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REVIEW

Protease Inhibitors and Renal Function in Patients with HIV Infection: a Systematic Review

Corinne Isnard Bagnis · Hans-Jürgen Stellbrink

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ABSTRACT

Introduction: Despite antiretroviral (ARV) therapy reducing renal disease in human immunodeficiency virus overall, there is concern that certain ARVs, particularly tenofovir disoproxil fumarate (TDF) with or without a boosted protease inhibitor (PI), may reduce renal function over time. It is not known whether effects seen with PI-based regimens are independent, result from interactions with TDF coadministration, or are artefactual owing to inhibition of renal tubular creatinine transport by ritonavir or cobicistat pharmacoenhancement. The aim of this review was to conduct a systematic review of studies, weighted toward high-quality evidence, examining changes in renal function over time with PI-based regimens.

Methods: PubMed, Embase, and Medline databases and conference abstracts were searched using pre-defined terms for English language articles, published up to and including August 12, 2013, describing changes in renal function over time with PI-based regimens. All available randomized controlled trials (RCTs) were selected; however, to reduce bias, only observational studies recruiting from more than one center and analyzing data from more than 1,000 patients were included. Evidence was qualitatively evaluated according to levels established by the Oxford Centre for Evidence-Based Medicine (OCEBM).

Results: A total of 2,322 articles were retrieved by the initial search. Of these, 37 were selected for full review, comprising 24 RCTs (OCEBM Level 1 evidence: 4 reports of fully double-blinded or blinded with respect to the PI component). The remaining 20 RCTs and 13 observational studies qualified as OCEBM Level 2 evidence. Level 1 evidence showed initial but non-progressive increases in serum creatinine and corresponding decreases in estimated glomerular filtration rate (eGFR), suggesting an

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C. I. Bagnis (✉)
Nephrology Department, Pitie Salpetriere Hospital and UPMC-CNAM-EHESS Research Chair for "Patient Education", Pierre et Marie Curie University, Paris, France
e-mail: corinne.bagnis@psl.aphp.fr

H.-J. Stellbrink
Infektions Medizinisches Centrum Hamburg Study Center, Hamburg, Germany

effect on renal tubular transport of creatinine. Level 2 evidence suggested that atazanavir and lopinavir especially in combination with TDF were associated with non-progressive reductions in eGFR over time, with a decreased risk for the development of chronic kidney disease (CKD) on cessation and without the development of advanced CKD or end-stage renal disease (ESRD); whether these reductions were independent or associated with interactions with coadministered TDF could not be established with certainty. Data on darunavir were insufficient to draw any conclusions. The principal limitation of the reviewed studies was the lack of standardization of creatinine measurements in virtually all studies and the lack of corroborative data on changes in proteinuria or other indices of renal function.

Discussion: In this review, there was little evidence for progressive changes in eGFR, or the development of advanced CKD, or ESRD with lopinavir or atazanavir. Further long-term studies, employing a wide range of validated renal function assessments, are required to fully evaluate potential association of PIs with CKD.

Keywords: Chronic kidney disease; Glomerular filtration rate; HIV infection; Protease inhibitors; Renal function

INTRODUCTION

Overall, chronic kidney disease (CKD) has declined in the combined antiretroviral therapy (cART) era owing to declines in human immunodeficiency virus (HIV)-associated renal disease [1]. However, because patients with HIV are now living longer [2], CKD disease is proportionally becoming an increasingly important cause of morbidity [3] and mortality [4] in this population. The prevalence of moderate or severe renal impairment in patients with HIV infection, defined as a sustained decrease in the estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2 for 3 months or more, ranges from 3.5 to 9.7% [5], with rates of mild renal impairment (eGFR 60–90 mL/min/m^2) being as high as 34.2% [6].

The causes of CKD in patients with HIV have shifted away from HIV-associated nephropathy (HIVAN) [7] toward associated coinfections, such as hepatitis B and/or C [8], behavioral risk factors, such as injecting drug use [9] or over-the-counter medication use [10], and probably most importantly, background factors that also affect the general population, such as aging, hypertension, and diabetes [11–13].

Despite the overall benefit of antiretroviral (ARV) therapy for the reduction of renal disease in HIV [14], there is emerging concern that certain ARVs [15], particularly tenofovir disoproxil fumarate (TDF) [16] with or without a boosted protease inhibitor (PI) [17], may be associated with declines in renal function over time.

Although some individual PIs such as indinavir (IDV) are well known to cause acute kidney injury (AKI) [18] and CKD [19], it is much less certain whether other PIs are associated with CKD either alone or in interaction with nucleoside/nucleotide reverse-transcriptase inhibitors (NRTI/NtRTIs) such as TDF. The recent surge of low-quality evidence in the form of small cohort studies and/or case series reporting renal changes with PI use have contributed to added concerns and confusion as to how clinicians should respond.

There is also additional confusion as to the most appropriate methods to measure renal function in patients with HIV because the commonly used creatinine-based estimating

equations for glomerular filtration rate can be biased in the context of HIV-related muscle wasting [20].

There is, therefore, a need for clarity, based on a review of high-quality evidence. The aims of the current literature review were as follows: via a qualitative data synthesis, to critically evaluate evidence for changes in renal function over time with the currently used PIs such as atazanavir (ATV), darunavir (DRV), fosamprenavir (FPV), lopinavir (LPV), or saquinavir (SQV), when analyzed individually, or as a class effect, or in interaction with TDF coadministration.

METHODS

English language articles on randomized controlled trials (RCTs) and observational studies published over the last 10 years containing data on changes in renal function with the use of ATV, DRV, FPV, LPV, or SQV were critically evaluated. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Definition of Renal Toxicity as Evaluated in this Review

Articles were selected for review if they contained longitudinal data examining CKD as follows: (i) an increase in serum creatinine; and/or (ii) a decrease in estimated creatinine clearance (eCC) as estimated by the Cockcroft–Gault (CG) equation [21]; and/or (iii) a decrease in eGFR as assessed by the Modification of Diet in Renal Disease (MDRD) [22], MDRD-4 [23], or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [24] estimating equations; and/or (iv) an increase in proteinuria or urinary albumin:creatinine ratio (ACR). In addition, we reported RCT discontinuation rates due to renal adverse events (AEs). Articles presenting data on AKI, HIVAN, tubulopathies, or nephrolithiasis were not selected.

In established guidelines from the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation CKD is defined as either kidney damage or decreased kidney function (decreased GFR <90 mL/min/1.73 m^2) for at least 3 months (Table 1) [25, 26]. More recently, the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines have introduced the concept of rapid progression, defined as a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year [27]. Specific issues relating to the measurement of renal function in patients with HIV-1 infection and the relative merits of estimating equations for creatinine clearance and GFR in this population are summarized in the online supplementary material section.

Other Inclusion and Exclusion Criteria

Further criteria for inclusion were as follows: patients with HIV-1 infection; use of PI(s) that are currently recommended in established US and EU treatment guidelines as part of an ARV regimen, either evaluated alone or in comparison with regimens containing other ARVs; RCTs (both double-blind or open-label designs), observational studies, and meta-analyses; English language articles; and a publication date within the last 10 years up to and including August 12, 2013. To reduce bias, observational studies were included only if they had recruited patients from more than one

Table 1 National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease

Stage	Description[a]	GFR (mL/min/1.73 m^2)[b]	Prevalence (%)[c]	Cumulative actions
1	Kidney damage with normal or increased GFR	>90	3.3	Diagnosis and treatment: Treatment of comorbid conditions Slowing progression Cardiovascular disease risk reduction
2	Kidney damage with mild decreased GFR	60–89	3.0	Estimating progression
3	Moderately decreased GFR	30–59	4.3	Evaluating and treating complications
4	Severely decreased GFR	15–29	0.2	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	0.1	Kidney replacement (if uremia present)

Adapted from Levey et al. [25]

[a] Chronic kidney disease is defined as either kidney damage or GFR less than 60 mL/min/1.73 m^2 for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. For stages 1 and 2, kidney damage is estimated using untimed urine samples to determine the albumin:creatinine ratios; greater than 17 mg/g in men or greater than 25 mg/g in women on two measurements indicates kidney damage

[b] Glomerular filtration rate is estimated from serum creatinine measurements using the Modification of Diet in Renal Disease study equation based on age, sex, race, and calibration for serum creatinine

[c] Prevalence for stage 5 is from the US Renal Data System (1998); it includes approximately 230,000 patients treated with dialysis and assumes 70,000 additional patients not receiving dialysis. Prevalence for stages 1–4 is from the Third National Health and Nutrition Examination Survey (1988–1994). Population of 177 million adults aged 20 or more years. *GFR* Glomerular filtration rate

center and had analyzed data on at least 1,000 patients.

Further criteria for exclusion were as follows: if the abstract was unavailable; animal studies; case reports; presenting data in children and/or adolescents <18 years of age; if a conference abstract was superseded by journal publication; if no useable AEs not leading to discontinuation; if the article PDF was unavailable; pharmacokinetic studies; articles examining renal function as a predictor of other outcomes, renal function in ART-naïve patients, or renal function posttransplantation; and other review articles.

Search Strategy

The databases searched were Embase/Medline through the OVID platform and PubMed over the last 10 years up to and including August 12, 2013. Detailed search terms used for both databases are shown in the online supplementary material. Abstracts from the Conference on Retroviruses and Opportunistic Infections (CROI) and the International AIDS Society (IAS) conference were also hand-searched according to the inclusion and exclusion criteria within the same time frame. US and EU treatment

guidelines were also consulted for relevant information.

Because it was not always apparent on abstract screening whether data on PI use would be contained within the main body of the article, a two-stage screening process was adopted. First, abstracts were selected for full-text retrieval according to the inclusion/exclusion criteria, irrespective of whether PIs were mentioned in the title/abstract or not. Second, full-text articles were screened again according to the inclusion/exclusion criteria and were specifically excluded if they did not contain data on currently recommended PIs.

Data Synthesis

Selected articles were weighted according the Oxford Centre for Evidence-Based Medicine Levels of Evidence 1 Table [28]: Level 1 evidence (meta-analyses and randomized double-blind controlled trials); Level 2 evidence (randomized open-label clinical trials or observational cohort studies with prospective cohort studies being weighted above retrospective studies); Level 3 evidence (case–control studies); Level 4 evidence (case series); Level 5 evidence (case reports or opinion). Level 4 or 5 evidence was not evaluated in this review. Within each level of evidence, articles were summarized using a clinically based approach: firstly, studies in treatment-naïve patients versus treatment-experienced patients; and second, studies without concomitant TDF use versus with concomitant TDF use. No quantitative data synthesis was performed. Finally, the evidence obtained above was balanced against indices of study quality known to potentially bias reported outcomes according to established methods [16, 29–32].

RESULTS

Articles Selected

A summary of the article selection process is shown in the PRISMA flow diagram (Fig. 1). Of the 37 articles selected for review, 24 described RCTs, but only 4 of these reported RCTs were fully double-blinded or blinded with respect to the PI component and therefore qualified as Level 1 evidence. The remaining 20 RCTs were not blinded to the PI component or were open-label studies and therefore qualified as Level 2 evidence. Observational studies meeting the criteria for inclusion comprised a further 13 articles.

Level 1 Evidence (Meta-Analyses and RCTs)

Meta-Analyses

No relevant meta-analyses were identified. However, in one meta-analysis of studies employing TDF, a subgroup analysis identified that RCTs showed significantly smaller falls in eGFR than observational studies [16]. This finding is of relevance to this review and could be interpreted in two ways. First, randomization better equilibrates background factors predisposing to CKD and, therefore, RCTs give a more specific evaluation of the influence of ARVs on kidney function; or second, that observational clinical populations contain real-life patients who may exhibit a wider variety of clinical comorbidities (often excluded in RCTs), which may interact with ARVs to increase the risk of CKD. Both of these interpretations may be valid in different circumstances and thus, both forms of evidence should be evaluated.

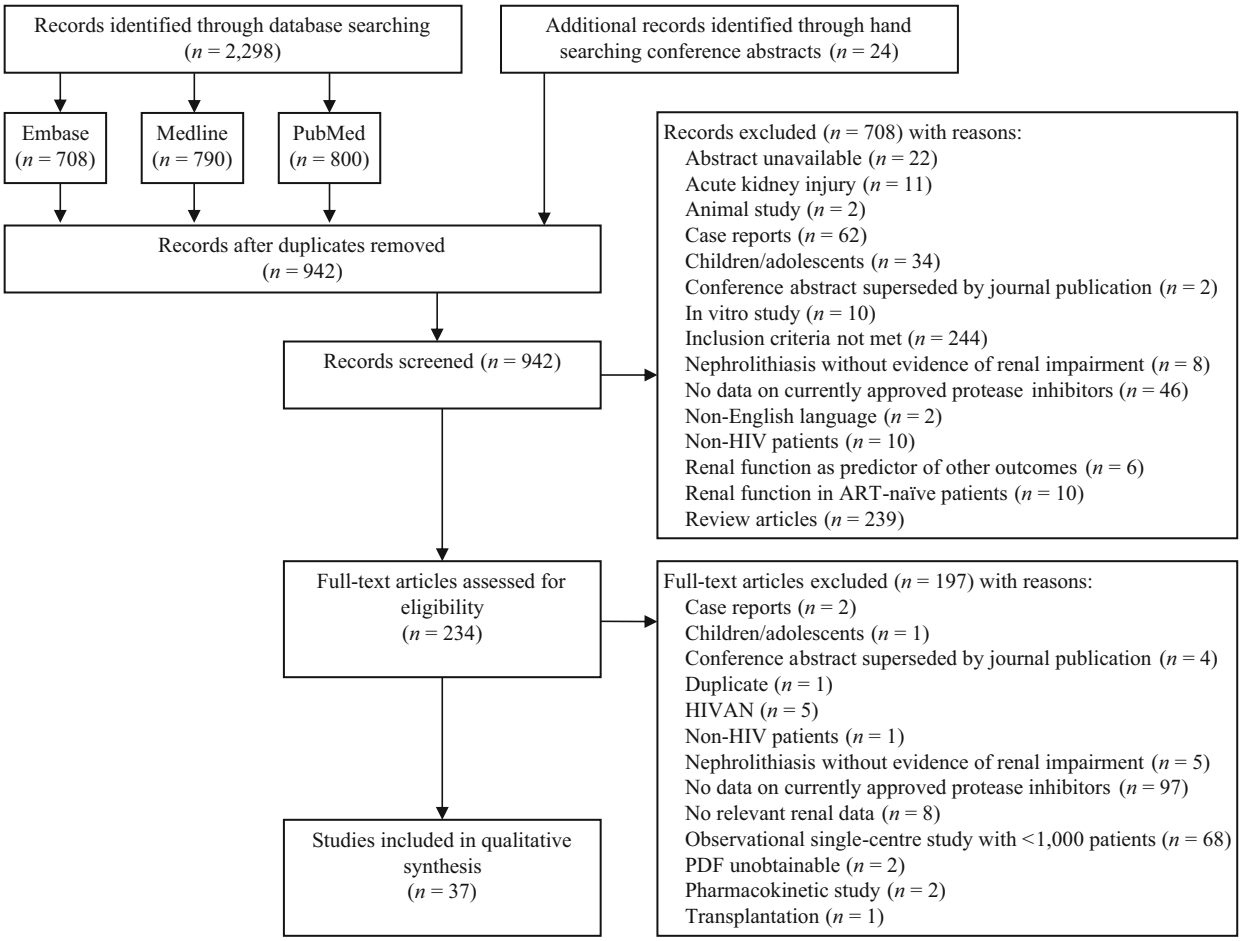

Fig. 1 PRISMA flow diagram. *HIV* Human immunodeficiency virus, *HIVAN* HIV-associated nephropathy

Randomized Double-Blind Controlled Trials

Very few RCT reports were fully double-blinded ($n = 4$), all concerned the use of ATV in combination with TDF in treatment-naïve adults with HIV-1 infection, and are summarized here under Level 1 evidence and in Table 2. The remaining RCT reports were randomized open-label studies ($n = 19$), which are summarized under Level 2 evidence.

In two RCTs, the first comparing cobicistat (COBI) versus ritonavir (RTV) as a pharmacoenhancer of ATV both in combination with emtricitabine (FTC) and TDF [33] and the second comparing the combined formulation 'quad' consisting of elvitegravir (EVG)/COBI/FTC/TDF with RTV-boosted ATV (ATV/r) + FTC/TDF [34], eCC, and eGFR were consistently decreased with both COBI-containing and to a lesser extent ATV/r-containing regimens at 48 weeks (Table 2). In contrast, serum creatinine was not elevated at 48 weeks with a regimen consisting of efavirenz (EFV)/FTC/TDF in a third RCT (Table 2). Given that both COBI and to a lesser extent RTV inhibit the active tubular secretion of creatinine [35], the changes in serum creatinine, eCC, and eGFR are a likely consequence of COBI and/or RTV components rather than a direct effect of ATV on kidney function. The rapid rise in serum creatinine

Table 2 Level 1 randomized controlled trials evaluating renal outcomes in treatment-naïve HIV-1 infected adults commencing PI-containing regimens

Study ID, references	Design	Regimen comparison	Renal outcome	Comment	Limitations
GS-US-216-0114, Gallant et al. [33]	48-week, double-blind, placebo-controlled, double-dummy, multicenter	ATV/COBI + FTC/TDF ($n = 334$) vs. ATV/r + FTC/TDF ($n = 348$)	Median changes from baseline at 48 weeks: Serum creatinine +11.5 μmol/L ATV/COBI group +8.0 μmol/L ATV/r group ($P < 0.001$ vs. ATV/COBI, Wilcoxon rank-sum test) eCC using CG equation −12.9 mL/min ATV/COBI group −9.1 mL/min ATV/r group ($P < 0.001$ vs. ATV/COBI, Wilcoxon rank-sum test)	Increases in serum creatinine and decreases in eCC in both groups stabilized by 8 weeks and did not change thereafter up to 48 weeks. Changes in the COBI arm significantly greater than in the ATV/r arm	No baseline serum creatinine or eCC values Patents with eCC <70 mL/min excluded Short follow-up
GS-236-0103, DeJesus et al. [34]	48-week, double-blind, placebo-controlled, quadruple-dummy, multicenter	EVG/COBI/FTC/TDF 'QUAD' ($n = 353$) vs. ATV/r + FTC/TDF ($n = 355$)	Median changes from baseline at 48 weeks: Serum creatinine +11.0 μmol/L QUAD group +7.0 μmol/L ATV/r group ($P < 0.001$, Wilcoxon rank-sum test) eCC using CG equation −12.7 mL/min QUAD group −9.5 mL/min ATV/r group ($P < 0.001$, Wilcoxon rank-sum test) eGFR using MDRD equation −14.1 mL/min/1.73 m^2 QUAD group −9.6 mL/min/1.73 m^2 ATV/r group ($P < 0.001$, Wilcoxon rank-sum test)	Increases in serum creatinine and decreases in eCC and eGFR occurred in both study groups by 2 weeks, which stabilized by 8 weeks and did not change thereafter up to 96 weeks. Changes in the QUAD arm significantly greater than in the ATV/r arm	Patents with eCC <70 mL/min excluded Few women were recruited (9.6%)
Rockstroh et al. [36]	96-week analysis of GS-236-0103		Median changes from baseline at 96 weeks: Serum creatinine +10.6 μmol/L QUAD group +7.1 μmol/L ATV/r group ($P < 0.001$, Wilcoxon rank-sum test)		

Table 2 continued

Study ID, references	Design	Regimen comparison	Renal outcome	Comment	Limitations
GS-236-0102, GS-236-0103, GS-236-0104, Fisher et al. [71]	48-week, pre-specified integrated analysis of one phase II and two phase III trials	EVG/COBI/FTC/TDF 'QUAD' vs. ATV/r + FTC/TDF vs. EFV + FTC/TDF	Median changes from baseline at 48 weeks: Serum creatinine +11.5 μmol/L QUAD group +7.1 μmol/L ATV/r group +0.9 μmol/L EFV group	Changes first observed by 2 weeks and stabilized by 48 weeks	Abstract presentation. No statistical comparisons quoted Short follow-up

ATV atazanavir, *ATV/r* ritonavir-boosted atazanavir, *eCC* estimated creatinine clearance, *CG* cockcroft–gault, *COBI* cobicistat, *eGFR* estimated glomerular filtration rate, *EFV* efavirenz, *EVG* elvitegravir, *FTC* emtricitabine, *MDRD* Modification of Diet in Renal Disease, *TDF* tenofovir disoproxil fumarate

over the first 2 weeks of treatment, followed by stabilization at 8 weeks (see figure four, page 2,434, in DeJesus et al. [34]), with no further change up to 96 weeks [36] would tend to support this conclusion. However, given that all regimens in these Level 1 studies also contained TDF, an interaction with TDF can neither be assumed nor ruled out.

Level 2 Evidence (Open-Label Clinical Trials or Observational Cohort Studies)

Randomized Open-Label Clinical Trials

Treatment-Naïve patients In studies comparing ATV/r-containing regimens with non-PI-containing regimens, the effect of ATV/r on indices of renal function depended upon the presence or absence of TDF coadministration with ATV/r (Table 3A). In the ARIES study (ClinicalTrials.gov #NCT00440947), neither unboosted ATV nor ATV/r was associated with changes in eGFR (MDRD) after 144 weeks of exposure [37]. Similarly, within the ATV/r + abacavir/lamivudine (ABC/3TC) arm of AIDS Clinical Trials Group (ACTG) A5202, eCC actually increased at 96 weeks [38]. In contrast, within the ATV/r + FTC/TDF arm of ACTG A5202, eCC significantly decreased [38]. Significant decreases in eGFR (CKD-EPI) within the ATV/r + FTC/TDF arms were also observed in the ALTAIR study (ClinicalTrials.gov #NCT00335322) [39] and in the Albini et al. [40] study, with the latter study employing isotope dilution mass spectrometry (IDMS) creatinine standardization and a confirmatory multivariate analysis. These findings suggest that ATV/r interacts with TDF resulting in reductions in eCC and/or eGFR. However, the Albini et al. [40] study did not demonstrate any associated significant change in proteinuria and it remains unclear whether the key interaction

Table 3 Level 2 randomized controlled trials evaluating renal outcomes in treatment-naïve HIV-1 infected adults commencing PI-containing regimens

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
A. Atazanavir					
ARIES, Young et al. [37]	144-week, open-label, multicenter, ABC/3TC +ATV/r for 36 weeks then randomized to maintain or discontinue RTV	ABC/3TC + ATV/r ($n = 419$) vs. ABC/3TC + ATV ($n = 369$)	Median changes from baseline at 144 weeks in eGFR using MDRD equation 0 mL/min/1.73 m^2 (IQR −10.4, 10.9) ATV group 0 mL/min/1.73 m^2 (IQR −9.2, 10.6) ATV/r group (NS, linear mixed-effects models) Proportion ≥25% decrease in eGFR from baseline <5% of patients Cox proportional hazards time to a ≥25% decrease in eGFR from baseline Lower baseline creatinine level ($P < 0.0001$) Higher baseline HIV-1 RNA level ($P = 0.0001$)	No statistically significant changes in eGFR over time or differences in change in eGFR between boosted or unboosted ATV	Abstract presentation Open-label No P values quoted for median change in eGFR No group differences quoted for proportion with ≥25% decrease in eGFR from baseline
ACTG A5202, Daar et al. [38]	96-week, open-label (EFV, ATV/r), double-blind, placebo-controlled (ABC/3TC, FTC/TDF), multicenter	ABC/3TC + EFV ($n = 465$) vs. ABC/3TC + ATV/r ($n = 463$) vs. FTC/TDF + EFV ($n = 464$) vs. FTC/TDF + ATV/r ($n = 465$)	Median changes from baseline at 96 weeks in eCC +7.8 mL/min ABC/3TC + EFV group +6.1 mL/min ABC/3TC + ATV/r group +4.6 mL/min FTC/TDF + EFV group −2.9 mL/min FTC/TDF + ATV/r group ($P < 0.001$ vs FTC/TDF + EFV, signed rank test)	Suggests that ATV/r interacts with TDF for a decline in renal function over time	Open-label Method for eCC not described 32% of patients discontinued third drug (ATV/r or EFV)

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
ACTG A5224s, Gupta et al. [67]	96-week, metabolic sub-study of ACTG A5202	As above, but eGFR endpoints available in 203 out of 269 sub-study participants	Mean change from baseline at 96 weeks in eGFR using the 2012 CKD-EPI-Creatinine–Cystatin-C equation HIV-1 RNA < 100,000 c/mL +10.1 mL/min/1.73 m^2 with EFV −0.6 mL/min/1.73 m^2 with ATV/r ($P < 0.001$ vs. EFV) HIV-1 RNA ≥ 100,000 c/mL +8.1 mL/min/1.73 m^2 with EFV +5.2 mL/min/1.73 m^2 with ATV/r ($P = 0.34$ vs. EFV) Urinary protein:creatinine or albumin:creatinine ratio No significant fold-change differences between ATV/r and EFV	Newer cystatin-C-based equations led to different results than older, creatinine-based equations, with the creatinine-based equations generally showing changes in eGFR of greater magnitude than the cystatin-C-based equations	Abstract presentation. Open-label. Small sample size No numeric data provided to assess changes with ATV/r with or without TDF

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
Elion et al. [72]	48-week, open-label (ATV, FTC/TDF), double-blind, placebo-controlled (COBI, RTV)	ATV/COBI + FTC/TDF ($n = 50$) vs. ATV/r + FTC/TDF ($n = 29$)	Mean percent change from baseline in eCC (CG equation) At 2 weeks −8% mL/min ATV/COBI group −3% mL/min ATV/r group ($P = 0.02$ vs. ATV/COBI, Wilcoxon rank-sum) At 48 weeks −12% mL/min ATV/COBI group −11% mL/min ATV/r group ($P = 0.8$ vs. ATV/COBI, Wilcoxon rank-sum)	eCC was reduced equally at 48 weeks with COBI or RTV enhancement of ATV	Open-label Small sample size Short follow-up
ALTAIR, Dazo et al. [39]	96-week, open-label	EFV + TDF/FTC ($n = 114$) vs. ATV/r + TDF/FTC ($n = 105$) vs. ZDV/ABC + TDF/FTC ($n = 103$)	Mean change from baseline in eGFR (CKD-EPI) At 48 weeks −4.1 mL/min (95% CI −6.8 to −1.4) on ATV/r No significant changes in other arms At 96 weeks No further reductions demonstrated Multivariate analysis; significant predictors of decrease in eGFR to week 48 were older age, higher baseline eGFR, being male, Asian, and on ATV/r	The short-term, non-progressive fall in eGFR in the ATV/r arm may represent a direct effect of ritonavir, ATV or an interaction with TDF	Abstract presentation Open-label Statistical methods not described

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
Albini et al. [40]	48-week, open-label, multicenter	EFV + TDF/FTC ($n = 43$) vs. ATV/r + TDF/FTC ($n = 48$)	Mean change from baseline at 48 weeks in eGFR CKD-EPI creatinine equation +1.7 mL/min/m^2 with EFV −4.9 mL/min/m^2 with ATV/r ($P = 0.009$ vs. EFV, linear mixed-effects model) CKD-EPI cystatin-C equation −5.8 mL/min/m^2 with EFV −14.9 mL/min/m^2 with ATV/r ($P = 0.02$ vs. EFV, linear mixed-effects model) Multivariate regression analysis, controlling for gender, age, hepatitis C virus coinfection, glycemia (≥110 mg/dL), hypophosphatemia (≤2.7 mg/dL), high systolic pressure (≥140 mmHg), CD4+ count (≤200 cells/mm^3), viral load (≥100,000 copies/mL), body mass index, trimethoprim/sulfamethoxazole prophylaxis, and the randomized treatment arm: ATV/r arm associated with an adjusted decrease in eGFR of −6.7 mL/min/m^2 ($P = 0.0046$) using the CKD-EPI creatinine equation but not the CKD-EPI cystatin-C equation Proteinuria No significant treatment group differences in change in proteinuria or microalbuminuria at 48 weeks	Multivariate analysis suggested that ATV/r has either independent or interactive effects with TDF for a decline in renal function over time, but only when assessed using creatinine-based estimating equations Used IDMS standardization of serum creatinine	Open-label Small sample size Short follow-up

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
B. Atazanavir vs. other protease inhibitors					
Aberg et al. [41]	48-week, open-label, multicenter	ATV/r + TDF/FTC ($n = 31$) vs. DRV/r + TDF/FTC ($n = 34$)	Mean change from baseline at 48 weeks in eCC −0.03 (SD: 0.244) mL/min ATV/r group −0.00 (SD: 0.288) mL/min DRV/r group	No effects of ATV or DRV with TDF on renal function decline	Open-label Small sample size Method for calculating CC not described Short follow-up
ALERT, Smith et al. [43]	48-week, open-label, multicenter	ATV/r + TDF/FTC ($n = 49$) vs. FPV/r + TDF/FTC ($n = 45$)	Proportion with >25% decline in eGFR at 48 weeks using the MDRD-4 equation 8.3% in each treatment group Discontinuation due to eGFR decreases <50 mL/min/1.73 m^2 3 patients in the FPV/r group 0 patients in ATV/r group	58% of patients had mild CKD at baseline (eGFR 60–89 mL/min/1.73 m^2)	Open-label Small sample size Short follow-up

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
CASTLE, Molina et al. [42]	96-week, open-label, multicenter	ATV/r + TDF/FTC ($n = 440$) vs. LPV/r + TDF/FTC ($n = 443$)	Mean change from baseline at 96 weeks in serum creatinine ≤3.1 μmol/L in both regimens Median percent change from baseline at 96 weeks in eCC using CG equation −1% in ATV/r group −2% in LPV/r group Proportion of patients with >50% reduction from baseline in eCC 0% in the ATV/r group <1% in the LPV/r group	Both the LPV/r and ATV/r groups showed limited evidence of a small decline in renal function over time, but the study design did not permit an assessment as to whether independent or interactive effects with TDF were present	Open-label Baseline creatinine or eGFR not described No statistical comparisons conducted

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
Vronenraets et al. [44]	48-week, open-label, multicenter	ATV/r + TDF/FTC ($n = 61$) vs. SQV/r + TDF/FTC ($n = 57$)	Mean change from baseline at 48 weeks in: Plasma creatinine +9 μmol/L in SQV/r group +6 μmol/L in ATV/r group ($P = 0.154$ vs. SQV/r, linear mixed-effects model) Increase over first 12 weeks, non-progressive thereafter Treatment difference in mean change from baseline at 48 weeks in: eCC using CG equation −9 mL/min/1.73 m^2 with SQV/r vs. ATV/r ($P = 0.009$, linear mixed-effects model) eGFR using MDRD, MDRD-4, CKD-EPI and cystatin-C No treatment differences identified Multivariate analysis baseline eCC using the CG equation and HIV-1 RNA were the only independent significant predictors for the change in eGFR; treatment group was no longer significant	Both the SQV/r and ATV/r treatment groups showed evidence of initial non-progressive declines in renal function, with limited evidence that this decline was slightly greater in the SPV/r group, but only with the CG equation. eGFR improved with the cystatin-C equation	Open-label Baseline creatinine or eGFR not described

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
C. Lopinavir					
ACTG A5142, Goicoechea et al. [45]	Post hoc analysis	LPV/r + TDF/3TC ($n = 56$) vs. EFV + TDF/3TC ($n = 60$) vs. LPV/r or EFV + 2NRTIs without TDF ($n = 201$) vs. LPV/r + EFV without NRTIs ($n = 157$)	Mean change from baseline at 96 weeks in eCC using the CG equation Univariate analysis −7.8 mL/min LPV/r + TDF/3TC [1] −9.0 mL/min EFV + TDF/3TC ($P = 0.21$ vs. [1]) −2.5 mL/min LPV/r + 2NRTIs ($P = 0.04$ vs. [1], linear mixed-effects models) Multivariate analysis adjusted for age, gender, baseline CD4 and HIV RNA, and pre-therapy eCC LPV/r + TDF/3TC group showed greater eCC declines than the EFV + TDF/3TC group (difference: −7.6 mL/min; 95% CI −12.6, −2.7; $P < 0.01$) Drug transporter polymorphisms ABCC2 3972C>T (rs3740066) was associated with preserved eCC (CC −6.4 mL/min, $n = 166$; CT −3.7 mL/min, $n = 142$; TT +4.4 mL/min, $n = 27$; $P = 0.021$)	Limited evidence that LPV/r may interact with TDF to produce greater declines in eCC, possibly via LPV/r inhibition of drug transporters	Abstract presentation Open-label. Although LPV/r use was subject to random allocation, the choice of the second NRTI, including tenofovir, was made by the study investigator prior to randomization, which could have influenced the assessment of interactive effects between LPV/r and TDF

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
PROGRESS, Reynes et al. [46]	96-week, open-label, multicenter	LPV/r + RAL ($n = 101$) vs. LPV/r + TDF/FTC ($n = 105$)	Mean change from baseline at 96 weeks in eCC using the CG equation −1.43 mL/min LPV/r + RAL group −7.3 mL/min LPV/r + FTC/TDF group ($P = 0.035$ vs. LPV/r + RAL, t test) Proportion of patients shifting from baseline CKD category (eCC ≥90, 60 to <90, and <60 mL/min) to a better CKD category at 96 weeks 9/14 (64.3%) LPV/r + RAL group 2/15 (13.3%) LPV/r + FTC/TDF group ($P = 0.008$, Fisher's exact test)	eCC declined to a greater extent in the TDF-containing regimen suggesting an interactive effect when LPV was administered with TDF	Open-label Baseline serum creatinine or eCC not described

Table 3 continued

Study ID, references	Design	Regimen comparison(s)	Renal outcome	Comment	Limitations
ACTG A5208, Mwafongo et al. [47]	Duration not specified. Open-label, multicenter. Women only. Pre-treatment eCC using CG equation of ≥ 60 mL/min	TDF/FTC + LPV/r ($n = 371$) vs. TDF/FTC + NVP ($n = 370$)	Proportion with events of renal insufficiency (defined as an occurrence of any grade 3 or 4 serum creatinine, or a per-protocol defined treatment modification due to reduced eCC using CG equation) 4.9% in LPV/r group 1.6% in NVP group Multivariate analyses (adjusted for treatment group, prior single dose NVP exposure, and baseline variables of age, Hb, CD4 cell count, BMI, eCC, and HIV-1 RNA load), significant predictors: Renal sufficiency event LPV/r (OR 3.12; 95% CI 1.21, 8.05) higher baseline HIV-1 RNA lower baseline eCC Renal events leading to treatment modification baseline HIV-1 RNA baseline eCC	In the context of a low rate of renal insufficiency events, LPV/r may increase this risk, either independently or in interaction with TDF	Abstract presentation Open-label Duration of exposure not specified Statistical methods not specified

ATV atazanavir, *ATV/r* ritonavir-boosted atazanavir, *BMI* body mass index, *eCC* estimated creatinine clearance, *CG* cockcroft–gault, *CI* confidence interval, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *COBI* cobicistat, *eGFR* estimated glomerular filtration rate, *EFV* efavirenz, *EVG* elvitegravir, *FPV* fosamprenavir, *FTC* emtricitabine, *Hb* hemoglobin, *IDMS* isotope dilution mass spectrometry, *IQR* interquartile range, *LPV* lopinavir, *MDRD* Modification of Diet in Renal Disease, *NS* not significant, *NVP* nevirapine, *RTV* ritonavir, *SD* standard deviation, *SQV* saquinavir, *TDF* tenofovir disoproxil fumarate, *ZDV* zidovudine

is between ATV and TDF or RTV and TDF. Further studies are required to resolve this question.

Regarding differences between ATV/r and other boosted PI regimens, all of these studies employed FTC/TDF backbones. For ATV/r versus RTV-boosted DRV (DRV/r), RTV-boosted FPV (FPV/r), or RTV-boosted LPV (LPV/r), the magnitude of changes from baseline in eCC or eGFR varied but were not significantly different between the two PI/r regimens [41–43]. Using mean change from baseline in eCC (CG), RTV-boosted SQV (SQV/r) appeared to show greater falls in eCC compared with ATV/r (Table 3B) [44].

In studies comparing LPV/r-containing regimens with non-PI-containing regimens, the effect of LPV/r on indices of renal function depended upon the presence or absence of TDF coadministration with LPV/r (Table 3C). In the post hoc analysis from ACTG A5142, a multivariate analysis showed greater declines in eCC with LPV/r + TDF/3TC compared with EFV + TDF/3TC [45]. Greater declines in eCC at 96 weeks were also observed in the LPV/r + TDF/FTC arm versus the LPV/r + raltegravir (RAL) arm in PROGRESS (ClinicalTrials.gov #NCT00711009), with a larger proportion of patients in the LPV/r + RAL arm shifting to a better CKD category at 96 weeks [46]. Similarly in ACTG A5208, events of renal insufficiency were higher in the LPV/r + TDF/FTC arm versus the nevirapine (NVP) + TDF/FTC arm, a finding that was confirmed on multivariate analyses [47]. These findings suggest a similar conclusion to that described for ATV/r, namely an interaction between LPV/r and TDF, especially since the post hoc ACTG A5142 analysis identified relevant drug transporter polymorphisms in whose presence TDF exposures may be increased by LPV/r inhibition of these transporters [45].

Treatment-Experienced Patients In six out of the seven treatment-experienced studies identified, there were no changes to the PI component of the regimen; thus, it was not possible to assess the contribution of the PI component to changes in eGFR or eCC in these studies [48–53].

In an open-label, randomized trial in treatment-experienced patients receiving highly active ARV therapy (HAART) for at least 6 months [the KITE study (ClinicalTrials.gov #NCT00700115)], patients were randomized to switch to RAL + LPV/r ($n = 40$) or to remain on their pre-existing HAART regimen ($n = 20$) [54]. At baseline, there were no statistically significant differences in regimen components between groups with approximately 40% receiving LPV/r, 20% receiving other PIs, 40% an NRTI and 60% TDF; however, baseline eCC (CG equation) was significantly higher in the RAL + LPV/r group. Mean eCC at 48 weeks adjusted for baseline value was 106.1 in the RAL + LPV/r group versus 115.9 mL/min in the continuing HAART group (mean difference 9.7 mL/min; 95% CI −4.7, 24.2; $P = 0.18$). Study limitations included open-label design, small sample size, baseline imbalance in eCC between groups, and the high proportion of patients continuing on a PI in the HAART group making changes in eCC consequent to switching to RAL + LPV/r difficult to interpret. In summary, although adjusted mean eCC was numerically higher in the continuing HAART versus the RAL + LPV/r group, absolute values for eCC were higher in the RAL + LPV/r group by virtue of the imbalance in baseline eCC between the two groups. In addition, the adjusted mean difference was not significant. It is, therefore, unlikely that the switch to LPV/r was associated with meaningful changes in kidney function.

Observational Cohort Studies

Owing to the wide variety of study designs and outcome measures employed, it was not possible to meaningfully tabulate the observational cohort studies. A summary description of these studies is provided as follows.

Treatment-Naïve Patients Studies examining individual PIs.

ATV with or without TDF: A population-based Danish cohort study ($n = 3{,}358$) was conducted to assess renal function and the incidence of CKD, defined as two consecutive eGFR values of <60 mL/min/1.73 m^2 measured >3 months apart, in patients with HIV infection over a 15-year period. At baseline, patients were stratified on the basis of an eGFR (MDRD-4 equation) of <90 mL/min/1.73 m^2 or ≥90 mL/min/1.73 m^2 [55]. In patients with a baseline eGFR of <90 mL/min/1.73 m^2, ATV (−2.00 mL/min/1.73 m^2; 95% CI −3.75, −0.25) and TDF + ATV (−4.06 mL/min/1.73 m^2; 95% CI −6.87, −1.25) were associated with reductions in eGFR from baseline (linear mixed-effects models). CKD incidence rate ratios (IRRs) were estimated using a time-updated Cox-regression model. The overall rate of CKD was low at 1.1 events per 100 patient-years. Female gender, diabetes, hypertension, hepatitis C infection, CD4 cell count <200 cells/μL at baseline, and HIV diagnosis before 1995 were associated with an increased risk of CKD, regardless of baseline eGFR stratum. For patients with baseline eGFR <90 mL/min/1.73 m^2, HAART exposure was associated with an increased risk of CKD (IRR 6.08; 95% CI 2.76–13.41), but event rates in those exposed to TDF ($n = 7$), TDF + PIs ($n = 4$), or TDF + ATV ($n = 10$) were very low limiting interpretability of findings in HAART subgroups.

TDF and amprenavir, ATV, FPV, LPV/r, IDV, nelfinavir, RTV, SQV, or tipranavir: The effects of cumulative and 'ever exposure' to TDF and interactions between TDF and PIs on renal outcomes were evaluated in a retrospective cohort study that included 10,841 patients (from the Veterans Health Administration), all of whom had started ARV treatment between 1997 and 2007 [56]. Associations between TDF and time to first occurrence of proteinuria, rapid decrease in renal function (≥3 mL/min/1.73 m^2 every year), and CKD (eGFR <60 mL/min/1.73 m^2) were assessed using Cox proportional hazards and marginal structural models. During a median follow-up of 3.9–5.5 years, every year of TDF exposure was associated with a 34% increase in proteinuria risk ($P < 0.0001$), a 33% increase in CKD risk ($P < 0.0001$), and an 11% increase in rapid decrease in renal function risk ($P = 0.0033$), which did not appear to lessen 6 months following TDF discontinuation. In analyses conducted to assess the effects of cumulative exposure to other ARV drugs (including PIs), IDV was the only PI that significantly increased the risk of CKD.

Studies analyzing PIs as a class effect.

In the multicenter Canadian Observational Cohort Study, patients with HIV infection starting triple ARV therapy ($n = 1{,}463$) were included in an analysis of markers of renal function after a mean duration of follow-up of 24.6 months [57]. An increase in serum creatinine to a level >120 μmol/L was seen more frequently in patients taking PIs compared with recipients of non-nucleoside(nucleotide) reverse-transcriptase inhibitors (NNRTIs); incidence rate (IR) 5.68 vs. 3.44 occurrences per 100 person-years of follow-up, $P = 0.02$; however, it was unclear whether PIs were used unboosted or boosted with RTV.

In the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) multicenter study, risk factors for chronic renal disease were evaluated in a large cohort of HIV-infected persons ($n = 3,329$) initiating ARV therapy and who were followed over 4 years [58]. RTV-boosted PI (PI/r) use (65% amprenavir/r, 35% LPV/r) with TDF was associated with a higher risk of moderate CKD (eGFR of <60 mL/min/1.73 m^2) and hazard odds ratio was 3.35 (95% CI 1.40–8.02) in multivariate-adjusted Cox proportional models. In contrast, PI/r use (19% ATV/r, 69% LPV/r, 6% other) without TDF was not associated with an increase in moderate CKD (hazard odds ratio 1.04; 95% CI 0.24–4.45). Other factors associated with an increased risk of CKD included Black race, coinfection with hepatitis C virus, lower time-varying CD4+ cell count and higher time-varying HIV-1 RNA load. In adjusted analyses of eGFR (MDRD and CKD-EPI equations) using linear mixed-effects models, ARV therapy overall was associated with a significantly slower rate of decrease in eGFR (from −2.18 pre ART to −1.37 mL/min/1.73 m^2 per year on ART; $P = 0.02$) without evidence of an increased rate of decline in the PI/r with TDF group.

In the ICONA Foundation cohort study, eGFR (MDRD equation) was measured in treatment-naïve patients ($n = 1,505$) pre- and post-ARV commencement [59]. Baseline eGFR was <90 mL/min/1.73 m^2 in 24% of patients; age, female gender, hepatitis, CD4 count, and diabetes pre-ARV therapy were significantly associated with this eGFR level at baseline (logistic regression). An eGFR decrease of >20% from pre-combination ARV therapy levels was identified in 96 patients (6.8 per 100 person-years); older age, female gender, higher baseline eGFR, and current treatment with didanosine (DDI), TDF, or PIs (either unboosted or boosted but not including IDV) were associated with an eGFR decrease of >20% (Poisson regression). However, the absence of ethnicity data to compute eGFR using the MDRD equation limited analysis validity, and the potential interaction between TDF and PIs was not specifically tested.

Patients with Mixed Treatment Experience Studies examining individual PIs.

ATV and LPV: In the EuroSIDA cohort study, HIV-infected patients were assessed for the development of CKD over time from 2004 onwards ($n = 6,843$) [60]. CKD was defined as either two measurements of ≤60 mL/min/1.73 m^2 taken ≥3 months apart for individuals with a baseline eCC of >60 mL/min/1.73 m^2, or a confirmed 25% decrease in eCC for individuals with a baseline eCC of ≤60 mL/min/1.73 m^2 (CG equation standardized for body surface area). Sensitivity analyses using the MDRD and CKD-EPI equations and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) definition of CKD were also performed. Factors associated with the development of CKD were analyzed using Poisson regression adjusted for traditional factors known to be associated with CKD and other potentially confounding variables. During a median 3.7 years duration of follow-up, 225 (3.3%) developed CKD, equating to an incidence of 1.05 per 100 person-years follow-up. With increasing cumulative exposure to TDF and ATV, there was an increased incidence of CKD. The multivariate-adjusted IRRs per year of exposure for TDF, ATV, and LPV/r were 1.16 (95% CI 1.06, 1.25; $P < 0.0001$), 1.21 (95% CI 1.09, 1.34; $P = 0.0003$), and 1.08 (95% CI 1.01, 1.16; $P = 0.03$), respectively. Among covariates included in the model, higher baseline eCC was associated with a reduced risk of CKD; female sex, older age, an AIDS-defining illness during

follow-up, malignancy, hepatitis C infection, hypertension, and diabetes were all associated with an increased risk of CKD.

These results were robust to several sensitivity analyses, using calculations based on the MDRD and CKD-EPI equations; in addition, possible interactive effects between regimen components were tested by censoring patient follow-up on starting TDF, ATV, or PI/r (see figure three, page 1673, in Mocroft et al. [60]). Thus for TDF-treated patients, the adjusted IRR was slightly increased in patients who had not started ATV, indicating that the increased incidence of CKD with TDF cannot be explained by concomitant ATV administration. Although there was a slight decrease in adjusted IRR in ATV-treated patients who had not started TDF, the confidence intervals were too wide to assess whether the increased incidence of CKD with ATV therapy was attributable to concomitant TDF administration.

Patients with prior but not current ATV or LPV/r exposure did not have an increased incidence of CKD compared with those with no prior exposure to ATV or LPV/r, whereas patients discontinuing TDF continued to have a significantly increased incidence of CKD for up to 12 months after discontinuation (see web figure one b in Mocroft et al. [60]). The authors concluded that changes in kidney function with LPV/r and ATV were generally reversible on cessation of these PIs.

In the prospective multinational D:A:D cohort study, eCC (CG equation standardized for body surface area) was used because ethnicity data were restricted in several study cohorts. Enrolled patients with HIV infection ($n = 22{,}603$) and normal baseline renal function (eCC of $\geq$90 mL/min/1.73 m^2) were followed from January 1, 2004 until they were identified as having a confirmed eCC of $\leq$70 mL/min/1.73 m^2 (the hypothesized point at which renal interventions and/or ARV switching may be required) or a confirmed eCC of $\leq$60 mL/min/1.73 m^2 (indicating moderately severe CKD) or until the final eCC measurement during the follow-up period [61]. Poisson regression models were used to determine predictors and eCC-related discontinuations of ARV treatment. During a median 4.5 years duration of follow-up, an eCC of $\leq$70 mL/min/1.73 m^2 occurred in 2.1% of patients (IR 0.478 cases/100 person-years). CKD was identified in 131 (0.6%) of patients (IR 0.133 cases/100 person-years). Compared with patients with a current eCC of $\geq$90 mL/min/1.73 m^2, significantly higher rates of TDF discontinuation (adjusted IRR 1.72; 95% CI 1.38, 2.14), but not other ARV drugs, were identified in patients with a current eCC of 60–70 mL/min/1.73 m^2. The cumulative use of TDF (adjusted IRR 1.18/year; 95% CI 1.12, 1.25) and ATV/r (adjusted IRR 1.19/year; 95% CI 1.09, 1.32) was independent predictor of a confirmed eCC of $\leq$70 mL/min/1.73 m^2, but not of CKD. LPV/r was a significant predictor for a confirmed eCC of $\leq$70 mL/min/1.73 m^2 (adjusted IRR 1.11/year; 95% CI 1.05, 1.17) and CKD (adjusted IRR 1.22/year; 95% CI 1.16, 1.28). Censoring for use of other ARV drugs (including abacavir) administered during the study or before the start of the study (in the case of treatment-experienced patients) did not affect these results. Cumulative exposure to TDF, ATV/r, and LPV/r increased IRRs for a change in eCC from 90 to $\leq$70 mL/min/1.73 m^2, which nevertheless fell back to values approaching unity at least 1 year after discontinuing therapy with these agents. In summary, TDF, ATV/r and LPV/r were independent predictors of chronic renal impairment in HIV-infected individuals without pre-existing impaired renal function.

In a subsequent analysis of data from the D:A:D study, 35,192 patients with HIV infection

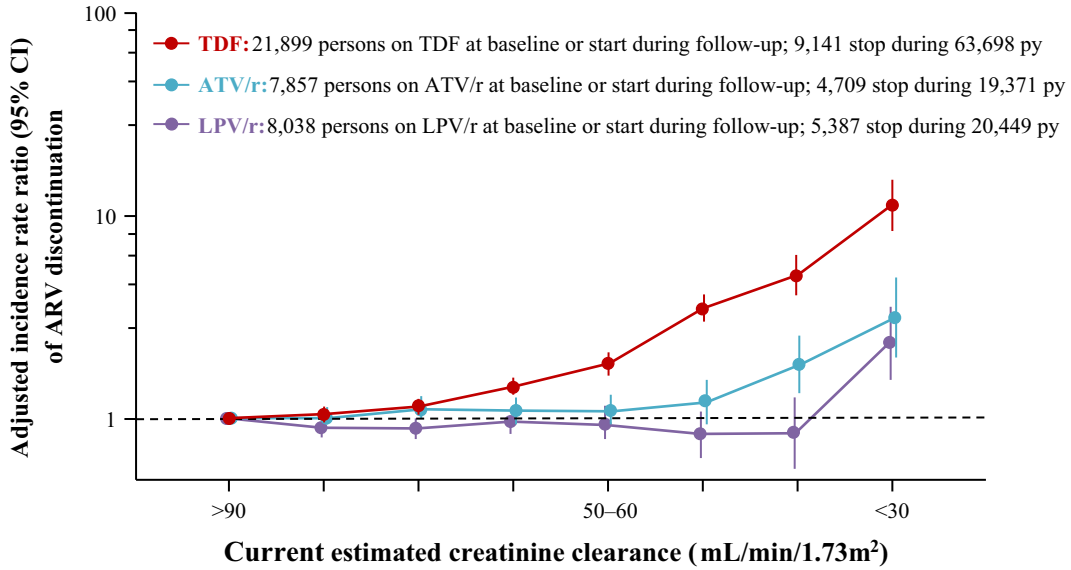

Fig. 2 ARV discontinuation according to current estimated creatinine clearance level in the D:A:D study. Models were adjusted for CD4 count nadir, gender, ethnicity, HIV transmission risk, enrollment cohort and prior acquired immune deficiency syndrome (all at baseline) and hepatitis B virus, hepatitis C virus, smoking status, hypertension, diabetes, cardiovascular events, age, and CD4 count (as time-updated values). Adapted from Ryom et al. [62]. *ARV* antiretroviral, *ATV/r* ritonavir-boosted atazanavir, *CI* confidence interval, *HIV* human immunodeficiency virus, *LPV/r* ritonavir-boosted lopinavir, *py* person-years, *TDF* tenofovir disoproxil fumarate

were followed up for several years [62]. Patients without advanced CKD or end-stage renal disease (ESRD) at the start of the study (January 2004) were included and followed up until a diagnosis of advanced CKD/ESRD was made 6 months after the final study visit or until January 2012. Advanced CKD was defined as two eCC results of <30 mL/min/1.73 m^2 ≥3 months apart and patients with ESRD were on dialysis for ≥3 months or had undergone renal transplantation. Poisson regression models were used to investigate ARV discontinuation rates in relation to the latest eCC assessment, and to identify variables associated with the development of advanced CKD/ESRD; the model included adjustments for various factors, including age, gender, ethnicity, HIV RNA level, CD4+ cell count, traditional risk factors (e.g., hypertension, diabetes), and treatment with TDF and PIs.

Over the median follow-up period of 6.2 years, 135 individuals (0.4%) developed CKD/ESRD (CDK, $n = 114$; and ESRD, $n = 21$) (IR 0.67 per 1,000 person-years). At the 5-year evaluation, progression to advanced CKD/ESRD was estimated to be 0.32 per 1,000 person-years. As the eCC declined, rates of switching from ATV/r, LPV/r, and TDF increased, but this was especially the case for TDF (Fig. 2). After adjustment, those exposed, but currently off TDF, had similar IRRs for advanced CKD compared to those unexposed, while those currently on TDF had reduced rates (note: that those with reduced eCC while on TDF were more likely to discontinue). None of the other ARV drugs included in the analysis showed a significant effect on IRRs for CKD/ESRD. However, the adjusted IRR of CKD/ESRD was increased with diabetes, hypertension, lower baseline eGFR, and decreased in those who had

never smoked and in patients with higher current CD4 counts. Of interest, as eCC fell so did rates of ARV discontinuation/switching, which would suggest that in a real-life setting, clinicians actively monitor renal function and largely prevent advanced ARV-related renal disease.

ATV, *LPV*, *FPV*, *SQV*, *IDV*, *nelfinavir:* In a retrospective cohort analysis, patients ($n = 7{,}378$) from seven large HIV reference centers (with prospective HIV databases) in France were assessed for risk factors for CKD from 1993 to 2006 [63]. The primary outcome was the time to CKD, which was defined as two consecutive measures of eGFR ≤60 mL/min/1.73 m^2 over ≥3 months (MDRD equation without the term for race as ethnicity data was unavailable). Factors predictive of time to CKD were assessed using a Cox proportional hazards model with delayed entry. In this study, time of entry was defined as the date of the first creatinine measurement. In real-life cohort data, it is common for patients to enter the study at varying time points. There is a substantial possibility that patients with delayed entries may have very different hazard ratios for CKD compared with those entering at the start of the study period; for example, only older potentially more nephrotoxic ARVs being available earlier versus newer potentially less nephrotoxic agents being available later. Allowing for delayed entry enables patients experiencing CKD events within a similar time period, during which ARV use is likely to have been more consistent, to be compared with each other. Patients entering and experiencing CKD events later in the study, during which ARV use may have changed, will also be compared with each other. Thus, hazard ratios for CKD events using this methodology will take into account changing patterns of ARV use over time. A wide variety of ARVs, including PIs (ATV, LPV, FPV, SQV, IDV, nelfinavir), were assessed for their potential association with CKD. CKD was identified in 4.7% of patients. In multivariate analyses, significant risk factors for CKD were the occurrence of AKI, hypertension, recent exposure to IDV, TDF or ABC, and past exposure to TDF. None of the other PIs tested were associated with CKD. However, the potential interaction between TDF and PIs was not assessed.

Studies analyzing PIs as a class effect.

Participants with HIV infection initiating TDF in combination with a PI- or NNRTI-based regimen were assessed in a large cohort study (NA-ACCORD), reported as an abstract [64]. At baseline, most of the 5,801 patients were treatment-experienced, and 3,575 patients initiated treatment with TDF in combination with a PI-based regimen. During 2.3 years (TDF + PI) and 2.1 years (TDF + NNRTI) of treatment, the median change in eGFR was −1%/year for both groups (adjusting for a history of hypertension and diabetes, age >50 years, and Black race). Among individuals with the most marked declines in renal function of ≥8%/year, those who received treatment with TDF + PI had the most marked decreases in eGFR. However, at baseline, the TDF + PI group was more likely to be of Black race ($P < 0.01$) and older in age ($P = 0.03$); given that both factors are associated with a higher risk of CKD, the clinical significance of changes in renal function in this study cannot be determined.

In a prospective study using data from the Swiss HIV Cohort Study database, patients were identified who were ARV-naïve or whose ARV therapy had been interrupted for ≥12 months ($n = 1{,}078$) [65]. Selected patients were required to have a baseline eCC (CG equation) and at least two eCC values after starting or restarting combination ARV therapy. The authors stated that the CG equation was preferred over the

Table 4 Discontinuation rates due to renal AEs from randomized trials in treatment-naïve patients examining TDF plus a boosted PI versus randomized trials in treatment-naïve patients examining TDF plus INSTI or NNRTI

Study	*n*	Follow-up (weeks)	Discontinuation due to renal AE (%)	Reason(s)
TDF + boosted PI				
ABT-730 (LPV/r) [73]	664	96	0	
ARTEMIS (DRV/r or LPV/r) [74]	689	96	0	
GEMINI (SQV/r or LPV/r) [75]	337	48	0	
ARTEN (ATV/r) [76]	193	48	0	
CASTLE (ATV/r) [42]	440	96	0.2%	Fanconi syndrome
CASTLE (LPV/r) [42]	443	96	0.2%	Proteinuria
HEAT (LPV/r) [77]	345	96	0.6%	ARF
ABT-418 (LPV/r) [78]	190	96	1.1%	ARF
GS-US–164–0115 (BATON) (ATV/r) [79]	100	48	1.0%	Grade 2 creatinine
GS-US-216-0114 (ATV/r) [33]	348	48	1.4%	↑ serum creatinine Proximal tubulopathy
GS-US-216-0114 (ATV/cobicistat) [33]	344	48	1.7%	↑ serum creatinine Proximal tubulopathy
ACTG 5202 (ATV/r) [38]	464	96	1.3%	↓ creatinine clearance
ALERT (ATV/r) [43]	53	48	0	
ALERT (FPV/r) [43]	53	48	5.7%	GFR <50 mL/min
TDF + INSTI or NNRTI				
STARTMRK (RAL or EFV) [80]	563	48	Not reported	
QDMRK (RAL) [81]	770	48	Not reported	
GS–99–903 (EFV) [82]	299	144	0	
GS–01–934 (EFV) [83]	257	144	0	
ECHO/THRIVE (RPV or EFV) [84]	1096	96	0	
ASSERT (EFV) [85]	193	96	0	
ARTEN (NVP) [76]	376	48	0.3%	↓ GFR
ACTG 5202 (EFV)	461	96	0.7%	↓ creatinine clearance

AE adverse event, *ATV/r* ritonavir-boosted atazanavir, *DRV/r* ritonavir-boosted darunavir, *EFV* efavirenz, *FPV/r* ritonavir-boosted fosamprenavir, *GFR* glomerular filtration rate, *INSTI* integrase strand inhibitor, *LPV/r* ritonavir-boosted lopinavir, *NNRTI* non-nucleoside(nucleotide) reverse-transcriptase inhibitor, *NVP* nevirapine, *PI* protease inhibitor, *RAL* raltegravir, *RPV* rilpivirine, *SQV/r* ritonavir-boosted saquinavir, *TDF* tenofovir disoproxil fumarate

MDRD equation as they considered it to correct for weight changes during the period of the study (the MDRD equation was used in secondary sensitivity analyses). However, the MDRD equation adjusts for body surface area, which is influenced by changes in weight. Over 24 months, TDF-containing regimes were associated with significant median reductions in eCC and shorter time to a sustained 10 mL/min reduction in eCC, regardless of treatment experience. In multivariate Cox proportional hazards models, TDF use (HR 1.84; 95% CI 1.35–2.51) and boosted PI use (HR 1.71; 95% CI 1.30–2.24) were significantly associated with time to a sustained 10 mL/min reduction in eCC; other significant associations were female gender, diabetes, and higher baseline eCC. The interaction term between TDF and boosted PI use was not significant ($P = 0.2$). Consistent results were reported using the DMDRD equation. However, follow-up was too short to assess whether initial reductions in eCC were stable or progressive.

The ANRS CO3 Aquitaine Cohort study, investigated the prevalence of renal impairment, defined as an eCC (CG equation) of 60–90 mL/min (mild), 30–60 mL/min (moderate), 15–30 mL/min (severe) or <15 mL/min (end-stage), in a cross-sectional retrospective survey of a French hospital-based cohort of patients with HIV infection ($n = 2{,}588$) [6]. Across the study cohort, the overall prevalence of renal impairment was very high at 39%; mild, moderate, severe, and ESRD were present in 34.2%, 4.4%, 0.3%, and, 0.2% of patients, respectively. In logistic regression models, increasing duration of TDF exposure was associated with an increased risk of mild renal impairment, whereas PIs (with the exception of IDV) were not associated with this outcome. However, no analysis of the potential interaction between TDF and PIs was presented. Other factors associated with an increased risk of renal impairment were female gender, older age, body mass index (BMI) <22 kg/m^2, and hypertension.

In a further prospective analysis of the ANRS CO3 Aquitaine Cohort, patients with HIV-1 infection and a baseline eGFR (MDRD equation) of >60 mL/min/1.73 m^2 ($n = 2{,}692$) were followed up for a median duration of 3.4 years [66]. At the end of the follow-up period, 95% of patients had received ARV therapy and among these patients 35% had received TDF in combination with a PI/r (ATV 41%, LPV 35%, FPV 11%, SQV 4%, others 9%) for >6 months. The determinants of CKD, defined as an eGFR of <60 mL/min/1.73 m^2 on two consecutive occasions ≥3 months apart, were assessed using a Poisson regression model. The IR of CKD, defined as an eGFR of <60 mL/min/1.73 m^2 on two consecutive occasions ≥3 months apart, was low at 1.01 cases per 100 patient-years. In univariate Poisson regression analysis, ever having been exposed to a PI was associated with an increased incidence of CKD (IRR 3.0; 95% CI 1.5, 5.7; $P = 0.008$). In multivariate analyses, an independent effect of PIs was no longer evident, but exposure to a PI in combination with TDF for at least 6 months appeared to increase the incidence of CKD [IRR for TDF without PI for ≥6 months 1.8 (95% CI 1.0, 3.3) vs. IRR for TDF with PI for ≥6 months 3.5 (95% CI 2.1, 6.1); P value for difference = 0.0006]. Other associated risk factors were ever having been exposed to TDF (IRR 2.5; 95% CI 1.5, 4.1; $P = 0.0002$), female gender, older age, low baseline eGFR, diabetes, hyperlipidemia, and low CD4 count. However, the median exposure to PIs (3.6 years) was longer than that for TDF (1.9 years) making interpretation of interactive effects difficult. The authors suggested that a combination of TDF with a PI requires careful

monitoring to prevent the development of CKD and that further studies are required to identify if the effect varies across individual PIs.

Level 3 Evidence (Case–Control Studies)

No case–control multicenter studies of sufficient sample size to meet the inclusion criteria of this review were identified.

Discontinuation Rates Due to Renal AEs in RCTs Involving PIs and Comparators

Discontinuation rates due to renal AEs from clinical trials in treatment-naïve patients receiving TDF plus a boosted PI versus trials in treatment-naïve patients receiving TDF plus an integrase strand inhibitor (INSTI) or NNRTI are summarized in Table 4. Discontinuation rates due to renal AEs with TDF plus LPV/r or ATV/r were low and ranged from 0 to 1.2%, and were similar to those with TDF plus an INSTI or NNRTI (0–0.7%). A single study in patients receiving FPV showed a discontinuation rate of 5.7% due to eGFR falling to below 50 mL/min.

DISCUSSION

Only four reports describing three studies were available that fell under the category of Level 1 evidence. All examined ATV in treatment-naïve patients who were also receiving concomitant TDF, and all used non-IDMS-standardized serum creatinine measurements and associated CG or MDRD estimating equations. Initial decreases in serum creatinine occurred in ATV/r + TDF-based regimens, but not in EFV + TDF-based regimens, that were nevertheless non-progressive after 8 weeks and up to 96 weeks. COBI as a pharmacoenhancer of ATV or EVG appeared to be associated with greater initial drops in eCC or eGFR vs ATV/r. Level 1 evidence would suggest that the changes in serum creatinine, eCC, or eGFR with ATV are largely determined by the inhibition of renal tubular creatinine secretion by RTV or COBI pharmacoenhancement rather than by any nephrotoxic effect of ATV. However, given that all regimens in these Level 1 studies contained TDF, an interaction with TDF can neither be assumed nor ruled out.

Regarding Level 2 RCT evidence, most studies were small (<100 patients per arm) and only one evaluated changes in proteinuria. These studies generally showed reductions in eGFR with PIs in combination with TDF. Of the larger studies reviewed, A5202 showed reductions in ATV/r in combination with TDF, but in ARIES, in which TDF was not used, no changes in eGFR were demonstrated with either RTV-boosted or unboosted ATV.

Taken together, the RCT data would suggest little evidence for an independent effect of PIs on decline in renal function, especially since studies examining changes in proteinuria with PIs without concomitant TDF use have shown no change in proteinuria with treatment [67, 68]. Evidence for an interactive effect of PIs with TDF on initial but non-progressive declines in eGFR was consistent and was demonstrated across ATV and LPV; however, few studies conducted multivariate analyses and of those that did, three showed that the PI effect remained significant after adjustment [39, 40, 47] and the fourth that it was no longer significant [44]. Regarding a potential mechanism for this PI–TDF interaction, the post hoc ACTG A5142 analysis suggested that LPV/r inhibition of drug transporters may increase TDF exposures [45]. It should also be noted that most RCTs excluded patients with baseline eGFR <70 mL/min, and that only one Level 2 RCT used IDMS-standardized creatinine measurements, limiting the generalizability of

these findings to the wider population of patients with HIV-1 infection. RCT data on DRV was insufficient to draw conclusions.

A vast literature constituting Level 2 observational evidence was identified, much of low quality. Therefore, to reduce bias, studies were only reviewed if they included more than 1,000 patients from more than 1 study center. In prospective cohorts of treatment-naïve patients with well-preserved renal function [58], ARV therapy overall was associated with a slower rate of decline in eGFR over time, in parallel with increases in CD4 count and decreases in HIV-1 RNA load. However, risk for CKD was increased with amprenavir/r and LPV/r in combination with TDF but not for ATV/r or LPV/r without TDF. In populations with greater proportions of patients having baseline renal impairment [55, 58, 59], PIs independently or in combination with TDF were associated with an increased risk of CKD. In prospective studies of patients with mixed treatment experience, consistent evidence emerged for an increased risk of CKD with TDF, but the clinical significance of changes in renal function with other PIs was less certain. Data from the EuroSIDA study indicated that any or cumulative exposure to TDF, ATV, and to a lesser extent LPV/r, was associated with an increased incidence of CKD on multivariate analyses [19, 60]. Testing possible interactions between TDF and PIs through censoring confirmed an independent effect of TDF, but could not provide certainty as to whether the effect of PIs was independent or better explained by an interaction with TDF. The increased risk of CKD with ATV, LPV/r, and TDF, however, returned to levels seen in patients never exposed to these agents immediately following discontinuation of ATV or LPV, and after 1 year following discontinuation of TDF. Data from the D:A:D study in patients with normal baseline renal function demonstrated that the increased risk of CKD with TDF, ATV/r and LPV/r was decreased to unity 1 year after discontinuing these ARVs [61]. These findings from the EuroSIDA and D:A:D cohorts could either suggest that the potential nephrotoxicity of these agents was reversible on cessation, or that for individuals who have not already developed CKD, the rate of developing CKD was reduced after cessation. Further analysis of appropriately designed long-term studies is required to resolve this question. A subsequent analysis of the D:A:D cohort suggested that ATV/r and LPV/r were not, however, associated with the development of advanced CKD or ESRD [62]; discontinuation analyses by current eGFR level suggested that TDF discontinuation may protect against the development of advanced CKD/ESRD in these patients. Data from other cohorts provided conflicting conclusions as to whether the increased risk of CKD was attributable to an independent effect of PIs as suggested in the Swiss Cohort study [65] or only in interaction with TDF as suggested in the CO3 Aquitaine Cohort study [66].

Taken together, the prospective observational data would suggest that currently used PIs such as ATV/r or LPV/r are associated with modest reductions in eGFR, which may or may not be associated with interactions with TDF, but do not appear to lead to advanced CKD/ESRD. Data on other currently used PIs such as DRV/r were completely lacking. Data from retrospective observational studies provided similar findings to those from prospective studies.

An initial drop in eGFR in the short term with stabilization thereafter was seen in many studies. Longer term studies are required to ascertain whether the rate of decline reached after leveling off is equivalent to the rate of

decline expected for age or whether the rate of decline remains elevated even when taking into account age and other HIV-related and general comorbidities. However, the general assumption that GFR decreases with age in a regular manner might be correct at a population level but not necessarily at the individual level where factors such as hyperfiltration may alter GFR estimates [69]. Therefore, short-term changes in estimates of renal function have to be viewed with some caution if not paralleled by other signs of renal dysfunction.

Differences in the interpretation of renal function changes between estimating equations were evident, particularly between the newer cystatin-C-based methods [40, 44, 67] and the older creatinine-based methods, which could have arisen from a number of different mechanisms. The initial decline in eGFR followed by stabilization observed in many studies using creatinine-based estimating equations, raise the possibility that the greater changes in eGFR with boosted PIs might be due to RTV- or COBI- induced inhibition of the renal tubular transport of creatinine rather than any effect on renal function per se. Given the fact that cystatin-C is elevated in untreated HIV infection and decreases on ART initiation [70], the cystatin-C-based equations actually led to an increase in eGFR in ACTG 5224s [67] and in another study [44]. This equation is probably not suitable for monitoring renal function in the dynamic situation of ART initiation, but might be suitable later on when HIV replication is suppressed. Only 2 of the reviewed studies provided data beyond creatinine, cystatin-C or their associated estimating equations, such as changes in proteinuria [40, 67]; thus, the clinical significance of these changes in eGFR remains uncertain.

The discontinuation rate from clinical trials due to renal events was very low and comparable between PIs + TDF versus INSTI or NNRTI + TDF, suggesting that PIs as a class (with the exception of IDV) do not cause clinically significant renal impairment. These RCT data are supported by analyses of discontinuations due to renal events in cohort studies, which indicate that the risk of CKD with LPV/r and ATV decreased on cessation of therapy, irrespective of baseline eGFR status [60, 61]. Taken together, these findings from RCTs and real-life cohort studies would suggest that the commonly used PIs, LPV/r, and ATV are not associated with progressive impairment in renal function.

This systematic review has a number of strengths. To our knowledge, this represents the most comprehensive review of the potential association of PIs with CKD undertaken. We attempted to summarize all available RCT data and, in order to reduce bias from small observational studies or case series, pre-defined criteria were established to select only those observational studies least likely to be subject to bias. We also structured our evaluation using the OCEBM levels of evidence criteria to allow readers to easily assess the strength of available evidence.

A number of limitations, inherent to the nature of the data being evaluated, were also noted. The available data on CKD were heavily influenced by year of introduction of ARVs, which could introduce bias; thus, many RCTs and cohort studies were identified using ATV/r or LPV/r, but only a single small RCT using DRV/r. RCT data should have been less subject to bias owing to the process of randomization; however, many of these trials were of small sample size, of short duration (48 weeks or less), showed a low rate of renal events, and few conducted multivariate analyses. All but one of the RCTs reviewed were in treatment-naïve patients, making it difficult to assess changes in renal

function, since there is an overlap between improvement in kidney function secondary to virological suppression and possible nephrotoxic effects of ARVs. Examining changes in renal function in treatment-experienced patients switched to a PI-containing regimen potentially provides useful information on changes attributable to PIs; however, renal function in this context is also difficult to assess because of the potential continuing nephrotoxic effects of prior ARV exposure. Only one RCT examined a PI-switch strategy, but the observed changes were uninterpretable owing to methodological difficulties [54]. Most of the published literature on renal function with ARVs was in the form of observational studies, the majority of which were small studies from single centers. Although our selection criteria excluded single-center studies with less than 1,000 participants, not all of the selected studies performed multivariate analyses, which in the observational study setting is essential to avoid potential bias arising from the lack of randomization. However, despite the use of multivariate analysis, it is nearly impossible to adequately control for all potential sources of baseline imbalances in observational studies. In addition, observational studies can be associated with other forms of bias or difficulties in interpretation as follows. Channeling bias may have influenced the assessment of changes in renal function for some PIs. For example, because ATV/r has a more favorable lipid profile than LPV/r, ATV/r may have been used more frequently in patients with metabolic/cardiovascular diseases (i.e., conditions that pre-dispose to kidney disease). In addition, ATV/r is commonly used in combination with TDF. The observational studies employed a wide range of statistical methodologies, ranging from Poisson regression models to Cox proportional hazards models with or without delayed entry. Flandre et al. [63] have argued that Cox proportional hazards models with delayed entry are essential to accurately assess CKD risk because of the changing pattern of ARV availability over time and the influence of cumulative exposure to prior ARVs. Thus, there are significant problems to establishing causality in observational studies with an associated risk of misattributing the development of CKD to ARV use. The majority of studies either used the CG equation (not best suited for assessing renal function in patients with HIV-1 infection and not IDMS-validated), or used the original MDRD equation (not IDMS-validated). The variability in eCC measurement in studies using the CG equation or in eGFR using the original MDRD equation, limits the interpretation of many of these studies; for example, the D:A:D cohort study, which used the CG equation in patients with normal baseline renal function for whom variability would be expected to be greater. Although some studies employed estimating equations that have been validated using IDMS standardization, CKD-EPI [39, 40, 44, 58, 60, 67] and MDRD-4 [43, 44, 55], only one of these studies specifically mentioned in the methods section that IDMS standardization of serum creatinine measurement had been employed [40]. Of note, many of the source publications described eGFR to be measured by the CG equation when this equation represents a measurement of eCC rather than eGFR; under these instances, we described these studies as having measured eCC. Finally, only two studies examined rapid progression of CKD with ARVs [56, 64].

CONCLUSIONS

This review identified limited evidence that currently used PIs, such as LPV/r and ATV/r were associated with non-progressive

reductions in eGFR without an elevated risk for the development of advanced CKD or ESRD. Whether the changes in eGFR with PIs were independent, or as a result of inhibition of renal tubular creatinine secretion by RTV or COBI pharmacoenhancement, or as a result of interactions with other ARVs such as TDF could not be established with certainty. Very few of the reviewed studies included a broader range of renal function assessments beyond serum creatinine, eCC/eGFR estimating equations; thus, the clinical significance of these findings remains uncertain. Further long-term clinical trials, employing a wide range of appropriate renal function assessments (e.g., IDMS-standardized creatinine measurement, IDMS-validated eGFR equations, ACR) and specific renal endpoints (e.g., rapid progression of CKD) analyzed with sufficient statistical power, are required to fully understand any potential nephrotoxic effects of PIs. However, to place these findings in context, it is important to highlight that a number of studies demonstrated that, overall, ARV therapy reduced the risk for CKD, and that HIV-related factors, such as low CD4 or high viral load, hepatitis coinfection, previous episodes of AKI, or traditional risk factors, such as advancing age, female gender, hypertension and diabetes significantly increased risk for CKD. Thus, potential changes in renal function with PIs should be assessed within the framework of the overall benefit of ARV therapy and the importance of addressing associated non-ARV therapy-related risk factors. Finally, in clinical practice regular monitoring of renal function should be undertaken for all patients with HIV infection, regardless of ARV therapy usage.

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