

## **Chronic kidney disease and exposure to antiretroviral drugs in a large cohort with long-term follow-up: the EuroSIDA Study**

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### **Questions and answers:**

#### **What are the main findings of this study?**

The study was designed – and powered - to analyse the role of antiretrovirals (ARVs) in the development of chronic kidney disease (CKD). About 4% of a heterogeneous patient population developed CKD within a 4-year period. We found that increasing exposure to some antiretrovirals (ARVs) were statistically linked to deterioration of renal function/CKD. These drugs were tenofovir (Viread and one of the components in Truvada and Atripla) and the protease inhibitors atazanavir (Reyataz) and indinavir (Crixivan). There was also some indication of an association for ritonavir boosted lopinavir (Kaletra), although the evidence for the latter was less clear.

There was no evidence of an association between exposure to other ARVs and CKD; although it should be pointed out that at present there is not sufficient follow-up to adequately address the role of newly introduced ARVs such as darunavir (Prezista), raltegravir (Isentress), etravirine (Intelence) and maraviroc (Celsentri).

#### **What is the context of these results?**

The study was performed within the framework of the EuroSIDA study, which, with more than 16,500 HIV-positive persons is one of the largest European observational studies. Initiated in 1994, the purpose of the EuroSIDA study is to analyse the clinical prognosis in the general HIV-positive population outside the randomised trials and to analyse the long-term clinical effect of ARV regimens.

Since 2004, the EuroSIDA study has collected serum creatinine measurements using a standardised data collection form. Renal disease has been a prioritised research area for EuroSIDA, which has previously published on this research issue.

This particular study was performed among adult HIV-positive persons who had risk factors for CKD. Therefore the results cannot be extrapolated to HIV-positive children, and long-term safety studies for children on ARVs are clearly needed.

This study prospectively collected 21,482 person-years of follow-up in patients with serial serum creatinine measurements with a median follow-up time of 3.7 years per person included in the study. A total of 225 persons developed CKD – of whom 203 fulfilled the first part of our CKD definition (i.e. a decrease in eGFR to below 60 ml/min/1.73m<sup>2</sup>).

### **What are the traditional risk factors for chronic kidney disease?**

Traditional risk factors for CKD are older age and chronic diseases such as arterial hypertension and diabetes mellitus.

### **Does HIV-infection cause CKD?**

HIV infection is associated with several types of renal dysfunction, including HIV-associated nephropathy (HIVAN), immune complex kidney disease and acute renal failure. The incidence of these has declined since the introduction of combination antiretroviral therapy (cART).

### **What are glomerular filtration rate (GFR) and estimated glomerular filtration rate (eGFR)?**

The glomerular filtration rate, or GFR, describes the flow rate of filtered fluid through the kidney and is a marker of kidney function.

A person's GFR can be evaluated in several ways.

The creatinine clearance rate, the volume of blood plasma that is cleared of creatinine per time unit, is a useful measure for approximating the GFR and can be assessed by analysing a urine sample collected over a 24-hour period. Other methods are injecting inulin or a radiolabelled isotope to determine inulin clearance or Chrome-EDTA clearance.

Alternatively, GFR can be estimated (eGFR) using various formulas – the first developed by Cockcroft and Gault more than 30 years ago, and more recently the Modification in Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. The formulas, all derived in HIV-negative persons, are based on commonly available data such as gender, age, height, body weight, ethnicity, and serum creatinine. A tool for calculating eGFR is available at [www.cphiv.dk](http://www.cphiv.dk) (Tools).

There is currently no consensus on which formula is best in estimating the GFR for HIV-positive persons.

### **What is chronic kidney disease (CKD)?**

CKD is defined as a persistent, often progressive, reduction in GFR (GFR below 60 mL/min/1.73m<sup>2</sup> at two measurements at least 3 months apart) and/or albuminuria (more than 30 mg of urinary albumin per gram of urinary creatinine). This definition of CKD is used in both HIV-positive and HIV-negative persons and has been developed by the National Institute of Diabetes and Digestive and Kidney Diseases, and 60 mL/min/1.73m<sup>2</sup> is generally agreed to be a useful cut-off for renal function.

In the present study we used the following definition: i) confirmed eGFR  $\leq 60$  mL/min/1.73m<sup>2</sup> (two measurements at least 3 months apart), if eGFR  $>60$  mL/min/1.73m<sup>2</sup> when the patient entered into the analysis or, ii) a confirmed 25% decline if baseline eGFR  $\leq 60$  mL/min/1.73m<sup>2</sup>.

The latter definition was used to include patients with CKD at entry into the study to reflect further meaningful deterioration of kidney function. Data on proteinuria is at present not available within the EuroSIDA study.

CKD is not identical to end stage renal disease, which is a fatal condition unless the person is dialysed (haemodialysis or peritoneal dialysis) or receives a renal transplant.

### **Does CKD cause any symptoms?**

Early stages of renal dysfunction may not cause clinical symptoms and are often only detectable through laboratory analyses. A decrease in GFR correlates with the severity of kidney disease and GFR typically decreases before the onset of symptoms of kidney failure and end stage renal disease.

### **How many people with CKD will develop kidney failure or end stage renal disease?**

The clinical prognosis after a diagnosis of CKD depends on a large number of factors – including the eGFR level, the level of proteinuria and the management of CKD and possible underlying diseases (e.g. diabetes and hypertension).

CKD is usually a progressive disease, although active intervention can stabilise the condition and prevent progression to end stage renal disease. Resolution of CKD is uncommon.

The mortality rate among persons with CKD is higher than among persons without CKD. A recent Canadian study on the general population documented all-cause mortalities between 2.9 and 10.4 per 1000 person-years of follow-up and a progression rate to end stage renal disease between 0.2 (eGFR 45-59.9 mL/min/1.73m<sup>2</sup>, and no proteinuria) and 65.9 per 1000 person-years of follow-up (eGFR 15-29.9 mL/min/1.73m<sup>2</sup> and heavy proteinuria).

### **What is new in the present findings?**

The present study is the first to report on a link between specific ARVs and CKD following longer-term exposure to the ARVs and CKD. The study considered the role of all available ARVs, and also considered the different ways in which ARVs are combined together in cART regimens. The ARVs found to be associated with CKD were tenofovir, atazanavir (whether used together with ritonavir or not), indinavir and perhaps also lopinavir/ritonavir. No other ARV, or different combinations of ARVs, was associated with CKD in this study.

Tenofovir has in a large number of studies been associated with acute renal impairment – in particular the Fanconi syndrome – caused by tubular dysfunction in the kidneys. Indinavir, and to some extent also atazanavir, has been linked with crystalluria, crystal nephropathy and nephrolithiasis.

To the best of our knowledge, no study so far has been able to demonstrate a link between cumulative longer-term exposure and risk of CKD for specific ARVs.

In the present study, use of tenofovir was associated with 16% increased risk of CKD per year of exposure, whereas exposure to indinavir, atazanavir and lopinavir/ritonavir were associated with a 12, 21, and 8% increased risk of CKD respectively.

### **What does an increased risk of 16% per year for patients exposed to tenofovir mean?**

A 16% increased risk per year means that the risk of developing CKD increases by 16% per year of exposure to tenofovir compared to the same person's underlying risk of CKD (and never exposed to tenofovir).

A person being treated with a regimen including tenofovir for 2 years has a 35% ( $1.16 \times 1.16 = 1.35$ ) increased risk of CKD compared with the same person not being treated with tenofovir. Naturally this has more severe implications for the person if the underlying risk of CKD is already high – e.g. for HIV-positive persons suffering from diabetes and arterial hypertension.

If a person has an underlying absolute risk of 0.50% for developing CKD within the next 12 months, one year of tenofovir exposure would, according to our results, lead to a 16% relative increase in the absolute risk of CKD – i.e. an absolute risk of 0.58% ( $0.5 \times 1.16$ ).

If a person has an underlying absolute risk of 20% for developing CKD in the next 12 months, one year of tenofovir exposure would lead to an increase in this absolute of CKD to 23.2%.

### **Was the tenofovir effect caused by simultaneous treatment with a boosted protease inhibitor and vice versa?**

There have been some reports that the effect of tenofovir on renal function is worse when co-administered with ritonavir-boosted PI, and that deteriorating renal function was greater in boosted-PI regimens than in non-nucleoside reverse-transcriptase inhibitor regimens.

We found that the association between CKD and tenofovir could not be explained by concomitant use of boosted PIs and that the association between CKD and atazanavir or lopinavir/ritonavir could not be explained by coadministration with tenofovir.

### **Does this effect continue on a longer term?**

The study is based on a median follow-up of 3.7 years, and further follow-up is needed to gain greater understanding of whether the association between cumulative exposure to a given ARV and CKD persists.

At present, we are unable to say whether the risk of CKD for persons treated with tenofovir, atazanavir, indinavir and lopinavir/ritonavir will continue to increase with longer exposure, but we cannot rule out that the risk continues to rise with increasing exposure either.

### **What are the mechanisms behind the present findings?**

The development of CKD is presumed to be due to glomerular and tubular dysfunction (tenofovir) or high renal excretion rates and crystalluria/ crystal nephropathy/ nephrolithiasis (PIs). Although these biological mechanisms are plausible based on the existing literature, they were not directly assessed in the study, and the exact pathogenesis behind our findings remains unclear.

### **Are the changes reversible?**

Preliminary analyses suggest that the risk of CKD is reversible, although it may take more than 12 months before those who stop tenofovir treatment are at similar risk of CKD as persons never exposed to tenofovir. For the other ARVs, the risk of CKD reverts quickly to a level of those never exposed to the specific ARV.

Further follow-up and additional data are warranted to better understand the clinical prognosis (including mortality, progression to end stage renal disease, reversion to near-normal renal function) for persons who have experienced CKD.

### **Which HIV-positive persons are at highest risk of developing CKD associated with ARVs?**

First of all, it is important to underline that the risk of adverse events of any ARV (e.g. CKD) should be balanced against the extremely positive effect of ARVs.

On a population level, the underlying risk of CKD is low. HIV-positive persons who were older and/or suffered from co-morbidities in terms of diabetes, arterial hypertension and hepatitis C coinfection all have a higher underlying risk of CKD.

Among patients who start tenofovir, those at highest risk of developing CKD are the persons suffering from one or more of the co-morbidities mentioned above - e.g. among HIV-positive persons receiving tenofovir, older patients, those with diabetes, hypertension and hepatitis coinfection were all at a higher risk of developing CKD.

Among persons with a normal or near-normal eGFR, the incidence rate of CKD is substantially lower. These low rates, however, do not exclude the possibility that the statistically significant associations between specific ARVs and CKD will also become evident in this sub-group, once longer follow-up has accumulated and persons have experienced declines in an initially higher eGFR.

### **What is the difference between the present findings and results from randomised trials?**

The randomised trials have not been able to detect a signal of CKD in patients treated with ARVs such as tenofovir, indinavir, atazanavir and lopinavir/ritonavir, although there have been reports from randomised trials on changes in eGFR for tenofovir and indinavir and on nephrolithiasis due to indinavir and atazanavir. Such trials, however, generally have limited follow-up periods and there are a number of exclusion criteria in the trials, meaning that patients with risk factors for CKD are not included in the trials (i.e. patients with hepatitis C co-infection are commonly excluded from the trials).

It is important to emphasise that this study is derived from an observational study, and hence carries all the limitations associated with this type of study design. As such, we have only observed associations and are unable to definitively demonstrate that these associations are causal; only randomised controlled trials are able to do so.

However, the advantage is that the study is based on a heterogeneous population of HIV-positive persons who are all under routine follow-up in clinics across Europe and that there is a considerable follow-up time available for the analyses, thus allowing us to detect the increase in CKD which may have been less clear in a randomised trial.

### **How solid are the findings?**

The data presented here are the results of a comprehensive analytic work. We have performed an extensive number of sensitivity analyses using alternative formulas for assessing eGFR, a large number of analyses with different censoring strategies and of different ways of modelling ARV regimens.

The findings were very solid and robust for tenofovir, this also being the case for indinavir and atazanavir, whereas the results for lopinavir/ritonavir were less clear and further research with lopinavir/ritonavir is warranted before a possible role in CKD can be determined.

Using the current definition of CKD with an arbitrary cut-off of 60 mL/min/1.73m<sup>2</sup> implies that a patient with an eGFR of 61 who drops to 59 mL/min/1.73m<sup>2</sup> on 2 consecutive occasions, at least 3 months apart, is defined as having CKD. However, most patients (74% of those with an initial eGFR > 60 mL/min/1.73m<sup>2</sup>) experienced a drop of at least 10 mL/min/1.73m<sup>2</sup>, and extensive sensitivity analyses looking at different endpoints and different derivations of eGFR were all consistent.

Further, some ARVs including tenofovir should be dosage-reduced as GFR decreases. At present, this type is not available, but collection of this data is ongoing and will be incorporated in future analyses.

It should also be emphasised that, although there were no significant associations between CKD and recently introduced ARVs like darunavir, etravirine and maraviroc, longer follow-up and more data are needed to sufficiently address the role of these ARVs – in particular the protease inhibitor darunavir.

#### **Were there other factors associated with CKD?**

In addition to traditional risk factors of CKD such as age, arterial hypertension and diabetes, we found that both an AIDS event and a non-AIDS malignancy are independent risk factors of CKD.

This may be due to the fact that persons suffering from these severe diseases are characterised by a general deterioration in health, immune function, or exposure to nephrotoxic drugs.

Hepatitis C co-infection was also an important risk factor for CKD – as has been the case for other studies on HIV-positive persons as well as in the general population.

#### **Which other ARVs can you exclude to be associated with excess risk of CVD?**

We studied all available ARVs, and only tenofovir, indinavir, atazanavir and lopinavir/ritonavir were significantly associated with CKD. However, for the more recently introduced drugs (darunavir, etravirine, maraviroc, raltegravir, tipranavir), there is insufficient follow-up to exclude the possibility that they maybe associated with excess risk of CKD. Only additional follow-up time into the future can inform this discussion.

#### **What are the implications of the present findings?**

The clinical implications of the development of CKD are not fully understood at present. Preliminary analyses show that for about one fourth of the persons suffering from CKD, the condition will actually resolve within one year.

Clearly, 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.

## **Additional questions – non-technical Q&A for HIV-positive readers**

### **What is the EuroSIDA study?**

The EuroSIDA study is a large observational, non-interventional study of more than 16,500 HIV-positive persons from 103 clinics in 35 countries in Europe, Israel and Argentina. The study was initiated in 1994 and data is collected every 6 months using a standardised data collection form.

As of early 2010, more than 125 articles have been published from the study; several of which have led to revisions of treatment guidelines and changes in clinical management of HIV-positive persons.

Since 2004, all creatinine measurements available have been collected on the follow-up forms, thus allowing for analyses of changes in renal function over time.

### **What did the study find?**

The study found an association between exposure to four ARVs and development of CKD. These drugs were tenofovir, atazanavir, indinavir and lopinavir/ritonavir. The effect was cumulative – that is, the risk of CKD increased with longer exposure to the individual drugs.

It should be emphasised that although there were no significant associations between CKD and recently introduced ARVs like darunavir, etravirine and maraviroc, longer follow-up and more data are needed to sufficiently address the role of these ARVs and to assess whether the risk continues to increase with even longer exposure to the ARVs.

The deterioration in renal function was reversible although for tenofovir it may take more than 12 months before the risk of CKD is back to the level of a person not exposed to tenofovir.

The long-term consequences for the patients remain to be elucidated.

### **What is the difference between relative risk and real risk?**

The real risk – or absolute risk – of developing CKD in this population was low: 225 of 6843 (3.3%) patients developed CKD over a median follow-up time of 3.7 years.

The relative risk indicates how one factor increases or decreases the chance of developing CKD compared to a person who does not have this factor. A person exposed to tenofovir for one year was at 16% higher risk of CKD compared to the same person without tenofovir exposure.

### **Is this the first time antiretroviral drugs have been reported to be associated with chronic kidney disease?**

To the best of our knowledge, this is the first time that cumulative exposure to specific ARVs is linked to a persistent and substantial impairment of renal function in terms of CKD.

There have been a large number of articles reporting on acute renal impairment within the first few months of exposure (Fanconi syndrome among persons treated with tenofovir)

and on crystalluria and nephrolithiasis among persons treated with indinavir and atazanavir).

**What do these findings mean for HIV-positive persons and their antiretroviral treatment?**

Adverse events potentially associated with antiretroviral therapy should be carefully balanced against the high efficacy of the antiretroviral treatment, and the virological effect of a person's treatment should in general take priority over concern of toxicity. However, if there are reasonable alternatives, it may be worth considering switching away from the above mentioned ARVs in patients with a very high underlying risk of CKD.

**The authors of the present presentation recommend that HIV-positive persons receiving tenofovir, atazanavir, indinavir or lopinavir/ritonavir should consult their doctor and discuss whether a change in their anti-HIV treatment regimen is appropriate. Persons receiving this type of treatment should NOT stop any drug without prior discussion with their doctor.**