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## Comparative effectiveness of immediate antiretroviral therapy versus CD4-based initiation in HIV-positive individuals in high-income countries: observational cohort study

The HIV-CAUSAL Collaboration\*

### Summary

**Background**—Recommendations have differed nationally and internationally with respect to the best time to start antiretroviral therapy (cART). We compared effectiveness of three strategies for initiation of cART in high-income countries for HIV-positive individuals who do not have AIDS: immediate universal cART initiation, cART initiation at a CD4 cell count below 500, and cART initiation at a CD4 cell count below 350 cells/mm<sup>3</sup>.

**Methods**—We used data from the HIV-CAUSAL collaboration of cohorts in Europe and the United States. We included 55,826 individuals diagnosed with HIV between 2000–2013, ART naïve, AIDS-free, aged 18 years and within 6 months of HIV diagnosis. We used the parametric g-formula to adjust for baseline and time-varying confounders to estimate the following quantities as would have been observed under each cART initiation strategy after 7 years of HIV diagnosis: relative risks of both death and of death or AIDS-defining illness, mean survival time, proportion in need of cART, and proportion with HIV RNA<50 copies/mL.

**Findings**—Median [interquartile range] CD4 at HIV diagnosis was 376 [222,551] cells/mm<sup>3</sup>. Compared with immediate initiation, the mortality risk ratio estimate (95% CI) was 1.02 (1.01,1.02) under initiation at CD4<500 cells/mm<sup>3</sup>, and 1.06 (1.04,1.08) under initiation at CD4<350 cells/mm<sup>3</sup>. The corresponding estimates were 1.06 (1.06,1.07) and 1.20 (1.17,1.23) for the combined endpoint. Compared with immediate initiation, the mean survival time at 7 years under initiation at CD4<500 cells/mm<sup>3</sup> and at CD4<350 cells/mm<sup>3</sup> was 2 (1,2) and 5 (4,6) days shorter. Seven years after HIV diagnosis, 100%, 99%, and 93% of individuals would have been in need of cART, and 87%, 87% and 84% would have HIV-RNA<50 copies/mL, under immediate initiation, initiation at CD4<500 and <350 cells/mm<sup>3</sup>, respectively.

**Interpretation**—The benefits of immediate initiation of cART, such as prolonged survival and AIDS-free survival and increased virological suppression, were small in this high-income setting with relatively low CD4 count at HIV diagnosis. The estimated beneficial effect on AIDS is less than in recently reported randomised trials. Increasing rates of HIV testing might be as important as a policy of early initiation of cART.

### Keywords

when to start; CD4 cell count; guidelines; mathematical models; causal inference; parametric g-formula; comparative effectiveness

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## Introduction

Recommendations have differed nationally and internationally with respect to the best time

All authors have contributed to the interpretation of the data and have read and approved the final version of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Principal contributions made by the authors

Data collection: Andrew Phillips, Ashley Olson, Dominique Costagliola, Sophie Abgrall, Ard van Sighem, Peter Reiss, José M. Miró, Elena Ferrer, Amy Justice, Heiner C. Bucher, Hansjakob Furrer, Santiago Moreno, Susana Monge, Giota Touloumi, Nikos Pantazis, Laurence Meyer, Rémonie Seng, Francois Dabis, Marie-Anne Vandenhede, Santiago Pérez-Hoyos, Inma Jarrín, Sophie Jose, Caroline Sabin; Study design: Sara Lodi, Miguel Hernan; Statistical analyses: Sara Lodi, Roger Logan, Jessica Young; Interpretation of results: All authors; Read and approved the manuscript: All authors; Revised the work for important intellectual content: All authors; Drafted the manuscript: Sara Lodi, Miguel Hernan. Sara Lodi, the corresponding author, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Declaration of interests

CS declares research grants from the MRC during this study; personal fees for membership of data safety and advisory boards and for development of educational materials from Gilead Sciences and Janssen-Cilag, outside the submitted work; and personal fees for speaking from Bristol-Myers Squibb and MSD, outside the submitted work. JS declares research grants from the National Institutes of Health during this study. AP declares personal fees for consultancy and speaking from Gilead Sciences, Abbvie, and GlaxoSmithKline, outside the submitted work. DC reports personal fees for travel from Gilead Sciences, outside the submitted work; and research grants and personal fees for travel, consultancy, and speaking from Janssen-Cilag, MSD, and ViiV Healthcare, outside the submitted work. PR reports unrestricted research grants to their institution from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceutica, Bristol-Myers Squibb, and Merck, outside the submitted work; and honoraria paid to their institution from Gilead Sciences and ViiV Healthcare, outside the submitted work. SJ declares research grants paid to their institution from MRC (UK) during this study. LM reports research grants from ANRS Inserm (France) during this study; and research grants from ANRS Inserm (France) and European FP7 through the MRC (UK), outside the submitted work. JMM declares personal fees for consultancy from Abbvie, Bristol-Myers Squibb, Cubist, Gilead Sciences, Merck, Novartis, and ViiV Healthcare, outside the submitted work; and research grants from Bristol-Myers Squibb, Cubist, Gilead Sciences, Merck, Novartis, and ViiV Healthcare, outside the submitted work. All other authors declare no competing interests.

### Panel: Research in context

#### Evidence before the study

Several observational studies and clinical trials have addressed the question of when to start combined antiretroviral therapy (cART). A summary of the evidence was presented in a systematic review and meta-analysis by WHO. Results of the TEMPRANO trial, and interim findings of the START trial, suggest that immediate initiation is the best cART initiation strategy. However, estimates from observational studies remain important to assess long-term outcomes of early cART initiation in populations representative of routine clinical practice.

#### Added value of this study

We have used data from a large collaboration of cohort studies in Europe and the USA to compare the effectiveness of three cART initiation strategies: immediate initiation; initiation at a CD4 count less than 500 cells/mm<sup>3</sup> or a diagnosis of AIDS; and initiation at a CD4 count less than 350 cells/mm<sup>3</sup> or a diagnosis of AIDS. The CD4 count at HIV diagnosis was low for many patients. In this population with a fairly low CD4 count at HIV diagnosis, immediate initiation increased survival and AIDS-free survival but, overall, the benefit was small. A strategy of immediate initiation of cART substantially increases the proportion of individuals with suppressed virological replication and the proportion of individuals in need of cART.

#### Implications of all the available evidence

Recent trials suggest that immediate initiation is the best ART initiation strategy. However, the benefits of a strategy of immediate initiation of cART, such as prolonged survival and AIDS-free survival and increased virological suppression, might be small in high-income settings with relatively low CD4 count at HIV diagnosis. More widespread and frequent HIV testing is likely to be at least as important as a policy of early cART initiation.

to start combined antiretroviral therapy (cART) in HIV-positive patients who do not have AIDS. In the most recent US guidelines,<sup>1,2</sup> initiation of cART is recommended for all individuals who have been newly diagnosed with HIV infection, irrespective of their CD4 count. By contrast with this guidance, WHO recommends initiation of cART when the patient's CD4 count has fallen below 500 cells/mm<sup>3</sup>. Moreover, in Europe, treatment initiation is recommended for all patients with a CD4 count less than 350 cells/mm<sup>3</sup> and should be considered for individuals with a CD4 count of 350–500 cells/mm<sup>3</sup>.

These discrepancies are attributable partly to different interpretations of available evidence. Over the past decade, findings of observational studies and clinical trials have shown that starting cART at CD4 counts of 350–500 cells/mm<sup>3</sup> is associated with reduced mortality and AIDS morbidity<sup>5–12</sup> and decreased transmission of HIV to other people.<sup>13</sup> The benefits of such early initiation on survival and transmission might be off set by development of toxicity and drug resistance.<sup>14</sup> Moreover, because treatment must be used for the rest of a patient's life without interruption,<sup>15</sup> immediate initiation would increase substantially the proportion of individuals in need of cART and the burden on available resources.

The results from the Temprano trial suggest that immediate universal initiation is the best cART initiation strategy in low-income countries with high risk of opportunistic infections<sup>12</sup>. Preliminary results from the Strategic Timing of Anti-Retroviral Treatment (START) trial also support the benefit of early initiation ([http://www.ctu.mrc.ac.uk/news/2015/start\\_results\\_28052015](http://www.ctu.mrc.ac.uk/news/2015/start_results_28052015)). However, there are no estimates of the relative effectiveness of immediate universal initiation versus initiation according to CD4 thresholds on the mortality and morbidity of populations representative of the clinical HIV practice in high-income countries. These estimates are important not only to patients and clinicians but also, to service providers and policy makers who require estimates of the proportions of individuals in need of treatment and with suppressed viral load to estimate the cost-effectiveness of current or future guidelines on cART initiation and to allocate resources between HIV treatment and other health priorities.

Here, we aimed to compare immediate initiation of cART with strategies for starting treatment based on CD4 thresholds of 350 cells/mm<sup>3</sup> and 500 cells/mm<sup>3</sup> in cohorts of HIV-positive individuals from Europe and the USA. We aimed to compare clinical outcomes and the proportions of patients in need of treatment and with suppressed virological replication under each initiation strategy up to 7 years after HIV diagnosis.

## Methods

### Study population

The HIV-CAUSAL collaboration is a consortium of prospective cohort studies from 6 European countries and the United States. All cohorts record routinely collected data in clinical practice within healthcare systems with universal access to care. Data collected include that related to patient characteristics (age, sex, geographical origin, and transmission category), use of cART (type of regimes and dates of start and discontinuation), CD4 cell counts, and plasma HIV-RNA, AIDS-defining illnesses, and deaths. Each cohort submits data in a standardized format (<http://www.hicdep.org/>) to the coordinating center. The

analyses presented here are based on data pooled in September 2013. Ethics approval was granted by the ethic committees of each of the participating cohorts according to country-specific regulations.

### Selection of patients

Analyses were restricted to individuals who met the following inclusion criteria: age 18 years; HIV diagnosis on or after January 1, 2000; AIDS-free; antiretroviral therapy naïve; CD4 cell count and HIV-RNA measurements within 3 months of each other and within 6 months of the date of HIV diagnosis. Follow-up started at baseline, defined as the date when all criteria were met, and ended at death (or AIDS when considering AIDS-free survival), 12 months after the most recent laboratory measurement, or cohort-specific administrative censoring (ranging from 2011 to 2013), whichever occurred first. Individuals with no CD4 cell count and HIV-RNA measurements after baseline were excluded. Since the relative effectiveness of initiation strategies will depend on CD4 count at HIV diagnosis, we also conducted two sensitivity analyses restricted to individuals with CD4>350 cells/mm<sup>3</sup> and CD4>500 cells/mm<sup>3</sup> at HIV diagnosis.

### cART initiation strategies

cART 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.

We compared the following three cART initiation strategies: i) immediate universal treatment, defined as initiation within 6 months of HIV diagnosis regardless of the CD4 count, ii) initiation within 6 months of a CD4 count <500 cells/mm<sup>3</sup> or an AIDS diagnosis, and iii) initiation within 6 months of a CD4 cell count <350 cells/mm<sup>3</sup> or an AIDS diagnosis.

### Outcomes

We considered the following clinical outcomes: all-cause mortality and a combined endpoint of AIDS-defining illness<sup>16</sup> or death. For each cART initiation strategy and outcome, we estimated the 7-year risk and the average restricted survival time<sup>17</sup>. In sensitivity analyses, we also considered a combined endpoint of death or severe or moderate AIDS-defining illness<sup>18</sup> (non-Hodgkin's lymphoma, progressive multifocal leukoencephalopathy, cryptococcosis, cerebral toxoplasmosis, AIDS dementia complex and disseminated *Mycobacterium avium* complex), and the outcome tuberculosis as later treatment initiation has been associated with increased risk of tuberculosis<sup>10,13</sup>.

We also estimated the proportion of individuals considered in need of treatment and with suppressed virological replication, defined as HIV-RNA<50 copies/mL, up to 7 years after baseline, assuming that cART is continued once it is started.

## Statistical methods

Our estimates need to be adjusted for the time-dependent confounders CD4 cell count, HIVRNA 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<sup>19,20</sup>, 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<sup>21</sup>.

The parametric g-formula is a generalization of standardization for time-varying treatments and confounders<sup>5,20,21</sup>. The estimation procedure for the HIV-CAUSAL Collaboration has been described elsewhere<sup>5</sup>. Briefly, the procedure has two steps. First, parametric regression models are used to estimate the probability density functions of the time-varying variables 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 cART initiation strategy.

For the first step, we fit separate logistic regression models for time-varying indicators of death, AIDS-defining illness, cART 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 two most recent values of these time-varying variables, time since last CD4 count and HIV-RNA measurements, and the following baseline variables: CD4 cell count (<50,50-99,100-199,200-349,350-499, 500 cells/mm<sup>3</sup>), HIV-RNA level (<4,4-5, >5 log<sub>10</sub> copies/mL), sex, transmission group (heterosexual, homo/bisexual, injecting drug users, or other/unknown), calendar year (2000-2004, 2005-2010, 2011-2013), age (<35,35-50, >50 years), geographical origin (Western countries, sub-Saharan Africa, other, unknown), and cohort. Models for CD4 cell count and HIV-RNA also included an interaction term for number of months since cART initiation. Like 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 (Appendix Figure 1).

We used a nonparametric bootstrap procedure based on 200 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

We conducted several sensitivity analyses in which we (i) adjusted for a time-fixed indicator of hepatitis C co-infection, (ii) included individuals with no CD4 cell count and HIV-RNA measurements after baseline, (iii) excluded the cohorts of HIV seroconverters (GEMES, PRIMO, SEROCO, UK Register of Seroconverters) who might have been treated with short-course antiretroviral treatment during primary HIV infection (shown to have immunological and virological benefits after treatment is stopped<sup>22-24</sup>), and (iv) computed the proportion of individuals with suppressed virological replication defined as HIV-RNA<400 copies/mL rather than <50 copies/mL.

## Role of funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

## Results

The HIV-CAUSAL collaboration included 70,488 HIV positive individuals with known date of HIV diagnosis between 2000-2013. We excluded 5,027 who had no CD4 count or HIV-RNA after baseline and 9,635 whose baseline date was >6 months after HIV diagnosis.

Table 1 shows the baseline characteristics of the 55,826 individuals eligible for our analyses: 77% were men, 73% started follow-up after 2004; their median [IQR] CD4 cell count, HIV-RNA and age at baseline were 376 [222,551] cells/mm<sup>3</sup>, 4.6 [4.0,5.1] log<sub>10</sub> copies/mL and 36 [30,44] years, respectively. During the follow-up 71% initiated cART. The median [IQR] CD4 cell count and HIV-RNA at cART initiation were 259 [161,355] cells/mm<sup>3</sup> and 4.8 [4.2,5.3] log<sub>10</sub> copies/mL, respectively. The median [IQR] time between HIV diagnosis and cART initiation was 2 [1,14] months, and the proportion of initiators with CD4 cell count >500 cells/mm<sup>3</sup> was 9%. Compared with individuals who initiated cART with CD4 cell count <500 cells/mm<sup>3</sup>, those who initiated cART with CD4 count >500 cells/mm<sup>3</sup> were less likely to be immigrants and more likely to be in the homosexual/bisexual transmission group (Appendix Table 1).

During 215,521 person-years of follow-up 1,737 individuals died and 3,472 developed an AIDS-defining illness or died. The estimated 7-year risk (95% CI) of death was 4.0% (3.8, 4.2) for immediate cART initiation, 4.0% (3.8, 4.3) for initiation at CD4<500 cells/mm<sup>3</sup>, and 4.2% (4.0, 4.5) for initiation at CD4<350 cells/mm<sup>3</sup>. Compared with immediate initiation, the risk ratio (95% CI) was 1.02 (1.01, 1.03) under initiation at CD4<500 cell/mm<sup>3</sup>, and 1.06 (1.03, 1.10) under initiation at CD4<350 cell/mm<sup>3</sup> (Table 2). Compared with immediate initiation, the mean survival time at 7 years under initiation at CD4<500 cells/mm<sup>3</sup> and at CD4<350 cells/mm<sup>3</sup> was 2 (1,2) and 5 (4,6) days shorter. The estimates did not materially change in sensitivity analyses (Appendix Table 2).

The estimated 7-year risk of the combined endpoint of AIDS-defining illness or death was 7.1% (6.8, 7.3) for immediate initiation, 7.5% (7.2, 7.8) for initiation at CD4<500 cell/mm<sup>3</sup>, and 8.5% (8.2, 8.8) for initiation at CD4<350 cell/mm<sup>3</sup>. Compared with immediate initiation, the risk ratio (95% CI) was 1.06 (1.06, 1.07) under initiation at CD4<500 cell/mm<sup>3</sup>, and 1.20 (1.17, 1.23) under initiation at CD4<350 cell/mm<sup>3</sup>. Figure 1 shows the estimated survival curves.

All estimated 7-year risks were lower in analyses restricted to the 17,612 individuals with baseline CD4 cell count >500 cells/mm<sup>3</sup> and the 30,558 individuals with baseline CD4 cell count >350 cells/mm<sup>3</sup> (Table 3).

The estimated 7-year risk of severe/moderate AIDS or death was 4.7% (4.3, 5.0) under immediate initiation, 4.8% (4.5, 5.1) under initiation at CD4<500 cells/mm<sup>3</sup>, and 5.2% (4.9,

5.4) under initiation at  $CD4 < 350$  cells/mm<sup>3</sup>. Compared with immediate initiation, the risk ratio was 1.03 (1.02, 1.04) under initiation at  $CD4 < 500$  cell/mm<sup>3</sup> and 1.11 (1.07, 1.15) under initiation at  $CD4 < 350$  cell/mm<sup>3</sup>. The estimated 7-year risk of tuberculosis was 1.20 (1.09, 1.36) under immediate initiation, and 1.24 (1.15, 1.41) and 1.34 (1.26, 1.51) under initiation at  $CD4$  initiation  $< 500$  and  $< 350$  cells/mm<sup>3</sup>.

Figure 2 shows the proportion of individuals considered in need of treatment by cART initiation strategy. At 1 year, 100%, 78%, and 58% of individuals were estimated to be on cART under immediate initiation, initiation at  $CD4 < 500$  cell/mm<sup>3</sup>, and initiation under  $CD4 < 350$  cell/mm<sup>3</sup>, respectively. The corresponding proportions at year 7 are 100%, 99%, and 92% (Appendix Table 3).

Figure 3 shows the proportion of individuals with virologically suppressed replication by cART initiation strategy. At 1 year, 58%, 46%, and 36% of individuals were estimated to be virologically suppressed under immediate initiation, initiation at  $CD4 < 500$  cell/mm<sup>3</sup>, and initiation under  $CD4 < 350$  cell/mm<sup>3</sup>, respectively. The corresponding proportions at year 7 are 87%, 87%, and 84% (Appendix Table 4). The estimates were larger when suppressed virological suppression was defined as HIV-RNA  $< 400$  copies/mL (Appendix Figure 2).

## Discussion

Our estimates from high-income countries in Europe and the USA indicate that, in a population with a fairly low  $CD4$  count at HIV diagnosis, immediate initiation of cART increases survival and AIDS-free survival compared with initiation strategies based on  $CD4$  count. However, over a 7 year period, the average benefit was small both for survival (5 days) and AIDS-free survival (21 days) when comparing immediate initiation with initiation at a  $CD4$  count of less than 350 cells/mm<sup>3</sup>. For individuals with a  $CD4$  count greater than 500 cells/mm<sup>3</sup> at HIV diagnosis, starting cART when the  $CD4$  count fell below 350 cells/mm<sup>3</sup> increased the relative risk of death or diagnosis of AIDS by more than 50% when compared with immediate initiation.

Our estimates also indicate that the proportion of individuals with suppressed virological replication was greater for immediate universal cART initiation earlier in the follow-up. By 7 years, all strategies resulted in estimated proportions of virological suppression between 83 and 87%. At that time between 93% and 99% of individuals were estimated to be receiving cART under both  $CD4$ -based strategies.

Our findings from high-income countries complement the results from the Temprano<sup>12</sup> and the HPTN 052<sup>10</sup> trials. The Temprano trial randomised individuals with nadir  $CD4$  cells count  $> 800$  cells/mm<sup>3</sup> to either immediate initiation or initiation when  $CD4$  count drops below the threshold recommended by WHO (between 200 and 500 cells/mm<sup>3</sup> depending of the year of recruitment). Immediate initiation reduced the risk of serious illness, including tuberculosis and death, by 44%. The HPTN 052 trial randomly assigned individuals in low and mid-income countries with  $CD4$  count between 350 and 550 cells/mm<sup>3</sup> to either immediate cART initiation or initiation at the earliest of  $CD4$  dropping below 250 cells/mm<sup>3</sup> or a diagnosis of an AIDS-defining illness. A secondary analysis found that immediate

initiation reduced the risk of several clinical outcomes. Though these trials cover a shorter period than our study (2.5 versus 7 years) and use outdated CD4 cell count thresholds, a comparison with our estimates suggests that immediate initiation may be more beneficial in low-income countries, where tuberculosis and bacterial infections are more frequent, than in the high-income countries represented in our study.

Our results will also complement the START trial results, when they become available, for the subset of trial participants in high-income countries.<sup>34</sup> In preliminary analyses, the data and safety monitoring board of the START trial reported that initiation of treatment at a CD4 count less than 350 cells/mm<sup>3</sup> substantially increased the incidence of death or serious disease when compared with immediate initiation in individuals with CD4 counts higher than 500 cells per  $\mu$ L at baseline. We also estimated an increased risk with deferral of cART (52% after 7 years), but of smaller magnitude, perhaps reflecting residual confounding, different populations and periods, or both. Our analysis also provides estimates for all-cause mortality over 7 year follow-up in high income countries. When full results of the START trial are released, we will be able to do a more formal comparison between a randomized and an observational study assessing the benefits of early initiation of cART, which will be useful in informing adjustments that may be required in future analyses of longer term outcomes

Besides the length of follow-up, the main strengths of our study are the large sample size of over 55,0000 individuals and the setting in HIV clinics in Europe and United States that are representative of routine clinical practice. Therefore, our results should be generalisable to a population of HIV-infected, AIDS-free patients in high-income countries. Other observational studies of ART-naïve patients have compared clinical outcomes for cART initiation at different CD4 count thresholds,<sup>5-8</sup> and have generally found that earlier initiation was beneficial. Of note, some of these observational studies included HIV cohorts that contributed data to our study, although we are using a more recent data update.

Our study has some limitations. First, we did not have information on non-fatal adverse effects. Because of longer exposure to antiretroviral treatment, patients who initiate cART early might be more susceptible to drug toxicity. Although the safety profiles of antiretroviral drugs has largely improved in the last decade, central nervous system,<sup>25,26</sup> renal,<sup>27-29</sup> bone<sup>30</sup> and cardiovascular<sup>31</sup> toxicities have been reported in relation to drugs currently used in high-income countries. Second, like all observational studies the validity of our estimates relies on the assumption of no unmeasured confounding. Although we adjusted our models for time-varying CD4 count, HIV-RNA levels and AIDS diagnosis, the most important factors used by clinicians to decide when to start cART, we cannot exclude the possibility that unmeasured prognostic factors (e.g., hepatitis co-infection) could have influenced the decision to start cART.

The debate on the optimal strategy to initiate cART needs to take into consideration both the public health benefits, i.e., reduction of HIV transmission, and the benefits for HIV-infected individuals, i.e., increase in healthy life years. Our findings help quantify both types of benefits. A public health benefit of earlier initiation is implied by the greater proportion of virologically suppressed individuals, which will result in lower transmission to others.



However, the success of cART to prevent transmission depends also on HIV testing strategies. Since at least 30% to 80%<sup>32,33</sup> of transmissions occur from individuals unaware of their HIV infection, early cART initiation, if implemented, should be put in place together with strategies to encourage HIV testing in early HIV disease.

Our findings also help quantify the individual benefits of earlier initiation in terms of slightly longer survival under the testing strategies present in the study populations. More work is needed to explore whether these small benefits are partly offset by higher risk of toxicity or development of drug resistance in the long term.

In analyses restricted to individuals with CD4 count >350 cells/mm<sup>3</sup> at HIV diagnosis, the estimated 7-year risks of mortality and combined outcome mortality or AIDS-defining illness were <3% and <7%, respectively, for all cART initiation strategies. The higher risks (<4.2% and <9%, respectively) in the main analyses, which included approximately 50% individuals with CD4 count <350 cells/mm<sup>3</sup> at HIV diagnosis, again suggest the importance of timely cART initiation and better HIV testing strategies.

Finally, our study enables us to quantify the degree to which earlier cART initiation results in increased proportions of individuals considered in need of treatment. The differences between cART initiation strategies decrease over time and become small at 7 years after HIV diagnosis. The early differences might be negligible when considering the total duration of cART, which is expected to be between 40 and 50 years<sup>35</sup>. More research is needed on the long-term cost-effectiveness of different cART initiation strategies after accounting for the impact on new transmissions.<sup>36,37</sup>

In conclusion, our estimates indicate that, compared with CD4-based strategies, immediate universal treatment slightly prolongs survival and AIDS-free survival and increases the proportions of individuals with suppressed virological replication and in need of treatment. However, a policy on whether cART is made available at HIV diagnosis irrespective of CD4 count needs to consider many pieces of information—eg, longterm all-cause mortality, AIDS and non-AIDS morbidity, HIV transmission, the health-care setting, and costs that no one study can provide. Results from recently presented randomised trials indicate that there is a health benefit from immediate initiation of cART. Observational studies will continue to have a role in understanding the long-term effects of initiation of cART at high CD4 counts in routine clinical settings. Our results suggest that a focus on better and innovative HIV testing strategies might be as important, if not more, than discussions about early initiation of treatment.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

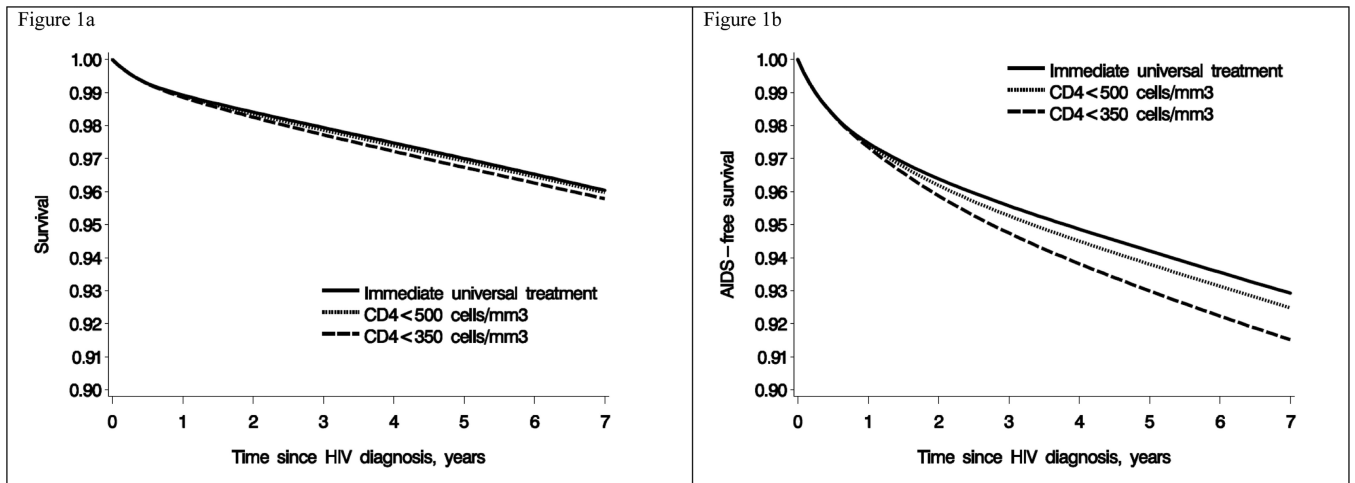
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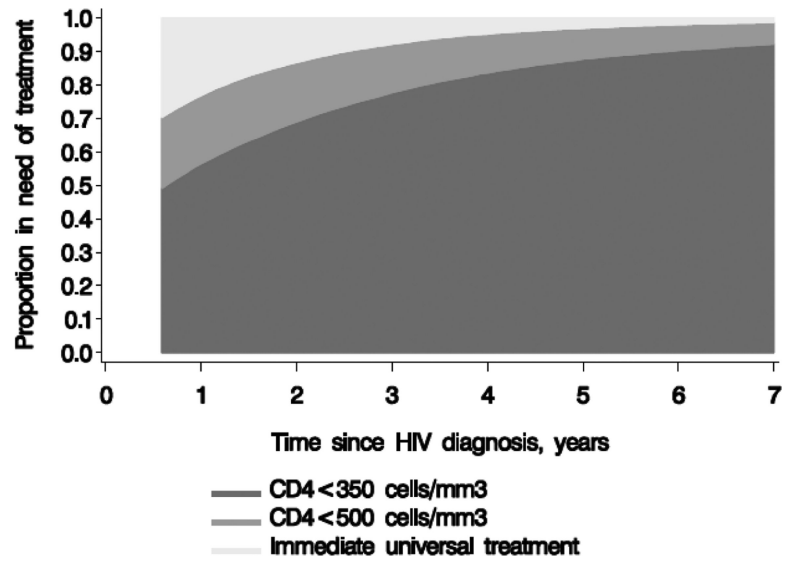
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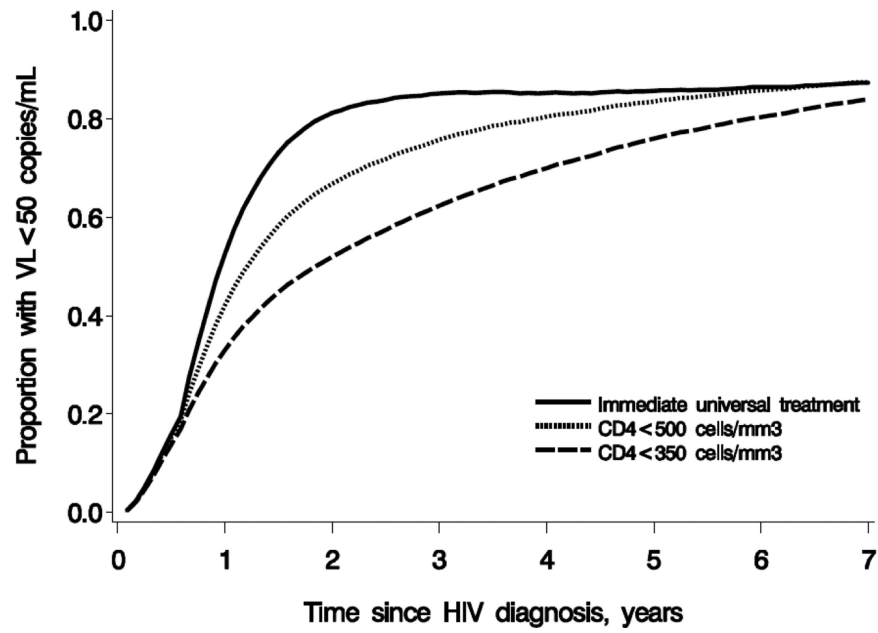
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**Figure 1.**  
Survival and AIDS-free survival estimates by cART initiation strategy, HIV-CAUSAL  
Collaboration 2000-2013



**Figure 2.** Proportions in need of antiretroviral treatment by cART initiation strategy\*, HIV-CAUSAL Collaboration 2000-2013



**Figure 3.** Proportion with suppressed virological replication, defined as HIV-RNA < 50 copies/mL by cART initiation strategy\*. HIV-CAUSAL Collaboration 2000-2013

Table 1

Baseline characteristics and incidence rates of mortality and of AIDS or mortality of 55,826 eligible individuals, HIV-CAUSAL Collaboration 2000-2013.

	No. individuals	Person-years	% cART initiators during follow-up	Median [IQR] follow-up time, months	No. deaths	Incidence rate of death, per 1000 person-years	No. AIDS events or deaths	Incidence rate of AIDS or death, per 1000 person-years
CD4 cell count, cells/mm <sup>3</sup>								
<50	3080	12960	95	43 [21,74]	323	24.9	521	49.4
50-100	2573	10906	96	44 [21,75]	197	18.1	330	34
100 - 200	6398	26321	95	41 [20,73]	291	11.1	534	21.6
200 - 350	13217	52259	86	39 [19,69]	351	6.7	757	15.1
350 - 500	12927	48826	67	36 [18,66]	272	5.6	608	12.9
>500	17631	64248	46	34 [18,63]	303	4.7	722	11.5
HIV-RNA, copies/mL								
<10,000	13631	49891	54	35 [18,62]	287	5.8	532	10.9
10,000 - 100,000	24702	95501	72	37 [19,68]	691	7.2	1469	16.1
>100,000	17493	70129	84	39 [19,71]	759	10.8	1471	22.7
Sex								
Male	42940	166625	70	38 [19,68]	1509	9.1	2787	17.6
Female	12886	48896	74	36 [18,67]	228	4.7	685	14.9
Age, years								
< 35	25359	93346	65	34 [18,64]	246	2.6	945	10.5
35 - 50	22722	92025	75	40 [20,71]	713	7.7	1535	17.7
>50	7745	30150	82	38 [19,69]	778	25.8	992	35
Transmission group								
Heterosexual	20567	80626	75	38 [19,69]	459	5.7	1243	16.4
Homo/bisexual	26547	102663	67	38 [19,67]	371	3.6	1093	11.1
Injection drug-use	1514	5530	66	32 [16,63]	119	21.5	171	32.9
Other/unknown	7198	26703	76	35 [18,65]	788	29.5	965	38.2
Geographical origin								
Western Countries	38122	149012	71	38 [19,68]	1414	9.5	2450	17.2
Sub-Saharan Africa	9713	37410	77	37 [19,68]	154	4.1	624	18
Rest of World	5235	18147	68	33 [17,59]	97	5.3	263	15.3
Unknown	2756	10951	65	35 [17,69]	72	6.6	135	12.9
Calendar year								
2000 - 2004	15180	90114	76	71 [31,109]	889	9.9	1644	19.5
2005 - 2010	35124	12517	73	37 [22,58]	826	6.8	1785	15.3
2011 - 2013	5522	3890	48	8 [4,12]	22	5.7	43	11.2

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	No. individuals	Person-years	% cART initiators during follow-up	Median [IQR] follow-up time, months	No. deaths	Incidence rate of death, per 1000 person-years	No. AIDS events or deaths	Incidence rate of AIDS or death, per 1000 person-years
Total	55826	215521	71	37 [19,68]	1737	8.1	3472	16.9



Table 2

Seven-year risks, risk ratios, and risk differences by cART initiation strategy, HIV-CAUSAL Collaboration 2000-2013.\*

Clinical Outcome	cART initiation strategy	Risk at 7 years, % (95% CI)	Risk Ratio (95% CI)	Risk difference, ** % (95% CI)	Difference in restricted mean survival time, ** days (95% CI)
All-cause mortality	Immediate universal	4.0 (3.8, 4.2)	1 (Ref.)	0 (Ref.)	0 (Ref.)
	<500 cells/mm <sup>3</sup>	4.0 (3.8, 4.3)	1.02 (1.01,1.03)	0.06 (0.02,0.11)	-2 (-2,-1)
	<350 cells/mm <sup>3</sup>	4.2 (4.0, 4.5)	1.06 (1.03,1.10)	0.25 (0.14,0.37)	-5 (-6,-4)
AIDS or death	Immediate universal	7.1 ( 6.8, 7.3)	1 (Ref.)	0 (Ref.)	0 (Ref.)
	<500 cells/mm <sup>3</sup>	7.5 (7.2, 7.8)	1.06 (1.06,1.07)	0.44 (0.37,0.51)	-7 (-8,-6)
	<350 cells/mm <sup>3</sup>	8.5 (8.2, 8.8)	1.20 (1.17,1.23)	1.41 (1.24,1.59)	-21 (-23,-19)

\* Estimates based on the parametric g-formula adjusted for measured time-varying confounders (CD4 count, HIV-RNA and AIDS) and baseline characteristics (calendar period and age of HIV diagnosis, risk group, gender, geographical origin, ethnicity and cohort).

\*\* The risk difference is the 7-year risk of death under each strategy minus the 7-year risk of death under immediate universal initiation. The difference in restricted survival time is the mean survival (up to 7 years) under each strategy minus the mean survival under the immediate initiation strategy.

Seven-year risks, risk ratios, and risk differences by cART initiation strategy for individuals with CD4 count >500 and >350 cells/mm<sup>3</sup> at HIV diagnosis, HIV-CAUSAL Collaboration 2000-2013.\*

Table 3

CD4 at HIV diagnosis	Clinical Outcome	cART initiation strategy	Risk at 7 years (95% CI)	Risk Ratio (95% CI)	Risk difference (95% CI)	Difference in mean survival time, days (95% CI)
>500 cells/mm <sup>3</sup>	All-cause mortality	Immediate universal	2.7 (2.2,3.5)	Ref.	Ref.	Ref.
		<500 cells/mm <sup>3</sup>	2.6 (2.2,3.1)	0.96 (0.87,1.05)	-0.10 (-0.42,0.12)	-1 (-4,-3)
		<350 cells/mm <sup>3</sup>	2.7 (2.3,3.1)	1.00 (0.84,1.14)	-0.01 (-0.49,0.34)	-3 (-7,-3)
>350 cells/mm <sup>3</sup>	AIDS or death	Immediate universal	4.9 (4.4,5.2)	Ref.	Ref.	Ref.
		<500 cells/mm <sup>3</sup>	5.7 (5.2,6.0)	1.21 (1.11,1.33)	1.00 (0.58,1.35)	-19 (-23,-15)
		<350 cells/mm <sup>3</sup>	7.1 (6.6,7.5)	1.52 (1.34,1.77)	2.45 (1.75,3.18)	-38 (-46,-31)
>350 cells/mm <sup>3</sup>	All-cause mortality	Immediate universal	2.9 (2.7,3.3)	Ref.	Ref.	Ref.
		<500 cells/mm <sup>3</sup>	2.9 (2.6,3.2)	0.99 (0.95,1.03)	-0.02 (-0.16,0.08)	-1 (-2,1)
		<350 cells/mm <sup>3</sup>	3.0 (2.7,3.3)	1.03 (0.92,1.13)	0.08 (-0.25,0.32)	-3 (-6,1)
<350 cells/mm <sup>3</sup>	AIDS or death	Immediate universal	4.9 (4.4,5.2)	Ref.	Ref.	Ref.
		<500 cells/mm <sup>3</sup>	5.5 (5.1,5.8)	1.13 (1.09,1.17)	0.62 (0.47,0.70)	-11 (-13,-9)
		7.0 (6.6,7.5)	1.43 (1.33,1.53)	2.11 (1.70,2.56)	-34 (-38,-28)	

\* Estimates based on the parametric g-formula adjusted for measured time-varying confounders (CD4 count, HIV-RNA and AIDS) and baseline characteristics (calendar period and age of HIV diagnosis, risk group, gender, geographical origin, ethnicity and cohort).