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Death rates in HIV-positive antiretroviral-naive patients with CD4 count greater than 350 cells per microL in Europe and North America: a pooled cohort observational study

Study Group on Death Rates at High CD4 Count in Antiretroviral Naïve Patients

Abstract

Background—It is unclear whether antiretroviral (ART) naive HIV-positive individuals with high CD4 counts have a raised mortality risk compared with the general population, but this is relevant for considering earlier initiation of antiretroviral therapy.

Methods—Pooling data from 23 European and North American cohorts, we calculated country-, age-, sex-, and year-standardised mortality ratios (SMRs), stratifying by risk group. Included patients had at least one pre-ART CD4 count above 350 cells/mm^3. The association between CD4 count and death rate was evaluated using Poisson regression methods.

Findings—Of 40,830 patients contributing 80,682 person-years of follow up with CD4 count above 350 cells/mm^3, 419 (1.0%) died. The SMRs (95% confidence interval) were 1.30 (1.06-1.58) in homosexual men, and 2.94 (2.28-3.73) and 9.37 (8.13-10.75) in the heterosexual and IDU risk groups respectively. CD4 count above 500 cells/mm^3 was associated with a lower death rate than 350-499 cells/mm^3: adjusted rate ratios (95% confidence intervals) for 500-699 cells/mm^3 and above 700 cells/mm^3 were 0.77 (0.61-0.95) and 0.66 (0.52-0.85) respectively.

Interpretation—In HIV-infected ART-naive patients with high CD4 counts, death rates were raised compared with the general population. In homosexual men this was modest, suggesting that a proportion of the increased risk in other groups is due to confounding by other factors. Even in this high CD4 count range, lower CD4 count was associated with raised mortality.

Introduction

Lower CD4 count is associated with an increased risk of death in HIV infection (1), and this trend has been observed even in the high CD4 count range (2;3). There is a growing understanding that the risk of non-AIDS death is associated with CD4 count, although not as strongly as for AIDS deaths (4). The optimal CD4 count at which to initiate antiretroviral therapy (ART) in HIV-positive individuals is, at present, unclear. Most current guidelines state that, in patients without a previous AIDS event, ART should be initiated when the CD4 count falls to 350 cells/mm^3 (5;6). Evidence as to whether initiating ART at higher CD4 counts may be beneficial is currently restricted to observational studies (7;8), and to a sub-analysis of the SMART trial (9). The observational studies have attempted to mimic the comparison made in a randomized trial, comparing outcomes from immediate versus deferred ART initiation, and have generally concluded that earlier initiation is likely to lead

Correspondence: Rebecca Lodwick, HIV Epidemiology & Biostatistics Group, Research Department of Infection & Population Health, UCL Medical School, Royal Free Campus, Rowland Hill Street, London NW3 2PF, UK, r.lodwick@ucl.ac.uk.

Conflict of interest statement

No member of the Analysis and Writing Committee has any financial or personal relationships with people or organizations that could inappropriately influence this work, although most members of the group have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements or consultancy fees.

to a lower risk of death, although there are inconsistencies in results (7;8). We sought to use observational data to address a more fundamental question concerning the potential for benefit of early use of ART: do ART-naïve patients with CD4 count above 350 cells/mm^3 experience a higher risk of death than the general population? It appears that there would need to be such a raised risk for there to be a potential benefit of early ART initiation.

We compared the mortality rates observed in a large multinational collaborative cohort study with those expected in the general population, standardized by age, sex, country, and year. Furthermore, we considered whether death rates in such HIV-infected patients differ according to CD4 count.

Methods

Data

Twenty-three cohorts and cohort collaborations contributed data for this analysis: 18 cohorts were based in Europe and 5 in North America. Data were requested in a standardised format (10), and duplicate records were removed where patients appeared in more than one cohort. Data requested from participating cohorts included demographic information, CD4 counts, viral load measurements, hepatitis C co-infection status, smoking status, date of death and whether AIDS-related or not. This analysis was restricted to patients aged 20 to 59 who had at least one CD4 count above 350 cells/mm^3 while ART naïve. All pre-ART CD4 counts above 350 cells/mm^3 from January 1990 to December 2004 were included: the exclusion of CD4 counts after 2005 was in order to mitigate the effect of any delay in reporting of deaths. All CD4 counts measured during prospective follow-up, i.e., after enrolment to a cohort while ART naive, were included.

Statistical methods

In each patient, included follow-up was counted from the date of each eligible CD4 count until the earliest of: next CD4 count; death; start of ART; or elapse of one year (Figure 1). Standardised mortality ratios were calculated by comparing observed death rates with those expected in the general population, standardised by age, sex, country, and year of CD4 count. The data used for calculation of the SMRs were restricted to those countries on which general population mortality data were available from the Human Mortality Database (11), and for which there was at least 2000 person-years of follow-up.

Poisson regression methods were used to investigate the relationship between death rate and CD4 count. In addition to CD4 count, factors included in the multivariable model were sex, risk group, age, current calendar year, and most recent viral load measurement (no earlier than six months before the date of the included CD4 count). Additionally, hepatitis C co-infection and smoking status were considered as factors in models restricted to data from cohorts able to provide such data.

Three sensitivity analyses were performed. In the first of these, follow-up was censored at six months after each CD4 count instead of at one year: this was to test the assumption implicit in the main analysis that the most recent CD4 count was valid for up to one year. In the second, the main analysis was repeated but only follow-up after CD4 counts above 500 cells/mm^3 was included: this was to determine whether there was a raised risk of death in this higher CD4 count range. In the third sensitivity analysis, to assess the impact of any possible underascertainment of deaths, the SMRs were calculated using data from only those cohorts which are known to be linked to national death registers.

All p-values are two sided. Analyses were performed using SAS version 9.1., Cary, North Carolina, United States.

Role of the funding source

The study sponsors had no role in the study design, analysis, interpretation of data, writing of the report or in the decision to submit the paper for publication. Final responsibility for the decision to submit for publication was made by the Analysis and Writing Committee.

Results

Included patients and follow-up

A total of 40,830 patients were included in the analysis, contributing 201,620 CD4 counts and 80,682 person-years of follow-up, with a median of 3 CD4 counts per patient (IQR: 1-6). The number of patients for whom follow-up was censored due to ART initiation was 11713 (28.7%; 5.8% of CD4 episodes). The distribution of follow-up according to patient characteristics is described in Table 1. Most follow-up was from male patients (59,774 person-years, 74.1%), approximately half of follow-up was from homosexual men (39,732 person-years, 49.2%), and approximately half of follow-up was from patients aged between 30 and 39 (38,112 person-years, 47.2%). The amount of follow-up with CD4 count above 500 cells/mm^3 was 50,357 person-years (62.4%). The most recent viral load was available for 48,487 person-years of follow up (60.1%). Around one third of follow-up was from patients within cohorts linked to national death registers (27,206 person-years, 33.7%). Data on hepatitis C co-infection status were available from 16 of the 23 participating cohorts (73,322 person-years; 90.9% of total follow-up) and on smoking from 9 cohorts (30,332 person-years; 37.6% of total follow-up).

Deaths

A total of 419 (1.0%) patients died during follow-up, giving an overall death rate of 5.2 per 1000 person-years (95% CI: 4.7-5.7). Of these, 61 (14.6%) deaths were categorised as AIDS-related, 188 (44.9%) were categorised as non-AIDS-related, and the cause was unknown for 170 (40.6%) of deaths.

Comparison of death rates with those expected from the general population

The SMR analysis for pre-ART CD4 counts above 350 cells/mm^3 included 38,997 patients (95.5% of the total: the SMR analysis was restricted to those countries on which data were available from the Human Mortality Database (11), and for which there was at least 2000 person-years of follow-up), with 77,936 person-years of follow-up (96.6% of the total) and 401 deaths (95.7% of the total). The observed death rates and age-, sex-, country-, and year-standardised SMRs for each risk group are displayed in Table 2. For homosexual men, the SMR was 1.30 (95% CI: 1.06-1.58). The SMRs in the other risk groups were greater in value, at 2.94 (95% CI: 2.28-3.73), 9.37 (95% CI: 8.13-10.75) and 4.57 (95% CI: 3.09-6.53) for the heterosexual, IDU and other/unknown risk groups respectively. When the analysis was restricted to CD4 counts above 500 cells/mm^3, the resulting SMRs were slightly lower at 2.83 (95% CI: 2.03-3.87), 7.97 (95% CI: 6.55-9.60) and 4.47 (95% CI: 2.61-7.16) for the heterosexual, IDU and other/unknown risk groups. For homosexual men, however, the SMR was 1.03 (95% CI: 0.76-1.37). Again considering CD4 counts above 350 cells/mm^3 but with follow-up censored at 6 months after each CD4 count instead of at 1 year, the SMRs were slightly lower than in the main analysis at 1.14 (95% CI: 0.90-1.43) for homosexual men, 2.74 (95% CI: 2.05-3.60) for the heterosexual risk group, 9.35 (95% CI: 7.93-10.94) for IDUs and 3.30 (95% CI: 1.96-5.22) for the other/unknown risk group. Restricting the analysis to follow-up from patients within cohorts linked to national death registers resulted in slightly higher SMRs than in the main analysis, at 1.52 (95% CI: 1.10-2.04) for homosexual men, 3.29 (95% CI: 2.09-4.94) for the heterosexual risk group, 15.85 (95% CI: 11.27-21.67) for IDUs and 6.99 (95% CI: 3.99-11.35) for the other/unknown risk group.

Association between CD4 count and risk of death

In a Poisson regression model fitted to the full dataset, a CD4 count above 500 cells/mm^3 was found to be associated with a lower risk of death than CD4 count between 350 and 499 cells/mm^3 (Figure 2). The unadjusted risk ratios were 0.75 (95% CI: 0.60-0.93) and 0.67 (95% CI: 0.52-0.86) for CD4 counts 500-699 cells/mm^3 and 700- cells/mm^3 respectively, compared to 350-499 cells/mm^3 (Table 3). Factors found in univariable analyses to be significant predictors of death were risk group and age. Sex and calendar year of CD4 count were not associated with the rate of death in univariable analyses, but were significant factors in the multivariable model. Viral load, which was only available for 60.1% of total follow-up, was not found to be associated with death rate. Following adjustment for the other factors in the model, the rate ratios for the CD4 count remained largely unchanged at 0.77 (95% CI: 0.61-0.95) and 0.66 (95% CI: 0.52-0.85) for CD4 counts 500-699 cells/mm^3 and 700-cells/mm^3 respectively, compared to 350-499 cells/mm^3.

In the two models fitted to subsets of the data to include hepatitis C and smoking covariates respectively, the associations between CD4 count and death rate were consistent with that in the main model.

In a sensitivity analysis where follow-up was censored at 6 months after each CD4 count instead of at 1 year, the association between CD4 count and the risk of death was similar. Compared to 350-499 cells/mm^3, the adjusted rate ratio for CD4 count 500-699 cells/mm^3 was 0.71 (95% CI: 0.55-0.92), and for CD4 count 700-cells/mm^3 was 0.67 (95% CI: 0.50-0.89). When the analysis was restricted to CD4 counts above 500 cells/mm^3, there was no significant difference in the risk of death between the CD4 count categories (adjusted risk ratio for CD4 count 700-cells/mm^3 compared to 500-699 cells/mm^3: 0.84, 95% CI: 0.65-1.10, p=0.22).

Discussion

In this large collaborative analysis, using data from industrialised countries, we found that death rates in ART-naïve patients with CD4 count above 350 cells/mm^3 tend to be raised compared to the general population. However, the extent of the increase in risk varied markedly with risk group, being substantial in IDU and heterosexuals but relatively small in homosexual men. This suggests that much of the raised risk in the former two risk groups is likely to be due to confounding by socio-economic and lifestyle factors (12;13), rather than due to effects of HIV infection itself. Consistent with this, an increased risk of death has been observed in the siblings of people with HIV compared with the siblings of a control population without HIV (14). We also observed that a higher CD4 count was associated with a lower risk of death, even in this high CD4 count range, a trend that has previously been observed in patients on ART (2;3). Taken together, it would seem that there is a risk of death due to HIV in antiretroviral-naïve people with high CD4 count, but this appears to be of modest magnitude. This is despite the very low risk of AIDS diseases at this CD4 count (15,16), and appears to be consistent with the hypothesis that in people with high CD4 count, HIV causes some appreciable increased mortality risk (2-4;17;18).

We observed a raised risk of death in men compared with women, consistent with the general population. When considering the association between CD4 count and risk of death, in multivariable models fitted to subsets of our data, we were able to adjust for two potential confounding factors (hepatitis C co-infection and smoking history): we found that the relationship between death rate and CD4 count remained. Interestingly, we did not observe an association between plasma viral load level and risk of death in the subset of patients with this information available. This appears inconsistent with data suggesting an

association between viral suppression and risk of non-AIDS diseases (4), although here we are comparing people with various levels of unsuppressed viral load.

Although, to our knowledge, there are no substantive studies restricted to ART naïve people, several studies have compared the death rate in HIV-positive individuals, including those on ART, with the general population, matched for factors such as age and sex (19-22). Although all such studies have demonstrated an excess risk of death in people with HIV, it has been observed that there are some successfully treated subgroups of patients for whom the death rate has been found to approach that of the general population. A study combining data from two French cohorts found that the death rate in patients with a CD4 count above 500 cells/mm^3 reached that of the general population by the sixth year after starting ART (19), while a study on a collaboration of HIV seroconverter cohorts observed that, in the most recent period of follow-up (where 73% of person-time was on ART), there was no excess mortality during the first five years after seroconversion in patients infected sexually when compared to the general population (22).

Patients included in this analysis had been diagnosed earlier than most HIV-positive people in these settings. Of patients presenting with HIV from 1996 to 2006 at selected clinics in the UK, 39% had an initial CD4 count above 350 cells/mm^3 (23). Patients who are diagnosed earlier may differ from patients diagnosed later with respect to their attitudes towards health and access to healthcare services.

Although several included cohorts are linked to national death registers, a further limitation is that possible under-ascertainment of deaths may have resulted in death rates being underestimated: this is supported by the slightly higher SMRs seen in the sensitivity analysis restricted to data from cohorts linked to national death registers. It may be the case that the decrease in risk of death over calendar time observed in the multivariable model (Table 3) is due, at least in part, to a delay in reporting of deaths.

Patients included in this study were under care at clinics linked to cohort studies and collaborations in Europe and North America. Results from this study may not be generalisable to all settings, either in clinics in these regions without research links, or in resource limited settings.

In conclusion, these data suggest that people with HIV who have not taken ART and have CD4 count above 350 cells/mm^3 have a raised risk of death compared with the general uninfected population, although this increased risk seems to be of modest magnitude. As ART may well reduce the risk of death in such patients, these findings support the need for ongoing studies (such as the START trial (24) and further exploration of existing observational databases) of the risks and benefits of initiation of ART at CD4 counts higher than 350 cells/mm^3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study Group on Death Rates at High CD4 Count in Antiretroviral Naïve Patients: Analysis and Writing Committee: Rebecca K. Lodwick, Caroline A. Sabin (UK CHIC), Kholoud Porter (CASCADE), Bruno Ledergerber (Swiss HIV Cohort Study), Ard van Sighem (Athena), Alessandro Cozzi-Lepri (ICONA), Pavel Khaykin (Frankfurt HIV Cohort), Amanda Mocroft (EuroSIDA), Lisa Jacobson (MACS), Stephane De Wit (Brussels St Pierre), Niels Obel (Danish HIV Cohort Study), Antonella Castagna (IDD-HSR), Jan-Christian Wasmuth (Cologne-Bonn), John Gill (Southern Alberta Cohort), Marina B. Klein (Montreal Chest Immunodeficiency Cohort), Stephen Gange (WIHS), Melchor Riera (PISCIS), Cristina Mussini (Modena), Félix Gutiérrez (CoRIS and CoRIS-MD), Giota Touloumi

(AMACS), Patrizia Carrieri (MANIF 2000), Jodie L. Guest (HAVACS), Norbert H. Brockmeyer (KOMPNET), Andrew N. Phillips.

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AMACS

Steering Committee: Antoniadou A., Gargalianos-Kakolyris P., Katsarou O., Kordossis T., Lazanas M., Panos G., Paparizos V., Paraskevis D., Petrikkos G., Sambatakou H., Skoutelis A., Touloumi G. (Chair). Coordinating Center: Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, Greece (Touloumi G., Paraskevis D., Pantazis N., Bakoyannis G, Gioukari V.)

ATHENA

The ATHENA database is supported by a grant from the Dutch Health Minister and was set up and is maintained by the Stichting HIV Monitoring. Director: F. de Wolf; data analysis: D.O. Bezemer, L.A.J. Gras, A.M. Kesselring, A.I. van Sighem, C. Smit, S. Zhang, S. Zaheri; site-coordinating physicians: J.M. Prins, G. Schreij, B. Bravenboer, M.E. van der Ende, R.H. Kauffmann, R.W. ten Kate, F.P. Kroon, W. Bronsveld, R. Vriesendorp, D. van Houte, C.H.H. ten Napel, K. Brinkman, A. van Eeden, J.W. Mulder, J.R. Juttmann, J. Veenstra, P.P. Koopmans, H.G. Sprenger, I.M. Hoepelman, S.A. Danner, C. Richter, A.A. Tanis.

Brussels St Pierre

The members of the Brussels Saint Pierre Cohort are N. Clumeck (Head of Unit), S. De Wit (Cohort Coordinator), M. Delforge (Biostatistician), C. Necsoi (Data Manager), R. Demeester, A-F. Gennotte, M. Gerard, M-P Guillaume, P. Hermans, K. Kabeya, D. Konopnicki, C. Martin, A. Libois, M-C Payen, P. Semaille, Y. Van Laethem.

CASCADE

Steering Committee: Julia Del Amo (Chair), Laurence Meyer (Vice Chair), Heiner C. Bucher, Geneviève Chêne, Deenan Pillay, Maria Prins, Magda Rosinska, Caroline Sabin, Giota Touloumi. Co-ordinating Centre: Kholoud Porter (Project Leader), Sara Lodi, Kate Coughlin, Sarah Walker, Abdel Babiker. Clinical Advisory Board: Heiner Bucher, Andrea de Luca, Martin Fisher, Roberto Muga.

Cologne-Bonn

Gerd Fätkenheuer, Jürgen Rockstroh, Jan-Christian Wasmuth. Data management: Janne Vehreschild and Caroline Hertenstein.

CoRIS and CoRIS-MD

Red de Investigación en SIDA-ISCIII-RETIC-RD06/0006. Steering commitee: Juan Berenguer, Julia del Amo, Federico García, Félix Gutiérrez, Pablo Labarga, Santiago Moreno y María Ángeles Muñoz. Field work, data management and statistical analyses: Ana M. Caro-Murillo, Paz Sobrino, Santiago Pérez-Cachafeiro, Inmaculada Jarrín, Belén Alejos. BioBank: María Ángeles Muñoz, Isabel García. Hospitals: Hospital Universitario de Canarias (Santa Cruz de Tenerife), Hospital Carlos III (Madrid), Hospital Doce de Octubre (Madrid), Hospital Donostia (San Sebastián), Hospital Universitario de Elche (Elche), Hospital Gregorio Marañón (Madrid), Hospital Universitari Joan XXIII (Tarragona), Hospital de la Princesa (Madrid), Hospital San Pedro (Logroño), Hospital de Navarra (Pamplona), Hospital Ramón y Cajal (Madrid), Hospital San Cecilio (Granada).

Danish HIV Cohort Study

Steering commitee and members of The Danish HIV Cohort Study are N. Obel, J Gerstoft, G. Kronborg, B. Røge, C.S.Larsen, G. Pedersen, A.L. Laursen, L. Nielsen, J. Jensen.

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Frankfurt HIV Cohort

Babacan E. (data management), Bickel M., Bodtländer A., Brodt H-R., Carlebach A., Gute P., Haberl A., Helm E., Khaykin P., Klauke S., Knecht G., Lennemann T., Locher L., Lutz T., Mösch M., Müller A., Nisius G., Staszewski S., Stephan C., Stürmer M. (Virology), von Hentig N., Wolf T.

HAVACS

The members of the HIV Atlanta VA Cohort Study (HAVACS) are: Guest JL, Rimland D, Moanna A, Moorfield M, Dorsey M, Desilva KE, Schlueter Wirtz S, Mindley R, Dozier R, Robinson Y, Brown P.

ICONA

Governing body: M Moroni (Chair), G Carosi, R Cauda, F Chiodo, A d'Arminio Monforte, G Di Perri, M Galli, R Iardino, G Ippolito, A Lazzarin, R Panebianco, G Pastore, CF Perno. Steering committee: A Ammassari, A Antinori, C Arici, C Balotta, P Bonfanti, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, A d'Arminio Monforte, A De Luca, C Gervasoni, E Girardi, S Lo Caputo, R Murri, C Mussini, M Puoti, C Torti. Funding: The Icona Foundation Study is supported by unrestricted educational grants from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Pfizer and Janssen-Cilag.

IDD-HSR

Representative of the cohort: Antonella Castagna. Data Managers: Stefania Salpietro, Mario Marangione. Statistician: Laura Galli. Scientific commmittee: Adriano Lazzarin (representative of the institution) Nicola Gianotti, Francesca Cossarini, Vincenzo Spagnuolo.

KOMPNET

Steering Committee: Gabriele Arendt(Speaker of the Clinical Science Board), Norbert H. Brockmeyer (Chair KompNet), Stefan Esser (Representative of the Sites), Annette Haberl(Speaker of the Gender & Pediatric Studies Board), Hans Jäger (Representative of the Sites), Siegfried Schwarze (Representative of the Patients Council), Matthias Stoll (Speaker of the Social Sciences & Public Health Board), Hans Wolf (Speaker of the Basic & Translational Research Board), Klaus Jansen (Cohort Manager), Claudia Michalik (Data Manager), Adriane Skaletz-Rorowski (Scientific Coordinator) Children Cohort: Christoph Königs (Speaker); Pregnant Women Cohort: Andrea Gingelmaier (Speaker) The KompNet is supproted by the Federal Ministry of Education and Research and the Ruhr-Universität Bochum.

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Website located at http://www.statepi.jhsph.edu/macs/macs.html

MANIF 2000

Cohort Management Team: C. Boirot, AD. Bouhnik, MP. Carrieri, JP. Cassuto, M. Chesney, J. Cohen, P. Dellamonica, P. Dujardin, H. Gallais, JA. Gastaut, P. Kurkdji, G. Lepeu, D. Mechali, JP. Moatti, J. Moreau, M. Nègre, Y. Obadia, I. Poizot-Martin, C. Pradier, M. Préau, D. Rey, P. Roux, C. Rouzioux, A. Sobel, B. Spire, F. Trémolières, V. Villes, E. Vincent, D. Vlahov.

Modena

Cohort representative: Cristina Mussini. Data management: Vanni Borghi.

Montreal Chest Immunodeficiency Cohort

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PISCIS

Coordinators: J. Casabona (CEEISCAT-Autonomous Universitat Autònoma de Barcelona –UAB-) Jose M. Miró (Hospital Clínic-Idibaps, Universitat de Barcelona – UB-). *Scientific committee*: JM Gatell, M López-Dieguez-Puerta (Hospital Clínic-Idibaps, -UB-), C. Tural, B. Clotet (Hospital Universitari Germans Trias i Pujol, -UAB-), D Podzamczer E. Ferrer (Hospital de Bellvitge, Hospitalet), M. Riera, J. Murillas (Hospital Son Dureta, Mallorca), F. Segura, G. Navarro (Corporació Parc Taulí, Sabadell), L. Force (Hospital de Mataró), J. Vilaró (Hospital de Vic), A. Masabeu (Hospital de Palamós), I. García (Hospital General d'Hospitalet), M.Guadarrama (Hospital Alt Penedès, Vilafranca), Alvaro J. Betancourt, A. Romero, C. Agustí (CEEISCAT), for the PISCIS cohort.

Southern Alberta Cohort

Cohort representative: John Gill.

Swiss HIV Cohort Study

Battegay M, Bernasconi E, Böni J, Bucher HC, Bürgisser P, Calmy A, Cavassini M, Dubs R, Egger M, Elzi L, Fischer M, Flepp M, Fontana A, Francioli P, Furrer H, Fux CA, Gorgievski M, Günthard HF, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Karrer U, Kind C, Klimkait T, Ledergerber B, Martinetti G, Martinez B, Müller N, Nadal D, Paccaud F, Pantaleo G, Rauch A, Regenass S, Rickenbach M, Rudin C, Schmid P,Schultze D, Schöni F, Schüpbach J, Speck R, Taffé P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

UK CHIC

Steering Committee: Jonathan Ainsworth, Jane Anderson, Abdel Babiker, Valerie Delpech, David Dunn, Philippa Easterbrook, Martin Fisher, Brian Gazzard, Richard Gilson, Mark Gompels, Teresa Hill, Margaret Johnson, Clifford Leen, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Kholoud Porter, Frank Post, Caroline Sabin, Achim Schwenk, John Walsh. Central Co-ordination: UCL Medical School, London (Caroline Sabin, Loveleen Bansi, Teresa Hill, Andrew Phillips, Susie Huntington); Medical Research Council Clinical Trials Unit (MRC CTU), London (David Dunn, Adam Glabay, Kholoud Porter). UK CHIC is funded by the Medical Research Council, UK.

WIHS

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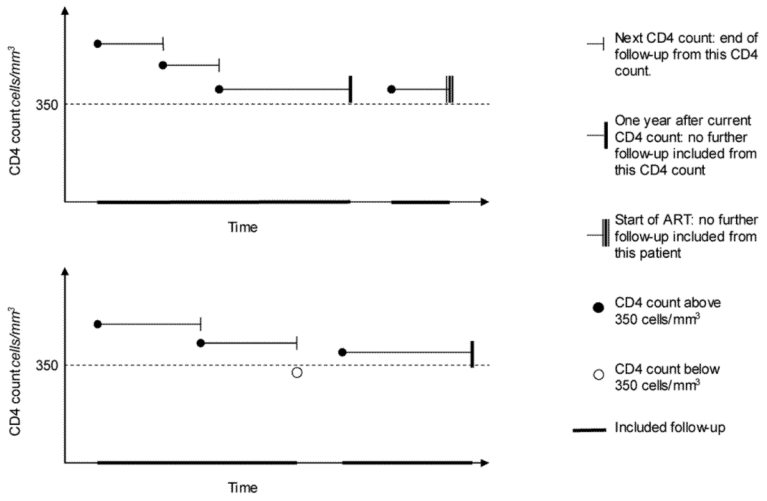

Figure 1.
Illustration of included follow-up for example patients.

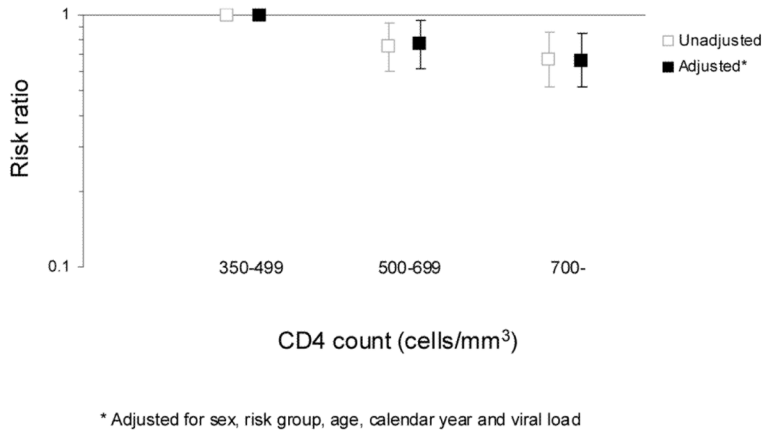

Figure 2.
Unadjusted and adjusted risk ratios from a Poisson regression model for the risk of death according to CD4 count. The number of patients was 40,830, contributing 80,682 person-years of follow-up and with 419 deaths.

Table 1

Characteristics of follow-up of the 40,830 included patients contributing 80,682 person-years of follow-up

Characteristics of follow-up		**Person-years**	**% of follow-up**
Sex	Male	59774	*74.1*
	Female	20908	*25.9*
Risk group	Homosexual men	39732	*49.2*
	Heterosexual	18955	*23.5*
	IDU	17543	*21.7*
	Other / Unknown	4452	*5.5*
Age *years*	20-29	22312	*27.7*
	30-39	38112	*47.2*
	40-49	15759	*19.5*
	50-59	4500	*5.6*
Calendar year	1990-1994	20857	*25.9*
	1995-1999	28325	*35.1*
	2000-2004	31501	*39.0*
CD4 count *cells/mm^3*	350-499	30325	*37.6*
	500-699	28565	*35.4*
	700-	21792	*27.0*
Viral load *log_{10} copies/ml*	−2.99	9479	*11.7*
	3.00-3.99	15586	*19.3*
	4.00-4.99	19220	*23.8*
	5.00-	4202	*5.2*
	Unknown	32195	*39.9*
Hepatitis C co-infection[1]	No previous infection	35313	*48.2*
	Current or previous infection	13991	*19.1*
	Unknown	24018	*32.8*
Smoking status[2]	Never smoked	6005	*19.8*
	Ever smoked	16783	*55.3*
	Unknown	7544	*24.9*

[1] Participating cohorts who were able to provide hepatitis data contributed a total of 73,322 person-years of follow up.

[2] Participating cohorts who were able to provide smoking data contributed a total of 30,332 person-years of follow up.

Table 2

Observed death rates and standardized mortality ratios based on 77,936 person-years of follow-up from 38,997 patients

Risk group	**Deaths** *observed*	**Follow-up** *person-years*	**Death rate (95% CI)** *per 1000 person-years*	**Deaths** *expected*	**SMR (95% CI)**
Homosexual men	100	38764	2.58 (2.07-3.09)	76.79	1.30 (1.06-1.58)
Heterosexual	68	18311	3.71 (2.83-4.60)	23.13	2.94 (2.28-3.73)
IDU	203	16725	12.14 (10.47-13.81)	21.77	9.37 (8.13-10.75)
Other / Unknown	30	4137	7.25 (4.66-9.85)	6.56	4.57 (3.09-6.53)

Table 3

Incidence rate ratios of death at CD4 count above 350 cells/mm^3 while ART näve, according to CD4 count and other patient characteristics. Results were obtained from Poisson regression models: there were 419 deaths in 80,682 person-years

	Univariable analyses		Multivariable analysis	
Characteristics	**Risk ratio (95% CI)**	**p-value**	**Risk ratio (95% CI)**	**p-value**
CD4 count *cells/mm^3*				
350-499	1	0.0019	1	0.0023
500-699	0.75 (0.60-0.93)		0.77 (0.61-0.95)	
700-	0.67 (0.52-0.86)		0.66 (0.52-0.85)	
Sex				
Male	1	0.78	1	0.015
Female	1.03 (0.83-1.28)		0.74 (0.57-0.94)	
Risk group				
Homosexual men	1	<0.0001	1	<0.0001
Heterosexual	1.37 (1.01-1.85)		1.83 (1.29-2.59)	
IDU	4.58 (3.63-5.78)		5.85 (4.54-7.53)	
Other / Unknown	2.53 (1.69-3.79)		2.97 (1.96-4.50)	
Age *years*				
20-29	1	<0.0001	1	<0.0001
30-39	1.38 (1.07-1.79)		1.41 (1.08-1.83)	
40-49	1.76 (1.32-2.35)		2.09 (1.55-2.82)	
50-59	2.21 (1.50-3.25)		3.24 (2.17-4.83)	
Calendar year				
1990-1994	1	0.091	1	0.035
1995-1999	0.84 (0.66-1.06)		0.71 (0.54-0.94)	
2000-2004	0.77 (0.61-0.98)		0.67 (0.48-0.93)	
Viral load *log_{10} copies/ml*				
−2.99	1	0.34	1	0.28
3.00-3.99	0.76 (0.53-1.10)		0.86 (0.59-1.23)	
4.00-4.99	1.00 (0.71-1.39)		1.20 (0.85-1.68)	

Characteristics	Univariable analyses		Multivariable analysis	
	Risk ratio (95% CI)	p-value	Risk ratio (95% CI)	p-value
5.00-	0.97 (0.59-1.60)		1.16 (0.70-1.91)	
Unknown	1.03 (0.76-1.41)		0.96 (0.68-1.37)	