Chronic kidney disease and antiretroviral therapy in HIV-positive individuals: recent developments.

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Short title: Renal toxicity of antiretroviral therapy

Word count: 3700 (limit 4000)

Abstract: 250 (limit 250)

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ABSTRACT

Chronic kidney disease (CKD) has emerged as an important health concern in HIV-positive individuals. Preventing long-term renal toxicity from antiretroviral therapy is therefore critical. Selected anti-retroviral agents, especially tenofovir disoproxil fumarate (TDF) and some ritonavir-boosted protease inhibitors (PI/rs), have been associated with increased risk of CKD. However the CKD risk attributable to these agents is overall small, especially in those with low baseline risk of CKD and normal renal function. CKD risk in HIV-positive individuals can be further minimized by timely identification of those with worsening renal function and discontinuation of potentially nephrotoxic agents. Clinicians can use several monitoring tools, including the D:A:D risk score and routine measurements of estimated glomerular filtration (eGFR) and proteinuria, to identify high-risk individuals who may require an intervention. The tenofovir alefenamide (TAF), a TDF alternative is now available which promises to be safer in terms of TDF-associated renal and bone toxicity. While the short term data on TAF does indicate lower eGFR decline and lower risk of proteinuria (vs. TDF), long-term data on renal safety of TAF is still awaited. Promising results have also emerged from recent trials on alternative dual-therapy antiretroviral regimens which exclude the nucleoside(tide) reverse transcriptase class as well as possibly the PI/rs, thereby reducing the drug burden, and possibly the toxicity. However, long-term safety or benefits of these dual-therapy regimens are still unclear and will need to be studied in future prospective studies. Finally, addressing life-style risk factors such as hypertension and diabetes will continue to be important in this population.

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Key words: HIV; HAART; cART; kidney; renal; tenofovir; antiretroviral therapy; dual therapy; GFR; proteinuria

INTRODUCTION

The introduction of combination antiretroviral therapy (cART) for HIV has changed the trajectory of HIV disease from that of an acute disease with high mortality to a chronic illness. Morbidity and mortality in HIV-positive individuals receiving cART is predominantly because of serious non-AIDS diseases, including liver, cardiovascular, and kidney disease.[1, 2] While aging, HIV infection, and other comorbidities such as diabetes and hypertension likely play an important role, long-term cART toxicity may also contribute to serious non-AIDS end-organ diseases.[3]

Of increasing interest in the ageing HIV-positive population is chronic kidney disease (CKD), which has been associated with long-term cART use. In a large Danish cohort, HIV-positive individuals had nearly 4 times the rate of CKD compared to HIV-negative population controls.[1] Moreover, HIV-positive individuals are increasingly reported to have a high prevalence of traditional and behavioral risk factors for CKD. For example, in the Strategic Timing of Antiretroviral Therapy (START) trial, the relatively young (mean age of 36 years) ART-naïve population with high CD4 counts had a high baseline prevalence of over-weight/obesity (45%), smoking (32%), hypertension (19%), and diabetes (3.5%), as well as a higher than expected prevalence of proteinuria (5.7%), even before initiating cART.[4] Even a relatively small incremental risk of CKD from cART toxicity could therefore play an important role in this high-risk population requiring life-long cART.

Several recent longitudinal studies have highlighted the potential role of cART in promoting CKD. In particular, renal toxicity from the use of tenofovir disoproxil fumarate (TDF) has been an issue of intense investigation. In this review, we will focus on recent (past 1-2 years) prospective studies (epidemiological/ cohort as well as randomised trials) evaluating the impact of anti-retroviral agents on CKD risk, with a particular focus on TDF, the new alternative prodrug tenofovir alafenamide (TAF), and PI/rs. Finally, we will review strategies for minimising the risk of CKD due to ART particularly for those with high baseline risk of CKD.

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RENAL TOXICITY FROM TDF AND OTHER ART AGENTS

TDF, a prodrug for the nucleotide analogue reverse transcriptase inhibitor (N(t)RTI) tenofovir, is a popular choice because of its potency, convenient once daily dosing, and relatively minimal adverse reactions. TDF is currently recommended by World Health Organization (WHO), the European AIDS Clinical Society (EACS) and United States Department of Health and Human Services (DHHS) guidelines as a component of the preferred first-line ART regimens, as well as a component of pre-exposure prophylaxis for HIV-infection.[5-7] Since 2006, it has been the most widely prescribed antiretroviral agent in the United States, and it is increasingly used in low-middle income countries.

Recent insights into the nature of TDF renal toxicity

Initial registration trials of TDF did not demonstrate any clinically relevant renal toxicity[8], possibly because of the relatively short follow-up in clinical trials or the exclusion of some patient groups who may be at a higher underlying risk of CKD. However, subsequent observational studies have reported a significant decline in the estimated glomerular filtration rate (eGFR) with cumulative use of TDF.[9-11] A meta-analysis of randomized trials and observational studies comparing individuals on TDF with those on alternative agents demonstrated a greater decrease in Cockcroft-Gault (CG)-eGFR over a median 48 weeks of follow-up; compared to individuals taking non-TDF regimens, eGFR declined by 3.92 ml/min more in those on TDF.[10] Most of the prior studies had a relatively short follow-up period of up to 3-4 years, and therefore could not properly analyze hard CKD endpoints which can take years to manifest.

Recent analyses from the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study--a large prospective international cohort study with well-validated outcomes--have provided a better understanding of how TDF may contribute to the risk of CKD, especially in those with normal baseline eGFR.[12] In D:A:D study participants with normal baseline eGFR followed for a median of over 7 years, TDF use was associated with about 14% more risk of CKD (defined as confirmed eGFR <60 mL/min) per year of use after adjusting for key confounders, with the relative risk nearly doubling in 5 years.[12] Because TDF is likely to have been stopped in those with declining eGFR, the actual relative risk could be even higher.

It is important to emphasize that while TDF does seem to be associated with higher relative risk of CKD, the absolute risk of CKD remains low, especially in those with normal (eGFR>90 mL/min) baseline eGFR. In the D:A:D study, the overall incidence of CKD was 0.18 per 100 person-years of follow-up in those with normal baseline eGFR.[12] In another D:A:D analysis[13], after 5 years, only 0.3% had progressed to advanced CKD or end stage renal disease (ESRD), including 6.6% of those with eGFR < 60ml/min and only 0.07% of those with baseline eGFR >90 ml/min. In this study, TDF was not associated with advanced CKD/ ESRD, although the number of events was low.[13] Similarly, early data from low-middle income countries suggest a low short-term absolute risk of significant decline in eGFR (<60 mL/min) with TDF.[14, 15] Furthermore, the risk of CKD appears to return to baseline levels in most patients if TDF is discontinued. In the D:A:D study, in those participants in whom TDF was discontinued in response to declining eGFR, the relative risk of CKD approached that of those never exposed to TDF after 12 months of TDF discontinuation.[16, 13] In a cohort from the UK, decline in eGFR while on TDF was

reversible (defined as within 5% of baseline eGFR) within 2 years after TDF discontinuation in a majority (62%) but not all participants.[17] Lack of reversibility was associated with lower eGFR at the time of TDF discontinuation (suggesting a late discontinuation of TDF or a presence of comorbid kidney disease), and concomitant use of PI/rs.[17]

In randomized trials of TDF-based pre-exposure prophylaxis (PrEP) in otherwise healthy populations, TDF use resulted in small but statistically significant declines in eGFR which were not deemed to be clinically relevant and which were largely reversible.[18-21] Available data also suggest no significant increase in proximal tubular dysfunction with TDF-based PrEP, although the Partners PrEP investigators recently reported a significant increase in the prevalence of proteinuria at 24 months in participants randomized to TDF/FTC versus placebo.[19,22] Because follow-up in these trials was short and several of the trials were limited by poor adherence to PrEP, longer follow-up in real world populations is needed to confirm the safety of TDF-based PrEP.

Other antiretrovirals affecting renal function

Cohort studies have also found several PI/rs to be associated with the risk of eGFR decline.[9] In most studies, however, PI/rs were used with concomitant TDF, making it difficult to delineate their independent effect on renal function. In the recent D:A:D study, where over 65,000 person-years of follow-up were available on contemporary non-TDF regimens, cumulative use of ritonavir-boosted atazanavir (ATV/r) and lopinavir (LPV/r) was associated with higher relative risk of CKD (about 22% and 13% higher per year of use, respectively).[12] The findings were consistent among those never exposed to TDF, which suggests that it is not coadministration with TDF explaining the increased risks of CKD seen with ritonavir-boosed atazanavir and lopinavir. Other PI/rs were not found to be associated with the risk of CKD.[11]

There have not been any consistent signals of nephrotoxicity with other antiretroviral agents. Although cohort data from modern integrase inhibitor based regimens are still awaited, there does not appear to be any concern for renal toxicity based on the initial safety data.[23]

Implications for monitoring renal function while on ART

Several guidelines including the Infectious Disease Society of America recommends that, for adults starting TDF with a baseline eGFR<90 mL/min, who are on other nephrotoxic medications or who have hypertension or diabetes, physicians check a baseline blood pressure, serum creatinine and urine protein, and monitor kidney function with biannual serum creatinine, serum phosphorous, and urinalysis for proteinuria and glycosuria.[24, 7] Guidelines recommend referral to a nephrologist for diagnostic evaluation when “there is a clinically significant decline in GFR (ie, GFR decline by >25% from baseline and to a level ≤60 mL/min) that fails to resolve after potential nephrotoxic drugs are removed, there is albuminuria in excess of 300 mg per day, hematuria is combined with either albuminuria/proteinuria or increasing blood pressure, or for advanced CKD management (GFR ≤30 mL/min)”.[24]

Moreover, an externally validated risk score, the D:A:D risk score, is now available for predicting the 5-year risk of CKD in HIV-positive individuals. This score takes in to account easily measurable key individual risk factors to identify HIV-positive individuals at a higher risk of developing CKD.[25] The score, available at

http://www.hivpv.org/Home/Tools/ChronicKidneyDiseaseTool.aspx, also estimates the risk for CKD for a given person, as well as how this risk changes if one of the potentially nephrotoxic antiretrovirals is started. Using this score can assist clinicians in ART regimen selection. Other markers of renal injury, including proteinuria and other urinary biomarkers, could potentially improve the risk prediction,[26] and should be evaluated in prospective studies.

While serum creatinine is routinely monitored in most settings, cohort data suggest that monitoring of proteinuria is still relatively infrequent despite general consensus in guidelines to include this as a marker of renal impairment. In a small clinical study reviewing cases of biopsy-proven TDF renal toxicity, 26% of individuals had manifested as chronic proteinuria without significant eGFR decline.[27] This study highlights the importance of monitoring proteinuria in HIV-positive individuals receiving TDF.

Finally, it is important to underline that given the low overall risk of toxicity and overwhelming benefits from ART, laboratory monitoring should not be a barrier to starting ART in HIV-positive individuals. This is of particular relevance to low-middle income countries where access to laboratory investigations can be a barrier to starting ART. Indeed, in the 5-year DART trial evaluating routine versus clinically driven laboratory monitoring in Africa, lack of routine monitoring did not impact survival on ART.[28] In such settings where laboratory monitoring is not easily available, use of clinical risk scores to identify high risk individuals could be a useful strategy.

STRATEGIES TO MINIMISE RENAL TOXICITY FROM ART

Novel ART options continue to be developed, which are potentially safer in terms of long-term end-organ toxicity.

Tenofovir alafenamide (TAF)

The mechanism of TDF toxicity seems to be related to the plasma concentration of tenofovir.[11] Higher tenofovir plasma concentration can lead to increased intracellular concentrations that cause depletion of mitochondrial DNA and dysfunction of the oxidative respiratory chain in proximal tubular epithelial cells. Theoretically, this leads to a depletion of intracellular ATP, which limits the proximal tubule's ability to reabsorb electrolytes and low molecular weight proteins.[29] The novel tenofovir prodrug, TAF, achieves higher intracellular concentrations of the active metabolite tenofovir-diphosphate in immune cells at a much lower dose and nearly 90% lower plasma concentration as compared to TDF.[29] Also, TAF does not appear to enter renal tubular cells, as it is not a substrate for the membrane transporters that facilitate tenofovir entry into these cells.[29] Owing to these properties, TAF holds promise as a safer alternative to TDF in terms of both renal and bone toxicity.[29]

The non-inferior virological efficacy of TAF vs TDF (both in combination with cobicistat boosted elvitegravir and emtricitabine, called E/C/F) as a first-line ART regimen has been proven in phase-3 double-blinded 48-week clinical trials.[30] This led to the approval of E/C/F/TAF, the first single-pill ART regimen approved for use in adults with baseline eGFR 30-50 ml/min.[31] Subsequently, non-inferior efficacy of E/C/F/TAF as initial ART has been shown at 96 weeks of follow-up in the same trial.[32] Furthermore, an open-label 48-week phase-3 study demonstrated non-inferior efficacy of TAF in virologically suppressed patients

switching to E/C/F/TAF from a TDF-containing regimen.[33] Finally, while the majority of published trials have evaluated TAF in combination with E/C/F, a recent large double-blinded trial demonstrated non-inferior efficacy of TAF with emtricitabine and any of a variety of third agents, with or without a PI/r.[34] Table-1 summarises key studies of TAF.

In the first-line trial of E/C/F/TAF, TAF was associated with a marginally smaller mean decrease in eGFR at week 48 (-6.4 in TAF group vs. -11.2 ml/min in the TDF group). Four participants in the TDF group and no participants in the TAF group discontinued study drug because of renal adverse events.[30] Findings were similar at week 96[32] (see Table-1). In the switch trial, TAF showed small improvements in eGFR only in those who switched from a PI/r based regimen[33]. Finally, a single-arm 48-week study evaluated the effect of switching to TAF (without dose adjustment) in participants with eGFR 30-69 mL/min at baseline.[35] This study did not report any significant change in eGFR at 48-weeks of follow-up.[35] Of note, changes in eGFR are difficult to interpret in these trials because the use of cobicistat can result in an artifactual rise in serum creatinine by inhibiting the tubular secretion of creatinine. However, in the study evaluating TAF in combination with any of the non-boosted agents, eGFR was slightly but significantly higher at 48 weeks in the TAF arm as compared to the TDF-arm.[34]

Importantly, all of these studies reported a lower relative risk of proteinuria as well as a better profile of markers of tubulopathy in the TAF arm vs the TDF arm (Table-1). For example, in the first-line trial, E/C/F/TAF was associated with a median 5% decline in urine albumin: creatinine ratio compared to a 7% increase in the E/C/F/TDF group.[30] Collectively, these initial data suggest that TAF could potentially offer a safer alternative to TDF in terms of long-term renal toxicity (Table-1).

TAF- important caveats

It is important to understand and explore several caveats about TAF before it is adopted for widespread use.

First, the reported follow-up in most of the initial TAF studies was only 48 weeks, and at best, 96-144 week (2-3 years) data are likely to be reported. Given the overall low risk of developing CKD, such a short follow-up is unlikely to inform whether TAF will truly result in a reduced risk of renal events compared to the TDF or may still harbor a significant risk of nephrotoxicity. Only long-term post-marketing studies will answer this question.

Second, the initial registration data suggest that TAF may have interaction with drugs interfering with P-glycoprotein (Pgp) as well as CYP450, which includes the anti-tuberculosis agent rifampicin. Rifampicin could potentially reduce plasma levels of TAF, resulting in loss of its therapeutic effect. The current TAF label states that rifampicin should not be used with TAF, although detailed pharmacokinetic data from these two agents together are still awaited.[31] If found to be correct; this would limit the use of TAF in regions where tuberculosis is endemic, including most of the low-middle income countries globally.

Third, initial trials indicate that use of TAF could result in loss of the lipid-lowering effect afforded by TDF. In both first-line and switch trials (Table-1), the TAF arms experienced a significant increase in the low-density lipoprotein (LDL)-cholesterol, total cholesterol and triglycerides, but not in the total cholesterol: high-density lipoprotein (HDL) cholesterol ratio.

Implications of these changes in lipids, in terms of risk of cardiovascular disease, will need to be studied in long-term post-marketing or cohort studies.

Finally, cost issues will need to be considered before the widespread use of TAF, especially in low-middle income countries. TDF-based regimens have been found to be cost-effective for use in low-middle income countries.[36] While TAF is expected to be priced similar to TDF[37], the currently approved TAF regimen includes integrase inhibitors which are more expensive. On the other hand, if TAF indeed offers improved renal and bone safety, it could potentially reduce monitoring costs and may turn out to be a more cost-effective agent. It is still unclear whether TAF regimens will provide incremental benefit or loss in terms of its cost-effectiveness. These issues will need to be carefully studied before the widespread use of TAF.

Alternative ART regimens

cART has conventionally consisted of a three drug regimen with two agents from the N(t)RTI class and one from an alternative class. However, concerns about long-term toxicities and cross-resistance within the N(t)RTI class, combined with the continuing development of newer and seemingly safer agents has led to a growing interest in the use of feasible, innovative, and appealing dual-therapy N(t)RTI-sparing regimens.[38] Such regimens could be especially appealing , especially in individuals who are at high risk of bone, renal, or cardiovascular disease (CVD), where using either TDF or abacavir (ABC, owing to its potential CVD toxicity[39]) would be of concern to providers and patient. Because of shared risk factors, providers will increasingly encounter individuals with, or at high risk for both CKD and CVD.[2, 40] Could carefully choosing N(t)RTTI-sparing regimens potentially prevent long-term renal and other toxicities from ART?

Several recent trials have examined the efficacy of dual-therapy N(t)RTI-sparing regimens in both treatment-naïve and treatment experienced individuals (reviewed here in details[38, 41]). For the first time, DHHS and EACS guidelines now recommend dual-therapy regimens of LPV/r with lamivudine (3TC) and boosted darunavir (DRV/r) with raltegravir (RAL) as alternative first-line therapy in selected individuals where TDF and ABC cannot be used.[5, 7] All of the trials we mention here have found N(t)RTI-sparing regimens to be virologically non-inferior to standard ART. With regards to renal toxicity, however, these trials have had mixed results (Table-2 summarizes selected dual-therapy studies which reported eGFR outcomes). In the 96-week NEAT001 trial (RAL + DRV/r vs. TDF/FTC + DRV/r), the dual-therapy arm was associated with a significantly higher mean eGFR as compared to the TDF-containing standard ART arm (which experienced a mean decline in eGFR).[42] Similar results were found in the PROGRESS trial (RAL + LPV/r vs. TDF/FTC+ LPV/r)[43] as well as the ATLAS-M trial (ATV/r + 3TC vs. ATV/r + 2 N(t)RTIs).[44] However, in SALT (individuals switching from a standard ART regimen to ATV/r + 3TC vs. 2N(t)RTIs+ ATV/r) and and OLE (individuals switching from a standard ART to a LPV/r + 3TC vs. 2N(t)RTIs+ LPV/r) trials, no such benefit was seen, although none of the trials have indicated additional renal harm from dual-therapy regimens.[45, 46] Of note, in both SALT and OLE, only 60-70% of individuals were using TDF in the control arm.[46, 45]

While the renal safety data from these studies have been inconclusive, almost all of these trials included PI/rs in their experimental dual-therapy regimen. PI/rs have been independently associated with both renal and cardiovascular toxicity.[39] With the availability of several agents in the integrase-inhibitor (INSTI) class, as well as newer non-nucleoside reverse transcriptase inhibitor (NNRTIs), there is ongoing interest in evaluating regimens which spare both PI/rs and N(t)RTIs. Several potential regimens that spare PI/rs, N(t)RTIs as well as efavirenz but still consist of 2 or 3 active agents could be constructed for HIV-positive individuals regardless of their treatment experience.[47] Indeed, a recent phase-3 trial has proved the non-inferior efficacy of long-acting injectable Cabotegravir (an INSTI) with rilpivirine (a newer NNRTI) vs. standard ART.[48] Ongoing studies are also evaluating dolutegravir (INSTI with a high genetic barrier to resistance and excellent safety profile) along with lamivudine or as monotherapy. Future studies will determine whether these novel regimens may be safer in the long-term compared to conventional ART, as well as reducing the drug burden and possibly the overall cost of ART.[49]

Other promising strategies

Recent studies have suggested the potential of pharmacokinetic monitoring of TDF in order to prevent toxicity. In one study of over 100 women receiving TDF, a single measure of area under the-time concentration curve (AUC) of TDF predicted renal toxicity for up to seven years of follow-up.[50] Women with higher TDF AUC tended to be older and with lower BMI.[50] Another study suggested that the TDF exposure, and consequently renal toxicity, is higher in those with low body weight.[51] Overall, these studies suggest that in individuals at high risk of CKD, pharmacokinetic monitoring with dose-adjustment of TDF could potentially thwart toxicity, although the overall efficacy and safety of such a strategy is yet to be studied.

Finally, it is important to emphasize that CKD and other serious events in HIV-positive individuals are still largely attributable to traditional risk factors, including diabetes, hypertension, physical inactivity, and smoking.[4, 40, 25, 39, 52] Moreover, renal toxicity from ART is likely to be of much lower concern if these risk factors are either prevented or managed. More research is therefore needed on best strategies to minimize traditional CKD and CVD risk factors in those at highest underlying risk of renal disease.

LIMITATIONS AND CONCLUSIONS

It should be noted that most of the studies discussed in this review have relatively short follow-up period, whereas ART toxicity can take years to manifest. Also, there is significant heterogeneity in how studies evaluated renal outcomes. Most studies have analysed surrogate renal end-points, which are usually a metric derived from serum creatinine, either eGFR with substantial variablity. While eGFR does predict future renal function and risk of CKD, it is unclear what small short-term changes in eGFR mean in the long run. Moreover, the eGFR measurement itself varies between studies depending on which equation is used for its estimation. The CKD-EPI or MDRD equations are thought to be most accurate,[53, 54] but require data on race/ethnicity which are often not available in large cohort studies,[12] thereby requiring use of the less accurate Cockcroft-Gault equation for eGFR estimation. Also, most studies do not report data on proteinuria or markers of tubular injury, which are thought to be important in terms of assessing renal toxicity of ART.

In conclusion, selected anti-retroviral agents, especially TDF and some PI/rs do seem to be associated with increased risk of CKD. However the risk is overall small, especially in those with low baseline risk of CKD. Risk can be further minimized by timely identification of those at high risk of CKD and discontinuation of potentially nephrotoxic agents. Clinicians can use several monitoring tools, including the D:A:D risk score and routine measurements of eGFR and proteinuria, to identify high-risk individuals. Meanwhile, progress is being made in developing newer, safer ART regimens to further minimize the risk of toxicity and improve durability. These include using TAF- a TDF alternative thought to be safer in terms of TDF-associated renal and bone toxicity. Also promising results have emerged from recent trials on unconventional ART regimens which exclude the N(t)RTI-class as well as possibly the PI class. Whether these modern regimens truly offer better safety profile over current regimens will need to be studied in carefully designed long-term cohort studies.

Table-1: Key renal findings of recent studies evaluating tenofovir alafenamide (TAF)

Author	Year	Population at baseline	Design	Comparison	N/weeks of follow-up	Key renal safety findings
Wohl et al[32]	2016	ART-naïve; eGFR>50	RCT, double-blinded	E/C/F/TAF vs. E/C/F/TDF	1733/96	➢ Median change in eGFR in TAF arm: -2 vs. -7.5 ml/min in TDF arm ➢ ↓UACR, UPCR, retinol binding protein and ß-2 microglobulin ➢ ↑LDL-C, total-C, triglycerides and HDL-C in TAF arm ➢ Discontinuation due to renal events in TAF arm: 0 (vs. 6 in TDF arm)
Mills et al[33]	2016	On TDF-based regimens, virologically suppressed, eGFR>50	RCT, open-label	E/C/F/TAF vs. Continue TDF-based regimen	1443/48	➢ Higher eGFR in TAF-arm only in those who switched from TDF and booster containing regimens ➢ ↓UACR, UPCR, retinol binding protein and ß-2 microglobulin in TAF arm ➢ ↑LDL-C, total-C, triglycerides and HDL-C in TAF arm ➢ Discontinuation due to renal events in TAF arm: 2 (vs. 5 in TDF arm)
Gallant et al[34]	2016	On TDF-based regimens, virologically suppressed, eGFR>50	RCT, double-blinded	TAF/F+ any 3rd agent vs. TDF/F + any 3rd agent	663/48	➢ Median change in eGFR in TAF arm: +8.4 vs. +2.8 ml/min in TDF arm ➢ ↓UACR, UPCR, retinol binding protein and ß-2 microglobulin in TAF arm ➢ ↑LDL-C, total-C, and triglycerides (but not TC: HDL-C ratio) in TAF arm
Pozniak et al[35]	2016	On stable ART, virologically suppressed, eGFR 30-69	Single-arm, open-label	Switch to E/C/F/TAF	70/48	➢ No change in eGFR, regardless of baseline eGFR ➢ ↓UACR, UPCR, retinol binding protein and ß-2 microglobulin

						➢ Lipids improved in those switching from no-TDF-based regimens but worsened in those switching from TDF-based regimens. No significant change in TC:HDL-C ratio

Note: TDF= tenofovir disoproxil fumarate; TAF= tenofovir alafenamide; eGFR= estimated glomerular filtration rate; E/C/F/TAF= elvitegravir+ cobicistat+emtricitabine+TAF; UACR= urinary albumin creatinine ratio; UPCR= urinary protein creatinine ratio; LDL-C= low-density lipoprotein cholesterol; TC= total cholesterol; HDL-C= high-density lipoprotein cholesterol

Table-2: Key renal findings of selected recent studies evaluating dual therapy regimens

Author	Year	Population at baseline	Design	Comparison	N/weeks of follow-up	Key renal safety findings*
Arribas[46]	2015	Virologically suppressed	Open-label RCT	LPV/r +3TC vs. 2N(t)RTIs + LPV/r	239/	➢ Mean change in MDRD-eGFR in dual-therapy arm: +5 vs. -2 mL/min in control arm, P=0.003
Molina[45]	2015	Virologically suppressed	Open-label RCT	ATV/r +3TC vs. 2N(t)RTIs + ATV/r	286/48	➢ Mean change in CKD-EPI-eGFR in dual-therapy arm: -1.1 vs. -0.5 mL/min in control arm, P=0.78
Giambenedetto[44]	2015	Virologically suppressed	Open-label RCT	ATV/r +3TC vs. 2N(t)RTIs + ATV/r	266/48	➢ Mean change in MDRD-eGFR in dual-therapy arm: +2 vs. -4 mL/min in control arm, P<0.001
Raffi[42]	2014	ART-naïve	Open-label RCT	RAL+DRV/r vs TDF/FTC + DRV/r	805/96	➢ Mean change in CG-eGFR in dual-therapy arm: +0.8 mL/min vs. -4.6 mL/min in control arm, P<0.001
Reynes[43]	2013	ART-naïve	Open-label RCT	RAL+LPV/r vs TDF/FTC + LPV/r	206/96	➢ Mean change in CG-eGFR in dual-therapy arm: -1.43 ml/min vs. -7.33 ml/min in control arm, P = 0.035 ➢ 1 treatment-related renal failure in dual therapy arm

Note: ATV/r= ritonavir boosted atazanavir; DRV/r= ritonavir boosted darunavir; LPV/r= ritonavir boosted lopinavir; N(t)RTI= nucleoside(tide) reverse transcriptase inhibitor; RAL=raltegravir; TDF/FTC= tenofovir/emtricitabine; 3TC= lamivudine

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