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

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Summary

Background Recommendations have differed nationally and internationally with respect to the best time to start antiretroviral therapy (ART). We compared effectiveness of three strategies for initiation of ART in high-income countries for HIV-positive individuals who do not have AIDS: immediate initiation, initiation at a CD4 count less than 500 cells per μL, and initiation at a CD4 count less than 350 cells per μL.

Methods We used data from the HIV-CAUSAL Collaboration of cohort studies in Europe and the USA. We included 55 826 individuals aged 18 years or older who were diagnosed with HIV-1 infection between January, 2000, and September, 2013, had not started ART, did not have AIDS, and had CD4 count and HIV-RNA viral load measurements within 6 months of HIV diagnosis. We estimated relative risks of death and of death or AIDS-defining illness, mean survival time, the proportion of individuals in need of ART, and the proportion of individuals with HIV-RNA viral load less than 50 copies per mL, as would have been recorded under each ART initiation strategy after 7 years of HIV diagnosis. We used the parametric g-formula to adjust for baseline and time-varying confounders.

Findings Median CD4 count at diagnosis of HIV infection was 376 cells per μL (IQR 222–551). Compared with immediate initiation, the estimated relative risk of death was 1·02 (95% CI 1·01–1·02) when ART was started at a CD4 count less than 500 cells per μL, and 1·06 (1·04–1·08) with initiation at a CD4 count less than 350 cells per μL. Corresponding estimates for death or AIDS-defining illness were 1·06 (1·06–1·07) and 1·20 (1·17–1·23), respectively. Compared with immediate initiation, the mean survival time at 7 years with a strategy of initiation at a CD4 count less than 500 cells per μL was 2 days shorter (95% CI 1–2) and at a CD4 count less than 350 cells per μL was 5 days shorter (4–6). 7 years after diagnosis of HIV, 100%, 98·7% (95% CI 98·6–98·7), and 92·6% (92·2–92·9) of individuals would have been in need of ART with immediate initiation, initiation at a CD4 count less than 500 cells per μL, and initiation at a CD4 count less than 350 cells per μL, respectively. Corresponding proportions of individuals with HIV-RNA viral load less than 50 copies per mL at 7 years were 87·3% (87·3–88·6), 87·4% (87·4–88·6), and 83·8% (83·6–84·9).

Interpretation The benefits of immediate initiation of ART, 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 ART.

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Introduction

Recommendations have differed nationally and internationally with respect to the best time to start antiretroviral therapy (ART) in HIV-positive patients who do not have AIDS. In the most recent US guidelines,[1,2] initiation of ART 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 ART when the patient's CD4 count has fallen below 500 cells per μL.[3] Moreover, in Europe, treatment initiation is recommended for all patients with a CD4 count less than 350 cells per μL[4] and should be considered for individuals with a CD4 count of 350–500 cells per μL.

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 ART at CD4 counts of 350–500 cells per μL is associated with reduced mortality and AIDS morbidity[5–12] and decreased transmission of HIV to other people.[13] The benefits of such early initiation on survival and transmission might be offset by development of toxicity and drug resistance.[14] Moreover, because treatment must be used for the rest of a patient's

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Research in context

Evidence before the study

Several observational studies and clinical trials have addressed the question of when to start antiretroviral therapy (ART). 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 ART initiation strategy. However, estimates from observational studies remain important to assess long-term outcomes of early ART 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 ART initiation strategies: immediate initiation; initiation at a CD4 count less than 500 cells per μL or a diagnosis of AIDS; and initiation at a CD4 count less than 350 cells per μL 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 ART substantially increases the proportion of individuals with suppressed virological replication and the proportion of individuals in need of ART.

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 ART, 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 ART initiation.

life without interruption,[15] immediate initiation would increase substantially the proportion of individuals in need of ART and the burden on available resources.

Results from The Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (TEMPRANO) trial[12] suggest that immediate initiation of ART is the best strategy for patients in low-income countries, where the risk of opportunistic infections is high. Preliminary findings of the Strategic Timing of Antiretroviral Treatment (START) trial[16] also support the benefit of early initiation with a large beneficial effect on risk of serious AIDS. However, no estimates are available of the relative effectiveness of immediate initiation versus starting treatment according to CD4 thresholds with respect to death and morbidity of patients with HIV infection, representative of clinical practice in high-income countries. These estimates are important not only for patients and clinicians but also for service providers and policy makers. Estimates of the proportions of individuals in need of treatment and with suppressed viral load are important to estimate the cost-effectiveness of strategies in current or future guidelines on ART initiation and to allocate resources between HIV treatment and other health priorities.

Here, we aimed to compare immediate initiation of ART with strategies for starting treatment based on CD4 thresholds of 350 cells per μL and 500 cells per μL 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 the USA and six countries in Europe (France, Greece, the Netherlands, Spain, Switzerland, and the UK). Data for every cohort are gathered routinely during clinical practice within health-care systems with universal access to care. Recorded data include patients' characteristics (age, sex, geographical origin, and transmission category), use of ART (type of regimens and dates of start and discontinuation), CD4 counts, plasma HIV-RNA viral load measurements, AIDS-defining illnesses, and deaths. Data for every cohort are submitted in a standardised format to the coordinating centre. Ethics approval was granted by the ethics committees of every one of the participating cohorts, according to country-specific regulations.

Procedures

We restricted our analyses to individuals who met the following inclusion criteria: aged 18 years or older; diagnosis of HIV-1 infection on or after Jan 1, 2000; did not have AIDS; had not started ART; and CD4 count and HIV-RNA viral load measurements within 3 months of each other and within 6 months of the date of HIV diagnosis. We followed up patients from baseline, which we defined as the date when all criteria were met, to death (or progression to AIDS when considering AIDS-free survival), 12 months after the most recent laboratory measurement, or cohort-specific administrative censoring (ranging from February, 2010, to March, 2013), whichever occurred first. We excluded individuals who had no data for CD4 count or HIV-RNA viral load after baseline.

Because the relative effectiveness of initiation strategies will depend on CD4 count at HIV diagnosis, we did two sensitivity analyses restricted to individuals with a CD4 count greater than 350 cells per μL at HIV diagnosis and a CD4 count greater than 500 cells per μL at HIV diagnosis.

ART consisted of a regimen of antiretroviral drugs including at least two nucleoside reverse transcriptase inhibitors (NRTIs) and either one or more protease

inhibitors, one non-nucleoside reverse transcriptase inhibitor (NNRTI), one entry or fusion inhibitor, or one integrase inhibitor. We compared three initiation strategies. First was immediate treatment, which we defined as initiation within 6 months of HIV diagnosis, irrespective of the CD4 count. The second strategy was initiation within 6 months of a CD4 count less than 500 cells per µL or a diagnosis of AIDS. Finally, we looked at initiation within 6 months of a CD4 count less than 350 cells per µL or a diagnosis of AIDS.

Outcomes

Our primary clinical outcomes were all-cause mortality and a combined endpoint of AIDS diagnosis[17] or death. For each initiation strategy and outcome, we estimated the 7 year risk and the restricted mean survival time.[18] In sensitivity analyses, we also considered a combined endpoint of death or severe or moderate AIDS-defining illness[19] (eg, non-Hodgkin lymphoma, progressive multifocal leukoencephalopathy, cryptococcosis, cerebral toxoplasmosis, AIDS dementia complex, and disseminated *Mycobacterium avium* complex), and we also assessed the outcome tuberculosis, because delayed initiation of treatment has been associated with increased risk of tuberculosis.[10,13] Other primary outcomes were the proportion of individuals in need of treatment and the proportion with suppressed virological replication, which we defined as HIV-RNA viral load less than 50 copies per mL, up to 7 years after HIV diagnosis, assuming that ART is continued once it is started.

Statistical analysis

We adjusted estimates for confounders measured at baseline and for time-dependent confounders (ie, CD4 count, HIV-RNA viral load, and AIDS diagnosis). However, standard statistical methods cannot adjust appropriately for time-dependent confounders affected by previous treatment.[20,21] Therefore, we applied the parametric g-formula[22] to obtain adjusted estimates for each treatment strategy under the assumptions of no residual confounding, no measurement error, and no model misspecification. We used a non-parametric bootstrap procedure based on 200 samples to obtain percentile-based 95% CIs. We did all analyses with SAS version 9.2 and the GFORMULA macro.[23]

The parametric g-formula is a generalisation of standardisation for time-varying treatments and confounders.[5,21,22] The estimation procedure for the HIV-CAUSAL Collaboration has been described elsewhere.[5] 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 with the above estimates is run to simulate the distribution of the post-baseline outcomes and time-varying covariates separately for each initiation strategy for ART.

For the first step of the estimation procedure, we fit separate logistic regression models for time-varying indicators of death, AIDS diagnosis, initiation of ART, CD4 count, and HIV-RNA viral load, in addition to linear regression models for CD4 count and HIV-RNA on the natural logarithm scale. All regression models included as covariates the two most recent values for these time-varying indicators, time since last CD4 count, and HIV-RNA viral load, and the following baseline variables: CD4 count per µL (<50, 50–99, 100–199, 200–349, 350–499, and ≥500), HIV-RNA viral load log copies per mL (<4, 4–5, and >5), sex, transmission group (heterosexual, homosexual or bisexual, injecting drug user, other or unknown), calendar year (2000–04, 2005–10, 2011–13), age in years (<35, 35–50, >50), geographical origin (Europe and the USA, sub-Saharan Africa, rest of the world, unknown), and cohort. Models for CD4 count and HIV-RNA also included an interaction term for the number of months since starting ART. Similar to 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 p 5).

We did several sensitivity analyses. First, we adjusted for a time-fixed indicator of co-infection with hepatitis C virus. Second, we included individuals with no CD4 count and HIV-RNA viral load measurements after baseline. Third, we excluded cohorts of HIV seroconverters (GEMES, PRIMO, SEROCO, UK Register of Seroconverters) who might have been treated with short-course ART during primary HIV infection (patients have immunological and virological benefits after treatment is stopped).[24–26] Finally, we calculated the proportion of individuals with suppressed virological replication, which we defined as HIV-RNA viral load less than 400 copies per mL rather than less than 50 copies per mL.

Role of the 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 a known date for diagnosis of HIV-1 infection between January, 2000, and September, 2013. The analyses presented here are based on data pooled in September, 2013. We excluded 5027 people who had no CD4 count or HIV-RNA viral load measurement after baseline and 9635 individuals whose baseline date was more than 6 months after HIV diagnosis. Therefore, 55 826 individuals were eligible for our analysis.

	Individuals (n)	Person-years	Proportion starting ART during follow-up (%)	Median (IQR) follow-up (months)	Deaths (n)	Incidence of death (per 1000 person-years)	AIDS events or deaths (n)	Incidence of AIDS events or death (per 1000 person-years)
Total	55 826	215 521	71%	37 (19–68)	1737	8·1	3472	16·9
CD4 cell count (cells per μL)								
<50	3080	12 960	95%	43 (21–74)	323	24·9	521	49·4
50–99	2573	10 906	96%	44 (21–75)	197	18·1	330	34·0
100–199	6398	26 321	95%	41 (20–73)	291	11·1	534	21·6
200–349	13 217	52 259	86%	39 (19–69)	351	6·7	757	15·1
350–499	12 927	48 826	67%	36 (18–66)	272	5·6	608	12·9
≥500	17 631	64 248	46%	34 (18–63)	303	4·7	722	11·5
HIV-RNA viral load (copies per mL)								
<10 000	13 631	49 891	54%	35 (18–62)	287	5·8	532	10·9
10 000–100 000	24 702	95 501	72%	37 (19–68)	691	7·2	1469	16·1
>100 000	17 493	70 129	84%	39 (19–71)	759	10·8	1471	22·7
Sex								
Men	42 940	166 625	70%	38 (19–68)	1509	9·1	2787	17·6
Women	12 886	48 896	74%	36 (18–67)	228	4·7	685	14·9
Age (years)								
<35	25 359	93 346	65%	34 (18–64)	246	2·6	945	10·5
35–50	22 722	92 025	75%	40 (20–71)	713	7·7	1535	17·7
>50	7745	30 150	82%	38 (19–69)	778	25·8	992	35·0
Transmission group								
Heterosexual	20 567	80 626	75%	38 (19–69)	459	5·7	1243	16·4
Homosexual or bisexual	26 547	102 663	67%	38 (19–67)	371	3·6	1093	11·1
Injecting drug user	1514	5530	66%	32 (16–63)	119	21·5	171	32·9
Other or unknown	7198	26 703	76%	35 (18–65)	788	29·5	965	38·2
Geographical origin								
Europe and the USA	38 122	149 012	71%	38 (19–68)	1414	9·5	2450	17·2
Sub-Saharan Africa	9713	37 410	77%	37 (19–68)	154	4·1	624	18·0
Rest of the world	5235	18 147	68%	33 (17–59)	97	5·3	263	15·3
Unknown	2756	10 951	65%	35 (17–69)	72	6·6	135	12·9
Calendar year								
2000–04	15 180	90 114	76%	71 (31–109)	889	9·9	1644	19·5
2005–10	35 124	12 517	73%	37 (22–58)	826	6·8	1785	15·3
2011–13	5522	3890	48%	8 (4–12)	22	5·7	43	11·2

ART=antiretroviral therapy.

Table 1: **Baseline characteristics and incidence of death and of AIDS events or death**

	Risk at 7 years (95% CI)	Relative risk (95% CI)	Risk difference (95% CI)*	Difference in restricted mean survival time (days; 95% CI)*
All-cause mortality				
Immediate treatment	4·0% (3·8–4·2)	1·00	..	..
CD4 count <500 cells per μL	4·0% (3·8–4·3)	1·02 (1·01–1·03)	0·06% (0·02–0·11)	−2 (−2 to −1)
CD4 count <350 cells per μL	4·2% (4·0–4·5)	1·06 (1·03–1·10)	0·25% (0·14–0·37)	−5 (−6 to −4)
AIDS diagnosis or death				
Immediate treatment	7·1% (6·8–7·3)	1·00	..	..
CD4 count <500 cells per μL	7·5% (7·2–7·8)	1·06 (1·06–1·07)	0·44% (0·37–0·51)	−7 (−8 to −6)
CD4 count <350 cells per μL	8·5% (8·2–8·8)	1·20 (1·17–1·23)	1·41% (1·24–1·59)	−21 (−23 to −19)

Estimates are based on the parametric g-formula, adjusted for measured time-varying confounders (CD4 count, HIV-RNA viral load, and AIDS diagnosis) and baseline characteristics (calendar period and age at HIV diagnosis, risk group, sex, geographical origin, ethnic origin, and cohort). ART=antiretroviral therapy. *Compared with immediate initiation.

Table 2: **Risk of all-cause mortality and AIDS diagnosis or death at 7 years, by ART initiation strategy**

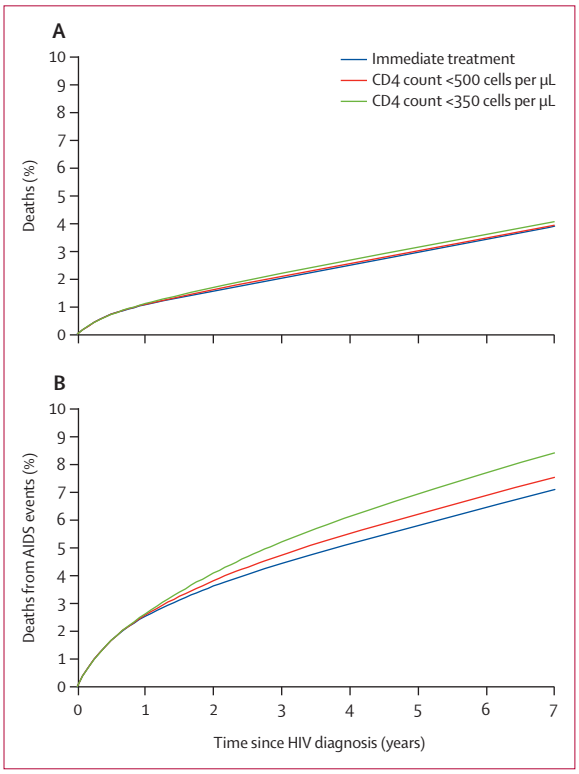

Figure 1: **Estimates of deaths and deaths from AIDS events with each ART initiation strategy**
ART=antiretroviral therapy.

77% of participants were men and 73% started follow-up after 2004 (table 1). The median CD4 count was 376 cells per µL (IQR 222–551), median HIV-RNA viral load was 4·6 log copies per mL (4·0–5·1), and median age at baseline was 36 years (30–44). During median follow-up of 37 months (IQR 19–68), 39 708 (71%) individuals started ART. Median CD4 count and HIV-RNA viral load at initiation of ART were 259 cells per µL (IQR 161–355) and 4·8 log copies per mL (4·2–5·3), respectively. The median time between HIV diagnosis and initiation of ART was 2 months (IQR 1–14), and 5136 (12%) people started ART when their CD4 count was greater than 500 cells per µL. Compared with individuals who initiated treatment with a CD4 count of 500 cells per µL or lower, people who initiated ART with a CD4 count greater than 500 cells per µL were less likely to come from a region outside Europe or the USA and more likely to be in the homosexual and bisexual transmission group (appendix p 1).

During 215 521 person-years of follow-up, 1737 people died and 3472 were diagnosed with AIDS or died (table 1). The estimated 7 year risk of death was 4·0% (95% CI 3·8–4·2) when ART was started immediately, 4·0% (3·8–4·3) for initiation of treatment at a CD4 count less than 500 cells per µL, and 4·2% (4·0–4·5) for initiation at a CD4 count less than 350 cells per µL (table 2). Compared with immediate initiation of treatment, the relative risk of death was 1·02 (95% CI 1·01–1·03) when ART was started at a CD4 count less than 500 cells per µL and 1·06

	Risk at 7 years (95% CI)	Relative risk (95% CI)	Risk difference (95% CI)*	Difference in mean survival time (days; 95% CI)*
CD4 count >500 cells per µL				
All-cause mortality				
Immediate treatment	2·7% (2·2–3·5)	1·00	..	..
CD4 count <500 cells per µL	2·6% (2·2–3·1)	0·96 (0·87–1·05)	−0·10 (−0·42 to 0·12)	−1 (−4 to 3)
CD4 count <350 cells per µL	2·7% (2·3–3·1)	1·00 (0·84–1·14)	−0·01 (−0·49 to 0·34)	−3 (−7 to 3)
AIDS diagnosis or death				
Immediate treatment	4·9% (4·4–5·2)	1·00	..	..
CD4 count <500 cells per µL	5·7% (5·2–6·0)	1·21 (1·11–1·33)	1·00 (0·58 to 1·35)	−19 (−23 to −15)
CD4 count <350 cells per µL	7·1% (6·6–7·5)	1·52 (1·34–1·77)	2·45 (1·75 to 3·18)	−38 (−46 to −31)
CD4 count >350 cells per µL				
All-cause mortality				
Immediate treatment	2·9% (2·7–3·3)	1·00	..	..
CD4 count <500 cells per µL	2·9% (2·6–3·2)	0·99 (0·95–1·03)	−0·02 (−0·16 to 0·08)	−1 (−2 to 1)
CD4 count <350 cells per µL	3·0% (2·7–3·3)	1·03 (0·92–1·13)	0·08 (−0·25 to 0·32)	−3 (−6 to 1)
AIDS diagnosis or death				
Immediate treatment	4·9% (4·4–5·2)	1·00	..	..
CD4 count <500 cells per µL	5·5% (5·1–5·8)	1·13 (1·09–1·17)	0·62 (0·47 to 0·70)	−11 (−13 to −9)
CD4 count <350 cells per µL	7·0% (6·6–7·5)	1·43 (1·33–1·53)	2·11 (1·70 to 2·56)	−34 (−38 to −28)

Estimates are based on the parametric g-formula, adjusted for measured time-varying confounders (CD4 count, HIV-RNA viral load, and AIDS diagnosis) and baseline characteristics (calendar period and age at HIV diagnosis, risk group, sex, geographical origin, ethnic origin, and cohort). ART=antiretroviral therapy. *Compared with immediate initiation.

Table 3: **Sensitivity analyses of risk of all-cause mortality and AIDS diagnosis or death at 7 years, by baseline CD4 counts and ART strategy**

(1·03–1·10) with initiation at a CD4 count less than 350 cells per µL. Compared with immediate initiation, mean survival at 7 years was 2 days shorter (95% CI 1–2) when treatment was started at a CD4 count less than 500 cells per µL and 5 days shorter (4–6) with initiation at a CD4 count less than 350 cells per µL. Estimates did not change by much in sensitivity analyses adjusting for co-infection with hepatitis C virus, no CD4 count and HIV-RNA viral load measurements after baseline, and excluding HIV seroconverters (appendix p 2).

The estimated 7 year risk of the combined endpoint of AIDS diagnosis or death was 7·1% (6·8–7·3) with an immediate start to treatment, 7·5% (7·2–7·8) for initiation at a CD4 count less than 500 cells per µL, and 8·5% (8·2–8·8) for initiation at a CD4 count less than 350 cells per µL. Compared with immediate initiation of ART, the relative risk of AIDS diagnosis or death was 1·06 (95% CI 1·06–1·07) with initiation at a CD4 count less than 500 cells per µL, and 1·20 (1·17–1·23) when ART was started at a CD4 count less than 350 cells per µL (figure 1).

In sensitivity analyses in individuals with baseline CD4 counts greater than 500 cells per µL and greater than 350 cells per µL (table 3) estimated 7 year risks of all-cause mortality and AIDS diagnosis or death were lower than in the overall cohort.

In further sensitivity analyses, the estimated 7 year risk of severe or moderate AIDS-defining illness or death was 4·7% (95% CI 4·3–5·0) with immediate initiation of ART, 4·8% (4·5–5·1) with initiation at a CD4 count less than 500 cells per µL, and 5·2% (4·9–5·4) with initiation at a CD4 count less than 350 cells per µL. Compared with an immediate start to treatment, the relative risk of severe or moderate AIDS-defining illness or death was 1·03 (95% CI 1·02–1·04) with initiation at CD4 count less than 500 cells per µL and 1·11 (1·07–1·15) with initiation at a CD4 count less than 350 cells per µL. The estimated 7 year risk of tuberculosis was 1·20 (1·09–1·36) with immediate initiation of ART, 1·24 (1·15–1·41) with initiation at a CD4 count less than 500 cells per µL, and 1·34 (1·26–1·51) with initiation at a CD4 count less than 350 cells per µL.

With a strategy of immediate initiation, 100% of patients needed ART (figure 2). With initiation at a CD4 count less than 500 cells per µL, at 1 year, 77·9% (95% CI 77·8–78·3) of individuals were estimated to need treatment, and at 7 years, 98·7% (98·6–98·7) would need treatment. With initiation at a CD4 count less then 350 cells per µL, at 1 year, 57·7% (57·3–58·2) of individuals were estimated to need ART and at 7 years, 92·6% (92·2–92·9) would need treatment (appendix p 3).

At 1 year, 57·5% (95% CI 57·1–58·1) of individuals were estimated to be virologically suppressed (ie, HIV-RNA viral load <50 copies per mL) when ART was started immediately (figure 3), 45·6% (45·5–46·2) had virological suppression when treatment was initiated at a CD4 count less than 500 cells per µL, and 35·5% (35·5–36·0) had a viral load less than 50 copies per mL with initiation at a CD4 count less than 350 cells per µL (appendix p 4). Corresponding proportions at year 7 were 87·3% (95% CI 87·3–88·6), 87·4% (87·4–88·6), and 83·8% (83·6–84·9). Estimates were larger when suppressed virological suppression was defined as HIV-RNA viral load less than 400 copies per mL (appendix p 6).

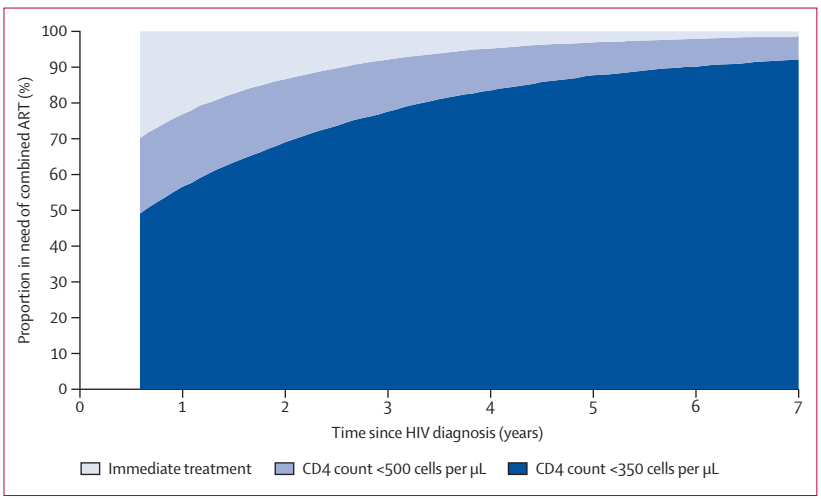

Figure 2: **Estimates of the need for ART, according to initiation strategy**
Estimates are based on the parametric g-formula, adjusted for measured time-varying confounders (CD4 count, HIV-RNA viral load, and AIDS diagnosis) and baseline characteristics (calendar period and age at HIV diagnosis, risk group, sex, geographical origin, ethnic origin, and cohort). ART=antiretroviral therapy.

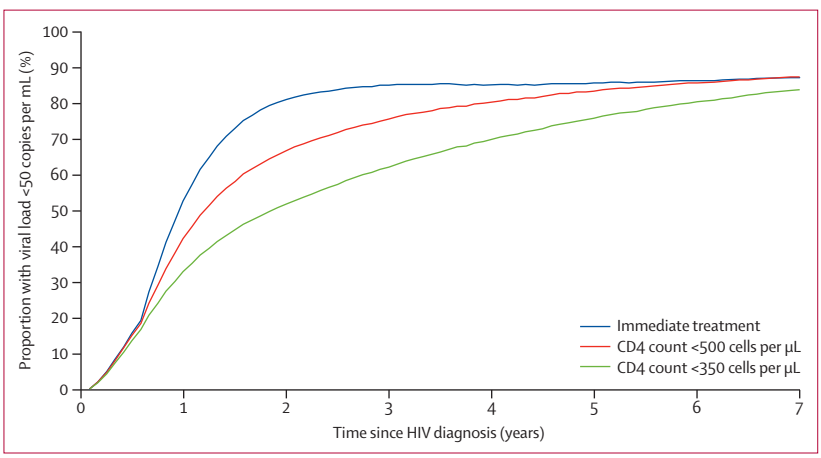

Figure 3: **Estimates of suppressed virological replication with each ART initiation strategy**
Suppressed virological replication was defined as an HIV-RNA viral load less than 50 copies per mL. Estimates are based on the parametric g-formula, adjusted for measured time-varying confounders (CD4 count, HIV-RNA viral load, and AIDS diagnosis) and baseline characteristics (calendar period and age at HIV diagnosis, risk group, sex, geographical origin, ethnic origin, and cohort). ART=antiretroviral therapy.

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 ART 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

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comparing immediate initiation with initiation at a CD4 count of less than 350 cells per µL. For individuals with a CD4 count greater than 500 cells per µL at HIV diagnosis, starting ART when the CD4 count fell below 350 cells per µL 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 initiation of ART earlier in the follow-up period. 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 ART under both CD4-based strategies.

Our findings in high-income countries complement results of the TEMPRANO[12] and HPTN 052[10] trials. In the TEMPRANO trial, individuals with nadir CD4 counts greater than 800 cells per µL were randomly allocated to either immediate initiation of treatment or initiation when the CD4 count dropped below the threshold recommended by WHO (200–500 cells per µL, depending on the year of recruitment). Immediate initiation reduced the risk of serious illness, including tuberculosis and death, by 44%.[12] In the HPTN 052 trial, individuals in low-income and middle-income countries with CD4 counts between 350 cells per µL and 550 cells per µL were randomly assigned to begin treatment immediately or at first occurrence of either the CD4 count dropping below 250 cells per µL or on diagnosis of AIDS. Findings of a secondary analysis showed that immediate initiation reduced the risk of several clinical outcomes.[10] Although these trials cover a shorter period than does our study (2·5 years *vs* 7 years) and use outdated CD4 thresholds, comparison with our estimates suggests that immediate initiation might be most beneficial in low-income countries, where tuberculosis and bacterial infections are frequent, rather 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 participants in high-income countries.[27] 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 per µL substantially increased the incidence of death or serious disease when compared with immediate initiation in individuals with CD4 counts higher than 500 cells per µL at baseline. We also estimated an increased risk with deferral of ART (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 randomised and an observational study assessing the benefits of early initiation of ART, 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 more than 55 000 individuals and the setting in HIV clinics in Europe and the USA, which are representative of routine clinical practice. Therefore, our results should be generalisable to a population with HIV infection without AIDS in high-income countries. In other observational studies of ART-naive patients, clinical outcomes for initiation of ART have been compared at different CD4 thresholds;[5–8] in general, earlier initiation of treatment 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 prolonged exposure to ART, patients who begin ART early might be more susceptible to drug toxic effects. Although the safety profiles of antiretroviral drugs have largely improved in the past decade, toxic effects on the CNS,[28,29] kidney,[30–32] bone,[33] and cardiovascular system[34] have been reported in relation to drugs currently used in high-income countries. Second, similar to other 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 viral load, and AIDS diagnosis, which are the most important factors used by clinicians to decide when to start ART, we cannot exclude the possibility that unmeasured prognostic factors (eg, hepatitis co-infection) could have affected the decision to start ART.

The debate about the best strategy for initiation of ART needs to account for the benefits not only to public health (eg, reduction of HIV transmission) but also to HIV-infected individuals (eg, increase in healthy life years). Our findings help quantify both types of benefits in high-income countries. A greater proportion of individuals who started ART immediately had virological suppression at 1 year (<50 copies per mL) than did those who initiated treatment when the CD4 count fell below a threshold (58% *vs* 36–46%), which will imply decreased transmission to other people. However, the success of combined ART to prevent transmission depends also on HIV testing strategies. 30–80% of transmissions happen because individuals are unaware they are infected with HIV;[35,36] therefore, early initiation of ART should be implemented together with strategies to encourage HIV testing. More work is needed to ascertain the extent to which the beneficial effects of early ART are offset by increased long-term toxic effects or development of drug resistance.

In analyses restricted to individuals with CD4 counts greater than 350 cells per µL at HIV diagnosis, the estimated 7 year risks of all-cause mortality were less

than 3% for all initiation strategies. For the combined outcome of death or AIDS-defining illness, estimated 7 year risks were less than 7%, irrespective of the initiation strategy. Corresponding 7 year risks in the primary analyses, which included about 50% of individuals with a CD4 count less than 350 cells per µL at HIV diagnosis, were less than 4% and less than 9%. These findings again suggest the importance of timely initiation of ART and better HIV testing strategies.

With respect to the proportions of individuals in need of treatment, the differences between initiation strategies fell over time and became small at 7 years after HIV diagnosis (100% with immediate initiation *vs* 58–78% at 1 year and 93–99% at 7 years with a CD4-based initiation strategy). The early differences might be negligible when considering the total duration of ART, which is expected to be between 40 and 50 years.[37] More research is needed on the long-term cost-effectiveness of different initiation strategies after accounting for the effect on new transmissions.[38,39]

In conclusion, our estimates indicate that, compared with CD4-based strategies, immediate initiation of ART slightly prolongs survival and AIDS-free survival and increases the proportions of individuals with suppressed virological replication (<50 copies per mL) and in need of treatment. However, a policy on whether ART is made available at HIV diagnosis irrespective of CD4 count needs to consider many pieces of information—eg, long-term 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 ART.[12,27] Observational studies will continue to have a role in understanding the long-term effects of initiation of ART 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.

Contributors

SL and MAH designed the study and wrote the report. AP, AO, DC, SA, AvS, PR, JMM, EF, AJ, HCB, HF, SMor, SMon, GT, NP, LM, RS, FD, M-AV, SP-H, IJ, SJ, NG, and CS contributed to data collection. SL, RL, and JGY did statistical analyses. All authors contributed to interpretation of data and revised and approved the report.

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.

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