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# Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B

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**Background & Aims**: Therapy of chronic hepatitis B with HBV-polymerase inhibitors, in particular tenofovir or adefovir, may affect renal function. To assess renal function more accurately in the normal range, we used the recently validated, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to calculate the estimated glomerular filtration rate (eGFR).

**Methods**: Patient subgroups included: patients with HBV-monoinfection treated with lamivudine ($n = 36$), adefovir ($n = 32$), entecavir ($n = 32$), or tenofovir ($n = 37$). HBsAg-positive untreated patients ($n = 60$) served as control. For comparison HIV-monoinfected patients treated with tenofovir ($n = 120$) or zidovudine ($n = 52$) based antiretroviral therapy and antiretroviral naive patients ($n = 109$) were assessed. CKD-EPI equation was used to calculate eGFR. In a more sensitive approach, we modeled the individual change in eGFR over time with linear mixed effects models (LME).

**Results**: Yearly predicted median changes in individual eGFR according to the LME model were: HBV untreated −2.05 ml/min, HBV lamivudine −0.92 ml/min, HBV adefovir −1.02 ml/min, HBV entecavir −1.00 ml/min, and HBV tenofovir −0.92 ml/min ($p < 0.01$ for HBV untreated *vs.* HBV treated). In HIV-monoinfected patients: HIV untreated −0.62 ml/min, HIV treated with tenofovir −2.64 ml/min, HIV treated with zidovudine −1.0 ml/min ($p = 0.017$ for tenofovir *vs.* no treatment, $p < 0.001$ for tenofovir *vs.* zidovudine).

**Conclusions**: Therapy of HBV infection irrespective of medication seems to result in a milder decrease of renal function. In contrast tenofovir as part of HIV combination therapy seems to impair renal function in this Caucasian population.



Keywords: HBV; Renal function; HBV-polymerase inhibitors; HIV; Tenofovir; Entecavir; Adefovir; Lamivudine.

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*Abbreviations:* HBV, hepatitis B virus; eGFR, estimated glomerular filtration rate; CKD-EPI equation, Chronic Kidney Disease Epidemiology Collaboration equation; HBsAg, surface antigen of hepatitis B virus; LME model, linear mixed effects model; MDRD equation, Modification of Diet in Renal Disease Study; HIV, human immunodeficiency virus; AIC, Akaike's information criterion is a measure for the goodness of fit; ALT, alanine transaminase; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; $CD4^+$ cells, helper cells with cluster of differentiation 4 glycoprotein expressed on the surface.

## Introduction

With the introduction of the HBV-polymerase inhibitors for treatment of chronic hepatitis B the proportion of treated patient has increased substantially. This is due to the convenience of a once daily, one pill oral drug regimen and reflected by the revision of the current treatment guidelines [1,2]. With higher numbers of patients treated for years, possible adverse events have gained more attention. One area of concern is renal function. Adefovir is dose limited by tubular toxicity [3,4]. Tenofovir is associated with increases in creatinine and anecdotal reports of kidney failure in HIV patients [5–14]. In addition chronic hepatitis B may cause membranoproliferative glomerulonephritis by HBs-antigen induced-immune complexes [15]. At last aging diminishes renal function.

In contrast to the experience with tenofovir in HIV, the pivotal phase 3 studies in HBV-monoinfected patients have not shown a clear signal of renal impairment [16,17]. The well established formulae using serum creatinine for the calculation of eGFR, such as Cockcroft-Gault or MDRD are validated only for patients with substantially impaired renal function and not for monitoring patients with normal renal function [18,19]. Therefore, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was introduced for more accurately estimating glomerular filtration rate in patients with normal or slightly impaired kidney function [20]. In addition we assessed the individual change in estimated glomerular filtration rate over time to better capture changes in renal function in patients with normal or slightly impaired renal function.

## Materials and methods

Patients with chronic hepatitis B virus (HBV) infection were recruited on a consecutive basis from two outpatient clinics. Patients with HBV-monoinfection were categorized according to therapy: lamivudine ($n = 36$), adefovir ($n = 32$), entecavir ($n = 32$), tenofovir ($n = 37$), and untreated HBsAg-positive patients ($n = 60$).

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As tenofovir has been associated with decreased renal function, patients with HIV-monoinfection on tenofovir ($n$ = 120) or zidovudine ($n$ = 52) based antiretroviral combination therapy were enrolled as comparators. In addition untreated HIV-monoinfected patients with moderate to high viral load (>5000 copies/ml, $n$ = 81) or low viral load (<5000 copies/ml, $n$ = 28) were added for comparison.

All treated patients were on first line therapy to exclude confounding by pretreatment. Dosing of all antiviral drugs was according to the label. No dose reduction of HBV-polymerase inhibitors was performed in the HBV or HIV cohorts.

Patients with pre-existing renal disease, Diabetes mellitus, or arterial hypertension were excluded from the analysis.

The baseline characteristics of the subgroups are shown in Tables 1 and 2. For minimizing a bias due to differences in the distribution of gender, age, HBV-DNA, ALT, HIV-RNA, or CD4+ cell count, two multivariate linear mixed effects models including these variables were developed.

Serum creatinine was analyzed as part of the clinical routine. The creatinine determination was carried out fully automatically on a ROCHE MODULAR P-model (Roche, Mannheim Germany) using a kinetic Jaffe test with rate-blanking and compensation. The method is based on the Jaffe reaction.

Formulae to estimate GFR (ml/min) in clinical practice use serum creatinine (crea, mg/dl)), age (years), and gender as variables. The MDRD equation (Modification of Diet in Renal Disease Study): eGFR = 186 × (crea) exp −1.154 × (age) exp −0.203 × 0.742 if female. MDRD formula is commonly used, but validated only for GFR <60 ml/min [19,21].

As second formula to calculate eGFR we used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation which was recently validated and is considered more accurate than MDRD in patients without renal impairment [20]. CKD-EPI formulae: female with creatinine ⩽0.7 mg/dl: eGFR = 144 × (crea/0.7) exp −0.329 × (0.993) exp age. Female with creatinine >0.7 mg/dl: eGFR = 144 × (crea/0.7) exp −1.209 × (0.993) exp age. Male with creatinine ⩽0.9 mg/dl: eGFR = 141 × (crea/0.9) exp −0.411 × (0.993) exp age. Male with creatinine >0.9 mg/dl: eGFR = 141 × (crea/0.9) exp −1.209 × (0.993) exp age.

The associations of the variables with the change of GFR levels over time were analyzed by two linear mixed effects models for the HBV-monoinfected cohort and for the HIV-monoinfected cohort. Thereby, a maximum likelihood approach was used for fitting and an AIC based stepwise regression method for variable selection.

**Table 1. Baseline characteristics of HBsAg-positive patients. Baseline data are given for untreated patients, HBV-monoinfected patients treated with lamivudine, adefovir, entecavir or tenofovir.**

| | HBV untreated | HBV lamivudine | HBV adefovir | HBV entecavir | HBV tenofovir |
|---|---|---|---|---|---|
| Total n | 60 | 36 | 32 | 32 | 37 |
| Observation (months) median and range | 24 (12-48) | 24 (12-48) | 24 (12-48) | 24 (6-48) | 12 (6-36) |
| Male | 33 (55%) | 23 (64%) | 21 (66%) | 23 (72%) | 31 (84%) |
| Age (years) median and range | 39 (21-62) | 41 (18-68) | 38 (18-63) | 43 (20-73) | 43 (19-75) |
| HBV-DNA log(IU/ml) median and range | 3.43 (<1.08-4.71) | 6.82 (3.12- >8.04) | 6.32 (2.98- >8.04) | 6.38 (3.49- >8.04) | 5.58 (2.41- >8.04) |
| ALT (U/L) median and range | 31 (11-93) | 121 (20-612) | 59 (16-1268) | 72 (18-2230) | 73 (21-528) |
| HBeAG positive | 1 (2%) | 8 (23%) | 15 (50%) | 16 (50%) | 11 (30%) |
| HBeAG negative | 59 (98%) | 27 (77%) | 15 (50%) | 16 (50%) | 26 (70%) |
| eGFR (ml/min) | 108 (47-139) | 107 (72-127) | 108 (77-134) | 108 (52-128) | 103 (65-133) |
| eGFR stage (%) | | | | | |
| ≥90 ml/min | 78 | 83 | 81 | 84 | 73 |
| 60-89 ml/min | 20 | 17 | 19 | 13 | 27 |
| 30-59 ml/min | 2 | 0 | 0 | 3 | 0 |

**Table 2. Baseline characteristics of HIV-monoinfected patient. Baseline data are given for untreated HIV-monoinfected patients and patients with tenofovir or zidovudine as part of the antiretroviral therapy.**

| | all HIV untreated | low HIV replication untreated | Moderate to high HIV replication untreated | HIV tenofovir | HIV zidovudine |
|---|---|---|---|---|---|
| Total n | 109 | 28 | 81 | 120 | 52 |
| Observation (months) median and range | 36 (12-48) | 48 (18-48) | 36 (12-48) | 24 (12-48) | 48 (12-48) |
| Male | 98 (90%) | 22 (79%) | 76 (94%) | 109 (91%) | 47 (90%) |
| Age (years) median and range | 35 (19-70) | 38 (24-70) | 34 (19-55) | 40 (20-64) | 37 (18-64) |
| HIV-RNA log(copies/ml) median and range | 4.11 (2.02-6.58) | 3.18 (2.17-3.65) | 5.00 (2.03-6.58) | 5.30 (3.05-6.80) | 5.60 (2.36-6.38) |
| CD4+cells ( /µl) median and range | 663 (96-1582) | 794 (285-1582) | 651 (96-1314) | 255 (14-834) | 230 (8-685) |
| eGFR (ml/min) median and range | 108 (70-144) | 106 (70-134) | 110 (79-144) | 108 (61-132) | 111 (75-131) |
| eGFR stage (%) | | | | | |
| ≥90 ml/min | 84 | 71 | 81 | 81 | 92 |
| 60-89 ml/min | 16 | 29 | 19 | 19 | 8 |
| 30-59 ml/min | 0 | 0 | 0 | 0 | 0 |

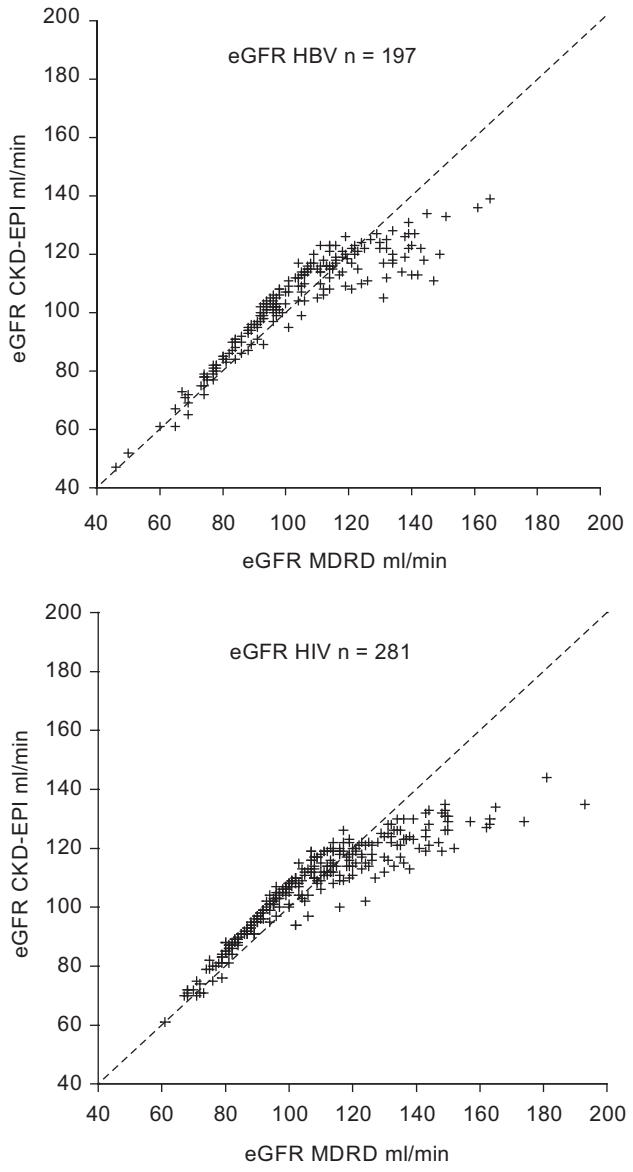


**Fig. 1. Comparison of eGFR at baseline estimated with MDRD-formula or CKD-EPI formula for HBV-monoinfected or HIV-monoinfected patient**s. At baseline all patients were untreated. Line of identity is shown.

Potential factors in the HBV model were: sex, age (in years), observation time (in years), treatment (yes/no), medication (lamivudine, adefovir, entecavir, tenofovir), baseline ALT, and baseline HBV-DNA. Potential factors in the HIV model were: sex, age (in years), observation time (in years), treatment (yes/no), medication (tenofovir, zidovudine), and baseline CD4+ cells and baseline HIV-RNA.

Both models accounted for treatment effects on eGFR levels by analyzing interactions between treatment and treatment time and also considered other possible up to threefold interactions. *F*-tests, *t* tests, and likelihood ratio tests for nested models were performed to test the effect of treatment in general as well the effect of different treatment types and other potential factors on GFR. We calculated the predicted individual change in eGFR for each subject from the fitted models to examine the impact on renal function over time. A linear association between age and GFR was assumed as established by Hoang *et al.* for healthy volunteers aged 18–88 [22].

Furthermore, non-parametric maximum likelihood estimation for interval censored data was performed to compare the proportion of patients maintaining normal eGFR ( $\geqslant$60 ml/min) over time between different treatment types (Fig. 3).

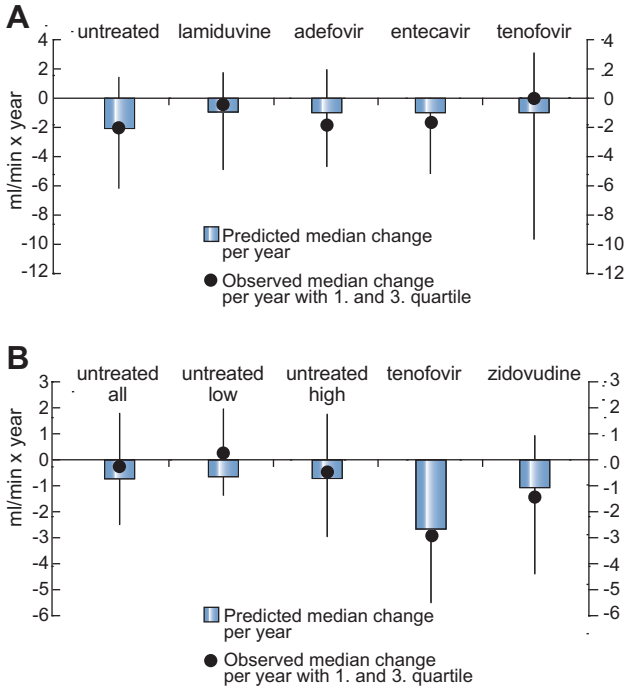


**Fig. 2. Predicted median change per year in individual eGFR**. (A) HBV-model: predicted change in eGFR per year of HbsAg-positive untreated patients was stronger compared to patients treated with HBV-polymerase inhibitors ($p$ <0.01). For comparison the observed median change and quartiles are shown. (B) HIV-model: predicted change in eGFR per year of all untreated HIV-monoinfected patients (untreated all), untreated with low (untreated low) or high (untreated high) viral replication, and patients with tenofovir or zidovudine as part of the antiretroviral therapy. For comparison the observed median change and quartiles are shown.

All tests were two-tailed and a $p$ value of less than 0.05 was considered as significant. All statistical analyses were performed using R software (packages nlme, lme4, survival, and interval, version 2.9.2, The R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org).

## Results

As expected the MDRD equation resulted in higher individual eGFR in study patients with normal renal function compared to the CKD-EPI formula. This finding was not different for patients with HBV- or HIV-infection (Fig. 1).

We used CKD-EPI to calculate the yearly change in individual eGFR. Using eGFR calculated with MDRD did alter the magnitude of the yearly change, but not the general pattern of the findings (not shown).

### *HBV-monoinfected patients*

In the linear mixed model, age (years), gender, and being on HBV-polymerase inhibitor therapy were significant predictors for eGFR over time. Therapy of HBV seems to have a beneficial effect on renal function assessed by eGFR levels over time compared to untreated HBsAg-positive patients in the linear mixed effects model ($p$ <0.01). Because of an additional interaction with age and gender, the beneficial effect was more pronounced in younger and female patients. We did not find

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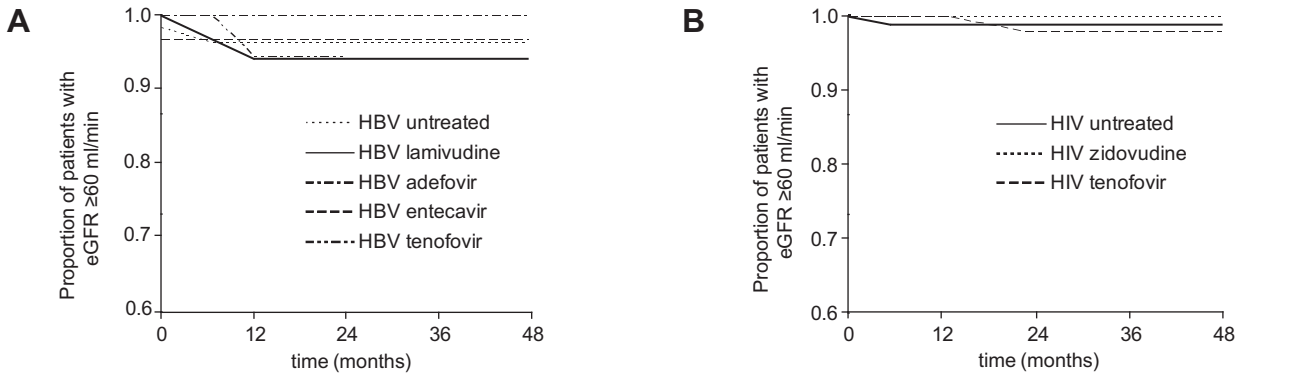


| Time (months) | Baseline | 6 | 12 | 18 | 24 | 36 | 48 |
|---|---|---|---|---|---|---|---|
| HBV untreated | 60 | 15 | 44 | 21 | 37 | 18 | 15 |
| HBV lamivudine | 36 | 35 | 35 | 26 | 26 | 15 | 10 |
| HBV adefovir | 32 | 32 | 30 | 20 | 19 | 12 | 4 |
| HBV entecavir | 32 | 30 | 31 | 20 | 21 | 13 | 2 |
| HBV tenofovir | 37 | 36 | 34 | 16 | 8 | 3 | - |

| Time (months) | Baseline | 6 | 12 | 18 | 24 | 36 | 48 |
|---|---|---|---|---|---|---|---|
| HIV untreated | 109 | 94 | 106 | 85 | 85 | 67 | 47 |
| HIV TDF | 120 | 118 | 120 | 102 | 98 | 59 | 35 |
| HIV AZT | 52 | 51 | 52 | 46 | 45 | 34 | 32 |

**Fig. 3. Non-parametric maximum likelihood estimation for the proportion of patients maintaining normal eGFR (⩾60 ml/min) over time**. (A) HBV-patients. (B) HIV-patients. Tables below the figure show number of patients which are under observation.

significant differences in the effect on renal function over time between the different HBV-polymerase inhibitor treatment groups.

The resulting model was:

$$(\text{eGFR})\exp 2.3 = 76500 - 810\times\text{age} - 9540\times\text{time} + 207\times\text{age}\times\text{time} + (\text{if female})(5320 - 2460\times\text{time} - 49\times\text{age} - 90\times\text{time}\times\text{age}) + (\text{if treatment})(7520\times\text{time} - 179\times\text{time}\times\text{age})$$

The yearly predicted median individual changes in eGFR (CKD-EPI formula) according to this model were: HBV untreated −2.05 ml/min, HBV lamivudine −0.92 ml/min, HBV adefovir −1.02 ml/min, entecavir −1.00 ml/min, and tenofovir −0.92 ml/min (Fig. 2A). Limiting the analysis to 24 months as a control for the decreasing number of patients under observation did not alter the results.

A decrease of eGFR >20 ml/min from baseline confirmed by two measurements was observed in 2/60 HBV untreated patients, in 2/36 HBV lamivudine treated patients, 2/32 HBV entecavir treated patients, 0/32 HBV adefovir treated patients, and 1/37 HBV tenofovir treated patients.

Patients achieving an eGFR of <60 ml/min (renal insufficiency stage 3) were infrequent and not different between HBV patient groups (Fig. 3A).

*HIV-monoinfected patients*

In the linear mixed effects model age (years), baseline CD4-positive cells and being on antiretrovirals (tenofovir, zidovudine) were significant predictors for eGFR over time.

In contrast to the HBV-monoinfected patients, we found significant differences between the different treatment groups ($p$ <0.001). Tenofovir seems to lead to a more rapid decline of renal function compared to patients treated with zidovudine as part of antiretroviral therapy ($p$ <0.001). In addition, tenofovir induced a more rapid decline of renal function compared to untreated patients ($p$ = 0.017) (Fig. 2B). Zidovudine shows no significant effect on renal function compared to patients with no treatment ($p$ >0.2) (Fig. 2B).

The resulting model was:

$$(\text{eGFR})\exp 2.3 = 80200 - 819\times\text{age} - 1540\times\text{time} - 5.67\times\text{CD4baseline} + 1.41\times\text{CD4baseline}\times\text{time} - (\text{if tenofovir})1220\times\text{time} + (\text{if zidovudine})208\times\text{time}$$

The yearly predicted median individual eGFR-changes in HIV-monoinfected patients (CKD-EPI) according to this model were as follows: HIV untreated moderate to high viral load (>5000 copies/ml) −0.63 ml/min, HIV untreated low viral load (⩽5000 copies/ml) −0.57 ml/min, HIV treated with tenofovir −2.64 ml/min, HIV treated with zidovudine −1.0 ml/min (Fig. 2B). As for the HBV-monoinfected patients, limiting the analysis to 24 months, as a control for the decreasing number of patients under observation, did not alter the results.

A decrease of eGFR >20 ml/min from baseline confirmed by two measurements was observed in 5/109 HIV untreated patients, in 3/52 zidovudine treated patients and 7/120 HIV tenofovir treated patients.

Patients achieving an eGFR of <60 ml/min (renal insufficiency stage 3) were few and not different between HIV patient groups (Fig. 3B).

## Discussion

In controlled prospective studies with a variety of HBV-polymerase inhibitors including tenofovir and dose adjusted adefovir, a marked renal impairment was not observed as a general effect of antiviral therapy [3,4,16,17]. These results are based on eGFR results calculated by MDRD or Cockcroft-Gault equations which are not validated for assessing changes in individuals with normal kidney function. Recently, CKD-EPI formula was validated

for calculation of eGFR both in patients with impaired and normal kidney function. In addition, we have evaluated the individual change in eGFR. Mean changes in eGFR are less sensitive to detect effects on kidney function. However, it seems to be important to detect low levels of renal toxicity for drugs, such as HBV-polymerase inhibitors, developed for long term therapy. After approval, these drugs may also be used in patients with renal impairment or in combination with potentially nephrotoxic drugs. This may result in renal impairment in some patients in particular with pre-existing co-morbidities as reported for adefovir by Ha and colleagues [23].

In contrast, in our observational cohort with relatively young patients without arterial hypertension or Diabetes mellitus the initiation of HBV-polymerase therapy seems to contribute to a milder decrease in renal function. This observation may be explained by an improvement of renal impairment by HBV-associated membranous nephropathy as reported from small patient series or individual cases [24–27]. However, in our multivariate linear mixed effects model HBV-DNA did not show a significant association with change in eGFR. In addition we did not observe any significant correlation between baseline HBV-DNA levels and baseline eGFR (Spearman's rho $-0.05$, $p = 0.53$).

The yearly decline of eGFR observed in all patient groups can be attributed to aging which results in a progressive loss of renal function [22,28–30].

In contrast to HBV-monoinfected patients, in HIV-monoinfected patients the use of tenofovir was associated with a more pronounced impairment of yearly change in eGFR which corresponds well with the published data [6–10].

An important detail of the study population is that all included patients are of Caucasian origin. In contrast to African and African–American patients HIV-associated nephropathy is rare in Caucasian populations [31,32]. This may explain differences in the results between this study and studies published from the United States and Africa reporting a beneficial effect of initiation of antiretroviral therapy on renal function in populations with a high prevalence of HIV-associated nephropathy [33,34].

An important difference between HIV-infected patients and HBV-monoinfected patients may be that HIV patients are exposed to antiviral combination therapy. Recent reports suggest interactions between tenofovir and at least some HIV-protease leading to a higher frequency of impaired glomerular filtration rate [35,36]. In contrast zidovudine was not associated with increased renal impairment [36]. The present study supports this observation.

The main limitations of this study are the limited number of patients per subgroup and the limited observational period. However, this study did not aim at detecting rare adverse events, but a general pattern of drug toxicity which is based on a uniform mechanism. This does not seem to be present with the current dose of the assessed HBV-polymerase inhibitors.

## Conflict of interest

S. Mauss speaks for Bristol-Myers-Squibb and Gilead Sciences, and is a member of the advisory board of Bristol-Myers-Squibb, Gilead Sciences, and ViiV.

E. Herrmann is a consultant for Roche Pharmaceuticals and Gilead Sciences.

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