Increased Risk of Chronic Kidney Disease Linked to Tenofovir and Atazanavir

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Continued use of two commonly used antiretrovirals (ARVs)--tenofovir (found in Viread, Truvada and Atripla) and atazanavir (Reyataz), along with the older protease inhibitor indinavir (Crixivan)--is associated with an increased risk of kidney function deterioration, according to an analysis of the large ongoing EuroSIDA study reported on Thursday, February 18, at the 17th Conference on Retroviruses and Opportunistic Infections (CROI). It is the first study reported to date linking the long-term use of specific ARVs and chronic kidney disease (CKD).

HIV infection is associated with several types of renal dysfunction, including HIV- associated nephropathy (HIVAN) and acute renal failure. The incidence of these kidney problems has declined since the introduction of combination antiretroviral therapy. Conversely, CKD remains a problem for people living with HIV, as it is associated with older age, chronic diseases such as hypertension and diabetes, and certain medications, including those used to treat HIV.

Most studies reported to date have looked at rates of acute kidney problems, such as a condition called Fanconi syndrome among those taking tenofovir and the development of kidney stones among those taking the indinavir and atazanavir. The data reported at CROI by Ole Kirk, MD, of the University of Copenhagen and his EuroSIDA study colleagues are among the first to evaluate the risk of CKD for every year a person remains on particular HIV drugs.

CKD is often defined as a persistent reduction in what is known as the glomerular filtration rate (GFR), which is basically an estimate of the fluid volume passing through the kidneys using measurements of serum creatinine levels. A diagnosis of CKD is made if a person's GFR is less than 60 after being measured twice at least three months apart. Kirk's group also defined CKD as a GFR above 60 at the time of entering the EuroSIDA study followed by a drop of at least 25 percent at some time point.

EuroSIDA is a large observational, non-interventional study of more than 16,500 HIV-positive people from 103 clinics in 35 countries in Europe, Israel and Argentina. The study was initiated in 1994, and data are collected from patients every six months.

The analysis reported by Kirk's group involved 6,843 patients--all of whom had regular creatinine

measurements on file--followed for an average of 3.7 years. A total of 225 people (3.3 percent) developed CKD during the follow-up period.

The study considered the role of all available ARVs, and it also took into account the different ways in which ARVs are combined with each other. The ARVs found to be associated with CKD were tenofovir, atazanavir, indinavir and, quite possibly, lopinavir/ritonavir (Kaletra).

Tenofovir was associated with a 16 percent increased risk of CKD per year of exposure to the drug, after adjusting the data for other risk factors for kidney disease (e.g., high blood pressure, diabetes, etc.). In other words, for every year a person living with HIV remains on tenofovir, the risk of CKD increases by 16 percent. This may not necessarily be a concern among people who don't have other health problems associated with CKD, but Kirk pointed out that those who have low GFRs before starting tenofovir and who have other traditional risk factors for kidney disease are at greatest risk for CKD.

Atazanavir was associated with a 12 percent increased risk of CKD for every year the drug was used. The annual risk with indinavir was 21 percent. These findings were highly statistically significant and, thus, weren't likely due to chance.

Lopinavir/ritonavir was associated with an 8 percent increased risk of CKD for every year the drug was used. However, this excess risk was considered marginal and was just barely statistically significant.

There was no evidence of an association between exposure to other ARVs and CKD. However, it is necessary to point out that, at least at the time these data were analyzed, there was not sufficient follow-up to adequately address the role of more recently approved ARVs such a darunavir (Prezista), raltegravir (Isentress), etravirine (Intelence) and maraviroc (Selzentry).

Kirk and his colleagues point out that the clinical implications of the development of CKD are not yet fully understood. They point out that for approximately 25 percent of people with CKD, the condition will actually resolve within one year.

In conclusion, Kirk's group argues that large-size studies with longer-term follow-up are warranted to better understand the longer-term consequences of CKD, including issues such as longer-term mortality, progression to end-stage renal disease and reversion of CKD.
