CROI 2005, Poster # 601a

Risk of AIDS/death According to Viral Load & CD4 Count Levels, Related to Specific Antiretroviral Drugs in Patients on cART

Christian Holkmann-Olsen*[1], Jose Gatell[2], Bruno Ledergerber[3], Christine Katlama[4], Nina Friis-Møller[1], Jonathan Weber[5], Andrzej Horban[6], Schlomo Staszewski[7], Jens Lundgren[1], Andrew Phillips[8], on behalf of the EuroSIDA study group

[1]Copenhagen HIV Programme, Hvidovre University Hospital, Denmark; [2]Hosp Clínic de Barcelona, Barcelona, Spain; [3]Univ Hosp, Zurich, Switzerland; [4]Hosp Pitie-Salpetriere, Paris, France; [5]St Mary's Hosp, London, UK; [6]Wojewodzki Szpital Zakazny, Warsaw, Poland; [7]JW Goethe Univ Hosp, Frankfurt, Germany; and [8]Royal Free and Univ Coll Med Sch, London, UK

Christian Holkmann Olsen
Copenhagen HIV Programme
Hvidovre University Hospital
Kettegaard Allé 30
DK-2650 Hvidovre
Phone no: +45 36 32 30 15
Fax no: +45 36 47 33 40
E-mail: cho@cphiv.dk

BACKGROUND

In the years prior to 1997, drug approval for antiretroviral therapy (ART) relied on trials showing a reduction in AIDS events or death; i.e. the clinical effect markers.

Several studies, mainly on mono and dual nucleoside therapy regimens, indicated that the effect of a drug regimen on the immunologic/virologic, surrogate markers, i.e. CD_4 count/ HIV-RNA levels, strongly correlated to the risk of clinical progression to AIDS or death.

As a result, the FDA decided in 1997 that it was sufficient for clinical trials to show that a new drug resulted in sustained suppression of plasma HIV-RNA levels and to rises in peripheral blood CD_4 lymphocyte count. [1]

Since 1997, the HIV community, industry and regulatory authorities have relied completely on the general assumption that the relationship between the HIV-RNA & CD_4 count levels and the risk of clinical disease continues to hold true for newer antiretroviral drugs (released after 1997), and that there is no additional effect of such drugs leading to a higher or lower AIDS/death risk for given HIV-RNA/CD_4 cell count levels compared to others.

Table 1

Time on cART & specific third drugs and CD_4 count change since drug initiation

Drug	Total number of patiens Taking drug	Total number Person-years on drug	Months from start of CART to initiation of drug (i)	Months from initiation of drug (ii)	Median CD_4 count at initiation of drug (IQR) (iii)	Median change in CD_4 count since initation of drug (IQR) (iv)
Indinavir (IDV)	3338	6729.1	0	16	167 (67, 296)	+98 (0 +240)
Ritonavir (RTV)	1231	1705.4	0	14	148 (56,264)	+86 (0, +242)
Saquinavir (SQV)	1257	1441.9	0	8	160 (68,270)	+0 (0, +102)
Nelfinavir (NFV)	1705	3194.5	12	15	265 (137,401)	+70 (0, +196)
IDV or SQV / r	1649	2637.8	12	18	218 (100,382)	+100 (0, +240)
Lopinavir (LPV)/ r	675	773.9	51	9	251 (132,420)	+46 (0, +149)
Abacavir (ABC) #	765	1217.8	34	14	377 (222, 578)	+35 (-12,+149)
Nevirapine (NVP)	1423	2629.6	18	16	325 (200,469)	+62 (0, +179)
Efavirenz (EFV)	1465	2436.5	29	13	342 (195,524)	+50 (0, +166)

'Drug x/r' means 'ritonavir boosted drug x'. # means counted only when third drug.
For (iii) median (IQR) is over all subjects who took the drug
For (iv) median (IQR) is over all person- months of use of the drug

HYPOTHESIS

The risk of clinical disease progression to AIDS or death according to specific CD_4 counts or HIV-RNA levels is similar for newer ART drugs.

OBJECTIVE

To determine and compare rate ratios of AIDS and death at given, latest HIV-RNA and CD_4 count levels according to various nucleoside pairs and specific third drugs.

METHODS

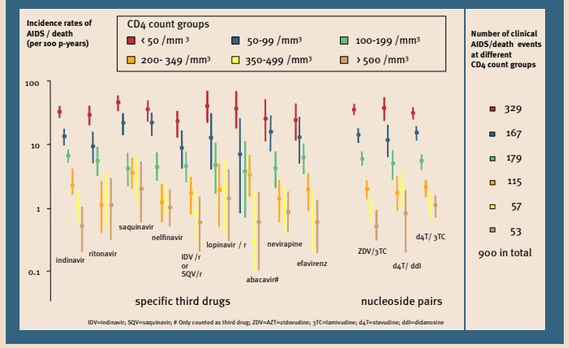
The EuroSIDA study is a prospective European cohort study initiated in 1994 of 9,802 HIV-1 infected patients followed in 72 clinics from 26 European countries. Patients included are considered a representative sample of the European HIV population.

Data are collected every 6 months on: clinical events (incl. AIDS or death); laboratory values (incl. CD_4 count and HIV-RNA measures), and drugs (incl. ART regimens) used.

1. Antiviral Drugs Advisory Committee. Meeting Start Date: 14th July 1997.
Transcripts made 140797 and 150797. www.fda.gov

Figure 1

Incidence rates of AIDS/death (95% CI) according to latest CD_4 count and specific drugs



Patients contributed to the analysis during periods of time during which they were on a combination antiretroviral therapy (cART) regimen containing at least three drugs, i.e. a non-abacavir nucleoside pair and one of the specific third drugs listed in table 1.

The events of interest were the development of any clinical AIDS defining illness (i.e. CDC stage C) or death.

Analysis & Statistical Methods

Person years at risk, numbers of AIDS and death events and rates of these events were calculated for specific categories of the latest CD_4 count and HIV-RNA, according to which drugs were currently used in the regimen. Person time was attributed to the current drug regimen only, not to any previous drug regimens.

Poisson Regression models in SAS were used to assess rate ratios of clinical progression to AIDS or death comparing specific third drugs and nucleoside pairs after adjusting for latest CD_4 count, latest HIV-RNA measure, and other factors listed in figure 3.

RESULTS

A total of 6,814 patients contributed observation time to the analysis, representing 94% of all the patients that had started cART; 6% were taking regimens not focused on. There was a total of 22,766.6 person years of follow up. The median date of starting cART was 1997, and 4,773 patients (70%) had used nucleoside mono- or dual therapy before starting cART.

A total of 900 events of AIDS or death were observed, of which 125 were deaths.

Table 1

As seen in table 1, showing the details relating to use of specific third drugs, the protease inhibitors, introduced in 1995/1996 – saquinavir, indinavir and ritonavir – were generally used as part of the initial cART regimen and when CD_4 counts were relatively low (around 150-160 cells/µL). In contrast, ritonavir-boosted indinavir/saquinavir or lopinavir, nelfinavir, nevirapine, efavirenz and abacavir, tended to be initiated some time after cART was started and at higher CD_4 counts.

The median degree of CD_4 count increase also varied with each drug, with lower increases for the drugs such as efavirenz, nevirapine and abacavir which were introduced when the CD_4 count was already relatively high.

Figure 2

Incidence rates of AIDS/death (95% CI) according to latest HIV-RNA levels and specific drugs

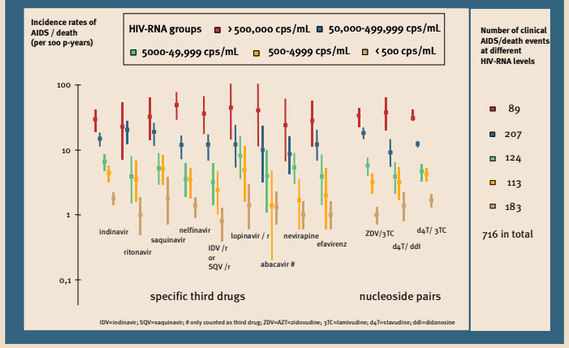


Figure 1 & 2

The crude incidence rates of AIDS/death for given, latest CD_4 count strata (figure 1) and latest HIV-RNA levels (figure 2) are shown according to:

- Specific third drugs (on the left side of the figures 1 and 2) and
- Nucleoside pairs (on the right side of figure 1 and 2).

Respectively, 900 and 716 events are in included in figure 1 and figure 2, due to availability of a current CD_4 count or HIV-RNA measure at the time of the event.

Please note the log 10 scale showing AIDS/death events per 100 person years of follow-up.

As seen in figure 1, the different drugs appear to have similar crude incidence rates of AIDS or death for a given CD_4 count strata, with the highest risk in groups of patients having lower CD_4 counts, regardless of regimen taken.

Likewise for figure 2, the different drugs appear to have similar crude incidence rates of AIDS or death for a given HIV-RNA level, with the highest risk in groups of patients having higher HIV-RNA levels, regardless of regimen taken.

Please note that the figures cannot be used to compare efficacy of drug regimens.

Figure 3

The adjusted rate ratios of AIDS/death (95%CI) comparing different nucleoside pairs and specific third drugs are shown in figure 3; the exact numbers are given in the multivariable analysis shown in the table of the corresponding abstract #K-177.

The reference group for the nucleoside pairs is the group of other nucleoside pairs, and the reference for specific third drugs is indinavir; for which clinical endpoint trials are available.

As seen, rate ratios for the different nucleoside pairs and specific third drugs are all close to 1 and the relatively narrow 95% confidence intervals are all overlapping 1, meaning that the risk of AIDS/death for given specific CD_4 count strata and HIV-RNA levels is fairly similar to the reference regimen, regardless of which nucleoside pair or specific third drug is being used.

Sensitivity analyses

The results of the main analysis were consistent with the results of the different sensitivity analyses performed, e.g. when restricting analyses to:

- person time in which the third drug had been used for at least 6 months
- person months when CD_4 and HIV-RNA were known within at most the past 3 months
- person time with a > 50 /mm^3 increase attained on the third drug
- person time when the specific third drug had been started when HIV-RNA was <500 cps/mL
- persons with CD_4 counts < 200 /mm^3 at cART initiation and a latest CD_4 count > 350 /mm^3

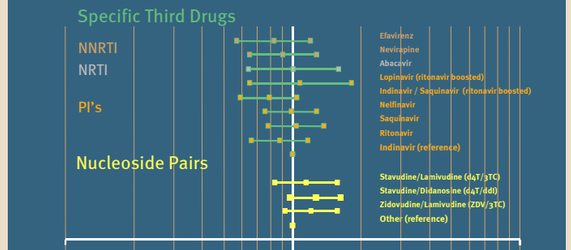
CONCLUSION

The results provide reassurance that HIV-RNA and CD_4 values in individual patients receiving newer drugs have the same meaning in terms of AIDS/death risk, regardless of the specific antiretroviral regimen.

Our results support the assumption that these markers have the same prognostic significance, regardless of the antiretroviral drugs being used.

Figure 3

Rate ratios of AIDS/death (95% CI) comparing different nucleoside pairs and specific third drugs



Multivariate analysis adjusted for: latest CD_4 count, HIV-RNA, age, exposure group, prior AIDS, calendar year, time from starting cART, and time on current combination

The multicentre study group on EuroSIDA (national coordinators in parenthesis).
Argentina (M Losso), A Duran, Hospital JM Ramos Mejia, Buenos Aires. **Austria** (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna. **Belarus** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk. **Belgium** (N Clumeck)/ S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp. **Czech Republic** (L Machala) , H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark** (J Nielsen) J Lundgren, T Benfield, O Kirk, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense. **Estonia** (K Zilmer) West-Tallinn Central Hospital, Tallinn. **France** (C Katlama) Hôpital de la Pitié-Salpetrière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; T Saint-Marc, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, Unité INSERM, Bordeaux. **Germany** M Dietrich, C Mansgold, Bernhard-Nocht-Institut for Tropical Medicine, Hamburg; J van Lunzen, H-J Stellbrink, Eppendorf Medizinische Kernklinik, Hamburg; S Staszewski, M Bickel, JW Goethe University Hospital, Frankfurt; F-D Goebel, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne; J Rockstroh, Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover. **Greece** (J Kosmidis) P Gargalianos, H Sambatakou, J Perdios, Athens General Hospital, Athens;G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital, Athens. **Hungary** (D Banhegyi) Szent Laszlo Hospital, Budapest. **Ireland** (F Mulcahy) St. James's Hospital, Dublin. **Israel** (I Yust) D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; Z Sthoeger, Kaplan Hospital, Rehovot; S Maayan, Hadassah University Hospital, Jerusalem. **Italy** (S Vella, A Chiesi) Istituto Superiore di Sanita, Rome; C Arici, Ospedale Riuniti, Bergamo; R Pristerà, Ospedale Generale Regionale, Bolzano; F Mazzetta, A Gabbuti, Ospedale S. Maria Annunziata, Florence; R Esposito, A Bedini, Università di Modena, Modena; A Chirianni, , E Montesarchio, Presidio Ospedaliero A.D. Cotugno, Naples; V Vullo, P Santopadre, Università di Roma La Sapienza, Rome; P Narciso, A Antinori, P Franci, M Zaccarelli, Ospedale Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; A D'Arminio Monforte, Osp. L. Sacco, Milan. **Latvia** (L Viksna) Infectology Centre of Latvia, Riga. **Lithuania** (S Chaplinskas) Lithuanian AIDS Centre, Vilnius. **Luxembourg** (R Hemmer), T Staub, Centre Hospitalier, Luxembourg. **Netherlands** (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway** (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo. **Poland** (B Knysz) I Gasiorowski, Medical University, Wroclaw; A Horban, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, A Wiercinska-Drapalo, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical University, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk. **Portugal** (F Antunes) F Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Matez, Hospital Curry Cabral, Lisbon. **Romania** (D Duiculescu) Spitalul de Boli Infectioase si Tropicale 'Dr. Victor Babes, Bucarest; A Streinu-Cercel, Institute of Infectious Diseases, Bucarest. **Russia** E Vinogradova, St Petersburg AIDS Centre; A Rakhmanova, Medical Academy Botkin Hospital, St Petersburg. **Serbia & Montenegro** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia** (M Mokráš) D Staneková, Dérer Hospital, Bratislava. **Spain** (J González-Lahoz) M Sánchez-Conde, T García-Benayas, L Martín-Carbonero, V Soriano, Hospital Carlos III, Madrid; B Clotet, A Jou, J Conejero, C Tural, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clínic i Provincial, Barcelona. **Sweden** (A Blaxhult) Karolinska University Hospital, Solna; A Karlsson, Karolinska University Hospital, Stockholm; P Pehrson, Karolinska University Hospital, Huddinge. **Switzerland** (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, A Telenti, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, V Sosvala-Dunand, Hospital Cantonal Universitaire de Geneve, Geneva; H Furrer, Inselspital Bern, Bern. **Ukraine** (N Chentsova) Kyiv Centre for AIDS, Kyiv. **United Kingdom** (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; R Brettle, Western General Hospital, Edinburgh.
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), J Gjørup, O Kirk, N Friis-Moeller, A Mocroft, A Cozzi-Lepri, W Bannister, D Mollerup, D Podlevskareva, C Holkmann Olsen, J Kjær.

www.cphiv.dk

CHIP COPENHAGEN HIV PROGRAMME