Time to virological failure, treatment change and interruption for individuals treated within 12 months of HIV seroconversion and in chronic infection

This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/140833 since 2021-11-02T11:36:36Z

Published version:
DOI:10.3851/IMP2312

Terms of use:
Open Access
Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)
This is the author's final version of the contribution published as:


Time to virological failure, treatment change and interruption for individuals treated within 12 months of HIV seroconversion and in chronic infection

Daniela Zugna, Ronald B Geskus, Bianca De Stavola, Magdalena Rosinska, Barbara Bartmeyer, Faroudy Boufassa, Marie-Laure Chaix, Abdel Babiker, Kholoud Porter, CASCADE Collaboration in EuroCoord

The publisher's version is available at:

http://hdl.handle.net/2318/140833

When citing, please refer to the published version.

Link to this full text:

http://hdl.handle.net/2318/140833

This full text was downloaded from iris-Aperto: https://iris.unito.it/
Time to virological failure, treatment change and interruption for individuals treated within 12 months of HIV seroconversion and in chronic infection

Daniela Zugna¹, Ronald B Geskus²,³, Bianca De Stavola³, Magdalena Rosinska⁴, Barbara Bartmeyer⁵, Faroudy Boufassa⁶, Marie-Laure Chaix⁷, Abdel Babiker⁸ and Kholoud Porter⁸ for the CASCADE Collaboration in EuroCoord*

1- Department of Biomedical Sciences and Human Oncology, University of Turin
2- Cluster of Infectious Diseases, Department of Research, Amsterdam Health Service, Amsterdam, the Netherlands
3- London School of Hygiene & Tropical Medicine, London, UK
4- National Institute of Public Health – National Institute of Hygiene, Warsaw, Poland
5- Robert Koch-Institut, Berlin, Germany
6- Inserm, CESP Centre for research in Epidemiology and Population Health, U1018, Epidemiology of HIV and STDs Team, F-94807, Villejuif, France
7- Université Paris Descartes, EA 3620, AP-HP, CHU Necker-Enfants Malades, Paris, France
8- MRC Clinical Trials Unit, London, UK
9- Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, the Netherlands

* see Appendix

Correspondence to: Dr K Porter, MRC Clinical Trials Unit, Aviation House, 125 Kingsway, London, WC2B 6NH, UK. Email: kp@ctu.mrc.ac.uk

Number of words: abstract (259), text (3702)
The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2011) under EuroCoord grant agreement n° 260694.
Abstract

**Introduction:** Estimates of treatment failure, change and interruption are lacking for individuals treated in early infection.

**Methods:** Using CASCADE data, we compared the effect of treatment in early infection (within 12 months of seroconversion) with that seen in chronic infection on risk of virological failure, change, and interruption. Failure was defined as two subsequent HIV RNA >1000 copies/ml following suppression (<500 copies/ml), or >500 copies/ml six months following initiation. Treatment change and interruption were defined as modification or interruption lasting >1 week. In multivariable competing risks proportional sub-distribution hazards models, we adjusted for: cART class, sex, risk group, age, and CD4, HIV RNA and calendar period at treatment initiation.

**Results:** Of 1627 initiating cART early (median 1.8 months from seroconversion), 159, 395 and 692 failed, changed and interrupted therapy, respectively. For 2710 initiating cART in chronic infection (median 35.9 months from seroconversion), the corresponding values were 266, 569 and 597. Adjusted hazard ratios (HR, 95%CI) for treatment failure and change were similar between the two treatment groups (0.93, 0.72-1.20 and 1.06, 0.91-1.24, respectively). Individuals treated early were increasingly more likely to interrupt, whereas for those who started during chronic infection this effect was reversed. Consequently, compared to chronic infection, treatment interruption was similar for early starters in the early cART period, but the relative hazard increased over calendar time (1.54, 1.33-1.79 in 2000 and 1.64, 1.42-1.90 in 2001).

**Conclusion:** Individuals initiating treatment in early infection are more likely to interrupt treatment than those initiating later. However, rates of failure and treatment change were similar between the two groups.
**Introduction**

Achieving undetectable plasma HIV RNA is the goal of combination anti-retroviral therapy (cART) (1-3) and is known to reduce the risk of clinical progression and mortality (4,5). Maintaining this state is an indication of drug activity but is challenging given that cART requires life-long commitment. In reality, drug-related toxicities necessitate regimen changes and treatment interruptions occur or are unavoidable, for example through drug stock-outs in resource-limited settings (6-9). Furthermore, therapeutic failure is observed if patients have sub-optimal adherence with the consequent detection of viral rebound leading to accumulation of resistance-conferring mutations (10). For these reasons treatment change, interruption and failure are not uncommon among HIV-infected individuals initiating cART.

It is estimated that a change in regimen is necessary for 15-25% within one year of initiating it (8,11). The most common reasons being intolerance and toxicities, including hypertriglyceridemia and hypercholesterolemia (11,12). Once viral suppression is achieved, around 30% rebound by one year (13-16). Before the results of SMART were known, a trial which evaluated the strategy of interrupting cART and restarting it each time CD4 count necessitated it, treatment interruption was fairly common (17). These studies are based, however, on data from individuals initiating treatment in chronic infection. Few estimates are available on virological suppression for individuals identified and treated in early infection, close to the time of HIV acquisition (18,19). These are in the order of 10-15 weeks median time, similar to that reported from chronic infection cohorts (20) although there are no estimates for rates of failure and change.

The time of primary HIV infection arguably presents a small window of opportunity in which to intervene and successfully achieve long-term immunological and virological control given that the immune system is fairly intact and viral diversity within the infected individual is limited (21-23). Adherence may be particularly challenging if cART is initiated at such an early stage, however, a concern which has led to the concept of administering cART of limited duration. Treated individuals are scheduled to interrupt and restart when clinically-indicated according to prevailing treatment guidelines having, hopefully, altered CD4 cell decline to such an extent that the need to restart cART is substantially delayed. We may, therefore, expect higher rates of cART interruption in patients initiating it close to HIV acquisition.

We aimed to describe the rate of treatment interruption after initiation of cART close to seroconversion and trends in this over time, and to estimate the rates of treatment failure and change accounting for the competing nature of all three events. We then compared these rates to those experienced by patients starting treatment during chronic infection.
Methods

Study population

We used data from the CASCADE Collaboration within EuroCoord (www.EuroCoord.net) of HIV infected persons with well-estimated dates of seroconversion. The study has been described in detail elsewhere (24) but briefly, it is a collaboration between the investigators of 28 cohorts in Europe, Australia, Canada and sub-Saharan Africa (details in Appendix A). Seroconverters are enrolled into national, regional and local cohorts and are typically followed up life-long. Follow-up data include all CD4 and HIV RNA measurements, all anti-retroviral drugs prescribed, vital status and date of last clinical assessment. Data pooled in 2011 were used for this study.

Patients were eligible if they were aged >15 years, antiretroviral treatment-naive when they started their first cART regimen and remained on cART for at least 90 days. Furthermore, data on specific drugs in the regimen, including changes and interruptions, had to be available. Patients diagnosed with clinical AIDS prior to treatment initiation and those infected through injecting drug use were excluded because their subsequent outcome is likely to differ from that of other patients (25). We also excluded data from two African cohorts as rates of treatment change, interruption and failure are likely to differ significantly from those observed in high-income country cohorts.

Seroconversion was estimated as the date of laboratory evidence for seroconversion, where available (12.5%), or else as the midpoint between the last negative and first positive antibody test dates ("HIV test window"), if within a maximum interval of 3 years. Treatment in early infection was defined as initiation of cART within one year of estimated seroconversion for individuals with a maximum HIV test window of 12 months. cART initiated by all other individuals was regarded as being in chronic infection.

All cohorts received approval from their individual human subjects review boards or from a national agency and were also approved to pool anonymised data for analyses and dissemination.

Statistical analysis

Outcomes definition and competing events analysis

We examined three outcomes of interest: treatment failure, treatment change, and treatment interruption. Treatment failure was defined as the second of two subsequent measurements in HIV RNA of >1000 copies/ml after previous viral suppression of <500 copies/ml, or HIV RNA of >500 copies/ml at 6 months following cART initiation. If no second HIV RNA value was available, but the
patient changed therapy, we considered that change as a failure. Treatment interruption occurred on the date at which cART was terminated for one week or longer. An interruption within 30 days following treatment failure was regarded as an interruption of treatment, rather than failure, as we judged it more likely for such individuals to have interrupted and then subsequently failed. In a sensitivity analysis we considered a definition of interruption of one month or longer. Treatment change was defined as a change of drug class without the occurrence of treatment failure or interruption.

All analyses were performed in a competing risks setting (26,27), with time since treatment initiation as the principal time-scale. Non-parametric cause-specific cumulative incidence functions, stratified by timing of cART administration, were calculated for all three competing events. The outcome-specific cumulative incidence curve represents the probability of that outcome occurring before either of the two other competing outcomes, expressed as a function of time since treatment initiation. When comparing treatment given in early versus chronic infection we adjusted for possible confounders in a multivariable competing risks proportional sub-distribution hazards model (“Fine and Gray model” (28,29)). This modelling allows us to estimate the hazard corresponding to the cause-specific cumulative incidence function in the presence of randomly right-censored and left-truncated data. Specifically, it leads to estimates of the sub-distribution hazard ratio of treatment in early relative to chronic infection separately for each event of interest. For simplicity, we refer to this throughout the manuscript as the hazard ratio (HR). The following potential confounders were included in the models: age, calendar year and biomarker (CD4 and HIV RNA) values at cART initiation, sex, HIV risk group, and class of regimen (non-nucleoside reverse transcriptase inhibitor (NNRTI)-based, protease inhibitor (PI)- based, 3-class regimens, 3 NRTIs and NRTI-sparing). Sex and risk group were re-categorised to form a single variable (sex between men, men infected through sex between men and women, women infected through sex between men and women, and others). To deal with non-linear trends, quadratic and cubic terms for age and calendar year were considered. To deal with potential effect modification of the effect of treatment in early versus chronic infection, interaction terms were included. To deal with possibly non-proportional hazard profiles by cohort, the models were stratified by cohort. We checked and tested whether the effect of the other variables was proportional by Schoenfeld’s residuals.

Information on all these variables was generally complete with the exception of the biomarkers at cART initiation because they were measured at irregular time intervals during follow-up. For this reason a multivariate imputation by chained equations (MICE) approach was adopted (30) assuming the data were missing at random (MAR) (31) (details in Appendix B).
Reported p-values are two-sided. Stata 11.0 (www.stata.com) and R 2.11.0 (www.r-project.org) were used to perform the analyses described above.

Results

Study population

Of the 25967 participants in CASCADE, 9795 initiated cART from naïve and had available data on specific drug regimens for at least 90 days. Of these, 1587 were excluded from analyses as they were infected through injecting drug use (n= 781), HIV risk group was not recorded (n= 290), or they had been diagnosed with AIDS prior to cART initiation (n=506), or were <16 years old (n=10). A further 3651 from one large cohort were excluded as treatment changes were not recorded within that cohort, and 81 from the two African cohorts. Finally 117 and 22 individuals were excluded because they had initiated cART before seroconversion, and had no HIV RNA measurements subsequent to cART initiation, respectively. Analyses were, therefore, based on 4337 patients, the characteristics of whom are described in Table 1. Specifically 1627 (37.5%) and 2710 (63.5%) patients initiated treatment in early and chronic infection, respectively. Individuals treated in chronic infection were more likely to be men, younger at seroconversion, and to have been prescribed NNRTI-based cART. Individuals treated in early infection were more likely to have been prescribed PI-based cART. The median time from seroconversion to the first cART regimen was 1.8 and 35.9 months for those treated in early and chronic infection, respectively. Among them 159 and 266 experienced treatment failure, 395 and 569 changed treatment, and 692 and 597 interrupted treatment, and 5 and 19 died, respectively (Table 2). CD4 values at cART interruption (within 6 months) were higher among early, compared to chronic, initiators (mean of 750 vs. 697 cells/mm³, p=0.02).

Missing data

CD4 count and HIV RNA at cART initiation (within 1 month) were known for 3013 and 2842 patients, respectively. The median (IQR) CD4 counts at cART initiation were 451 (297-645) and 322 (211-581) cells/cm³, and the median HIV RNA at cART initiation was 5.24 (4.66-5.78) log₁₀ copies/mL and 4.86 (4.30-5.28), for patients treated in early and chronic infection, respectively. Patients treated in chronic infection, those who started treatment in earlier calendar years and those who failed treatment were more likely to have incomplete data on biomarker values at treatment initiation.

Competing events
The non-parametric cumulative incidence estimates (with their 95% confidence intervals) of treatment failure, change, and interruption are shown in Figure 1 separately for individuals treated in early and in chronic infection. Adjusted hazard ratios for each competing event are given in Table 3.

Treatment failure

There was no evidence of modification of the effect of treatment group on treatment failure by any of the potential confounders (overall p-value for all interactions with exposure: p=0.29) and no evidence of departure from linearity for the effects of age (p=0.26). As there was strong evidence for departure from linearity for the effect of calendar time (p<0.001), a model with a quadratic term was used. The adjusted hazard for treatment failure was slightly lower for patients treated in early infection compared to chronic infection, but not significantly so (HR=0.93, 95% CI: 0.72-1.20). However, the adjusted hazard of treatment failure significantly decreased over calendar time (HR=0.81 per year, 95% CI=0.78-0.85) and increased with increasing HIV RNA at cART initiation (HR=1.29, 95%CI =1.09-1.53). We found no evidence that age, CD4 cell count at cART initiation, sex, risk group, or cART class were independently associated with the hazard of treatment failure.

Treatment change

There was no evidence of modification of the effect of treatment group on treatment change by any of the potential confounders examined (p=0.76) and no evidence of departure from linearity for the effects of age and calendar time (p=0.17 and p=0.13). Also again, the adjusted hazard for treatment change was similar for the two groups (HR=1.06, 95% CI: 0.91-1.24). We found an effect of cART class, however, with patients treated with PI-based (HR=1.87, 95%CI:1.59-2.19), 3 NRTIs (2.23, 1.65-3.03) and 3-class regimens (8.26, 5.74-11.90) having higher hazards of treatment change than those treated with NNRTI-based regimens. None of the other factors examined were independently associated with the hazard of treatment change.

Treatment interruption

We found evidence that the effect of treatment group on treatment interruption was significantly modified by calendar time (p<0.001), but not by any of the other potential confounders (comparison between the model with all interactions and the model with a single interaction between calendar time and exposure: p=0.12). Moreover, there was evidence of a departure from linearity for the effect of calendar time (p<0.001) but not of age (p=0.71). Thus the model was fitted allowing for a quadratic term of calendar time and an interaction between the linear term of calendar time and treatment group. Figure 2 shows the hazard ratios for treatment interruption over calendar year relative to the year 2000 separately for the two treatment groups indicating that, for both treatment
groups, interruption rates have peaked and fallen over calendar time. Apart from the first years of the cART era, patients treated in early infection were significantly more likely to interrupt treatment. For example, treatment interruption rates in early starters were 54% higher than in those treated in chronic infection in 2000 (HR=1.54, 95% CI: 1.33-1.79) and increased by 6% for every additional calendar year (e.g. HR=1.64, 95% CI: 1.42-1.90, in 2001, see fig. 3). Furthermore, older patients were less likely to interrupt (0.91, 0.85-0.96 per 10-year increase), and women infected through sex between men and women were more likely to, compared to those infected through sex between men (1.46, 1.25-1.71). Compared to those initiating on NNRTI-based regimens, those on PI-based regimens were more likely to interrupt and those on 3-class regimens less likely to interrupt. Finally, CD4 cell count at cART initiation (HR=1.03, 95% CI:1.02-1.04), but not HIV RNA, was also independently associated with interruption of treatment.

Estimates for failure, change and interruption were similar when we considered a definition of interruption of one month or more (data not shown).

**Discussion**

To our knowledge, this is the first study to report on the risk of treatment failure, change and interruption for persons initiating therapy close to HIV seroconversion and how they compare to those initiating it later in infection. Surprisingly, given the more augmented/intact immune system present in early infection, we found no evidence to suggest that the risk of treatment failure differs between individuals treated in early and chronic infection. The period of acute infection represents a small window in the natural history of HIV disease, however, and our definition of early treated individuals, within one year of estimated seroconversion, will have allowed the inclusion of individuals who may have already lost their early immune status advantage. Given that 75% of our early treated individuals had initiated therapy within 162 days of seroconversion, however, it is difficult to conceive a better definition of early treated whilst attempting to ensure that results are of practical significance to the HIV clinic population.

Another explanation is that all our analyses were performed in a competing risks setting, with three types of outcome: a biological (treatment failure), a behavioural (interruption) and a clinical (change) outcome. Our results also show that individuals treated in early infection are more likely to interrupt therapy than those treated in chronic infection in the presence of treatment failure and change. Hence different scenarios can be envisaged according to the reasons leading patients to interrupt their therapy. If individuals interrupt therapy because they are responding well, rather than simply because they are scheduled to do so, and response to therapy is greater in those initiating in early vs. chronic infection, we could presume that the former would be less likely to fail
treatment than the latter. In this case, the overall (marginal) hazard ratio of failing treatment when
given in early vs. chronic infection, which cannot be estimated from data affected by competing
events like ours, would be smaller than the one we report (i.e. further away from 1). On the other
hand, early starters may change or interrupt therapy more frequently than chronic starters because
of toxicities and, had they not changed/interrupted therapy, they may have been more likely to fail
treatment, which could imply a greater overall hazard ratio of treatment failure than the one we
report.

The risk of treatment failure decreased over calendar time, even after controlling for changes in
cART classes which took place over that period. This is likely to reflect wider changes in treatment
management, including use of resistance testing to inform treatment decisions, and the availability
of new formulations with a reduced pill burden. The risk of failure was higher at high HIV RNA at
baseline, in line with findings from ART-CC of higher risk of treatment success with lower HIV RNA
(32). Finally, we found a non-significant effect of age, with older individuals being slightly at lower
risk of treatment failure. Such a finding is in agreement with that reported by several investigators
and is likely to be due to the relatively poor levels of adherence to cART observed in young adults
(33).

There was no evidence to suggest that the risk of treatment change differed between individuals
treated in early and chronic infection. However the risk of treatment change was higher for PI-
based and 3-class cART compared to NNRTI-based regimens, which may suggest better
tolerability for NNRTI drugs.

Treatment interruption was far more likely in individuals treated in early, compared to chronic,
infection and its rate increased over calendar time. This probably reflects a deliberate
management decision of prescribing a short-course cART regimen as reported by us previously
(34) and others (35). Structured treatment interruptions had also been proposed in chronic
infection to decrease exposure to antiretroviral drugs, and thus reduce the risk of drug-associated
toxicities and cardiovascular events (36) but is no longer recommended in adults with chronic HIV
infection following the SMART trial (37). It is not surprising that interruption was more likely at
higher CD4 counts, as the risk of disease progression would have been judged by the clinician to
be low (4,5). It is of interest, however, that we found a higher risk of interruption for women. This
is in agreement with previous reports and may be related to a lower Body Mass Index for women,
compared to men, and hence a greater likelihood of over-dosing in women leading to
complications which, in turn, lead to interrupting cART (17,38). It may also be because cART
taken as prophylaxis to prevent mother-to-child HIV transmission by some of these women. As no
data on pregnancies were collected within CASCADE we were unable to verify this. Interruption
was much less likely with increasing age, possibly reflecting clinical concerns about interrupting
therapy for older patients or, simply, the effect of better adherence with increasing age. The finding of higher interruption rates for patients on PI-based regimens, and lower rates for those on 3-class regimens is interesting and merits further exploration.

Our study has a number of limitations worthy of discussion. Firstly, we used data from an observational cohort to estimate the effect of timing of cART on the three types of outcome which is best estimated through a randomised controlled trial. Such a trial is clearly not feasible, however, as individuals would have to be randomly assigned at the time of seroconversion to initiating cART early or at a random later date. The occurrence of all three events is clearly conditional on initiation of treatment, hence our choice of time since cART initiation as the time-scale for our analyses. We also controlled for factors that may have influenced the actual treatment allocation as potential confounders, including the established markers of disease progression CD4 cell count and HIV RNA. Residual confounding may still be present, however, as well as survival bias for those initiating cART in chronic infection.

Secondly, our estimates also include those who never suppressed by 6 months which will have inflated the risk of treatment failure compared to that reported from other studies. Censoring their follow-up at 6 months, rather than treating them as failures, would have little effect on estimates, however, given that proportions are similar in both treatment groups (8.2% for both).

Thirdly, as seroconverters, our patient population has been monitored from early infection and may well have been treated differently from the majority of individuals presenting in the clinic. Indeed, we have shown previously that seroconverters included in CASCADE tend to be treated at higher CD4 counts than is recommended by the prevailing treatment guidelines (24). Individuals treated in chronic infection included here may have better prognosis, and different risk of treatment failure, change and interruption, compared to the wider infected patient population receiving treatment in chronic infection.

Fourthly, we do not have information on the reasons for interruption. It may be that interruption is more likely in chronic infection to be a sign of poor adherence. Although mean CD4 values at interruption were, indeed, lower for those interrupting in chronic infection compared to early infection, absolute levels were high for both groups (750 and 697 cells/mm³ for early and late initiators, respectively). It is unlikely, therefore, that poor adherence was the driving factor for cART interruption in the latter group.

Finally data on two of the most important potential confounders, CD4 count and HIV RNA at treatment initiation, were missing for some individuals. Since excluding subjects with missing data may lead to loss of efficiency and to potential bias due to differences between unobserved and observed data, we adopted a multiple imputation approach under the assumption that missingness
was at random (MAR), i.e. missing values depended on observed subject characteristics. We examined the appropriateness of the assumed multiple imputation model, under the MAR assumption, graphically as described by Raghunatan and Bondarenko (39) and found no evidence that it was inappropriate. It is possible, however, to under-estimate failure rates if HIV RNA is measure infrequently. This potential source of bias is unlikely to have greatly affected our findings, however, given that during a median period of 1.4 years of follow-up, there were 2.7 HIV RNA measurements, on average, per year.

In summary, we found no evidence of a difference in rates of treatment failure or change between individuals treated close to seroconversion and those treated later within a competing events analysis. The difference in treatment interruption rates was large, however, the consequences of which warrants investigation. Results from SMART of higher rates of cardiovascular events in the drug conservation arm compared to the viral suppression arm are supported by higher levels of the inflammatory and coagulation markers C-reactive protein, IL-6 and D-dimer, measured one month after randomization (40). As the SPARTAC trial has recently reported (41), an evaluation of whether stopping therapy given in early HIV infection elicits the same response in these markers is urgently needed.

Author contributions

ICMJE criteria for authorship read and met: DZ RBG BDS MR BB FB MC AGB KP. Agree with the manuscript's results and conclusions: DZ RBG BDS MR BB FB MC AGB KP. Designed the experiments/the study: DZ RBG BDS. Analyzed the data: DZ. Collected data/did experiments for the study: DZ RBG BDS AB KP. Enrolled patients: BB FB MC. Secured funding for the study: KP. Wrote the first draft of the paper: KP. Contributed to the writing of the paper: DZ RBG BDS MR BB FB MC AB KP. KP had full access to all data in the study and had final responsibility for the decision to submit this report for publication.

Figure 1. Non-parametric estimate of cumulative incidence curves with their confidence intervals for treatment failure, change, and interruption. Solid lines denote treatment in early infection, dashed lines denote treatment in chronic infection.

Figure 2. Estimated effect of calendar year by treatment group on treatment interruption rates with confidence intervals estimated by the proportional subdistribution hazards model. Solid lines denote treatment in early infection, dashed lines denote treatment in chronic infection.
Note: the hazard ratios for treatment interruption is shown separately for the two treatment groups relative to the year 2000. It indicates that, for both treatment groups, interruption rates have peaked and fallen over calendar time.

Figure 3. Effect of treatment group over calendar year on treatment interruption rates with confidence intervals.

Note: effect of early vs. chronic cART initiation on treatment interruption rates increased by 6% (95% CI 3-10%) for every additional calendar year
Appendix A

CASCADE Steering Committee: Julia Del Amo (Chair), Laurence Meyer (Vice Chair), Heiner C. Bucher, Geneviève Chêne, Osamah Hamouda, Deenan Pillay, Maria Prins, Magda Rosinska, Caroline Sabin, Giota Touloumi.

CASCADE Co-ordinating Centre: Kholoud Porter (Project Leader), Ashley Olson, Kate Coughlin, Sarah Walker, Abdel Babiker.

CASCADE Clinical Advisory Board: Heiner C. Bucher, Andrea De Luca, Martin Fisher, Roberto Muga

CASCADE Collaborators: Austria: Austrian HIV Cohort Study (Robert Zangerle); Australia PHAEDRA cohort (Tony Kelleher, David Cooper, Pat Grey, Robert Finlayson, Mark Bloch) Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (Tony Kelleher, Tim Ramacciotti, Linda Gelgor, David Cooper, Don Smith); Canada South Alberta clinic (John Gill); Estonia Tartu Ülikool (Irja Lutsar); France ANRS CO3 Aquitaine cohort (Geneviève Chêne, Francois Dabis, Rodolphe Thiebaut, Bernard Masquelier), ANRS CO4 French Hospital Database (Dominique Costaglolia, Marguerite Guiguet), Lyon Primary Infection cohort (Philippe Vanhems), French ANRS CO6 PRIMO cohort (Marie-Laure Chaix, Jade Ghosn), ANRS CO2 SEROCO cohort (Laurence Meyer, Farouidy Boufassa); Germany German cohort (Osamah Hamouda, Claudia Kücherer, Barbara Bartmeyer); Greece AMACS (Paparizos V, Gargalianos-Kakolyris P, Lazanas M); Greek Haemophilia cohort (Giota Touloumi, Nikos Pantazis, Olga Katsarou); Italy Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucci), ICONA cohort (Antonella d’Arminio Monforte, Andrea De Luca.) Netherlands Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, Ronald Geskus, Jannie van der Helm, Hanneke Schuitemaker); Norway Oslo and Ulleval Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, Anne-Marte Bakken Kran); Poland National Institute of Hygiene (Magdalena Rosinska); Spain Badalona IDU hospital cohort (Roberto Muga, Jordi Tor), Barcelona IDU Cohort (Patricia Garcia de Olalla, Joan Cayla), CoRIS-scv (Julia del Amo, Santiago Moreno, Susana Monge; Madrid cohort (Julia Del Amo, Jorge del Romero), Valencia IDU cohort (Santiago Pérez-Hoyos); Switzerland Swiss HIV Cohort Study (Heiner C. Bucher, Martin Rickenbach, Patrick Francioli); Ukraine Perinatal Prevention of AIDS Initiative (Ruslan Malyuta); United Kingdom Health Protection Agency (Gary Murphy), Royal Free haemophilia cohort (Caroline Sabin), UK Register of HIV Seroconverters (Kholoud Porter, Anne Johnson, Andrew Phillips, Abdel Babiker), University College London (Deenan Pillay). African cohorts: Genital Shedding Study (US: Charles Morrison; Family Health International, Robert Salata, Case Western Reserve University, Uganda: Roy Mugerwa, Makerere University, Zimbabwe: Tsungai Chipato, University of Zimbabwe); International AIDS Vaccine Initiative (IAVI)
Early Infections Cohort (Kenya, Rwanda, South Africa, Uganda, Zambia: Pauli N. Amornkul, IAVI, USA; Jill Gilmour, IAVI, UK; Anatoli Kamali, Uganda Virus Research Institute/Medical Research Council Uganda; Etienne Karita, Projet San Francisco, Rwanda).

**EuroCoord Executive Board**: Geneviève Chêne, University Bordeaux Segalen, France; Dominique Costagliola, Institut National de la Santé et de la Recherche Médicale, France Julia Del Amo, Instituto de Salud Carlos III, Spain; Carlo Giaquinto, Fondazione PENTA, Italy; Di Gibb, Medical Research Council, UK; Jesper Grarup, Københavns Universitet, Denmark; Ole Kirk, Københavns Universitetet, Denmark; Bruno Ledergerber, University of Zurich, Switzerland; Laurence Meyer, Institut National de la Santé et de la Recherche Médicale, France; Alex Panteleev, St. Petersburg City AIDS Centre, Russian Federation; Andrew Phillips, University College London, UK, Kholoud Porter (Chair), Medical Research Council, UK; Caroline Sabin (Scientific Coordinator), University College London, UK; Claire Thorne, University College London, UK; Stephen Welch, Fondazione PENTA, UK.

**EuroCoord Council of Partners**: Jean-Pierre Aboulker, Institut National de la Santé et de la Recherche Médicale, France; Jan Albert, Karolinska Institute, Sweden; Silvia Asandi, Romanian Angel Appeal Foundation, Romania; Geneviève Chêne, University Bordeaux Segalen, France; Dominique Costagliola, INSERM, France; Antonella d’Arminio Monforte, ICoNA Foundation, Italy; Stéphane De Wit, St. Pierre University Hospital, Belgium; Frank De Wolf (Chair), Stichting HIV Monitoring, Netherlands; Julia Del Amo, Instituto de Salud Carlos III, Spain; José Gatell, Fundació Privada Clínic per a la Recerca Biomèdica, Spain; Carlo Giaquinto, Fondazione PENTA, Italy; Osamah Hamouda, Robert Koch Institut, Germany; Igor Karpov, University of Minsk, Belarus; Bruno Ledergerber, University of Zurich, Switzerland; Jens Lundgren, Københavns Universitetet, Denmark; Ruslan Malyuta, Perinatal Prevention of AIDS Initiative, Ukraine; Claus Møller, Cadpeople A/S, Denmark; Andrew Phillips, University College London, UK; Kholoud Porter, Medical Research Council, United Kingdom; Maria Prins, Academic Medical Centre, Netherlands; Aza Rakhmanova, St. Petersburg City AIDS Centre, Russian Federation; Jürgen Rockstroh, University of Bonn, Germany; Magda Rosinska, National Institute of Public Health, National Institute of Hygiene, Poland; Claire Thorne, University College London, UK; Giota Touloumi, National and Kapodistrian University of Athens, Greece; Alain Volny Anne, European AIDS Treatment Group, France.

**EuroCoord External Advisory Board**: David Cooper, University of New South Wales, Australia; Nikos Dedes, Positive Voice, Greece; Kevin Fenton, Centers for Disease Control and Prevention, USA; David Pizzuti, Gilead Sciences, USA; Marco Vitoria, World Health Organisation, Switzerland.
**EuroCoord Secretariat:** Kate Coughlin, MRC Clinical Trials Unit, UK; Michelle Ellefson, Københavns Universitet, Denmark; Silvia Faggion, Fondazione PENTA, Italy; Lorraine Fradette, MRC Clinical Trials Unit; Richard Frost, MRC Regional Centre London, UK; Christine Schwimmer, University Bordeaux Segalen, France; Martin Scott, UCL European Research & Development Office, UK.
Appendix B

The imputation model involved regression of the two biomarkers on the other potential confounders, plus the exposure (early/late treatment), the biomarker values collected up to 6 months before initiation, the elapsed time between seroconversion and cART initiation and the survival data, which included the event indicator (having been censored or having experienced one of the competing events), the overall cumulative hazard at the time of entry for all events combined (estimated using the Nelson-Aalen method, to take into account left truncation), and the difference between the estimated cumulative hazard at the exit time and that at entry (42). Square root transformation for CD4 count and log$_{10}$ transformation for HIV RNA were used in order to normalize their distribution, while a natural log transformation of elapsed time between seroconversion and cART initiation was used as suggested by Royston and Sauerbrei (43). Once the regression model was fitted, imputed values for the missing data were created using predictive mean matching.

For each imputed dataset, proportional sub-distribution hazards models were fitted to obtain estimates of the adjusted hazard ratios for the effect of each variable on the three competing events using the Fine and Gray proportional subdistribution hazards model, as described in the main text. These were then combined into overall estimates, with standard errors, confidence intervals and p-values calculated using Rubin’s rule (44). Similarly, likelihood ratio tests (45) were combined to assess significance of interaction terms between the exposure and other covariates.
References


39. Raghunathan T, and Bondarenko I. Diagnostics for Multiple Imputations. SSRN


41. Fidler S. The effect of short-course ART in PHI: final results from an international randomised controlled trial; SPARTAC. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome July 2011 [WELBX].

Table 1. Descriptive characteristics of the 4337 individuals treated in early (within 12 months of HIV seroconversion) and chronic (after 12 months) HIV infection

<table>
<thead>
<tr>
<th></th>
<th>Treated in early infection</th>
<th>Treated in chronic infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No(%)</td>
<td>No(%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td></td>
<td>1627(37.5%)</td>
<td>2710(62.5%)</td>
<td>4337(100.0)</td>
</tr>
</tbody>
</table>

**Sex**

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1414 (86.9)</td>
<td>213 (13.1)</td>
</tr>
</tbody>
</table>

**Sex and Risk Group**

<table>
<thead>
<tr>
<th></th>
<th>Male: MSW</th>
<th>Female: MSW</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>196 (12.0)</td>
<td>207 (12.7)</td>
<td>19 (1.2)</td>
</tr>
</tbody>
</table>

**Age at seroconversion (yrs)**

<table>
<thead>
<tr>
<th></th>
<th>16-24</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>653 (40.1)</td>
<td>1233 (45.5)</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>16-24</td>
<td>630 (14.5)</td>
</tr>
<tr>
<td>Age at cART initiation (yrs)</td>
<td>25-34</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>16-24</td>
<td>500(30.7)</td>
</tr>
<tr>
<td>25-34</td>
<td>281(17.3)</td>
</tr>
<tr>
<td>35-44</td>
<td>131(4.8)</td>
</tr>
<tr>
<td>45+</td>
<td>312(7.2)</td>
</tr>
<tr>
<td>cART class</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>410(25.2)</td>
</tr>
<tr>
<td>PI</td>
<td>1142(70.2)</td>
</tr>
<tr>
<td>3 NRTIs</td>
<td>44(2.7)</td>
</tr>
<tr>
<td>3 classes</td>
<td>29(1.8)</td>
</tr>
<tr>
<td>NRTI-sparing</td>
<td></td>
</tr>
<tr>
<td>Cohort region</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>1487(91.4)</td>
</tr>
<tr>
<td>Canada</td>
<td>21(1.3)</td>
</tr>
<tr>
<td>Australia</td>
<td>119(7.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at seroconversion (yrs)</td>
<td>34.4(28.8,41.6)</td>
<td>32.2(26.9,39.3)</td>
</tr>
<tr>
<td>Age at cART initiation (yrs)</td>
<td>34.7(29.0,41.8)</td>
<td>36.8(31.2,43.3)</td>
</tr>
<tr>
<td>Years from seroconversion to cART</td>
<td>0.15(0.0,0.4)</td>
<td>3.0(1.6,5.6)</td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>1.0(0.5,2.1)</td>
<td>1.9(0.6,4.0)</td>
</tr>
<tr>
<td>Calendar year of seroconversion</td>
<td>2002(99,06)</td>
<td>2000(95,04)</td>
</tr>
<tr>
<td>Calendar year of cART initiation</td>
<td>2003(00,06)</td>
<td>2004(00,08)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>CD4 at cART initiation (cells/µL)*</td>
<td>451(297,645)</td>
<td>322(211,581)</td>
</tr>
<tr>
<td>HIV RNA at cART initiation (log10)*</td>
<td>5.24(4.66,5.78)</td>
<td>4.86(4.30,5.28)</td>
</tr>
<tr>
<td>Number of CD4s per unit-time of observational period (yr))</td>
<td>2.5(1.7-3.4)</td>
<td>2.6(1.8-3.4)</td>
</tr>
<tr>
<td>Number of HIV RNAs per unit-time of observational period (yr))</td>
<td>2.6(1.7-3.5)</td>
<td>2.7(1.7-3.5)</td>
</tr>
</tbody>
</table>

MSW- Sex between men & women

* 21% and 36% with missing values for individuals treated in early and chronic infection respectively

# 22% and 42% with missing values for individuals treated in early and chronic infection respectively
Table 2. Causes of end of follow-up by treatment group

<table>
<thead>
<tr>
<th>Cause of exit</th>
<th>Treated in early infection</th>
<th>Treated in chronic infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Administrative censoring/loss to follow-up*</td>
<td>376 (23.1)</td>
<td>1259 (46.5)</td>
<td>1635 (37.7)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>159 (9.8)</td>
<td>266 (9.8)</td>
<td>425 (9.8)</td>
</tr>
<tr>
<td>Two HIV RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=1000 copies after suppression</td>
<td>51 (67.9)</td>
<td>106 (39.8)</td>
<td>157 (36.9)</td>
</tr>
<tr>
<td>HIV RNA &gt;=500 copies/ml after 6 months</td>
<td>108 (32.1)</td>
<td>160 (60.2)</td>
<td>268 (63.1)</td>
</tr>
<tr>
<td>Change of cART</td>
<td>395 (24.3)</td>
<td>569 (21.0)</td>
<td>964 (22.2)</td>
</tr>
<tr>
<td>Interruption of cART</td>
<td>692 (42.5)</td>
<td>597 (22.0)</td>
<td>1289 (29.7)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.3)</td>
<td>19 (0.7)</td>
<td>24 (0.5)</td>
</tr>
</tbody>
</table>

* Loss to follow-up was assumed to have occurred if patient had left cohort, withdrawn consent or no new information was available for the preceding 12 months
Table 3. Mutually adjusted hazard ratios for treatment failure, change of treatment, and treatment interruption *

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment failure</th>
<th>Change of treatment</th>
<th>Treatment interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Test for heterogeneity (p-value)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Early/chronic</td>
<td>0.93 (0.72-1.20)</td>
<td>0.86</td>
<td>1.06 (0.91-1.24)</td>
</tr>
<tr>
<td>Sex and Risk Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex between men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, Sex between men &amp; women</td>
<td>0.91 (0.65-1.27)</td>
<td>0.97 (0.79-1.19)</td>
<td>0.98 (0.81-1.18)</td>
</tr>
<tr>
<td>Women, Sex between men &amp; women</td>
<td>1.07 (0.80-1.43)</td>
<td>0.84 (0.69-1.03)</td>
<td>1.46 (1.25-1.71)</td>
</tr>
<tr>
<td>Other</td>
<td>0.89 (0.33-2.45)</td>
<td>0.80 (0.44-1.48)</td>
<td>1.50 (0.96-2.34)</td>
</tr>
<tr>
<td>cART class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>0.77</td>
<td>0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>PI</td>
<td>1.04 (0.82-1.33)</td>
<td>1.87 (1.59-2.19)</td>
<td>1.31 (1.14-1.50)</td>
</tr>
<tr>
<td>3 NRTIs</td>
<td>1.07 (0.60-1.91)</td>
<td>2.23 (1.65-3.03)</td>
<td>0.80 (0.57-1.13)</td>
</tr>
<tr>
<td>3 classes</td>
<td>0.65 (0.23-1.78)</td>
<td>8.26 (5.74-11.90)</td>
<td>0.47 (0.25-0.89)</td>
</tr>
<tr>
<td>Year of cART initiation**</td>
<td>0.81 (0.78-0.85)</td>
<td>1.00 (0.98-1.02)</td>
<td>1.01 (0.98-1.04)</td>
</tr>
<tr>
<td>Year of cART initiation^2</td>
<td>1.01 (1.01,1.02)</td>
<td>1.02 (0.96-1.09)</td>
<td>0.91 (0.85-0.96)</td>
</tr>
<tr>
<td>Age at cART initiation</td>
<td>0.93 (0.83,1.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(per 10-year increase)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Treatment group/calendar year interaction</th>
<th>HIV RNA at cART initiation (log_{10} copies/ml)</th>
<th>CD4 at cART initiation (square root cells/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.29 (1.09-1.53)</td>
<td>0.98 (0.96-1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.07 (0.98-1.17)</td>
<td>1.00 (0.98-1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.95 (0.89-1.02)</td>
<td>1.03 (1.02-1.04)</td>
</tr>
</tbody>
</table>

* Estimated using subdistribution proportional hazards models stratified by cohort and defined on the time since treatment initiation time scale

# Likelihood ratio test for the heterogeneity across the variable’s categories

** Hazard ratio is centred at 2000