Nephrotoxicity of Antiretroviral Agents: Is the List Getting Longer?

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(See the major article by Ryom et al on pages 1359–69.)

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The article by Ryom and colleagues [1] in this issue of the Journal is another in an expanding literature on the effects of antiretroviral agents on the kidney. With prolonged exposure to effective long-term antiretroviral therapy (ART), we are now in an era in which complications of therapy have become more important than the consequences of human immunodeficiency virus (HIV) infection itself.

A number of factors make the kidneys particularly vulnerable to potential toxins. High renal blood flow (20% of cardiac output) delivers large quantities of toxins to the kidney. Toxins are concentrated in the ultrafiltrate because of absorption of water and solute, exposing epithelial cells to high concentrations and allowing crystallization. Finally, reabsorption or secretion of toxins allows high concentrations within tubular epithelial cells. It is not surprising that we may be seeing kidney toxicity as a result of prolonged exposure to a number of antiretroviral agents.

The current study of D:A:D cohort participants includes a large number (22,603) of ART-exposed individuals with normal baseline kidney function (estimated glomerular filtration rate [eGFR], >90 mL/min). The decline in eGFR by >20 mL/min, to <70 mL/min (an arbitrary cutoff that the authors deemed to be one at which interventions would begin to occur), was associated with the use of tenofovir (TDF), ritonavir-boosted atazanavir (ATV/r), and ritonavir-boosted lopinavir (LPV/r). Moderately severe chronic kidney disease (CKD), defined as an eGFR of ≤60 mL/min, was associated with only LPV/r use. Not surprisingly, TDF was more likely to be discontinued in patients with an eGFR of 60–70 mL/min. An earlier study by the EuroSIDA cohort (a subset of the D:A:D cohort) by Mocroft and several of the authors of the current study [2] demonstrated similar results in a smaller population (n = 6843). The EuroSIDA study, despite several limitations discussed by the authors, was the first large study to demonstrate high rates of CKD (1.05 cases per 100 person-years), with a strong association between CKD and TDF and, unexpectedly, between CKD and ATV/r. There was also an association of marginal statistical significance between CKD and LPV/r. Of note, this earlier study included patients with abnormal baseline kidney function and defined CKD as an eGFR of <60 mL/min, for those with a baseline value of >60 mL/min, and as an eGFR change of 25%, for those with a baseline value of <60 mL/min. In the current study, the investigators chose to look at a more homogenous population with normal baseline eGFR, which included a greater number of ART-naive patients, perhaps more closely reflecting the present-day ART-treated population.

A limitation acknowledged by the authors is their use of the Cockcroft-Gault formula to calculate eGFRs. They were limited to the use of this formula because of the unavailability of race data, which are needed for the other estimating formulas. The Cockcroft-Gault formula, which estimates the creatinine clearance rate, has not performed as well as the Modification of Diet in Renal Disease (MDRD) formula in the general population, and since its initial publication in 1999 [3], the MDRD formula has become widely accepted as a more accurate estimate of GFR than the Cockcroft-Gault formula [4]. The MDRD formula subsequently came under scrutiny because of its derivation from a population with CKD and its inaccuracy in populations with an eGFR of >60 mL/min/1.73 m² [4]. Recent nephrology literature has focused on a newer estimating formula, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [5], which is now recognized as providing a more accurate estimate of
GFR than either the Cockcroft-Gault or MDRD formulas. A recent study of HIV-infected patients suggested that the CKD-EPI formula is more accurate in this population, as well [6]. In addition to its wide acceptance in the nephrology research community, the CKD-EPI formula is now replacing the MDRD formula in clinical practice in the United States, as major commercial laboratories adopt it as the GFR estimation formula of choice [7]. It is likely that this is not the last of the GFR estimation formulas, as we search for better ways to accurately assess this important parameter. The cystatin C level, a marker widely used in research settings, has shown recent promise as a marker of renal health in the non–HIV-infected population [8], but its clinical usefulness remains to be assessed. In limited studies of HIV-infected patients, it has not been shown to have significant advantages over the creatinine level [6]. Effects of viral load on cystatin C levels may be an additional limitation [9].

Another limitation, also noted by the authors, is the inability to measure other markers of kidney disease, including serum phosphate and urine protein levels, as measures of tubular toxicity. TDF-associated nephrotoxicity is attributed to damage to proximal renal tubule cells. Measurement of serum creatinine level can be both insensitive for tubular toxicity, which can occur before changes in eGFR, and nonspecific, since changes in eGFR without evidence of tubular damage may be have other causes. Data on race would also have been helpful, because those of African ancestry are at significantly greater risk of kidney disease, largely because of the risk associated with the presence of APOL1 risk alleles [10].

The association between TDF and kidney disease in this study is not surprising. The potential for nephrotoxicity was apparent in early case reports, case-control studies, and observational cohorts. The EuroSIDA study confirmed that TDF was associated with the development of CKD [2], and more recently a study from a Veterans Health Administration (VA) population showed similar findings [11]. TDF in the VA study was associated with a rapid decline in eGFR, development of proteinuria, and development of CKD. However, the effects of long-term TDF use are not well described, and the current article suggests that they exist. In contrast to the EuroSIDA and VA studies, the current study found no association with CKD, which may reflect discontinuation of TDF as renal function declined. Indeed, there was greater drug discontinuation due to declining eGFR with TDF than with other drugs, presumably reflecting the awareness of TDF toxicity on the part of clinicians. Recovery of renal function could not be adequately studied in this cohort, although discontinuation of TDF (defined as cessation of TDF >12 months ago) was not associated with an eGFR of <70 mL/min. The long-term effects of TDF withdrawal on kidney function deserve further study.

The association of ATV with decrease in eGFR and development of CKD in this and the EuroSIDA study [2] are surprising, because it was not expected or observed in earlier studies. Prospective trials have not shown renal effects. Interestingly, the VA study, which focused predominantly on TDF toxicity, did demonstrate an association between ATV use and rapid decline in renal function but not CKD. A recent, small retrospective cohort study compared ATV/r (n = 78) to both efavirenz (n = 82) and LPV/r (n = 75) in combination with TDF/emtricitabine and found greater decline in renal function at 1 year with ATV/r as compared to the 2 other agents [12]. There was also a higher incidence of proximal tubular dysfunction, suggesting a possible interaction with TDF, so attributing the renal effects to ATV is difficult. Tenofovir levels are elevated by >30% when these drugs are combined [13]. Because this regimen is so widely used, separating the effects of either drug can be difficult. The authors of the current study do adjust for the use of other medications. If the renal effects of ATV are real, then the reason for the lack of a toxicity signal in earlier studies may be related to the shorter duration of therapy. There is a plausible mechanism for nephrotoxicity based on the propensity of the drug to crystallize. ATV has been shown to form crystals and stones [14], although to a lesser extent than the older protease inhibitor indinavir (IDV), which frequently caused interstitial nephritis, crystallization in the kidney, and stone formation. A recent Japanese study found a significant increase in stone formation in individuals receiving ATV, although the stones were not analyzed [15]. Other features that might be expected if this is a true drug effect would include a reduction in risk with unboosted dosing and a cumulative increase in risk over time. The latter was seen in the earlier EuroSIDA study. There is no study to date showing more intrarenal crystals in kidney biopsy specimens among patients receiving ATV. Nevertheless, this study, together with others, raises the possibility of toxicity in the context of a plausible mechanism and merits further study.

Most surprising was the suggestion of a LPV/r effect. This medication has been around for a long time, with little suggestion of renal toxicity. Both this study and the EuroSIDA study demonstrated a risk for CKD, although the association was weaker in the EuroSIDA study [2]. The VA study found no risk of rapid decline in eGFR or in CKD development with LPV/r but did find an association with proteinuria. Although LPV can crystallize [16], this has not been widely demonstrated and certainly occurs less commonly than with ATV and IDV. One must question whether the LPV/r-treated population is comparable to the other patients in the study. In EuroSIDA and the current study, study of patients began in January 2004. There is no measure of the duration of drug exposure prior to that time, although Table 1 shows that individuals receiving LPV/r were more experienced and receiving drugs for a longer duration. It is also likely that they had a longer duration of
HIV infection. It is possible that individuals with longer durations of drug exposure and HIV disease have less renal reserve. Since the creatinine level rises only after a significant proportion of glomeruli have been lost, patients with longer durations of disease and drug exposure may start with fewer nephrons despite having normal eGFRs, putting them at greater risk. Despite the study limitations and the lack of a plausible mechanism of toxicity with LPV/r, it is clear that further study is warranted.

Should the findings of this study affect our current practice? The D:A:D study supports the importance of renal monitoring in patients receiving TDF and discontinuation of the drug, when possible, in those who may be experiencing nephrotoxicity. Monitoring should include not only the serum creatinine level (assessed in the current study) but also periodic measurement of makers of tubular function: serum phosphate level, proteinuria, and glycosuria. With an increasing number of studies showing an association of nephrotoxicity with use of ATV/r, and with a plausible mechanism of toxicity, it is also appropriate to monitor renal function in ATV-treated patients and to consider switching treatment to an alternative agent in those experiencing a decline in eGFR. The data linking LPV/r with nephrotoxicity are far more limited, so it is difficult to make specific recommendations. More study is clearly needed to better define the potential nephrotoxicity of both protease inhibitors. We must also remember that decline in kidney function can occur over time in HIV-infected patients taking other ART agents, in HIV-infected patients not being treated with ART, and in HIV-negative patients. The assumption that such declines are due to drug toxicity is not always correct. An evaluation for other causes is usually appropriate.

Note

Potential conflicts of interest. Joel Gallant, MD, has served as a consultant or member of a scientific advisory board for Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Therapeutics, and Merck & Co. Johns Hopkins University has received grant support from Gilead Sciences for research he has conducted. Derek Fine, MD, has served as a consultant for Bristol-Myers Squibb and Viiv Pharmaceuticals, on the lecturers/speaker’s bureau for Viiv Pharmaceuticals and Abbott Pharmaceuticals, and a reviewer for educational materials for Bristol-Myers Squibb.

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