



EuroSIDA

a multicentre study

**Tracking HIV/AIDS
Across Europe
2003**

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Preface

The EuroSIDA study has expanded and reorganised itself considerably since 1999 when we first released a report comparable to this.

The leading body of the study – the steering committee – was elected by the participating sites in 2001. Dr Bruno Ledergerber is now heading this committee. Two central EuroSIDA virological laboratories were started by Clive Loveday in London and Lidia Ruiz in Badalona, and are now fully operational. Additional clinical sites and patients were added to the study in 2001 and further replenishment of the cohort is planned by the end of this year. The statistical and the coordinating centres in London and Copenhagen, respectively, were staffed up to deal with the increasing workload.

Over this time, the scientific productivity continues. In addition to the internal scientific process within the EuroSIDA study group, we have also launched successful collaborations with several cohort studies like the *Data collection of Adverse events of anti-HIV drugs* (the *D:A:D* study), the *ART Cohort Collaboration* and the *Intercohort Collaboration on the Safety of Interrupting Disease Specific Maintenance Therap*".

At the European AIDS Clinical Society conference in Warsaw in October 2003, the EuroSIDA study is presenting new data on the clinical implications of co-infection with hepatitis, among other things.

This booklet will summarize all these activities and the status of the study as of October 2003. Many people and organisations have contributed to the progress of the study and deserve our gratitude. The clinical sites and their patients have of course been essential. The various academic groups handling and analysing the data and biological material centrally are also vital components, as well as the financial sponsors of the study: the European Commission and four pharmaceutical companies – GlaxoSmithKline, Roche, Boehringer-Ingelheim and Bristol-Myers Squibb.

The daily EuroSIDA coordinator at the coordinating centre at the Copenhagen HIV Programme, Cristina Oancea, and Ole Kirk have compiled this booklet skilfully.

Jens D. Lundgren, MD
head, coordinating office

Andrew Phillips, PhD
head, statistical centre

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The EuroSIDA Study Group

The multicentre study group on EuroSIDA (national coordinators in parenthesis)

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Virology group

C Loveday, B Clotet (Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study.

Steering committee

Francisco Antunes; Anders Blaxhult; Nathan Clumeck; Jose Gatell; Andrzej Horban; Anne Johnson; Christine Katlama; Bruno Ledergerber (chair); Clive Loveday; Andrew Phillips; Peter Reiss; Stefano Vella.

Coordinating centre staff

J Lundgren (project leader), I Gjørup, O Kirk, C Oancea, N Friis-Møller, A Mocroft, A Cozzi-Lepri, W Bannister, D Mollerup, M Nielsen, A Hansen, D Kristensen, L Hansen, J Kjær.

The EuroSIDA study

HISTORY

The EuroSIDA Study was initiated in May 1994 as the successor of the *AIDS in Europe* study. It is a prospective observational cohort study, which now includes more than 9.800 patients followed in 72 hospitals in 26 European Countries (including Israel). Argentina also participates in the study since an EuroSIDA satellite has been established there. All participating HIV-clinics and countries are shown in the section of “EuroSIDA study group” and “EuroSIDA map”.

The main objective of the study is to follow the long-term clinical prognosis for the general population of HIV-infected patients living in Europe and to assess the impact of antiretroviral drugs on the outcome.

Since the very beginning, The European Commission BIOMED 1 (CT94-1637) and BIOMED 2 (CT97-2713) and the 5th framework (QLK2-2000-00773) programs have been the primary sponsors of the study. GlaxoSmithKline, Roche, Boehringer-Ingelheim, and Bristol-Myers Squibb also provided unrestricted grants. The participation of centers from Switzerland was supported by a grant from the Swiss Federal Office for Education and Science.

ORGANISATION

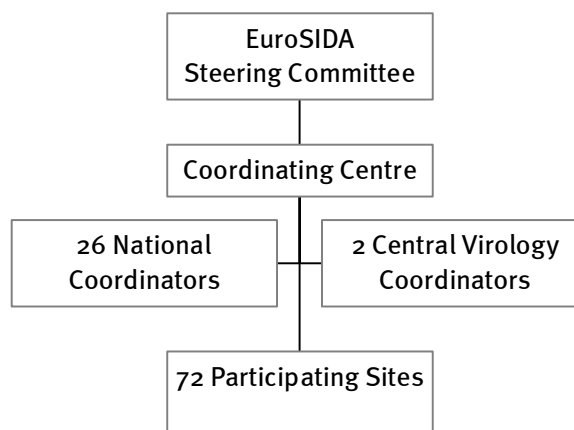
The study is headed by the steering committee, which consists of 12 members, elected by the EuroSIDA investigators for a 4-year period on a regional distribution according to the number of patients included in the study in 2000/2001. Members of the current steering committee are listed in the section “A note from the Steering Committee” (page 10). The chair of the EuroSIDA steering committee is Bruno Ledergerber from Zürich in Switzerland. Each of the 26 countries has a national coordinator, and more than 100 investigators participate in the EuroSIDA study group. The overall coordination of the study is performed by the Copenhagen HIV Programme (CHIP), at Hvidovre University Hospital in Copenhagen, Denmark.

CURRENT STATUS OF THE EUROSIDA STUDY SEPTEMBER 2003

The study has enrolled five cohorts of adult patients (*Cohort I* identified in summer of 1994 (n=3.116), *Cohort II* in winter 1995/96 (n=1.365), *Cohort III* in spring of 1997 (n=2.839), *Cohort IV* in spring of 1999 (n=1.225) and *Cohort V* in fall of 2001 (n=1.257)). Patient inclusion is done in pre-determined time periods from outpatient clinics in a way which ensures a random selection of patients under current follow-up at the clinics and therefore being as representative data from participating clinics as possible.

This is the largest international cohort study, and there are only few other studies available on a global scale of a comparable design. Until now, a total of 38.851 person-years of patient experience have been collected. There are now 168,680 CD4 cell measurements and 134,128 viral loads in the database. A central plasma repository has been established and now includes 25,772 plasma samples. Two EuroSIDA laboratories have been set up in London, UK and Badalona, Spain; more than 1400 samples have already been analyzed and an additional of 5000 are planned for the coming 2 years, thus bringing the total number of resistance tests up to approximately 6500. This number will be boosted substantially by results of resistance tests already performed locally in the clinics. At present, results of more than 1000 tests have been registered in the database.

Organisation of EuroSIDA study



An extensive quality assurance program has been implemented and now includes data checking at the coordinating office as well as regular monitoring visits with source verification of all new major events (e.g. new AIDS defining events and myocardial infarction) plus a random selection of patients followed at the clinics.

A new cohort will start recruiting approximately 1200 new patients by November/December 2003. In this process, we will include a substantial number of patients from already participating clinics in the Baltic countries and Ukraine, and hopefully new sites in Russia and Belarus. Thereafter, about 1300 participants in the study will come from the eastern part of Europe, enabling the study to better follow the dramatic epidemic in this geographical area.

SCIENTIFIC PRODUCTION

Production of scientific papers is the primary objective for the study. As of September 2003, 37 articles have been published in peer-reviewed journals. Abstracts and the key tables and figures of these articles are listed on pages 22-62. As illustrated by the publication list, the EuroSIDA study has, in the last few years, participated in and initiated international inter-cohort collaborations to address issues, which cannot readily be answered within the EuroSIDA study itself. Such collaborations include *the DAD study* and *the ART Cohort Collaboration*, and *the Intercohort Collaboration on the Safety of Interrupting Disease Specific Maintenance Therapy*, and are likely to be even more important in the coming years, as several key questions cannot be answered in even a large-size cohort study such as EuroSIDA.

EuroSIDA has presented abstracts at all the major conferences related to HIV since 1997. At the Ninth European Conference on Clinical Aspects and Treatment of HIV-Infection in Warsaw, October 25-29 2003, the EuroSIDA study presents 7 abstracts – of which 5 are oral presentations. These abstracts are all listed on pages 14-20.

FUTURE OBJECTIVES

The study will be able, in the coming years, to address the following key items:

- I) Hepatitis B and C co-infection
- II) Association between presence of virological resistance and virological, immunological and clinical outcome
- III) The epidemic in the eastern part of Europe
- IV) Long-term and rare toxicity of antiretroviral therapy

The important foundation for a study such as EuroSIDA remains the data provided by the participating clinics from across Europe – and now also Argentina.

Many people have over the last 9 years done a dedicated work by completing follow-up forms in a timely and accurate manner to allow the study to provide updated information on clinical practice in HIV-clinics across Europe. The rate of loss-to-follow-up is as low as approximately 2% per year, which is lower than or at the same level as mono-centric or national cohort studies and randomized studies.

In addition to the high data quality, the active participation of many EuroSIDA investigators in specific scientific projects is another cornerstone of the study, making this multi-national cohort study a true teamwork of European clinicians.

We would like to take this opportunity to express our gratitude for this immense work done in the clinics without which the study would never have achieved the many merits listed in the present booklet.

Updated information on the EuroSIDA study is available at: www.cphiv.dk. Should you need further information on the study, please contact:

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A note from the Steering Committee

The Steering Committee consists of regional representatives from across Europe complemented with a statistical and virological expert. The current members were elected in Fall 2001 for a four-year term by the participating sites. Our mission is to guide and assist the project leader and his team in Copenhagen and London in the scientific conduct of the study. In addition, we are here to help you by providing information, links or scientific support. Therefore, please find our e-mail addresses and phone numbers in the table below.

We would like to encourage all investigators and also researchers from outside the group to submit scientific proposals. We are convinced that EuroSIDA provides a great opportunity especially for young fellows. Proposals can be as short as one page (including background, hypotheses, questions) and will be evaluated by the Steering Committee within less than two months. For the analyses we are in the unique position to call upon the experienced statistical team of Amanda Mocroft and Andrew Phillips in London.

Bruno Ledergerber , Chair
EuroSIDA Steering Committee

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C = Central Europe; **E** = East Europe;
N = North Europe; **S** = South Europe

EuroSIDA Statistical Center

The statistical center for EuroSIDA is physically based at the Royal Free and University College Medical School (RFUCMS) in London, but has very close links with the Coordinating Center in Copenhagen.

Several statisticians contribute to the analysis of the data: Amanda Mocroft, Alessandro Cozzi Lepri, Zoe Fox, Colette Smith and Andrew Phillips. A new statistician, Wendy Bannister, will be joining the group in October.

When a clinician or virologist within the group makes a proposal for an analysis, we assign one statistician at the statistical center to work on the project with them, jointly developing an analysis plan. A set of results is produced and discussed with the project leading investigators who then draft a manuscript. We also develop proposals of our own and lead on certain projects. Areas of statistical expertise encompass analysis of virological data, including analysis of resistance data, analysis of toxicities potentially associated with HAART, such as lactic acidosis and pancreatitis, and the statistical analysis of more general questions associated with disease progression and the response to HAART.

Current projects include the response to HAART and clinical disease progression among patients infected with both HIV and hepatitis B or hepatitis C, the factors associated with triple-drug class treatment failure, disease progression among patients who stop HAART for 3 months or more, continued monitoring of the incidence of AIDS and/or death, and investigation of the durability of HAART.

In addition, a short two-day introductory course in statistical methods for HIV research is run each year by statisticians within the group along with colleagues at RFUCMS. This is intended for clinicians or laboratory scientists working in HIV to help gain basic understanding of relevant statistical issues.

On behalf of the statistical center,

Amanda Mocroft

Andrew Phillips

The EuroSIDA Virology Laboratory Group

The EuroSIDA Virology Laboratory Group is constituted by two interactive centers, one in the UK: *ICVC international clinical virology center, London* and another one in Spain: *IrsiCaixa Foundation, Badalona*.

OBJECTIVES

The main objective of our current studies is to evaluate the genotypic resistance as a factor associated to the virological, immunological and/or clinical outcome.

Other objectives:

- Supporting the development of the plasma bank.
- Defining the prevalence of resistance in Europe in untreated patients.
- Understanding resistance in specific therapeutic settings.
- Database entry and analyses using different rules algorithms. Tracking key mutations in Europe in time and space.
- Characterization of subtype diversity in time and space in Europe and understanding the implications in virological and clinical terms.
- Understanding the impact of chronic viral co-infections on virological and clinical responses in HIV/AIDS.
- Maintain the highest quality for virological data that will be used to serve the EuroSIDA database.

OUR RESEARCH AREAS

- Resistance
- Subtypes
- Provision of processes for a unique database for interpretation

Scientifically, the virology group interacts with other groups within EuroSIDA (statisticians and clinicians) and contributes to proposing new projects according to the EuroSIDA data.

THE EUROSIDA VIROLOGY GROUP

Virologists and lab technicians contributing to the laboratory and scientific work are:

- Virologists: Cecilia Cabrera, Vincent Calvez, Bonaventura Clotet, Clive Loveday, Janucz Stanczak, Amalio Telenti, Lidia Ruiz, Katja Wolthers
- Technicians: Elisabeth García and Teresa Puig
- Central plasma repository, coordination and data management: Cristina Oancea, Ole Kirk, Jesper Kjær, Lena Hansen and Jens D Lungren
- Statisticians: Alessandro Cozzi-Lepri, Andrew Phillips

On behalf of the virology group,

Lidia Ruiz, Bonaventura Clotet & Clive Loveday

**Abstracts from the EuroSIDA group
accepted for the 9th European AIDS
Conference (EACS) on Clinical Aspects and
Treatment of HIV-Infection, Warsaw 2003**

Virologic outcome of patients with virologic failure who start a regimen containing Abacavir: EuroSIDA Study

Cabrera C. (1), Cozzi-Lepri A. (2), Phillips A.N. (2), Loveday C. (3), Puig T. (1), Kirk O. (4), Ait-Khaled M. (5), Ledergerber B. (6), Lundgren J. (4), Clotet B. (1), Ruiz L. (1)

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BACKGROUND:

There are various measures of abacavir (ABC) resistance obtainable from genotypes and these require evaluation.

OBJECTIVES:

To assess the association between baseline resistance and viral load outcome in ART-experienced, ABC-naïve people starting an ABC-containing regimen in EuroSIDA.

PATIENTS AND METHODS:

Patients VL > 1,000 copies/mL and plasma sample at baseline were included. Genotyping was determined using TrueGene HIV-1 assay. Resistance to ABC was measured by number of abacavir-related mutations (using IAS-USA guidelines), VGI, Rega 4.0 rules and number of TAMs.

RESULTS:

Baseline median VL was 4.41 log₁₀ copies/mL for the 115 patients included. For 31 patients ABC was the only drug added, 1 started ABC with two recycled drugs, and 83 with 1 ≥ new

antiretroviral. The median (range) number of ABC mutations was 3 (0-8) - around half had ABC resistance according to VGI/Rega scores. Overall median VL week 24 decline was 2.76 log₁₀ copies/mL (95%CI:2.38-3.07). The VGI, number of TAMs and number of abacavir-related mutations, but not the Rega system were significantly univariably associated with outcome. After adjustment for baseline VL, number of active drugs started (other than ABC, according to Rega system) and number of drugs previously received there was a 0.09 cps/ml less VL reduction per additional IAS mutation (p=0.09) and a 0.10 cps/ml less reduction per additional TAM (p=0.08). Rega and VGI showed little association.

CONCLUSIONS:

The ABC measures were not clearly associated with response, suggesting that these algorithms may need further improvements. The predictive value of other ABC resistance measures will be presented.

Hepatitis B (HBV) in the EuroSIDA Cohort: prevalence and impact on mortality, AIDS progression and response to HAART

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BACKGROUND:

Whether HBV co-infection affects outcome of patients treated with HAART remains unclear.

OBJECTIVES:

We assessed HBsAg prevalence and survival, clinical progression and response to HAART according to HBsAg status.

RESULTS:

Among 5,883 patients tested for HbsAg at time of recruitment in EuroSIDA, 530 patients (9%) were positive. The highest prevalence was found in Argentina (17.8%) vs Northern (9.7%), Central (9.2%), Southern (9.1%) and Eastern Europe (6%) ($p=0.0016$). There were more males and HIV homosexual transmission among HbsAg-pos subjects ($p<0.0001$). Median CD4 count at recruitment was lower in HbsAg-pos persons (234) vs HBsAg-neg ($274 \times 10^6/l$; $p<0.0001$). Coinfection with HCV was found in 158 HbsAg-pos (29.8%) and 1363 HBsAg-neg patients (25.5%) ($p=0.023$). Incidence of any new AIDS diagnosis was higher for HbsAg-pos vs HbsAg-

neg subjects (13.1 vs 4.1/100 person-years) but this was not significant after adjustment for CD4, age, AIDS diagnosis, HAART, risk group, gender, ethnic origin, region of Europe, date of recruitment, and HCV status (Poisson regression model). The incidence of global and liver-related mortality were significantly higher in HbsAg-pos vs HbsAg-neg patients (12 vs 2.6 and 0.5 vs 0.2 /100 person-years respectively), and remained significantly higher in multivariate analysis (including HCV status) with incidence rate ratios of 1.55 (global; 95%CI:1.24-1.93) and 3.77 (liver-related mortality; 2.07-6.87). HbsAg status did not influence virological or immunological response among the 1752 subjects starting HAART.

CONCLUSION:

The prevalence of HBV-HIV co-infection is 9% in the EuroSIDA cohort. HBV status does not influence virological and immunological responses to HAART but significantly increases overall and liver-related mortality.

Changing incidence of central nervous system (CNS) AIDS-related diseases in the EuroSIDA cohort

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OBJECTIVE:

To assess the trend of incidence of CNS diseases (CNS-D) among 9,803 patients within EuroSIDA during 1994-2002.

METHODS:

All patients without CNS-D at recruitment were included. Incidences were calculated using a person-years (py) analysis, Cox models were used to investigate progression to CNS-D, either separately (AIDS Dementia Complex, ADC and opportunistic CNS diseases, CNS-OIs) or as a whole.

RESULTS:

Overall, 568 patients (5.8%) were diagnosed with a new CNS-D. Incidence decreased significantly from 5.9 per 100 py in 1994 to 0.5 in 2002. The decrease was 40% per calendar year, it was similar to that of non-CNS-D and less evident after year 1998. The annual decrease rate was significantly higher in ADC than in CNS OIs (45% vs. 37%). In multivariable

models, low CD4 cell count and high plasma viral load, but not calendar year, HAART or any components thereof, were significantly associated with development of CNS-D, indicating that the effect of HAART was likely mediated by improved immunological status and inhibition of viral replication. In contrast, use of NRTIs, irrespective of use of PIs or NNRTIs, appeared to protect specifically against ADC (RH=0.59, 95%-CI: 0.39-0.90), but not against other CNS-D (RH=1.06, 95%-CI: 0.80-1.40), suggesting that, in ADC, therapy might have a direct, additive effect in the CNS.

CONCLUSIONS:

The incidence of CNS-D across Europe decreased following the introduction of HAART, immune reconstitution being the main responsible. A direct effect of antiretroviral therapy on virus replication in CNS might have also accounted for the incidence decline in ADC.

Relative risk of any CNS-D after recruitment to the EuroSIDA study.

	Univariable model RH and 95%-CI	P/value	Multivariable model* RH and 95%-CI	P/value
CD4 cell count (per 50% higher)	0.60 (0.58-0.62)	< 0.0001	0.57 (0.53-0.62)	< 0.0001
HIV/RNA (per 1 log higher)	2.29 (2.02-2.60)	< 0.0001	1.43 (1.22-1.65)	< 0.0001
Started NRTIs	1.08 (0.86-1.35)	0.51	0.94 (0.62-1.43)	0.76
Started PI-HAART	0.36 (0.29-0.45)	< 0.0001	0.93 (0.65-1.35)	0.71
Started NNRTI-HAART	0.59 (0.42-0.82)	0.0016	0.77 (0.48-1.22)	0.26

Model with time-dependent variables.

*model also adjusted for calendar year and HIV transmission category

Changes in hospital admissions across Europe in 1995-2002

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OBJECTIVE:

To describe changes in the proportions of patients admitted to hospital and duration of admission during the month of March 1995-2002 in 9803 patients from the EuroSIDA cohort and factors related to admission.

METHODS:

Linear regression was used to describe changes in the proportion of patients admitted and the duration of admission. Logistic regression was used to determine factors related to admission in 1995, 1998 and 2001.

RESULTS:

The proportion of patients admitted declined from 7.4% in 1995 to 2.6% in 2002; the estimated reduction was 0.77%/year (95%-CI 0.45#1.09%, $p = 0.0032$). The median duration of admission declined from 12 days in 1995

(interquartile range, IQR 5 - 19) to 6 days during 2002 (IQR 3 - 11), a decline of 1.00 days/year (95%-CI 0.48 # 1.52, $p = 0.0090$). Patients with a lower CD4 count, and with a recent AIDS diagnosis were more likely to be admitted during March 1995, 1998 or 2001. In March 1998 and 2001, patients who made a change to their treatment-regimen were more likely to be admitted (odds ratio (OR) 2.44; 95%-CI 1.68 # 3.53, $p < 0.0001$ and OR 3.08; 95% CI 1.31 # 7.18, $p = 0.010$ respectively). In 2001, patients coinfecting with Hepatitis C had an increased risk of admission (OR 1.78; 95% CI 1.11 # 2.86, $p = 0.018$).

CONCLUSIONS:

There has been a considerable decline in both the proportion of patients admitted to hospital and the median duration of the stay.

Influence of Hepatitis C coinfection on HIV disease progression within the EuroSIDA Cohort

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OBJECTIVES:

We assessed HCV prevalence and survival, clinical progression, HIV suppression and CD4-cell recovery under HAART according to HCV status in the EuroSIDA-cohort.

RESULTS:

Results of HCV serology were available for 4,957 patients; 1,685 (34 %) patients were HCV-positive (75% IVDU) and 3,272 (66 %) HCV-negative. The highest HCV-prevalence was found in Southern and Eastern Europe with 44.9 % (623/1387) and 47.7% (412/864) versus 22.9 % (280/1221) in Central and 24.5 % (346/1410) in Northern Europe. There was a higher incidence of AIDS or death in HCV-positive versus HCV-negative patients (5.6 vs. 4.2 per 100 PYFU $p < 0.0001$). After adjustment for CD4, age, prior AIDS, HAART, recruitment date, hepatitis B status, gender and ethnic origin however, no significant difference in incidence

of AIDS or death was observed in HCV-positive vs HCV-negative patients (incidence rate ratio 0.92; 95% CI 0.79 - 1.07, $p = 0.27$). In further multivariate analyses, there was an increased risk of liver-related deaths in HCV-positive versus HCV-negative patients (IRR 3.18, 95% CI 1.23 - 6.18, $p = 0.014$) but not of AIDS ($p = 0.061$) or global-mortality ($p = 0.4$). No significant difference in the median time to viral load < 400 copies/ml or time to 50% increase in CD4 was found comparing HCV-negative and HIV/HCV-coinfected patients ($p = 0.77$ and $p = 0.13$).

CONCLUSIONS:

1/3 of HIV-infected patients in the EuroSIDA Cohort are coinfecting with HCV. HCV-coinfection doesn't influence virological and immunologic response to HAART. HCV-positive patients however, experience a higher mortality rate due to liver disease related causes.

Use of and response to antiretroviral therapy in regions of Europe. The EuroSIDA Study

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OBJECTIVES:

To analyse the use of HAART in regions of Europe, as well as response to HAART.

METHODS:

Analysis of patients under active follow-up in January 2002 within the EuroSIDA study; 907, 1580, 1583, 1538 and 100 in Eastern (EE), Southern (SE), Central (CE), Northern Europe (NE) and Argentina, respectively.

RESULTS:

The proportions of treatment naïve patients in January 2002 were 23 (EE), 1 (SE), 2 (CE), 4 (NE), and 4% (Argentina); $p < 0.001$, whereas 63, 80, 81, 81 and 88% were on HAART; $p < 0.001$. After adjustment for gender, age, ethnic origin, HIV transmission group, prior AIDS diagnosis, nadir CD4, peak viral load and date of recruitment in EuroSIDA, the regional differences in use of HAART diminished (table). Within EE the percentages on HAART varied from 2 to 91%

according to the HIV-clinic and country analysed. Newer drugs such as tenofovir and amprenavir were less commonly used in EE. As of 2002-2003, there were no indications of an inferior virological response to HAART in EE compared to the other regions. Further, within the available prospective follow-up the incidences of new AIDS events or death did not differ significantly across the regions.

CONCLUSIONS:

HAART was less commonly used in EE compared to other regions of Europe, primarily explained by regional differences in patient characteristics. Use of HAART varied substantially across the individual countries within EE. On a regional level, there were no differences in response to HAART at present, neither in laboratory response nor clinical outcome. Continuous follow-up is warranted.

Odds ratio of being on HAART in January 2002

	Univariable model (odds ratio and 95%-CI)	p-value	Multivariable model* (odds ratio and 95%-CI)	p-value
EE	1.00	-	1.00	-
SE	2.39 (1.99-2.87)	< 0.0001	1.26 (1.00-1.62)	0.055
CE	2.46 (2.09-2.96)	< 0.0001	1.15 (0.90-1.47)	0.26
NE	2.54 (2.13-3.03)	< 0.0001	1.12 (0.88-1.43)	0.37
Argentina	4.40 (2.37-8.16)	< 0.0001	3.20 (1.66-6.16)	0.0005

* model adjusted for gender, risk group, ethnic origin, prior AIDS diagnosis, nadir CD4, peak viral load, age and date of recruitment into EuroSIDA.

Regional differences in characteristics of HIV-patients from across Europe. The EuroSIDA study

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BACKGROUND OF STUDY:

Patient characteristics may well differ across Europe.

OBJECTIVES:

To compare characteristics of HIV-patients recruited to EuroSIDA in regions of Europe.

METHODS:

Analysis of 5708 HIV-patients under active follow-up in January 2002 within the EuroSIDA study, which includes 70 HIV-clinics across Europe and in Argentina.

RESULTS:

907 were under follow-up in Eastern Europe (EE), 1580 in Southern Europe (SE), 1583 in Central Europe (CE), 1538 in Northern Europe (NE), and 100 in Argentina (A). In EE, intravenous drug use (IVDU) was the most common HIV transmission category, and a higher proportion was coinfecting with hepatitis C virus (HCV). Moreover, patients in EE were younger and had

a slightly lower CD4 cell count compared with other regions of Europe. In addition, the time since first positive HIV-1 test was shorter in EE. A lower proportion in EE had a prior diagnosis of AIDS, and the pattern of AIDS events also differed across regions: a diagnosis of pulmonary and/or extrapulmonary tuberculosis were more common in EE, SE and A (6.3, 6.8, 5.0, 3.7 and 12.0% with a diagnosis of tuberculosis before January 2002 in EE, SE, CE, NE and A, respectively; $p=0.12$), whereas *Pneumocystis carinii* pneumonia was less common in EE (4.6, 7.3, 8.8, 12.2 and 10.0%; $p<0.001$).

CONCLUSIONS:

Substantial regional differences in demographic and clinical characteristics were observed within EuroSIDA. In EE, a higher proportion was infected by IVDU, were coinfecting with HCV, were younger, had a higher nadir CD4 cell count and a shorter history of known HIV-infection.

Patient characteristics in regions of EuroSIDA.

	EE	SE	CE	NE	A	p-value
Gender (% female)	27	27	24	16	42	$P < 0.001$
IVDU (%)	38	33	16	11	17	$P < 0.001$
HCV+ (%)	41	34	20	13	24	$P < 0.001$
Prior AIDS (%)	24	28	32	36	32	$P < 0.001$
Age (years; median, IQR)	34 (28-42)	40 (36-46)	42 (38-49)	43 (38-50)	36 (31-42)	$P < 0.001$
CD4 count (cells/mm ³ ; median, IQR)	390 (246-577)	437 (380-635)	432 (270-609)	410 (270-593)	332 (164-503)	$P < 0.001$
Nadir CD4 count (cells/mm ³ ; median, IQR)	175 (69-323)	136 (45-252)	128 (41-225)	110 (40-200)	113 (39-232)	$P < 0.001$
Months since HIV diagnosis (median, IQR)	37 (9-81)	40 (14-82)	53 (22-96)	53 (20-99)	40 (16-76)	$P < 0.001$

IQR: interquartile range.

Abstracts of publications by the EuroSIDA Study Group

Regional differences in use of antiretroviral agents and primary prophylaxis in 3122 European HIV-infected patients. EuroSIDA Study Group.

Lundgren JD, Phillips AN, Vella S, Katlama C, Ledergerber B, Johnson AM, Reiss P, Gatell J, Clumeck N, Dietrich M, Benfield TL, Nielsen JO, Pedersen C.

Little is known about how widely HIV-related drugs are used outside controlled clinical trials. We therefore assessed factors associated with use of antiretroviral (ARV) therapy and primary prophylactic regimens to prevent HIV-associated opportunistic infections. Baseline data from a prospective study from May to August 1994, on 3122 consecutive HIV infected patients with a CD4 count <500 cells/microl, followed in 37 centers from 16 European countries, were analyzed.

Two thousand and twenty patients (65%) were receiving at least 1 ARV drug at the time of the study. ARV therapy was more frequently used among patients from southern and central Europe as compared with patients from northern Europe, especially among patients with CD4 counts >200 cells/microl (73%, 57%, and 42%, respectively, $p < 0.0001$). Of patients on ARV therapy, 34% received open-label combination therapy. This proportion was higher in central Europe compared with other regions (27%, 50%,

and 31% for southern, central, and northern Europe, respectively, $p < 0.0001$). Primary prophylaxis against *Pneumocystis carinii* pneumonia (PCP) was used by 85% of patients with a CD4 count <200 cells/microl, without marked regional differences. In patients without esophageal candidiasis or other invasive fungal infections, antifungal drugs were far less frequently used in patients from southern and central Europe compared with patients from northern Europe (10%, 10%, and 25%, respectively, $p < 0.0001$).

Only 5% of patients with a CD4 count <100 cells/microl received rifabutine as primary prophylaxis against nontuberculous mycobacterioses. ARV and antifungal therapies are used differently in different parts of Europe, whereas primary PCP prophylaxis is uniformly administered to most at-risk patients. U.S. recommendations on the use of antimycobacterial prophylaxis have not been implemented in Europe.

Odds ratio (95% confidence interval) for use of primary prophylaxis against *Pneumocystis carinii* pneumonia and esophageal/pulmonary/systemic fungal infections in central and southern Europe compared with northern Europe.

	PCP prophylaxis (n=1433)		Antifungal prophylaxis (n=2840)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
North	1 (-)	1 (-)	1 (-)	1 (-)
Central	0.75 (0.54, 1.05)	0.98 (0.67, 1.43)	0.32 (0.24, 0.43)	0.34 (0.25, 0.47)
South	1.45 (1.04, 2.03)	1.93 (1.28, 2.92)	0.32 (0.25, 0.41)	0.31 (0.23, 0.42)

* Adjusted for gender, transmission category, CD4 count, age prior diagnosis of AIDS. Patients included in the two models are those presented in the corresponding sections in Table 2. Except that for PCP prophylaxis.

Patients with a CD4 count > 200 cell/μl (i.e. not at risk patients) are excluded.

PCP = *Pneumocystis carinii* pneumonia

Survival in 2367 zidovudine-treated patients according to use of other nucleoside analogue drugs. The EuroSIDA Study Group.

Phillips AN, Katlama C, Barton S, Vella S, Blaxhult A, Clotet B, Goebel FD, Hirschel B, Pedersen C, Lundgren JD.

To evaluate survival according to use of different nucleoside drugs in a routine clinical setting, we studied a large group of zidovudine-treated patients seen in clinics across Europe. A total of 3128 subjects was recruited to the observational, prospective EuroSIDA study in May 1994. These were consecutive patients (up to a predefined limit) seen at outpatient clinics in 37 centers from 16 European countries and followed at 6-month intervals by use of standardized forms completed by clinicians at the respective centers. This report concerns 2367 subjects who began antiretroviral therapy with a regime that included zidovudine either before study entry or during the course of follow-up. Cox proportional hazards models were fitted, with use of other antiretroviral drugs, CD4 count, and date of development of AIDS fitted as time-dependent covariates. Survival times from start of therapy were left truncated at study entry to avoid survival bias. In addition to zidovudine, antiretroviral drugs used included didanosine (ddl) (n = 1119;

median 1.6 years after starting zidovudine), dideoxycytidine (ddC) (n = 592; median 1.9 years after starting zidovudine), stavudine (d4T) (n = 241; median 2.9 years after starting zidovudine) and lamivudine (3TC) (n = 33 ; median 2.7 years after starting zidovudine). Of the 2367 patients, 613 died during follow-up. Overall, risk of death was reduced in those zidovudine-treated patients who began at least one other nucleoside analogue drug with or after taking zidovudine (relative hazard [RH], 0.61; 95% confidence interval [CI], 0.51-0.72, adjusting for CD4 count, development of AIDS, and age). Fitting each drug separately, there was a larger association with reduced mortality for starting 3TC (RH, 0.41; 95% CI, 0.28-0.62) than for starting ddl (RH, 0.79; 95% CI, 0.67-0.93), ddC (RH, 0.74; 95% CI, 0.59-0.92) or d4T (RH, 0.67; 95% CI, 0.49-0.91). These results suggest that the beneficial effect of nucleoside combination therapy identified in controlled trials can be seen in routine clinical practice.

Number of deaths, person-years of follow-up, death rate, rate ratio, and unadjusted and adjusted relative hazard, according to whether each drug has ever been taken.

	ddl		ddC		3TC		d4T		Any additional nucleoside	
	yes	no	yes	no	yes	no	yes	no	yes	no
Person-years of follow-up	1157	1754	507	2404	229	2682	236	2675	1713	1198
Number of deaths	288	325	100	513	27	586	44	569	372	241
Death rate per year (95% CI)	0.25 (0.22-0.28)	0.19 (0.17-0.21)	0.20 (0.16-0.24)	0.21 (0.19-0.23)	0.12 (0.07-0.16)	0.22 (0.20-0.24)	0.19 (0.13-0.24)	0.21 (0.20-0.23)	0.22 (0.20-0.24)	0.20 (0.18-0.23)
Death rate ratio (yes vs. no)	1.34		0.92		0.54		0.88		1.08	
Relative hazard of death, unadjusted (95% CI)	1.04 (0.89-1.23)		0.78 (0.63-0.97)		0.41 (0.28-0.61)		0.68 (0.50-0.94)		0.76 (0.65-0.90)	
Relative hazard of death, adjusted * (95% CI)	0.79 (0.67-0.93)		0.74 (0.59-0.92)		0.41 (0.28-0.62)		0.67 (0.49-0.91)		0.61 (0.51-0.72)	

* Adjusted for aged, current CD4 count and current AIDS status (i.e., AIDS yes/no), and whether started other drugs. CI, confidence interval; 3TC, lamivudine; d4T, stavudine; ddC, dideoxycytidine; ddl, didanosine.

Changes in use of antiretroviral therapy in regions of Europe over time.
EuroSIDA Study Group.

Kirk O, Mocroft A, Katzenstein TL, Lazzarin A, Antunes F, Francioli P, Brettle RP, Parkin JM, Gonzales-Lahoz J, Lundgren JD.

OBJECTIVES:

To analyse use of antiretroviral therapy within Europe between 1994 and 1997.

DESIGN AND METHODS:

From September 1994, the EuroSIDA study (cohorts I-III) has prospectively followed unselected HIV-infected patients from 50 clinical centres in 17 European countries (total, 7230). Patients under follow-up at half-year intervals from September 1994 (n=2871) to September 1997 (n=3682) were classified according to number of drugs currently used (none, one, two, three, four or more). Use of antiretroviral therapy was stratified by CD4 cell count (< 200 versus ≥ 200 × 10⁶/l) and by region of Europe (south, central, or north). Frequency data were compared by chi² test and logistic regression modelling.

RESULTS:

The proportion of patients on antiretroviral monotherapy diminished over time (1994, 42%; 1997, 3%), as did the proportion of patients without therapy (from 37 to 9%). Over time, the proportion of patients on triple (from 2 to 55%)

and quadruple (from 0 to 9%) therapy increased, whereas use of dual therapy peaked in 1996 and subsequently fell. In the three regions of Europe, changes in use of antiretroviral therapy differed substantially. However, as of September 1997, only minor differences persisted. The proportion of patients on dual, triple, and quadruple therapy were as follow: south, 33, 52 and 5%, respectively; central, 23, 55 and 14%, respectively; north, 16, 59 and 10%, respectively. In September 1997, odds for use of three or more drugs including at least one protease inhibitor did not differ significantly between regions.

CONCLUSIONS:

Use of antiretroviral therapy in Europe has changed dramatically towards combination treatment in the last few years. Regional differences in use of antiretroviral therapy have decreased, and by September 1997 only minor differences remained. Antiretroviral therapy with three or more drugs and use of protease inhibitors has become more common in all regions of Europe.

Odds ratio (95% confidence intervals) for patients on triple ARVT including a protease inhibitor (PI) (≥ 3 drugs including ≥ 1 PI Vs. < 3 drugs, or = 3 but without any PI) in Central and North Europe compared South Europe.

Adjustment was made for gender, age, transmission category, CD4 cell count, AIDS (yes/no), and duration of infection. Patients included in this analysis are those presented in table 1 and 2. Data from before 03-96 has been excluded, as very few patients received triple therapy in this period.

Time	Central Europe		North Europe	
03-96	2.38	(1.69-3.36)	2.10	(0.99-4.47)
09-96	2.91	(2.49-3.40)	4.11	(2.98-5.66)
03-97	1.30	(1.18-1.42)	1.40	(1.17-1.69)
09-97	0.95	(0.87-1.21)	1.03	(0.87-1.21)

Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group.

Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, d'Arminio Monforte A, Yust I, Bruun JN, Phillips AN, Lundgren JD.

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:

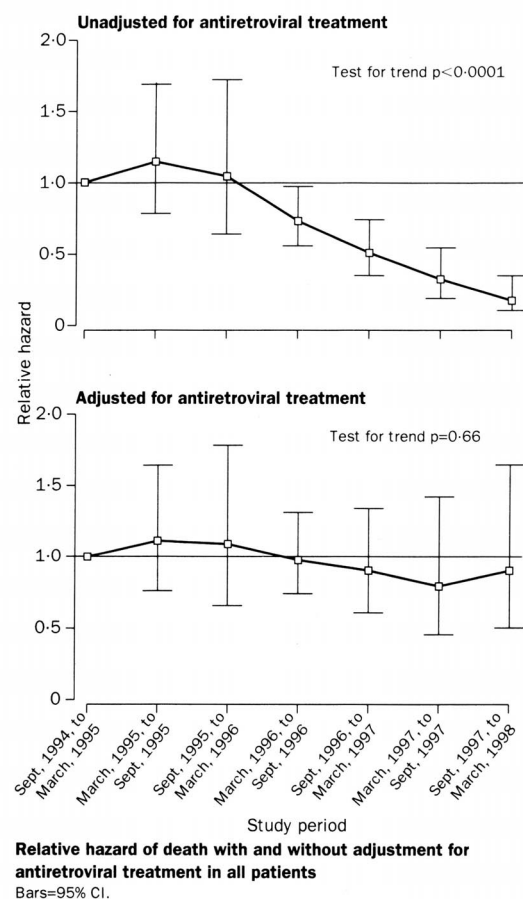
We analysed data from EuroSIDA, which is a prospective, observational, European, multi-centre cohort of 4270 HIV-1-infected patients. We compared death rates in each 6 month period from September, 1994, to March, 1998.

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 beginning 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.



Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study.

Miller V, Mocroft A, Reiss P, Katlama C, Papadopoulos AI, Katzenstein T, van Lunzen J, Antunes F, Phillips AN, Lundgren JD.

BACKGROUND:

The effect of previous CD4 cell count nadir on clinical progression in patients with increases in CD4 cell counts has not been investigated.

OBJECTIVE:

To assess risk for progression of HIV disease in patients with CD4 counts of at least 200 cells/mm³ (stratified by the lowest previous CD4 count) and compare the rate of progression in patients with CD4 counts less than 50 cells/mm³ with that in patients whose CD4 counts rebounded from less than 50 cells/mm³ to at least 200 cells/mm³.

DESIGN:

Prospective, observational multicenter study.

SETTING:

52 HIV outpatient clinics in Europe.

PATIENTS:

Two groups were identified: those with CD4 counts of at least 200 cells/mm³ (group A) and those with CD4 counts less than 50 cells/mm³ (group B). Group A was stratified according to the lowest previous CD4 count: at least 150 cells/mm³ (stratum 1), 100 to 149 cells/mm³ (stratum 2), 50 to 99 cells/mm³ (stratum 3), and 1 to 50 cells/mm³ (stratum 4).

MEASUREMENTS:

Patients were followed until a progression event occurred (first AIDS-defining event, new AIDS-defining event, or death) or until the CD4 count decreased to less than 200 cells/mm³ (group A) or increased to more than 50 cells/mm³ (group B). Incidence rates were based on a patient-years analysis and reported as events per 100 patient-years of follow-up; the relative hazards for progression were based on Cox proportional hazards models.

RESULTS:

The overall rate of disease progression in group A was 3.9 per 100 patient-years (95% CI, 3.5 to 4.3 per 100 patient-years), whereas in group B it was much higher (72.9 per 100 patient-years [CI, 69.0 to 76.8 per 100 patient-years]). In group A, the rate increased in patients with previous low CD4 cell count nadirs, resulting in a significant increase in the relative hazard for progression. The relative hazards for strata 2, 3, and 4 were 2.29 (CI, 1.30 to 4.03), 3.65 (CI, 1.94 to 6.85), and 2.94 (CI, 1.44 to 6.00), respectively.

CONCLUSIONS:

Increases in CD4 counts from very low levels to at least 200 cells/mm³ are associated with a much reduced rate of disease progression. However, a previously low CD4 cell count nadir remains associated with a moderately higher risk for disease progression among patients with CD4 counts of at least 200 cells/mm³.

Relative Hazard of Disease Progression for Patients in Group A *

Variable	Univariate Analysis		Multivariate Analysis	
	Relative Hazard (95% CI)	P Value	Relative Hazard (95% CI)	P Value
CD4 cell nadir †				
≥ 150 cells/mm ³	1.00	—	1.00	—
100–149 cells/mm ³	1.61 (0.95–2.72)	0.078	2.29 (1.30–4.03)	0.0042
50–99 cells/mm ³	2.16 (1.27–3.66)	0.0045	3.65 (1.94–6.85)	< 0.001
< 50 cells/mm ³	1.56 (0.86–2.80)	0.14	2.94 (1.44–6.00)	0.0031
Age ‡	1.12 (1.01–1.25)	0.040	1.19 (1.06–1.34)	0.0033
Baseline CD4 cell count (per 50% lower)	1.25 (1.01–1.55)	0.042	1.24 (0.99–1.57)	0.065
AIDS	1.61 (1.19–2.17)	0.0019	1.48 (1.05–2.09)	0.024
Antiretroviral drug therapy				
No antiretroviral drugs	1.00	—	1.00	—
1 antiretroviral drug	1.08 (0.84–1.39)	> 0.2	0.89 (0.67–1.17)	> 0.2
2 antiretroviral drugs	0.58 (0.41–0.83)	0.0026	0.54 (0.36–0.80)	0.0024
≥ 3 antiretroviral drugs	0.57 (0.37–0.88)	0.012	0.20 (0.07–0.58)	0.0032
Highly active antiretroviral therapy ◇				
No	1.00	—	1.00	—
Yes	0.72 (0.45–1.14)	0.16	1.70 (0.57–5.01)	> 0.2

* Estimates are the relative hazard of disease progression. For CD4 nadir, CD4 ≥150 is the reference group. The relative hazard for age at first CD4 ≥200 is per 10 year age difference. The model has also been adjusted for the logarithm (base 2) of the first CD4 lymphocyte count at or above 200/mm³ and whether AIDS had been diagnosed by this date or not. At the date of first CD4 ≥200/mm³, the number of concurrent antiretrovirals being used was calculated and adjusted for, with the reference category being zero. In addition, whether the patient was on HAART at the date of first CD4 ≥200 (HAART was defined as a minimum of a PI or NN in combination with 2 nucleosides). The model has been stratified for centre and adjusted for calendar time, use of PCP prophylaxis and is left censored. Demographic variables, such as gender, ethnic origin and exposure group were of no significance in the univariate analysis and have not been included in the final multivariate model.

† Reference group: ≥ 150 cells/mm³

‡ Per 10-year age difference

◇ Defined as a minimum of one protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus two nucleoside reverse transcriptase inhibitors.

Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group.

Mocroft A, Kirk O, Barton SE, Dietrich M, Proenca R, Colebunders R, Pradier C, dArminio Monforte A, Ledergerber B, Lundgren JD.

OBJECTIVES:

To describe changes in haemoglobin over time and to determine the joint prognostic value of the current haemoglobin, CD4 lymphocyte count and viral load among patients from across Europe.

PATIENTS:

The analysis included 6725 patients from EuroSIDA, an observational, prospective cohort of patients with HIV from across Europe.

METHODS:

Normal haemoglobin was defined as haemoglobin greater than 14 g/dl for men and 12 g/dl for women; mild anaemia was 8-14 g/dl for men and 8-12 g/dl for women; severe anaemia was defined as less than 8 g/dl for both males and females. Linear regression techniques were used to estimate the annual change in haemoglobin; standard survival techniques were used to describe disease progression and risk of death.

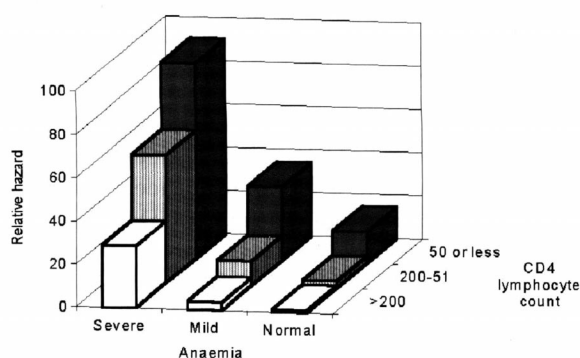
RESULTS:

At recruitment to the study, 40.4% had normal levels of haemoglobin, 58.2% had mild anaemia and 1.4% had severe anaemia. At 12 months after recruitment, the proportion of patients estimated to have died was 3.1% [95% confidence interval (CI) 2.3-3.9] for patients without anaemia, 15.9% for patients with mild anaemia (95% CI 14.5-17.2) and 40.8% for patients with severe anaemia (95% CI 27.9-53.6; $P < 0.0001$). In a multivariate, time-updated Cox proportional hazards model, adjusted for

demographic factors, AIDS status and each antiretroviral treatment as time-dependent covariates, a 1 g/dl decrease in the latest haemoglobin level increased the hazard of death by 57% [relative hazard (RH) 1.57; 95% CI 1.41-1.75; $P < 0.0001$], a 50% drop in the most recent CD4 lymphocyte count increased the hazard by 51% (RH 1.51; 95% CI 1.35-1.70; $P < 0.0001$) and a log increase in the latest viral load increased the hazard by 37% (RH 1.37; 95% CI 1.15-1.63; $P = 0.0005$).

CONCLUSIONS:

Severe anaemia occurred infrequently among these patients but was associated with a much faster rate of disease progression. Among patients with similar CD4 lymphocyte counts and viral load, the latest value of haemoglobin was a strong independent prognostic marker for death.



Relative hazard of death. The multivariate Cox model from Table 2 was repeated using discrete clinical cut-offs for CD4 cell count and haemoglobin and each category was modelled as time dependent. (See Table 2 for definition of anaemia)

Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. EuroSIDA Study Group.

Weverling GJ, Mocroft A, Ledergerber B, Kirk O, Gonzales-Lahoz J, d'Arminio Monforte A, Proenca R, Phillips AN, Lundgren JD, Reiss P.

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/microL and 270 cells/microL, the median plasma HIV-1 RNA load 500 copies/mL, and the median lowest recorded CD4-lymphocyte counts 123 cells/microL and 60 cells/microL. 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/microL, is sufficiently low to warrant discontinuation of primary PCP prophylaxis. Longer follow-up is needed to confirm a similarly low risk for stopping secondary PCP prophylaxis.

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

	Any PCP				Secondary PCP			Any PCP, bacterial pneumonia or toxopl.			Any AIDS defining event			Deaths		
	Cases	PYFUP	ID	95% CI	PYFUP	ID	95% CI	Cases	ID	95% CI	Cases	ID	95% CI	Cases	ID	95% CI
All	0	247	0	(0 – 1.5)	50	0	(0 – 7.4)	1	0.4	0 – 2.3	5	2.0	0.7 – 4.7	10	4.1	(1.9 – 7.5)
Latest CD4																
<= 100	0	21.7	0	(0 – 17.0)	8.2	0	(0 – 45.0)	0	0	0-1.7	3	13.8	0-1.7	9	41.5	(19.0 – 78.8)
101 – 200	0	37.4	0	(0 – 9.9)	6.1	0	(0 – 60.5)	0	0	0-9.9	0	0	0-9.9	0	0	(0 – 9.9)
201 – 300	0	70.4	0	(0 – 5.2)	8.7	0	(0 – 42.4)	0	0	0-5.2	0	0	0-5.2	1	1.4	(0 – 7.9)
> 300	0	115.1	0	(0 – 3.2)	17.1	0	(0 – 21.6)	1	0.9	0.2-4.8	2	1.7	0.2-4.8	0	0	(0 – 3.2)
Latest VL																
< 500	0	114.9	0	(0 – 3.2)	18.1	0	(0 – 20.4)	0	0	0-3.2	3	2.6	0-3.2	1	0.9	(0 – 4.8)
500 – 9,999	0	60.4	0	(0 – 6.1)	11.3	0	(0 – 32.6)	1	1.7	0.4-9.2	1	1.7	0.4-9.2	1	1.7	(0 – 9.2)
10,000 – 49,999	0	26.0	0	(0 – 14.2)	2.8	0	(0 – 131.8)	0	0	0-14.2	1	3.8	0-14.2	1	3.8	(0.1 – 21.4)
>= 50,000	0	28.9	0	(0 – 12.8)	4.9	0	(0 – 75.3)	0	0	0-12.8	0	0	0-12.8	4	13.8	(0.1 – 35.4)
CD4 Nadir																
<= 50	0	59.7	0	(0 – 6.2)	18.8	0	(0 – 19.6)	0	0	0-6.2	3	5.0	0-6.2	7	11.7	(4.7 – 24.2)
51-100	0	49.6	0	(0 – 7.4)	9.0	0	(0 – 41.0)	0	0	0-7.4	1	2.0	0-7.4	2	9.0	(0.5 – 14.6)
> 100	0	131.5	0	(0 – 2.8)	12.2	0	(0 – 30.2)	1	0.8	0-4.2	1	0.8	0-4.2	1	0.8	(0 – 4.2)
Time on HAART																
< 10 mths	0	179.2	0	(0 – 2.1)	33.3	0	(0 – 11.1)							9	5.0	(2.3 – 9.5)
>=10 mths	0	67.3	0	(0 – 5.5)	6.7	0	(0 – 55.1)							1	1.5	(0 – 8.3)

cases number of cases; pyfup person years of follow-up; ID 95%CI incidence density and 95%confidence interval. Any PCP, bacterial pneumonia or toxoplasmosis cerebri: 1 case of bacterial pneumonia. Any AIDS defining event: 1 case each of bacterial pneumonia, oesophageal candidiasis, cryptosporidiosis, wasting and PML.

Regional survival differences across Europe in HIV-positive people: the EuroSIDA study.

Chiesi A, Mocroft A, Dally LG, Miller V, Katlama C, Ledergerber B, Pedersen C, Phillips AN, Arcieri R, Lundgren JD.

OBJECTIVES:

To analyse the survival differences between macro-regions of Europe (northern, central and southern Europe) between 1994 and early 1999, and their possible association with antiretroviral treatment differences. DESIGN: From September 1994 the EuroSIDA study has prospectively followed non-selected HIV-infected people from 50 clinical sites in 18 European countries (n = 7331).

METHODS:

Cox proportional hazards models were used to compare death rates between regions and to investigate the relationship between treatment usage and regional mortality rates. Kaplan-Meier curves were used to compare survival from the first CD4 lymphocyte count of < 200 x 10(6)/l or < 50 x 10(6)/l.

RESULTS:

At the time of analysis, the median follow-up was 21 months and there was a total of 1544 deaths. In people with a CD4+ cell count that fell below 200 or 50 x 10(6)/l those from central Europe had a better prognosis compared with those from the two other regions (P < 0.05). Patients from central Europe were more frequently exposed to reverse transcriptase inhibitors and protease inhibitors compared with patients from other regions (P < 0.001).

There was a significant difference in risk of death between regions after adjustment for baseline differences in demography, presence of AIDS and level of immunodeficiency (risk of death in central Europe was 37% lower than that in southern Europe (P < 0.0001) and 33% lower than in northern Europe (P < 0.0001)). After adjustment for use of individual antiretroviral agents, intensity of treatment regimen, CD4 lymphocyte count, weight, haemoglobin and development of AIDS as time-dependent covariates, the differences became much smaller (risk in central Europe 13% lower than that in southern Europe (P = 0.071) and 15% lower than in northern Europe (P = 0.054)).

CONCLUSION:

Antiretroviral therapy has been used more aggressively in Europe in recent years, resulting in improved prognosis. In this study we observed that the HIV mortality rate in central Europe was significantly lower than those in northern and southern Europe in the period 1994 to early 1999. This finding appears to be due to the effect on survival of different treatment policies and drug availability in the three regions of Europe during this time period, with central European countries, on average, having introduced more aggressive treatment strategies earlier.

Cox proportional hazards model of death

Variables included*	Regions	RH	95% CI	P
AIDS status and CD4 fixed	Central/south	0.63	0.53-0.74	0.0001
	Central/north	0.67	0.57-0.78	0.0001
	South/north	1.07	0.93-1.23	0.37
AIDS status, CD4, and treatments time updated	Central/south	0.87	0.73-1.02	0.071
	Central/north	0.85	0.73-1.01	0.054
	South/north	0.92	0.80-1.05	0.22
AIDS status and CD4 time updated	Central/south	0.65	0.56-0.70	0.0001
	Central/north	0.63	0.54-0.73	0.0001
	South/north	0.96	0.84-1.10	0.57

*All models presented are multivariate and are adjusted for age, exposure category, and sex. In first model, AIDS status, haemoglobin, weight and CD4 lymphocyte count at recruitment to EuroSIDA were adjusted for as fixed factors at recruitment. In the second model, AIDS status, CD4 lymphocyte count, weight, haemoglobin, *Pneumocystis carinii* pneumonia prophylaxis, and treatment with each of zidovudine, didanosine, zalcitabine, lamivudine, stavudine, indinavir, zalcitabine, and saquinavir were adjusted for as time-dependent covariates, as was intensity of treatment regimen (0, 1, 2 or > 3 antiretroviral agents used consecutively). The third model is identical to the second, except that no adjustment has been made for any antiretroviral treatments or treatment regimens. RH, relative hazard; CI, confidence interval.

Use of observational databases to evaluate the effectiveness of antiretroviral therapy for HIV infection: comparison of cohort studies with randomized trials. EuroSIDA, the French Hospital Database on HIV and the Swiss HIV Cohort Study Groups.

Phillips AN, Grabar S, Tassie JM, Costagliola D, Lundgren JD, Egger M.

OBJECTIVES:

It is important to assess the extent of bias when comparing the clinical efficacy of antiretroviral regimens in observational databases because, with the current lack of planned large trials, such analyses may represent the only means of assessing the risk of serious clinical events associated with new regimens. We aimed to compare the results from observational databases with those from randomized trials.

METHODS:

Three treatment comparisons from randomized trials [Delta, AIDS Clinical Trials Group (ACTG) 175, Community Programs for Clinical Research on AIDS (CPCRA) 007 and ACTC 320] were mimicked in cohorts: (i) zidovudine monotherapy versus combination regimens of two nucleoside analogues; (ii) zidovudine combined with either didanosine or zalcitabine; and (iii) a dual combination versus a triple regimen including a protease inhibitor. Data for over 10 000 patients from the French Hospital Database on HIV, the EuroSIDA study and the Swiss HIV cohort study were analysed for each of the comparisons. Progression to AIDS disease or death was analysed in Cox models,

adjusting for baseline differences, and results compared with randomized trials.

RESULTS:

For comparison (i) the adjusted relative risk estimates from cohorts were between 0.61 and 0.84, favouring combinations over monotherapy, compared with 0.57 to 0.63 for trials. For comparison (ii) relative risk estimates from cohorts ranged from 0.81 to 1.01 compared with 0.77 to 0.92 for trials. For comparison (iii), two of the cohorts showed similar results to the ACTG 320 trial but one indicated a higher risk of progression on triple therapy [relative risk 1.20, 95% confidence interval (CI) 1.01-1.441, in direct contrast to the trial result (relative risk 0.50, 95% CI 0.33-0.76).

CONCLUSION:

Serious biases can be present when comparing outcomes from the use of antiretroviral regimens in observational studies. However, such bias is not inevitable and careful interpretation of the results from several observational studies considered together is likely to be informative, guiding the design of new trials.

Comparison of relative risks for AIDS or death in cohort studies and randomized trials. In the upper panel, top lines for trials, relate to zidovudine and zalcitabine, lower lines to zidovudine and didanosine. These groups were combined in the EuroSIDA and Swiss cohorts. The French data relate to zidovudine and didanosine.

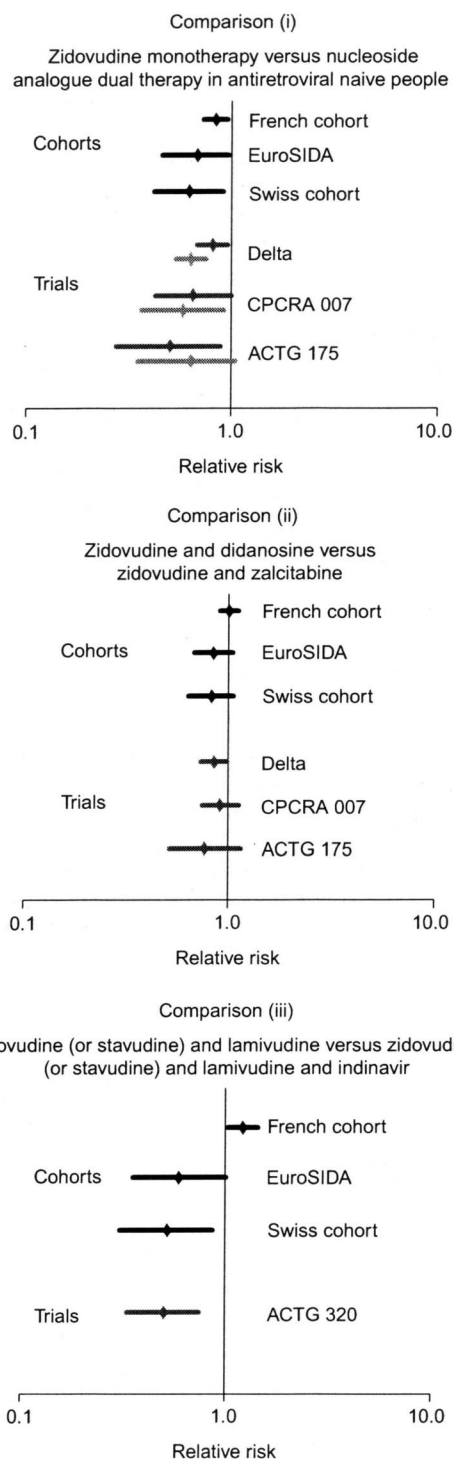


Fig. Comparison of relative risks for AIDS or death in cohort studies and randomized trials. In the upper panel, top lines for trials, relate to zidovudine and zalcitabine, lower lines to zidovudine and didanosine. These groups were combined in the EuroSIDA and Swiss cohorts. The French data relate to zidovudine and didanosine.

Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study.

Paredes R, Mocroft A, Kirk O, Lazzarin A, Barton SE, van Lunzen J, Katzenstein TL, Antunes F, Lundgren JD, Clotet B.

BACKGROUND:

Predictors of virological response to highly active antiretroviral therapy (HAART) have never been systematically evaluated in a large continental multicenter cohort of unselected human immunodeficiency virus (HIV)-infected people.

OBJECTIVE:

To determine the factors related to achieving and maintaining undetectable plasma HIV-1 RNA levels among HIV-1-infected patients first starting protease inhibitor- or nonnucleoside retrotranscriptase inhibitor-containing HAART in Europe.

DESIGN AND SETTING:

Prospective multicenter cohort study. Fifty-two clinical centers in 17 European countries included in the EuroSIDA Study Group, from August 1996 to April 1999.

PATIENTS:

A total of 1469 HIV-positive patients first starting HAART recruited from an unselected cohort of more than 7300 HIV-positive patients.

MAIN OUTCOME MEASURE:

Detection of factors related to virological success after first starting HAART (baseline) and ensuing failure by standard survival techniques, including Kaplan-Meier techniques and Cox proportional hazards models. All analyses were intention to treat.

RESULTS:

Most patients (80%) achieved plasma HIV-1 RNA levels of less than 500 copies/mL during follow-up (60.4% at 6 months from the onset of HAART). Patients with higher baseline HIV-1 RNA levels (relative hazard [RH], 0.76 per log higher; 95% confidence interval [CI], 0.69-0.84;

$P < 0.001$) and those taking saquinavir mesylate hard gel as a single protease inhibitor (RH, 0.62; 95% CI, 0.47-0.82; $P < 0.001$) were less likely to reach undetectable HIV-1 RNA levels. Conversely, higher CD4+ lymphocyte counts (RH per 50% higher, 1.09; 95% CI, 1.02-1.16; $P = .008$) and the initiation of 3 or more new antiretroviral drugs (RH, 1.29; 95% CI, 1.03-1.61; $P = .02$) were independent predictors of higher success. Once success was achieved, HIV-1 RNA levels rebounded in more than one third of all patients during follow-up (24% at 6 months). Antiretroviral-naïve patients (RH, 0.50; 95% CI, 0.29-0.87; $P = .01$), older patients (RH, 0.86 per year older; 95% CI, 0.75-0.99; $P = .04$), and those starting a protease inhibitor other than saquinavir hard gel (RH, 0.66; 95% CI, 0.44-0.98; $P = .04$) were at decreased hazard for virological failure. Higher baseline HIV-1 RNA level (RH, 1.18 per log higher; 95% CI, 0.99-1.40; $P = .06$) and a longer time to achieve virological success (RH per 12 months, 1.53; 95% CI, 0.99-2.38; $P = .06$) were marginally significant predictors of a decreased hazard of ensuing virological failure.

CONCLUSIONS:

HAART is associated with a favorable virological response if started when the baseline HIV-1 RNA level is low, if at least 2 new nucleoside retrotranscriptase inhibitors are added, and if standard doses of saquinavir hard gel capsule are avoided as a single protease inhibitor. Older patients are more likely to achieve virological success. Thereafter, the higher durability of virological response is predicted by an antiretroviral-naïve status and by the use of specific regimens. Lower baseline HIV-1 RNA levels and rapid maximal viral suppression seem to be other important factors in the durability of virological response.

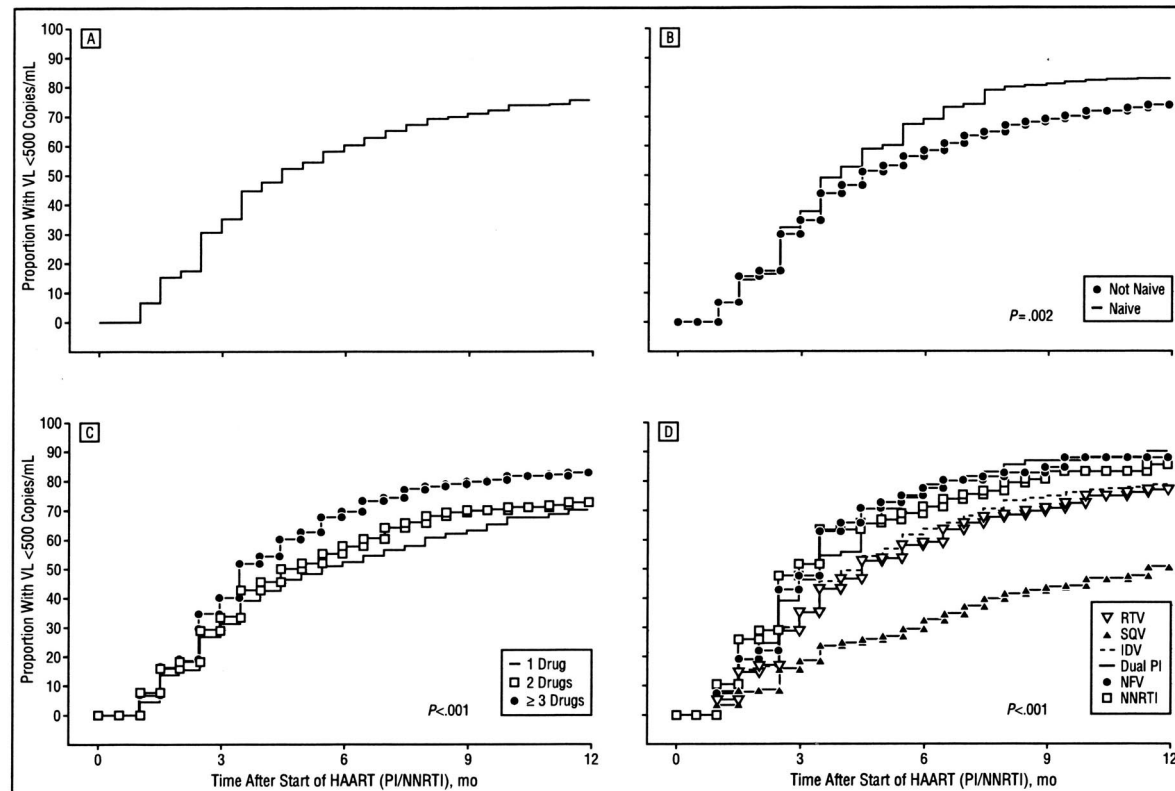
Kaplan-Meier plots for the time to plasma human immunodeficiency virus 1 RNA levels below 500 copies/mL after first starting highly active antiretroviral therapy (HAART) for all patients

(A); those with nucleoside retrotranscriptase inhibitor–naïve vs –experienced status

(B); patients starting 1, 2, and 3 or more drugs

(C); and patients including particular protease inhibitors (PIs) (RTV indicates ritonavir; SQV, saquinavir; IDV, indinavir; and NFV, nelfinavir) or nonnucleoside retrotranscriptase inhibitors (NNRTIs)

(D). VL indicates viral load.



Does European or non-European origin influence health care and prognosis for HIV patients in Europe? The EuroSIDA Study Group.

Blaxhult A, Mocroft A, Phillips A, van Lunzen J, Bentwich Z, Stergiou G, Colebunders R, Benfield TL, Mulcahy F, Lundgren JD.

BACKGROUND:

Previous studies, especially in North America, have shown that socio-economic factors may influence the prognosis for patients with HIV. This study was performed in order to determine if European or non-European origin influence provision of health-care and survival among HIV patients in Europe.

METHODS:

Fifty HIV clinics in 17 European countries are involved in a European prospective, observational multicentre study. In total, 7230 consecutive patients with HIV attending a routine clinic visit were included in the study. Data on demographics, treatment and laboratory results were collected at time of recruitment into the study and thereafter every 6 months.

RESULTS:

The median CD4+ lymphocyte count at AIDS diagnosis was 60/mm³, and was similar for all

ethnic groups (P = 0.87, Kruskal-Wallis test). The median terminal CD4+ lymphocyte count was 17/mm³ and, again, there was no significant difference between continents of origin (P = 0.35, Kruskal-Wallis test). Antiretroviral drugs were initiated at similar median CD4+ lymphocyte counts and there was no statistically significant difference in survival after a diagnosis of AIDS.

CONCLUSIONS:

AIDS was diagnosed at the same level of immunodeficiency independent of European or non-European origin and antiretroviral drugs were provided at similar levels of immunodeficiency. No differences in survival depending on continent of origin was found. In spite of these encouraging findings concerns remain that belonging to an ethnic minority can be an obstacle in getting into contact with treatment facilities and thus benefiting from developments in the management of HIV.

Relative risk of death for HIV patients in groups with different origins using the Cox proportional hazards models

	Relative hazard	95% confidence interval	P-value
Univariate			
European	1.00	-	-
African	0.51	0.37-0.68	0.0001
Asian	0.66	0.35-1.22	0.19
Other	0.91	0.68-1.22	0.55
Multivariate			
European	1.00	-	-
African	0.80	0.56-1.15	0.22
Asian	1.18	0.59-2.36	0.65
Other	1.24	0.90-1.71	0.18
In the multivariate analysis adjustment is made for age, gender, risk group, region of Europe, CD4 count, and cohort.			

A comparison of exposure groups in the EuroSIDA study: starting highly active antiretroviral therapy (HAART), response to HAART, and survival.

Mocroft A, Madge S, Johnson AM, Lazzarin A, Clumeck N, Goebel FD, Viard JP, Gatell J, Blaxhult A, Lundgren JD.

BACKGROUND:

Concerns have been raised that intravenous drug users may be less likely to start highly active antiretroviral therapy (HAART) and that adherence to therapy may be poor among this group of patients. Given the decreased mortality and incidence of AIDS-defining illnesses among patients with HIV who start HAART, this may lead to a poorer prognosis among intravenous drug users.

PURPOSE:

To compare homosexual men, intravenous drug users, and heterosexuals in EuroSIDA, a prospective European cohort of 7331 patients with HIV in terms of starting a HAART treatment regimen, immunologic and virologic response to therapy, and survival.

METHODS:

6645 patients were included in this analysis. Logistic regression and Cox proportional hazards models were used to investigate the factors associated with use of HAART regimens and survival following recruitment to the EuroSIDA study.

RESULTS:

In a multivariate logistic regression model, intravenous drug users were significantly less likely to be receiving HAART at recruitment to EuroSIDA (odds ratio [OR], 0.48; 95% confidence

interval [CI], 0.37-0.62; $p < .0001$) when compared with homosexual men. Similarly, during follow-up, intravenous drug users were at a 27% reduced risk of starting HAART, after adjustment for other factors related to starting HAART (relative hazard [RH], 0.73; 95% CI, 0.64-0.82; $p < .0001$). There were no differences between heterosexual and homosexual patients, and similar results were found within regions of Europe (South, Central and Northern). Among those patients who started HAART, there were no significant differences between exposure groups in CD4 lymphocyte count response to HAART or virologic response to HAART. After adjustment for factors related to survival, intravenous drug users were at a small, but nonsignificant increased risk of death compared with homosexuals (RH 1.16; 95% CI, 0.99-1.38; $p = .074$).

CONCLUSIONS:

Intravenous drug users were significantly less likely to start HAART, but among those who did, response to therapy was similar to that of other exposure groups. There were no differences in risk of death. If intravenous drug users continue to use HAART less commonly than other exposure groups, it may result in a poorer prognosis, a different spectrum of AIDS-defining illnesses, and differential long-term clinical needs.

Relative hazard (RH) of death

	Homosexual	IDU			Heterosexual		
	RH	RH	95% CI	p value	RH	95% CI	p value
Univariate	1.00	1.07	0.95-1.20	.27	0.62	0.54-0.72	<.0001
Adjusted for factors known at recruitment ^a	1.00	1.16	0.99-1.38	.074	0.88	0.72-1.00	.054
Adjusted for factors measured during follow-up ^b	1.00	0.97	0.81-1.15	.69	0.85	0.69-1.05	.10
Adjusted additionally for viral load ^c	1.00	1.11	0.74-1.65	.62	0.85	0.55-1.30	.45

^a Model was stratified for center and cohort, and adjusted for calendar year, gender, race, AIDS diagnosis, age at recruitment, as well as CD4 lymphocyte count, weight, hemoglobin, and treatment regimen at recruitment to EuroSIDA.

^b As model 1, but factors that change after recruitment were included as time-dependent variables; thus CD4, AIDS diagnosis, hemoglobin, weight, and treatment regimen were modelled as time-dependent.

^c As model 2, but an additional adjustment was made for viral load as a time-dependent covariate. IDU, intravenous drug user; CI, confidence interval

Infections with *Mycobacterium tuberculosis* and *Mycobacterium avium* among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group.

Kirk O, Gatell JM, Mocroft A, Pedersen C, Proenca R, Brettle RP, Barton SE, Sudre P, Phillips AN, Lundgren JD.

BACKGROUND:

The impact of highly active antiretroviral therapy (HAART) among human immunodeficiency virus (HIV)-infected patients on the incidences of mycobacterial infections has not been studied in detail.

PATIENTS AND METHODS:

We assessed incidences of mycobacterial diseases among HIV-infected patients following the introduction of HAART, using data from the EuroSIDA study, a European, multicenter observational cohort of more than 7,000 patients.

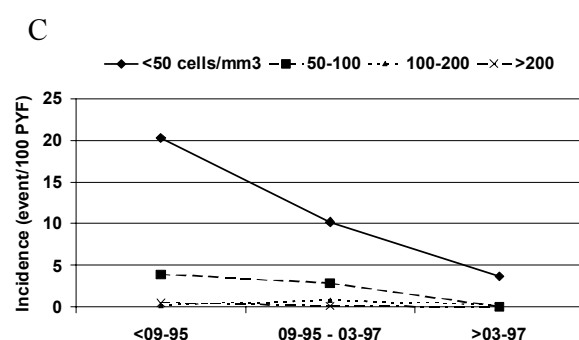
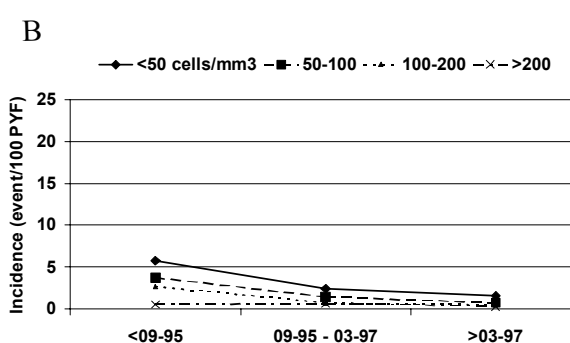
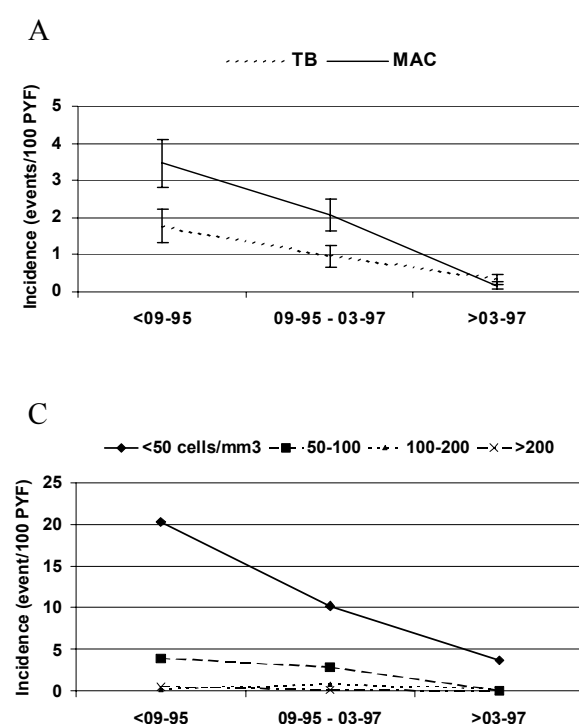
RESULTS:

Overall incidences of *Mycobacterium tuberculosis* (TB) and *Mycobacterium avium* complex (MAC) were 0.8 and 1.4 cases/100 person-years of follow-up (PYF), decreasing from 1.8 (TB) and 3.5 cases/100 PYF (MAC) before September 1995 to 0.3 and 0.2 cases/100 PYF

after March 1997. After adjustment for changes in CD4 cell count and use of antiretroviral treatment in Cox proportional hazards models, the risk of MAC decreased with increasing calendar time (hazard ratio per calendar year; HR = 0.58 [95% confidence intervals: 0.45-0.74], whereas this was not the case for TB; 0.95 [0.74-1.22]).

CONCLUSION:

In conclusion, we documented marked decreases in the incidence of TB and to an even larger extent of MAC among HIV-infected patients from 1994 to 1999. The decrease in TB was associated with the introduction of HAART and changes in CD4 cell count. These factors could also explain some of the decrease in MAC over time, though there remained a significantly lower risk of MAC than expected.



Changes in incidence per 100 person years of follow-up (100 PYF) of *Mycobacterium tuberculosis* (TB) and *Mycobacterium avium* complex (MAC) among patients in the EuroSIDA study: A) Changes over calendar time, $p < 0.001$ in a test for trend for both diseases. B) Changes in the incidence of TB within CD4 strata over calendar time. Within each of the periods <09-95 and 09-95 - 03-97: $p < 0.0001$ in a test for trend, and for the period after 03-97: $p = 0.002$, and C) Changes in the incidence of MAC within CD4 strata over calendar time, $p < 0.001$ for each of the 3 time intervals.

AIDS across Europe, 1994-98: the EuroSIDA study.

Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, Chiesi A, Phillips AN, Kirk O, Lundgren JD.

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.

PATIENTS AND 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.

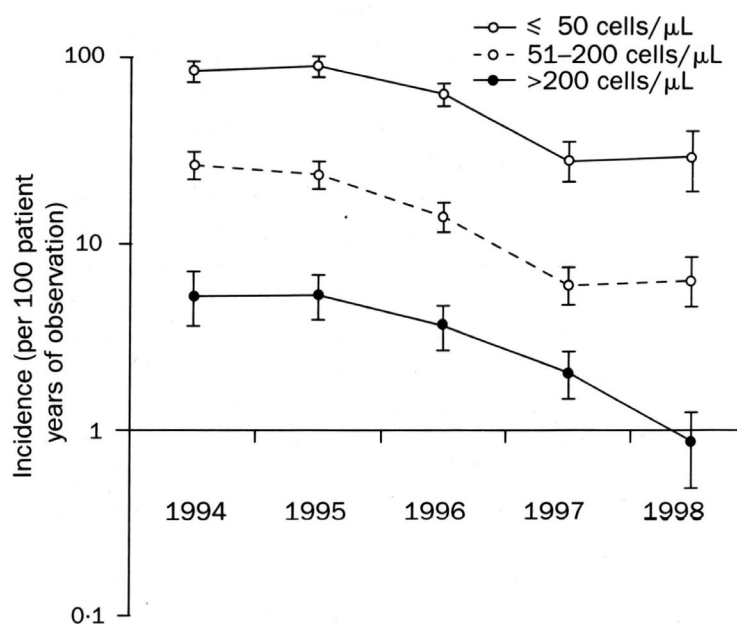
RESULTS:

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/microL to 125 cells/microL 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 ($< \text{or} = 50$, 51-200, and > 200 cells/microL). 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.

CONCLUSION:

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.



Virological failure among patients on HAART from across Europe: results from the EuroSIDA study.

Mocroft A, Miller V, Chiesi A, Blaxhult A, Katlama C, Clotet B, Barton S, Lundgren JD.

BACKGROUND:

To monitor the response to highly active antiretroviral therapy (HAART) over time and the proportions of patients with poor virological control in order to help provide some insight into drug resistance. DESIGN: Analysis of data from the EuroSIDA study; an observational study initiated in 1994 of almost 8500 patients with HIV from across Europe.

PATIENTS AND METHODS:

Patients who initiated HAART, and had both a CD4 lymphocyte count and viral load measured in the 3 months prior to starting HAART, were included in analyses. The proportion of patients with a poor virological response (defined as a viral load of $> 10,000$ copies/ml, using either a single measure or two consecutive measures) at 16 and 48 weeks was determined. Multivariate logistical regression was used to determine the factors associated with a poor virological response at both time points.

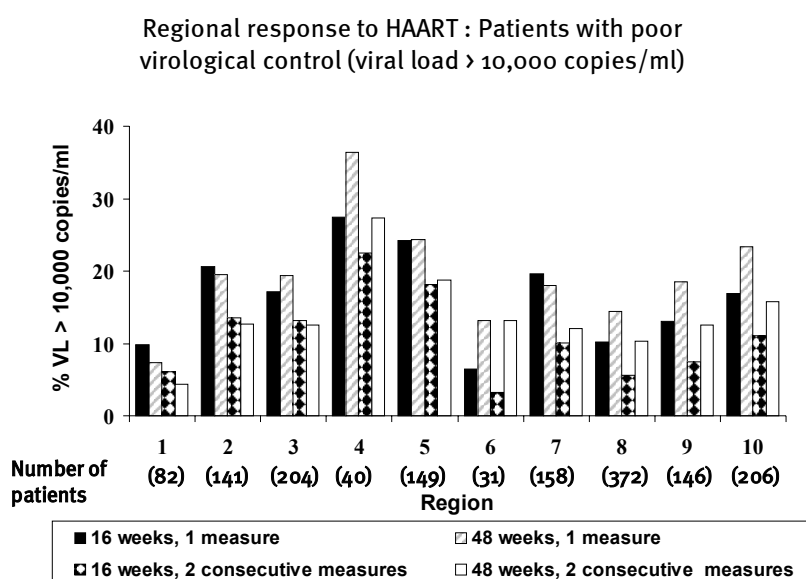
RESULTS:

Median CD4 cell count at starting HAART was 218 cells/mm³ [interquartile range (IQR), 113-327 cells/mm³] and median viral load was 4.36 log₁₀ copies/ml (IQR, 3.57-5.04 log₁₀ copies/ml). At 16 weeks, 16% had a viral load of

$> 10,000$ copies/ml based on a single viral load measure and 10% if the more stringent definition of two consecutive viral loads above this level was used. At 48 weeks these proportions were 19% and 13%, respectively. Compared with patients from Southern Europe, patients from both Central and Northern Europe had approximately half the chance of a poor virological response at 16 weeks (odds ratios 0.53 and 0.47, $P = 0.0015$ and $P < 0.0001$, respectively), while at 48 weeks both regions still had approximately a 25% reduced chance of a poor virological response, but this was no longer statistically significant (odds ratio 0.77 and 0.75, $P = 0.17$ and $P = 0.13$, respectively).

CONCLUSION:

There were marked difference in virological response to HAART across regions of Europe, which may be partly explained by regional differences in access to HAART and utilisation. If drug resistance is closely related to virological failure, these results may help to provide an early insight into the potential problem of drug resistance across Europe. Continued follow-up is essential to monitor patients with poor virological control.



Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy.

Ledergerber B, Mocroft A, Reiss P, Furrer H, Kirk O, Bickel M, Uberti-Foppa C, Pradier C, D'Arminio Monforte A, Schneider MM, Lundgren JD; Eight European Study Groups.

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.

PATIENTS AND 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.

CHARACTERISTICS OF THE 325 STUDY PATIENTS DURING FOLLOW-UP.	
CHARACTERISTIC	VALUE
Duration of follow-up — mo	
Median	13
Interquartile range	7–19
Total follow-up — person-yr*	374
Incidence of recurrent <i>P. carinii</i> pneumonia — per 100 person-yr†	0
Upper 95% confidence limit	0.8
Upper 99% confidence limit	1.2
Incidence of bacterial pneumonia — per 100 person-yr‡	2.7
95% confidence interval	1.1–5.6
99% confidence interval	0.8–6.6
New AIDS-defining events — no. of patients§	5
Death — no. of patients¶	4
Patients lost to follow-up — no. (%)	23 (7)
Patients in whom CD4 counts dropped below 200 cells/mm3 — no. (%)	27 (8)
Patients with reinstitution of secondary prophylaxis — no. (%)	15 (5)
Patients with reinstitution of secondary prophylaxis after CD4 counts dropped below 200 cells/mm3 — no. (%)	4 (1)

*For 355 years of follow-up, CD4 cell counts were at or above 200 per cubic millimeter, resulting in a 99 percent confidence interval for the incidence of recurrent *P. carinii* pneumonia of 0 to 1.3 per 100 person-years.

†The exact Poisson confidence limits are one-sided.

‡Seven patients had bacterial pneumonia 0.4, 1, 6, 7, 9, 10, and 29 months after the discontinuation of secondary prophylaxis. One patient had a clinical diagnosis only; bacterial pneumonia was confirmed in all other patients by evidence of infiltrates on chest radiographs and good responses to antibacterial-drug treatment. This analysis is based on 222 patients, who accounted for 258 person-years of follow-up, since not all cohorts were able to provide data on single episodes of bacterial pneumonia.

§One patient each had candida esophagitis two weeks after the discontinuation of secondary prophylaxis, wasting syndrome at four months, atypical mycobacteriosis at six months, Kaposi's sarcoma at eight months, and indeterminate intracerebral lesions at nine months.

¶Deaths occurred 11, 13, 14, and 18 months after the discontinuation of secondary prophylaxis and were due to laryngeal carcinoma, bacterial pneumonia (3 months after the reinstitution of secondary prophylaxis), liver cirrhosis, and an unknown cause, respectively.

The use of and response to second-line protease inhibitor regimens: results from the EuroSIDA study.

Mocroft A, Phillips AN, Miller V, Gatell J, van Lunzen J, Parkin JM, Weber R, Roze B, Lazzarin A, Lundgren JD; EuroSIDA study group.

BACKGROUND:

To describe the use of second line protease-inhibitor (PI) regimens across Europe and to determine factors associated with virological and immunological response.

DESIGN:

Analysis of data from 984 patients with a median follow-up of 21 months enrolled in EuroSIDA. Patients started their second PI-containing regimen at least 16 weeks after starting the first PI-containing regimen and with viral load > 1000 copies/ml.

METHODS:

Virological response was defined as a viral load < 500 copies/ml and immunological response as an increase of 50×10^6 /l or more in CD4 lymphocyte count.

RESULTS:

The median CD4 cell count at starting the second PI was 171×10^6 cells/l; viral load was 4.45 log copies/ml. As a second PI regimen,

45% were using a dual PI, while of those on one PI, indinavir (42%) and nelfinavir (34%) were most common. In multivariate Cox models, a higher viral load at starting the second PI [relative hazard (RH), 0.67 per 1 log higher; 95% confidence interval (CI), 0.58-0.77; $P < 0.0001$] and a lower CD4 cell count (RH, 1.15 per 50% higher; 95% CI, 1.06-1.26; $P = 0.0014$) were associated with a reduced probability of virological response. Those who had achieved viral suppression on the first PI-regimen were more likely to respond to the second (RH, 1.65; 95% CI, 1.30-2.10; $P < 0.0001$) as were those who added one or two new nucleosides to their second PI.

CONCLUSIONS:

Patients who initiate a second PI regimen at lower viral load, higher CD4 cell count or who added new nucleosides tended to be more likely to achieve a viral load < 500 copies/ml. The roles of cross-resistance and adherence in response to second-line regimens needs further investigation.

Factors associated with a viral load < 500 copies/ml after starting a second-line protease inhibitor (PI) regimen: results from a multivariate Cox proportional hazards model.

		RH	95% CI	P
Viral load	per log higher	0.67	0.58 - 0.77	< 0.0001
Viral load < 500 copies/ml on first PI		1.65	1.30 - 2.10	< 0.0001
CD4 cells	per 50% higher	1.15	1.06 - 1.26	0.0014
CD4 cells increase > 50×10^6 cells/l on first PI		0.86	0.67 - 1.09	0.20
Time since first PI	(per 6 months)	0.96	0.83 - 1.10	0.54
No. new nucleosides	0	1.00	---	---
	1	1.22	0.96 - 1.56	0.10
	2	1.99	1.45 - 2.73	< 0.0001
First PI	Ritonavir	1.00	---	---
	Saquinavir (HGC)	1.59	1.15 - 2.21	0.0055
	Indinavir	1.16	0.81 - 1.66	0.42
Second PI	Dual	1.00	---	---
	Ritonavir	1.29	0.86 - 1.95	0.22
	Saquinavir (HGC)	1.01	0.55 - 1.83	0.99
	Indinavir	1.06	0.83 - 1.51	0.31
	Nelfinavir	0.93	0.69 - 1.25	0.62
Nucleoside combinations	ZDV / 3TC	1.00	---	---
	3TC / D4T	0.93	0.68 - 1.28	0.67
	DDI / D4T	0.76	0.52 - 1.10	0.15
	Other	1.04	0.70 - 1.54	0.87

The relative hazards are from a multivariate Cox proportional hazards model, stratified by centre. RH, relative hazards; CI, confidence interval; HGC, hard gel capsule; ZDV, zidovudine; 3TC, lamivudine; D4T, stavudine; DDI, didanosine.

Influence of age on CD4 cell recovery in human immuno-deficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study.

Viard JP, Mocroft A, Chiesi A, Kirk O, Røge B, Panos G, Vetter N, Bruun JN, Johnson M, Lundgren JD; EuroSIDA Study Group.

PATIENTS AND METHODS:

Influence of age on the CD4 cell response to highly active antiretroviral therapy (HAART) was examined in 1956 patients (median age, 37.2 years) in the EuroSIDA study. Median initial CD4 cell count was 192×10^6 cells/L, follow-up was 31 months, and time to maximum CD4 cell response was 20 months. Age groups were not different for baseline CD4 cell count, baseline human immunodeficiency virus RNA load, or treatment history.

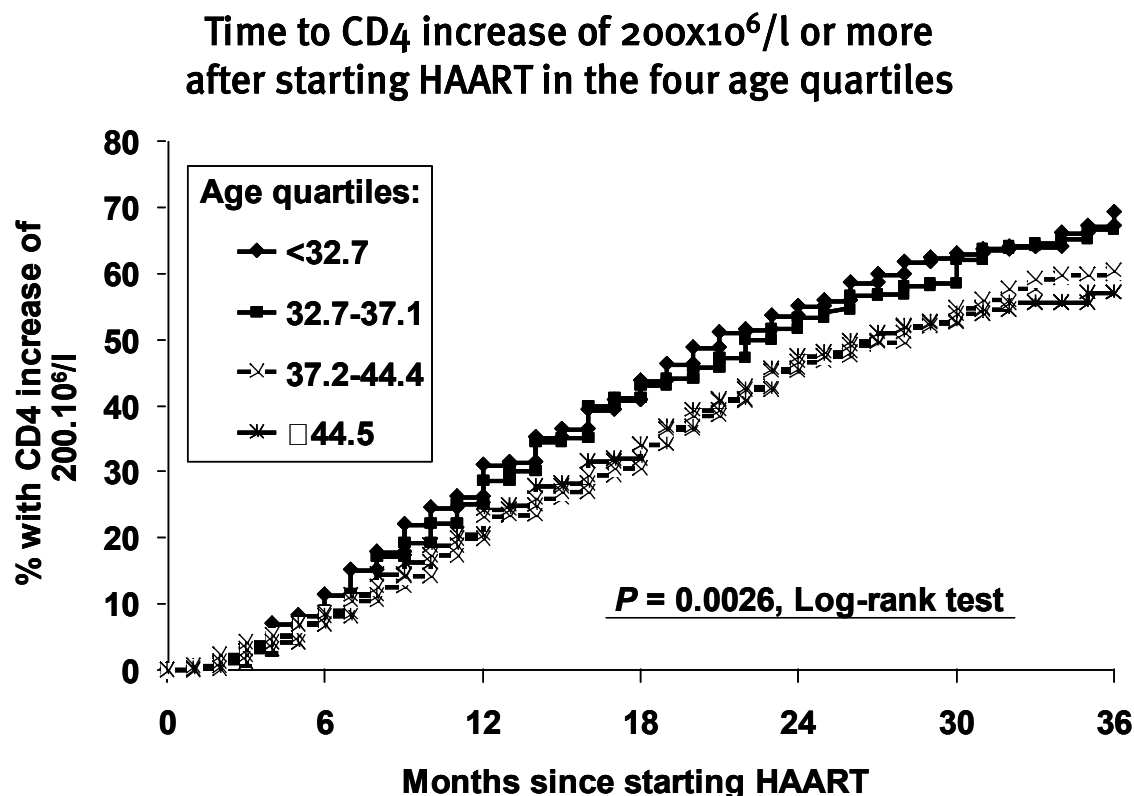
RESULTS:

CD4 cell increase, stratified by age quartiles,

differed during months 3-36 of HAART ($P = 0.023$). Maximum CD4 cell increase from start of HAART differed by age group ($P = 0.0003$), as did maximum CD4 cell count ($P < 10^{-4}$). Multivariate analysis confirmed the inverse relationship between age and maximum CD4 cell response ($P = 0.023$). Time to a CD4 increase of $>200 \times 10^6$ cells/L was shorter for patients in the younger age groups ($P = 0.0026$), as confirmed by multivariate analysis ($P < 10^{-4}$).

CONCLUSION:

Younger age may favor CD4 cell restoration because of preserved thymic function.



Clinical outcome among HIV-infected patients starting saquinavir hard gel compared to ritonavir or indinavir.

Kirk O, Mocroft A, Pradier C, Bruun JN, Hemmer R, Clotet B, Miller V, Viard JP, Phillips AN, Lundgren JD; EuroSIDA Study Group

OBJECTIVE:

To compare the clinical response among patients who initiate protease inhibitor therapies with different virological potency.

DESIGN:

We analysed patients who started indinavir, ritonavir or saquinavir hard gel capsule (hgc) as part of at least triple therapy during prospective follow-up within the EuroSIDA study.

METHODS:

Changes in plasma viral load (pVL) and CD4 cell count from baseline were compared between treatment groups. Time to new AIDS-defining events and death were compared in Kaplan-Meier models, and Cox models were established to further assess differences in clinical progression (new AIDS/death). Adjustment was made for differences in baseline parameters, in particular pVL, CD4 cell count, and region of Europe.

RESULTS:

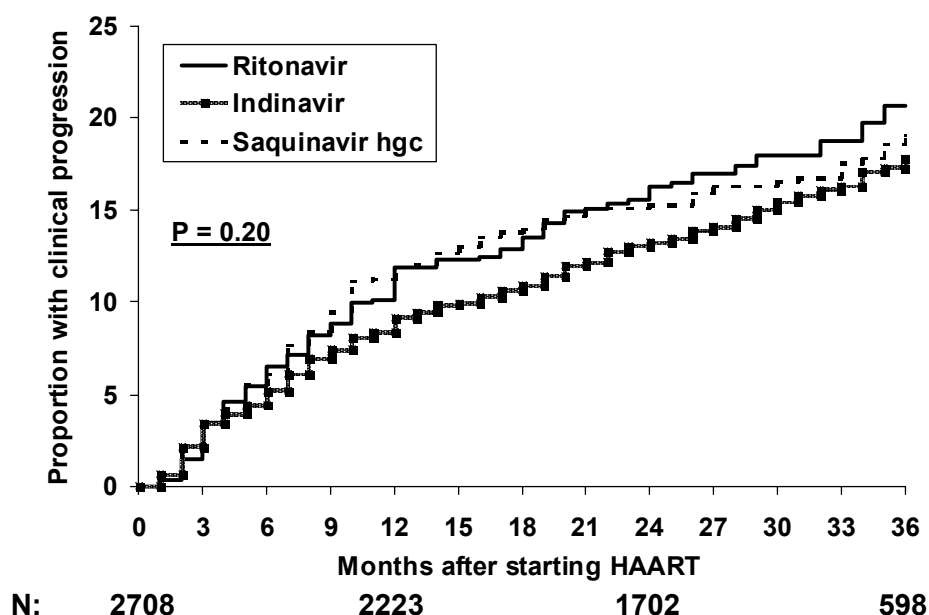
A total of 2708 patients (median follow-up: 30 months) were included, of which 556 started

ritonavir (21%), 1342 indinavir (50%), and 810 saquinavir hgc (30%). The three groups were fairly evenly balanced at baseline regarding CD4 count, previous diagnosis of AIDS and pVL. After 12 months, the median changes in CD4 cell count were 90, 96 and 74 $\times 10^6$ cells/l, respectively; $P < 0.001$, the proportions of patients with pVL < 500 copies/ml were 47, 54 and 41%; $P < 0.001$, and the proportions with clinical progression were 11.9, 9.2 and 11.9%, respectively; $P = 0.20$ (log-rank test). In multivariate models the relative risk of clinical progression for indinavir compared with saquinavir hgc was: 0.77 (0.60-0.99); $P = 0.043$, and for ritonavir 0.83 (0.62-1.11); $P = 0.20$.

CONCLUSIONS:

Saquinavir hgc was associated with an inferior long-term clinical response relative to indinavir, which was consistent with the observed differences in virological and immunological responses.

Time to clinical progression (new AIDS defining event or death) according to the initial protease inhibitor used.



Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens for 2203 mainly antiretroviral-experienced patients.

Phillips AN, Pradier C, Lazzarin A, Clotet B, Goebel FD, Hermans P, Antunes F, Ledergerber B, Kirk O, Lundgren JD; EuroSIDA Study Group

OBJECTIVE:

To assess the factors associated with virologic response to non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens in a large clinic cohort.

DESIGN:

Inception cohort. SETTING: HIV clinics in Europe PATIENTS: We identified all patients in EuroSIDA who began a regimen including either nevirapine or efavirenz (not both) after July 1997 and for whom pre-therapy viral load and CD4 cell count were known. MAIN OUTCOME MEASURES: Virological failure.

RESULTS:

A total of 1325 patients initiated nevirapine and 878 efavirenz. Respectively, median start dates were October 1998 and May 1999. Other factors at baseline, including CD4 cell count, viral load, previous AIDS, previous antiretroviral drug use and make-up of the NNRTI-containing regimen were all approximately similar between the nevirapine and efavirenz groups. A total of 669 patients experienced virological failure during

follow-up. In a Cox model, less protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs) previously used, higher CD4 nadir, lower viral load at baseline, a previous AIDS diagnosis and less NRTIs in the regimen were associated with lower risk of virological failure. The relative hazard of virological failure comparing those on efavirenz with those on nevirapine was 0.57 (95% confidence interval, 0.47-0.69; $P < 0.0001$).

CONCLUSIONS:

The difference in virologic outcome between those using nevirapine and efavirenz in this almost entirely drug-experienced population could reflect differences in effectiveness of the drugs in this setting but, despite the similarity between groups at baseline, bias cannot be excluded as an explanation. Replication of these findings in randomized trials and other cohort studies is required. Factors associated with virological failure after starting a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen.

	Unadjusted		Adjusted	
No. previous NRTIs (per extra drug)	1.30 (1.22 - 1.39)	$P < 0.0001$	1.17 (1.08 - 1.26)	$P < 0.0001$
No. previous PIs (per extra drug)	1.33 (1.25 - 1.43)	$P < 0.0001$	1.17 (1.07 - 1.27)	$P = 0.0006$
Previous AIDS	1.07 (0.92 - 1.25)	$P = 0.39$	0.78 (0.66 - 0.92)	$P = 0.004$
Calendar year at baseline (per year)	0.82 (0.71 - 0.94)	$P = 0.006$	1.11 (0.94 - 1.30)	$P = 0.21$
CD4 count (per 100 x 10 ⁶ cells/l higher)				
Baseline	0.86 (0.82 - 0.90)	$P < 0.0001$	1.03 (0.96 - 1.09)	$P = 0.45$
Nadir	0.74 (0.69 - 0.80)	$P < 0.0001$	0.84 (0.75 - 0.94)	$P = 0.002$
Viral load (per log copies/ml higher)				
Baseline	1.38 (1.29 - 1.47)	$P < 0.0001$	1.28 (1.18 - 1.38)	$P < 0.0001$
Max. ever	1.38 (1.27 - 1.50)	$P < 0.0001$	1.09 (0.99 - 1.21)	$P = 0.10$
No. NRTIs in regimen (per extra drug)	1.36 (1.25 - 1.48)	$P < 0.0001$	1.15 (1.06 - 1.26)	$P = 0.002$
No. PIs in regimen (per extra drug)	1.37 (1.27 - 1.48)	$P < 0.0001$	1.02 (0.93 - 1.12)	$P = 0.62$
Use of efavirenz (versus nevirapine)	0.67 (0.56 - 0.80)	$P < 0.0001$	0.57 (0.47 - 0.69)	$P < 0.0001$

Data are: relative hazard, 95% confidence interval; P-value. PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

Non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy.

Kirk O, Pedersen C, Cozzi-Lepri A, Antunes F, Miller V, Gatell JM, Katlama C, Lazzarin A, Skinhoj P, Barton SE; EuroSIDA Study Group.

OBJECTIVE:

This study was designed to assess the influence of highly active antiretroviral therapy (HAART) on non-Hodgkin lymphoma (NHL) among patients infected with human immunodeficiency virus (HIV).

PATIENTS AND METHODS:

Within EuroSIDA, a multicenter observational cohort of more than 8500 patients from across Europe, the incidences of NHL and subtypes (Burkitt, immunoblastic, primary brain lymphoma [PBL], and other/unknown histology) were determined according to calendar time of follow-up, and for those who initiated HAART (> or =3 drugs) also time on HAART. Potential predictive factors of NHL were evaluated in Cox proportional hazard models.

RESULTS:

Over 26 764 person-years of prospective follow-up (PYF) from May 1994 to December 2000, the incidence of NHL decreased from 1.99 (95% confidence interval, 1.51-2.47) before September

1995 to 0.30 (0.19-0.42) cases/100 (PYF) after March 1999 ($P < .001$). The incidence of all subtypes of NHL decreased significantly and most pronouncedly for PBL. Among patients who started HAART, the incidence of NHL decreased from 0.88 (0.60-1.16) within the first 12 months after starting HAART to 0.45 (0.31-0.60) cases/100 PYF after more than 24 months ($P = .004$). In an adjusted Cox model for patients on HAART, the latest CD4 cell count and plasma viral load were both significantly associated with diagnosis of NHL; the relative hazard was 1.39 (range, 1.14-1.69) per 50% lower CD4 cell count, and 1.51 (range, 1.21-1.88) per 1 log higher plasma viral load.

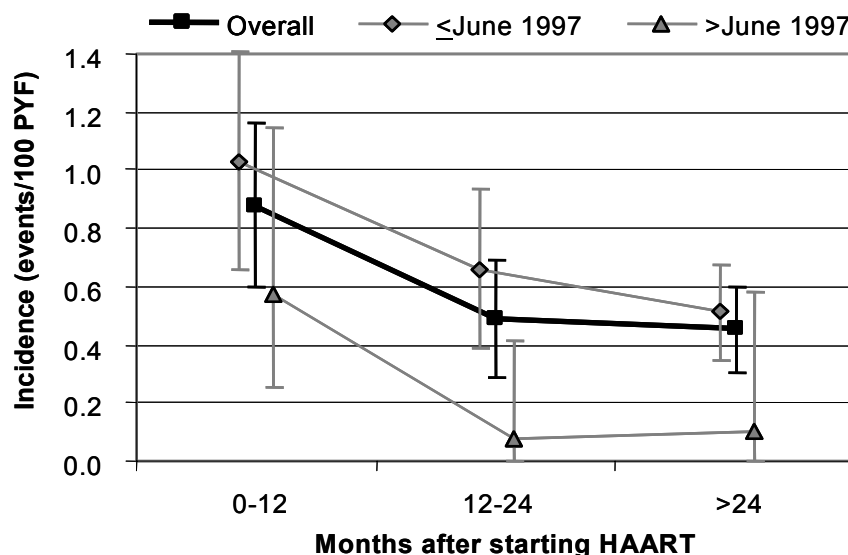
CONCLUSION:

In conclusion, the incidence of NHL among HIV-infected patients has decreased significantly after the introduction of HAART, and the decline was most pronounced for PBL. After starting HAART, patients with insufficient immunologic and virologic responses were at highest risk of NHL.

Incidence of NHL according to the calendar time of starting HAART and the time after starting HAART.

Overall: $p=0.027$ for 0-12 months versus 12-24 months and $p=0.004$ for 0-12 months versus >24 months.

Bars: 95% confidence intervals.



HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load.

Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, Vernazza P, Lundgren JD, Ledergerber B; Swiss HIV Cohort Study; Frankfurt HIV Clinic Cohort; EuroSIDA Study Group.

BACKGROUND:

It is unclear whether delay in initiation of antiretroviral therapy (ART) may lead to a poorer viral load response for patients with human immunodeficiency virus (HIV).

OBJECTIVE:

To characterize the relationship of viral load response to ART with baseline CD4 cell count and baseline viral load.

DESIGN:

Inception cohort of 3430 therapy-naive patients with HIV, of whom 3226 patients had at least 1 viral load count after the start of ART. SETTING: Three cohort studies of patients cared for in HIV clinics in Europe between 1996 and 2000.

PATIENTS: All patients initiating ART consisting of at least 3 drugs initiated in or after 1996 and for whom CD4 cell count and viral load were available in the prior 6 months (at most).

MAIN OUTCOME MEASURES: Viral load decrease to below 500 copies/mL; viral load rebound to above 500 copies/mL (2 consecutive values).

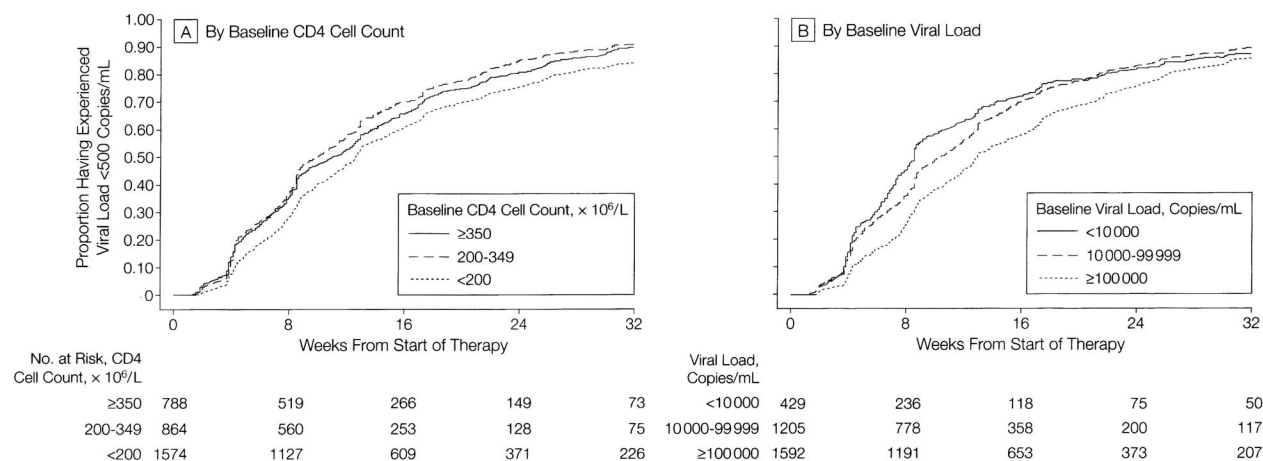
RESULTS: Of 3226 patients during the median follow-up of 119 weeks, 2741 (85%) experienced

viral suppression to less than 500 copies/mL by 32 weeks. Relative hazards (RHs) of achieving this were 1.08 (95% confidence interval [CI], 0.98-1.21) and 0.94 (95% CI, 0.84-1.04) for baseline CD4 cell counts between 200 and $349 \times 10^6/L$ and baseline CD4 cell counts lower than $200 \times 10^6/L$, respectively, compared with baseline CD4 cell counts of $350 \times 10^6/L$ or higher, after adjustment for several factors including baseline viral load. For baseline viral load, the RHs were 0.95 (95% CI, 0.84-1.07) and 0.65 (95% CI, 0.58-0.74), for 10,000 to 99,999 and 100,000 copies/mL or greater, respectively, compared with less than 10,000 copies/mL, but the probability of viral load lower than 500 copies/mL at week 32 was similar in all 3 groups. Subsequent rebound above 500 copies/mL was no more likely with a lower baseline CD4 cell count or higher viral load.

CONCLUSION:

In this study, lower CD4 cell counts and higher viral loads at baseline were not associated with poorer virological outcome of ART. Those with baseline viral loads of greater than 100 000 copies/mL had a slower rate of achieving viral suppression.

Proportion of patients who achieved a viral load of less than 500 Copies/ml



A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study.

Lundgren JD, Mocroft A, Gatell JM, Ledergerber B, D'Arminio Monforte A, Hermans P, Goebel FD, Blaxhult A, Kirk O, Phillips AN; EuroSIDA Study Group.

BACKGROUND:

The risk of clinical progression for human immunodeficiency virus (HIV)-infected persons receiving treatment with highly active antiretroviral therapy (HAART) is poorly defined.

PATIENTS AND METHODS:

From an inception cohort of 8457 HIV-infected persons, 2027 patients who started HAART during prospective follow-up were examined. Results were validated in another 2 groups of patients (n=1946 and n=1442).

RESULTS:

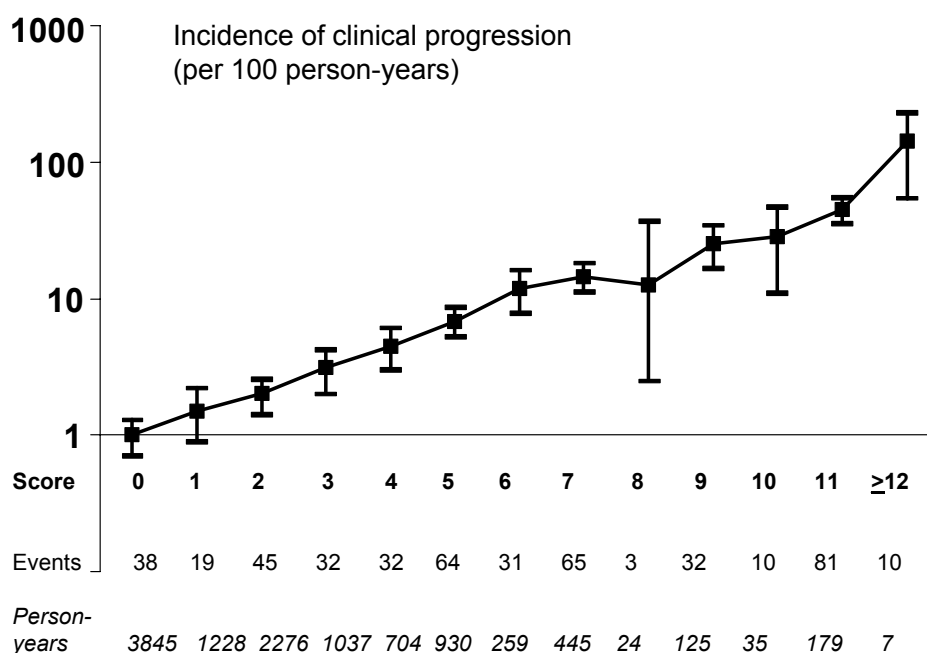
In total, 200 patients (9.9%) experienced clinical progression during 5177 person-years (incidence, 3.9/100 years). The most recently

measured CD4 cell count, virus load, and hemoglobin level all were independently related to the risk of clinical progression, as was a diagnosis of severe AIDS before the start of HAART. On the basis of these findings, a scoring system was derived (range, 0-17). A single unit increase in the score was associated with a 38% increased risk of clinical progression (relative hazard, 1.38; 95% confidence interval, 1.33-1.43; $P < 0.0001$). The scoring system was validated with remarkably good agreement in the 2 other cohorts.

CONCLUSION:

This system can be used in patient and resource management.

Incidence (95% CI) of clinical progression (a new AIDS defining event or death) for each value of the score in individuals starting HAART. Data from all three cohorts (see table 3) were combined in this analysis, and it is thus based on experience from 5415 persons. The number of events and person-years of follow-up on which the incidence estimates are based on is also indicated.



Response to antiretroviral therapy among patients exposed to three classes of antiretrovirals: results from the EuroSIDA study.

Mocroft A, Phillips AN, Friis-Moller N, Colebunders R, Johnson AM, Hirschel B, Saint-Marc T, Staub T, Clotet B, Lundgren JD; EuroSIDA study group.

BACKGROUND:

There is an increasing proportion of HIV-positive patients exposed to all licensed classes of antiretrovirals, and the response to salvage regimens may be poor.

PATIENTS AND METHODS:

Among over 8500 patients in EuroSIDA, the proportion of treated patients exposed to nucleosides, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitor (NNRTI) increased from 0% in 1996 to 47% in 2001. Four-hundred-and-thirteen patients, who had failed virologically two highly active antiretroviral therapy (HAART) regimens and experienced all three main drug classes, started a salvage regimen of at least three drugs, in which at least one new PI or NNRTI was included.

RESULTS:

Median viral load was 4.7 log copies/ml [Interquartile range (IQR) 4.2-5.2], CD4 lymphocyte count 150/mm³ (IQR 60-274/mm³) and follow-up 14 months. Of these patients, 283 (69%) subsequently experienced at least a 1 log decline in viral load and 202 (49%) achieved a

viral load < 500 copies/ml. Conversely, the CD4 count halved from the baseline value in 88 (21%), and 45 (11%) experienced a new AIDS-defining disease. In multivariable analyses, a 1 log viral load reduction was related to baseline viral load [relative hazard (RH) 1.27 per 1 log higher; P = 0.008], a previous viral load of less than 500 copies/ml (RH 1.69; P = 0.002), more recent initiation of the regimen (RH 1.36 per year more recent; P = 0.02), number of new drugs in the regimen (RH 1.20 per drug; P = 0.02), time since start of antiretroviral therapy (RH 0.94 per extra year; P = 0.035) and time spent on HAART with viral load > 1000 copies/ml (RH 0.96 per extra month; P = 0.0001). Analysis of factors associated with CD4 count decline and new AIDS disease also indicated improved outcomes in more recent times and a tendency for a better response in those starting more new drugs, but no relationship with the total number of drugs.

CONCLUSION:

Outcomes in people starting salvage regimens appear to depend on the number of new drugs started but not on the total number of drugs being used.

Factors associated with time to a 1 log reduction in viral load (283 / 413 with event). Results from univariate and multiple Cox regression models.

	Relative hazard (95% CI) p-value			
	Univariate		Adjusted	
Baseline viral load (per 1 log higher)	1.01 (0.86 – 1.18)	p=0.91	1.27 (1.06 – 1.50)	p=0.008
Date of starting salvage (per 1 year more recent)	1.32 (1.12 – 1.55)	p=0.001	1.36 (1.05 – 1.77)	p=0.02
No. of drugs in regimen (per extra drug)	0.90 (0.84 – 0.98)	p=0.01	0.97 (0.89 – 1.06)	p=0.53
No. of new drugs in regimen (per extra drug)	1.29 (1.11 – 1.50)	p=0.0009	1.20 (1.03 – 1.40)	p=0.02
Time since start of ART (per extra year)	0.95 (0.90 – 0.99)	p=0.03	0.94 (0.89 – 1.00)	p=0.035
Months since starting 1 st HAART	1.01 (1.00 – 1.02)	p=0.19	1.00 (0.98 – 1.02)	p=0.88
Months since starting 2 nd HAART	1.00 (0.99 – 1.02)	p=0.61	1.02 (1.00 – 1.03)	p=0.11
Time spent on HAART with viral load > 1000 cps/ml (per extra month)	0.97 (0.96 – 0.98)	p<0.0001	0.96 (0.95 – 0.98)	p=0.0001
Viral load ever < 500 cps/mL on ART	1.94 (1.53 – 2.46)	p<0.0001	1.69 (1.28 – 2.22)	p=0.002

Results from univariate and multiple Cox regression models. HAART, highly active antiretroviral therapy; ART, antiretroviral therapy.

Association of virus load, CD4 cell count, and treatment with clinical progression in human immunodeficiency virus-infected patients with very low CD4 cell counts.

Miller V, Phillips AN, Clotet B, Mocroft A, Ledergerber B, Kirk O, Ormaasen V, Gargalianos-Kakolyris P, Vella S, Lundgren JD.

OBJECTIVE:

This study prospectively assessed the impact of treatment modality, virus load, and CD4 cell count of <50 cells/mm³ on human immunodeficiency virus disease progression.

RESULTS:

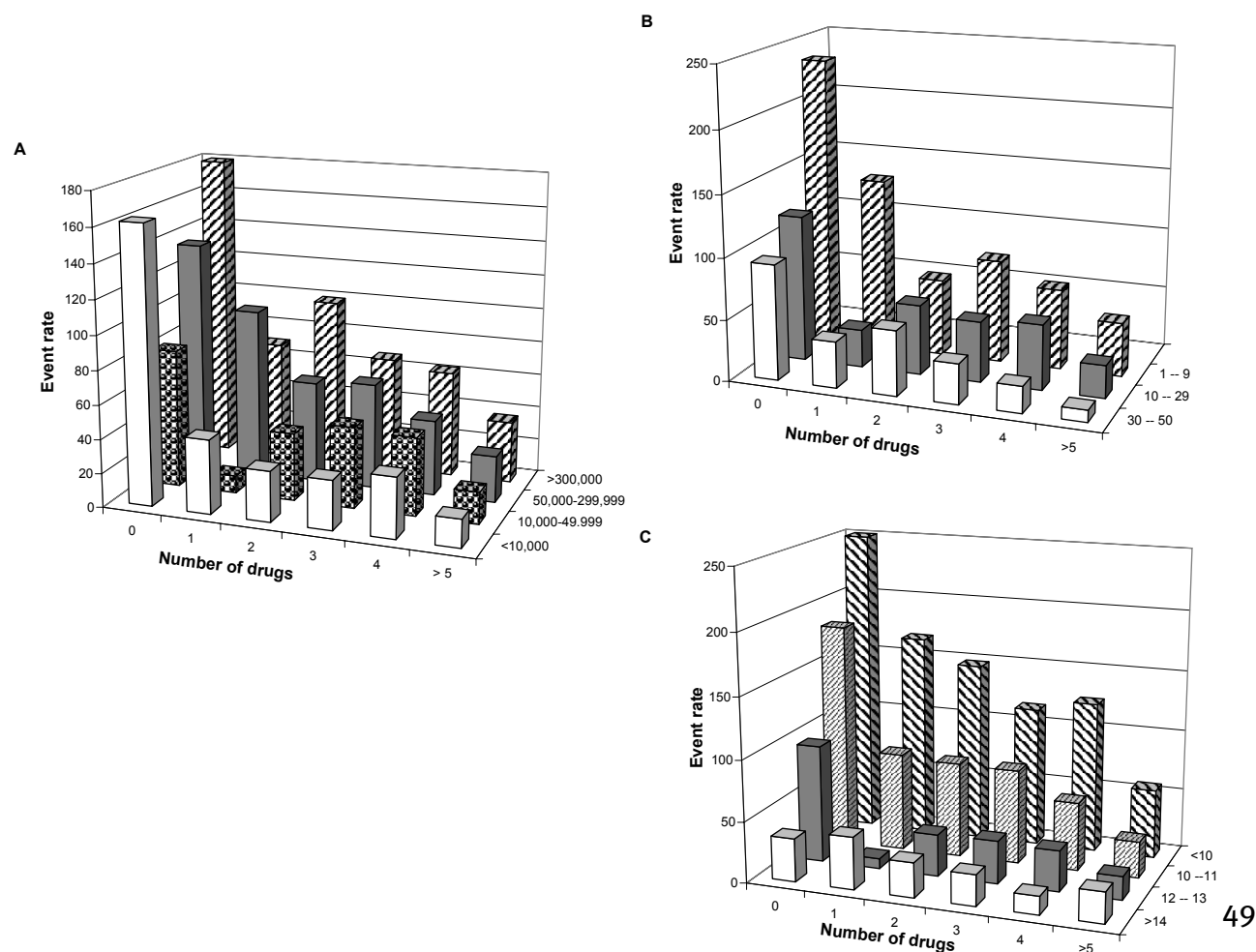
The incidence rate of new AIDS disease or death was 54.8 (95% confidence interval, 48.7-59.9) per 100 person-years of follow-up. Independent predictors related to progression were latest CD4 cell count (relative risk [RR], 0.84/10 mm³ higher; $P<.0001$), latest hemoglobin level (RR, 0.79/g/L higher; $P<.0001$), Pneumocystis carinii

pneumonia prophylaxis (RR, 0.49; $P<.0001$), latest body mass index (RR, 0.93/kg/m² higher; $P=.002$), latest virus load (RR, 1.11/log(10) higher; $P=.03$), and intensity of treatment (RR, 1.82, $P=.004$; RR 2.27, $P<.0001$; RR 2.46, $P=.0001$; RR 2.33, $P<.0006$; 5.10, $P<.0001$, respectively, for 4, 3, 2, 1, or no drugs vs. ≥ 5 drugs).

CONCLUSION:

Although reverse causality cannot be excluded, more intense antiviral treatment appears to decrease the risk of progression in immunocompromised patients.

Event rate (new AIDS defining illnesses or death) per 100 person years of follow-up according to number of antiviral drugs and latest viral load (A), latest CD4 cell count (B) and latest haemoglobin (C)



Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study.

Mocroft A, Brettle R, Kirk O, Blaxhult A, Parkin JM, Antunes F, Francioli P, D'Arminio Monforte A, Fox Z, Lundgren JD; EuroSIDA study group.

OBJECTIVES:

The causes of death among HIV-positive patients may have changed since the introduction of highly active antiretroviral therapy (HAART). We investigated these changes, patients who died without an AIDS diagnosis and factors relating to pre-AIDS deaths.

METHODS:

Analyses of 1826 deaths among EuroSIDA patients, an observational study of 8556 patients. Incidence rates of pre-AIDS deaths were compared to overall rates. Factors relating to pre-AIDS deaths were identified using Cox regression.

RESULTS:

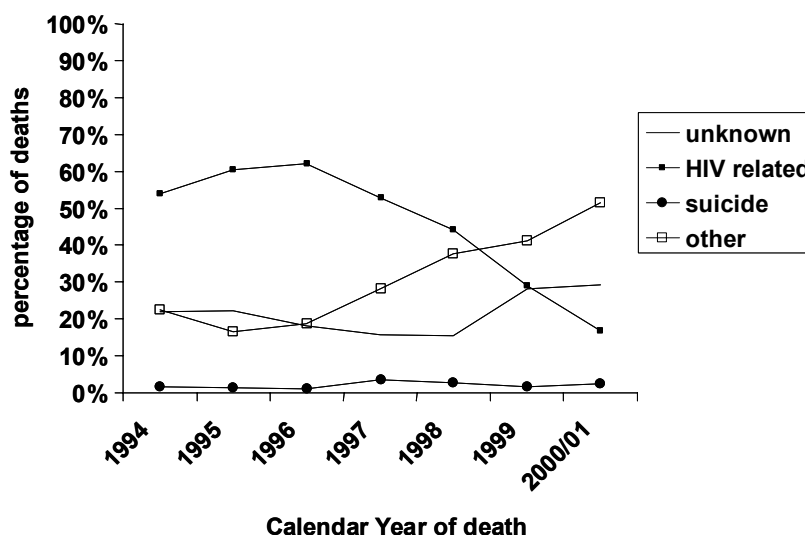
Death rates declined from 15.6 to 2.7 per 100 person-years of follow-up (PYFU) between 1994 and 2001. Pre-AIDS incidence declined from 2.4 to 1.1 per 100 PYFU. The ratio of overall to pre-AIDS deaths peaked in 1996 at 8.4 and dropped to < 3 after 1998. The adjusted odds of dying following one AIDS defining event (ADE) increased yearly (odds ratio, 1.53; $P < 0.001$),

conversely the odds of dying following three or more ADE decreased yearly (odds ratio, 0.79; $P < 0.001$). The proportion of deaths that followed an HIV-related disease decreased by 23% annually; in contrast there was a 32% yearly increase in the proportion of deaths due to known causes other than HIV-related or suicides. Injecting drug users (IDU) were significantly more likely to die before an ADE than homosexuals (relative hazard, 2.97; $P < 0.0001$) and patients from northern/eastern Europe (relative hazard, 2.01; $P < 0.0001$) were more likely to die pre-AIDS than southern patients.

CONCLUSIONS:

The proportion of pre-AIDS deaths increased from 1994 to 2001; however, the incidence of pre-AIDS deaths and deaths overall declined. IDU and subjects from northern/eastern Europe had an increased risk of pre-AIDS death. HIV-positive patients live longer therefore it is essential to continue to monitor all causes of mortality to identify changes.

The yearly change in the cause of death within the EuroSIDA study



Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy.

Kirk O, Reiss P, Uberti-Foppa C, Bickel M, Gerstoft J, Pradier C, Wit FW, Ledergerber B, Lundgren JD, Furrer H; European HIV Cohorts.

BACKGROUND:

The safety of interrupting maintenance therapy for previous opportunistic infections other than *Pneumocystis carinii* pneumonia among patients with HIV infection who respond to potent antiretroviral therapy has not been well documented.

OBJECTIVE:

To assess the safety of interrupting maintenance therapy for cytomegalovirus (CMV) end-organ disease, disseminated *Mycobacterium avium* complex (MAC) infection, cerebral toxoplasmosis, and extrapulmonary cryptococcosis in patients receiving antiretroviral therapy.

DESIGN:

Observational study.

PATIENTS AND METHODS:

Seven European HIV cohorts. **PATIENTS:** 358 patients taking potent antiretroviral therapy ($>$ or $=$ 3 drugs) who interrupted maintenance therapy at a CD4 lymphocyte count greater than 50×10^6 cells/L.

MEASUREMENTS: Recurrence of opportunistic infection after interruption of maintenance therapy.

RESULTS:

379 interruptions of maintenance therapy were identified: 162 for CMV disease, 103 for MAC infection, 75 for toxoplasmosis, and 39 for cryptococcosis. During 781 person-years of

follow-up, five patients had relapse. Two relapses (one of CMV disease and one of MAC infection) were diagnosed after maintenance therapy was interrupted when the CD4 lymphocyte count was less than 100×10^6 cells/L or when only one recent measurement exceeded this value. Two relapses (one of CMV disease and one of MAC infection) were diagnosed after maintenance therapy was interrupted once CD4 counts were greater than 100×10^6 cells/L for 10 and 8 months, respectively. One relapse (toxoplasmosis) was diagnosed after maintenance therapy interruption at a CD4 lymphocyte count greater than 200×10^6 cells/L for 15 months. The overall incidences of recurrent CMV disease, MAC infection, toxoplasmosis, and cryptococcosis were 0.54 per 100 person-years (95% CI, 0.07 to 1.95 per 100 person-years), 0.90 per 100 person-years (CI, 0.11 to 3.25 per 100 person-years), 0.84 per 100 person-years (CI, 0.02 to 4.68 per 100 person-years), and 0.00 per 100 person-years (CI, 0.00 to 5.27 per 100 person-years), respectively.

CONCLUSION:

Maintenance therapy against previous infection with CMV, MAC, *Toxoplasma gondii*, or *Cryptococcus neoformans* in patients with HIV infection can be interrupted after sustained CD4 count increases to greater than 200 (or possibly 100 to 200) $\times 10^6$ cells/L for at least 6 months after the start of potent antiretroviral therapy.

Incidence of recurrent opportunistic infections among patients on potent ART who interrupted maintenance therapy while taking potent antiretroviral therapy.

Characteristic	CMV End-Organ Disease		Cryptococcosis		Disseminated MAC Infection		Toxoplasmosis	
	Events/ PYF	Incidence and 95%-CI*	Events/ PYF	Incidence and 95%-CI*	Events/ PYF	Incidence and 95%-CI*	Events/ PYF	Incidence and 95%-CI*
<i>Overall (n=379)</i>	2/370	0.54 (0.07-1.95)	0/70	0.00 (0.00-5.27)	2/222	0.90 (0.11-3.25)	1/119	0.84 (0.02-4.68)
<i>CD4 lymphocyte count at interruption (x 10 cells/L)</i>								
50-99 x 10 ⁶ cells / L (n=39)	1/34	2.9 (0.1-16.4)	0/5	0.0 (0.0-73.8)	0/37	0.0 (0.0-10.0)	0/11	0.0 (0.0-33.5)
100-199 x 10 ⁶ cells / L (n=109)	0/134	0.0 (0.0-2.8)	0/16	0.0 (0.0-23.1)	1/92	1.1 (0.0-6.1)	0/17	0.0 (0.0-21.7)
≥200 x 10 ⁶ cells / L (n=231)	1/202	0.5 (0.0-2.8)	0/49	0.0 (0.0-7.5)	1/93	1.1 (0.0-6.0)	1/92	1.1 (0.0-6.1)
<i>Plasma HIV-RNA at interruption (copies/mL)</i>								
≤500 copies / mL (n=204)	1/185	0.5 (0.0-3.0)	0/40	0.0 (0.0-9.2)	1/109	0.9 (0.0-5.1)	1/60	1.7 (0.0-9.3)
>500 copies / mL (n=108)	1/103	1.0 (0.0-5.4)	0/17	0.0 (0.0-21.7)	1/66	1.5 (0.0-8.4)	0/52	0.0 (0.0-7.1)

*Incidence in events/100 person-years of follow-up (PYF) with 95%-confidence intervals.

CMV = cytomegalovirus; MAC = Mycobacterium avium complex; PYF = Person Years of Follow-up

Analysis of virological efficacy in trials of antiretroviral regimens: drawbacks of not including viral load measurements after premature discontinuation of therapy.

Kirk O, Pedersen C, Law M, Gulick RM, Moyle G, Montaner J, Eron JJ Jr, Phillips AN, Lundgren JD.

OBJECTIVES:

To compare two analytic approaches to assess the virological effect of HAART according to the intention-to-treat (ITT) principle.

PATIENTS AND METHODS:

Data from 2318 patients enrolled in 10 randomised clinical trials (RCTs) and from 3091 patients followed in an observation cohort (EuroSIDA) starting their first HAART regimen. Two classifications of defining virological response 48 weeks after starting the therapy to be evaluated were compared: 1) only patients remaining on the therapy and having a plasma viral load (pVL) below a given cut-off level at week 48 were classified as responders (ITT/s=f); and 2) patients with a pVL below a given cut-off at week 48 whether they remained on initial assigned therapy or switched therapy were responders (ITT/s incl). In both analyses, patients with missing data at week 48 were classified as failures (i.e., non-responders).

RESULTS:

According to ITT/s=f, 22-70% of the patients starting a HAART regimen in a RCT experienced a virological response at week 48. Only two RCTs

had complete follow-up data (n=424): between 29 and 62% achieved a virological response at week 48 in the six treatment arms evaluated in the studies according to ITT/s=f, and 41-72% according to ITT/s incl. Among those who discontinued the therapy to be evaluated in these two trials, 13-45% (cohort: 39-74%) subsequently experienced a virological response at week 48. The subsequent response rates were associated with the reason for discontinuation (toxicity versus confirmed virological failure: 63 vs 33%), varied largely across regimens and were not associated with the discontinuation rate.

CONCLUSIONS:

Discontinuation of follow-up at switch from the therapy to be evaluated remains common in antiretroviral treatment trials, but leads to an imprecise and incomplete assessment of the intrinsic effect of a given regimen. Complete follow-up of all patients should be encouraged strongly as this will allow for several complementary analytic approaches and a focus on optimal treatment strategies rather than specific regimens.

Virological response after 48 weeks of HAART assessed according to the principles of ITT/s=f and ITT/s incl. Results from the EuroSIDA study.

Type of PI/NNRTI in HAART regimen	Number of patients	Disc. of PI/NNRTI %	Disc. of any component of regimen %	ITT/s=f (based on PI/NNRTI disc.)	ITT/s=f (based on any disc.) % of patients with pVL≤500 copies/mL	ITT/s incl	Virological response after premature disc. of initial PI/NNRTI*
Nelfinavir	310	25.5	30.7	47.4	43.9	57.4	39.2
Indinavir	1390	25.8	35.3	45.5	40.2	56.4	42.5
Efavirenz	60	31.7	40.0	41.7	35.0	65.0	73.7
Nevirapine	265	32.1	38.5	33.6	30.6	49.4	49.4
Ritonavir/ saquinavir hgc	114	36.0	43.0	46.5	40.4	64.0	48.8
Saquinavir hgc	462	48.1	55.6	14.7	12.6	34.2	40.5
Ritonavir	490	52.5	57.1	30.0	26.9	52.0	42.0

Abbreviations: *disc.*: discontinuation of original PI/NNRTI before week 48 (deaths not included), *hgc*: hard gel capsule, *NNRTI*: non-nucleoside reverse transcriptase inhibitor. *PI*: protease inhibitor.

499 patients (including 47 deaths) had no pVL measurement at week 48 and were in both ITT/s=f and ITT/s incl classified as virological failures.

*: among patients who discontinued original HAART regimen before week 48.

Regional and temporal changes in AIDS in Europe before HAART.

Blaxhult A, Fox Z, Colebunders R, Francioli P, Ben-Ishai Z, Fatkenheuer G, Parkin JM, Vanhems P, Phillips AN, Kirk O; EuroSIDA Study Group.

PATIENTS AND METHODS:

In a prospective observational study 4,485 patients from 46 clinical centres in 17 European countries were followed between April 1994 and November 1996. Information on AIDS-defining events (ADEs) were collected together with basic demographic data, treatment history and laboratory results. The centres were divided into four geographical regions (north, central, south-west and south-east) so that it was possible to identify any existing regional differences in ADEs.

RESULTS:

The regional differences that we observed included a higher risk of all forms of *Mycobacterium tuberculosis* infections (Tb) and wasting disease in the south-west and an increased risk of infections with the

Mycobacterium avium complex (MAC) in the north. In Cox multivariable analyses, where north was used as the reference group, we observed hazard ratios of 6.87, 7.77, 2.29 and 0.16 ($P < 0.05$ in all cases) for pulmonary Tb, extrapulmonary Tb, wasting disease and MAC respectively in the south-west. *Pneumocystis carinii* pneumonia (PCP) was less commonly diagnosed in the central region (RH = 0.51, 95% CI 0.32-0.79, $P = 0.003$) and most common in the south-east (RH = 1.04, 95% CI 0.71-1.51, $P = 0.85$).

CONCLUSION:

Comparisons with a similar 'AIDS in Europe' study that concentrated on the early phase of the epidemic reveal that most of the regional differences that were observed in the 1980s still persist in the mid-1990s.

Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies.

Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, Costagliola D, D'Arminio Monforte A, de Wolf F, Reiss P, Lundgren JD, Justice AC, Staszewski S, Leport C, Hogg RS, Sabin CA, Gill MJ, Salzberger B, Sterne JA; ART Cohort Collaboration.

BACKGROUND:

Insufficient data are available from single cohort studies to allow estimation of the prognosis of HIV-1 infected, treatment-naïve patients who start highly active antiretroviral therapy (HAART). The ART Cohort Collaboration, which includes 13 cohort studies from Europe and North America, was established to fill this knowledge gap.

PATIENTS AND METHODS:

We analysed data on 12,574 adult patients starting HAART with a combination of at least three drugs. Data were analysed by intention-to-continue-treatment, ignoring treatment changes and interruptions. We considered progression to a combined endpoint of a new AIDS-defining disease or death, and to death alone. The prognostic model that generalised best was a Weibull model, stratified by baseline CD4 cell count and transmission group.

RESULTS:

During 24,310 person-years of follow up, 1094 patients developed AIDS or died and 344 patients died. Baseline CD4 cell count was strongly associated with the probability of

progression to AIDS or death: compared with patients starting HAART with less than 50 CD4 cells/microL, adjusted hazard ratios were 0.74 (95% CI 0.62-0.89) for 50-99 cells/microL, 0.52 (0.44-0.63) for 100-199 cells/microL, 0.24 (0.20-0.30) for 200-349 cells/microL, and 0.18 (0.14-0.22) for 350 or more CD4 cells/microL. Baseline HIV-1 viral load was associated with a higher probability of progression only if 100,000 copies/microL or above. Other independent predictors of poorer outcome were advanced age, infection through injection-drug use, and a previous diagnosis of AIDS. The probability of progression to AIDS or death at 3 years ranged from 3.4% (2.8-4.1) in patients in the lowest-risk stratum for each prognostic variable, to 50% (43-58) in patients in the highest-risk strata.

CONCLUSION:

The CD4 cell count at initiation was the dominant prognostic factor in patients starting HAART. Our findings have important implications for clinical management and should be taken into account in future treatment guidelines.

Incidence rates of progression to AIDS or death at baseline and different points during follow-up according to baseline CD4 cell count. Note logarithmic scale for incidence rates.

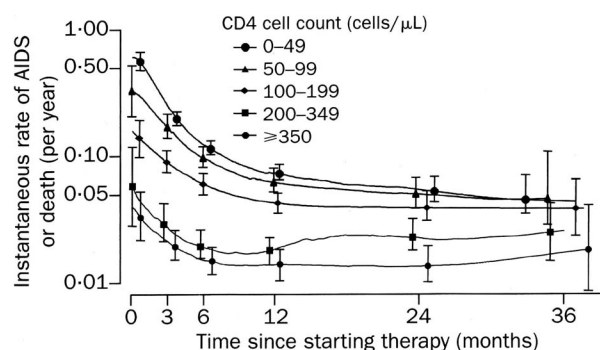


Figure 2: Incidence rates of progression to AIDS or death at baseline and different points during follow-up according to baseline CD4 cell count

Note logarithmic scale for incidence rates.

Virologic, immunologic, and clinical response to highly active antiretroviral therapy: the gender issue revisited.

Moore AL, Kirk O, Johnson AM, Katlama C, Blaxhult A, Dietrich M, Colebunders R, Chiesi A, Lungren JD, Phillips AN; EuroSIDA group.

BACKGROUND:

Highly active antiretroviral therapy (HAART) has dramatically improved the prognosis for patients with HIV. There is ongoing debate over a potential gender effect on patient outcome after HAART.

METHODS:

Individuals were from the EuroSIDA cohort, naive to protease inhibitors and nonnucleoside reverse transcriptase inhibitors, and had at least one viral load and CD4 measurement prior to starting HAART. Endpoints were virologic (time to <500 copies/mL, time to rebound [first of two consecutive viral loads >500 copies/mL]), immunologic (time to a 100/mm cell rise in CD4 count) and clinical (time to new AIDS and death). Hazard ratios (HR), derived using Cox regression models, compared female to male rates of achieving endpoints.

RESULTS:

Of 2547 patients, 20% (511) were female. Significantly more females than males were

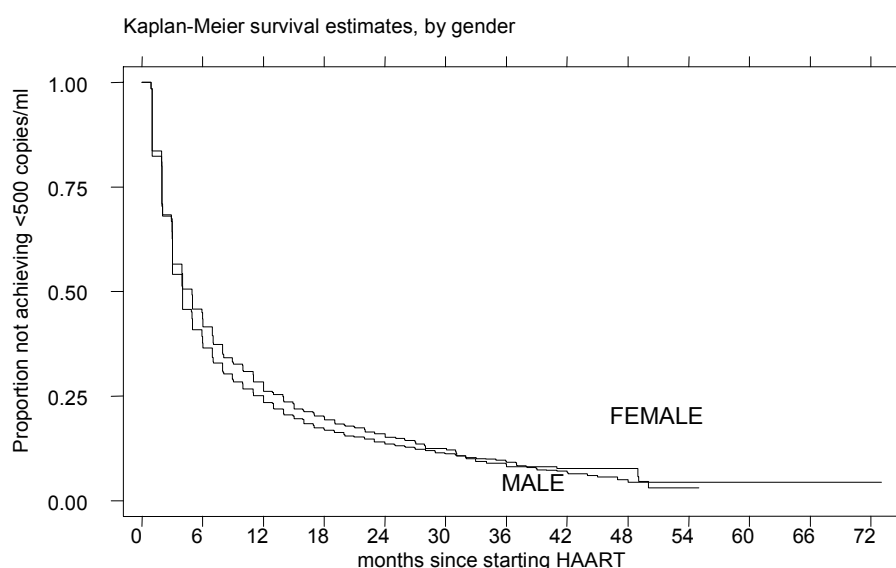
nonwhite (24% vs. 10%, $p < .001$). Males were older (median age 39 vs. 35 years, $p < 0.0001$), had lower CD4 counts (211 vs. 240/mm, $p = .03$), higher viral loads (4.6 vs. 4.4 log copies/mL, $p < .0001$), were more likely to have a history of AIDS (26% vs. 18%, $p < .001$) and were more likely to be treatment-naïve (34% vs. 29%, $p = .03$). Adjusted HR for association between gender (comparing females with males) and the outcomes studied were as follows: for reaching <500 copies/mL 0.91 (0.81-1.03, $p = .17$), rebound 1.17 (0.95-1.44, $p = .15$), for 100 cell CD4 count rise 1.02 (0.88-1.14, $p = .99$), for progression to new AIDS 1.12 (0.73-1.71, $p = .59$) and for time to death 1.15 (0.69-1.92, $p = .57$).

CONCLUSION:

We found no significant evidence of a gender difference in virologic, immunologic, or clinical outcomes after starting HAART.

Kaplan Meier graph showing time to virological outcomes.

Achievement of < 500 copies



Modelling the 3-year risk of myocardial infarction among participants in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study.

Law M, Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Calvo G, El-Sadr W, De Wit S, Sabin CA, Lundgren JD; DAD Study Group.

OBJECTIVES:

To estimate the 3-year risk of myocardial infarction (MI) among participants in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study.

METHODS:

Conventional cardiovascular risk equations were applied to baseline data from the DAD study to estimate the 3-year risk of MI. Best estimates were obtained by simply applying the risk equations, with upper and lower limits based on worst case and optimistic case scenarios. Three-year risks of AIDS or death were also estimated based on a prognostic scoring system for patients receiving antiretroviral (ARV) treatment, and on estimated AIDS rates in untreated people with HIV for those patients not on ARVs or if they were to cease ARVs.

RESULTS:

Analyses were based on 17 600 patients (24.3% female) recruited into the DAD study with baseline data and no previous MI. The overall 3-year risk of MI was estimated to be 0.72% (lower limit 0.35, upper limit 1.12%), corresponding to a total predicted 127 (65-197) MIs over a 3-year

follow-up period. The risk was much greater for men than women (0.92% vs. 0.07%), with only three (2-8) MIs predicted in women. The 3-year risk of MI was estimated to increase from 0.30% (0.20-0.38%) in ARV naive patients to 1.07% (0.43-1.77%) in patients receiving ARVs from all three drug classes. The estimated 3-year risk of AIDS or death was in the range 6.2% to 11.1% in patients receiving ARVs if they continued treatment, and 22.5% to 29.4% if they ceased ARVs.

CONCLUSION:

These models suggest that although the increase in relative risk of MI as a result of ARV treatment may be as high as threefold in a worst case scenario, the absolute risk is modest with a best estimate of 3-year risk less than or equal to 1% in all groups of patients, and is outweighed by the benefits of ARV treatment in terms of reduced risk of AIDS and death in most patients. As estimates are based on models not validated for people receiving ARV drugs, all estimates should be interpreted cautiously.

Best estimate of cumulative risk of MI by ARV drug class to 10 years.

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

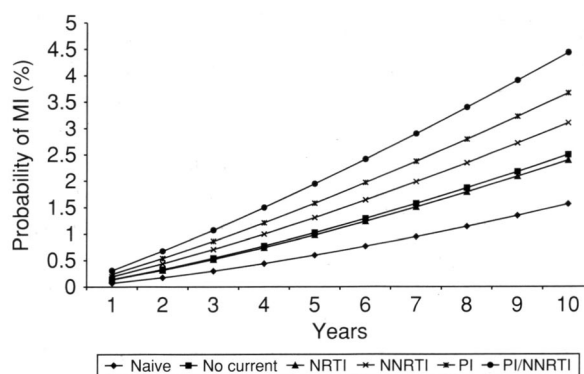


Fig. Best estimate of cumulative risk of MI by ARV drug class to 10 years.
NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Changes in viral load in people with virological failure who remain on the same HAART regimen.

Cozzi-Lepri A, Phillips AN, Miller V, Katlama C, Ledergerber B, Vella S, Weber J, Bruun JN, Kirk O, Clotet B, Lundgrens JD.

OBJECTIVES:

To assess the rate of change in viral load and CD4 count over time in HIV-infected patients experiencing virological failure on a HAART regimen.

PATIENTS AND METHODS:

Study population included patients from EuroSIDA, a large, multicentre, observational study enrolling HIV-infected patients across Europe. Median change in viral load and CD4 count per month were estimated using the viral load and CD4 measurements obtained over a 12-month period after confirmed virological failure between 3 and 4 log₁₀ copies/ml in a population of 488 HIV-infected patients who were left on a failing HAART regimen.

RESULTS:

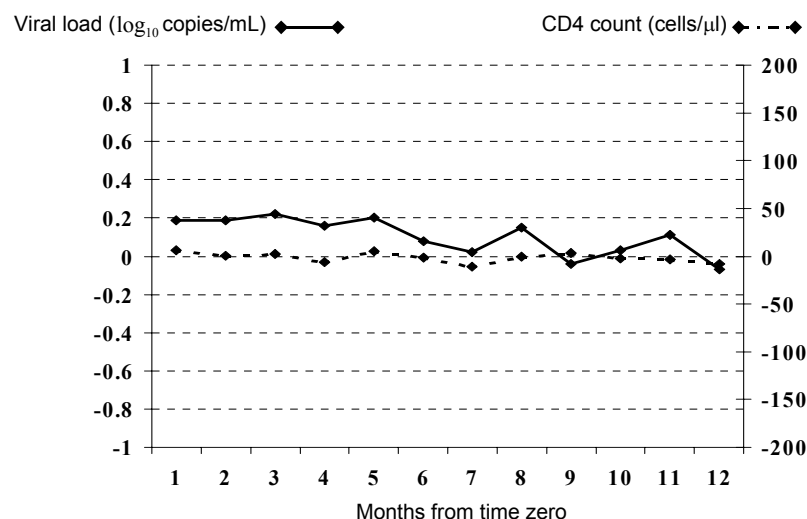
The estimated median viral load change in our study population was 0.024 log₁₀ copies/ml per month, statistically different from 0 (P=0.0001). In 20.9% of the patients studied viral load

showed a tendency to decrease, in 47.8% showed a tendency to increase by a positive rate no higher than 0.04 log₁₀ copies/ml per month and in the remaining 31.3% showed a tendency to increase by a rate greater than 0.04 log₁₀ copies/ml per month. On average, CD4 counts were estimated to remain stable (decrease at a slow rate of about -0.53 cells/microl per month).

CONCLUSIONS:

In patients that remained on a stable, but virologically failing HAART regimen (with viral load ranging 1000-10000 copies/ml), the viral load over the ensuing 12-month period increased at a relatively slow rate. In contrast, the CD4 count remained stable, possibly because of partial but sustained viral suppression below the viral load natural set-point. The time-course of selecting more replication-competent virus in patients with virological failure remains to be fully clarified.

Mean viral load (solid line) and CD4 count (dotted line) raw changes from baseline. Individual observations are the difference between the viral load at each month and the viral load at time zero.



Patients included													
VL	64	122	182	161	130	166	150	115	134	137	136	146	
CD4 count	58	124	170	145	97	112	98	80	92	82	81	81	

Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study.

Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Mateu S, Law M, El-Sadr W, De Wit S, Sabin CA, Phillips AN, Lundgren JD; DAD study group.

OBJECTIVE:

To determine the prevalence of risk factors for cardiovascular disease (CVD) among HIV-infected persons, and to investigate any association between such risk factors, stage of HIV disease, and use of antiretroviral therapies.

PATIENTS AND METHODS:

Baseline data from 17,852 subjects enrolled in DAD, a prospective multinational cohort study initiated in 1999. Cross-sectional analyses of CVD risk factors at baseline. The data collected includes data on demographic variables, cigarette smoking, diabetes mellitus, hypertension, dyslipidaemia, body mass index, stage of HIV infection, antiretroviral therapy.

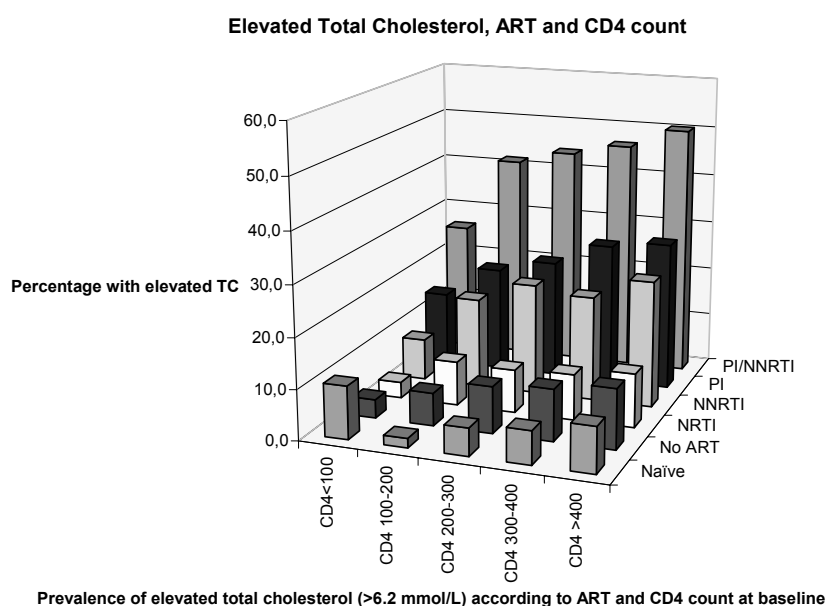
RESULTS:

Almost 25% of the study population were at an age where there is an appreciable risk of CVD, with those receiving a protease inhibitor (PI) and/or non-nucleoside reverse transcriptase inhibitor (NNRTI) tending to be older. 1.4% had a previous history of CVD and 51.5% were cigarette smokers. Increased prevalence of elevated total cholesterol (\geq or = 6.2 mmol/l) was observed among subjects receiving an

NNRTI but no PI [odds ratio (OR), 1.79; 95% confidence interval (CI), 1.45-2.22], PI but no NNRTI (OR, 2.35; 95% CI, 1.92-2.87), or NNRTI + PI (OR, 5.48; 95% CI, 4.34-6.91) compared to the prevalence among antiretroviral therapy (ART)-naive subjects. Subjects who have discontinued ART as well as subjects receiving nucleoside reverse transcriptase inhibitors had similar cholesterol levels to treatment-naive subjects. Higher CD4 cell count, lower plasma HIV RNA levels, clinical signs of lipodystrophy, longer exposure times to NNRTI and PI, and older age were all also associated with elevated total cholesterol level.

CONCLUSION:

HIV-infected persons exhibit multiple known risk factors for CVD. Of specific concern is the fact that use of the NNRTI and PI drug classes (alone and especially in combination), particularly among older subjects with normalized CD4 cell counts and suppressed HIV replication, was associated with a lipid profile known to increase the risk of coronary heart disease.



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

Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, Knysz B, Dietrich M, Phillips AN, Lundgren JD; 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.

PATIENTS AND 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).

RESULTS:

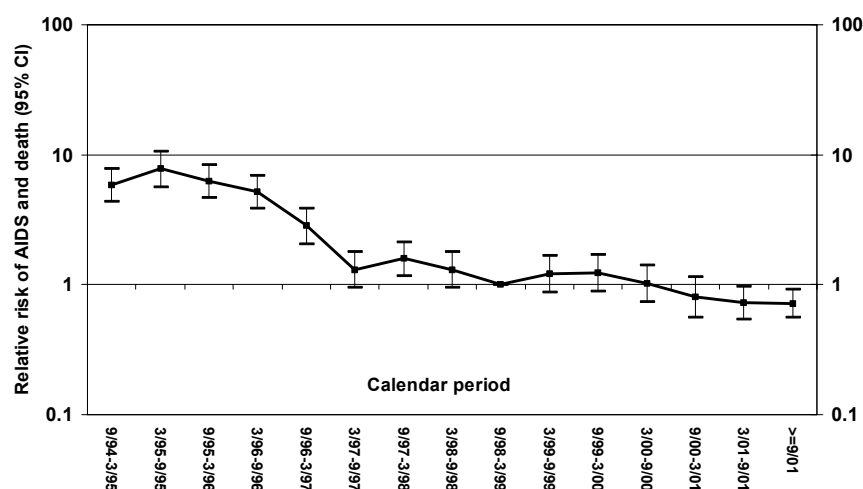
The incidence of AIDS or death fell after September, 1998, by 8% per 6-month period (rate ratio 0.92, 95% CI 0.88-0.95, $p<0.0001$). When AIDS and death were analysed separately, the incidence of all deaths during the late-HAART era was significantly lower than that

during the early-HAART era in patients whose latest CD4 count was 20 cells/microL 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.

CONCLUSION:

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.

Adjusted relative risk of AIDS or death



Adjusted for CD4 count at recruitment, age, prior HAART treatment, AIDS status (yes/no)

Virological rebound after suppression on highly active antiretroviral therapy.

Mocroft A, Ruiz L, Reiss P, Ledergerber B, Katlama C, Lazzarin A, Goebel FD, Phillips AN, Clotet B, Lundgren JD; EuroSIDA study group.

OBJECTIVE:

To determine the rate of virological rebound and factors associated with rebound among patients on highly active antiretroviral therapy (HAART) with previously undetectable levels of viraemia.

DESIGN:

An observational cohort study of 2444 patients from the EuroSIDA study.

METHODS:

Patients were followed from their first viral load under 400 copies/ml to the first of two consecutive viral loads above 400 copies/ml. Incidence rates were calculated using person-years of follow-up (PYFU), Cox proportional hazards models were used to determine factors related to rebound.

RESULTS:

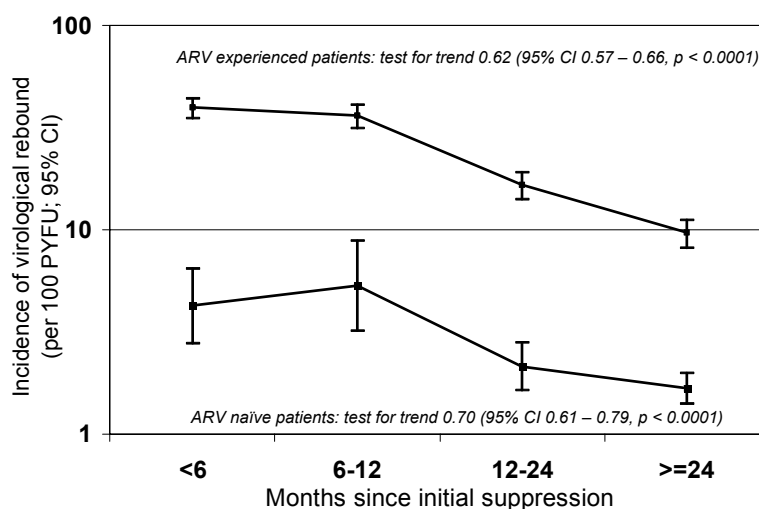
Of 2444 patients, 1031 experienced virological rebound (42.2%). The incidence of rebound decreased over time; from 33.5 in the first

6 months after initial suppression to 8.6 per 100 PYFU at 2 years after initial suppression ($P, 0.0001$). The rate of rebound was lower for treatment-naïve compared with treatment-experienced patients. In multivariate models, patients who changed treatment were more likely to rebound, as were patients with higher viral loads on starting HAART. Treatment-naïve patients were less likely to rebound. Among pretreated patients, those who were started on new nucleosides were less likely to rebound.

CONCLUSION:

The rate of virological rebound decreased over time, suggesting that the greatest risk of treatment failure is in the months after initial suppression. Treatment naïve patients were at a lower risk of rebound, but among drug-experienced patients, those who added new nucleosides had a lower risk of rebound, as were patients with a good immunological response.

Incidence of virological rebound (> 400 copies/ml)



Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study.

Florence E, Lundgren J, Dreezen C, Fisher M, Kirk O, Blaxhult A, Panos G, Katlama C, Vella S, Phillips A; The EuroSIDA Study Group.

OBJECTIVES:

To describe the prevalence and risk factors of poor CD4 count rise despite a good virological response on highly active antiretroviral treatment (HAART).

PATIENTS AND METHODS:

The patients from the EuroSIDA study who started HAART with a baseline CD4 count of <350 cells/microL and where all viral load (pVL) measures remained below 500 HIV-1 RNA copies/mL between 6 and 12 months after the start of HAART were included. The risk factors for poor CD4 count rise were analyzed by multiple regression.

RESULTS:

Seven hundred and eighty patients were included. A low CD4 count response was observed in 225 patients (29%). The risk factors

for this condition were older age, lower CD4 count at baseline, higher increase from the nadir to baseline CD4 count and lower pVL at baseline. Patients taking >=one drug from each of the three antiviral classes were more likely to have a good CD4 response but a minority of the study participants was taking this treatment regimen (3.1%) and the confidence interval was large.

CONCLUSIONS:

A poor immune reconstitution despite a good virological control is frequent after initiation of HAART among patients with a baseline CD4 count of <350 cells/microL. The underlying mechanisms leading to this condition seems mainly driven by the age and the baseline immunological and virological status of the patients.

Univariable and multivariable odd ratios of a low (paradoxical) CD4+ lymphocyte count response

Odds ratio (95% CI); p value				
Univariable			Multivariable	
*Age (per 10 years older)	1.52 (1.29-1.79)	p < 0.0001	1.49 (1.26-1.78)	p < 0.0001
Female	0.91 (0.61-1.35)	p = 0.63	0.87 (0.57-1.34)	p = 0.53
Naïve at start of HAART	0.59 (0.43-0.83)	p = 0.002	1.08 (0.73-1.61)	p = 0.69
Number of NRTI previously experienced (per extra drug)	1.19 (1.07-1.31)	p = 0.001	0.99 (0.87-1.12)	p = 0.84
Time from start of ART (per year)	1.12 (1.05-1.19)	p = 0.0003	1.04 (0.97-1.11)	p = 0.30
CD4 nadir (per 100 cells/mm ³ higher)	0.78 (0.66-0.93)	p < 0.0001	0.52 (0.38-0.72)	p < 0.0001
* CD4 at HAART (per 100 cells/mm ³ higher)	0.99 (0.85-1.16)	p = 0.92	0.77 (0.63-0.93)	p = 0.006
* Increase from CD4 nadir at HAART (per 100 cells/mm ³ higher)	1.91 (1.44-2.52)	p < 0.0001	1.92 (1.39-2.67)	p < 0.0001
Viral load max ever (per 1 log higher)	0.70 (0.60-0.83)	p < 0.0001	0.87 (0.68-1.11)	p = 0.26
* Viral load at HAART (per 1 log higher)	0.68 (0.58-0.80)	p < 0.0001	0.70 (0.60-0.83)	p < 0.0001
Date of start of HAART (per year more recent)	0.89 (0.75-1.06)	p = 0.19	0.92 (0.76-1.10)	p = 0.35
Month of response-defining CD4 count (per month later)	0.97 (0.87-1.07)	p = 0.53	0.98 (0.88-1.10)	p = 0.77
Type of HAART				
PI and NNRTI	0.22 (0.05 - 0.96)	p = 0.04	0.15 (0.03 - 0.70)	p = 0.02
NNRTI no PI	1.22 (0.75 - 0.98)	p = 0.41	1.21 (0.72 - 2.02)	p = 0.48
PI no NNRTI	1.00		1.00	
Previous PCP	0.57 (0.27 - 1.19)	p = 0.13	0.48 (0.22 - 1.06)	p = 0.07
Previous KS	2.35 (1.05 - 5.22)	p = 0.04	2.48 (1.01 - 6.41)	p = 0.05

95% CI: 95% confidence interval. IDU: Intravenous Drug User. NRTI: Nucleoside Reverse Transcriptase Inhibitor. HAART: Highly Active Antiretroviral Treatment. PI: Protease Inhibitor. NNRTI: Not-Nucleoside Reverse Transcriptase Inhibitor.

HCV: Hepatitis C Virus. PCP: Pneumocystis carinii Pneumonia. KS: Kaposi's Sarcoma.

Factors marked with * are included in all multivariable models. Multivariable models also included HIV exposure group, previous AIDS, hepatitis C antibody status and hepatitis B S-antigene status. Choice of inclusion of increase from CD4 nadir rather than CD4 nadir was arbitrary. Multivariable odds ratio for CD4 nadir does not include adjustment for increase in CD4 count from nadir.

Cash invigorates European AIDS study

The world's largest multinational cohort study of HIV-infected patients has received a funding boost from the European Commission (EC) in Brussels. A new four year grant of 1.2 million EUROS (\$1.8 million) from the commission will help EuroSIDA—a study originated in 1979 and headed by Jens D. Lundgren of Hvidovre University Hospital in Denmark—to continue assessing how anti-HIV therapies affect the course of chronic infection based on 8,500 patients in 20 countries. Particular focus will be placed on the treatment of HIV in Eastern Europe, where AIDS is increasing through intravenous drug use. Although a number of Eastern European countries are already involved in the project, Lundgren says that additional countries, such as the Baltic States and hopefully the Ukraine, will be added over the next four years. Eventually the number of patients covered by the study is expected to increase to 12,000. "This new money is valuable because it will allow us to initiate an extensive analysis of the plasma bank that we have built up from volunteers participating in the study," says Lundgren. He adds, "Such an analysis will provide us with important information about the role of

resistance to antiretroviral therapies." In addition to funding from the EC's Biomed programs, EuroSIDA receives a similar level of support from the pharmaceutical companies GlaxoSmithKline, Roche and Boehringer Ingelheim. Another goal is to assess the patterns of HIV-related diseases. The study has already shown that the pattern in patients receiving highly active antiretroviral therapy (HAART) is changing, with relatively more cases of non-Hodgkin lymphoma and an increase in the number of patients who are dying without having experienced a so-called 'AIDS-defining' disease. One possible explanation is the late-onset side effects from HAART, such as increased risk of cardiovascular disease. "The possible long-term side effects are something that the new money will allow us to study more closely," says Lundgren. EuroSIDA's data on the effectiveness of HAART have already had implications for treatment guidelines. For example, the information that HAART induced reconstitution of the immune system—as indicated by a rise in blood C4⁺ lymphocyte levels—enabled chemoprophylaxis of opportunistic infections to be safely discontinued and have contributed to the recent revision of treatment guidelines in the US (<http://hivatis.org/trtgdlns.html>).

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