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Original article

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Lars Peters[1], Amanda Mocroft[2], Daniel Grint[3], Santiago Moreno[4], Alexandra Calmy[5], Djordje Jevtovic[6], Helen Sambatakou[7], Karine Lacombe[8], Stephane De Wit[9], Jürgen Rockstroh[10], Jelena Smidt[11], Igor Karpov[12], Anna Grzeszczuk[13], Vesnadarjan Haziosmanovic[14], Magnus Gottfredsson[15], Roxana Radoi[16], Elena Kuzovatova[17], Chloe Orkin[18], Anna Lisa Ridolfo[19], Jose Zapirain[20], Jens Lundgren[1]*

[1]CHIP, Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark

[2]University College London Medical School, Primary Care and Population Sciences, London, United Kingdom

[3]London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, United Kingdom

[4]Hospital Universitario Ramón y Cajal-IRYCIS, Infectious Diseases Department, Madrid, Spain

[5]University Hospital Geneva, Geneva, Switzerland

[6]The Institute for Infectious & Tropical Diseases, Belgrade, Serbia

[7]Athens Medical School, Hippokration General Hospital, Athens, Greece

[8]Hopital Saint-Antoine, Paris, France

[9]CHU Saint-Pierre Hospital, Brussels, Belgium

[10]University of Bonn, Department of Medicine I, Bonn, Germany

[11]Narva AIDS Centre, Kohtla-Järve, Estonia

[12]Belarus State Medical University, Minsk, Belarus

[13]Uniwersytet Medyczny w Bialymstoku, Department of Infectious Diseases, Bialystok, Poland

[14]Klinicki Centar Univerziteta Sarajevo, Sarajevo, Bosnia & Herzegovina

[15]University of Iceland and Landspitali University Hospital, Reykjavik, Iceland

[16]Dr. Victor Babes Hospital, Spitalul de Boli Infectioase si Tropicale, Bucarest, Romania

[17]Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology, Nizhny Novgorod, Russia

[18]Royal London Hospital, London, United Kingdom

[19]Osp. L. Sacco, Milan, Italy

[20]Hospital Universitario de Alava, Vitoria-Gasteiz, Spain

*Corresponding author e-mail: lars.peters@regionh.dk

Abstract

Background: According to guidelines all HIV/HBV co-infected patients should receive tenofovir-based combination antiretroviral therapy (cART). We aimed to investigate uptake and outcomes of tenofovir-based cART among HIV/HBV patients in the EuroSIDA study.

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Methods: All HBsAg+ patients followed up after 1 March 2002 were included. Changes in the proportion taking tenofovir-based cART over time were described. Poisson regression was used to investigate the relationship between tenofovir use and clinical events.

Results: 953 HIV/HBV patients were included. Median age was 41 years and patients were predominantly male (85%), white (82%) and ART experienced (88%). 697 and 256 were from Western and Eastern Europe, respectively. Fifty-five started cART during follow-up, the proportion starting with CD4<350 cells/mm3 decreased from 85% to 52% in the periods 2002-2006 to 2007-2015. Tenofovir use, among those taking cART, increased from 4% in 2002 to 73% in 2015. Compared to West, tenofovir use was lower in East in 2005 (7% vs. 42%), and remained lower in 2015 (63% vs. 76%). Among 602 patients taking tenofovir-based cART during follow-up, 155 (26%) discontinued tenofovir. Twenty-seven of all discontinuations were due to adverse effects. Only 14 started entecavir and/or adefovir after tenofovir discontinuation, whereas ten started PEG-IFN. Tenofovir use was not significantly associated with lower risk of liver-related clinical events (N=51), adjusted IRR 0.64 (95% CI 0.35–1.18) for comparing patients on tenofovir with those off tenofovir.

Conclusions: Although use of tenofovir-based cART among HIV/HBV patients has increased across Europe, a substantial proportion are still starting cART late and are receiving suboptimal HBV therapy

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BACKGROUND

For patients co-infected with HIV and hepatitis B virus (HBV), potent and durable treatment against both pathogens first became available with the introduction of tenofovir disoproxil fumarate (TDF). The European Medicines Agency approved TDF for treatment of HIV-1 infection in February 2002 [1], and for treatment of HBV in April 2008 [2]. Until 2002 HBV treatment options were limited to interferon, which has low tolerability and a low likelihood of durable suppression of HBV-DNA [3], or lamivudine, which has limited potency and confers a high rate of HBV resistance development if used as the only HBV active drug [4,5].

TDF is a nucleotide reverse transcriptase inhibitor (NRTI) with activity against both HIV and HBV. In 2005 the European Consensus Conference on treatment of HBV and HCV in HIV co-infected patients recommended that all HIV/HBV co-infected patients with an indication for antiretroviral therapy (ART) should include TDF and lamivudine or emtricitabine in their ART regimen, while in patients already receiving lamivudine, TDF should be added or replace lamivudine [6].

These recommendations have been advocated by the European AIDS Clinical Society (EACS) since the 2007 version of their treatment guidelines [7]. In the 2016 edition of the EACS guidelines it is recommended that all HBsAg positive HIV patients, irrespective of CD4 cell count, should receive ART including TDF + lamivudine or emtricitabine unless there are contra-indications [7,8,8]. If TDF needs to be discontinued due to toxicity, entecavir and adefovir can be used instead, whereas in co-infected patients who require a switch of their antiretrovirals because of HIV resistance

to TDF and/or lamivudine/emtricitabine, should continue their active HBV therapy (TDF with or without lamivudine/emtricitabine) and suitable anti-HIV agents added.

In addition to concerns about tenofovir-associated renal toxicity and bone demineralization, there may be other reasons why not all co-infected patients are receiving the optimal HBV treatment, including lack of awareness of concurrent HBV infection, regional differences in the time point when TDF was registered and prescribable.

In this study we aimed to investigate regional differences in uptake of TDF-based ART and factors associated with its use among HIV/HBV co-infected patients across Europe.

METHODS

Study population and data collection

Patients were recruited from the EuroSIDA study, a large prospective observational cohort of more than 22000 patients followed in 100 hospitals in 35 European countries plus Israel and Argentina [9]. At recruitment, in addition to demographic and clinical data, a complete ART history is obtained together with the most recent CD4 cell count and HIV-RNA measurements. Data is collected prospectively at clinical sites and sent to the coordinating centre at 6 monthly intervals. At each follow-up visit, details on all CD4 cell count and HIV-RNA values measured since last follow-up are collected, as are the dates of starting and stopping each antiretroviral drug used. Information about hepatitis B surface antigen (HBsAg), HBV-DNA and HCV serology have been collected since 1997. In 2006, all patients with unknown status for HBsAg or anti-HCV, and store plasma available, were tested for these markers in a central laboratory. All patients who were positive for HBsAg were further tested for quantitative plasma HBV-DNA and anti-HDV. Among 18943 patients with some follow up after 1/1/2002 only 1419 (7.5%) have never been tested for HBsAg.

All HBsAg positive patients, with prospective follow up after March 2002 (the date of EMA approval of TDF) were eligible for this study. Patients were followed up to a median last visit date of June 2015. Combination antiretroviral therapy (cART) was defined as a minimum of 3 antiretrovirals from any class. Liver fibrosis stage, according to the METAVIR classification [10], was defined using data from liver biopsies, the AST to platelet ratio index (APRI) or from plasma hyaluronic acid levels, as previously described [11]. In brief, values at baseline were the last values measured in the 2 years prior to baseline, and where more than one measurement of fibrosis was recorded, the biopsy was assumed to be the gold standard, followed by APRI then hyaluronic acid.

Statistical analysis

Baseline was defined as the latest of 1 March 2002, recruitment to EuroSIDA, or testing HBsAg positive. Baseline characteristics of included persons were summarized using proportions or medians and interquartile ranges (IQR). Regions of Europe were classified as in previous studies [12]. Argentina was excluded from analyses. The proportions of persons starting cART, and the CD4 count at cART initiation (and in the 12 months prior to initiation), were compared across regions of Europe and in

different calendar periods using chi-squared tests. The proportion of persons on cART at 1 March in each calendar year, amongst those under follow-up at that date, was compared between regions.

Changes in the proportion of all patients taking HBV active cART over time were described. In all analyses, use of tenofovir was defined as “tenofovir +/- lamivudine or emtricitabine” whereas other HBV active cART was defined as “lamivudine or emtricitabine without tenofovir”. Factors associated with starting TDF were investigated using Poisson regression with separate models for East and West regions. In this analysis all patients with exposure to TDF prior to baseline were excluded. A priori, due to limited power, we decided to adjust models for age, ethnicity, gender, year of follow-up, mode of HIV transmission, current CD4 count and viral load, current estimated glomerular filtration rate (eGFR) using CKD-EPI formula, current liver fibrosis, current ALT levels, current HBV-DNA and hepatitis C (included as hepatitis C antibody negative, hepatitis C antibody positive and HCV-RNA negative, hepatitis C antibody positive and HCV-RNA positive, hepatitis C antibody positive and unknown HCV-RNA, and unknown hepatitis C serology).

Changes in ALT and HBV-DNA after stopping TDF, for those that stopped during prospective follow-up were calculated at 1 year intervals before and after stopping TDF. At each time point, the latest ALT and HBV-DNA in the 6 months prior to the date were used, and where these were missing, the first measurements after the time point of interest were used. ALT and HBV-DNA measured after in those subsequently restarting TDF were excluded.

Liver related clinical events encompassed ascites, end stage hepatic encephalopathy, bacterial peritonitis, esophageal variceal bleeding, hepatorenal syndrome, liver transplantation, death from any liver related cause [13], and hepatocellular carcinoma [14]. Poisson regression was used to investigate the relationship between use of TDF and liver related events or non-liver related death among those persons on cART. Models were adjusted for age, calendar year of follow-up, HIV transmission group, and CD4, HIV viral load, fibrosis stage, HBV-DNA level, diagnosis of an AIDS defining event and the use of TDF as time-updated variables. Use of TDF was investigated as cumulative exposure as well as categorical (never exposed, started but not currently on, currently on). The analysis was repeated using fixed covariates at baseline for all variables. In a sensitivity analysis we expanded the definition of liver-related events to all also include compensated cirrhosis as an end-point.

An overview of the number of patients included in the different analyses described above is shown in supplementary figure 1.

All analyses were performed using SAS version 9.4 (Statistical Analysis Software, Cary, NC, US).

RESULTS

Baseline characteristics

We included 953 HIV/HBV co-infected patients who were followed up after March 2002. Median (IQR) baseline date was December 2004 (March 2002 – March 2012). Their characteristics at baseline are

shown in table 1. Patients were predominantly white (82%) males (85%) with a median age of 41 years. Almost a third of all patients were infected with HIV via injection drug use (IDU), 49% were anti-HCV positive and 11% and 16% were from EuroSIDA region East Central and East, respectively. At baseline, only 122 (12%) were ART naïve. Among 774 patients receiving cART at baseline, 252 (32.6%) were taking TDF with or without lamivudine/emtricitabine, and 383 (49.5%) were taking lamivudine or emtricitabine without TDF.

CD4 count at cART initiation

Fifty-five out of 122 antiretroviral naive HIV/HBV patients started cART during prospective follow-up. The CD4 cell count at cART initiation increased over time, with median (IQR) CD4 cell count increasing from 257 cells/µl (150 – 312) in 34 patients initiating cART during 2002-2006, to 345 cells/µl (218 – 403) in 21 patients starting cART in 2007 and later (p=0.05). The proportion starting cART with ≤350 CD4 cells/µl has decreased from 85.3% in 2002-2006 to 52.4% in 2007 or later (p=0.0078), with a similar increase seen in both West and Eastern regions.

Use of HBV active antiretrovirals over time

Among all patients on cART on 1 March 2002 (n=316), 4.1% were receiving a TDF based regimen, while 67.7% were receiving lamivudine as the only HBV active drug. 28.2% were on cART with no HBV active drugs. Overall use of TDF regimens increased substantially over the study period to the point where 72.9% of all HIV/HBV patients on cART were taking TDF on 1 March 2015. However, the levels of TDF use remained very low in Eastern Europe (East Central and East) until 2005/2006, and even though TDF use picked up rapidly thereafter (figure 1a), it remained significantly lower compared to Western Europe (figure 1b) (p<0.05 for 2004-2015). On 1 March 2015, use of TDF-based cART was 76.4% and 62.7% in Western and Eastern Europe, respectively (p<0.0001). Only 9.6% and 4.2% of those on cART in West and East received no HBV active antiretrovirals.

TDF was licensed for treatment of HIV-1 infection in 2002 in all countries in Western Europe, but not until May 2004 in eight out of 16 countries in Eastern Europe, and later in the remaining eight countries (Gilead Sciences Denmark, personal communication). In a sensitivity analysis, where use of HBV active antiretrovirals over time was calculated with left-censoring at date of licensing, the results changed little (supplementary figure 2). The proportion of patients in Eastern Europe receiving TDF in 2005 with vs. without left-censoring was 6.1% vs. 7.1% in 2005 and 48.0% vs. 41.4% in 2010.

Factors associated with starting tenofovir

Among 659 included patients, 373 (56.6%) started TDF during 2141 PYFU [incidence starting TDF 174.2/1000 PYFU; 95% CI 156.5 – 191.9, a median follow-up of 2.5 years (IQR 1.1 – 5.5) per person]. Generally, the adjusted point estimates for the different variables were similar when comparing Eastern and Western Europe, but few of them reached statistical significance due to the limited statistical power, particularly for East Europe (figure 2a and 2b). Calendar year of follow-up of 2007 or later was associated with increased incidence of starting TDF, in West [IRR 1.52 (95% CI 1.11 – 2.09)] but not East [IRR 1.05 (95% CI 0.55 – 2.00)], possibly due to the lower numbers starting TDF in Eastern

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Europe. Lower CD4 cell count, increasing HIV-RNA viral load, elevated HBV-DNA levels (≥2000 vs <2000 IU/ml) and elevated ALT levels were also associated with similarly increased incidence of starting TDF in both regions, but the association did not reach statistical significance for CD4, ALT and HBV-DNA in East.

Reasons for stopping tenofovir

Sixty five patients had started and stopped TDF before baseline. Of the 888 remaining patients, 602 (67.8%) took TDF during prospective follow up; of these, 229 (38.0%) were on TDF at baseline and 373 (62.0%) started during follow up. Among the 602 patients on TDF during follow up, 155 (25.7%) stopped TDF for the reasons shown in table 2, of which 48 (31.0%) stopped only TDF. Twenty-seven (17.4%) of all TDF discontinuations were due to toxicity/intolerance, with renal toxicity being the most common cause (n=14; 9.0%).

Of the 155 patients who stopped TDF during prospective follow up, only two started adefovir, eleven started entecavir, and one person started both adefovir and entecavir (after stopping TDF), and none started telbivudine. Six of the 14 starting adefovir or entecavir started in the 6 months immediately after stopping TDF. Ten patients started interferon or PEG-interferon after stopping TDF, of whom two started within six months of stopping TDF; all were co-infected with HCV.

88 persons (56.8%) restarted TDF during follow up, of which 44 (50.0%) restarted within 6 months of stopping. Among those that restarted, the median time to restarting TDF was 6.5 months (IQR 2.4 – 18.6 months). Eleven out of 27 (40.7%) who stopped TDF due to toxicity restarted TDF, compared to 41/64 (64.1%) for patient/physician choice and 36/64 (56.3%) for other reasons, p=0.12.

Changes in HBV-DNA and ALT levels after stopping tenofovir

Among the 155 patients who discontinued TDF, sixty-six (42.6%) and 10 (6.5%) patients had an ALT and HBV-DNA measurement, respectively, within 12 months after stopping TDF. Among the 66 patients with ALT measurements, 30 did not receive any HBV active drugs within 12 months after stopping TDF. Both percent with HBV-DNA >3000 IU/ml and percent with ALT levels >5 times upper level of normal did not change over time (supplementary figure 3). Only 1/66 (1.5%) patient had an ALT level >5 times upper level of normal within 12 months after stopping TDF, and had also stopped all other HBV active drugs when TDF was stopped.

Clinical events in HIV/HBV co-infected patients

Fifty-one liver-related clinical events occurred (18 deaths, 20 cases of liver failure and 13 with hepatocellular carcinoma) during 5411 person-years follow-up (median 5.8 per person, IQR 1.8 – 11.8 years) on cART. The characteristics at time of the liver-related event or at last follow-up visit for those who did not experience an event are shown in supplementary table 2. Patients with a liver-related clinical event were more likely to receive no HBV active antiretroviral drugs, less likely to receive TDF-based cART (41.2% vs. 60.8%), less likely to have suppressed HIV-RNA (62.8% vs. 77.3%) and had much lower median (IQR) CD4 cell count [250 (169 – 387) vs. 470 (294 – 689) cells/µl), but were equally likely to be anti-HCV positive (54.9% vs. 53.9%). The rate (per 1000 PYFU) of liver-related events

was lower when comparing patients on TDF (7.1, 95% CI 4.0 – 10.1) with those off TDF (12.3, 95% CI 7.9 – 16.7), p=0.051. The adjusted IRR was 0.64 (95% CI 0.35 – 1.18) for comparing patients on TDF with those off TDF (reference). Current CD4 cell count (per doubling) (IRR 0.68, 95% CI 0.57 – 0.82), current fibrosis stage (F2-4 vs. F0/1) (IRR 6.46, 95% CI 3.12 – 13.36) and older age (IRR 1.26, 95% CI 1.08 – 1.47 per 10 years older) were the only factors that were statistically significantly associated with risk of a liver related event. Current HBV-DNA was marginally significant when comparing >2000 IU/ml with < 2000 IU/ml (IRR 2.29 (0.88 – 5.94, p=0.089).

Analyzing use of TDF as a continuous variable gave similar results (not shown).

Including compensated cirrhosis as a liver endpoint increased the total number of events to 175 during 7642.8 PYFU (95% CI 32.1 - 43.3); 9 liver deaths, 12 liver failures, 7 HCC, and 148 compensated cirrhosis. 113 events occurred during 2144.3 PYFU in patients off TDF (IR 52.7; 95% CI 43.0 - 62.4) and 62 events during 2498.5 PYFU in patients on TDF (IR 24.8; 95% CI 18.6 - 31.0). The univariate and multivariate IRR were 0.47 (0.35 - 0.64, p<0.0001) and 0.29 (0.13 - 0.68, p=0.0042), respectively. Other factors were similar to when using only clinical endpoints as reported in primary analysis (results not shown) except relationship with current CD4 slightly less strong (aIRR 0.83; 95% CI 0.62 - 1.11, p=0.21).

877 patients had at least one ALT measurement during follow up; 32/877 (3.7%) experienced a grade 4 ALT flare (defined as ALT >10x upper level of normal). Among the 32 with a grade 4 flare, nine were on TDF +/- lamivudine/emtricitabine, 10 were on lamivudine/emtricitabine without TDF and 13 did not receive HBV active drugs.

A total of 99 non-liver-related deaths occurred during follow up. The most common causes of death were AIDS (n=28), non-AIDS defining cancers (n=18), and other infections (n=11). There was no significant association between use of TDF and non-liver-related deaths either, adjusted IRR 0.76 (95% CI 0.48 – 1.19).

Both analyses were repeated using only baseline covariates with similar results (data not shown).

DISCUSSION

The nucleotide reverse transcriptase inhibitor tenofovir has dual activity against HIV and HBV, and has become the mainstay for HIV/HBV co-infected patients receiving cART due to its ability to maintain long-term HBV-DNA suppression, the lack of resistance development so far and its relatively favorable safety profile.

In this study of 953 HIV/HBV co-infected patients we investigated use of TDF-based cART across Europe since the approval TDF by the European Medicine Agency in early 2002. As EuroSIDA is an observational study, we cannot say why some patients starting cART were not prescribed TDF. Possible reasons include drug access, fear of adverse effects of TDF, unawareness of HBV co-infection or other factors not collected in the EuroSIDA study. Although improvements were seen over

time, a significant proportion of patients were still starting cART late (CD4 cell count <350 cells/µl) and with suboptimal coverage against HBV, in particular in the Eastern regions (East Central and East) of EuroSIDA where among those on cART in 2015 only 63% received TDF. In the Western regions of EuroSIDA 76% of those on cART in 2015 received a TDF based regimen. Factors associated with starting tenofovir were similar in Eastern and Western EuroSIDA and included lower CD4 cell counts, higher HIV-RNA and ALT as marker of HBV induced liver injury, but in Eastern Europe, for which we had limited statistical power, the association was only statistically significant for HIV-RNA. Since plasma HBV-DNA levels were only available in a minority of patients, we are, however, not able to determine to which extent patients not receiving TDF had ongoing viral replication and therefore could have benefitted from access to TDF. We were also not able to say whether patients received other nephrotoxic drugs or had co-morbidities that could have made the clinician refrain from prescribing TDF.

Around a quarter of all patients discontinued TDF during follow up, with around 20% of all discontinuations due to toxicity/intolerance. The most common cause of toxicity was renal toxicity. Around 41% stopped TDF due to “physician decision” or “patient wish”. Although EuroSIDA investigators are instructed to not use these reasons for stopping treatment in case of toxicity we might be underestimating toxicities which are captured by patient wish or physician decision.

Only 5% of patients who discontinued TDF started adefovir, entecavir or PEG-interferon within six months of stopping TDF. Despite these deviations from guidelines, there were few ALT flares. However, since ALT levels are only collected every six months in EuroSIDA, we could have underestimated the number of flares if it they occurred outside the time of data collection.

There is accumulating evidence supporting that long-term antiviral therapy against HBV reduces the risk of liver failure and liver-related death (reviewed in ref [15].), but a sufficiently powered head-to-head comparison of the clinical effectiveness of TDF versus lamivudine/emtricitabine is lacking. Among patients receiving cART in our study, we did not find any evidence that patients on TDF were at lower risk of liver-related clinical events (death, HCC or liver failure) than patients not on TDF, but with only 51 liver-related clinical events, our study was also inadequately powered to answer this question. However, when we included compensated cirrhosis in the clinical end-point, patients receiving TDF had a significantly lower risk of the end-point compared with those not receiving TDF.

In conclusion, in this large pan-European observational study we have shown a large proportion of HIV/HBV co-infected patients have started cART late and seem to receive sub-optimal coverage against HBV, in particular in Eastern Europe. Discontinuations of TDF without replacement with antiviral agents with sufficient antiviral coverage against HBV are common, and put the patients at risk of hepatic flares and progression of liver disease. Longer follow up is warranted to investigate whether treatment with less potent HBV active antivirals translates into greater risk of clinical liver disease and death among HIV/HBV co-infected patients.

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Academy Botkin Hospital, St Petersburg; T Trofimora, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology named after Academician I.N. Blokhina, Nizhny Novogrod; E Borodulina, E Vdoushkina, Samara State Medical University, Samara. Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. Spain: (JM Gatell), JM Miró, Hospital Clinic Universitari de Barcelona, Barcelona; S Moreno, J. M. Rodriguez, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz. Sweden: (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; A Blaxhult, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö. Switzerland: (A Scherrer), R Weber, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen. Ukraine: A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv. United Kingdom: (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh. The following centers have previously contributed data to EuroSIDA: Infectious Diseases Hospital, Sofia, Bulgaria; Hôpital de la Croix Rousse, Lyon, France; Hôpital de la Pitié-Salpétière, Paris, France; Unité INSERM, Bordeaux, France; Bernhard Nocht Institut für Tropenmedizin, Hamburg, Germany; 1st I.K.A Hospital of Athens, Athens, Greece Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy; Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy; Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy; Dérer Hospital, Bratislava, Slovakia; Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain; Kiev Centre for AIDS, Kiev, Ukraine; Luhansk State Medical University, Luhansk, Ukraine; Odessa Region AIDS Center, Odessa, Ukraine. EuroSIDA Steering Committee: Steering Committee:: J Gatell, B Gazzard, A Horban, I Karpov, B Ledergerber, M Losso, A d'Arminio Monforte, C Pedersen, M Ristola, A Phillips, P Reiss, J Lundgren, J Rockstroh. Chair: J Rockstroh. Study Co-leads: A Mocroft, O Kirk. EuroSIDA Representatives to EuroCoord: O Kirk, A Mocroft, P Reiss, A Cozzi-Lepri, R Thiebaut, J Rockstroh, D Burger, R Paredes, L Peters EuroSIDA staff: Coordinating Centre Staff: O Kirk, L Peters, C Matthews, AH Fischer, A Bojesen, D Raben, D Kristensen, K Grønborg Laut, JF Larsen, D Podlekareva. Statistical Staff: A Mocroft, A Phillips, A Cozzi-Lepri, L Shepherd, A Schultze.

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Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy
Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy
Dérer Hospital, Bratislava, Slovakia
Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain
Odessa Region AIDS Center, Odessa, Ukraine

EuroSIDA Steering Committee

Steering Committee:: J Gatell, B Gazzard, A Horban, I Karpov, B Ledergerber, M Losso, A d'Arminio Monforte, C Pedersen, M Ristola, A Phillips, P Reiss, J Lundgren, J Rockstroh

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EuroSIDA staff

Coordinating Centre Staff: O Kirk, L Peters, C Matthews, AH Fischer, A Bojesen, D Raben, D Kristensen, K Grønborg Laut, JF Larsen, D Podlekareva

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Disclosures

Jürgen Rockstroh has received honoraria for speaking at educational events or counselling from Abbott, Abbvie, Abivax, Gilead, Janssen, Merck and ViiV

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FIGURE LEGENDS

Figure 1: **HBV active antiretrovirals used in HIV/HBV coinfected people over time in Eastern (figure 1a) and Western (figure 1b) Europe**

The figures show use of HBV active antiretroviral drugs among patients taking combination antiretroviral therapy

Abbreviations: TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine

Figure 2: Factors associated with starting tenofovir in Eastern (figure 2a) and Western (figure 2b) Europe

The figures show the incidence rate ratios of starting tenofovir

Footnote: Following factors were not associated with starting tenofovir in both regions ($p>0.1$), but were adjusted for: Unknown ALT, eGFR $\leq$ 60, unknown eGFR, unknown fibrosis stage, HBV-DNA unknown, anti-HCV+/HCV-RNA negative anti-HCV+/HCV-RNA unknown and anti-HCV unknown.

Abbreviations: IDU, injection drug use; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate

Supplementary figure 1: Flowchart of HBsAg positive patients included in different analyses

Abbreviations: HBsAg, hepatitis B surface antigen; TDF, tenofovir

Supplementary Figure 2: **HBV active antiretrovirals used in HIV/HBV coinfected people over time in Eastern Europe left-censored at date of tenofovir licensing**

The figure shows use of HBV active antiretroviral drugs among patients taking combination antiretroviral therapy in Eastern Europe. The figure is left-censored at date of tenofovir licensing in the individual countries

Abbreviations: TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine

Supplementary Figure 3: Change in ALT and HBV-DNA levels before and after stopping tenofovir

The figure shows the median HBV-DNA and ALT levels at different time points before and stopping tenofovir among patients who discontinued tenofovir

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Table 1. Baseline characteristics of 953 HIV/HBV coinfected individuals in EuroSIDA

Parameter		***N=953 (100)***
Age, years, median (IQR)		41 (35 – 48)
Male gender, N (%)		813 (85.3)
White race, N (%)		780 (81.9)
HIV transmission group, (N (%)	Injection drug use	288 (30.2)
	MSM	410 (43.0)
	Heterosexual	180 (18.9)
	Other	63 (8.0)
Prior AIDS, N (%)		279 (29.3)
Region of EuroSIDA, N (%)	South	211 (22.1)
	West	286 (30.0)
	North	200 (21.0)
	East Central	107 (11.2)
	East	149 (15.6)
HBV DNA, N (%)	≤2000 IU/ml	153 (16.1)
	>2000 IU/ml	72 (7.6)
	Unknown	728 (76.4)
Anti-HCV, N (%)	Negative	485 (48.8)
	Positive	400 (42.0)
	Unknown	88 (9.2)
eGFR, N (%)	≥90 ml/min/1.73^2	277 (28.5)
	<90 ml/min/1.73^2	124 (13.0)
	Unknown	557 (58.5)
Liver fibrosis, N (%)	F0/F1	378 (39.7)
	F2/F3/F4	87 (9.1)
	Unknown	488 (51.2)
ARV naïve, N (%)		122 (12.0)
On cART, N (%)		774 (81.2)
On TDF +/- 3TC/FTC, N (%)		252 (32.6)
On 3TC/FTC without TDF, N (%)		383 (49.5)
HIV-RNA, N (%)	<500 copies/ml	614 (64.4)
	≥500 copies/ml	229 (24.0)
	Unknown	110 (11.5)
CD4 cell count nadir, cells/µl, median (IQR)		153 (60 – 259)
CD4 cell count, cells/ µl, median (IQR)		414 (251 – 591)
Baseline date, median (IQR)		December/2004 (March/2002 – March/2012)

Abbreviations: IQR, inter-quartile range; MSM, men who have sex with men; eGFR, estimated glomerular filtration rate; ARV, antiretroviral drug; cART, combination antiretroviral therapy; HCV, hepatitis C virus; HBV, hepatitis B virus.

HIV-RNA, CD4, and eGFR were the latest results determined within 12 months before baseline. HBV-DNA and fibrosis was the latest result determined up to 24 months before baseline.

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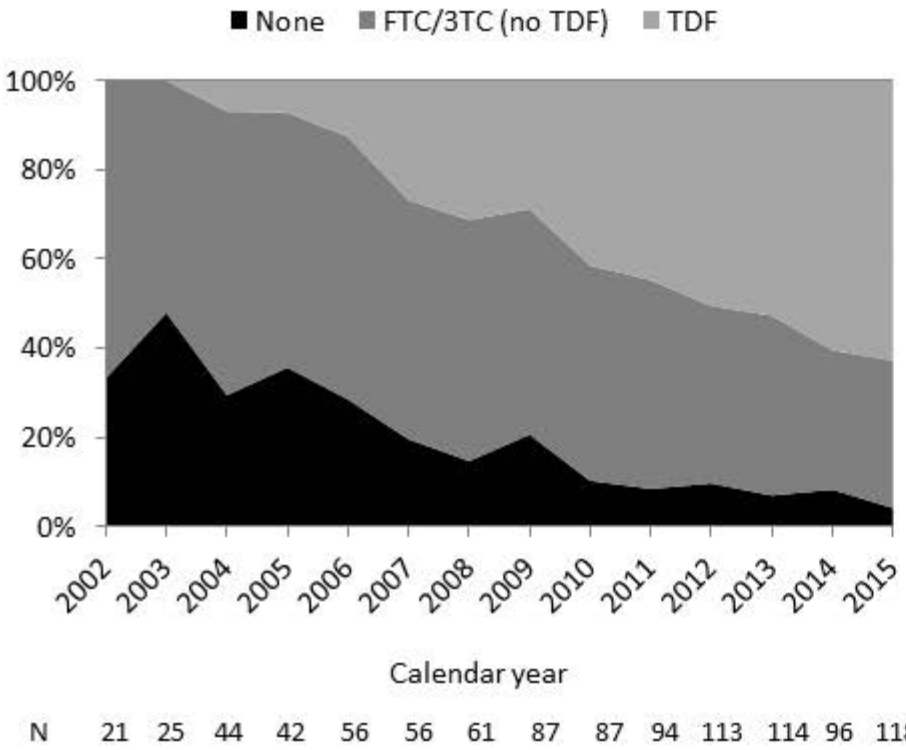
Table 2. Reasons for stopping tenofovir

Reason	N (%)
Renal toxicity/intolerance	14 (9.0)
Hypersensitivity reaction	3 (1.9)
Hepatic toxicity/intolerance	3 (1.9)
Endocrinological toxicity/intolerance	1 (0.7)
Haematological toxicity/intolerance	1 (0.7)
Gastrointestinal toxicity/intolerance	1 (0.7)
Toxicity not specified	4 (2.6)
Physician decision	21 (13.6)
Patient wish	43 (27.7)
Other causes	19 (12.3)
HIV treatment failure[1]	13 (8.4)
Drug out of stock	2 (1.3)
Concerns of cardiovascular disease	1 (0.7)
Unknown	29 (18.7)
Total	**155 (100%)**

[1]virological, immunological, and/or clinical failure

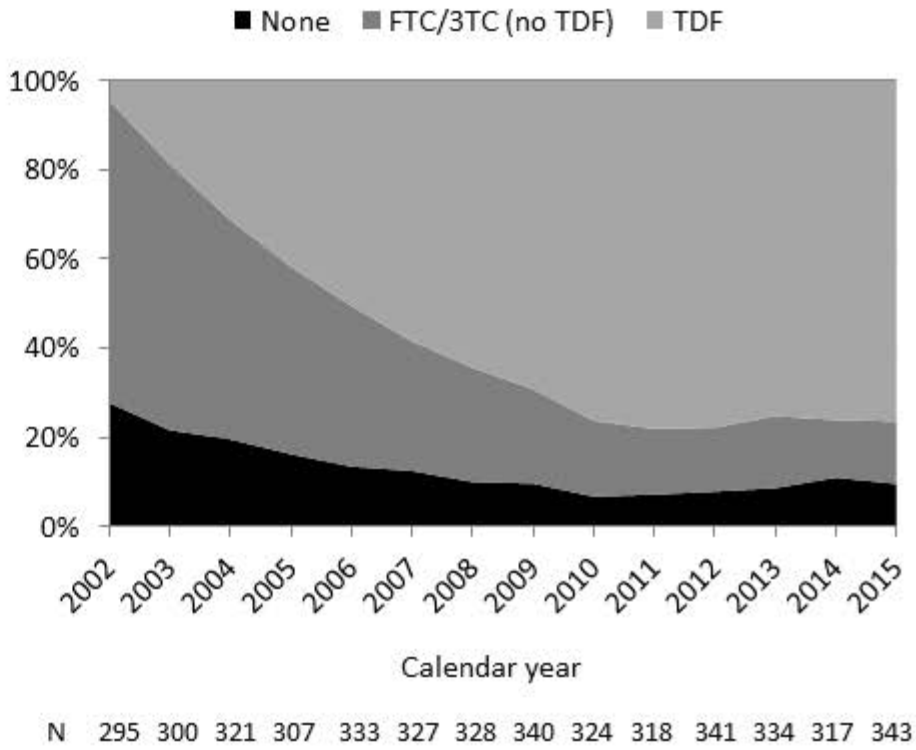
HBV active antiretrovirals used in HIV/HBV coinfected people over time in Eastern Europe (figure 1a) and Western Europe (figure 1b)

Figure 1a



N	21	25	44	42	56	56	61	87	87	94	113	114	96	118

Figure 1b



N	295	300	321	307	333	327	328	340	324	318	341	334	317	343

Figure 2a

Factors associated with starting tenofovir in Eastern Europe

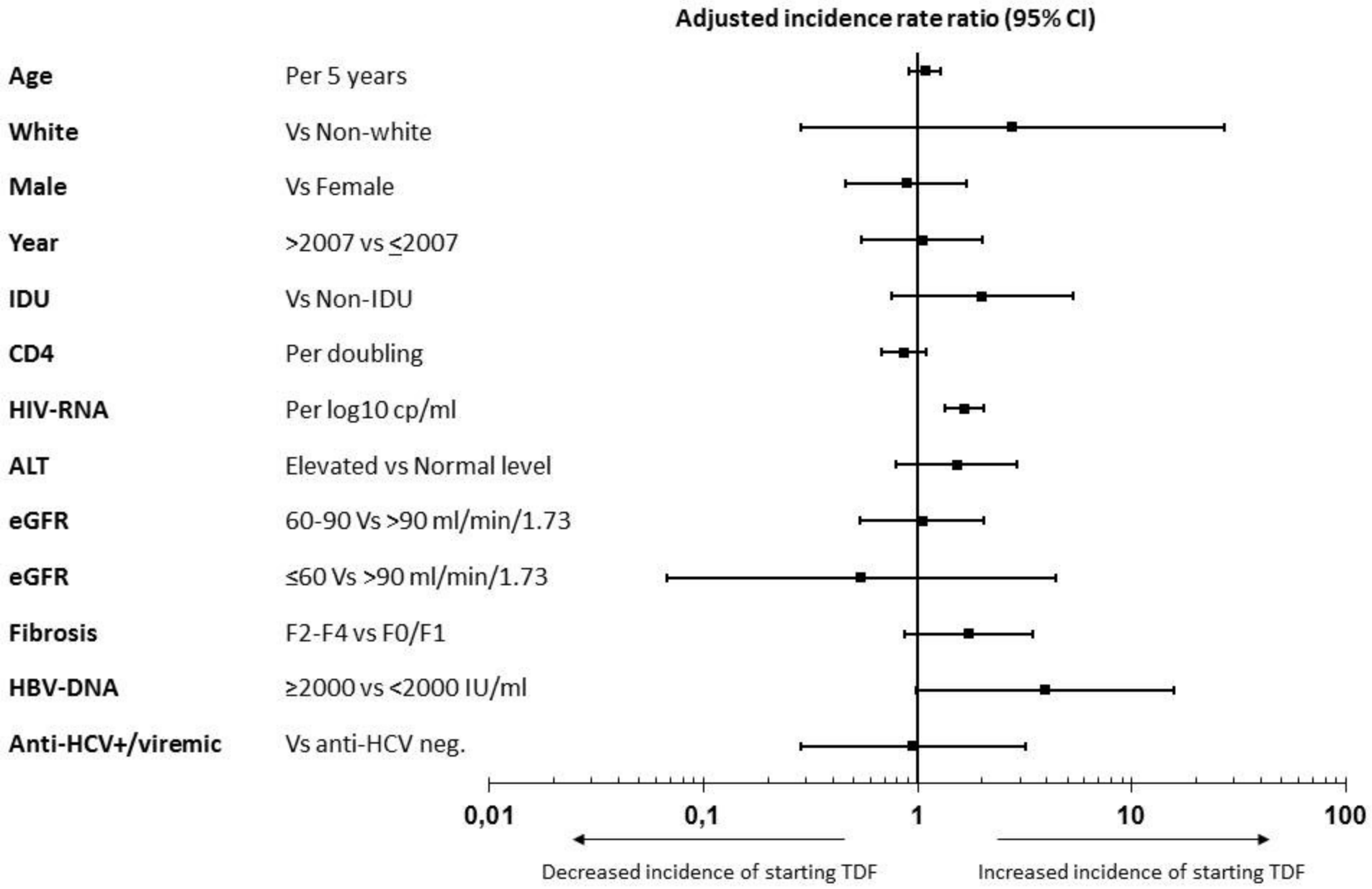
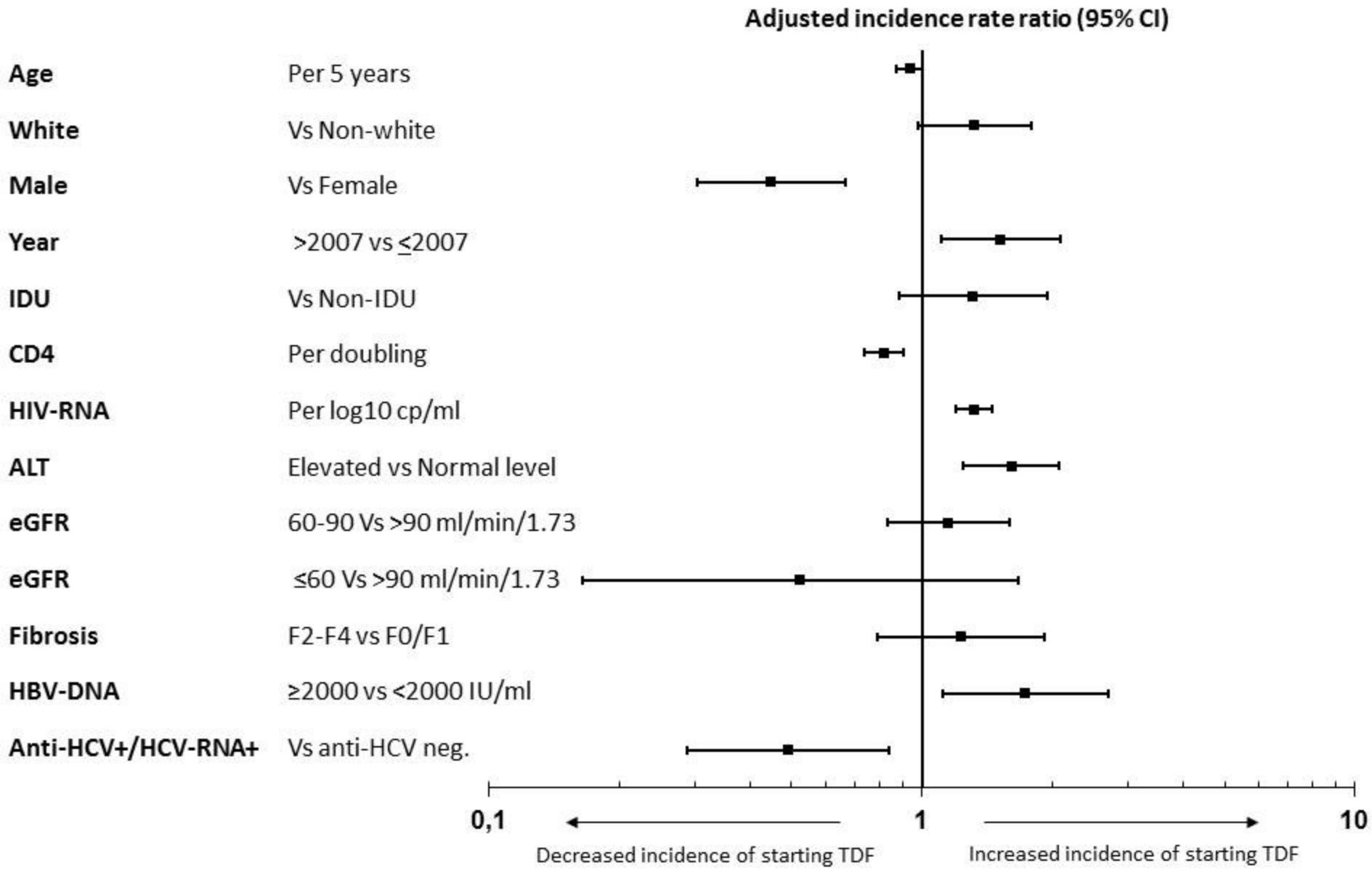


Figure 2b

Factors associated with starting tenofovir in Western Europe



Characteristics at last visit or clinical event for 882 HIV/HBV coinfected individuals in EuroSIDA on cART at last follow-up

Parameter		*N=831 (94.2%)*	*N=51 (5.8%)*	*p*
		No event	*Liver related event*	
Age, years, median (IQR)		49 (41 – 54)	50 (43 – 54)	0.92
Male gender, N (%)		709 (85.3)	43 (84.3)	0.84
White race, N (%)		680 (81.8)	49 (96.1)	0.0091
HIV transmission group, (N (%)	Injection drug use	224 (27.0)	15 (29.4)	0.41
	MSM	381 (45.9)	27 (29.4)	
	Heterosexual	159 (19.1)	5 (9.8)	
	Other	67 (8.1)	4 (7.8)	
Prior AIDS, N (%)		289 (34.8)	7 (41.2)	0.35
Region of EuroSIDA, N (%)	South	187 (22.5)	9 (17.7)	0.083
	West	258 (31.1)	11 (21.6)	
	North	189 (22.7)	20 (39.2)	
	East Central	98 (11.8)	7 (13.7)	
	East	99 (11.9)	4 (7.8)	
HBV-DNA, N (%)	$\leq$2000 IU/ml	141 (17.0)	7 (17.7)	<0.0001
	>2000 IU/ml	32 (3.9)	9 (17.7)	
	Unknown	658 (79.2)	33 (64.7)	
Anti-HCV, N (%)	Negative	448 (53.9)	28 (54.9)	0.81
	Positive	352 (42.4)	22 (43.1)	
	Unknown	31 (3.7)	1 (2.0)	
eGFR, N (%)	$\geq$90 ml/min/1.73^2	380 (45.7)	17 (33.3)	0.18
	<90 ml/min/1.73^2	263 (31.7)	18 (35.3)	
	Unknown	188 (22.6)	16 (31.4)	
Liver fibrosis, N (%)	F0/F1	564 (67.9)	15 (29.4)	<0.0001
	F2/F3/F4	92 (11.1)	17 (33.3)	
	Unknown	175 (21.1)	19 (37.3)	

Parameter		*N=831 (94.2%)*	*N=51 (5.8%)*	*p*
		No event	*Liver related event*	
On ARV no HBV active drugs, N (%)		134 (16.1)	14 (27.5)	0.017
On TDF +/- 3TC/FTC, N (%)		505 (60.8)	21 (41.2)	
On 3TC/FTC without TDF, N (%)		192 (23.1)	16 (31.4)	
HIV-RNA, N (%)	<500 copies/ml	642 (77.3)	32 (62.8)	0.017
	≥500 copies/ml	100 (12.0)	13 (25.5)	
	Unknown	89 (10.7)	6 (11.8)	
CD4 cell count nadir, cells/µl, median (IQR)		149 (60 – 246)	95 (50 – 199)	0.021
CD4 cell count, cells/ µl, median (IQR)		470 (294 – 689)	250 (169 – 387)	<0.0001
Baseline date, median (IQR)				

Abbreviations: IQR, inter-quartile range; MSM, men who have sex with men; eGFR, estimated glomerular filtration rate; ARV, antiretroviral drug; cART, combination antiretroviral therapy; HCV, hepatitis C virus; HBV, hepatitis B virus.

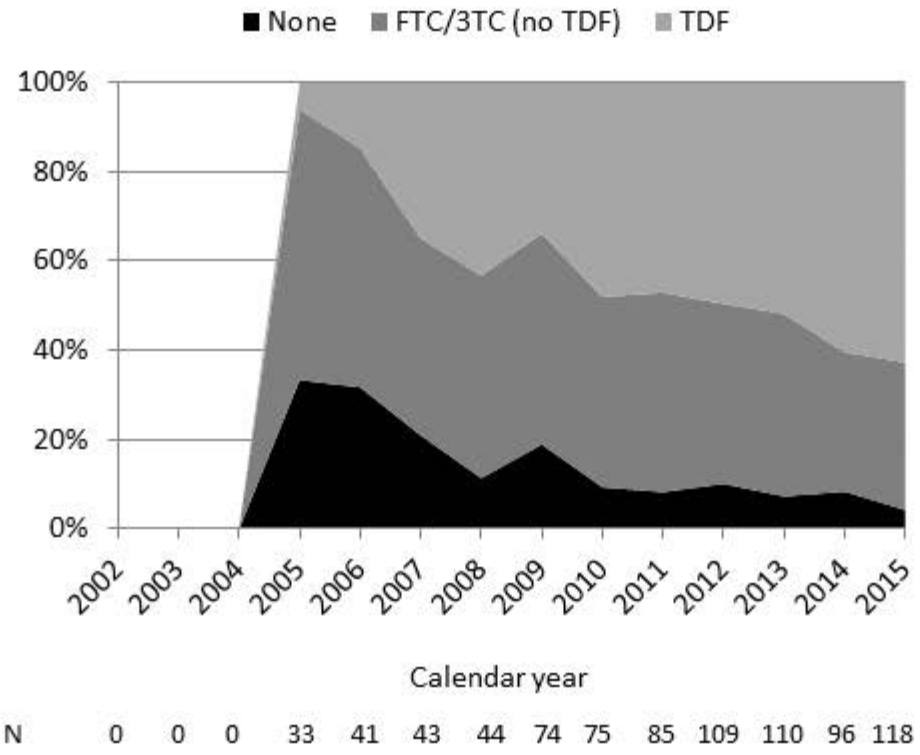
HIV-RNA, CD4, and eGFR were the latest results determined within 12 months before event or last follow-up. HBV-DNA and fibrosis was the latest result determined up to 24 months before event or last follow-up.

Supplementary Figure 1

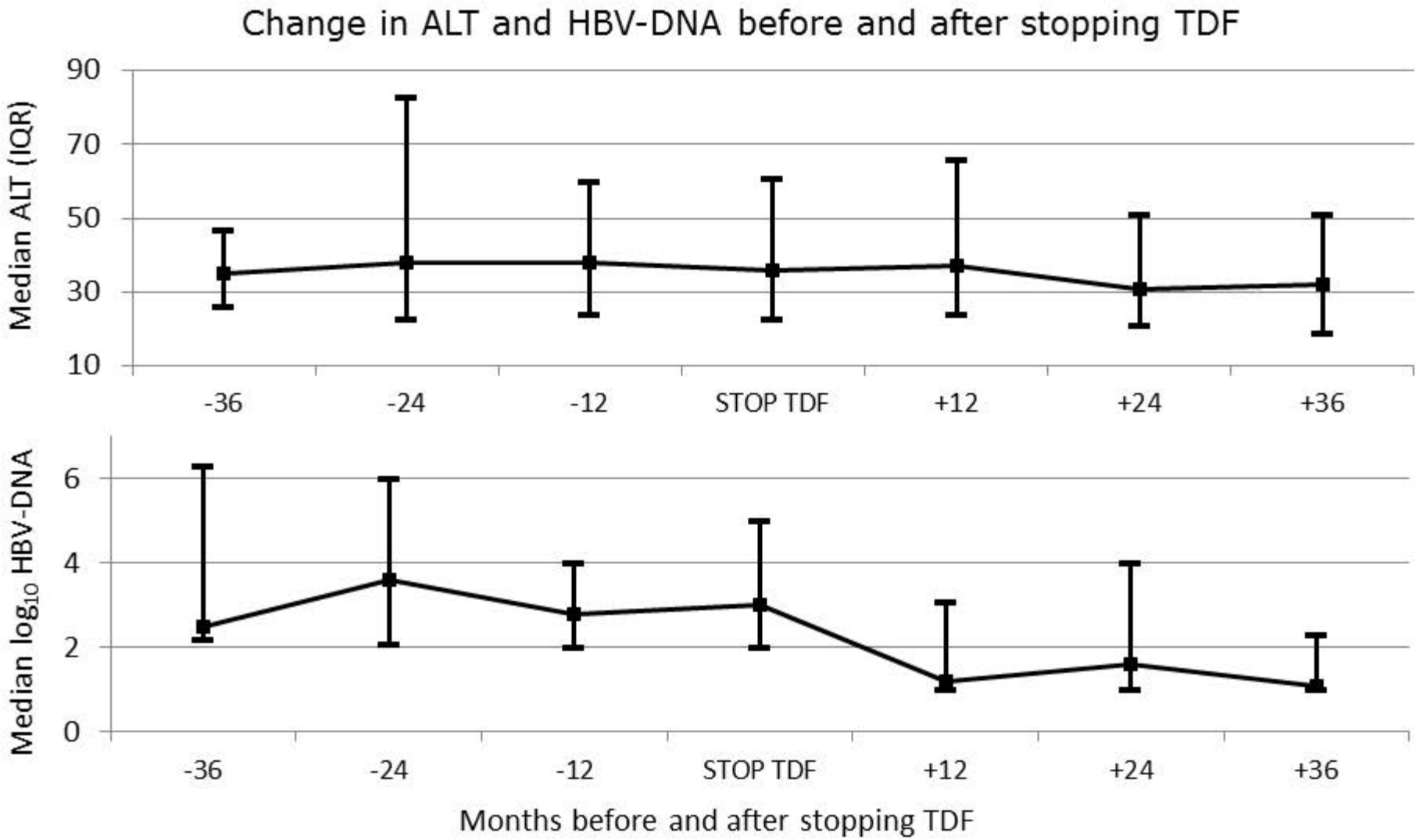
Flowchart of HBsAg positive patients included in different analyses

Supplementary Figure 2

HBV active antiretrovirals used in HIV/HBV coinfected people over time in Eastern Europe – left censoring at date of TDF licensing



Supplementary Figure 3



N	38	62	97	155	77	51	37
With ALT	29	49	86	136	66	43	27
With DNA	10	12	16	30	10	11	5
On HBV Rx[1]					36	28	18

[1]Of those with ALT values at timepoint; on lamivudine, emtricitabine, adefovir, entecavir, interferon