Prognosis of Renal Function, Risk of Dialysis and Mortality in HIV Patients Developing Moderate Impaired Renal Function During Treatment with Tenofovir or Abacavir

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Abstract: *Background*: Impaired renal function is a concern in HIV-infected patients treated with tenofovir. We undertook this study to investigate the prognosis ofrenal function, risk of dialysis and mortality in HIV patients developing moderately reduced renal function while on tenofovir or abacavir.

Methods: From a population based cohort of Danish HIV patients, we identified all patients who for the first time had an estimated glomerular filtration rate (eGFR)<50 ml/min per 1.73 m^2 while on tenofovir or abacavir. We calculated median eGFR and the fraction of patients with eGFR<60 ml/min per 1.73 m^2 during followup in the two groups. Cox regression was used to estimate unadjusted and adjusted mortality rate ratios (MRR).

Results: We identified 61 patients on tenofovir and 55 on abacavir who developed impaired renal function. Throughout the 2-year study period, the tenofovir group contributed with 87.6 years and the abacavir group with 79.4 years of follow-up. We found no difference between the groups regarding median eGFR or proportions of patients having eGFR <60 ml/min per 1.73 m^2 over time. Five patients in the tenofovir group and two in the abacavir group initiated dialyses within two years after study inclusion. Our study did not indicate that the tenofovir group had increased risk of death (adjusted MRR=0.66, 95% CI: 0.37-1.17).

Conclusions: Within the current clinical setting, we were not able to detect a statistical significant difference in renal outcome and mortality between patients developing reduced renal function while on tenofovir or abacavir.

Keywords: HIV, tenofovir, renal function, mortality, dialysis.

INTRODUCTION

With the introduction of highly active antiretroviral therapy (HAART), there has been a dramatic decrease in mortality and morbidity in HIV patients. Several effective combinations of treatment are available, making it increasingly important to monitor side effects [1-2]. HIV patients loose renal function faster than the general population [3], but the mechanism for this decline is not fully understood.

Several case reports and cohort studies have shown that exposure to tenofovir, which is commonly included in first-line HAART regimens, is associated with acute and chronic renal impairment [4-6]. Nevertheless, the magnitude of this problem and its clinical impact is still debated. A recent study from the Danish HIV Cohorte Study [7] failed to demonstrate any association between development of acute or chronic renal replacement therapy and tenofovir treatment.

Although the mild-to-moderate renal impairment in HIV patients on tenofovir is well documented, few studies have evaluated the long-term prognosis of renal function in HIV patients developing impaired renal function while on tenofovir treatment. A study by Horberg *et al.* [8] investigated the impact of different antiviral therapies on forthcoming renal function in HIV patients. This study found that patients on tenofovir with a baseline eGFR between 50 and 79 ml/min per 1.73 m^2 had a significantly decreased eGFR through a 52 and 104-week period compared to tenofovir-spared patients. A study by DAD/Eurosidainvestigated the outcome for advanced chronic kidney disease (CKD). They found that 19% of the patients had died within the first year after having suffered from advanced CKD or end stage renal disease [9].

To better understand the risks of antiviral therapy we aimed to assess the prognosis for patients who develop moderate to severe impaired renal function during treatment with tenofovir. In a population-based cohort of HIV patients we identified all patients who developed moderate renal impairment while on tenofovir and compared renal function, risk of dialysis and mortality with a cohort of HIV infected patients who developed impaired renal function while on abacavir treatment.

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METHODS

Study Design

We performed a population based cohort study including HIV infected patients who for the first time had a single eGFR<50 ml/min per 1.73 m^2 while on tenofovir or abacavir treatment and in opposition to some previous studies we thereby included patients with chronic as well as acute renal failure. This cut-off value of eGFR<50 ml/min per 1.73 m^2 was used since it defines patients with a moderate to severe reduced renal function [10]. We compared changes in eGFR over time by assessing the fraction of patients with eGFR<60 ml/min per 1.73 m^2 in the two groups, and by comparing changes in median eGFR. The endpoint of 60 ml/min per 1.73 m^2 was used to ensure that a rise in eGFR was a result of actual improvement in renal function and not only due to fluctuation in creatinine measurements. We also estimated time from study inclusion to dialysis and time to death.

Setting

Denmark has a population of 5.6 million people, with an HIV prevalence of approximately 0.1% in the adult population. All Danish HIV patients are seen in one of eight departments of infectious diseases specialized in HIV. In the study period the patients were seen regularly (at 12-24 weeks intervals) and s-creatinin and thereby eGFR was estimated at each visit. Antiretroviral treatment is provided free of charge, and more than 80% of the HIV population is treated with HAART; of these, more than 80% are virally suppressed [11].

Data Sources

We used the unique 10-digit personal identification number, assigned to all Danish citizens at birth and immigrants to avoid multiple registrations. This identification number was used to link data from the following registers: the Danish HIV Cohort Study (DHCS), Danish National Hospital Registry (DNHR) and Danish Civil Registration System (DCRS). The Danish HIV Cohort Study (DHCS) is a prospective study of all HIV patients aged ≥ 16 years at diagnosis who have been treated at Danish HIV centers after 1 January 1995 [2]. DHCS is still ongoing and patients are consecutively enrolled. Data are collected annually and include demographics, date of HIV infection, AIDS-defining events, date and causes of death, and antiretroviral treatment. CD4 cell counts, viral loads and serum creatinine measurements are extracted electronically from laboratory data files. Multiple registrations are avoided through the use of the unique civil registration number. Data on renal replacement therapy (dialysis) were extracted from the Danish National Hospital Registry (DNHR) and data on vital status, residency and migration from the Danish Civil Registration System (DCRS).

HIV Study Population

Patients were recruited from 3 major HIV treatment centers covering the geographical areas of Seeland and Funen (54% of the total Danish population and 73% of the HIV population living in Denmark). In this study we included all patients who: (1) for the first time had an eGFR<50 ml/min per 1.73 m^2 while on treatment with tenofovir or abacavir, (2) had a Danish unique person identification number, (3) were aged≥16 years at HIV diagnosis, (4) started tenofovir or abacavir treatment after 31 December, year 2001, (5) had not previously been on renal replacement therapy. Study inclusion was the first date the patient had an eGFR<50 ml/min per 1.73 m^2.

Calculation of eGFR

We calculated eGFR using the MDRD formula: eGFR (MDRD) = 32788 x serum creatinine $^{-1.154}$ x age $^{-0.203}$ x 0.742 (if female) x 1.21 (if black) [12-13].

Data Management and Statistical Analysis

We determined the median eGFR and fraction of patients with eGFR<60 ml/min per 1.73 m^2 in relation to time after study inclusion. Observation time was divided into time intervals of 0.25 year. Time to dialyses or death was calculated from study inclusion to first of the following: 1 July 2013, two years after study inclusion, lost to follow up (as defined in DCRS), emigration or death. Stop of treatment was not a criterion of exclusion. To estimate risk of dialysis and mortality we constructed Kaplan-Meier curves stratified on tenofovir or abacavir treatment at study inclusion. We used Cox-regression to determine mortality rate ratios (MRR) between the two groups. The following covariates were included in the adjusted model: age (continuous variable), gender and CD4 cell count (<200 vs >=200cells/mL). Time on tenofovir and abacavir treatment before study inclusion was calculated for the period from HAART initiation to the date the patients first developed eGFR<50.Statistical analyses were performed using SPSS for windows version 11.5 (Norusis; SPSS Inc., Chicago, IL, USA;).

RESULTS

A total of 4683 patients registered in The Danish HIV Cohort Study had initiated tenofovir or abacavir treatment after 2001. From this population we identified 61patients on tenofovir and 55 patients on abacavir who developed moderate to severe reduced renal function (eGFR < 50 ml/min per 1.73 m^2). The tenofovir and abacavir groups contributed with87.6 and 79.4

Table 1: Demographic Characteristic of Study Subjects by Regimen

Characteristics	Regimen	
	Tenofovir	Abacavir
Total number of study subjects	61	55
Observation time (years)	87.6	79.4
Number of patients according to the year of study inclusion (n, %)		
2002-2006	15 (24.6%)	26 (47.3%)
2007-2012	46 (75.4%)	29(52.7%)
Start of HAART before study inclusion, *n (%)*	61 (100%)	55 (100%)
AIDS diagnosis before study inclusion, *n (%)*	18 (29.5%)	18 (32.7%)
Number of patients on tenofovir before study inclusion, *n (%)*	61 (100%)	5 (9.1%)
Male, *n (%)*	46 (75.4%)	42 (76.4%)
Age at study inclusion, *median (IQR)*	51.8 (46.4-61.5)	51.6 (43.6-62.1)
Route of HIV infection, *n (%)*		
MSM	26 (42.6%)	24 (43.6%)
IDU	12 (19.6%)	6 (10.9%)
Heterosexually	20 (32.8%)	19 (34.6%)
Other/unknown	3 (4.9%)	6 (10.9%)
Race, *n (%)*		
Caucasian	56 (91.8%)	45 (81.8%)
Asian	3 (4.9%)	0 (0%)
Black	2 (3.3%)	7 (12.8%)
Other/unknown	0 (0%)	3 (5.4%)

Table 2: Clinical Characteristics of Study Subjects

Clinical characteristics	Regimen	
	Tenofovir	Abacavir
eGFR (ml/min per 1.73 m^2) at study inclusion, *median (IQR)*	46.3 (41.2-48.4)	42.5 (37.5-46.2)
CD4 cell count at study inclusion, *cells/mL, median (IQR)*	426 (248-621)	400 (180-530)
VL at study inclusion, copies/mL, *(n, %)*		
<400	48 (78.7%)	42 (76.4%)
400-100000	11 (18.0%)	9 (16.4%)
>100000	2 (3.3%)	4 (7.3%)
Start of HAART before study inclusion, *n (%)*	61 (100%)	55 (100%)
AIDS diagnosis before study inclusion, *n (%)*	18 (29.5%)	18 (32.7%)
Number of patients on tenofovir before study inclusion, *n (%)*	61 (100%)	5 (9.1%)
Number of patients on abacavir before study inclusion, *n (%)*	33 (54.1%)	55 (100%)
Time on tenofovir before study inclusion (years), *median (IQR)*	1.93 (0.64-4.12)	0 (0-0)
Time on abacavir before study inclusion (years), *median (IQR)*	0.08 (0-2.93)	2.74 (1.24-4.51)
Number of patients on tenofovir within 12 months of study inclusion, *n (%)*	61 (100%)	4 (7.3%)
Number of patients on abacavir within 12 months of study inclusion, *n (%)*	20 (32.8%)	55 (100%)
Time on tenofovir within 12 months of study inclusion (years), *median (IQR)*	1 (0.6-1)	0 (0-0)
Time on abacavir within 12 months of study inclusion (years), *median (IQR)*	0 (0-0.69)	1 (0.82-1)

person-years at risk with no lost to follow up. Median age at study inclusion was 51.8 years and 51.6 years and 75.4% and 76.4 % were males for the tenofovir and the abacavir groups. Median CD4 cell counts at study inclusion were 426 cells/μL and 400 cells/μL for the tenofovir and the abacavir groups. Characteristics of the study populations are shown in Table **1** and the clinical characteristics in Table **2**.

We also calculated time on abacavir and tenofovir before study inclusion. Patients developing reduced renal function on tenofovir had received tenofovir for a median (IQR) time period of 1.93 years (0.64-4.12), while patients developing reduced renal function on abacavir had received abacavir for a median (IQR) time period of 2.74(1.24-4.51) years.

Figures **1** and **2** illustrates the fraction of patients having an eGFR<60 ml/min per 1.73 m^2 and the patients median eGFR up to two years after study inclusion stratified on the tenofovir and abacavir groups and demonstrates that the two groups did not differ markedly in renal function throughout the study period.

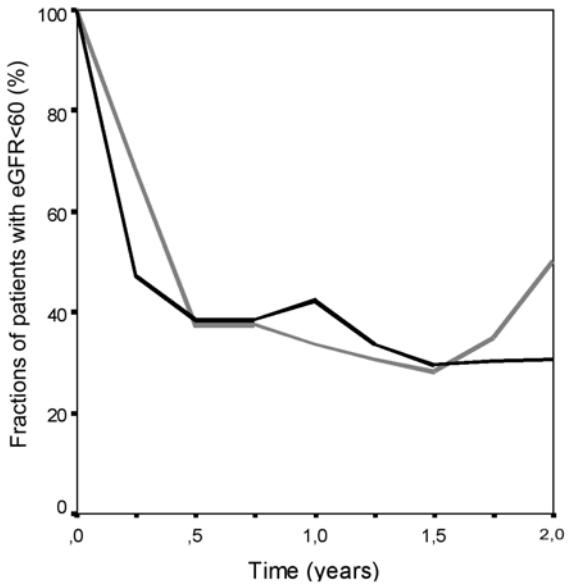


Figure 1: Fraction of patients with eGFR<60 ml/min per 1.73 m^2 stratified on antiviral treatment by time after first eGFR<50 ml/min per 1.73 m^2. Tenofovir treatment (grey full line), abacavir treatment (black full line).

The two year risk of renal replacement therapy was low in both groups (Figure **3**) and although the number of endpoints were small (5 in the tenofovir group and 2 in the abacavir group) it did not indicate a substantial increased risk in the tenofovir group.

In the first two years after study inclusion, we found no increased risk of death in the tenofovir group

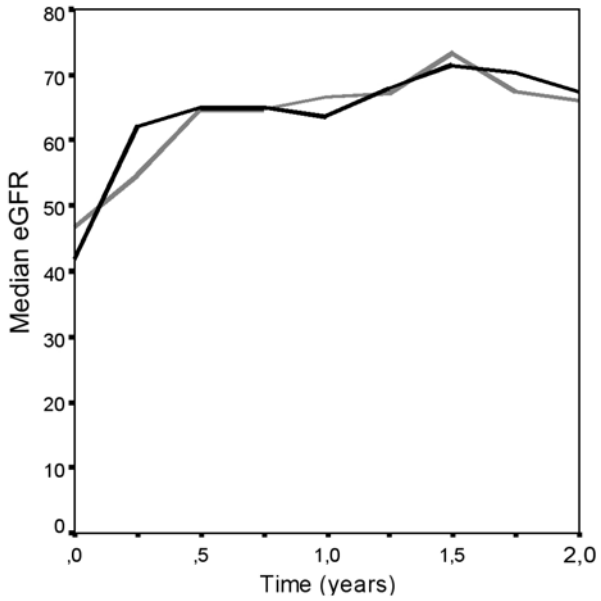
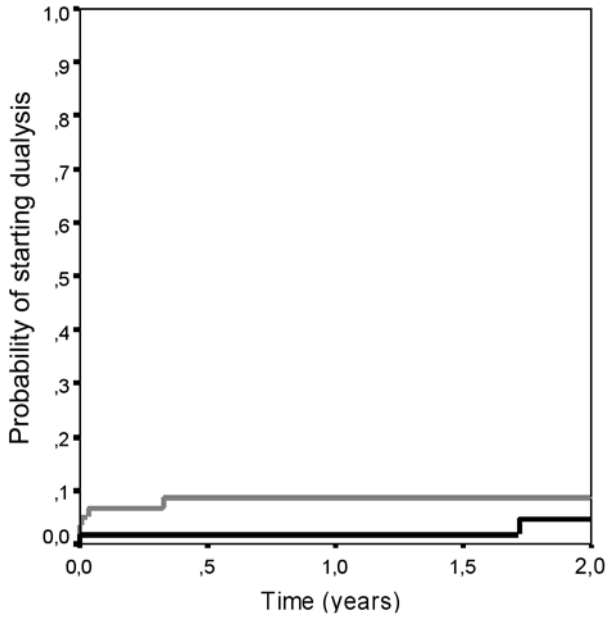


Figure 2: Median eGFR after first eGFR<50 ml/min per 1.73 m^2 stratified on antiviral treatment. Tenofovir treatment (grey full line), abacavir treatment (black full line).



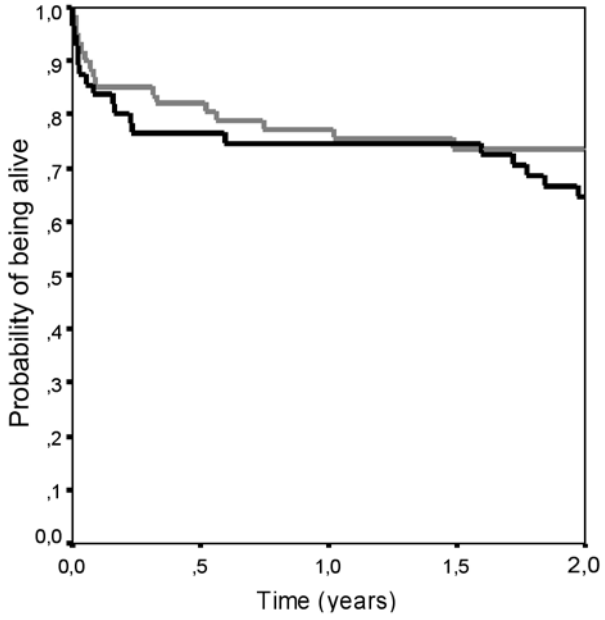
Persons under observation

Tenofovir	61	44	38
Abacavir	55	40	31

Figure 3: Kaplan Meier estimate of risk of starting dialysisin patients with a baseline GFR<50 ml/min per 1.73 m^2 stratified by antiviral treatment. Tenofovir treatment (grey full line), abacavir treatment (black full line).

(unadjusted MRR=0.62, 95% CI: 0.35-1.1) adjusted MRR=0.66, 95% CI: 0.37-1.17) (Figure **4**). In both groups of patients, we found the mortality rate to be the highest throughout the first months of study inclusion.

Two years after study inclusion, themortality was 26.4% (95% CI:15,3%-37.5%) for the patients in the tenofovir group and 35.5% (95% CI: 22,6%-48.4%) for the patients in the abacavir group.



Persons under observation

Tenofovir	61	46	40
Abacavir	55	40	31

Figure 4: Kaplan-Meier estimates of fraction alive in patients with a baseline GFR<50 ml/min per 1.73 m^2 stratified by antiviral treatment. Tenofovir treatment (grey full line), abacavir treatment (black full line).

DISCUSSION

In this Danish, population-based cohort study we found that patients who develop moderate to severe reduced renal function while on tenofovir or abacavir therapy did not differ in risk of 2-year impairment of renal function defined as persistent eGFR < 50 ml/min. Both groups suffered from high mortality (>25%), but had a relatively low risk of dialysis (<10%) throughout the first two years of study inclusion. Both groups also showed a substantial improvement in renal function (eGFR).

Assessing the risk of adverse events associated with specific antiretroviral therapies in observational studies can be difficult due to the risk of confounding by indication. The current knowledge on tenofovir's impact on patients' renal function indicates that patients on tenofovir have an increased risk of developing reduced renal function [4-6]. Also the focus on renal impairment in patients on tenofovir may have led to stop of this drug in fragile patients with eGFR higher than 50 ml/min, which may have confounded the study. We did not include the impact of specific antiretroviral drugs used after study inclusion. We found that the size of the study populations did not allow inclusion of further potential confounders in the analyses. The results of the present study combined with analyses of the clinical handling of patients, who develop decreased renal function while on tenofovir [14], indicates that when these patients develop reduced renal function, the 2-year prognosis concerning renal function, risk of dialysis and mortality are not markedly different compared to patients on other antiretrovirals.

In contrast to tenofovir, abacavir does not have a record of being nephrotoxic. It is therefore reasonable to assume, that reduced renal function developing during tenofovir treatment may be a consequence of either tenofovir related side effects or other factors, while reduced renal function developing during abacavir treatment is not a consequence the abacavir treatment. In consequence, patients who develop reduced renal function during tenofovir may have a beneficial effect on renal function when switching from tenofovir to abacavir or other drugs without significant impact on renal function. Abacavir was used as comparator, as this has been the main NRTI used in Denmark in the period in which tenofovir has been used in HAART.

It is well known, that decreased renal function in HIV patients increases risk of death. A previous study by Ibahimet *et al*. [15] examined the impact of baseline eGFR on all-cause mortality in an HIV cohort from UK. They found that HIV patients with an eGFR between 30-44 ml/min per 1.73 m^2 had a 1.7 higher mortality than HIV patients with an eGFR between 90-104 ml/min per 1.73 m^2. Also, previous studies have shown that HIV-infected patients with chronic renal disease have an increased risk of hospitalization, are less likely to receive ART (antiretroviral therapy), and have a higher mortality [16-18]. A study by George et. al. found that HIV patients with an eGFR<60 ml/min per 1.73 m^2 was associated with a 15.9-fold increased odds of a cardiovascular events compared with an eGFR of at least 60 ml/min per 1.73 m^2 [19]. However, to our knowledge, no previous studies have compared mortality in HIV patients who develop impaired renal function while on tenofovir or abacavir. Risk of myocardial infarction has been reported to be increased in patients on abacavir, which may subsequently have led to increased mortality in this fragile group of patients [20].

A study by O'Donnell *et al.* [21] found that advanced age, diabetes, decreased weight and CD4≤200 cells/m^3 predict renal impairment in HIV patients. A study by Tordatoet *et al.* [22] also found that absence of ART was associated with higher risk of decreased renal function. This is comparable with the findings in a Danish study [7], finding that patients on tenofovir did not have an increased risk of starting dialysis compared to patients on other types of HAART.

Our study found no association between the type of antiviral therapy at study inclusion and the patients' prognosis on renal function. We have not been able to find any studies with similar study design. However, several studies have explored the long-term effects of continuous tenofovir use. A study by Jones *et al.* [23] investigated the overall incidence and risk of renal dysfunction in individuals receiving tenofovir compared to other antiretrovirals. They found that tenofovir is not associated with renal dysfunction more frequently than other antiretroviral drugs. Similar findings were made by Gallant *et al*. [24] who evaluated the changes in renal parameters in 1111 patients who were enrolled in two randomized controlled trails comparing tenofovir patients against other ART. This study found small differences in glomerular filtration rate over time. Other studies have found conflicting results on tenofovirs 2-year effect on renal function. A retrospective cohort study performed by Horberg *et al*. [8] found that tenofovir patients had a higher decline in renal function compared to tenofovir spared patients through a 104-week period.

Limitations and Strength of the Study

Our study also has some limitations. The number of patients and number of outcome events were rather low, and too low to determine whether the outcome was similar in the two groups. Smaller differences between the groups concerning dialysis or death may not have been detected. Larger studies will be needed to examine this. Despite the lag of power in our study, we found that both tenofovir and abacavir patients with an impaired renal function have a high mortality rate and a low risk of dialysis. However, as a consequence of the lag of power, our estimates on death and dialyses have broad confidence intervals. Another limitation was that serum creatinine values were measured by different testing methods over the 12.5-year study period and we therefore cannot exclude some intra- and inter-laboratory variation. Since patient' weight were not measured regularly, we used the MDRD formula to calculate eGFR [12-13]. Thus the eGFR in patients with a high muscle mass may be underestimated, and overestimated in patients who as a result of illness have lower muscle mass. We do not suppose this had a major impact on the study results. We followed our patients up to 2 years and cannot exclude that differences between the two groups may be more pronounced after longer time of follow up. Also we cannot exclude that our estimates suffer from potential residual confounding.

Major strength of this study is its population-based cohort design with a long observation period and complete follow-up. The study design enabled us to extract data on study outcomes from three well-established Danish databases, the DHCS, DNHR and the DCRS, insuring that extracted data on renal function, dialysis rates and mortality had high validity. The access to the nationwide DHCS allowed us to extract a control cohort of HIV infected patients who developed reduced renal function while on another nucleotide reverse transcriptase (abacavir), which is not considered to impair renal function. In our study we used both hard and indisputable end points as dialysis and mortality and softer end points as eGFR. Despite eGFR being a softer end point, it is an important index of renal function and it provides a crucial tool for clinicians in detection of renal disease, understanding its severity and making decisions about treatment.

CONCLUSIONS

Within the current clinical setting, we were not able to detect statistical significant differences in renal outcome and mortality between patients developing reduced renal function while on tenofovir or abacavir.

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and Hvidovre (G Kronborg), Odense University Hospital (C Pedersen), Aarhus University Hospitals, Skejby (CS Larsen) and Aalborg (G Pedersen), Herning Hospital (AL Laursen), Helsingør Hospital (L Nielsen) and Kolding Hospital (J Jensen).

AUTHOR CONTRIBUTIONS

Conception and design: Dissing A, Obel N, Pedersen C.

Analysis and interpretation of the data: All authors

Drafting of the article: Dissing A.

Critical revision of the article for important intellectual content: All authors.

Final approval of the article: All authors.

Provision of study materials or patients: All authors.

Statistical expertise: Dissing A, Obel N.

Obtaining of funding: Obel N, Pedersen C, Kronborg G, Gerstoft J.

Collection and assembly of data: All authors.

POTENTIAL CONFLICTS OF INTEREST

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Dissing A, Legarth R, Helleberg M, Kronborg G, report no conflicts of interest.

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