chip
Centre of Excellence for
Health, Immunity and Infections

25 YEARS ANNIVERSARY

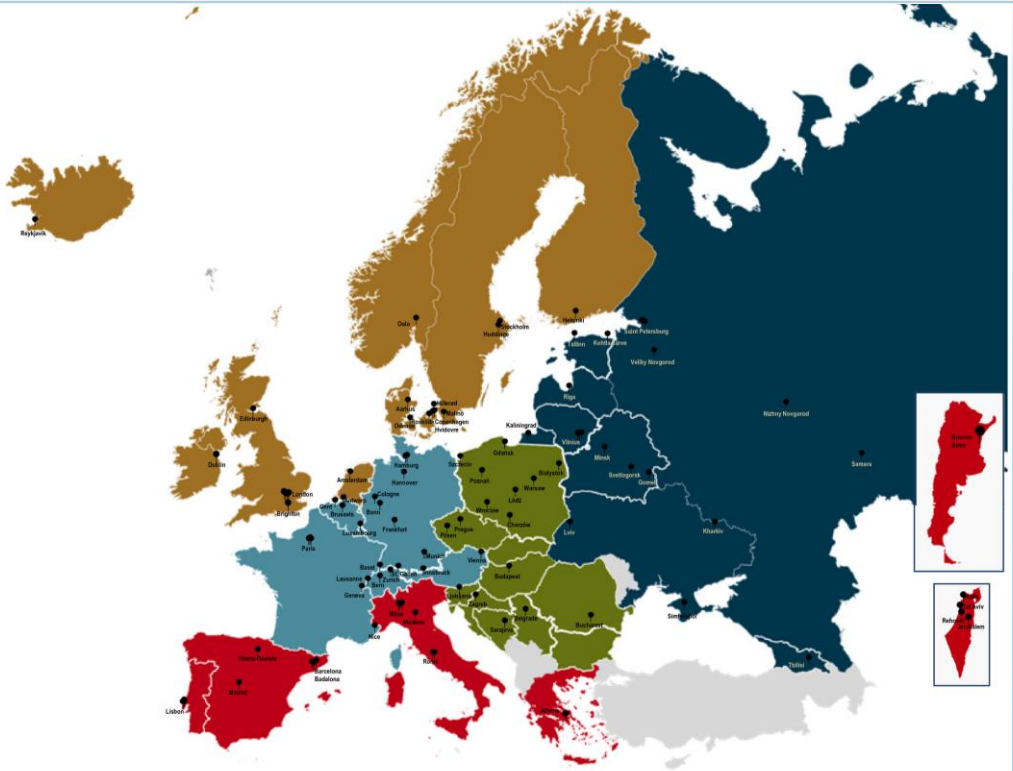
Major achievements in EuroSIDA

Prof Alison Rodger
Institute for Global Health
University College London

European AIDS Clinical Society Conference, Basel, 2019

EuroSIDA

- Established 1994 to study virological, immunological & clinical outcomes in PLWH, monitor temporal changes and regional differences across Europe
- Large prospective observational cohort: 100 collaborating clinics in 35 countries
- 2016 dataset held
  - 23,000 HIV-positive individuals, 174,481 person-years
  - 46% of participants HIV/HCV
  - Repository >160,000 samples



- **South:** Argentina, Greece, Israel, Italy, Portugal, Spain
- **Central West:** Austria, Belgium, France, Germany, Luxembourg, Switzerland
- **North:** Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, UK
- **East/Central East:** Belarus, Bosnia-Herzegovina, Croatia, Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Slovenia

Data available in EuroSIDA

Demographics/Clinical	Laboratory Values	Treatments	Plasma Repository
Date of birth Sex Country of origin Ethnicity Date first seen Date most rece Date first positi Date last negat Mode HIV-infec Mode HCV-infe Body weight Height Blood pressure Smoking status Alcohol abuse Injection drug use Pregnancy MTCT	HIV-RNA, resistance test CD4,CD8 cell count Haemoglobin Serum creatinine Platelets HBsAg, HBV-DNA, anti-HBs, HBc-IgG, anti-HBc Anti-HCV IgG, HCV-RNA HCV genotype and subtype Parathyroid hormone Prostate specific antigen Fibroscan/liver biopsy/CT/US	Antiretroviral therapy Start/stop-dates Reason discontinuation Adherence Hypersensitivity reactions Fractures Avascular necrosis Pancreatitis Lipodystrophy Treatment related to • Cardiovascular disease • Hepatitis C	Samples collected annually Centrally tested • Prostate specific antigen • HCV RNA and HCV els id a

EuroSIDA has published 300 articles (h-index 52) since 1997

http://www.chip.dk/eurosida

ART and declines in morbidity and mortality

Articles

Changing patterns of mortality across Europe in patients infected with HIV-1

A Mocroft, S Vella, T L Benfield, A Chiesi, V Miller, P Gargalianos, A d'Arminio Monforte, I Yust, J N Bruun, A N Phillips, J D Lundgren, for the EuroSIDA Study Group*

Summary

Background The introduction of combination antiretroviral therapy and protease inhibitors has led to reports of falling mortality rates among people infected with HIV-1. We examined the change in these mortality rates of HIV-1-infected patients across Europe during 1994–98, and assessed the extent to which changes can be explained by the use of new therapeutic regimens.

Methods We analysed data from EuroSIDA, which is a prospective, observational, European, multicentre cohort of 4270 HIV-1-infected patients. We compared death rates in each 6 month period from September, 1994, to March, 1998.

Findings By March, 1998, 1215 patients had died. The mortality rate from March to September, 1995, was 23·3 deaths per 100 person-years of follow-up (95% CI 20·6–26·0), and fell to 4·1 per 100 person-years of follow-up (2·3–5·9) between September, 1997, and March, 1998. From March to September, 1997, the death rate was 65·4 per 100 person-years of follow-up for those on no treatment, 7·5 per 100 person-years of follow-up for patients on dual therapy, and 3·4 per 100 person-years of follow-up for patients on triple-combination therapy. Compared with patients who were followed up from September, 1994, to March, 1995, patients seen between September, 1997, and March, 1998, had a relative hazard of death of 0·16 (0·08–0·32), which rose to 0·90 (0·50–1·64) after adjustment for treatment.

Interpretation Death rates across Europe among patients infected with HIV-1 have been falling since September, 1995, and at the begining of 1998 were less than a fifth of their previous level. A large proportion of the reduction in mortality could be explained by new treatments or combinations of treatments.

Lancet 1998; **352:** 1725–30

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Introduction

AIDS is one of the leading causes of premature death worldwide[1-3] and since the early 1980s such deaths have been steadily increasing in most countries.[4] An estimated 30 million or more adults and children had HIV-1 infection or AIDS by the end of 1997, of whom almost 2% were from western Europe. Since the start of the epidemic, more than 11 million people have died. As the number of patients with AIDS continues to increase, future mortality from the disease will increase unless treatment of the disease improves and survival increases.[5]

Treatment of HIV-1 has changed rapidly since 1994, particularly as a result of combination therapy which reduces the risk of death.[5-10] The most recent class of drugs to be approved are protease inhibitors, which have been shown to increase survival in patients with advanced immunodeficiency.[11-14] Improvements in prophylaxis of opportunistic infections, better access to care, and changes in treatment options may all have contributed to the falling death rates.[15-18]

We aimed to find out whether mortality rates had fallen between 1994 and 1998 across Europe in a group of prospectively followed patients infected with HIV-1. We also examined whether the changing mortality rates could be attributed to the introduction of new treatments.

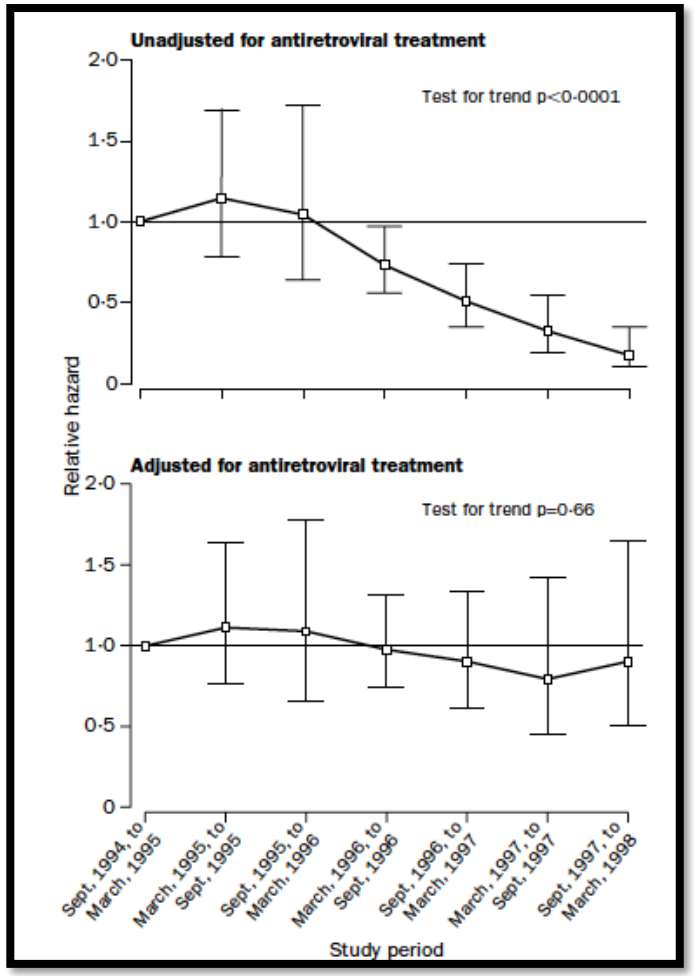
Methods

Patients

The EuroSIDA study is a prospective, pan-European study of patients with HIV-1 in 50 centres across Europe (including Israel). Details of the study have been published elsewhere.[19] In brief, centres provided data on consecutive patients seen in the outpatient clinic from May 2, 1994, until a predefined number of patients had been enrolled from each centre. This cohort of 3122 patients is the EuroSIDA I cohort. In December, 1995, a further 1369 patients were enrolled to the EuroSIDA II cohort.

Eligible patients in both cohorts were those with a CD4 lymphocyte count below 500/μL in the previous 4 months and age older than 16 years at enrolment. Information was collected from patients' case notes and by interviews with patients and recorded on a standard data-collection form at baseline and every 6 months thereafter. Information from up to seven follow-up forms is available for cohort I, and from up to four forms for cohort II. For this analysis we included data up to the last follow-up which ended in March, 1998. For each patient, we recorded the date of starting each antiretroviral, including protease inhibitors. The dates of diagnosis of all AIDS-defining diseases have also been recorded, according to the 1993 clinical definition of AIDS from the US Centers for Disease Control and Prevention.[20] Members of the EuroSIDA coordinating team visited all centres to ensure correct selection of patients and accurate provision of data.

Each of the participating centres sought ethical clearance according to local ethical regulations and laws and if requested, patients gave their informed consent to take part in the study.



Relative hazard of death with and without adjustment for ART in all patients

Lancet 1998; **352:** 1725–30

ART and declines in morbidity and mortality

Articles

Changing patterns of mortality ac infected with HIV-1

*A Mocroft, S Vella, T L Benfield, A Chiesi, V Miller, P Gargall A N Phillips, J D Lundgren, for the EuroSIDA Study Group**

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Methods We analysed data from EuroSIDA, which is a prospective, observational, European, multicentre cohort of 4270 HIV-1-infected patients. We compared death rates in each 6 month period from September, 1994, to March, 1998.

Findings By March, 1998, 1215 patients had died. The mortality rate from March to September, 1995, was 23·3 deaths per 100 person-years of follow-up (95% CI 20·6–26·0), and fell to 4·1 per 100 person-years of follow-up (2·3–5·9) between September, 1997, and March, 1998. From March to September, 1997, the death rate was 6·5·4 per 100 person-years of follow-up for those on no treatment, 7·5 per 100 person-years of follow-up for patients on dual therapy, and 3·4 per 100 person-years of follow-up for patients on triple-combination therapy. Compared with patients who were followed up from September, 1994, to March, 1995, patients seen between September, 1997, and March, 1998, had a relative hazard of death of 0·16 (0·08–0·32), which rose to 0·90 (0·50–1·64) after adjustment for treatment.

Interpretation Death rates across Europe among patients infected with HIV-1 have been falling since September, 1995, and at the begining of 1998 were less than a fifth of their previous level. A large proportion of the reduction in mortality could be explained by new treatments or combinations of treatments.

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AIDS across Europe, 1994–98: the EuroSIDA study

*A Mocroft, C Katlama, A M Johnson, C Pradier, F Antunes, F Mulcahy, A Chiesi, A N Phillips, O Kirk, J D Lundgren, for the EuroSIDA Study Group**

Summary

Background The clinical presentation of HIV-1 related diseases could have changed after the introduction of highly active antiretroviral treatment (HAART). We aimed to assess changes over time in the incidence of ADIs overall and within CD4 lymphocyte count strata, the relationship with treatment and degree of immunodeficiency at diagnosis of ADIs.

Methods We did a prospective observational multicentre study of over 7300 patients in 52 European HIV-1 outpatient clinics. Incidence rates per 100 patient-years of observation were calculated.

Findings In total, we recorded 1667 new ADIs; the incidence of ADIs declined from 30·7 per 100 patient-years of observation during 1994 (95% CI 28·0–33·4) to 2·5 per 100 patient-years of observation during 1998 (95% CI 2·0–3·0, p<0·0001, test for trend). Median CD4 lymphocyte count at diagnosis of a new ADI increased from 28 cells/μL to 125 cells/μL between 1994 and 1998 (p<0·0001), yet a steep decline in the rate of ADIs was seen after stratification by latest CD4 lymphocyte count within each year (≤50, 51–200, and >200 cells/μL). Patients on HAART had a lower rate of ADIs than patients not on this treatment within each CD4 lymphocyte count strata. The proportion of ADIs attributable to cytomegalovirus retinitis and *Mycobacterium avium* complex declined over time (p=0·0058 and 0·0022, respectively), whereas the proportion of diagnoses attributable to non-Hodgkin lymphoma has increased (p<0·0001). In 1994, less than 4% of ADIs were non-Hodgkin lymphoma, in 1998 the proportion was almost 16%. This condition has become one of the most common ADIs in patients on HAART.

Interpretation Our findings lend support to the idea that treatment regimens can lower the incidence of ADIs. The immediate risk of an ADI for a given CD4 lymphocyte count has declined over time and is lower among patients on HAART. Long-term follow-up of patients on combination treatment is essential to monitor the incidence of new and emerging diagnoses.

Lancet 2000; **356:** 291–96

*A list of study participants appears on *The Lancet*'s website

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Introduction

Until 1995, HIV was seen as a progressive disease with few treatments to prevent development of immunodeficiency and subsequent AIDS-defining illnesses (ADIs). Patients tended to have several ADIs before death, and each additional diagnosis was associated with an increased risk of death.[1–4] The incidence of ADIs within groups of patients varied before the introduction of combination treatment, and was dependent on the degree of immunodeficiency of patients included in studies.[4–6] However, the risk of ADIs was known to be very small at a CD4 lymphocyte count of above 200 cells/μL.[7,8] Some ADIs, such as Kaposi's sarcoma and tuberculosis, frequently arose at higher CD4 lymphocyte counts, whereas others, such as cytomegalovirus and mycobacterial disease, were associated with profound immunosuppression.[4,6,7] With the introduction of double and then highly active antiretroviral treatment (HAART) regimens during 1996 and 1997, the incidence of ADIs has greatly declined.[9–11]

There have been reports of ADIs arising at higher than expected CD4 lymphocyte counts after the start of treatment, as a result of immune reactivation or the development of symptom-free disease,[12,13] which has to led to debate about the prognostic value of the CD4 lymphocyte count. There are uncertainties about whether to use the same CD4 lymphocyte count value for patients given HAART when instituting prophylaxis, and treatment or investigation of specific symptoms, because current guidelines are mainly based on data obtained from patients before the introduction of HAART.[14] In addition, there have been reports that the CD4 lymphocyte count at diagnosis of ADIs has increased,[15] and conflicting reports that the incidence of some ADIs has declined to a greater extent than others.[16,17] Although smaller observational studies can monitor the incidence of more common ADIs or AIDS overall, larger studies with long follow-up are needed to monitor the occurrence of less common diagnoses. Such studies will also help to identify new and emerging diagnoses that might arise among patients who survive for longer than we have previously seen, or because of drug-related toxicities.

The aims of this study were, therefore, to describe the change in incidence of ADIs within the EuroSIDA study, both overall and within CD4 lymphocyte count strata. We also looked for temporal changes in the CD4 lymphocyte count at diagnosis and to assess whether an increase at diagnosis was as a result of patients living longer with higher CD4 lymphocyte counts. Our final objective was to establish whether the relative proportion of specific diagnoses was changing over time.

Methods

Patients

The EuroSIDA study is a prospective, European study of patients with HIV-1 in 51 centres across Europe (including Israel).[22,23] In brief, centres provided data for consecutive patients seen in the outpatient clinic from May 2, 1994,

Lancet 1998; **352:** 1725–30

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Association between latest CD4 count, treatment regime and incidence of ADIs

	Incidence (per 100 patient-years of observation)			
	≤50 cells/μL	51–200 cells/μL	>200 cells/μL	Overall
Any diagnosis				
Non-HAART	98·0	20·5	3·6	18·9
HAART	29·2	6·2	1·4	5·1
Oesophageal candidiasis				
Non-HAART	18·5	4·0	0·8	4·0
HAART	7·7	1·5	0·2	1·3
Pneumocystis carinii				
Non-HAART	13·1	2·7	0·3	2·5
HAART	4·4	0·4	0·1	0·6
CMV retinitis				
Non-HAART	17·1	1·7	0·1*	2·9
HAART	5·6	0·6	0·0	0·8
Wasting				
Non-HAART	10·5	1·8	0·2*	2·1
HAART	3·0	0·4	0·1	0·5
Kaposi's sarcoma				
Non-HAART	7·2	2·1	0·4	1·8
HAART	4·7	0·5	0·1	0·7
AIDS dementia				
Non-HAART	9·5	1·8	0·2	2·0
HAART	1·4	0·3	0·1	0·3
*M avium**				
Non-HAART	13·4	1·2	0·1*	2·3
HAART	4·0	0·3	0·0	0·5
Non-Hodgkin lymphoma				
Non-HAART	6·6	1·4*	0·3*	1·5
HAART	2·6	1·1	0·4	0·9
All other diagnoses				
Non-HAART	40·4	9·4	1·5	9·0
HAART	13·7	2·5	0·7	2·5

ART and declines in morbidity and mortality

EuroSIDA

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ARTICLES

Decline in the AIDS and death rates in the EuroSIDA study: an observational study

A Mocroft, B Ledergerber, C Katlama, O Kirk, P Reiss, A d'Arminio Monforte, B Knysz, M Dietrich, A N Phillips, J D Lundgren, for the EuroSIDA study group*

Background Since the introduction of highly active antiretroviral therapy (HAART), little is known about whether changes in HIV-1 mortality and morbidity rates have been sustained. We aimed to assess possible changes in these rates across Europe.

Methods We analysed data for 9803 patients in 70 European HIV centres including ones in Israel and Argentina. Incidence rates of AIDS or death were calculated for overall and most recent CD4 count in 6-monthly periods and in three treatment eras (pre-HAART, 1994–1995; early-HAART, 1996–1997; and late-HAART, 1998–2002).

Findings The incidence of AIDS or death fell after September, 1998, by 8% per 6-month period (rate ratio 0·92, 95% CI 0·88–0·95, p<0·0001). When AIDS and death were analysed separately, the incidence of all deaths during the late-HAART era was significantly lower than that during the early-HAART era in patients whose latest CD4 count was 20 cells/μL or less (0·43, 0·35–0·53, p<0·0001), but at higher CD4 counts, did not differ between early-HAART and late-HAART. Incidence of AIDS was about 50% lower in late-HAART than in early-HAART, irrespective of latest CD4 count (p<0·0001). In multivariate Cox's models, with early-HAART as the reference, there was an increased risk of AIDS (relative hazard 1·39; 95% CI 1·16–1·67, p=0·0004) and all deaths (1·29; 1·08–1·56, p=0·0065) in the pre-HAART era, and a reduced risk of AIDS (0·62; 0·50–0·77, p<0·0001) and all deaths (0·66; 0·53–0·82, p=0·0002) in the late-HAART era.

Interpretation The initial drop in mortality and morbidity after the introduction of HAART has been sustained. Potential long-term adverse effects associated with HAART have not altered its effectiveness in treating AIDS.

Lancet 2003; **362:** 22–29

*For list of members see
http://image.thelancet.com/extras/02art10332webappendix.pdf

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Introduction

The introduction of highly active antiretroviral therapy (HAART) during 1996 and 1997 led to a well-documented reduction in mortality and risk of AIDS-defining illnesses.[1-4] The death rate across Europe dropped rapidly, and within 2 years of the widespread availability of HAART,[3] the number of deaths were less than a fifth of those before HAART.[1] The initial success associated with HAART might not have continued, and high levels of treatment failure have been reported,[5,6] which has been associated with serious adverse events, emergence of drug resistance, difficulties in maintenance of long-term adherence, and the few types of drugs available.[6-10]

The EuroSIDA study was started in 1994 and provides an ideal opportunity to follow a large cohort of patients to describe patterns of mortality and morbidity in the era of HAART. The aims of this study were to examine changes in AIDS and death rates during this time.

Methods

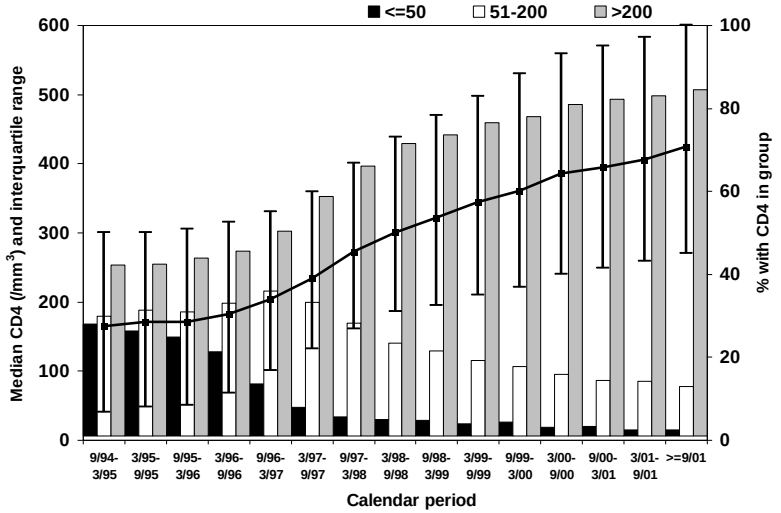
Patients

The EuroSIDA study is a prospective study of patients with HIV-1 in 70 centres across Europe, and now includes Argentina and Israel.[11] The centres provided data for consecutive patients seen in outpatient clinics from May, 1994, until a predefined number of patients was enrolled from each centre. To be eligible for inclusion, patients needed to have a prebooked clinic appointment and be aged over 16. The EuroSIDA I cohort was the first 3116 patients enrolled. The second cohort (n=1365) was enrolled between November, 1995, and April, 1996, the third (n=2839) between February, 1997, and September 1997, the fourth (n=1225) between January, 1999 and December, 1999, and the fifth (n=1258) between November, 2001, and April, 2002. For cohorts I–III, eligible patients were those with a CD4 count less than 500 cells/μL in the previous 4 months at enrolment. The threshold CD4 count was removed for cohorts IV and V. Information from patient notes was provided on a standardised data collection form at baseline and every 6 months thereafter. Follow-up was to September, 2002 with information available from up to 16 forms for cohort I, 13 for cohort II, ten for cohort III, five for cohort IV, and one for cohort V. At every follow-up visit, data were obtained for all CD4 counts measured since last follow-up and for viral load measurements. Height, weight, haemoglobin, and other laboratory indices were also routinely measured.

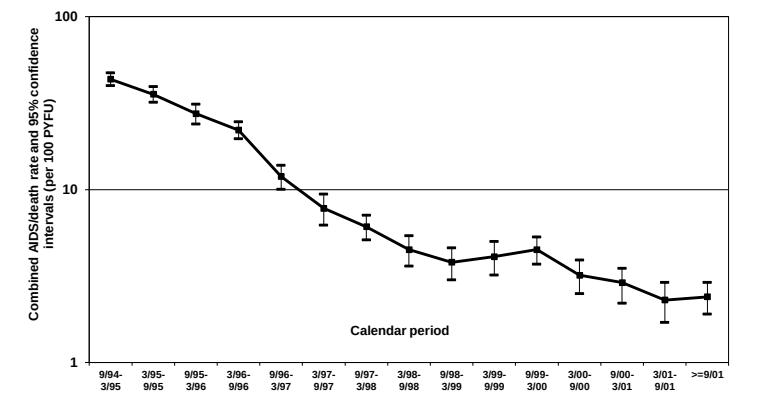
For all patients, the date of starting and stopping every antiretroviral drug was recorded, as was the use of drugs for prophylaxis against opportunistic infections. Dates of diagnosis of all AIDS-defining illnesses were also recorded, including subsequent diagnoses, by use of the 1993 clinical definition of AIDS from the Centers for Disease Control, USA.[12] Date variables were recorded as

Lancet 2003; **362:** 22–29

Changing population CD4 lymphocyte count (1995-2001)



Combined AIDS/death rates (1995 to 2001)



Interruption of OI prophylaxis

EuroSIDA

Articles

Discontinuation of *Pneumocystis c* after start of highly active antiretro

Gerrit J Weverling, Amanda Mocroft, Bruno Ledergerber, Ole Kirk, Rui Proenca, Andrew N Phillips, Jens D Lundgren, Peter Reiss, f

Summary

Background Highly active antiretroviral therapy (HAART) has improved rates of CD4-lymphocyte recovery and decreased the incidence of HIV-1-related morbidity and mortality. We assessed whether prophylaxis against *Pneumocystis carinii* pneumonia (PCP) can be safely discontinued after HAART is started.

Methods We investigated 7333 HIV-1-infected patients already enrolled in EuroSIDA, a continuing prospective observational cohort study in 52 centres across Europe and Israel. We did a person-years analysis of the rate of discontinuation of PCP prophylaxis and of the incidence of PCP after the introduction of HAART into clinical practice from July, 1996.

Findings The rate of discontinuation of primary and secondary PCP prophylaxis increased up to 21·9 discontinuations per 100 person-years of follow-up after March, 1998. 378 patients discontinued primary (319) or secondary (59) prophylaxis a median of 10 months after starting HAART. At discontinuation for primary and secondary prophylaxis, respectively, the median CD4-lymphocyte counts were 274 cells/μL and 270 cells/μL, the median plasma HIV-1 RNA load 500 copies/mL, and the median lowest recorded CD4-lymphocyte counts 123 cells/μL and 60 cells/μL. During 247 person-years of follow-up, no patient developed PCP (incidence density 0 [95% CI 0–1·5]).

Interpretation The risk of PCP after stopping primary prophylaxis, especially in patients on HAART with a rise in CD4-lymphocyte count to more than 200 cells/μL, is sufficiently low to warrant discontinuation of primary PCP

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THE LANCET

DISCONTINUATION OF SECONDARY PROPHYLAXIS AGAINST *PNEUMOCYSTIS CARINII* PNEUMONIA IN PATIENTS WITH HIV INFECTION WHO HAVE A RESPONSE TO ANTIRETROVIRAL THERAPY

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ABSTRACT

Background Patients with human immunodeficiency virus (HIV) infection and a history of *Pneumocystis carinii* pneumonia are at high risk for relapse if they are not given secondary prophylaxis. Whether secondary prophylaxis against *P. carinii* pneumonia can be safely discontinued in patients who have a response to highly active antiretroviral therapy is not known.

Methods We analyzed episodes of recurrent *P. carinii* pneumonia in 325 HIV-infected patients (275 men and 50 women) in eight prospective European cohorts. Between October 1996 and January 2000, these patients discontinued secondary prophylaxis during treatment with at least three anti-HIV drugs after they had at least one peripheral-blood CD4 cell count of more than 200 cells per cubic millimeter.

Results Secondary prophylaxis was discontinued at a median CD4 cell count of 350 per cubic millimeter; the median nadir CD4 cell count had been 50 per cubic millimeter. The median duration of the increase in the CD4 cell count to more than 200 per cubic millimeter after discontinuation of secondary prophylaxis was 11 months. The median follow-up period after discontinuation of secondary prophylaxis was 13 months, yielding a total of 374 person-years of follow-up; for 355 of these person-years, CD4 cell counts remained at or above 200 per cubic millimeter. No cases of recurrent *P. carinii* pneumonia were diagnosed during this period; the incidence was thus 0 per 100 patient-years (99 percent confidence interval, 0 to 1.2 per 100 patient-years, on the basis of the entire follow-up period, and 0 to 1.3 per 100 patient-years, on the basis of the follow-up period during which CD4 cell counts remained at or above 200 per cubic millimeter).

Conclusions It is safe to discontinue secondary prophylaxis against *P. carinii* pneumonia in patients with HIV infection who have an immunologic response to highly active antiretroviral therapy. (N Engl J Med 2001; 344:168-74.)

THE life expectancy of patients with human immunodeficiency virus (HIV) infection has dramatically improved,[1-4] and the risk of opportunistic infections, including *Pneumocystis carinii* pneumonia, has markedly declined in industrialized countries since 1996[1,5] because of the widespread use of highly active antiretroviral therapy. This decline has suggested that highly active antiretroviral therapy results in clinically important immune reconstitution. The absolute risk of the progression of HIV disease was markedly lower in patients who had an increase in CD4 cell counts in peripheral blood to more than 200 per cubic millimeter than in patients who had no such increase.[6] The degree of protection conferred could have been overestimated in these studies, because the majority of patients continued to use standard prophylactic medication against various opportunistic infections, including *P. carinii* pneumonia. However, several studies have subsequently indicated that the reduction in the risk of primary *P. carinii* pneumonia is maintained after the discontinuation of specific chemoprophylaxis.[7-10] These findings resulted in recommendations for the discontinuation of primary prophylaxis against *P. carinii* pneumonia in patients who have a response to antiretroviral therapy.[11]

The risk of recurrence of *P. carinii* pneumonia is substantially higher than the risk of primary *P. carinii* pneumonia.[12] This increase in risk is almost certainly due to the fact that the immune system is more profoundly compromised in patients in whom pneumonia has already developed, and to the presence of residual *P. carinii* organisms in the lungs despite a clinical response to therapy.[13] Thus, recommendations regarding the safety of discontinuing primary prophylaxis cannot simply be extrapolated to the discontinuation of secondary prophylaxis.

We therefore analyzed data on eight European cohorts of HIV-infected patients who had been successfully treated for an episode of *P. carinii* pneumonia, whose CD4 cell count had risen to more than 200 per cubic millimeter, and who subsequently discontinued chemoprophylaxis against recurrent *P. carinii* pneumonia.

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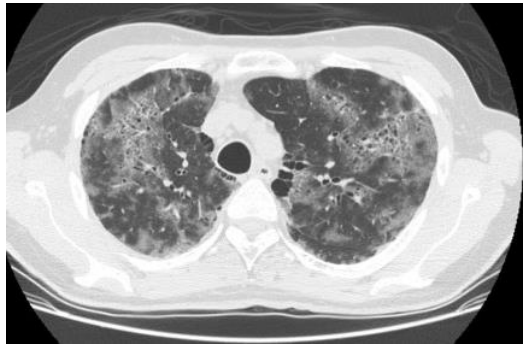

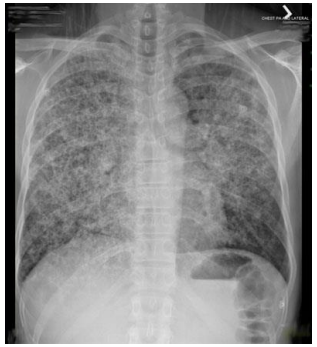

	PCP		
	Cases	PYFU	ID (95% CI)
All	0	247	0 (0–1·5)
Latest CD4-lymphocyte count (cells/μL)			
≤100	0	21·7	0 (0–17·0)
101–200	0	37·4	0 (0–9·9)
201–300	0	70·4	0 (0–5·2)
>300	0	115·1	0 (0–3·2)
Latest HIV-1 RNA load (copies/mL)			
<500	0	114·9	0 (0–3·2)
500–9999	0	60·4	0 (0–6·1)
10 000–49 999	0	26·0	0 (0–14·2)
≥50 000	0	28·9	0 (0–12·8)
CD4-lymphocyte nadir (cells/μL)			
≤50	0	59·7	0 (0–6·2)
51–100	0	49·6	0 (0–7·4)
>100	0	131·5	0 (0–2·8)
Time on HAART			
<10 months	0	179·2	0 (0–2·1)
≥10 months	0	67·3	0 (0–5·5)

Incidence of PCP and deaths among patients who stop any PCP prophylaxis after treatment with cART

ART related adverse events

Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients

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Objectives: Chronic kidney disease (CKD) in HIV-positive persons might be caused by both HIV and traditional or non-HIV-related factors. Our objective was to investigate long-term exposure to specific antiretroviral drugs and CKD.

Design: A cohort study including 6843 HIV-positive persons with at least three serum creatinine measurements and corresponding body weight measurements from 2004 onwards.

Methods: CKD was defined as either confirmed (two measurements ≥3 months apart) estimated glomerular filtration rate (eGFR) of 60 ml/min per 1.73 m^2 or below for persons with baseline eGFR of above 60 ml/min per 1.73 m^2 or confirmed 25% decline in eGFR for persons with baseline eGFR of 60 ml/min per 1.73 m^2 or less, using the Cockcroft–Gault formula. Poisson regression was used to determine factors associated with CKD.

Results: Two hundred and twenty-five (3.3%) persons progressed to CKD during 21 482 person-years follow-up, an incidence of 1.05 per 100 person-years follow-up [95% confidence interval (CI) 0.91–1.18]; median follow-up was 3.7 years (interquartile range 2.8–5.7). After adjustment for traditional factors associated with CKD and other confounding variables, increasing cumulative exposure to tenofovir [incidence rate ratio (IRR) per year 1.16, 95% CI 1.06–1.25, $P < 0.0001$), indinavir (IRR 1.12, 95% CI 1.06–1.18, $P < 0.0001$), atazanavir (IRR 1.21, 95% CI 1.09–1.34, $P = 0.0003$) and lopinavir/r (IRR 1.08, 95% CI 1.01–1.16, $P = 0.030$) were associated with a significantly increased rate of CKD. Consistent results were observed in wide-ranging sensitivity analyses, although of marginal statistical significance for lopinavir/r. No other antiretroviral dugs were associated with increased incidence of CKD.

Conclusion: In this nonrandomized large cohort, increasing exposure to tenofovir was associated with a higher incidence of CKD, as was true for indinavir and atazanavir, whereas the results for lopinavir/r were less clear.

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Keywords: antiretroviral drugs, chronic kidney disease, estimated glomerular filtration rate

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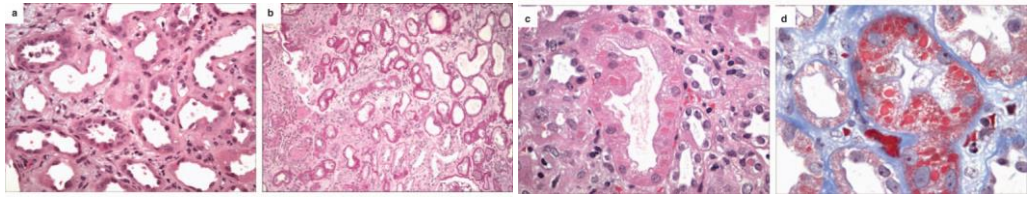

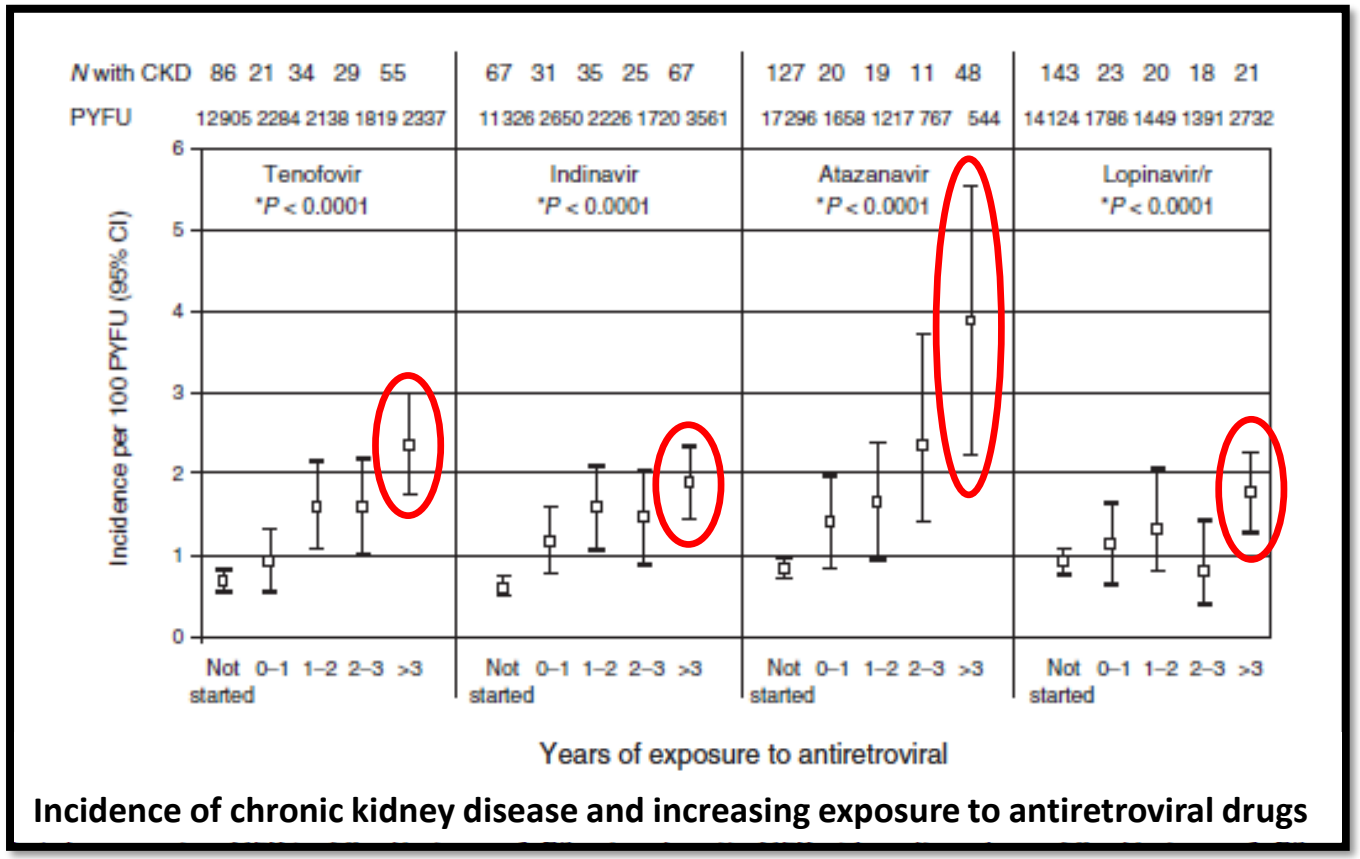

Incidence of chronic kidney disease and increasing exposure to antiretroviral drugs

ART related adverse events

Clinical Infectious Diseases

MAJOR ARTICLE

Antiretrovirals, Fractures, and Osteonecrosis in a Large International HIV Cohort

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Background. Antiretrovirals (ARVs) affect bone density and turnover, but their effect on risk of fractures and osteonecrosis of the femoral head is less understood. We investigated if exposure to ARVs increases the risk of both bone outcomes.

Methods. EuroSIDA participants were followed to assess fractures and osteonecrosis. Poisson regression identified clinical, laboratory and demographic predictors of either bone outcome. Ever, current, and cumulative exposures to ARVs were assessed.

Results. During 86118 PYFU among 11820 included persons (median age 41y, 75% male, median baseline CD4 440/mm^3, 70.4% virologically suppressed), there were 619 fractures (incidence/1000 PYFU 7.2; 95% CI 6.6–7.7) and 89 osteonecrosis (1.0; 0.8–1.3). Older age, white race, lower BMI, IV drug use, lower baseline CD4, HCV coinfection, prior osteonecrosis, prior fracture, cardiovascular disease, and recent non-AIDS cancer (last 12 months) were associated with fractures. After adjustment, persons who had ever used tenofovir disoproxil fumarate (TDF) (1.40; 1.15–1.70) or who were currently on TDF (1.25; 1.05–1.49) had higher incidence of fractures. There was no association between cumulative exposure to TDF and fractures (1.08/5 y exposure; 0.94–1.25). No other ARV was associated with fractures (all $P > .1$). Risk of osteonecrosis was associated with white race, lower nadir CD4, prior osteonecrosis, prior fracture, and prior AIDS. After mutual adjustment, no ARV was associated with osteonecrosis.

Conclusions. In human immunodeficiency virus (HIV) infection, host factors, HIV-specific variables, and comorbidities contribute to risk of fractures and osteonecrosis. Exposure to TDF, but not other ARVs, was an independent risk factor for fractures.

Keywords. fractures; osteonecrosis; avascular necrosis; bone; HIV.

Fractures and osteonecrosis of the femoral head have emerged as important manifestations of bone disease during treated human immunodeficiency virus (HIV) infection. According to population-based studies [1–3], HIV-positive persons have a 1.5–3.0 greater risk of fractures than the general population. Osteonecrosis of the femoral head, although a rare bone disease, also disproportionally affects HIV-positive persons. In the setting of HIV infection, it was estimated that osteonecrosis has a 100-fold excess risk when compared to the general population [4].

Initiation of antiretroviral therapy (ART) is associated with reduction in bone mineral density [5–7] and increases levels of markers of bone turnover [5, 8]. The loss of bone mineral density following ART initiation is comparable in magnitude to that occurring during the perimenopausal period [9] and treatment with corticosteroids [10]. Changes in bone mineral density and turnover are observed irrespective of ART regimen, but tenofovir disoproxil fumarate (TDF)-containing regimens causes greater bone loss [6, 11] whereas integrase inhibitor-based regimens may cause less bone loss [7]. However, the direct clinical consequences of this are yet to be determined because changes in bone mineral density are not perfect predictors of fracture risk [12], and the effect of ART exposure on the risk of fractures and osteonecrosis remain poorly understood. In a large HIV cohort, we set out to study the association of exposure to antiretroviral drugs with incident fractures and osteonecrosis of the femoral head and to determine factors independently associated with these two bone outcomes.

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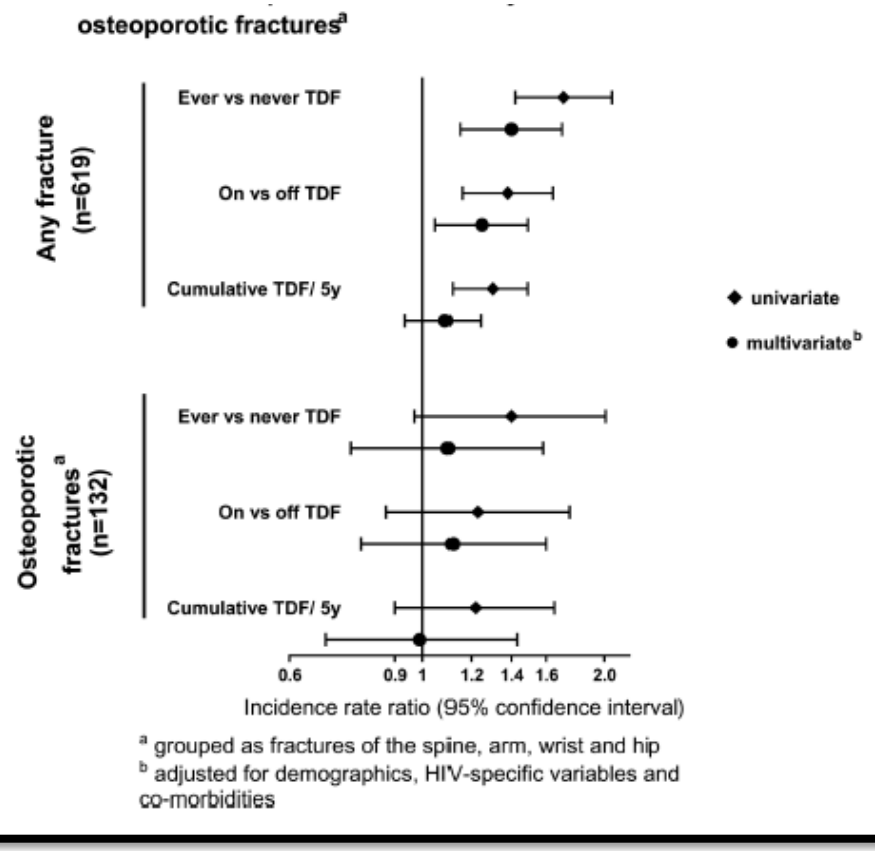
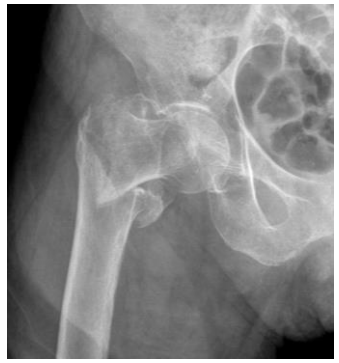
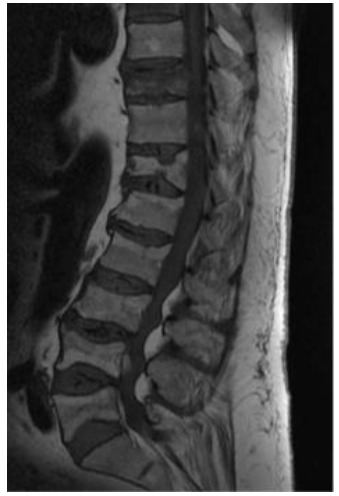
Effect of TDF exposure on risk of any fracture and of osteoporotic fracture



[a] grouped as fractures of the spine, arm, wrist and hip
[b] adjusted for demographics, HIV-specific variables and co-morbidities





Regional differences across Europe in quality of care

RESEARCH ARTICLE

Persistent disparities in antiretroviral treatment (ART) coverage and virological suppression across Europe, 2004 to 2015

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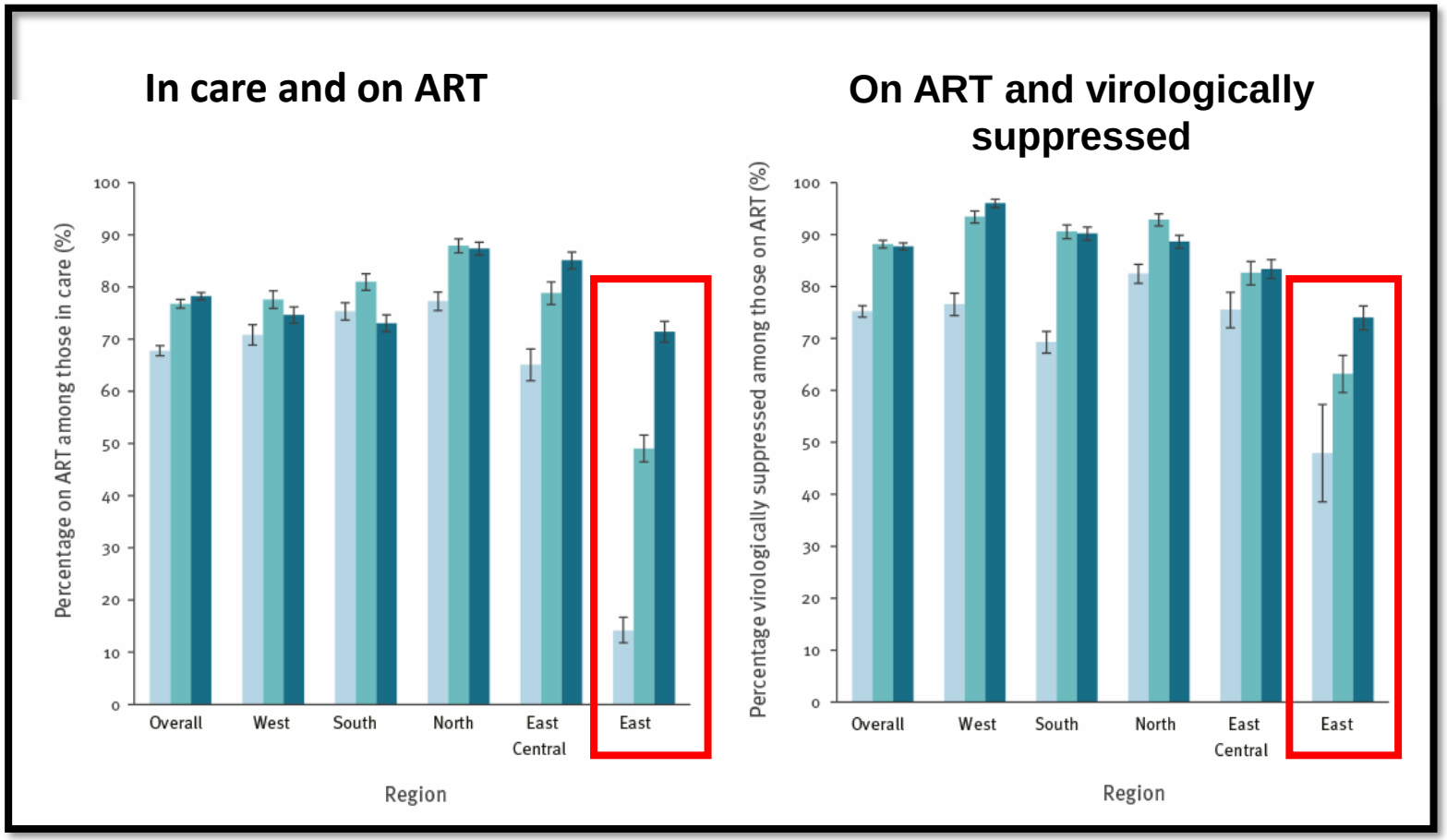
Background: Direct comparisons between countries in core HIV care parameters are often hampered by differences in data collection. **Aim:** Within the EuroSIDA study, we compared levels of antiretroviral treatment (ART) coverage and virological suppression (HIV RNA < 500 copies/mL) across Europe and explored temporal trends. **Methods:** In three cross-sectional analyses in 2004–05, 2009–10 and 2014–15, we assessed country-specific percentages of ART coverage and virological suppression among those on ART. Temporal changes were analysed using logistic regression. **Results:** Overall, the percentage of people on ART increased from 2004–05 (67.8%) to 2014–15 (78.2%), as did the percentage among those on ART who were virologically suppressed (75.2% in 2004–05, 87.7% in 2014–15). However, the rate of improvement over time varied significantly between regions ($p < 0.01$). In 2014–15, six of 34 countries had both ART coverage and virological suppression of above 90% among those on ART. The pattern varied substantially across clinics within countries, with ART coverage ranging from 61.9% to 97.0% and virological suppression from 32.2% to 100%. Compared with Western Europe (as defined in this study), patients in other regions were less likely to be virologically suppressed in 2014–15, with the lowest odds of suppression (adjusted odds ratio = 0.16; 95% confidence interval (CI): 0.13–0.21) in Eastern Europe. **Conclusions:** Despite overall improvements over a decade, we found persistent disparities in country-specific estimates of ART coverage and virological suppression. Underlying reasons for this variation warrant further analysis to identify a best practice and benchmark HIV care across EuroSIDA.

Background

It is documented that large health inequalities exist across Europe among people living with HIV (PLHIV) as well as for other diseases [1-4]. In recent years, comparing and characterising differences in healthcare between countries has received growing interest and



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Regional differences in quality of care

EuroSIDA

Variation in antiretroviral treatment coverage and virological suppression among three HIV key populations

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Objectives: We assessed differences in antiretroviral treatment (ART) coverage and virological suppression across three HIV key populations, as defined by self-reported HIV transmission category: sex between men, injection drug use (IDU) and heterosexual transmission.

Design: A multinational cohort study.

Methods: Within the EuroSIDA study, we assessed region-specific percentages of ART-coverage among those in care and virological suppression (<500 copies/ml) among those on ART, and analysed differences between transmission categories using logistic regression.

Results: Among 12 872 participants followed from 1 July 2014 to 30 June 2016, the percentages of ART-coverage and virological suppression varied between transmission categories, depending on geographical region (global *P* for interaction: $P = 0.0148$ for ART-coverage, $P = 0.0006$ for virological suppression). In Western [adjusted odds ratio (aOR) 1.41 (95% confidence interval 1.14–1.75)] and Northern Europe [aOR 1.68 (95% confidence interval 1.25–2.26)], heterosexuals were more likely to receive ART than MSM, while in Eastern Europe, there was some evidence that infection through IDU [aOR 0.60 (95% confidence interval 0.31–1.14)] or heterosexual contact [aOR 0.58 (95% confidence interval 0.30–1.10)] was associated with lower odds of receiving ART. In terms of virological suppression, people infected through IDU or heterosexual contact in East Central and Eastern Europe were around half as likely as MSM to have a

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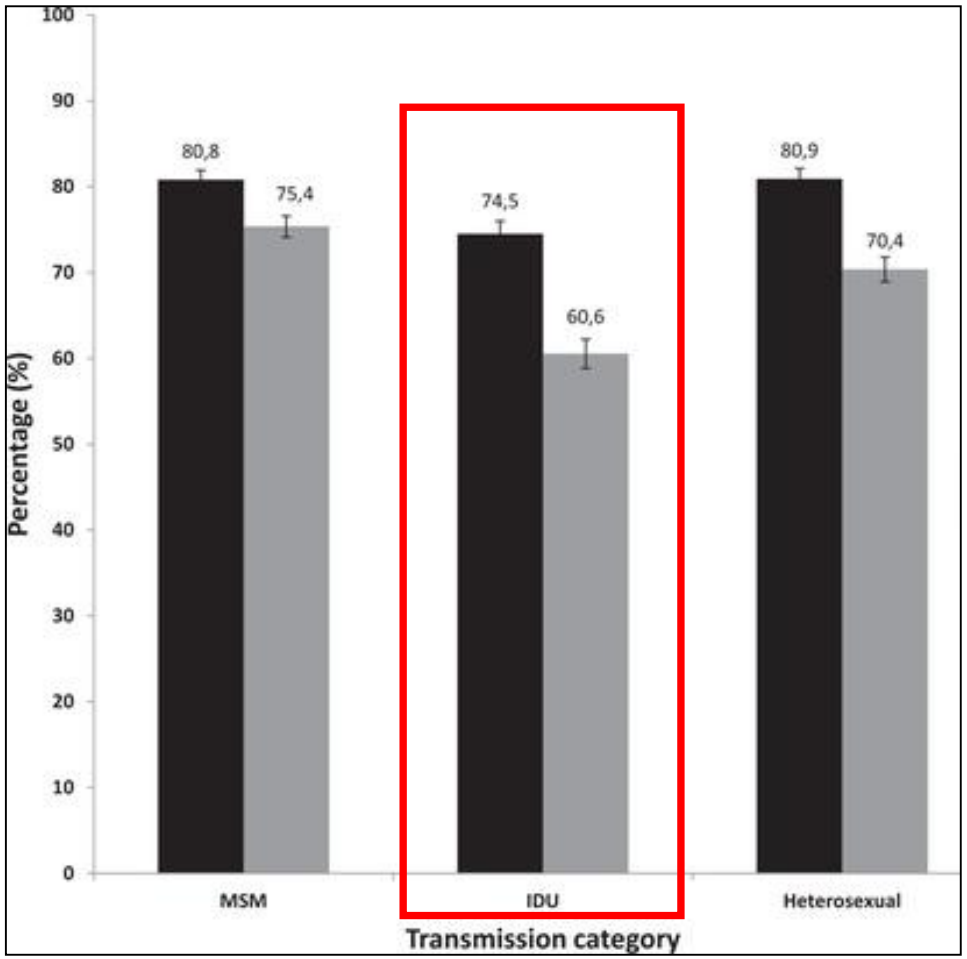

■ On ART among those in care

■ Virologically suppressed among those in care

Regional differences in quality of care

EuroSIDA

Variation in antiretroviral treatment coverage and virological suppression among three HIV key populations

Kamilla Grønborg Laut[a], Leah Shepherd[b], Magnus Gottfredsson[c,d], Dalibor Sedlacek[e], Brygida Knysz[f], Josip Begovac[g], Roxana Radoi[h], Brigitte Schmied[i], Nikoloz Chkhartishvili[j], Eric Florence[k], Matti Ristola[l], Gerd Fätkenheuer[m], Fiona Mulcahy[n], Patrick Schmid[o], Elena Kuzovatova[p], Dzmitry Paduta[q], Jelena Smidt[r], Pere Domingo[s], Janos Szlávik[t], Jens Lundgren[a], Amanda Mocroft[b], Ole Kirk[a], on behalf of the EuroSIDA study group

Objectives: We assessed differences in antiretroviral treatment (ART) coverage and virological suppression across three HIV key populations, as defined by self-reported HIV transmission category: sex between men, injection drug use (IDU) and heterosexual transmission.

Design: A multinational cohort study.

Methods: Within the EuroSIDA study, we assessed region-specific percentages of ART-coverage among those in care and virological suppression (<500 copies/ml) among those on ART, and analysed differences between transmission categories using logistic regression.

Results: Among 12 872 participants followed from 1 July 2014 to 30 June 2016, the percentages of ART-coverage and virological suppression varied between transmission categories, depending on geographical region (global *P* for interaction: $P = 0.0148$ for ART-coverage, $P = 0.0006$ for virological suppression). In Western [adjusted odds ratio (aOR) 1.41 (95% confidence interval 1.14–1.75)] and Northern Europe [aOR 1.68 (95% confidence interval 1.25–2.26)], heterosexuals were more likely to receive ART than MSM, while in Eastern Europe, there was some evidence that infection through IDU [aOR 0.60 (95% confidence interval 0.31–1.14)] or heterosexual contact [aOR 0.58 (95% confidence interval 0.30–1.10)] was associated with lower odds of receiving ART. In terms of virological suppression, people infected through IDU or heterosexual contact in East Central and Eastern Europe were around half as likely as MSM to have a

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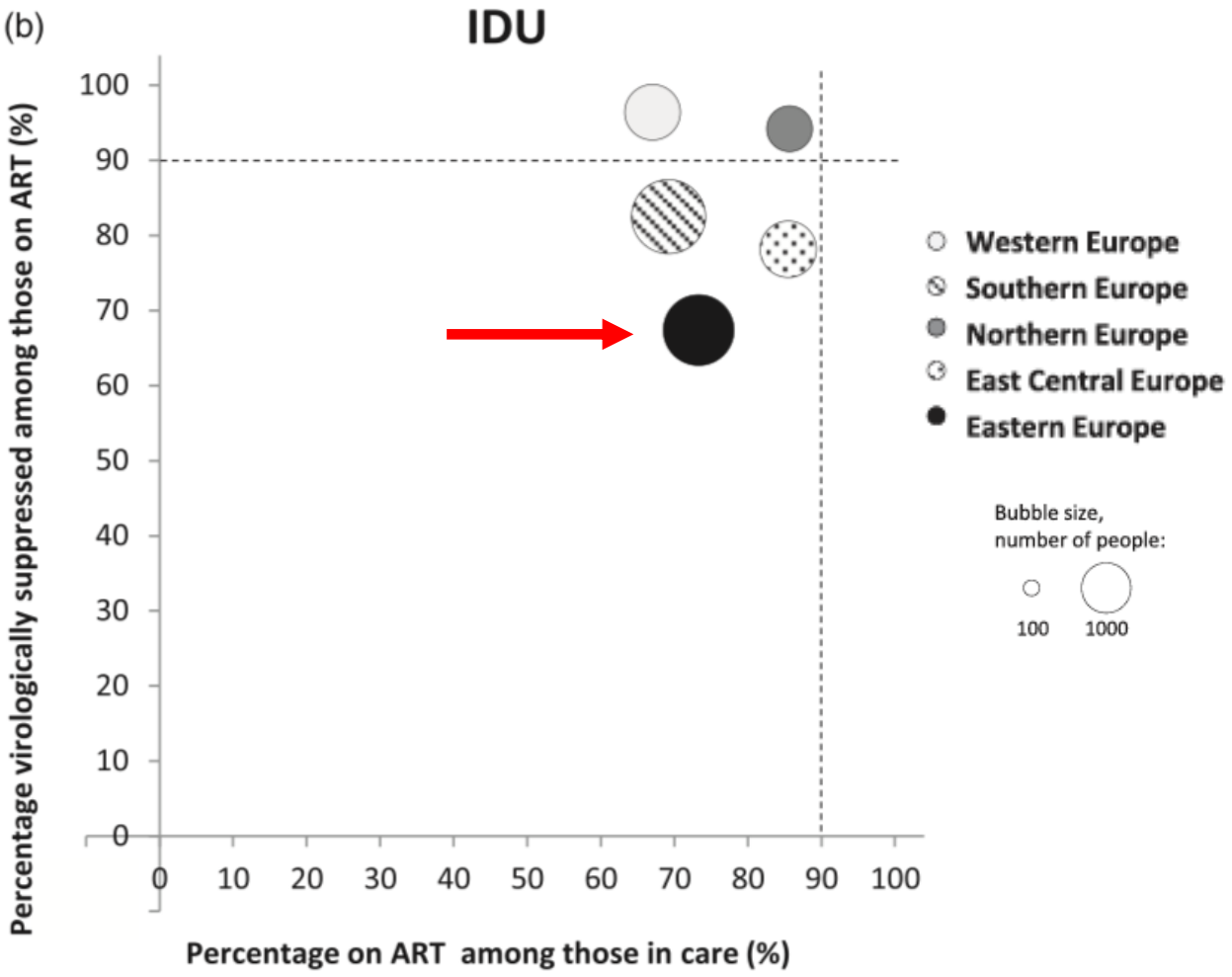

Viral hepatitis co-infection

MAJOR ARTICLE

Influence of Hepatitis C Virus Infec
Disease Progression and Response t
Antiretroviral Therapy

Jürgen K. Rockstroh,[1] Amanda Mocroft,[2] Vincent Soriano,[3] Cristina Tural,[4] Mar
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Objective. To assess hepatitis C virus (HCV) antibody prevalence in the
human immunodeficiency virus (HIV)–1 disease progression, virologic respo
copies/mL), and CD4 cell count recovery by HCV serostatus in patients
therapy (HAART).

Results. HCV serostatus at or before enrollment was available for 5957
were HCV seropositive and seronegative, respectively. No association betwe
immunodeficiency syndrome-defining illnesses or death and HCV serostatu
prognostic risk factors known at baseline (adjusted incidence rate ratio [IRR
0.81–1.16]). However, there was a large increase in the incidence of liver disea
patients in adjusted models (IRR, 11.71 [95% CI, 6.42–21.34]). Among 22
initiating HAART, after adjustment, there was no significant difference betwe
patients with respect to virologic response (relative hazard [RH], 1.13 [95
response, whether measured as a ⩾50% increase (RH, 0.94 [95% CI, 0.77–1
0.92 [95% CI, 0.77–1.11]) in CD4 cell count after HAART initiation.

Conclusions. HCV serostatus did not affect the risk of HIV-1 disease pr
related deaths was markedly increased in HCV-seropositive patients. The o
sponses to HAART were not affected by HCV serostatus.

Hepatitis C virus (HCV) coinfection has become one of the most challenging clinical situations to manage in HIV-1–infected individuals. Indeed, at present, end-stage liver disease is the cause of 17%–45% of in-hospital deaths in HIV-1–infected individuals in the West [1–3]. Because of shared routes of transmission, an estimated 30% of HIV-1–infected individuals are coinfected with HCV
epidemiologic di
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of HCV coinfecti
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-bonn.de).

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Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort

Deborah Konopnicki[a], Amanda Mocroft[b], S. de Wit[a], Francisco Antunes[c], Bruno Ledergerber[d], Christine Katlama[e], K. Zilmer[f], Stefano Vella[g], Ole Kirk[h] and Jens D. Lundgren[h] for the EuroSIDA Group

Background: Whether hepatitis B (HBV) coinfection affects outcome in HIV-1-infected patients remains unclear.

Objective: To assess the prevalence of HBV (assessed as HBsAg) coinfection and its possible impact on progression to AIDS, all-cause deaths, liver-related deaths and response to highly active antiretroviral therapy (HAART) in the EuroSIDA cohort.

Methods: Data on 9802 patients in 72 European HIV centres were analysed. Incidence rates of AIDS, global mortality and liver-related mortality, time to 25% CD4 cell count increase and time to viral load < 400 copies/ml after starting HAART were calculated and compared between HBsAg-positive and HBsAg-negative patients.

Results: HBsAg was found in 498 (8.7%) patients. The incidence of new AIDS diagnosis was similar in HBsAg-positive and HBsAg-negative patients (3.3 and 3.4/100 person-years, respectively) even after adjustment for potential confounders: the incidence rate ratio (IRR) was 0.94 [95% confidence interval (CI), 0.74–1.19; $P = 0.61$]. The incidences of all-cause and liver-related mortalities were significantly higher in HBsAg-positive subjects (3.7 and 0.7/100 person-years, respectively) compared with HBsAg-negative subjects (2.6 and 0.2/100 person-years, respectively). The adjusted IRR values were 1.53 for global (95% CI, 1.23–1.90; $P = 0.0001$) and 3.58 for liver-related (95% CI, 2.09–6.16; $P < 0.0001$) mortality. HBsAg status did not influence viral or immunological responses among the 1679 patients starting HAART.

Conclusions: The prevalence of HBV coinfection was 9% in the EuroSIDA cohort. Chronic HBV infection significantly increased liver-related mortality in HIV-1-infected patients but did not impact on progression to AIDS or on viral and immunological responses to HAART.

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Keywords: hepatitis B virus, coinfection, liver disease, mortality, HAART

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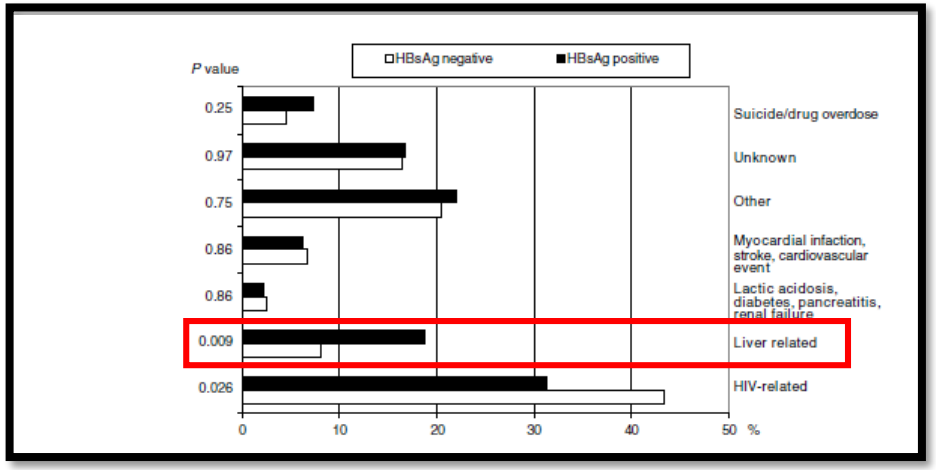
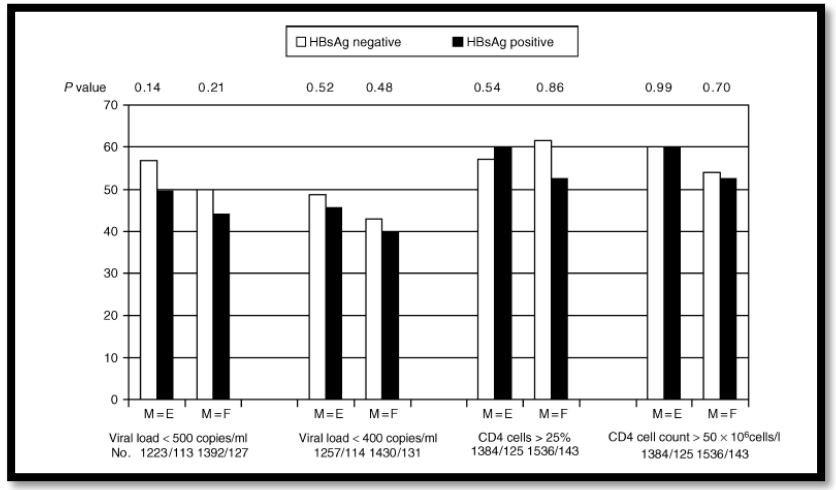
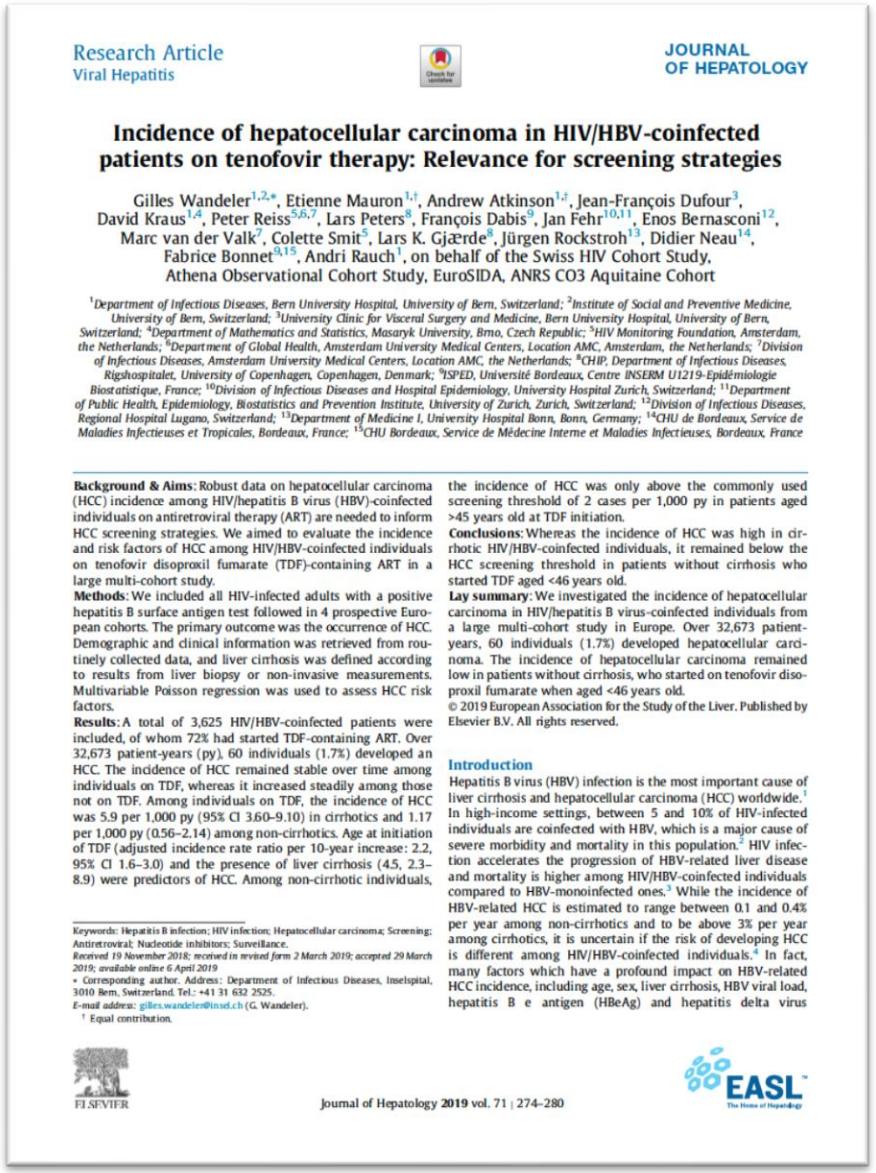
Cause of death - HBV Coinfection



Proportion responding to ART by HBsAg status



Viral hepatitis co-infection



Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies

Gilles Wandeler[1,2,*], Etienne Mauron[1,†], Andrew Atkinson[1,†], Jean-François Dufour[3], David Kraus[1,4], Peter Reiss[5,6,7], Lars Peters[8], François Dabis[9], Jan Fehr[10,11], Enos Bernasconi[12], Marc van der Valk[7], Colette Smit[5], Lars K. Gjærde[8], Jürgen Rockstroh[13], Didier Neau[14], Fabrice Bonnet[9,15], Andri Rauch[1], on behalf of the Swiss HIV Cohort Study, Athena Observational Cohort Study, EuroSIDA, ANRS CO3 Aquitaine Cohort

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Background & Aims: Robust data on hepatocellular carcinoma (HCC) incidence among HIV/hepatitis B virus (HBV)-coinfected individuals on antiretroviral therapy (ART) are needed to inform HCC screening strategies. We aimed to evaluate the incidence and risk factors of HCC among HIV/HBV-coinfected individuals on tenofovir disoproxil fumarate (TDF)-containing ART in a large multi-cohort study.

Methods: We included all HIV-infected adults with a positive hepatitis B surface antigen test followed in 4 prospective European cohorts. The primary outcome was the occurrence of HCC. Demographic and clinical information was retrieved from routinely collected data, and liver cirrhosis was defined according to results from liver biopsy or non-invasive measurements. Multivariable Poisson regression was used to assess HCC risk factors.

Results: A total of 3,625 HIV/HBV-coinfected patients were included, of whom 72% had started TDF-containing ART. Over 32,673 patient-years (py), 60 individuals (1.7%) developed an HCC. The incidence of HCC remained stable over time among individuals on TDF, whereas it increased steadily among those not on TDF. Among individuals on TDF, the incidence of HCC was 5.9 per 1,000 py (95% CI 3.60–9.10) in cirrhotics and 1.17 per 1,000 py (0.56–2.14) among non-cirrhotics. Age at initiation of TDF (adjusted incidence rate ratio per 10-year increase: 2.2, 95% CI 1.6–3.0) and the presence of liver cirrhosis (4.5, 2.3–8.9) were predictors of HCC. Among non-cirrhotic individuals, the incidence of HCC was only above the commonly used screening threshold of 2 cases per 1,000 py in patients aged >45 years old at TDF initiation.

Conclusions: Whereas the incidence of HCC was high in cirrhotic HIV/HBV-coinfected individuals, it remained below the HCC screening threshold in patients without cirrhosis who started TDF aged <46 years old.

Lay summary: We investigated the incidence of hepatocellular carcinoma in HIV/hepatitis B virus-coinfected individuals from a large multi-cohort study in Europe. Over 32,673 patient-years, 60 individuals (1.7%) developed hepatocellular carcinoma. The incidence of hepatocellular carcinoma remained low in patients without cirrhosis, who started on tenofovir disoproxil fumarate when aged <46 years old.

Keywords: Hepatitis B infection; HIV infection; Hepatocellular carcinoma; Screening; Antiretroviral; Nucleotide inhibitors; Surveillance.
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Introduction

Hepatitis B virus (HBV) infection is the most important cause of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide.[1] In high-income settings, between 5 and 10% of HIV-infected individuals are coinfected with HBV, which is a major cause of severe morbidity and mortality in this population.[2] HIV infection accelerates the progression of HBV-related liver disease and mortality is higher among HIV/HBV-coinfected individuals compared to HBV-monoinfected ones.[3] While the incidence of HBV-related HCC is estimated to range between 0.1 and 0.4% per year among non-cirrhotics and to be above 3% per year among cirrhotics, it is uncertain if the risk of developing HCC is different among HIV/HBV-coinfected individuals.[4] In fact, many factors which have a profound impact on HBV-related HCC incidence, including age, sex, liver cirrhosis, HBV viral load, hepatitis B e antigen (HBeAg) and hepatitis delta virus

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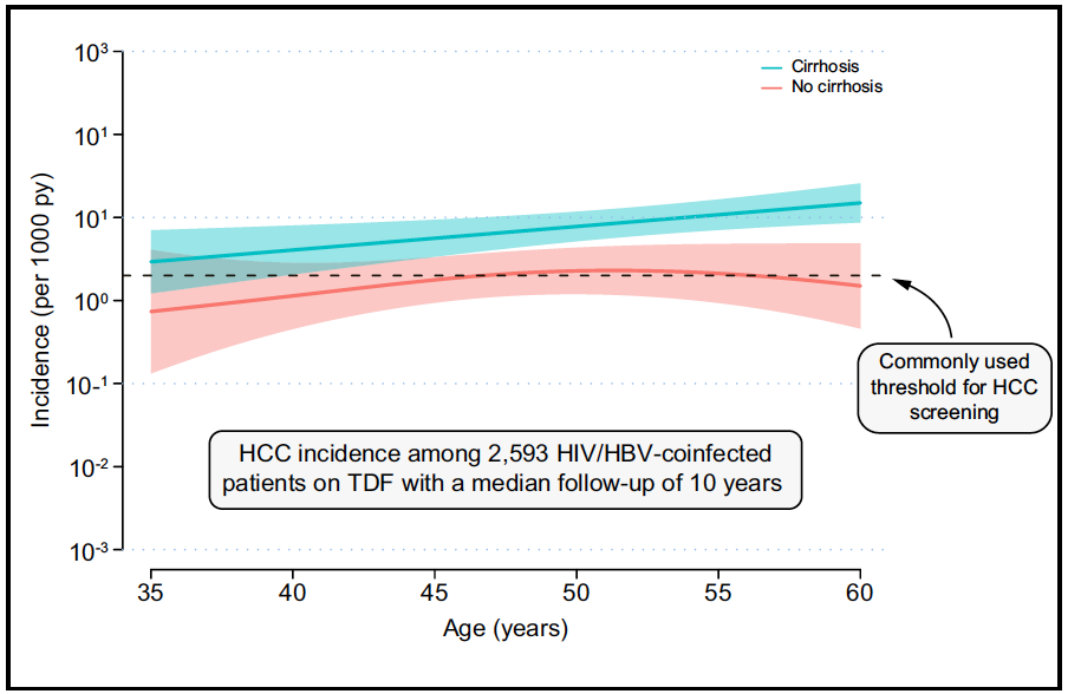

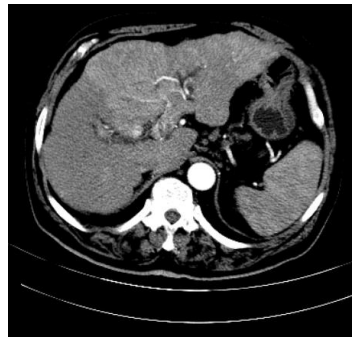

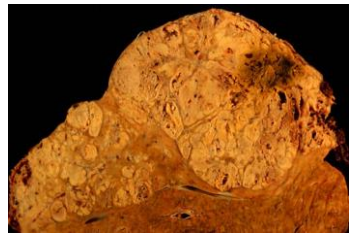

Incidence HCC among HIV/HBV coinfected individuals at initiation of ART

- 33,000 years follow up, HIV/HBV coinfected individuals
- 60 (1.7%) cases HCC
- Incidence: Cirrhotic patients 5.90/1,000 py; Non-cirrhotic 1.17/1,000 py.
- HCC incidence below screening threshold in non-cirrhotic HIV/HBV coinfected individuals starting TDF when <46 years old.

Major achievements in EuroSIDA

"Eurosida was initiated in 1994 with the aim of studying long-term virological, immunological and clinical outcomes of HIV positive individuals and assessing the impact of ART on the outcomes of PLWH across Europe"

Produced multiple key research outputs on the clinical implications of the HIV epidemic in Europe

- **Informed international guidelines on best practice in HIV care and management**
- **Monitors regional European differences in HIV care and management**
- **Recruiting the largest cohort of hepatitis co-infected patients to monitor uptake and outcomes of HCV therapy, particularly DAAs**

EuroSIDA will remain at the forefront of answering the scientific questions most meaningful for HIV and PLWH in the coming years