Tenofovir alafenamide revisited

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INTRODUCTION

Antivirals belonging to the class of nucleoside/nucleotide reverse transcriptase inhibitors (N/NtRTIs) maintain a pivotal position in the treatment of both HIV and HBV infection [1, 2]. Beyond the historical position of N/NtRTIs as part of any approved antiretroviral combination, the importance of the biosynthetic step inhibited by N/NtRTIs has been highlighted in the last decade by several attempts of developing antiretroviral strategies based on two instead of three drugs. While even a single drug might work in selected circumstances, in most studies only dual regimens including a reverse transcriptase inhibitor (RTI) were found to provide adequate viro-immunological results [3]. A major reason possibly accounting for the need of RTIs in any antiretroviral regimen is that RT activity covers more than 50% of the time required for a complete HIV replicative cycle [4].

The long story of N/NtRTIs started in 1987, when azidothymidine (AZT) was introduced into clinical use for the treatment of HIV infection [5]. Since that time, many other N/NtRTIs have been developed, with consistent improvements in both efficacy and safety. Today, the N/NtRTIs fulfilling the currently required risk/benefit standard for long-term treatment are the cytidine analogues lamivudine (3TC) and emtricitabine (FTC), the adenine analogues pro-drugs of tenofovir, namely tenofovir disoproxil fumarate (TDF) and its newer and safer evolution represented by tenofovir alafenamide (TAF), and the guanosine analog abacavir (ABC) [6].

SUMMARY

Two Tenofovir pro-drugs are available for the treatment of HIV and HBV infection. Tenofovir Alafenamide (TAF) was clinically developed as a safer alternative to the older Tenofovir Disoproxil Fumarate (TDF) as the latter was consistently found to be associated to proximal renal tubule dysfunction and decrease in bone mineral density (BMD). As compared to TDF, the pharmacological properties of TAF are such that a more active drug is delivered into target cells while much less is measurable in general circulation. This translates into an antiretroviral action comparable to TDF with a significantly lower impact on proximal renal tubular function and bone structural integrity. The lipid-lowering effects of TDF as well as its lesser tendency to be associated to undesired body weight increase have raised some doubts about the substitution of TDF with TAF. Both issues, whose genesis is multifactorial, are strictly linked to the hypothesis of increased cardiovascular risk that might follow the switch from TDF to TAF. However, the long-term impact of decreasing renal function on cardiovascular risk must also be considered, especially in aging patients. It is thus a matter of balance: while the action on modifiable behavioural variables may well reduce lipid levels and body weight, the permanent dysfunctional pressure exerted by TDF on the proximal renal tubule could cause irreversible damage to both kidneys and bones. Therefore, all things considered, avoidance of TDF, particularly when aging patients are concerned, appears the preferable approach.

Keywords: Tenofovir, HIV, HBV.

Basic comparative pharmacology of tenofovir pro-drugs

The nature of an antiviral pro-drug entails the need of undergoing molecular transformation in...
order to acquire the chemical structural having the property to inhibit the target replicative step of the sensitive microorganisms. This is to say that two different pro-drugs of the same active molecule will follow different metabolic steps whose final product is the same. In this case the final active moiety is tenofovir (TFV) that undergoes double phosphorylation at the intracellular level where it competes with the natural RT substrate (adenosine-triphosphate) in the chain process of RNA assembly. In the early phases of TFV development it was found that any oral pharmaceutical form of the drug, in order to be absorbed at the intestinal level, requires to be formulated with a salt [7]. In the pioneer work by Lee, the pharmacokinetics of TFV administered intravenously was compared with that resulting from oral administration of TDF and TAF. Intravenous (iv) TFV was given at the dose of 1mg/kg body weight, while TDF and TAF were orally administered at the doses of 300 mg (245 mg of TFV) and 25 mg, respectively. The highest pharmacokinetic exposure of TFV in the plasma, as measured by the AUC (area under the concentration/time curve), was found to be associated to iv administration, while the values achieved by oral intake were 60% and 95% lower with TDF and TAF respectively. However, such hierarchy turned to be the opposite when intracellular TFV diffusion was measured by means of the PBMC/plasma ratio; the latter was equal to 1 in case of IV administration, while TDF oral intake led to a value of 5 and a PBMC/plasma ratio as high as 140 was measured in case of TAF oral intake (8). These numbers clearly suggest a much higher intracellular penetration of TFV when orally administered as TAF, as also testified by the ten and thousand times lower in vitro EC50 of TAF when compared respectively to oral TDF and iv TFV [8]. The reason of such dissimilar pharmacokinetic profile and distribution between the two oral TFV pro-drugs lies in the properties of the salts to which the two oral TFV formulations are associated. In case of TDF, soon after intestinal passage most of the disoproxil fumarate salt dissolves from its pharmaceutical link with TFV, thus leaving the latter free to circulate and distribute throughout the vascular network [9]. Following TAF intestinal absorption the link between the alafenamide salt and TFV is much more stable, and only a negligible amount of free TAF is found in plasma. Further to the greater stability of the alafenamide/TFV link, the alafenamide salt has the property to selectively convey TFV to cells expressing high levels the lysosomal carboxypeptidase cathepsin A (CatA), such as lymphoid cells, monocyte derived macrophages and hepatocytes. When compared to TDF, this selective distribution translates into a higher intracellular availability of active TFV, such as where the virus replicates, and a much lower pharmacokinetic exposure in plasma. Whatever is the pro-drug administered, the catabolism and clearance of TFV is the same; once de-phosphorylated the drug undergoes renal clearance by both glomerular filtration (approx. 2/3) and secretion by proximal renal tubule (1/3). TFV in the efferent arterioles undergoes uptake by the organic anionic transporters 1 & 3 (OAT1-3) in the basolateral side of tubular epithelial cells and MRP2-4 efflux pumps are responsible for extrusion of the drug through the apical side of tubular cells into urine [9]. Based on the experience so far gathered in the study of TFV clearance, the uptake of the drug from the blood seems actually to be a more efficient process than its extrusion into urine. As a consequence, such limited capacity of the tubular secretion of TFV identifies a major difference between the two pro-drugs, as the plasma concentration of TFV is much higher when the drug is administered as TDF, and this proportionally accounts for some degree of accumulation into proximal tubular epithelial cells which may result in tubular dysfunction. This is the basic reason why TAF, the 2nd TFV pro-drug released into the market, was developed to substitute its predecessor.

Tenofovir renal toxicity
Tenofovir belongs to a unique class of nucleotide analogs, the acyclic nucleosides phosphonates (ANPs). This class is characterized by the presence in the original molecular structure of a phosphate group which is attached to the nucleoside analogue to form a phosphonomethyl ether [10]. Unlike the phosphate groups of common nucleosides, whose attachment occurs intracellularly by the catalytic action of kinases through an ester bound, such linkage is much more robust and is thought to resist the attack of any esterase or other catabolic enzyme. ANPs also include cidofovir (CDV) and adefovir disoproxil (ADV), which are licensed for the treatment of CMV and HBV infection, respectively [11, 12]. As outlined for Tenofo-
vir, a common feature of ANPs is to undergo renal clearance, both by means of glomerular filtration and tubular secretion [10]. Uptake of ANPs by proximal renal tubule occurs through the OAT1-3 transporters, and no differences across the three marketed ANPs were detected in terms of transmembrane transport efficiency [10, 13]. This suggests that the significant difference in renal toxicity seen with the three ANPs (CDV > ADV > TFV) is not attributable to a different uptake capacity by the tubule, but rather to the intrinsic properties of these drugs. The cytotoxic effects of ANPs was measured in human renal proximal proximal tubule epithelial cells (RPTECs), and CDV was found to be associated to the highest degree of growth inhibition of RPTECs (CC₅₀ of 260 μM), followed by ADV (CC₅₀ of 500 μM) and TDF (no effect at doses up to 2mM) (10, 13). Such hierarchy seen in renal toxicity is translated into the clinic by the strict indication to co-administer CDV with probenecid (OAT inhibitor) and by the dose reduction of ADV that took place in the clinical development of the drug [14, 15]. The latter was also initially developed as antiretroviral at daily doses of 60-120 mg, but it was only marketed as anti-HBV medication at a much lower dose (10 mg/d) [16]. It must be considered, however, that these in vitro data refer to drug exposure lasting 5 days, while the clinical use of TDF implies years of continuous administration.

Although the use of TDF in clinical practice has been fully successful for almost two decades, a series of studies describing the development of alterations in renal function markers in association with the decrease of bone mineral density (BMD) have been consistently reported since few years following the release of TDF in the market. As early as in the registration studies 903 and 904, TDF recipients were found to generate a statistically significant greater decrease in the estimated glomerular filtration rate (eGFR) as compared to controls [17]. In the post-marketing phase a higher incidence of renal failure, increased creatinine plasma levels, Fanconi’s Syndrome, reduced bone mineral density (BMD) and tubular dysfunction have been repeatedly associated to TDF intake, although the most severe forms of such untoward events were rather rare [18]. The way renal toxicity associated to TDF has been studied and reported is actually heterogeneous, as initial reports were only based on increases in creatininemia and related decreases of glomerular filtrate estimation [19]. Also depending on the drugs being associated to TDF, a consistent finding in TDF intakers is a 10-15% increase in plasma creatinine levels taking place soon after the drug is introduced [20]. Such increased levels tend to remain rather stable over time, with only minor further increases occurring in the short-midterm. The pathophysiological interpretation of increased creatinine levels lies in the mechanisms of clearance of creatinine. Although the latter has always been considered as a marker of renal filtration, it must be noted that 15% of creatinine clearance takes place through secretion by the proximal renal tubule [21]. While in most clinical circumstances creatinine plasma levels are nevertheless considered as a valid 1st line screening marker for gross estimation of renal function, in the case of TDF a distinction is worth to be made. The average magnitude of creatinine increase following TDF initiation well fits with the hypothesis that the functional impairment of proximal renal tubule is responsible for such consistent abnormality [22]. According to the results of clinical studies in which a pure filtration marker was used instead of creatinine, the true glomerular filtration was found to be actually unaffected by TDF intake, and this might well explain why no further significant creatinine increases take place in short-mid-term following the initial rise upon TDF introduction [23]. As a consequence, the increase in creatininemia and the magnitude of such increase in TDF intakers appear to be actually compatible with the functional impairment of the proximal tubule and its decreased capacity to secrete creatinine into urine. The dynamics of creatinine increase once TDF is introduced in therapy follows a bi-exponential pattern, with a steep initial increase followed by a plateau phase, with only minor increases taking place subsequently [24]. The same applies when TDF is discontinued, as a major decrease in creatinine levels occurs in few weeks, although the full recovery of initial values is not the rule. This suggests that the mechanism/s responsible for tubular toxicity in TDF recipients is/are to some extent reversible [25]. The first studies that focused on markers of tubular function in TDF intakers were published in 2009 and found a consistent decrease in the tubular capacity of reabsorbing low-molecular weight proteins (LMWP) following TDF initiation [26].
entirely reabsorbed by the proximal tubule, so that no such molecules should be found in the urine in normal conditions. Excess urinary loss of both Beta-2 microglobulin (B2M) and Retinol-binding protein (RBP) were consistently found in TDF recipients, along with the tendency to phosphate loss. The first comparative analysis on the effects of TDF on tubular function was made in a randomized open-label clinical study, the ASSERT Study [27]. In the latter, patients taking EFV as “third drug” were randomized to receive either TDF/FTC or ABV/3TC. Although no difference was seen between the two arms in terms of eGFR decrease, a significantly higher urine loss of both RBP and B2M was measured in patients treated with TDF/FTC. Since the nature of the third drug being associated to TDF/FTC was subsequently found to influence the magnitude of tubular dysfunction, it seems plausible that the intake of EFV in the ASSERT study was the likely reason why no differences in eGFR were measured between the two study arms. EFV was proven to be the drug whose administration with TDF is associated to little or no impact on creatinine and eGFR, while boosted - protease inhibitors (PIs/r) are instead responsible for the greatest changes [28]. The difference between EFV and PI/r in generating the reduction of eGFR was highlighted by the ACTG 5202 study. In this clinical trial, in which almost 2000 participants were randomized to receive either EFV or ATV in association with ABC/3TC or FTC/TDF, the only combination resulting in significant eGFR decrease was found to be ATV/r - FTC/TDF [29]. By considering both the results of the ASSERT and of the ACTG 5202 studies it is evident that TDF-associated tubular dysfunction may pass unnoticed unless urinary markers are also measured. The different sensitivity of creatinine-based measures and urinary markers in disclosing the presence of tubular dysfunction was also made evident by the results of a cohort comparative study in which various renal parameters were investigated in middle-aged 5% HIV-infected and 544 age-matched uninfected subjects [30]. In the HIV-infected arm 73.3% of patients were taking (and 12% had taken) TDF and such variable was significantly associated to proximal renal tubular dysfunction, while the association between TDF intake and eGFR <60 mL/min showed only a non-statistically significant trend toward lower eGFR values in TDF recipients. A rather similar evidence was provided by a cross-sectional clinical survey in which 54% of 289 long-term TDF recipients (median exposure duration of 52.4 months) had pathologic RBP urinary findings in spite of normal creatinine clearance values (mean 89.4 mL/min, all >60) [31].

TAF development

The decision to develop TAF as an alternative to TDF was not taken for reasons of viro-immunologic efficacy but to overcome the renal and bone toxicities associated to TDF intake and the related uncertainties concerning its prolonged use in a progressively aging HIV-infected population. The clinical development of TAF followed thus a rather consistent design in which specific markers of proximal renal tubular function and bone density were regularly assessed in the comparative studies with TDF. Urinary markers of tubular function together with BMD measurements were thus always included in TAF development trials, and the expected differences between TAF and TDF were consistently confirmed, both in terms of reduced impact on proximal renal tubular function and BMD.

The first registration trials were designed to compare the existing single-tablet regimen (STR) based on elvitagravir (ELV), the new booster cobicistat (COBI), TDF and FTC with the same co-formulation in which TAF was included instead of TDF. Both studies on treatment-naïve and experienced patients switching from TDF-containing regimens were designed to demonstrate virologic non-inferiority at week 48, but in both trials the TAF-based STR was found to achieve superior virological results at week 144 and week 48 respectively [32, 33]. In both studies significantly better renal and BMD figures were found for TAF vs TDF. It’s worth noting that in the treatment-experienced trial, patients included in the study arm (ELV/COBI/FTC/TAF) had evidence of significant improvement both in renal function markers and BMD values, which testifies that the TDF-associated abnormalities in renal tubular function and bone structural parameters recorded in the control arm are significantly improvable by switching from TDF to TAF [33].

The development of TAF in the treatment of HIV infection also included the new drug in a fixed-dose co-formulation (FDC) with 200 mg of FTC; according to the third drug to be combined with
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this FDC, the dose of co-formulated TAF was 10 mg (with third drugs requiring a booster agent) or 25 mg (integrase inhibitors, NNRTIs). In a small study on treatment-naive patients FTC/TAF was compared to FTC/TDF, both in association with darunavir/COBI. As seen in prior trials, a significantly better tubular function profile and BMD figures were associated to TAF [34].

In a study on virologically suppressed patients, participants were randomized to continue ABC/3TC or switching to the FDC consisting of FTC and TAF while maintaining the third agent in both arms. Virological non-inferiority was demonstrated at week 48 while no differences were recorded in terms of tubular function [35].

To further explore the impact of TAF on bone formation and renal function in specific conditions, additional small-sized, single-arm studies were also performed to provide data on TAF use in patients with mild to moderate and end-stage renal disease. Virologically suppressed patients with eGFR values between 30 and 69 mL/min were switched to the STR consisting of ELV/COBI/FTC/TAF and virological suppression was maintained in 83.1% patients at week 144 [36]. No significant changes were measured in creatinine-based parameters, but tubular function was significantly improved. Patients with end-stage renal disease (on dialysis) and stable virological suppression were also switched to ELV/COBI/FTC/TAF and 81.8% of them maintained virologic suppression at week 48, with no relevant changes in renal parameters [37].

A further small single-arm study was devoted to adolescents (mean age 15) who were given the STR consisting of ELV/COBI/FTC/TAF. Virologic suppression was achieved in 925 of patients at week 48 and no specific remarks emerged on the safety side [38].

TAF also underwent clinical development for the treatment of chronic HBV infection and two major phase III trials were carried in HBeAg-negative and positive patients, respectively [39]. With the exception of the HBeAg status, the two studies had quite a similar design, and a total of 866 patients were randomized to TAF and 432 to TDF. Virologic non-inferiority was achieved in both trials by TAF as established by a cut off of 29 HBV-DNA IU/mL. As expected, eGFR decrease was significantly higher in TDF recipients and the urinary markers of tubular function behaved accordingly, with significantly better findings for the TAF arm. BMD decrease was also significantly higher in the TDF group in both studies.

New issues in the TAF vs TDF choice

While the better safety profile of TAF in terms of proximal renal tubular function and structural bone measures has been fully and repeatedly proven, new objections have been raised to challenge this otherwise straightforward switch from the old to the newer TFV pro-drug.

The first point concerns the impact on lipids by TDF, whose withdrawal is regularly followed by small but consistent increases in several lipid parameters [40]. While TAF may be considered as a lipid-neutral medication, there are claims to keep TDF on board in order to take advantage of its lipid-lowering effect. The effect of TDF as “lipid-lowering agent” seems to be, however, quite modest, especially if the key combined parameter of total cholesterol/HDL ratio is considered. The cleanest experimental scenario providing information on the effects on lipids by the two different TFV pro-drugs is the one of chronic HBV infection, as there are not interferences from HIV infection or additional antiretrovirals. In the two phase III studies on chronic HBV infection, in spite of better values of total cholesterol and LDL for TDF intakers, the change in the total cholesterol/HDL ratio was found to be exactly the same in the TAF and TDF arms (39). In an aging population, the fraction, if any, of those who might avoid statin supplementation because of such TDF effect would therefore be rather limited [41]. Since the purpose of any lipid-lowering intervention is to reduce the risk of cardiovascular events, the other side of the coin is that by keeping TDF on board a continuous dysfunctional pressure on proximal renal tubule would remain active and thus contribute to increase the individual cardiovascular risk by the progressive impairment of renal function. In addition to this we must also consider, particularly in an aging population, the long-term effects on bone structural integrity. Cohort studies on the frequency of pathologic fractures in long-term TDF recipients started to disclose a tendency to increase as compared to intakers of TDF-free regimens [42]. The use of statins, when required, in association to a tubule-sparing drug looks thus as a preferable solution in the long-term. A second point is the concern around recent find-
nings on significant body weight increase in patients receiving TAF, an issue also involving the intake of integrase inhibitors (INSTIs). In late 90s, when the first triple antiretroviral combinations were found to be both virologically and immunologically effective, the increase in body weight following treatment initiation was considered as a basic sign of health recovery, especially in those who started treatment while in a very advanced stage of the disease. It must be remembered that AIDS was also called “slim disease” in some African countries [43]. In a subsequent phase, loss of fat in the limbs and increase in abdominal fat were described as lipodystrophy syndrome and the responsibility of thymidine analogs (stavudine and zidovudine) and 1st generation protease inhibitors were recognized [44]. Newer drugs belonging to these classes were found to be much less associated to such fat changes and the frequency of the lipodystrophy syndrome is truly low nowadays. No major attention was afterwards paid to body weight changes until last year when weight gain associated to INSTIs and TAF became an increasingly debated topic. The first major signals concerning the impact of INSTIs and TAF on body weight came from the South African study ADVANCE, in which three treatment arms in naïve patients were compared [45]. Two arms were treated with Dolutegravir (DTG), in association with FTC/TAF and FTC/TDF, respectively, while the third arm consisted of EFV, and FTC/TDF. A significant body weight increase was recorded at week 144 in patients receiving DTG, FTC/TAF (+7.2 and +12.3 kg in men and women respectively), vs those under treatment with DTG, FTC/TDF (+5.5 and +7.4 kg in men and women respectively) or EFV, FTC/TDF (+2.6 and +5.5 kg in men and women respectively). Further to the treatment to which patients were randomized, additional factors associated to body weight increase were female gender, baseline lower CD4+ T-cell count and higher viral load and older age. Other studies also showed similar associations between INSTI and/or TAF intake and increase in body weight, although the magnitude of such increase varied across different case series.

In a more recent large-scale survey that covered nearly 8% of US citizens living with HIV (the OPERA study), the electronic health records from 115,000 HIV-infected patients were evaluated in order to longitudinally verify body weight changes according to the regimens to which patients were exposed [46]. Among virologically suppressed patients who were receiving TDF as component of their 3-drug regimens, those who switched to TAF while maintaining the other components or also switched from a non-INSTI third drug to an INSTI underwent analysis for weight change. In the 9 months following the switch to TAF the magnitude of weight gain ranged from 1.8 to 4.47 kg/yr across all regimens, with a curve which slowed or plateaued after the first 9 months after switch.

It must be noted however that in the studies so far performed, mostly retrospective, a series of potentially significant parameters were not considered, and the main variable investigated was just the regimen to which patients were exposed. Among the neglected significant variables, it’s relevant to note that no studies have so far been published in which dietary intake and/or physical activity were monitored. An exception is a recent report that described the retrospective evaluation of 281 patients under long-term follow-up in a setting specialized in the study of HIV-associated metabolic alterations [47]. The outcome measure was the occurrence of significant weight gain as defined by an increase of ≥5% from 1st visit over a mean 4 years follow-up, and both physical activity (according to the International Physical Activity Questionnaire - IPAQ - as metabolic equivalent of task - MET) and daily caloric intake (DCI - 3-day food diary) were evaluated. The first factor associated to increased body weight was found to be a baseline body mass index (BMI) greater than 25, which means that not only obesity but also an overweight baseline status is associated to the risk of weight gain as here defined. The second factor was a low physical activity, which was defined in combination with dietary intake (MET) and daily caloric intake (DCI - 3-day food diary) were evaluated. The first factor associated to increased body weight was found to be a baseline body mass index (BMI) greater than 25, which means that not only obesity but also an overweight baseline status is associated to the risk of weight gain as here defined. The second factor was a low physical activity, which was defined in combination with dietary intake (MET), while the third was a suboptimal immunologic status. These findings actually widen the overall scope of the ongoing debate about the responsibility of antiretroviral treatment in the generation of undesirable increase in body weight and prompt to take into consideration a wider number of factors, particularly the conventional determinants of weight gain.

To what extent specific drugs are actually responsible for the increase in body weight is yet to be determined as plausible pathophysiolog-
weight gain are yet to be identified. However, the overall impression is that of a multifactorial phenomenon on which several mechanisms might have a different relative responsibility in the generation of weight increase according to individual circumstances. Immune reconstitution is often associated to weight gain which might simply represent the recovery from a so called “wasting syndrome”, as seen in advanced AIDS patients, but such increase might turn to an overweight status in those more prone to obesity for dietary and/or genetic reasons. Increased appetite has been suggested for INSTIs, but the drug levels normally measured in humans are considered insufficient to determine such effect in vivo. The class of INSTIs has also been suggested to be possibly responsible for increased fat storage and associated alterations of fat metabolism, but this hypothesis does not explain why weight gain is greater when TAF is also part of the regimen. An additional factor that might also contribute to the currently described findings concerns a possible suppressive effect on weight gain by older drugs whose substitution with new ones (lacking such suppressive action) might participate in the generation of the reported increases in body weight. The question remains largely unanswered, but it seems unlikely that a single drug may account alone for the issue here concerned [48, 49]. Dietary and lifestyle corrections appear to be the most rationale options to compensate for weight imbalance in most patients, thus avoiding unnecessary changes of otherwise well tolerated regimens whose lesser impact on renal function and bone integrity provides a solid chance for an uneventful long-term control of HIV infection.

CONCLUSIONS

The development of TAF, and the consistent evaluation made on tubular function and structural bone parameters provided unambiguous data on the safer profile of the newer TFV pro-drug as compared to TDF. Such differences must be contextualized according to the time when these two TFV pro-drugs were released into the international market. TAF was made available when the HIV-infected population had significantly aged and the rationale for preferring it to TDF is vividly reinforced by the greater vulnerability of aged and aging patients to decreasing renal function and bone fragility. Indeed, in the era when TDF was released the age of HIV-infected patients was well lower than today and it is likely that most of the major long-term consequences of chronic TDF intake were avoided because of the younger age of patients. The properties of TAF vs TDF are thus more suitable to make the chronic intake of antiretroviral therapy more compatible with the age-related decline of human physiology. The attempts to revive the position of TDF are largely due to its lower price as generic, although the issue of lipids and its association to weight gain have raised some conservative claims about its reconsideration. However, alterations of the lipid profile and weight gain are amenable to valid correction in the vast majority of individual circumstances, while long-term dysfunction of proximal renal tubule by TDF has the potential to generate poorly reversible reductions in renal function and bone integrity. In consideration of the variety of age-related medical issues to face today, a step-back to TDF does not seem to fit with the consistent improvement in safety the evolving field of antiretroviral therapy has consistently guaranteed.

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