug of TFV, with a more stable blood and plasma pharmacokinetic profile that allows targeted intracellular accumulation of TDF and consequent phosphory-

lation to the active metabolite TFV-DP Figure 1⁶. Due to higher intracellular levels of TFV-DP and lower circulating levels of TFV compared to TDF, TAF has shown a more favorable pharmacological profile and a higher antiviral activity at lower doses than its parent drug¹¹. Moreover, due to lower circulating levels of TFV, TAF minimizes the short- and long-term impact on estimated creatinine clearance, renal tubular proteinuria, and bone mineral density (BMD), thus, certifying its superiority compared to TDF¹².

In vitro studies have demonstrated a higher inhibitory quotient of TAF than TDF, the implication of this on clinical practice may result in the potential of TAF to inhibit HIV-1 viruses resistant to TDF¹³.

Initial cART with TAF-based regimen in naïve patients

TAF-based options for initial cART in naïve adults patients include an STR with E/c/FTC/TAF, or dolutegravir (DTG) plus the backbone with FTC/TAF or raltegravir (RAL) plus FTC/TAF or in patients with HIV-RNA load < 100,000 copies/mL, and CD4+ cell count > 200 cells/mm³ a rilpivirine based STR (RPV/FTC/TAF)²⁻¹⁴.

E/c/FTC/TAF, named Genvoya[®] by Gilead Sciences, was approved by FDA and by EMA in November 2015 in naïve adults and adolescent patients (12 years and older and of at least 35 Kg body weight)^{15,16}, in this STR the TAF dose is 10 mg. RPV/F/TAF, named Odefsey[®] by Gilead Sciences, was approved by FDA in March 2016, and by EMA in April 2016, for the use in adults and adolescents (aged 12 years and older with body weight at least 35 kg) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor class (NNRTI), TDF or FTC and with a VL ≤ 100,000 copies/mL.^{17,18} RPV/FTC/TAF

Table 1. TAF cascade in Europe

Drug	EMA approved	Therapeutic area	Study patients
EVG/c/FTC/TAF	November 2015	HIV	Naïve and experienced
FTC/TAF (25 mg or 10 mg)	April 2016	HIV	Switch studies
RPV/FTC/TAF	June 2016	HIV	Bioequivalence
TAF	January 2017	HBV	Naïve and experienced
Darunavir/c/FTC/TAF	na	HIV	Naïve
Bictegravir/FTC/TAF	na	HIV	Naïve

Figure 1. Mechanism of action for tenofovir disoproxil fumarate and tenofovir alafenamide.

contains 25 mg of TAF. The new backbone combination FTC/TAF, named Descovy® by Gilead Sciences, was approved by FDA and by EMA in April 2016 in combination with other antiretroviral agents in adults and adolescents patients (12 years of age and older)^{3,19}. Descovy may be used either with 25 mg (when an unboosted third agent is associated) or 10 mg of TAF. In the next future, a new STR containing darunavir 800 mg/c/FTC/TAF, by Janssen-Cilag International NV, will be available²⁰. This new fixed-dose combination contains 10 mg of TAF.

Why a TAF-based regimen in naïve patients?

Efficacy and safety of TAF compared to TDF have been established, creating the necessary conditions for the transition to the new backbone with FTC/TAF^{21,22}.

The first two clinical efficacy trials that compared TAF with TDF, in naïve patients, were two controlled, double-blind phase 3 noninferiority studies, registered on ClinicalTrials.gov, numbers NCT01780506 and NCT01797445²³. 1,733 treatment naïve patients with an HIV-RNA > 1,000 copies/mL, no resistance to E, FTC and TDF in GRT and estimated glomerular filtration of 50 mL/min or higher from 178 outpatient centers in 16 countries were randomly assigned E/c/FTC/TAF (866 patients) or E/c/FTC/TDF (867 patients). The primary outcomes were the percentage of patients with HIV-RNA < 50 copies/mL at week 48, as defined by the FDA snapshot analysis (noninferiority margin of 12%) and renal and bone safety endpoints at week 48. After

48 weeks of treatment, efficacy profiles were comparable with a HIV-RNA < 50 copies/mL in more than 90% of patients in the E/c/F/TAF arm (differences 2.0%, 95% confidence interval [CI] - 0.7-4.7%). E/c/F/TAF noninferiority was also observed in relation to HIV-RNA < 20 copies/mL with very high 96 weeks virologic suppression rates (84.4%: differences 0.4%, 95% CI: -3.0-3.8% and 81.5%: differences 1.5%, 95% CI - 2.2-5.2%), respectively. At week 48, the mean CD4 count increase was higher in the TAF based regimen arm: 230 cell/mm³ versus 211 cell/mm³ ($p = 0.024$). Virological failure occurred in 4% of HIV-infected patients in each treatment arm, and resistance in 7 patients (0.8%) in the TAF-based regimen arm versus 5 (0.6%) in the TDF based arm. At week 96, the results were confirmed (86.6% in TAF arm vs. 85.2% in TDF based arm with HIV-RNA < 50 copies/mL; difference 1.5%, 95% CI - 1.8-4.8%). The adverse event rates through 96 weeks were similar in two groups, and most events reported were mild or moderate. However, renal side effects were decreased in the E/C/F/TAF arm with a median increase of serum creatinine of 0.08 for the TAF arm compared to 0.12 mg/dL in the TDF arm ($p < 0.0001$) and a median % change in proteinuria of -3 in the TAF arm compared to 20 in the TDF arm ($p < 0.0001$). In the TAF arm, a significant smaller decrease in BMD at spine and hip was noticed after 48 weeks of therapy²³. Furthermore, no cases of proximal tubulopathy for TAF were noticed, while four cases in the TDF arm. The safety and efficacy were preserved after 144 weeks of therapy²⁴.

Similarly, fixed-dose STR containing TAF/FTC has been studied in a randomized, double-blinded multi-

center active-controlled study (ClinicalTrials.gov, number NCT01565850). 232 treatment-naïve adults were screened, 153 were randomized 2:1 to Darunavir/c/F/TAF ($n = 103$) versus Darunavir/c + F/TDF ($n = 50$). At both weeks 24 and 48, there were no significant differences in virologic suppression: 76.7% on TAF versus 84.0% on TDF by pre-specified subgroup analyses by demographic and disease characteristics, or adherence.

The AMBER study registered at clinicaltrials.com as NCT02431247 is evaluating noninferiority in efficacy and safety of darunavir/c/FTC/TAF fixed-dose combination versus darunavir/c/FTC/TDF in naïve patients²⁵.

The TAF arm had significantly improved renal and bone safety parameters: less proteinuria and less change in hip and spine BMD, consistent with results from a similarly designed study of the E/c/F/TAF^{26,27}. Moreover, long-term safety, durability as well as tolerability make TAF/FTC based regimen a favorable and desirable choice for initial cART with a low risk of developing drug resistance¹⁴⁻³⁰. To date, studies are ongoing in naïve patients evaluating the efficacy and safety of TAF in fixed-dose combination with FTC and a novel INSTI, named bictegravir (GS-9883), compared to TAF/FTC plus DTG³¹.

This recommendation follows the fact that TAF/FTC, as just recalled, has shown non-inferior efficacy as compared to TDF/FTC in combination with EVG/cobicistat and, in a smaller study, with darunavir/cobicistat. Given these results and the reduced renal and bone toxicity, this combination should be preferred to TDF/FTC for all first-line regimens, particularly, those with a boosted protease inhibitor or integrase inhibitor as third agent. Compared with the other nucleoside fixed-dose combination available on the market (i.e. lamivudine [3TC]/abacavir [ABC]), TAF/FTC should be evaluated on the assumption that TDF/FTC is a different prodrug of TFV, with the same active compound involved (even though with much lower concentrations in plasma and 2.5 times higher in cells). While some data may be still conflicting, recent reviews on different initial ARV regimens pointed out that TDF/FTC may have higher efficacy than 3TC/ABC³². Furthermore, the on-going signal of an increased cardiovascular risk in patients taking an ABC-containing regimen beyond and in addition to the well known D:A:D analyses³³ makes the FTC/TAF option the safest as far as the NRTIs are concerned.

To date, according to current available data, TAF should be part of cART starting regimens in all naïve patients, with specific consideration to the people over the age of 50.

cART optimization with TAF-based regimens in experienced patients

Inexperienced patients, efficacy, and safety of TAF compared to TDF have been established^{34,35}. The first randomized, double-blind, controlled study that explored the efficacy and safety of switching to a TAF/FTC based backbone in combination with a third agent (boosted protease inhibitor, integrase inhibitor, or NNRTI), from TDF/FTC in combination with a third agent, showed noninferiority at 48 weeks, with 94% of patients in the TAF group being virologically suppressed compared with 93% in the TDF group (difference 1.3%, 95% CI - 2.5-5.1)³⁴. Moreover, in the same study, with 333 treated in the TAF group and 330 in the TDF group, a low drug discontinuation rate due to adverse events (2.1% in TAF group compared to 0.9% in the TDF group) and no cases of proximal renal tubulopathy in either group proved the durability of FTC/TAF as a backbone and its suitability for future switching strategies regardless the chosen third agent³⁴.

The fixed-dose combination of E/c/FTC/TAF is indicated for simplification strategies in virologically suppressed patients (HIV-1 RNA < 50 copies/mL) for at least 6 months, with no history of treatment failure or resistance to its individual components^{15,16}; this switching strategy ensures high rate of efficacy and improvement in proteinuria, albuminuria, and BMD⁵. This option can be safely applied in patients with mild (eGFR 50-69 mL/min) or moderate (eGFR 30-49 mL/min) renal impairment without dose adjustment⁵. Likewise, studies 1216 and 1160 are evaluating efficacy and safety of a switching strategies from RPV/FTC/TDF (the first) or EFV/FTC/TDF (the latter) to RPV/FTC/TAF in adults virologically suppressed (HIV-1 RNA < 50 copies per mL) for at least 6 months and with creatinine clearance > 50 mL/min. At week 48, preliminary results showed the switching to RPV/FTC/TAF was well tolerated, with a high rates of virological suppression (> 94%) and with a statistically significant ($p < 0.001$) decrement of total and tubular proteinuria as well as an increment in BMD at hip and spine³⁵.

TAF does not exhibit OAT-dependent cytotoxicity, and it does not accumulate in renal proximal tubules in an OAT-dependent manner, thus justifying the potential benefit on renal function compared to TDF³⁶. Moreover, a meta-analysis by Wang et al., including data from six different trials, highlighted the lower decrease in eGFR_{CG} and a lower increase of serum creatinine in the TAF group compared to TDF⁴. Renal tu-

bular proteinuria (retinol binding protein/creatinine and b-2-microglobulin/creatinine) was markedly increased in the TDF group, while this trend was reverted in the TAF group⁴. An on-going trial, registered as NCT02881320, is currently evaluating safety and efficacy in virologically suppressed children and adolescent of Bictegravir/FTC/TAF³⁷.

Why TAF-based regimen in experienced patients?

Patients with stable HIV-RNA suppression, chronic kidney disease (CKD), comorbidity, with an high medication-related burden are all suitable to switch from a TDF based regimen with INSTI or boosted protease inhibitors to a TAF based STR, to ensure long-term benefit on renal function and urinary markers of proximal tubulopathy as well as a significant improvement of BMD^{38,39}.

Even in adult patients with mild to moderately impaired renal function (glomerular filtration rate, GFR, between 30 and 69 mL/min), E/c/FTC/TAF regimen has shown stable and durable improvement of proteinuria and albuminuria³⁸.

Due to provide safety and efficacy, TAF should be promptly considered for efficient switching strategies in all experienced patients currently on treatment with FTC/TDF FDC and E/c/FTC/TDF. An on-going study, named NCT02469246, aims to evaluate the efficacy, safety, and tolerability of switching ABC/3TC to FTC/TAF versus maintaining ABC/3TC in virologically suppressed adults and may expand indications for future switching strategy to TAF⁴⁰.

Altogether, these data suggest that switching from TDF to TAF in treatment-experienced patients should minimize the risks of renal impairment and bone mass loss that affect regimens based on TDF; they also suggest that switching from TDF to TAF, not only minimizes these risks but also improves renal tubular function and bone mass density in patients with current, drug-related, unapparent renal and bone damage.

Looking in perspective, the availability of TAF for many simple (often STR) regimens could prompt physicians to switch back to triple standard regimens patients who, because of renal or bone toxicity, were switched in the past to dual regimens; however, this option should be explored in clinical trials before it can be routinely implemented in clinical practice.

Inexperienced patients, TAF should be preferred if the eGFR is decreased more than > 5 mL/min and/or the eGFR is < 60 mL/min. Likewise, osteoporotic pa-

tients and postmenopausal woman should benefit of TAF based regimen.

TAF-based regimen in heavily treatment-experienced patients

Even in heavily treatment-experienced adults, with a high pills burden, a E/c/FTC/TAF plus darunavir 800 mg can reduce the daily intake of pills, improving quality of life and renal function as well as maintaining efficacy and durability⁴¹. In a phase 3, open-label, randomized multicenter study, participants were enrolled if were two virological failure and confirmed resistance by historical genotype to at least two different classes of antiretrovirals, no history of INSTI resistance or be INSTI naïve, or be currently suppressed following INSTIs. The primary endpoint was the percentage of participants with HIV-RNA < 50 copies/mL at week 24 using the US-FDA snapshot algorithm.

Treatment with E/c/FTC/TAF plus darunavir resulted in high rates of virologic suppression (94% in new regimen arm vs. 76% in maintaining cART arm with HIV-RNA < 50 copies/mL; difference 3.5%; 95% CI -3.5% to 33%, $p = 0.04$). Most adverse events were mild or moderate in severity, and no participants discontinued study drug because of an adverse event. No participants had any serious renal adverse event nor discontinued study drugs because of a renal event.

TAF-based regimen use and metabolic profile

The advents of TAF imply the need to study its metabolic impact, which will need to be considered in PLHIV with diverse baseline cardiovascular risk profile.

The metabolic parameters reported in five RCTs^{12,23-27,34-42} during 48 weeks of therapy showed increased fasting lipid from baseline in the TAF group compared with the TDF group. There were significant differences between the TAF group and the TDF group in the mean changes in total cholesterol (33 vs. 12 mg/dL, $p = 0.014$) and HDL (7 vs. 3.3 mg/dL, $p = 0.008$), whereas no statistically significant differences between groups were observed in LDL (20 vs. 4.5 mg/dL, $p = 0.124$), triglycerides (24 vs. 1.5 mg/dL, $p = 0.111$), and total cholesterol/HDL ratio (0.1 vs. 0.0, $p = 0.435$) in the naïve patients. Moreover, for experienced patients, there were significant differences between the TAF group and the TDF group in the mean changes in total cholesterol (17 vs. 1.5 mg/dL, $p = 0.036$) and triglyceride (10.5 vs. -2 mg/dL, $p = 0.002$), where-

as no significant differences between groups were observed in LDL (11 vs. 1 mg/dL, $p = 0.109$), HDL (2 vs. 0 mg/dL, $p = 0.184$), and total cholesterol/HDL ratio (0.15 vs. 0.0, $p = 0.095$). These results underline that TAF is lipid-neutral and do not share the “statin-like” phenomenon which characterized TDF.

Nevertheless, CVD prevention cannot be limited to antiretroviral switching versus metabolic friendly drugs but rather introducing statin as a key strategy for cardiovascular risk reduction.

During the aforementioned studies, 5.7% of all participants in the TAF group and 4.0% of all participants in the TDF group started lipid-lowering drugs, and no statistically significant difference was found between the groups.

TAF-based regimen use to help BMD

TAF, regardless BMD reduction at baseline, should be preferred in naive patients as first-regimen to slow diminution in BMD during the following years of treatment. Likewise, due to the reversible nature of the loss bone mass, TAF should be used for switching strategies, disregarding previous cART regimens, both in osteopenia/osteoporotic patients and patients with a consistent BMD reduction greater than physiologically expected. Moreover, adolescents with HIV infection that has not reached the BMD peak yet, may remarkably benefit of TAF based regimen.

TAF-based regimen use to preserve renal function

In the light of the data showed above, the switch to TAF is, nowadays, mandatory in patients with overt renal impairment, documented by eGFR between 30 and 60 mL/min (i.e., CKD Stage III-V), albuminuria, or signs of proximal renal tubular impairment (low molecular weight proteinuria, hypophosphatemia/hyperphosphaturia, normoglycemic glycosuria, and hypouricemia/hyperuricuria), or in patients with a rapid decline of eGFR, although within the normal ranges. However, regardless the renal function, this switch should be also considered in patients with normal renal function but presenting risk factors for kidney diseases such as diabetes, high blood pressure, coinfection with hepatitis viruses, and ART with atazanavir or lopinavir. Moreover, elderly patients should be considered for a switch to TAF. A switch performed before the onset of an eGFR decline in patients at risk could be of strategic importance, considering that in a certain percent-

Table 2. Proposed Agenda for TAF based of patients

When should you definitely use TAF over TDF?

- Patient with low BMD, osteoporosis on DEXA a high risk of major fracture as determined by FRAX.
- Patient with eGFR between 30 and 90 mL/min or evidence for proximal tubular dysfunction (e.g., proteinuria) or renal toxicity or other intolerance secondary to TDF
- Older adults
- When the switch is cost-neutral

When should you definitely not use TAF?

- Patient on rifamycin, phenobarbital, carbamazepine
- Pregnant women
- Pre-exposure prophylaxis
- Patients with CKD Stage 4 or 5
- Patients with proven or suspected resistance to the component drugs in any TAF-containing FDC or STR

age of patients the TDF-related renal toxicity is incompletely reversible⁴³.

The benefits of a shift in preventing renal disease in patients with normal kidney function are less clear and, at present, we have no data to support a possible substitution of TDF with TAF in this case.

Conclusions

With the advent of effective cART, steady viral suppression has become a common event⁴⁴, and the lifespan of PLWHIV has expanded^{45,46}. The spectrum of diseases experienced by PLWHIV has changed, too. AIDS-defining events have become rare^{45,47}, while aging with HIV has been linked to non-infectious comorbidities, including cardiovascular disease and hypertension, diabetes mellitus, CKD, osteopenia/osteoporosis, and non-AIDS cancers^{45,46,48}.

Chronic HIV infection appears to exacerbate those pathophysiologic processes associated with aging and to increase vulnerability in PLWHIV compared to demographically similar uninfected individuals⁴⁹.

Despite the improvement of long-term tolerability of currently used antiretroviral drugs, long-lasting cART along with aging presumably act as independent risk factors in determining these heterogeneous comorbidities that tend to aggregate into complex multimorbidity patterns⁵⁰. TAF is a relevant adjunct to the current antiretroviral armamentarium as minimizes the long-term effects of cART both on BMD and on renal function that in the past years acted as potential limiting factors of long-lasting cART. Current evidence indicates that switching TDF to TAF is not just a clini-

Table 3. Proposed Agenda for TAF based on cART regimens

Which patients already treated should change immediately?	
Current cART-based regimen or population	Future cART-based regimen
E/c/FTC/TDF	E/c/FTC/TAF
Boosted PI plus TDF/FTC	boosted PI plus FTC/TAF
Patients coinfecting HBV treated with TDF or entecavir	TAF based regimens
Rilpivirine/FTC/TDF	Rilpivirine/FTC/TAF
Efavirenz/FTC/TDF	Rilpivirine/FTC/TAF
Darunavir/c plus FTC/TDF	Darunavir/c/FTC/TAF
Which patients already treated might expect to change?	
cART-based regimen with virologic success	
Raltegravir plus TDF/FTC	
Dolutegravir plus TDF/FTC	
Boosted PI plus 3TC or FTC	
Dolutegravir plus 3TC	

cally sound option but is an ethically correct approach, too table 3.

The TAF cascade should be different for low-income countries (LIC). In fact, a generic formulation of TDF should become available by early 2018,^{51,52} while FTC/TDF in 2021. The price of generic TDF should be relevant in delaying the introduction of TAF in these countries. However, it is necessary to avoid the same mistake made in the past years with other antiretrovirals (i.e., stavudine) maintained with clear evidence of side effects. This Agenda could also aid to prioritize TAF use in patients living in LIC.

Conflicts of interest

Dr. De Andrea Luca reports grants from ViiV Healthcare, grants from Gilead, personal fees from ViiV Healthcare, personal fees from Gilead, personal fees from Merck Sharp and Dohme, personal fees from Janssen Cilag, outside the submitted work; Dr. Nicola Gianotti

reports grants and personal fees from Gilead Science, during the conduct of the study; Dr. Stefano Rusconi grants and personal fees from BMS, grants, personal fees and non-financial support from ViiV, personal fees from MSD, grants, personal fees and non-financial support from Gilead, grants, personal fees and non-financial support from Janssen, outside the submitted work, Dr. Antonio Di Biagio, Dr. Franco Maggiolo, Dr. Giovanni Guaraldi, Dr. Niccolò Riccardi, Dr. Paolo Maggi, Dr. Renato Maserati, Sergio Lo Caputo and Dr. Marco Borderi have nothing to disclose.

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