HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2017 November 01; 76(3): 311–318. doi:10.1097/QAI.0000000000001498.

Correspondence: Dr Sara Lodi, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, Massachusetts 02115, United States. slodi@hsph.harvard.edu, Phone: +16174322652.

*Writing committee: Sara Lodi PhD [1], Dominique Costagliola PhD [2], Caroline Sabin PhD [3], Julia del Amo PhD [4,5], Roger Logan PhD [1], Sophie Abgrall MD [2,6], Peter Reiss [7,8,9], Ard van Sighem PhD[7], Sophie Jose MSc [3], Jose-Ramon Blanco MD,PhD [10], Victoria Hernando PhD [4,5], Heiner C. Bucher MD MPH [11], Helen Kovari MD [12], Ferran Segura MD [13], Juan Ambrosioni MD PhD [14], Charalambos A. Gogos MD PhD [15], Nikos Pantazis PhD [16], Francois Dabis MD PhD [17,18], Marie-Anne Vandenhende MD PhD [17,18,19], Laurence Meyer PhD [20,21,22], Rémonie Seng MD MPH [21,22], M. John Gill MB[23,24], Hartmut Krentz PhD [23,24], Andrew N. Phillips PhD [4], Kholoud Porter PhD [4], Beatriz Grinsztejn MD [25], Antonio G. Pacheco MD PhD [26], Roberto Muga MD [27], Janet Tate ScD [28], Amy Justice MD, PhD [28,29], and Miguel A. Hernán MD PhD [1,30,31].

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, US;
[2]Sorbonne Universités, INSERM, UPMC Univ Paris 06, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), F75013, Paris, France
[3]Institute of Global Health, University College London, United Kingdom;
[4]Centro Nacional de Epidemiologia, Instituto de Salud Carlos III, Madrid, Spain;
[5]CIBERESP, Instituto de Salud Carlos III, Madrid, Spain;
[6]AP-HP, Hôpital Antoine Béclère, Service de Médecine Interne, Clamart, France;
[7]Stichting HIV Monitoring, Amsterdam, the Netherlands;
[8]Academic Medical Centre, Department of Global Health and Division of Infectious Diseases, University of Amsterdam, the Netherlands;
[9]Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands;
[10]Hospital San Pedro – CIBIR, Logroño, Spain;
[11]Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, University of Basel, Switzerland;
[12]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Switzerland;
[13]Hospital Parc Tauli, Infectious Disease Department, Sabadell, Spain;
[14]Hospital Clinic-IDIBAPS, Barcelona, Spain;
[15]Division of Infectious Diseases, Patras University Hospital, Greece;
[16]National and Kapodistrian University of Athens, Faculty of Medicine, Dept. of Hygiene, Epidemiology and Medical Statistics Greece;
[17]Université de Bordeaux, ISPED, Centre INSERM U1219-Epidemiologie-Biostatistique, Bordeaux, France;
[18]Centre INSERM U1219– Centre Inserm Epidémiologie et Biostatistique, Université de Bordeaux, Bordeaux, France;
[19]Bordeaux University Hospital, Department of Internal Medicine, Bordeaux, France;
[20]Université Paris Sud, UMR 1018, le Kremlin Bicêtre, France;
[21]Inserm, UMR 1018, le Kremlin Bicêtre, Paris, France;
[22]AP-HP, Hôpital de Bicêtre, Service de Santé Publique, le Kremlin Bicêtre, Paris, France;
[23]Southern Alberta Clinic, Calgary, Canada;
[24]Department of Medicine, University of Calgary, Canada;
[25]Instituto Nacional de Infectologia Evandro Chagas, Fundacao Oswaldo Cruz, Rio de Janeiro, Brasil;
[26]Programa de Computação Científica, Fundacao Oswaldo Cruz, Rio de Janeiro, Brasil;
[27]Hospital Universitari Germans Trias i Pujol, Badalona, Spain;
[28]Yale University School of Medicine, Department of Internal Medicine, New Haven, US;
[29]VA Connecticut Healthcare System, West Haven, US;
[30]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, US;
[31]Harvard-MIT Division of Health Sciences and Technology, Boston, US;

Meetings at which parts of the data were presented. Conference on Retroviruses and Opportunistic Infections, February 22–25, 2016, Boston, USA.

Authors' contributions

Acquisition of data: Dominique Costagliola, Caroline Sabin, Julia del Amo**,** Sophie Abgrall, Peter Reiss**,** Ard van Sighem, Sophie Jose, Jose-Ramon Blanco, Victoria Hernando, Heiner C. Bucher, Helen Kovari, Ferran Segura, Juan Ambrosioni, Charalambos Gogos, Nikos Pantazis, Francois Dabis, Marie-Anne Vandehende, Laurence Meyer, Rémonie Seng, John Gill, Hartmut Krentz, Andrew Phillips, Kholoud Porter, Beatriz Grinsztejn, Antonio G. Pacheco, Roberto Muga, Janet Tate, Amy Justice; Study design: Sara Lodi, Miguel Hernan; Statistical analyses: Sara Lodi, Roger Logan; Drafted the manuscript: Sara Lodi, Miguel Hernan. Interpretation of results: All authors; Read and approved the manuscript: All authors; Revised the work for important intellectual content: All authors; Sara Lodi, the corresponding author, had complete access to all data on the study and takes responsibility for the integrity of the data and the accuracy of any data analysis.

The list of contributors to the HIV-CAUSAL Collaboration is in Appendix 5.

Disclosure of potential conflict of interest

HC Bucher or his institution has received honorarium, support to attend conferences or unrestricted research grants from Gilead Sciences, BMS, Viiv Healthcare, Janssen, Abbvie, MSD in the last 3 years preceding the submission date of this manuscript.

JR Blanco has carried out consulting work for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare; has received compensation for lectures from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare, as well as grants and payments for the development of educational presentations for Gilead Sciences, Bristol-Myers Squibb, and VIIV Healthcare.

AN Phillips has received payment for invited presentations from Gilead Sciences. S Jose received speakers fees from Gilead.

Effect of immediate initiation of antiretroviral treatment in HIV-positive individuals aged 50 years or older

The HIV-CAUSAL Collaboration*

Abstract

Background—Clinical guidelines recommend immediate initiation of combined antiretroviral therapy (ART) for all HIV-positive individuals. However, those guidelines are based on trials of relatively young participants.

Methods—We included HIV-positive ART-naïve, AIDS-free individuals aged 50–70 years after 2004 in the HIV-CAUSAL Collaboration. We used the parametric g-formula to estimate the 5-year risk of all-cause and non-AIDS mortality under: i) immediate initiation at baseline, and initiation at CD4 count ii) <500 cells/mm^3, and iii) <350 cells/mm^3. Results were presented separately for the general HIV population and for a US Veterans cohort with high mortality.

Results—The study included 9596 individuals (28% US Veterans) with median [interquantile range] age of 55 [52,60] years and CD4 count 336 [182,513] at baseline. The 5-year risk of all-cause mortality was 0.40% (95% CI 0.10,0.71) lower for the general HIV population and 1.61% (95% CI 0.79,2.67) lower for US Veterans when comparing immediate initiation vs initiation at CD4<350 cells/mm^3. The 5-year risk of non-AIDS mortality was 0.17% (95% CI −0.07,0.43) lower for the general HIV population and 1% (95% CI 0.31,2.00) lower for US Veterans when comparing immediate initiation vs initiation at CD4<350 cells/mm^3.

Conclusions—Immediate initiation appears to reduce all-cause and non-AIDS mortality in patients aged 50–70 years.

Keywords

Aging; when to start; antiretroviral treatment; CD4 cell count; causal inference; parametric g-formula; comparative effectiveness

---

C Sabin received funding from Gilead Sciences, ViiV Healthcare and Janssen-Cilag for the membership of Data Safety and Monitoring Boards, Advisory Boards, Speaker Panels and for the preparation of educational materials.
A van Sighem reports grants from Dutch Ministry of Health, Welfare and Sport, during the conduct of the study; grants from European Centre for Disease Prevention and Control, personal fees from ViiV Healthcare, personal fees from Gilead Sciences, personal fees from Janssen-Cilag, outside the submitted work.
Marie-Anne Vandehende received travel/meeting expenses from Gilead and Jansen-Cilag during the 36 months prior to submission.
J Ambrosioni received travel Grants from Gilead, ViiV and Janssen, symposium honoraria from Gilead and Janssen and research Grants from ViiV and is part of the advisory boards for Janssen.
K.Porter received personal fees from ViiV healthcare. J.del Amo has received research grants awarded to her team from Companies BMS, MSD, Gilead, ViiV.
J del Amo has received teaching fees from Companies MSD, Gilead, ViiV. MJ Gill has been on National HIV advisory boards to Gilead ViiV and Merck.
D. Costagliola reports grants from Merck-Sharp & Dohme-Chibret (2014–2016), ViiV (2015), and Janssen (current), personal fees from Janssen-Cilag (2016), and Merck-Sharp & Dohme-Chibret (2015) for lectures, personal fees from ViiV (2015), for travel/accomodations/meeting expenses, personal fees from Gilead France from july 2011 until december 2015 for being a member of the French HIV board, personal fees from Innavirvax (in 2015 and in 2016) for consultancy, outside the submitted work.

Introduction

Two randomized clinical trials have shown that combined antiretroviral therapy (ART) initiation at high CD4 counts reduces the risk of serious AIDS and non-AIDS events and death in HIV-positive individuals [1,2]. As a result, clinical guidelines have been updated to recommend ART initiation in all HIV-positive individuals regardless of their CD4 cell count[3–5]. However, these trials were comprised of relatively young participants (median age 36 years) and the number of deaths was too small to examine effects on mortality. Thus, estimates of the impact of the new recommendations on mortality among older HIV-positive individuals, whose prognosis may be different, are currently lacking.

The number of patients diagnosed with HIV at older ages has increased over time [6]. Currently, between 12 and 18% of newly diagnosed HIV-positive individuals are over 50 years of age in high-income countries [7,8]. Compared with younger HIV-positive patients, those who enter HIV care at older ages are often diagnosed with late or advanced HIV disease [6], have a diminished immunological response to treatment [9–11], and are therefore at higher risk of progressing to AIDS or death. The clinical management of these patients is further complicated by a higher prevalence of comorbidities, including hyperlipidaemia, cardiovascular disease, cancer, and diabetes[12]. The benefits of immediate ART initiation might be partially or totally offset by polypharmacy, i.e. taking a large number of different medicines [13], that can make adherence to ART more difficult and can increase the risk of drug toxicities and drug interactions [14].

It is therefore important to quantify the impact of immediate ART initiation in patients who enter into HIV care at older ages. Here we estimate the 5-year risk of all-cause mortality and non-AIDS mortality among ART-naïve, AIDS-free individuals aged between 50 and 70 years using data from the HIV-CAUSAL Collaboration of HIV cohorts from Europe and the Americas. More specifically, we estimated and compared the mortality risks if all participants had started ART (i) immediately, (ii) when their CD4 count dropped below 500 cells/mm^3, and (iii) when their CD4 count dropped below 350 cells/mm^3. We present the results separately for HIV-positive patients from the general population and for United States (US) Veterans with high mortality.

Methods

Selection of patients

We included individuals aged between 50 and 70 years, who had at least one CD4 cell count and one HIV-RNA measured within 3 months of each other while ART-naïve and AIDS-free after December 31, 2004. Baseline was defined as the earliest of the date when all the inclusion criteria were met. Individuals aged more than 70 years at baseline were rare in our cohorts and were not included because their clinical management might be different due to a higher burden of comorbidities. We considered two populations with different background mortality: HIV-positive patients from the general population and US Veterans known to have higher mortality[15]. Individuals from the general HIV population were enrolled in the following cohorts: AMACS (Greece), ANRS CO3 Aquitaine, French Hospital Database, PRIMO, SEROCO (France), ATHENA (The Netherlands), CoRIS, GEMES, PISCIS

(Spain), IPEC (Brazil), Southern Alberta Clinic Cohort (Canada), Swiss HIV Cohort study (Switzerland), UK CHIC and the UK Register of Seroconverters (United Kingdom). The population of US Veterans included individuals from the Veterans Aging Cohort Study (US).

ART initiation strategies

ART was defined as a combination of antiretroviral drugs including at least two nucleoside reverse transcriptase inhibitors plus either one or more protease inhibitors, one nonnucleoside reverse transcriptase inhibitor, one entry/fusion inhibitor, or one integrase inhibitor.

For each population, we estimated the 5-year risk of all-cause mortality and non-AIDS mortality if all participants had started ART within 3 months of baseline (immediate ART initiation). We compared these estimates with those estimated under ART initiation within 3 months of an AIDS diagnosis or CD4 count i) <500 and ii) <350 cells/mm^3, the ART initiation strategies recommended in different settings before the changes in guidelines. We did not account for episodes of ART discontinuation and we assumed that once ART was started patterns of treatment discontinuation were the same as in the observed data for each of the two populations.

Follow-up

Follow-up started at baseline and ended at the earliest of death, 12 months after the most recent laboratory measurement, cohort-specific administrative censoring, date of pregnancy when known, 5 years after baseline or the date a patient initiated antiretroviral therapy with a combination other than our definition of ART.

Outcomes

The outcomes, which were analysed separately, were all-cause mortality and non-AIDS mortality up to 5 years after baseline. For each ART initiation strategy and outcome, we estimated the 5-year risk and risk difference. Non-AIDS mortality was defined as any known cause of death other than AIDS-defining conditions [16]. Cause of death was based on the International Classification of Diseases 10th Revision (ICD-10) and formatted according to CODE (http://www.hicdep.org/). Two cohorts, UK CHIC and IPEC, did not provide data on cause of death and were excluded from the non-AIDS mortality analyses. For all cohorts death ascertainment and cause of death were based on hospital records and cross-matching with national and local registries[15].

Statistical methods

Our estimates had to be adjusted for the time-dependent confounders CD4 cell count, HIV-RNA level and AIDS, as well as for confounders measured at baseline. Because standard statistical methods cannot appropriately adjust for time-dependent confounders affected by prior treatment [17,18], we applied the parametric g-formula to obtain adjusted estimates for each treatment strategy under the assumptions of no residual confounding, no measurement error, and no model misspecification [19].

The parametric g-formula is a generalization of standardization for time-varying treatments and confounders [17,20]. The parametric g-formula is used to estimate the risk of mortality that would have been observed if all patients in the study had perfectly complied with a particular treatment initiation strategy and none had been lost to follow-up. The estimation procedure for the HIV-CAUSAL Collaboration has been described elsewhere [21]. Briefly, the procedure has two steps. First, parametric regression models are used to estimate the joint distribution of the outcome, treatment and time-varying covariates conditional on previous treatment and covariate history. Second, a Monte Carlo simulation using the above estimates is run to simulate the distribution of the post-baseline outcomes and time-varying covariates separately under each ART initiation strategy.

For the first step, we fit separate logistic regression models for time-varying indicators for the outcome event, AIDS, ART initiation, measurement of CD4 cell count, measurement of HIV-RNA, and linear regression models for CD4 cell count and HIV-RNA on the natural logarithm scale. All regression models included as covariates the most recent value of these time-varying variables, time since last CD4 count and HIV-RNA measurements, and the following baseline variables: CD4 cell count (<100, 100–199, 200–349, 350–499, ≥500 cells/mm^3), HIV-RNA level (<10000,10000–100000, >100000 copies/mL), age (<60,≥60 years), sex, mode of acquisition (heterosexual, homo/bisexual, injecting drug users, or other/unknown), calendar year (2005–2009, 2010–2015), geographical origin (Western countries, sub-Saharan Africa, other, unknown), and cohort. All models also included an interaction term for number of months since ART initiation.

In the analyses where the outcome was non-AIDS mortality, AIDS mortality and mortality due to unknown cause where treated as competing events. The g-formula estimates of risk in the presence of competing risks should be interpreted as an extension of the sub-distribution cumulative incidence function to the setting of time-varying treatments and confounders[20].

As in all regression-based methods, the parametric g-formula relies on correct model specification. To explore the validity of our parametric assumptions, we compared the observed means of the outcome and time-varying covariates with those predicted by our models. We used a nonparametric bootstrap procedure based on 500 samples to obtain percentile-based 95% confidence intervals (CIs). All analyses were conducted with the publicly available SAS macro GFORMULA (http://www.hsph.harvard.edu/causal/software/).

Sensitivity analyses

Since our main analyses included all ART-naive patients regardless of CD4 count at baseline in a sensitivity analysis we restricted to the subset of individuals in the general HIV population with a CD4 count≥500 cells/mm^3 at baseline. This sensitivity analysis was conducted only in the general HIV population since there were not enough patients and death cases to achieve good model fit in the US Veterans.

Since a non-negligible proportion of death events had unknown cause of death, as a sensitivity analysis we estimated the risks, risk difference and risk ratio of non-AIDS mortality assuming that all deaths due to unknown cause were non-AIDS related. This

extreme case scenario is unrealistic in practice, but provides an illustration of how sensitive the analyses may be to assumptions regarding the missing data on cause-specific mortality.

Results

Table 1 shows the baseline characteristics of the 9,599 eligible individuals, of whom 2672 (28%) were US Veterans. Patients were predominantly males and started follow-up before 2010. The median [interquartile range (IQR)] age at baseline was 55 years [52,59] in the general HIV population and 56 years [53,60] in US Veterans. The median [IQR] CD4 count at baseline was 354 cells/mm^3 [203,530] in the general HIV population and 284 cells/mm^3 [128,471] in US Veterans (Appendix Table 1).

During a follow-up of 31,989 person years, 7,247 individuals initiated ART, 295 individuals died in the general HIV population and 339 died in the US Veterans cohort. In the general population, there were 124 (55%) non-AIDS deaths, 47 (21%) AIDS deaths, and 54 (24%) deaths with unknown cause. The most common non-AIDS causes of death were non-AIDS cancer (70 events) and cardiovascular disease (21 events). In US Veterans, there were 136 (40%) non-AIDS deaths, 157 (47%) AIDS deaths and 46 (14%) deaths with unknown cause. Sixty-two non-AIDS deaths were attributed to non-AIDS cancer and 45 to cardiovascular disease.

Rates of all-cause mortality and non-AIDS mortality per 1000 person-years were 12.3 and 6.3 for the general HIV population, and 42.4 and 9.7 for US Veterans (Figure 1). In both populations, the observed rates of all-cause and non-AIDS mortality were higher for males and for individuals with lower CD4 count and older age at baseline.

The estimated 5-year risk of all-cause mortality under immediate ART initiation was 5.3% (95% CI 4.5, 6.2) in the general HIV population and 14.4% (12.6, 16.7) in the US Veterans (Table 2). The 5-year risk of all-cause mortality was 0.40% (0.10, 0.71) lower for the general HIV population and 1.61% (0.79, 2.67) lower for US Veterans when comparing immediate initiation vs initiation at CD4 below 350 cells/mm^3. The estimated risk of non-AIDS mortality was lower for immediate ART initiation compared with initiation at CD4<500 and <350 cells/mm^3 in both populations (Table 2). More specifically, the 5-year risk of non-AIDS mortality was 0.17% (−0.07,0.43) lower for the general HIV population and 1.0% (0.31,2.0) lower for US Veterans when comparing immediate initiation vs. initiation at a CD4 of 350 cells/mm^3. The effect estimates were similar in a sensitivity analysis that classified all unknown-cause deaths as non-AIDS related (Appendix Table 2). Among individuals in the general HIV population with baseline CD4 count ≥500 cells/mm^3, the estimated risks of all-cause mortality were 2.8% (1.5,4.5) under immediate ART initiation, 3.7% (2.5,4.5) under initiation at CD4<500 cells/mm^3, and 4.4% (3.1,5.9) under initiation at CD4<350 cells/mm^3 (Table 3).

The time-varying means predicted by our models under observed ART initiation were similar to the observed means in the original data (Appendix Figure 1–3).

Discussion

We estimated the effect of immediate ART initiation in HIV-positive patients between the ages of 50 and 70 years who were entering routine HIV clinical care. The 5-year risk of all-cause mortality was 0.40% lower for the general HIV population and 1.61% lower for US Veterans when comparing immediate initiation vs. initiation at a CD4 count of 350 cells/mm^3. This means that in a hypothetical cohort of 1000 patients, immediate initiation would prevent between 4 and 16 deaths over a 5-year period. The reduction in absolute risk was smaller for non-AIDS mortality. While small, the estimated benefits of immediate initiation on the all-cause mortality of these older populations are larger than those estimated among all individuals in the HIV-CAUSAL Collaboration (median age 37 years) [22]: the 7-year risk of all-cause mortality for immediate initiation was only 0.25% (95% CI 0.40,0.37) lower than the risk under initiation at CD4 count<350 cells/mm^3. These findings suggest that in older HIV-positive patients the benefits of immediate ART initiation on mortality are not offset by age-related comorbidities and potential effects of polypharmacy.

Our findings expand results from randomized controlled trials such as Temprano and START, in which older HIV-positive patients were underrepresented and death events were too few to examine the effect of immediate initiation on mortality [1,2]. Our results are also compatible with those of a subgroup analysis in patients with age ≥50 in START, which showed an increase of 2.24 events of serious diseases per 100 years for deferred versus immediate ART initiation [23].

Our analysis estimates the risk that would have been observed if all patients in the study, regardless of their CD4 cell count at baseline, had followed each ART initiation strategy. The small magnitude of the benefit of immediate initiation is not surprising as more than half of the included patients had a CD4 cell count <350 cells/mm^3 at baseline. In analyses including only individuals in the general HIV population with CD4 cell count ≥500 cells/mm^3 at baseline, the risk differences were larger: 1.62% for immediate initiation versus initiation with CD4<350 cells/mm^3. This finding suggests that the benefit of immediate ART initiation in older HIV patients is greater when HIV infection is diagnosed early, which stresses the importance of scaling up testing programs. The high proportion of patients with low CD4 cell count at baseline observed in our data is consistent with reports of late HIV diagnosis among older HIV patients in observational studies and surveillance data [7,24–27]. Lower CD4 cell count at entry into care in older patients can be due to long periods of time being unaware of their positive HIV status as well as faster progression of the HIV disease in patients who become infected at older ages [28–30].

The rates of all-cause and non-AIDS mortality were higher for the US Veterans than for the general HIV population which included individuals in Europe, Canada and Brazil. The difference in mortality is likely due to a combination of heterogeneity in the data collection protocols and individual characteristics. A contributing factor is the ascertainment of death cases, which has been shown to be more complete in the cohort of US Veterans [15]. In addition to this, in our study, the US Veterans had larger proportions of individuals older than 60 years at study entry and of HCV co-infected persons. Also, the US Veterans present

substantial morbidity and poor health compared with the general population [31]. However, despite the difference in mortality, our effect estimates were similar in both populations.

Our conclusions indicating the benefits of immediate initiation are compatible with the results from a study using routinely collected data in the United States [32] and extend this study by looking at more recent calendar period, an older age group and non-AIDS mortality. Of note, the observed and estimated 5-year risks under all ART initiation strategies in the general HIV population were lower in our study. The better prognosis demonstrated by our study may be due to the more recent follow-up period (2005–2015 in our study and 1998–2010 in the American study) and a smaller proportions of injecting drug users (2% in our study and 22% in the American study).

Our study has several limitations. First, as in all non-randomized studies, the validity of our estimates relies on the assumption of no unmeasured confounding. We adjusted for the most important factors used to decide when to initiate ART such as CD4 count, HIV-RNA and AIDS. However, we did not collect information on age-related comorbidities and concomitant treatments. Had these characteristics influenced the decision to initiate ART in older HIV positive patients then our estimates could be biased. Second, our methods require that all models are correctly specified. This condition cannot be guaranteed, but it seems plausible because our models resulted in simulated data sets with average outcome and time-varying covariates similar to those in the original data. Third, cause-specific mortality was unknown for a substantial proportion of patients. Therefore, our estimates might underestimate the risk of non-AIDS mortality. As expected, the estimated absolute risks of non-AIDS mortality were higher in the sensitivity analysis assuming that all deaths for unknown cause were non-AIDS deaths, although risk differences and risk ratios were similar. Moreover, it has been shown that the ICD10 classification for cause of death in individuals known to be HIV-positive tends to misclassify liver disease-related mortality into AIDS-related mortality [33]. Finally, the cohorts included in the HIV-CAUSAL Collaboration are not based on random samples of the HIV population, tend to include many HIV seroconverters and might therefore not be fully representative of HIV patients in care in high-income countries. However, this concern is not supported by a recent study showing that individuals enrolled in European cohorts tend to have broadly similar characteristics at HIV diagnosis and the HIV-positive individuals in European Surveillance registries. [34].

In conclusion, immediate initiation of ART appears to be beneficial in reducing all-cause mortality in AIDS-free patients aged 50 years or older, despite their low baseline CD4 count. More effort should be made into diagnosing HIV earlier, particularly in older patients in order to ensure timely initiation of treatment and follow-up for concomitant comorbidities, thereby maximising the benefit of early treatment for HIV.

Acknowledgments

Sources of funding and support. The HIV-CAUSAL Collaboration is funded by NIH grant R01 AI102634. UK CHIC is funded by the UK Medical Research Council (Grant numbers G0000199, G0600337, G0900274 and M004236). The views expressed in this manuscript are those of the researchers and not necessarily those of the Medical Research Council.

References

1. Insight Start Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015; 373(9):795–807. [PubMed: 26192873]
2. Temprano ANRS Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015; 373(9):808–822. [PubMed: 26193126]
3. [Accessed 30 November 2016] Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf
4. World Health Organization (WHO). [Accessed 30 November 2016] Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. 2016. http://apps.who.int/iris/bitstream/10665/246200/1/9789241511124-eng.pdf?ua=1
5. European AIDS clinical society (EACS). [Accessed 30 November 2016] European guidelines for treatment of HIV infected adults in Europe. 2016. http://www.eacsociety.org/files/guidelines_8.1-english.pdf
6. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. Clin Infect Dis. 2010; 50(11):1512–1520. [PubMed: 20415573]
7. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2012. Stockholm: European Centre for Disease Prevention and Control; 2013.
8. Center for Disease Control C. HIV Surveillance Report: Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas. 2013
9. Sabin CA, Smith CJ, et al. Collaboration of Observational HIV Epidemiological Research Europe Study Group. Response to combination antiretroviral therapy: variation by age. Aids. 2008; 22(12): 1463–1473. [PubMed: 18614870]
10. Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. Aids. 2004; 18(15):2029–2038. [PubMed: 15577624]
11. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis. 2005; 41(3):361–372. [PubMed: 16007534]
12. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis. 2014; 59(12):1787–1797. [PubMed: 25182245]
13. Krentz HB, Gill MJ. The Impact of Non-Antiretroviral Polypharmacy on the Continuity of Antiretroviral Therapy (ART) Among HIV Patients. AIDS Patient Care STDS. 2016; 30(1):11–17. [PubMed: 26544766]
14. Greene M, Justice AC, Lampiris HW, Valcour V. Management of human immunodeficiency virus infection in advanced age. Jama. 2013; 309(13):1397–1405. [PubMed: 23549585]
15. May MT, Hogg RS, Justice AC, et al. Heterogeneity in outcomes of treated HIV-positive patients in Europe and North America: relation with patient and cohort characteristics. Int J Epidemiol. 2012; 41(6):1807–1820. [PubMed: 23148105]
16. Ancelle-Park R. Expanded European AIDS case definition. Lancet. 1993; 341(8842):441.
17. Robins, J., Hernan, M. Estimation of the causal effects of time-varying exposures. In: Fitzmaurice, GD.Verbeke, M., Molenberghs, G., editors. Advances in longitudinal data analysis. Boca Raton: Chapman and Hall/CRC Press; 2009. p. 553-599.
18. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004; 15(5):615. [PubMed: 15308962]
19. Robins JM. A new approach to causal inference in mortality studies with a sustained exposure period: application to the healthy worker survivor effect. Mathematical Modelling. 1986; 7(9–12): 1393–1512.
20. Taubman SL, Robins JM, Mittleman MA, Hernan MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. Int J Epidemiol. 2009; 38(6):1599–1611. [PubMed: 19389875]

21. Young JG, Cain LE, Robins JM, O'Reilly EJ, Hernan MA. Comparative effectiveness of dynamic treatment regimes: an application of the parametric g-formula. Stat Biosci. 2011; 3(1):119–143. [PubMed: 24039638]
22. Lodi S, Phillips A, Logan R, et al. Comparative effectiveness of strategies for antiretroviral treatment initiation in HIV-positive individuals in high-income countries: an observational cohort study of immediate universal treatment versus CD4-based initiation. Lancet HIV. 2015; 2(8):e335–e343. [PubMed: 26423376]
23. Molina, JM., Grund, B., Gordin, F., et al. Who benefited most from immediate treatment in START? A subgroup analysis. 21st International AIDS Conference; 2016; Durban.
24. Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med. 2013; 10(9):e1001510. [PubMed: 24137103]
25. Center for Disease Control C. Diagnoses of HIV infectons in the United States and dependent areas, 2014. 2015
26. Lodi S, Dray-Spira R, Touloumi G, et al. Delayed HIV diagnosis and initiation of antiretroviral therapy: inequalities by educational level, COHERE in EuroCoord. Aids. 2014; 28(15):2297–2306. [PubMed: 25313585]
27. Center for Disease Control C. Diagnoses of HIV infection among adults aged 50 years and older in the United States and dependent areas, 2010–2014. 2016
28. Babiker AG, Peto T, Porter K, Walker AS, Darbyshire JH. Age as a determinant of survival in HIV infection. J Clin Epidemiol. 2001; 54(Suppl 1):S16–21. [PubMed: 11750205]
29. Lodi S, Phillips A, Touloumi G, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm(3): assessment of need following changes in treatment guidelines. Clin Infect Dis. 2011; 53(8):817–825. [PubMed: 21921225]
30. Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS. 2014; 9(4):294–301. [PubMed: 24824889]
31. Kramarow, E., Pastor, P. The Health of Male Veterans and Nonveterans Aged 25–64: United States, 2007–2010. Hyattsville, MD: National Center for Health Statistics; 2012. Vol NCHS Data Brief
32. Edwards JK, Cole SR, Westreich D, et al. Age at Entry Into Care, Timing of Antiretroviral Therapy Initiation, and 10-Year Mortality Among HIV-Seropositive Adults in the United States. Clin Infect Dis. 2015; 61(7):1189–1195. [PubMed: 26082505]
33. Hernando V, Sobrino-Vegas P, Burriel MC, et al. Differences in the causes of death of HIV-positive patients in a cohort study by data sources and coding algorithms. Aids. 2012; 26(14):1829–1834. [PubMed: 22410685]
34. Touloumi, G. Assessing the representativeness of European HIV cohorts participants as compared to HIV Surveillance data-an ECDC Project. HepHIV 2017 Conference: HIV and Viral Hepatitis: Challenges of Timely Testing and Care; 2016; Malta.

Appendix 5. Contributors to the HIV-CAUSAL Collaboration

AMACS

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

Participating Centers: 4th Dept of Internal Medicine, Athens Medical School, Attikon University Hospital (Antoniadou A, Papadopoulos A, Petrikkos G); Infectious Disease Unit, "Tzaneio" General Hospital of Pireaus (Chrysos G, Paraskeva D, Hatziastros P); 1st Dept of

Propedeutic Medicine, Athens University, Medical School “Laikon” General Hopsital (Daikos G, Psichogiou M); 1st Dept of Medicine, Infectious Diseases Unit, “G. Gennimatas” Athens General Hospital (Gargalianos-Kakolyris P, Xylomenos G); 1st Dept of Internal Medicine, Infectious Diseases Section, Patras University Hospital (Gogos HA, Marangos MN, Panos G); Haemophilia Centre, 2nd Blood Transfusion Centre, “Laikon” Athens General Hospital (Katsarou O, Kouramba A, Ioannidou P); AIDS Unit, Dept of Pathophysiology, “Laikon” Athens General Hospital and Athens University, Medical School (Kordossis T, Kontos A); Infectious Diseases Unit, Red Cross General Hospital of Athens (Lazanas M, Chini M, Tsogas N); 1st Dept of Internal Medicine, Infectious Diseases Devision, AHEPA University Hospital, Aristotle University HIV Unit (Nikolaidis P, Kolaras P, Metallidis S); 2nd Internal Medicine Clinic, 1st IKA (Panos G, Haratsis G); AIDS Unit, Clinic of Venereologic & Dermatologic Diseases, Athens University, Medical School, Syngros Hospital (Paparizos V, Leuow K, Kourkounti S); HIV Unit, 2nd Dpt. of Internal Medicine, Athens University, Medical School, Hippokration General Hospital (Sambatakou H, Mariolis I); Infectious Diseases & HIV Division, Dept of Internal Medicine, Evaggelismos Athens General Hospital (Skoutelis A, Papastamopoulos V, Baraboutis I).

AQUITAINE

Principal investigator: Pr F. Dabis. Scientific committee: Prs F. Bonnet, D. Breilh, F. Dabis, M. Dupon, G. Chêne, H. Fleury, D. Malvy, P. Mercié, I. Pellegrin, P. Morlat, D. Neau, JL. Pellegrin, R. Thiébaut; Drs S. Bouchet, V. Gaborieau, D. Lacoste, S. Tchamgoué. Epidemiology and biostatistics: Prs G. Chêne, F. Dabis, R. Thiébaut, Drs M. Bruyand, S. Lawson-Ayayi, L. Wittkop. Clinical and biological hospital units: Bordeaux University Hospital: Pr P. Morlat (Pr F. Bonnet, Drs N. Bernard, M. Hessamfar, D. Lacoste, MA. Vandenhende); Pr M. Dupon (Drs FA. Dauchy, H. Dutronc), Pr M. Longy-Boursier (Pr P. Mercié, Drs P. Duffau, J. Roger Schmeltz), Pr D. Malvy (Drs T. Pistone, MC Receveur), Pr D. Neau (Drs C. Cazanave, A. Ochoa, MO. Vareil), Pr JL. Pellegrin (Pr JF. Viallard, Drs C. Greib, E. Lazaro); Pr H. Fleury (Pr ME. Lafon, Drs S. Reigadas, P. Trimoulet); Pr D. Breilh; Pr M. Molimard (Drs S. Bouchet, K. Titier); Pr JF. Moreau (Dr I. Pellegrin); Drs F. Haramburu, G. Miremont-Salamé. Arcachon Hospital: Dr A. Dupont. Dax Hospital: Dr Y. Gerard (Drs L. Caunègre, K. André). Bayonne Hospital: Dr F. Bonnal (Drs S. Farbos, MC. Gemain). Libourne Hospital: Dr J. Ceccaldi (Dr S. Tchamgoué). Mont-de-Marsan Hospital: Dr S. De Witte (Dr C. Courtault). Pau Hospital: Drs E. Monlun (Dr V. Gaborieau). Périgueux Hospital: Dr P. Lataste (Dr JP. Meraud). Villeneuve-sur-Lot Hospital: Dr I. Chossat. Permanent team: MJ. Blaizeau, M. Bruyand, V. Conte, M. Decoin, J. Delaune, S. Delveaux, F. Diarra, C. D’Ivernois, A. Frosch, S. Geffard, C. Hannapier, S. Lawson-Ayayi, E. Lenaud, O. Leleux, F. Le Marec, J. Leray, I. Louis, G. Palmer, A. Pougetoux, X. Sicard, D. Touchard B. Uwamaliya-Nziyumvira.

ATHENA

The ATHENA database is maintained by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment. CLINICAL CENTRES (* denotes site coordinating physician). Academic Medical Centre of the

University of Amsterdam: HIV treating physicians: J.M. Prins*, T.W. Kuijpers, H.J. Scherpbier, J.T.M. van der Meer, F.W.M.N. Wit, M.H. Godfried, P. Reiss, T. van der Poll, F.J.B. Nellen, S.E. Geerlings, M. van Vugt, D. Pajkrt, W.J. Wiersinga, M. van der Valk, A. Goorhuis, J.W. Hovius. HIV nurse consultants: M.A.H. Bijsterveld, J. van Eden, A.M.H. van Hes, M. Mutschelknauss, H.E. Nobel, F.J.J. Pijnappel, A.M. Weijsenfeld. HIV clinical virologists/chemists: S. Jurriaans, N.K.T. Back, H.L. Zaaijer, B. Berkhout, M.T.E. Cornelissen, C.J. Schinkel, X.V. Thomas. Admiraal De Ruyter Ziekenhuis, Goes: HIV treating physicians: M. van den Berge, A. Stegeman. HIV nurse consultants: S. Baas, L. Hage de Looff. HIV clinical virologists/chemists: B Wintermans, J Veenemans. Catharina Ziekenhuis, Eindhoven: HIV treating physicians: M.J.H. Pronk*, H.S.M. Ammerlaan. HIV nurse consultants: E.S. de Munnik, E. van Beek. HIV clinical virologists/chemists: A.R. Jansz, J. Tjhie, M.C.A. Wegdam, B. Deiman, V. Scharnhorst. Elisabeth-TweeSteden Ziekenhuis, Tilburg: HIV treating physicians: M.E.E. van Kasteren*, A.E. Brouwer. HIV nurse consultants: R. van Erve, B.A.F.M. de Kruijf-van de Wiel, S.Keelan-Pfaf, B. van der Ven. Data collection: B.A.F.M. de Kruijf-van de Wiel, B. van der Ven. HIV clinical virologists/chemists: A.G.M. Buiting, P.J. Kabel, D.Versteeg. Emma Kinderziekenhuis: HIV nurse consultants: A. van der Plas, A.M. Weijsenfeld. Erasmus MC, Rotterdam: HIV treating physicians: M.E. van der Ende*, H.I. Bax, E.C.M. van Gorp, J.L. Nouwen, B.J.A. Rijnders, C.A.M. Schurink, A. Verbon, T.E.M.S. de Vries-Sluijs. HIV nurse consultants: N. Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld. Data collection: H.J. van den Berg-Cameron, F.B. Bruinsma-Broekman, J. de Groot, M. de Zeeuw-de Man. HIV clinical virologists/chemists: C.A.B. Boucher, M.P.G Koopmans, J.J.A van Kampen, S.D. Pas. Erasmus MC–Sophia, Rotterdam: HIV treating physicians: G.J.A. Driessen, A.M.C. van Rossum. HIV nurse consultants: L.C. van der Knaap, E. Visser. Flevoziekenhuis, Almere: HIV treating physicians: J. Branger*, A. Rijkeboer-Mes. HIV nurse consultant and data collection: C.J.H.M. Duijf-van de Ven. HagaZiekenhuis, Den Haag: HIV treating physicians: E.F. Schippers*, C. van Nieuwkoop. HIV nurse consultants: J.M. van IJperen, J. Geilings. Data collection: G. van der Hut. HIV clinical virologist/chemist: P.F.H. Franck. HIV Focus Centrum (DC Klinieken): HIV treating physicians: A. van Eeden*. HIV nurse consultants: W. Brokking, M. Groot, L.J.M. Elsenburg. HIV clinical virologists/chemists: M. Damen, I.S. Kwa. Isala, Zwolle: HIV treating physicians: P.H.P. Groeneveld*, J.W. Bouwhuis. HIV nurse consultants: J.F. van den Berg, A.G.W. van Hulzen. Data collection: G.L. van der Bliek, P.C.J. Bor. HIV clinical virologists/chemists: P. Bloembergen, M.J.H.M. Wolfhagen, G.J.H.M. Ruijs. Leids Universitair Medisch Centrum, Leiden: HIV treating physicians: F.P. Kroon*, M.G.J. de Boer, H. Jolink, A.M. Vollaard. HIV nurse consultants: W. Dorama, N. van Holten. HIV clinical virologists/chemists: E.C.J. Claas, E. Wessels. Maasstad Ziekenhuis, Rotterdam: HIV treating physicians: J.G. den Hollander*, K. Pogany, A. Roukens. HIV nurse consultants: M. Kastelijns, J.V. Smit, E. Smit, D. Struik-Kalkman, C. Tearno. Data collection: M. Bezemer, T. van Niekerk. HIV clinical virologists/chemists: O. Pontesilli. Maastricht UMC+, Maastricht: HIV treating physicians: S.H. Lowe*, A.M.L. Oude Lashof, D. Posthouwer. HIV nurse consultants: R.P. Ackens, J. Schippers, R. Vergoossen. Data collection: B. Weijenberg-Maes. HIV clinical virologists/chemists: I.H.M. van Loo, T.R.A. Havenith. MCH-Bronovo, Den Haag: HIV treating physicians: E.M.S. Leyten*, L.B.S. Gelinck. HIV nurse consultants: A.Y. van Hartingsveld, C. Meerkerk, G.S. Wildenbeest. HIV clinical virologists/chemists: J.A.E.M. Mutsaers, S.Q. van Veen. MC

Slotervaart, Amsterdam: HIV treating physicians: J.W. Mulder*, S.M.E. Vrouenraets, F.N. Lauw. HIV nurse consultants: M.C. van Broekhuizen, H. Paap, D.J. Vlasblom. HIV clinical virologists/chemists: P.H.M. Smits. MC Zuiderzee, Lelystad: HIV treating physicians: S. Weijer*, R. El Moussaoui. HIV nurse consultant: A.S. Bosma. Medisch Centrum Leeuwarden, Leeuwarden: HIV treating physicians: M.G.A.van Vonderen*, D.P.F. van Houte, L.M. Kampschreur. HIV nurse consultants: K. Dijkstra, S. Faber. HIV clinical virologists/chemists: J Weel. Medisch Spectrum Twente, Enschede: HIV treating physicians: G.J. Kootstra*, C.E. Delsing. HIV nurse consultants: M. van der Burg-van de Plas, H. Heins. Data collection: E. Lucas. Noordwest Ziekenhuisgroep, Alkmaar: HIV treating physicians: W. Kortmann*, G. van Twillert*, J.W.T. Cohen Stuart, B.M.W. Diederen, R. Renckens. HIV nurse consultant and data collection: D. Ruiter-Pronk, F.A. van Truijen-Oud. HIV clinical virologists/chemists: W. A. van der Reijden, R. Jansen. OLVG, Amsterdam: HIV treating physicians: K. Brinkman*, G.E.L. van den Berk, W.L. Blok, P.H.J. Frissen, K.D. Lettinga W.E.M. Schouten, J. Veenstra. HIV nurse consultants: C.J. Brouwer, G.F. Geerders, K. Hoeksema, M.J. Kleene, I.B. van der Meché, M. Spelbrink, H. Sulman, A.J.M. Toonen, S. Wijnands. HIV clinical virologists: M. Damen, D. Kwa. Data collection: E. Witte. Radboudumc, Nijmegen: HIV treating physicians: R. van Crevel*, M. Keuter, A.J.A.M. van der Ven, H.J.M. ter Hofstede, A.S.M. Dofferhoff. HIV nurse consultants: M. Albers, K.J.T. Grintjes-Huisman, M. Marneef, A. Hairwassers. HIV clinical virologists/chemists: J. Rahamat-Langendoen. HIV clinical pharmacology consultant: D. Burger. Rijnstate, Arnhem: HIV treating physicians: E.H. Gisolf*, R.J. Hassing, M. Claassen. HIV nurse consultants: G. ter Beest, P.H.M. van Bentum, N. Langebeek. HIV clinical virologists/chemists: R. Tiemessen, C.M.A. Swanink. Spaarne Gasthuis, Haarlem: HIV treating physicians: S.F.L. van Lelyveld*, R. Soetekouw. HIV nurse consultants: L.M.M. van der Prijt, J. van der Swaluw. Data collection: N. Bermon. HIV clinical virologists/chemists: W.A. van der Reijden, R. Jansen, B.L. Herpers, D.Veenendaal. Medisch Centrum Jan van Goyen, Amsterdam: HIV treating physicians: D.W.M. Verhagen. HIV nurse consultants: M. van Wijk. Universitair Medisch Centrum Groningen, Groningen: HIV treating physicians: W.F.W. Bierman*, M. Bakker, J. Kleinnijenhuis, E. Kloeze, H. Scholvinck, Y. Stienstra, C.L. Vermont, K.R. Wilting. HIV nurse consultants: A. Boonstra, H. de Groot-de Jonge, P.A. van der Meulen, D.A. de Weerd. HIV clinical virologists/chemists: H.G.M. Niesters, C.C. van Leer-Buter, M. Knoester. Universitair Medisch Centrum Utrecht, Utrecht: HIV treating physicians: A.I.M. Hoepelman*, J.E. Arends, R.E. Barth, A.H.W. Bruns, P.M. Ellerbroek, T. Mudrikova, J.J. Oosterheert, E.M. Schadd, M.W.M. Wassenberg, M.A.D. van Zoelen. HIV nurse consultants: K. Aarsman, D.H.M. van Elst-Laurijssen, E.E.B. van Oers-Hazelzet. Data collection: M. van Berkel. HIV clinical virologists/chemists: R. Schuurman, F. Verduyn-Lunel, A.M.J. Wensing. VUmc, Amsterdam: HIV treating physicians: E.J.G. Peters*, M.A. van Agtmael, M. Bomers, J. de Vocht. HIV nurse consultants: M. Heitmuller, L.M. Laan. HIV clinical virologists/chemists: C.W. Ang, R. van Houdt, A.M. Pettersson, C.M.J.E. Vandenbroucke-Grauls. Wilhelmina Kinderziekenhuis, UMCU, Utrecht: HIV treating physicians: S.P.M. Geelen, T.F.W. Wolfs, L.J. Bont. HIV nurse consultants: N. Nauta. COORDINATING CENTRE. Director: P. Reiss. Data analysis: D.O. Bezemer, A.I. van Sighem, C. Smit, F.W.M.N. Wit, T.S. Boender. Data management and quality control: S. Zaheri, M. Hillebregt, A. de Jong. Data monitoring: D. Bergsma, A. de Lang, S. Grivell, A. Jansen, M.J. Rademaker, M. Raethke, R. Meijering, S. Schnörr. Data collection: L. de Groot,

M. van den Akker, Y. Bakker, E. Claessen, A. El Berkaoui, J. Koops, E. Kruijne, C. Lodewijk, L. Munjishvili, B. Peeck, C. Ree, R. Regtop, Y. Ruijs, T. Rutkens, L. van de Sande, M. Schoorl, A. Timmerman, E. Tuijn, L. Veenenberg, S. van der Vliet, A. Wisse, T. Woudstra. Patient registration: B. Tuk.

CoRIS/CoRIS-MD

Steering committee: S Moreno, J del Amo, D Dalmau, ML Navarro, MI González, JL Blanco, F Garcia, R Rubio, JA Iribarren, F Gutiérrez, F Vidal, J Berenguer, J González. Field work, data management, and statistical analyses: P Sobrino, I Jarrín, B Alejos, V Hernando, D Alvarez, C Moreno. Participating centres: Hospital General Universitario de Alicante, Alicante (J Portilla, E Merino, S Reus, V Boix, L Giner, C Gadea, I Portilla, M Pampliega, M Díez, JC Rodríguez, J Sánchez-Payá) ; Hospital Universitari de Bellvitge, Badalona (D Podzamczer, E Ferrer, A Imaz, E Van Den Eyncle, S Di Yacovo, M Sumoy); Hospital Universitario de Canarias, Santa Cruz de Tenerife (JL Gómez, J Hernández, MR Alemán, MM Alonso, MI Hernández, F Díaz-Flores, D García, R Pelazas) ; Hospital Universitario Central de Asturias, Oviedo (V Asensi, E Valle, JA Cartón); Hospital Clínico San Carlos, Madrid (V Estrada, MJ Téllez, J Vergas, E Pérez-Cecila); Hospital Doce de Octubre, Madrid (R Rubio, F Pulido, O Bisbal, M Matarranz, M Lagarde, R Rubio-Martín, A Hernando, L Bermejo, L Dominguez); Hospital Universitario Donostia, San Sebastián (JA Iribarren, J Arrizabalaga, MJ Aramburu, X Camino, F Rodríguez-Arrondo, MÁ von Wichmann, L Pascual, MÁ Goenaga, MJ Bustinduy, H Azkune, M Ibarguren, M Aguado, M Umerez); Hospital General Universitario de Elche, Elche (F Gutiérrez, M Masiá, C López, S Padilla, A Navarro, F Montolio, C Robledano, JG Colomé, A Adsuar, R Pascual, F Carlos, M Martinez, J Llenas, M Fernández, E García); Hospital Germans Trías i Pujol, Badalona (R Muga, J Tor, A Sanvisens); Hospital General Universitario Gregorio Marañón, Madrid (J Berenguer, JC López Bernaldo de Quirós, P Miralles, I Gutiérrez, M Ramírez, B Padilla, P Gijón, A Carrero, T Aldamiz-Echevarría, F Tejerina, FJ Parras, P Balsalobre, C Diez; Hospital Universitari de Tarragona Joan XXIII, IISPV, Universitat Rovira i Virgili, Tarragona (F Vidal, J Peraire, C Viladés, S Veloso, M Vargas, M López-Dupla, M Olona, A Aguilar, JJ Sirvent, V Alba, O Calavia; Hospital Universitario La Fe, Valencia (M Montero, J Lacruz, M Blanes, E Calabuig, S Cuellar, J López, M Salavert) ; Hospital Universitario La Paz/IdiPaz, Madrid (J González, I Bernardino, JR Arribas, ML Montes, JM Peña, B Arribas, JM Castro, FJ Zamora, I Pérez, M Estébanez, S García, M Díaz, NS Alcáriz, J Mingorance, D Montero, A González, MI de José); Hospital de la Princesa, Madrid (I de los Santos, J Sanz, A Salas, C Sarriá, A Gómez-Berrocal, L Garcia-Fraile; Hospital San Pedro-CIBIR, Logroño (JA Oteo, JR Blanco, V Ibarra, L Metola, M Sanz, L Pérez-Martínez) ; Hospital Universitario Miguel Servet, Zaragoza (A Pascual, C Ramos, P Arazo, D Gil); Hospital Universitari Mutua de Terrassa, Terrassa (D Dalmau, A Jaén, M Cairó, D Irigoyen, Q Jordano, M Xercavins, J Martinez-Lacasa, P Velli, R Font, M Sanmartí, L Ibáñez; Complejo Hospitalario de Navarra, Pamplona (M Rivero, MI Casado, JA Díaz, J Uriz, J Repáraz, C Irigoyen, MJ Arraiza); Hospital Parc Taulí, Sabadell (F Segura, MJ Amengual, G Navarro, M Sala, M Cervantes, V Pineda, V Segura, M Navarro, E Antón, MM Nogueras); Hospital Ramón y Cajal, Madrid (S Moreno, JL Casado, F Dronda, A Moreno, MJ Pérez Elías, D López, C Gutiérrez, N Madrid, A Lamas, P Martí, A de Diaz, S Serrrano, L Donat); Hospital

Reina Sofía, Murcia (A Cano, E Bernal, Á Muñoz); Hospital San Cecilio, Granada (F García, J Hernández, A Peña, L Muñoz, J Parra, M Alvarez, N Chueca, V Guillot, D Vinuesa, JA Fernández); Centro Sanitario Sandoval, Madrid (J Del Romero, C Rodríguez, T Puerta, JC Carrió, M Vera, J Ballesteros); Hospital de la Santa Creu i Sant Pau, Barcelona (P Domingo, MA Sambeat, K Lamarca, G Mateo, M Gutiérrez, I Fernández); Hospital Universitario Santiago de Compostela, Santiago de Compostela (A Antela, E Losada); Hospital Son Espases, Palma de Mallorca (M Riera, M Peñaranda, M Leyes, MA Ribas, AA Campins, C Vidal, L Gil, F Fanjul, C Marinescu); Hospital Universitari Vall d'Hebron, Barcelona (E Ribera); Hospital Virgen de la Victoria, Málaga (J Santos, M Márquez, I Viciana, R Palacios, I Pérez, CM González); Hospital Universitario Virgen del Rocío, Sevilla (P Viciana, M Leal, LF López-Cortés, N Espinosa); Hospital Universitario de Basurto, Bilbao (J Muñoz, M Zuriñe Zubero, J Mirena, S Ibarra, O Ferrero, J López de Munain, MM Cámara, I López, M de la Peña); Hospital Universitario Infanta Sofía, San Sebastián de los Reyes (I Suárez-García, E Malmierca); Hospital Universitario Costa del Sol, Marbella (J Olalla, A del Arco, J de la Torre, JL Prada, Z Caracuel); Hospital del Poniente, El Ejido (AM Lopez-Lirola, AB Lozano, E Fernández, I Pérez, JM Fernández); Hospital Universitario Santa Lucia, Cartagena (OJ Martínez, FJ Vera, L Martínez, J García, B Alcaraz, A Jimeno); INIBIC-Complejo Hospitalario Universitario de A Coruña, A Coruña (E Poveda, B Pernas, A Mena, M Grandal, A Castro, JD Pedreira); Hospital Clínico Universitario Virgen de la Arrixaca, Murcia (C Galera, H Albendin, A Iborra, A Moreno, MA Campillo, A Vidal); Hospital Marina Baixa, Villajoyosa (C Amador, F Pasquau, J Ena, C Benito, V Fenoll); Complejo Hospitalario de Jaén, Jaén (MO Mohamed-Balghata, MA Gómez); Hospital San Agustín de Avilés, Avilés (MA de Zarraga, ME Rivas); Fundación Jiménez Diaz,Madrid (M Górgolas).

FHDH-ANRS CO4

Scientific committee: S Abgrall, F Barin, M Bentata, E Billaud, F Boué, C Burty, A Cabié, D Costagliola, L Cotte, P De Truchis, X Duval, C Duvivier, P Enel, L Fredouille-Heripret, J Gasnault, C Gaud, J Gilquin, S Grabar, C. Katlama, MA Khuong, JM Lang, AS Lascaux, O Launay, A Mahamat, M Mary-Krause, S Matheron, JL Meynard, J Pavie, G Pialoux, F Pilorgé, I Poizot-Martin, C Pradier, J Reynes, E Rouveix, A Simon, P Tattevin, H Tissot-Dupont, JP Viard, N Viget. DMI2 coordinating center: French Ministry of Health (Valérie Salomon), Technical Hospitalization Information Agency, ATIH (N Jacquemet). Statistical analysis center: U943 INSERM et UPMC (S Abgrall, D Costagliola, S Grabar, M Guiguet, E Lanoy, L Lièvre, M Mary-Krause, H Selinger-Leneman), INSERM Transfert (JM Lacombe, V Potard). COREVIH: Paris area: Corevih Ile de France Centre (GH Pitié-Salpétrière: F Bricaire, S Herson, C Katlama, A Simon; Hôpital Saint-Antoine: N Desplanque, PM Girard, JL Meynard, MC Meyohas, O Picard; Hôpital Tenon: J Cadranel, C Mayaud, G Pialoux), Corevih Ile de France Est (Hôpital Saint-Louis: JP Clauvel, JM Decazes, L Gerard, JM Molina; GH Lariboisière-Fernand Widal: M Diemer, P Sellier; Hôpital Avicenne: M Bentata, P Honoré; Hôpital Jean Verdier: V Jeantils, S Tassi; Hôpital Delafontaine: D Mechali, B Taverne), Corevih Ile de France Nord (Hôpital Bichat-Claude Bernard: E Bouvet, B Crickx, JL Ecobichon, S Matheron, C Picard-Dahan, P Yeni), Corevih Ile de France Ouest (Hôpital Ambroise Paré: H Berthé, C Dupont; Hôpital Louis Mourier: C

Chandemerle, E Mortier; Hôpital Raymond Poincaré: P de Truchis), Corevih Ile de France Sud (Hôpital Européen Georges Pompidou: D Tisne-Dessus, L Weiss; GH Tarnier-Cochin: D Salmon; Hôpital Saint-Joseph: I Auperin, J Gilquin; Hôpital Necker adultes: L Roudière, JP Viard; Hôpital Antoine Béclère: F Boué, R Fior; Hôpital de Bicêtre: JF Delfraissy, C Goujard; Hôpital Henri Mondor: C Jung, Ph Lesprit; Hôpital Paul Brousse: D Vittecoq). Outside Paris area: Corevih Alsace (CHRU de Strasbourg: P Fraisse, JM Lang, D Rey; CH de Mulhouse: G Beck-Wirth), Corevih de l'Arc Alpin (CHU de Grenoble: JP Stahl, P Lecercq), Corevih Auvergne-Loire (CHU de Clermont-Ferrand: F Gourdon, H Laurichesse; CHRU de Saint-Etienne: A Fresard, F Lucht); Corevih Basse-Normandie (CHRU de Caen: C Bazin, R Verdon), Corevih Bourgogne (CHRU de Dijon: P Chavanet), Corevih Bretagne (CHU de Rennes: C Arvieux, C Michelet), Corevih Centre (CHRU de Tours: P Choutet, A Goudeau, MF Maître), Corevih Franche-Comté (CHRU de Besançon: B Hoen; CH de Belfort: P Eglinger, JP Faller); Corevih Haute-Normandie (CHRU de Rouen: F Borsa-Lebas, F Caron), Corevih Languedoc-Roussillon (CHU de Montpellier: J Reynes; CHG de Nîmes: JP Daures), Corevih Lorraine (Nancy Hôpital de Brabois: T May, C Rabaud; CHRU de Reims: JL Berger, G Rémy), Corevih de Midi-Pyrénées (Toulouse CHU Purpan: E Arlet-Suau, L Cuzin, P Massip, MF Thiercelin Legrand; Toulouse Hôpital la Grave: G Pontonnier; Toulouse CHU Rangueil), Corevih Nord-Pas de Calais (CH de Tourcoing: N Viget, Y Yasdanpanah), Corevih PACA Est (Nice Hôpital Archet 1: P Dellamonica, C Pradier, P Pugliese; CHG Antibes-Juan les Pins: K Aleksandrowicz, D Quinsat), Corevih PACA Ouest (Marseille Hôpital de la Conception: I Ravaux, H Tissot-Dupont; Marseille Hôpital Nord: JP Delmont, J Moreau; Marseille Institut Paoli Calmettes: JA Gastaut; Marseille Hôpital Sainte-Marguerite: I Poizot-Martin, F Retornaz, J Soubeyrand; Marseille Centre pénitentiaire des Baumettes: A Galinier, JM Ruiz; CHG d'Aix-En-Provence: T Allegre, PA Blanc; CH d'Arles: D Bonnet-Montchardon; CH d'Avignon: G Lepeu; CH de Digne Les Bains: P Granet-Brunello; CH de Gap: JP Esterni, L Pelissier; CH de Martigues: R Cohen-Valensi, M Nezri; CHI de Toulon: S Chadapaud, A Laffeuillade), Corevih Pays de la Loire (CHRU de Nantes: E Billaud, F Raffi), Corevih de la Vallée du Rhône (Lyon Hôpital de la Croix-Rousse: A Boibieux, D Peyramond; Lyon Hôpital Edouard Herriot: JM Livrozet, JL Touraine; Lyon Hôtel-Dieu: L Cotte, C Trepo). Overseas: Corevih Guadeloupe (CHRU de Pointe-à-Pitre: M Strobel; CH Saint-Martin: F Bissuel), Corevih Guyane (CHG de Cayenne: R Pradinaud, M Sobesky), Corevih Martinique (CHRU de Fort-de-France: A Cabié), Corevih de La Réunion (CHD Félix Guyon: C Gaud, M Contant).

Swiss HIV Cohort Study (SHCS): Aubert V, Barth J, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kovari H, Kouyos R, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Staehelin C, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

GEMES

Principal Investigator: R Muga/S Pérez-Hoyos. Data analysis center: S Pérez-Hoyos, A Schiaffino Centro Nacional de Epidemiología: J del Amo, D Alvarez, S Monge. Participating centres: Cohorte del Hospital Germans Trias I Pujol, Badalona (R Muga, A Sanvisens, B Clotet, J Tor, F Bolao, I Rivas, D Fuster), Cohorte de Madrid-Sandoval (J del Romero, P Raposo, C Rodríguez, M Vera), Cohorte de los CIPS de la Comunidad Valenciana (I Hurtado, J Belda, E Fernandez, I Alastrue, C Santos, T Tasa, A Juan, J Trullen), Cohortes de los CAS, de las Prisiones de Cataluña y de hemofílicos del Hospital Vall d'Hebron, Barcelona (P Garcia de Olalla, J Cayla, E Masdeu, H Knobel, JM Mirò, MA Sambeat, R Guerrero, E Rivera), Cohorte de hemofílicos del Hospital La Paz, Madrid (M Quintana, C Gonzalez), Cohorte de Navarra (J Castilla, M Guevara). Laboratory: C de Mendoza, N Zahonero, M Ortíz.

IPEC

Principal investigators: Beatriz Grinsztejn and Valdiléa G Veloso. Collaborators: Lara Coelho, Raquel De Boni, Dayse P Campos, Antonio G Pacheco, Paula M Luz, Rodrigo de C. Moreira, Ronaldo I Moreira, Ruth K Friedman, Marilia Santini-Oliveira, Sandra W Cardoso, Monica Derrico, Sayonara R Ribeiro, Leonardo Eksterman, Hugo Perazzo, Estevão P. Nunes, Maria R. Guimarães, Rodolfo Castro, Marcelo Ribeiro-Alves, Katia Lemos, Jose Roberto Grangeiro, Mario Sergio Pereira, Luciane Velasque, Jose Ricardo Coutinho, Angela Cristina Andrade, Juliana Netto, Rodrigo Otavio Escada, Desiree Gomes Santos, Flaviana Pavan.

PISCIS

Coordinators: J. Casabona, Centre d'Estudis Epidemiològics les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Jose M. Miró (Hospital Clínic de Barcelona-Idibaps, Universitat de Barcelona, Barcelona, Spain). Field coordinator: A. Gallois (CEEISCAT). Steering committee: J. Casabona, A. Gallois, A. Esteve (CEEISCAT), Jose M. Miró (Hospital Clínic de Barcelona-Idibaps, Universitat de Barcelona), D. Podzamczer (Hospital de Bellvitge de Barcelona), J. Murillas (Hospital Son Espases). Scientific committee: JM Gatell, C. Manzardo (Hospital Clínic-Idibaps, Universitat de Barcelona), C. Tural, B. Clotet (Hospital Universitari Germans Trias i Pujol, Universitat Autónoma de Barcelona), E. Ferrer (Hospital de Bellvitge), M. Riera (Hospital Son Espases), F. Segura, G. Navarro (Corporación Sanitaria Universitaria Parc Taulí, Universitad Autónoma de Barcelona), L. Force (Hospital de Mataró), J. Vilaró (Hospital General de Vic), A. Masabeu (Hospital de Palamós), I. García (Hospital General d'Hospitalet), M.Guadarrama (Hospital Alt Penedès de Vilafranca), C. Cifuentes (Hospital Son Llàtzer), D. Dalmau, À. Jaen (Hospital Universitari Mútua de Terrassa), C. Agustí (CEEISCAT). Data Management and statistical analysis: A. Esteve, A. Montoliu (CEEISCAT), I. Pérez (Hospital Clínic-Idibaps, Universitat de Barcelona). Technical support: I. Pérez (Hospital Clínic de Barcelona-Idibaps, Universitat de Barcelona), Freyra Gargoulas (Hospital Son Espases and Hospital Son Llàtzer). Clinicians involved: JL Blanco, F. Garcia-Alcaide, E. Martínez, J. Mallolas, M. López-Dieguez, JF García-Goez, (Hospital Clínic-Idibaps, Universitat de Barcelona), G.

Sirera, J. Romeu, A. Jou. E. Negredo, C. Miranda, MC Capitan (Hospital Universitari Germans Trias i Pujol, Universitat Autónoma de Barcelona), M. Saumoy, A. Imaz, JM Tiraboschi, O. Murillo, F. Bolao, C. Peña, C. Cabellos, M Masó, A. Vila (Hospital Universitari de Bellvitge), M. Sala, M. Cervantes, Mª Jose Amengual, M. Navarro, E Penelo (Corporación Sanitaria Universitaria Parc Taulí, Universitad Autónoma de Barcelona), P. Barrufet, G. Bejarano (Hospital de Mataró, Barcelona), J. Molina, M. Guadarrama, M. Alvaro, J. Mercadal (Hospital Alt Penedès de Vilafranca). Civil society representatives: Juanse Fernández (Comitè 1er de Desembre), Jesús E. Ospina (RedVIH).

PRIMO

JM Molina, B Loze (St Louis - Paris), P Morlat, M Bonarek, F Bonnet, C Nouts, I Louis (St André - Bordeaux), F Raffi, V Reliquet, F Sauser, C Biron, O Mounoury, H Hue, D Brosseau (Hotel Dieu - Nantes), JF Delfraissy, C Goujard, J Ghosn, MT Rannou (Bicêtre – Le Kremlin Bicêtre), JF Bergmann, E Badsi, A Rami, M Diemer, MParrinello (Lariboisière - Paris), PM Girard, D Samanon-Bollens, P Campa, M Tourneur, N Desplanques (St Antoine - Paris), JM Livrozet, F Jeanblanc, P Chiarello, D Makhloufi (E Herriot - Lyon), AP Blanc, T Allègre (CHG - Aix en Provence), J Reynes, V Baillat, V Lemoing, C Merle de Boever, C Tramoni (Gui de Chauliac - Montpellier), A Cabié, G Sobesky, S Abel, V Beaujolais (CHU - Fort de France), G Pialoux, L Slama, C Chakvetadze, V Berrebi (Tenon - Paris), P Yeni, E Bouvet, I Fournier, J Gerbe (Bichat - Paris), C Trepo, K Koffi, C Augustin-Normand, P Miailhes, V Thoirain, C Brochier (Hotel Dieu - Lyon), R Thomas, F Souala, M Ratajczak (Pontchaillou - Rennes), J Beytoux, C Jacomet, F Gourdon (G Montpied - Clermont-Ferrand), E Rouveix, S Morelon, C Dupont, C Olivier (A Paré - Boulogne), O Lortholary, B Dupont, JP Viard, A Maignan (Necker - Paris), JM Ragnaud, I Raymond (Pellegrin - Bordeaux), C Leport, C Jadand, C Jestin, P Longuet, S Boucherit (Bichat - Paris), D Sereni, C Lascoux, F Prevoteau (St Louis - Paris), A Sobel, Y Levy, JD Lelièvre, AS Lascaux, S Dominguez, C Dumont (H Mondor - Créteil), H Aumaître, B Delmas, M Saada, M Medus (St Jean - Perpignan), L Guillevin, D Salmon, T Tahi (Cochin - Paris), Y Yazdanpanah, S Pavel, MC Marien (CH Dron - Tourcoing), B Drenou, G Beck-Wirth, C Beck, M Benomar (E Muller - Mulhouse), C Katlama, R Tubiana, H Ait Mohand, A Chermak, S Ben Abdallah (Pitié-Salpétrière - Paris), M Bentata, F Touam, (Avicenne - Bobigny), B Hoen, C Drobacheff, A Folzer (St Jacques - Besançon), P Massip, M Obadia, L Prudhomme, E Bonnet, F Balzarin (Purpan - Toulouse), E Pichard, JM Chennebault, P Fialaire, J Loison (CHR - Angers), P Galanaud, F Boué, D Bornarel (Béclère - Clamart), R Verdon, C Bazin, M Six, P Ferret (CHR Côte de Nacre - Caen), L Weiss, D Batisse, G Gonzales-Canali, D Tisne-Dessus (HEGP - Paris), A Devidas, P Chevojon, I Turpault (Corbeil Essonnes), A Lafeuillade, A Cheret, G Philip (Chalucet - Toulon), P Morel, J Timsit (St Louis - Paris), S Herson, N Amirat, A Simon, C Brancion (Pitié-Salpétrière - Paris), J Cabane, O Picard, J Tredup, N Desplanques (St Antoine - Paris), A Stein, I Ravault (La Conception - Marseille), C Chavanet, M Buisson, S Treuvetot (Bocage - Dijon), P Choutet, P Nau, F Bastides (Bretonneau - Tours), T May, L Boyer, S Wassoumbou (CHU - Nancy), E Oksenhendeler, L Gérard (St Louis - Paris), L Bernard, P De Truchis, H Berthé (R Poincaré - Garches), Y Domart, D Merrien (CH - Compiègne), A Greder Belan, (A Mignot - Le Chesnay), M Gayraud, L Bodard, A Meudec (IMM Jourdan - Paris), C Beuscart, C Daniel, E Pape (La

Beauchée - St Brieuc), P Vinceneux, AM Simonpoli, A Zeng (L Mourier - Colombes), L Fournier (M Jacquet - Melun), JG Fuzibet, C Sohn, E Rosenthal, M Quaranta (L'Archet - Nice), P Dellamonica, S Chaillou, M Sabah (L'Archet - Nice), B Audhuy, A Schieber (L Pasteur - Colmar), P Moreau, M Niault, O Vaillant (Bretagne Sud - Lorient), G Huchon, A Compagnucci (Hotel-Dieu - Paris), I De Lacroix Szmania, L Richier (Intercommunal - Créteil), I Lamaury (Abymes - Pointe à Pitre), F Saint-Dizier, D Garipuy (Ducuing – Toulouse), JA Gastaut, MP Drogoul, I Poizot Martin, G Fabre (St Marguerite – Marseille), G Lambert de Cursay, B Abraham, C Perino (CH - Brives), P Lagarde, F David (CH - Lagny), J Roche-Sicot, JL Saraux, A Leprêtre (S Veil - Eaubonne), B Fampin, A Uludag, AS Morin (Beaujon – Clichy), O Bletry, D Zucman (Foch - Suresnes), A Regnier (CH - Vichy), JJ Girard (CH - Loches), DT Quinsat, L Heripret (CH - Antibes), F Grihon (Haute Vallée de l'Oise - Noyon), D Houlbert (CH - Alençon), M Ruel, K Chemlal (CH - Nanterre), F Caron, Y Debab (C Nicolle - Rouen), F Tremollieres, V Perronne (F Quesnay - Mantes La Jolie), G Lepeu, B Slama (H Duffaut - Avignon), P Perré (Les Oudairies - La Roche sur Yon), C Miodovski (Paris), G Guermonprez, A Dulioust (CMC Bligny - Briis s/Forges), P Boudon, D Malbec (R Ballanger - Aulnay s/bois), O Patey, C Semaille (CH - Villeneuve St Georges), J Deville, G Remy, I Béguinot (CH - Reims).

SEROCO

Hopital Antoine Beclere, Clamart (P Galanaud, F Boue, V Chambrin, C Pignon, GA Estocq, A Levy), Hopital de Bicetre, Le Kremlin Bicetre (JF Delfraissy, C Goujard, M Duracinsky, P Le Bras, MS Ngussan, D Peretti, N Medintzeff, T Lambert, O Segeral, P Lezeau, Y Laurian), Hopital Europeen Georges Pompidou, Paris (L Weiss, M Buisson, C Piketty, M Karmochkine, D Batisse, M Eliaszewitch, D Jayle, D Tisne- Dessus, M Kazatchkine), Hopital Bichat Claude Bernard, Paris (C Leport, U Colasante, C Jadand, C Jestin, X Duval, W Nouaouia, S Boucherit, JL Vilde), Hopital Saint Antoine, Paris (PM Girard, D Bollens, D Binet, B Diallo, MC Meyohas, L Fonquernie, JL Lagneau), Hopital Cochin, Paris (D Salmon, LGuillevin, T Tahi, O Launay, MP Pietrie, D Sicard, N Stieltjes, J Michot), Hopital Henri Mondor, Creteil (A Sobel, Y Levy, F Bourdillon, AS Lascaux, JD Lelievre, C Dumont), Hopital Necker, Paris (B Dupont, G Obenga, JP Viard, A Maignan), Hopital Paul Brousse, Villjuif (D Vittecoq, L Escaut, C Bolliot), Hopital Pitie Salpetriere, Paris (F Bricaire, C Katlama, L Schneider, S Herson, A Simon, M Iguertsira), Hopital de la Conception, Marseille (A Stein, C Tomei, I Ravaux, C Dhiver, H Tissot Dupont, A Vallon, J Gallais, H Gallais), Hopital Sainte Marguerite, Marseille (JA Gastaut, MP Drogoul, G Fabre), Hopital de L'Archet, Nice (P Dellamonica, J Durant, V Mondain, I Perbost, JP Cassuto, JM Karsenti, H Venti, JG Fuzibet, E Rosenthal, C Ceppi, M Quaranta), Hopital Avicenne, Bobigny (JA Krivitsky, M Bentata, O Bouchaud, P Honore), Hopital Saint Louis, Paris (D Sereni, C Lascoux, J Delgado), ACCTES / Hopital Necker, Paris (C Rouzioux, M Burgard, L Boufassa), Hopital Mignot, Le Chesnay (J Peynet).

SOUTHERN ALBERTA CLINIC COHORT

John Gill, Hartmut Krentz and Ron Read (Southern Alberta Clinic, Calgary, Canada).

SWISS HIV COHORT STUDY

Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

UK CHIC

Steering Committee: Jonathan Ainsworth, Sris Allan, Jane Anderson, Abdel Babiker, David Chadwick, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard, Richard Gilson, Mark Gompels, Phillip Hay, Teresa Hill, Margaret Johnson, Sophie Jose, Stephen Kegg, Clifford Leen, Fabiola Martin, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Frank Post, Jillian Pritchard, Caroline Sabin, Achim Schwenk, Anjum Tariq, Roy Trevelion, John Walsh. Central Co-ordination: University College London (Teresa Hill, Sophie Jose, Andrew Phillips, Caroline Sabin); Medical Research Council Clinical Trials Unit at UCL (MRC CTU at UCL), London (David Dunn, Adam Glabay). Participating Centres: Brighton and Sussex University Hospitals NHS Trust (M Fisher, N Perry, S Tilbury, E Youssef, D Churchill); Chelsea and Westminster Hospital NHS Foundation Trust, London (B Gazzard, M Nelson, R Everett, D Asboe, S Mandalia); King's College Hospital NHS Foundation Trust, London (F Post, H Korat, C Taylor, Z Gleisner, F Ibrahim, L Campbell); Mortimer Market Centre, University College London (R Gilson, N Brima, I Williams); Royal Free NHS Foundation Trust/University College London (M Johnson, M Youle, F Lampe, C Smith, R Tsintas, C Chaloner, S Hutchinson, C Sabin, A Phillips T Hill, S Jose); Imperial College Healthcare NHS Trust, London (J Walsh, N Mackie, A Winston, J Weber, F Ramzan, M Carder); Barts and The London NHS Trust, London (C Orkin, J Lynch, J Hand, C de Souza); Homerton University Hospital NHS Trust, London (J Anderson, S Munshi); North Middlesex University Hospital NHS Trust, London (J Ainsworth, A Schwenk, S Miller, C Wood); The Lothian University Hospitals NHS Trust, Edinburgh (C Leen, A Wilson, S Morris); North Bristol NHS Trust (M Gompels, S Allan); Leicester, University Hospitals of Leicester NHS Trust (A Palfreeman, K Memon, A Lewszuk); Middlesbrough, South Tees Hospitals NHS Foundation Trust, (D Chadwick, E Cope, J Gibson); Woolwich, Lewisham and Greenwich NHS Trust (S Kegg, P Main, Dr Mitchell, Dr Hunter), St. George's Healthcare NHS Trust (P Hay, M Dhillon); York Teaching Hospital NHS Foundation Trust (F Martin, S Russell-Sharpe); Coventry, University Hospitals Coventry and Warwickshire NHS Trust (S Allan, A Harte, S Clay); Wolverhampton, The Royal Wolverhampton Hospitals NHS Trust (A Tariq, H Spencer, R Jones); Chertsey, Ashford and St.Peter's Hospitals NHS Foundation Trust (J Pritchard, S Cumming, C Atkinson); Public Health England, London (V Delpech); HIV i-base (R Trevelion).

UK Register of HIV Seroconverters

Steering Committee: Andrew Phillips (Chair), University College London (UCL), London; Abdel Babiker, MRC CTU, London; Valerie Delpech, Public Health England, London; Sarah Fidler, St. Mary's Hospital, London; Martin Fisher, Brighton & Sussex University Hospitals NHS Trust, Brighton; Julie Fox, Guys and St Thomas' NHS Trust/ Kings College, London; Richard Gilson, West London Centre for Sexual Health, London; David Goldberg, Health Protection Scotland, Glasgow; David Hawkins, Chelsea & Westminster NHS Trust, London; Anne Johnson, UCL, London; Margaret Johnson, UCL and Royal Free NHS Trust, London; Ken McLean, West London Centre for Sexual Health, London; Deenan Pillay, UCL, London; Frank Post, Kings College, London. Collaborating clinical centres: N Kennedy, Monklands Hospital, Airdrie; J Pritchard, Ashford Hospital, Ashford; U Andrady, Ysbyty Gwynedd, Bangor; N Rajda, North Hampshire Hospital, Basingstoke; C Donnelly, S McKernan, Royal Victoria Hospital, Belfast; S Drake, G Gilleran, D White, Birmingham Heartlands Hospital, Birmingham; J Ross, J Harding, R Faville, Whittall Street Clinic, Birmingham; J Sweeney, P Flegg, S Toomer, Blackpool Victoria Hospital, Blackpool; H Wilding, R Woodward, Royal Bournemouth Hospital, Bournemouth; G Dean, C Richardson, N Perry, Royal Sussex County Hospital, Brighton; M Gompels, L Jennings, Southmead Hospital, Bristol; D Bansaal, Queens Hospital, Burton-upon-Trent; M Browing, L Connolly, Cardiff Royal Infirmary, Cardiff; B Stanley, North Cumbria Acute Hospitals NHS Trust, Carlisle; S Estreich, A Magdy, St. Helier Hospital, Carshalton; C O'Mahony, Countess of Chester Hospital, Chester; P Fraser, Chesterfield & North Derbyshire Royal Hospital, Chesterfield; SPR Jebakumar, Essex County Hospital, Colchester; L David, Coventry & Warwickshire Hospital, Coventry; R Mette, Mayday University Hospital, Croydon; H Summerfield, Weymouth Community Hospital, Dorset; M Evans, Ninewells Hospital, Dundee; C White, University Hospital of North Durham, Durham; R Robertson, Muirhouse Medical Group, Edinburgh; C Lean, S Morris, Western General Hospital, Edinburgh; A Winter, Gartnavel General Hospital & Glasgow Royal Infirmary, Glasgow; S Faulkner, Gloucestershire Royal Hospital, Gloucester; B Goorney, Salford Hope Hospital, Greater Manchester; L Howard, Farnham Road Hospital, Guildford; I Fairley, C Stemp, Harrogate Hospital, Harrogate; L Short, Huddersfield Royal Infirmary, Huddersfield; M gomez, F young, St Mary's Hospital Isle of Wight; M Roberts, S Green, Kidderminster General Hospital, Kidderminster; K Sivakumar, The Queen Elizabeth Hospital, King's Lynn; J Minton, A Siminoni, Leeds General Infirmary, Leeds; J Calderwood, D Greenhough, J Minton, St. James Hospital, Leeds; C DeSouza, Lisa Muthern, C Orkin, Barts & The London NHS Trust, London; S Murphy, M Truvedi, Central Middlesex Hospital, London; K McLean, Charing Cross Hospital, London; D Hawkins, C Higgs, A Moyes, Chelsea & Westminster Hospital, London; S Antonucci, S McCormack, Dean Street Clinic, London; W Lynn, Ealing Hospital, London; M Bevan, J Fox, A Teague, Guy's & St. Thomas NHS Trust, London; J Anderson, S Mguni, Homerton Hospital, London; F Post, L Campbell, E Wandolo King's College Hospital, London; C Mazhude, H Russell, Lewisham University Hospital, London; R Gilson, G Carrick, C Young Mortimer Market Centre, London; J Ainsworth, A Waters, North Middlesex Hospital, London; P Byrne, M Johnson, Royal Free Hospital, London; London; S Fidler, K Kuldanek, S Mullaney, St. Mary's Hospital, London; V Lawlor, R Melville, Whipps Cross Hospital, London; A Sukthankar, S Thorpe,

Manchester Royal Infirmary, Manchester; C Murphy, E Wilkins, North Manchester General Hospital, Manchester; S Ahmad, P Green, Withington Hospital, Manchester; S Tayal, James Cook Hospital, Middlesbrough; E Ong, Newcastle General Hospital, Newcastle; J Meaden, Norfolk & Norwich University Hospital, Norwich; L Riddell, City Hospital, Nottingham; D Loay, K Peacock, George Eliot Hospital, Nunneaton; H Blackman, V Harindra, St. Mary's Hospital, Portsmouth; AM Saeed, Royal Preston Hospital, Preston; S Allen, U Natarajan, East Surrey Hospital, Redhill; O Williams, Glan Clwyd District General, Rhyl; H Lacey, Baillie Street Health Centre, Rochdale; C Care, C Bowman, S Herman, Royal Hallamshire Hospital, Sheffield; S V Devendra, J Wither, Royal Shrewsbury Hospital, Shrewsbury; A Bridgwood, G Singh, North Staffordshire Hospital, Stoke-on-Trent; S Bushby, Sunderland Royal Hospital, Sunderland; D Kellock, S Young, King's Mill Centre, Sutton-in-Ashfield; G Rooney, B Snart, The Great Western Hospital, Swindon; J Currie, M. Fitzgerald, Taunton & Somerset Hospital, Taunton; J Arumainayyagam, S Chandramani, Manor Hospital, Walsall; S Rajamanoharan, T Robinson, Watford General Hospital, Watford; M Roberts, Worcester Royal Infirmary, Worcester; O Williams, Maelor Hospital, Wrexham; B Taylor, Wycombe General Hospital, Wycombe; C Brewer, I Fairley, Monkgate Health Centre, York Hospital NHS Trust, York.

Veterans Aging Cohort Study-Virtual Cohort

Principal investigator and co-principal investigator: AC Justice, DA Fiellin. Participating VA centers: Atlanta, GA (D. Rimland, C Jones-Taylor), Baltimore, MD (KA Oursler, R Titanji), Bronx, NY (S Brown, S Garrison), Houston, TX (M Rodriguez-Barradas, N Masozera), Los Angeles, CA (M Goetz, D Leaf), Manhattan-Brooklyn, NY (M Simberkoff, D Blumenthal, J Leung), Pittsburgh, PA (A Butt, E Hoffman), and Washington, DC (C Gibert, R Peck). Core Faculty: K Mattocks (Deputy Director), S Braithwaite, C Brandt, K Bryant, R Cook, J Conigliaro, K Crothers, J Chang, S Crystal, N Day, J Erdos, M Freiberg, M Kozal, N Gandhi, M Gaziano, M Gerschenson, B Good, A Gordon, JL Goulet, MA Hernán, K Kraemer, J Lim, S Maisto, P Miller, L Mole, P O'Connor, R Papas, JM Robins, C Rinaldo, M Roberts, J Samet, B Tierney, J Whittle.

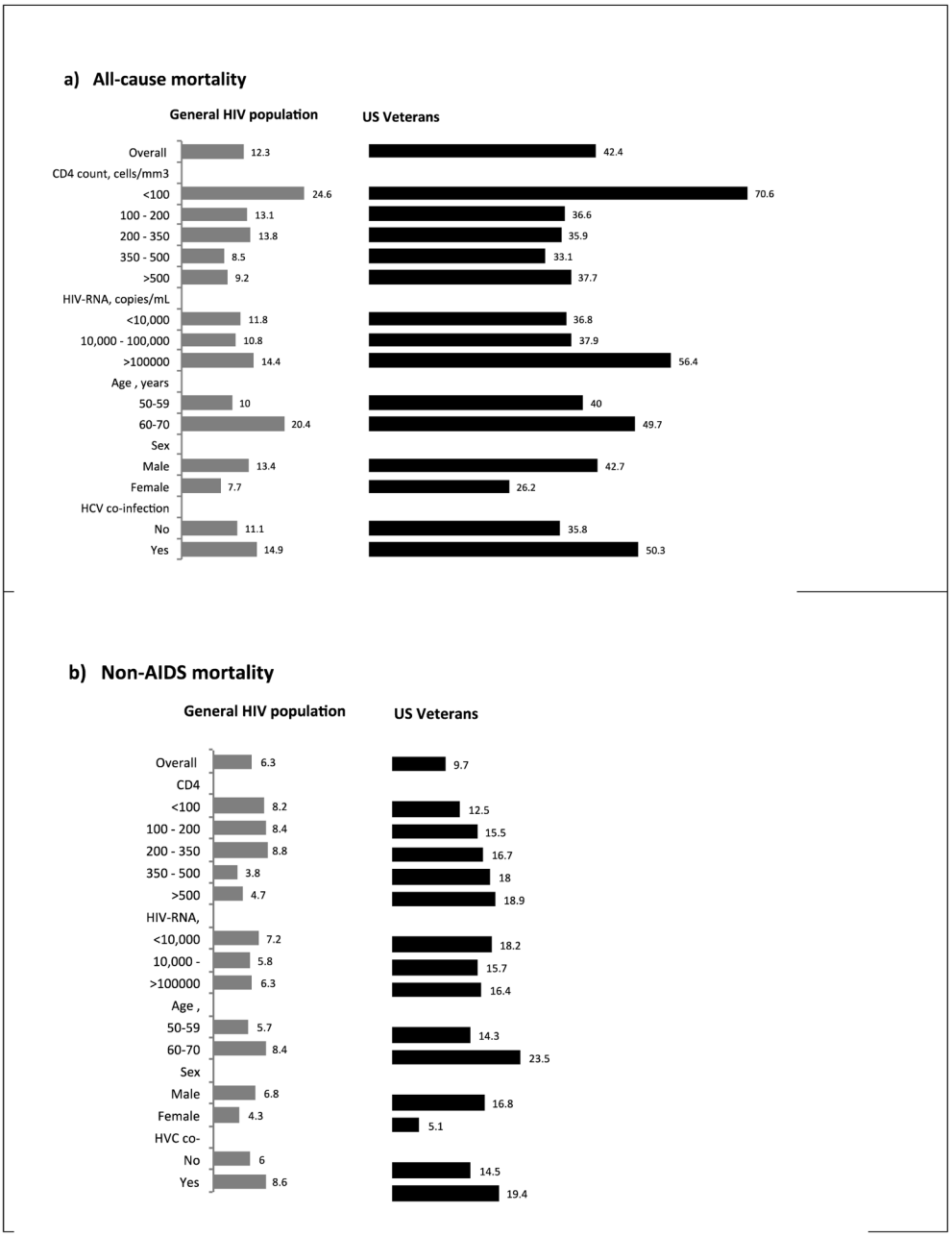
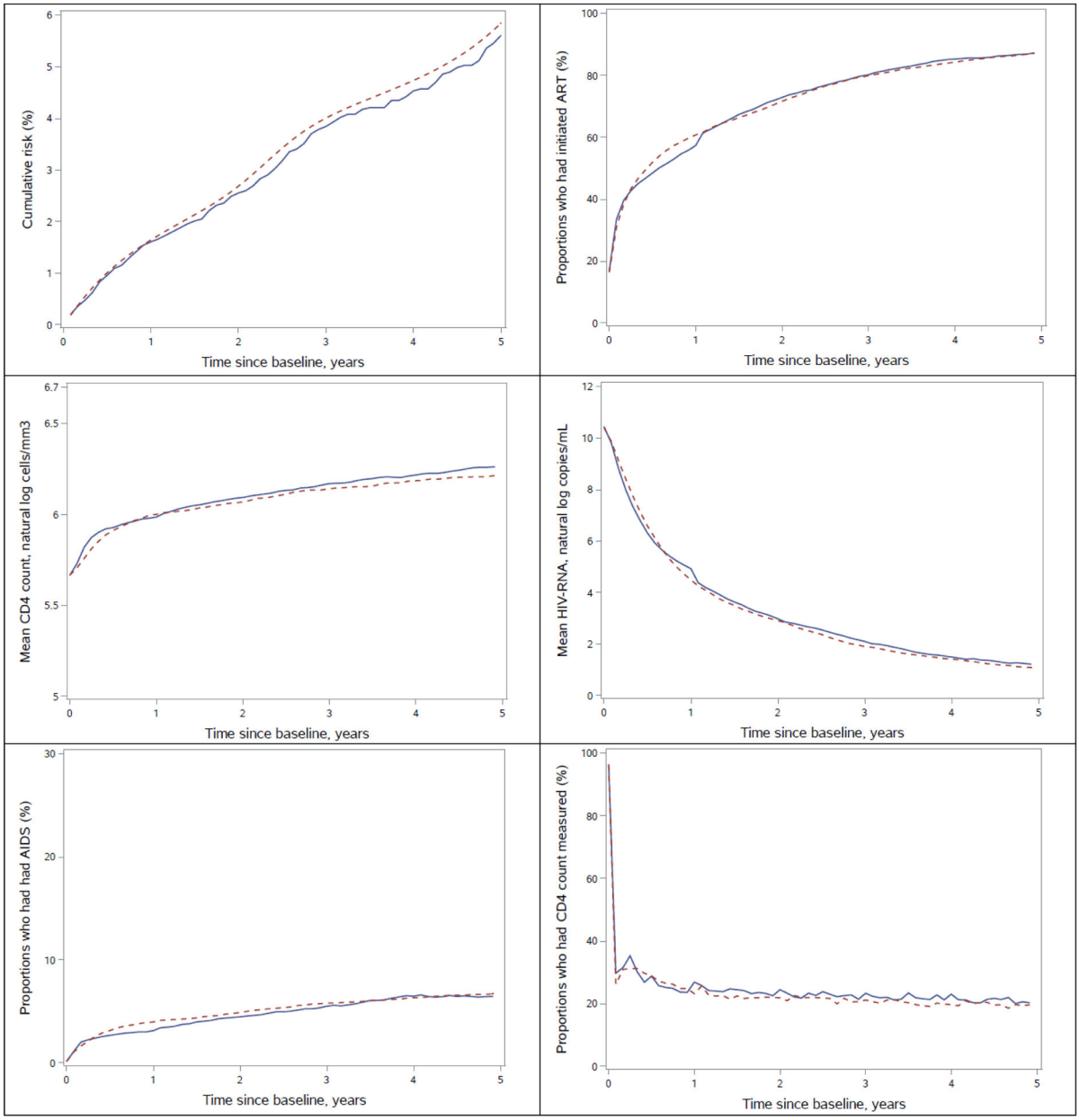


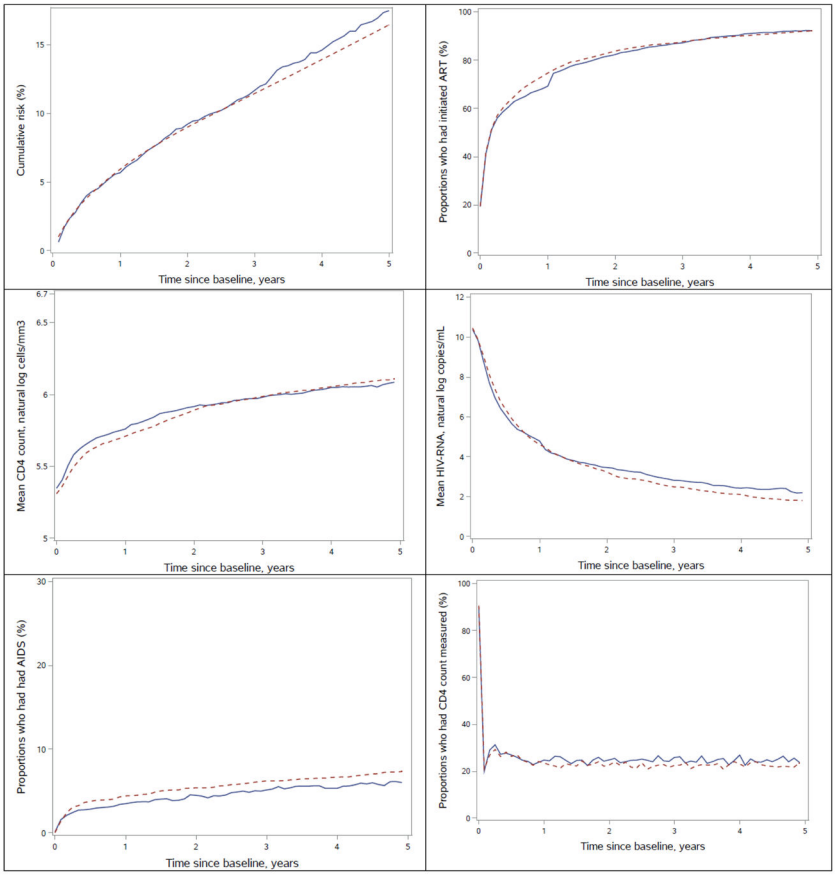
Figure 1.

Rates (number of events per 1000 person-years) of (a) all-cause mortality and (b) non-AIDS mortality by baseline characteristics and by background mortality group, HIV-CAUSAL Collaboration 2005–2015.

Appendix Figure 1. a



Appendix Figure 1. b

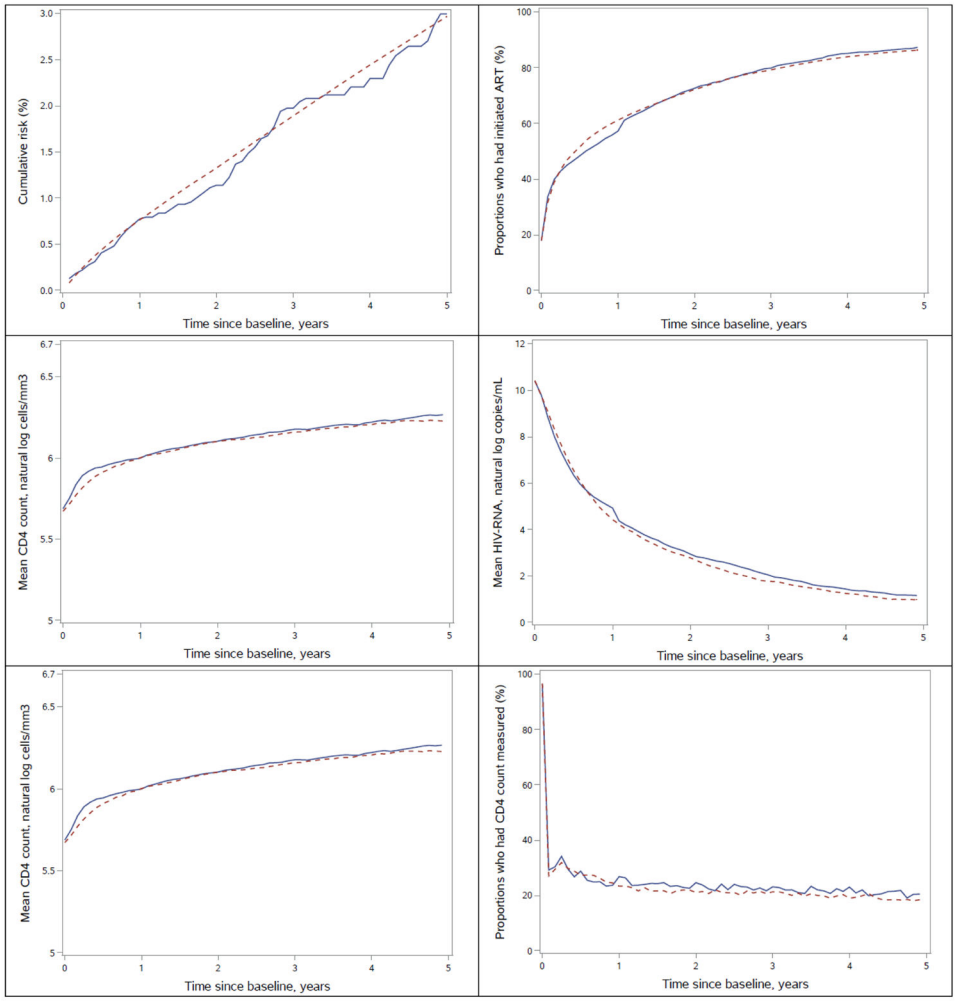


Appendix Figure 1.

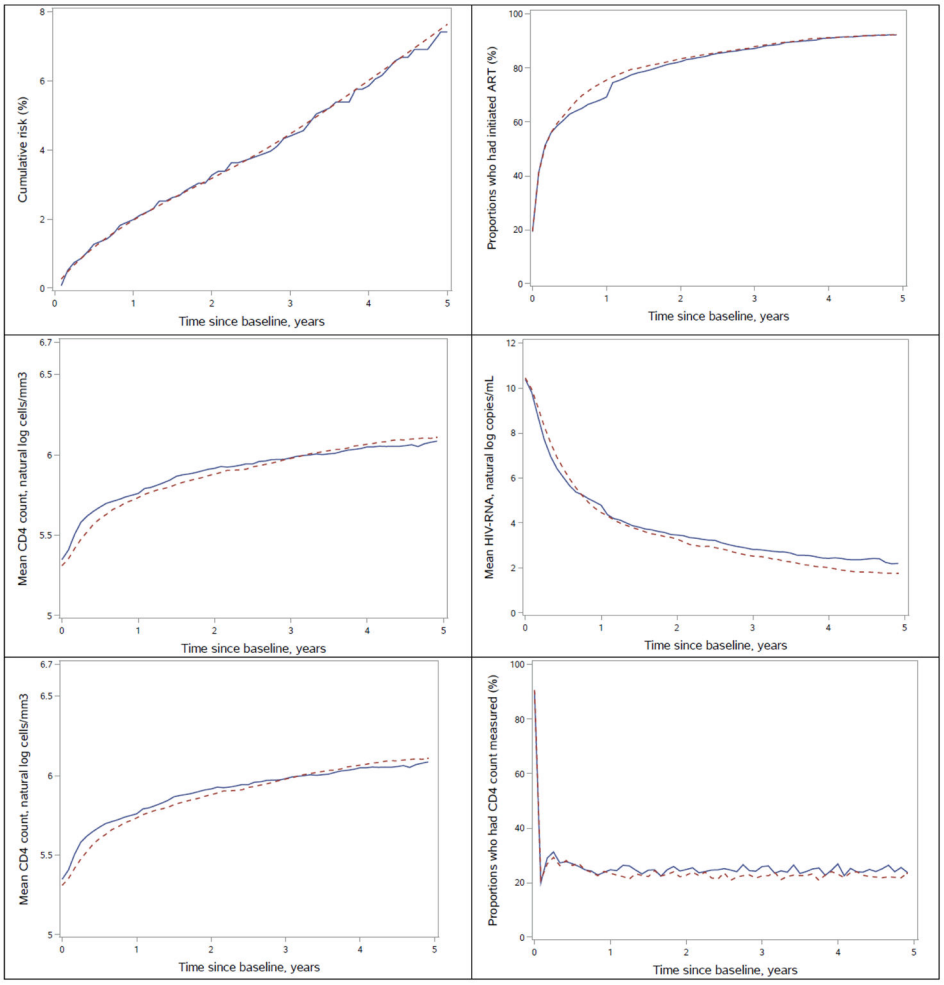
Appendix Figure 1a. Mean of the all-cause mortality outcome and time-varying variables in the general HIV population: observed (solid line) and simulated via the parametric g-formula (dashed line).

Appendix Figure 1. b. Mean of the all-cause mortality outcome and time-varying variables in the US Veteran population: observed (solid line) and simulated via the parametric g-formula (dashed line).

Appendix Figure 2. a



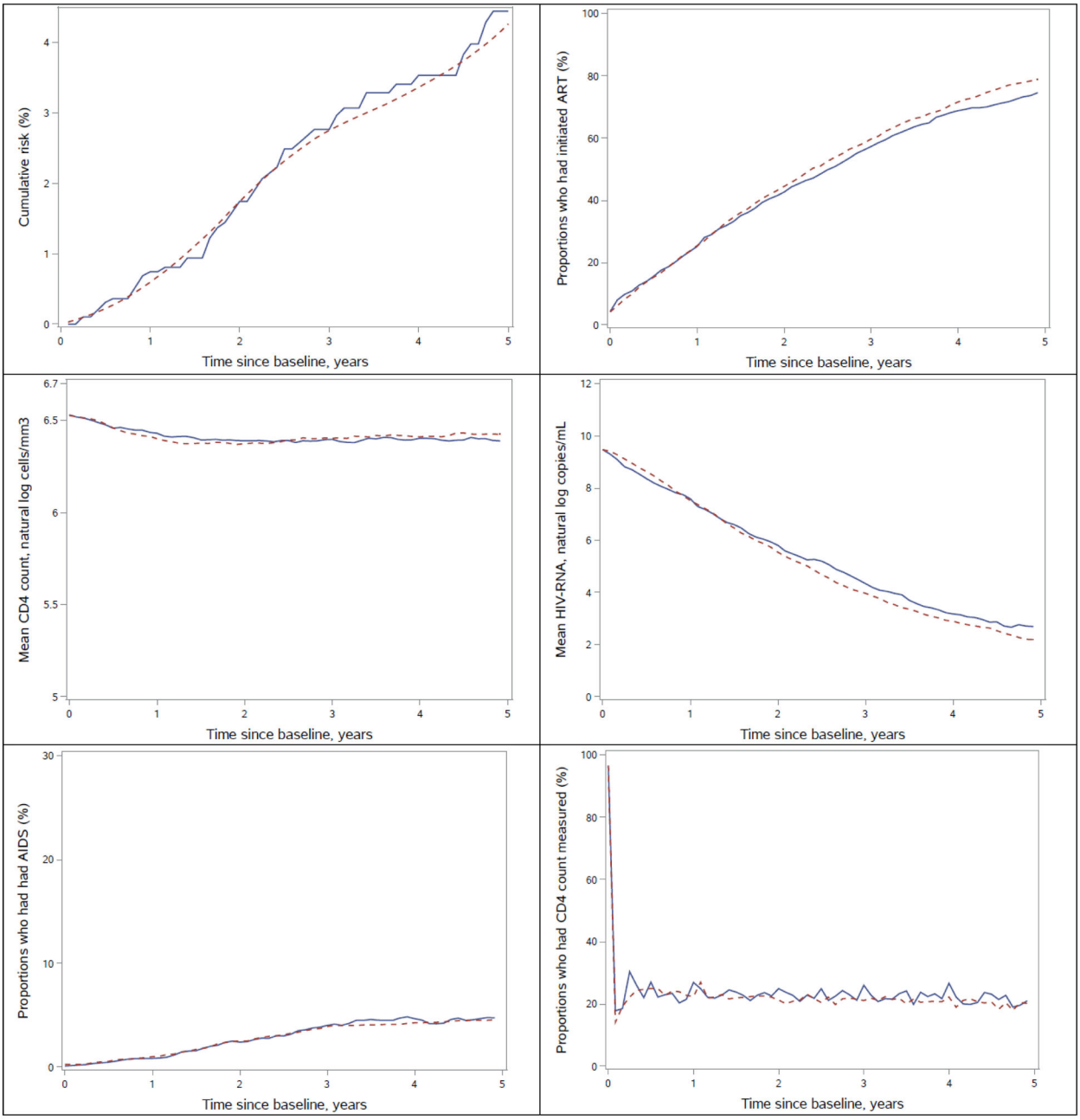
Appendix Figure 2. b



Appendix Figure 2.

Appendix Figure 2. a. Mean of the non-AIDS mortality outcome and time-varying variables in the general HIV population: observed (solid line) and simulated via the parametric g-formula (dashed line).

Appendix Figure 2. b. Mean of the non-AIDS mortality outcome and time-varying variables in the US Veteran population: observed (solid line) and simulated via the parametric g-formula (dashed line).



Appendix Figure 3.

Mean of the all-cause mortality outcome and time-varying variables in the general HIV population with baseline CD4 cell count≥500 cells/mm^3: observed (solid line) and simulated via the parametric g-formula (dashed line).

Table 1

Baseline characteristics by background mortality group, HIV-CAUSAL Collaboration 2005–2015.

Baseline characteristics		General HIV population			U.S. Veterans		
		Included (%)	Initiators of ART during follow-up	Median [IQR] follow-up, months	Included (%)	Initiators of ART during follow-up	Median [IQR] follow-up, months
CD4 count, cells/mm^3	<100	798 (12%)	88%	30 [13,54]]	532 (20%)	87%	26 [12,53]
	100 – 200	878 (13%)	89%	33 [15,57]	435 (16%)	87%	27 [14,54]
	200 – 349	1725 (25%)	85%	35 [17,64]	626 (23%)	83%	29 [14,55]
	350 – 499	1534 (22%)	71%	34 [15,62]	495 (19%)	76%	29 [13,60]
	≥500	1992 (29%)	57%	34 [15,62]	584 (22%)	60%	29 [14,57]
HIV-RNA, copies/mL	<10,000	1612 (23%)	58%	35 [15,66]	686 (26%)	63%	38 [11,53]
	10,000 – 100,000	2855 (41%)	75%	33 [15,62]	1266 (47%)	81%	30 [15,58]
	>100,000	2460 (36%)	85%	33 [16,59]	720 (27%)	87%	27 [12,52]
Sex	Male	5493 (79%)	76%	34 [16,63]	2607 (98%)	78%	28 [13,56]
	Female	1434 (21%)	70%	31 [14,58]	65 (2%)	74%	30 [15,50]
Mode of acquisition	Heterosexual	3149 (45%)	73%	32 [15,59]			
	Homo/bisexual	2960 (43%)	77%	39 [18,69]			
	Injection drug use	161 (2%)	67%	21 [11,45]			
	Other/unknown	657 (9%)	70%	26 [11,50]	2672 (100%)	78%	28 [13,56]
Geographical origin	Western Countries	4386 (63%)	76%	36 [16,66]			
	Sub-Saharan Africa	415 (6%)	69%	26 [11,51]			
	Rest of World	611 (9%)	72%	28 [14,51]			
	Unknown country	1515 (22%)	73%	31 [14,60]	2672 (100%) (100%R	74%	28 [13,56]
Calendar year	2005–2009	4212 (61%)	77%	52 [26,79]	1791 (67%)	86%	45 [23,67]
	2010 – 2015	2715 (39%)	71%	19 [11,33]	88 (33%)	80%	15 [9,22]
Age at enrollment, years	50–59	5384 (78%)	74%	34 [15,63]	1964 (73%)	83%	29 [13,58]
	60–70	1543 (22%)	78%	34 [15,59]	708 (27%)	87%	25 [13,48]
HCV co-infection status	No	5201 (75%)	80%	35 [17,63]	1555 (58%)	81%	29 [14,56]
	Yes	891 (13%)	74%	36 [17,72]	1069 (40%)	75%	28 [13,56]
	Unknown	835 (12%)	59%	22 [11,46]	48 (2%)	56%	11 [8,18]
All patients		6927	74%	34 [15,62]	2672	78%	28 [13,56]

Table 2

Estimated 5-year risks of all-cause mortality under three ART initiation strategies, HIV-CAUSAL Collaboration 2005–2015.

		All-cause mortality			Non-AIDS mortality		
Population	**ART initiation strategy**	**5-year risk, % (95% CI)**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**	**5-year Risk, % (95% CI)**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**
General HIV population (N=6927)	Immediate universal	5.3% (4.5,6.2)	0 (Ref.)	1 (Ref.)	2.7% (2.1,3.4)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	5.5% (4.8,6.3)	0.14 (0.04,0.28)	1.03 (1.01,1.06)	2.8% (2.2,3.5)	0.07 (−0.03,0.16)	1.03 (0.99,1.06)
	<350 cells/mm^3	5.7% (5.1,6.6)	0.40 (0.10,0.71)	1.07 (1.02,1.15)	2.9% (2.3,3.7)	0.17 (−0.07,0.43)	1.06 (0.97,1.16)
US Veterans (N=2669)	Immediate universal	14.4% (12.6,16.7)	0 (Ref.)	1 (Ref.)	6.6% (5.2,8.9)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	15.1% (13.3,17.4)	0.69 (0.32,1.13)	1.05 (1.02,1.08)	7.0% (5.6,9.2)	0.40 (0.13,0.84)	1.06 (1.02,1.13)
	<350 cells/mm^3	16.0% (14.5,18.4)	1.61 (0.79,2.67)	1.11 (1.05,1.18)	7.6% (6.4,9.9)	1.00 (0.31,2.00)	1.15 (1.04,1.30)

Table 3

Estimated 5-year risks of all-cause mortality under three ART initiation strategies for individuals with CD4 cell count ≥ 500 cells/mm^3 at baseline in the general HIV population, HIV-CAUSAL Collaboration 2005–2015.

		All-cause mortality		
Population	**ART initiation strategy**	**5-year risk, % (95% CI)**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**
General HIV population (N=2072)	Immediate universal	2.8% (1.6,4.4)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	3.7% (2.5,5.0)	0.86 (0.10,1.45)	1.30 (1.03,1.72)
	<350 cells/mm^3	4.4% (3.3,5.9)	1.62 (0.17,2.82)	1.56 (1.05,2.41)

Appendix Table 1

Characteristics of patients at baseline, ART initiation, death, non-AIDS death, HIV-CAUSAL Collaboration 2005–2015.

		General HIV population	U.S. Veterans
At baseline	N	6927	2672
	CD4 count	354 [203,530]	284 [128,471]
	Calendar year	2008 [2006,2011]	2008 [2006,2010]
	Age	55 [52,59]	56 [53,60]
	HIV-RNA	50946 [11700,207703]	37859 [9653,112879]
At ART initiation	N	5160	2087
	CD4 count	272 [171,375]	229 [108,356]
	HIV-RNA	71559 [17000,220895]	57600 [14652,161000]
At death	N	295	339
	CD4 count	340 [180,498]	225 [84,441]
	HIV-RNA	90 [40,20400]	2392 [50,60500]
At non-AIDS death	N	124	136
	CD4 count	360 [240,497]	329 [179,520]
	HIV-RNA	50 [40,22803]	344 [48,18323]

Appendix Table 2

Estimated 5-year risks of non-AIDS mortality under three ART initiation strategies assuming that deaths due to an unknown cause were non-AIDS deaths, HIV-CAUSAL Collaboration 2005–2015.

		Non-AIDS mortality (main analysis)			Non-AIDS mortality (sensitivity analysis)		
Population	**ART initiation strategy**	**5-year Risk, % (95% CI)**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**	**5-year Risk, % (95% CI)**	**Risk difference (95% CI)**	**Risk ratio (95% CI)**
General HIV population (N=6927)	Immediate universal	2.7% (2.1,3.4)	0 (Ref.)	1 (Ref.)	3.8% (3.3,4.6)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	2.8% (2.2,3.5)	0.07 (−0.03,0.16)	1.03 (0.99,1.06)	3.9% (3.4,4.6)	0.10 (−0.02,0.22)	1.02 (1.1,1.06)
	<350 cells/mm^3	2.9% (2.3,3.7)	0.17 (−0.07,0.43)	1.06 (0.97,1.16)	4.0% (3.7,4.8)	0.21 (−0.05,0.61)	1.05 (0.99,1.17)
US Veterans (N=2669)	Immediate universal	6.6% (5.2,8.9)	0 (Ref.)	1 (Ref.)	9.2% (8.2,11.5)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	7.0% (5.6,9.2)	0.40 (0.13,0.84)	1.06 (1.02,1.13)	9.6% (8.7,11.8)	0.39 (0.17,0.61)	1.04 (1.02,1.17)
	<350 cells/mm^3	7.6% (6.4,9.9)	1.00 (0.31,2.00)	1.15 (1.04,1.30)	10.2% (9.0,12.3)	1.03 (0.48,1.58)	1.11 (1.05,1.18)