Which HIV-infected adults with high CD4 T-cell counts benefit most from immediate initiation of antiretroviral therapy? A post-hoc subgroup analysis of the START trial

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Summary

Background Immediate initiation of antiretroviral therapy (ART) in asymptomatic adults with CD4 counts higher than 500 cells per μL, as recommended, might not always be possible in resource-limited settings. We aimed to identify subgroups of individuals who would benefit most from immediate treatment.

Methods The START trial was a randomised controlled trial in asymptomatic, HIV-positive adults previously untreated with ART. Participants with CD4 counts higher than 500 cells per μL were randomly assigned to receive immediate ART or to defer ART until CD4 counts were lower than 350 cells per μL. The primary endpoint of the study was serious AIDS-defining illnesses or death from AIDS and serious non-AIDS illnesses or non-AIDS-related death. In this post-hoc analysis, we estimated event rates and absolute risk reduction with immediate versus deferred ART, overall and by subgroup. Subgroups were prespecified in the study protocol or formed post hoc on the basis of baseline characteristics associated with morbidity and mortality in people with HIV. For continuous characteristics, approximate terciles were chosen as subgroup cutoff points, unless different cutoffs were clinically meaningful (eg, age ≥50 years). We estimated the number needed to treat immediately with ART for 1 year to prevent one primary event. Heterogeneity in the absolute risk reduction between subgroups was assessed with bootstrap tests. The START trial is registered with ClinicalTrials.gov, number NCT00867048.

Findings Between April 15, 2009, and Dec 23, 2013, we enrolled 4684 participants from 35 countries across five continents, of whom 2325 were assigned to immediate ART and 2359 were assigned to deferred ART. The primary endpoint occurred in 42 participants in the immediate ART group (0·58 events per 100 person-years) and 100 participants in the deferred ART group (1·37 events per 100 person-years). The absolute risk reduction was 0·80 (95% CI 0·48–1·13) per 100 person-years with immediate treatment, and the number needed to treat immediately to prevent one event was 126 (95% CI 89–208). Significant heterogeneity in absolute risk reduction with immediate ART was found across subgroups according to age (p=0·0022), CD4 to CD8 ratio (p=0·0007), and plasma HIV RNA viral load (p=0·033) at baseline. The highest absolute risk reductions and the lowest numbers needed to treat were found in participants aged 50 years or older, those with CD4 to CD8 ratios of less than 0·5, and those with plasma HIV RNA viral loads of 50 000 copies per mL or higher.

Interpretation Asymptomatic, ART-naive adults with CD4 counts higher than 500 cells per μL who are older, have a low CD4 to CD8 ratio, or a high plasma HIV RNA viral load benefit most from immediate initiation of ART and should be prioritised for treatment.

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Introduction

The Strategic Timing of AntiRetroviral Treatment (START) trial was designed to establish the risks, benefits, and appropriate timing of initiation of antiretroviral therapy (ART) in asymptomatic, HIV-positive individuals with CD4 counts greater than 500 cells per μL.[1] This international trial showed that immediate initiation of treatment reduced the risk of serious AIDS, serious non-AIDS conditions, and death by 57% compared with deferral of therapy until CD4 counts were lower than 350 cells per μL or AIDS had developed. These findings have led to rapid changes in international guidelines, which now recommend immediate ART for people with HIV regardless of CD4 cell count.[1–4] The clinical benefit of immediate ART was also confirmed in a randomised trial done in Côte d'Ivoire.[5] In addition to reducing morbidity and mortality, ART substantially reduces infectivity, an important public health benefit.[6,7]

In the START trial,[1] hazard ratios for the primary outcome were similar across subgroups formed by demographic and clinical baseline characteristics, with the same relative benefits seen with early treatment initiation. By contrast, event rates differed between subgroups. Given similar relative risk reductions, individuals at higher absolute risk would benefit more from immediate ART than individuals at lower absolute

Research in context

Evidence before this study

We searched PubMed without language restrictions for articles published up to Aug 25, 2017, using the search terms "HIV", "ART or antiretroviral", "CD4", "early or immediate", and "trial". Eligible studies compared early with deferred combination antiretroviral therapy (ART) in HIV-infected, ART-naive adults with high CD4 cell counts (>350 cells per μL) for the clinical outcomes of AIDS, serious non-AIDS conditions, and all-cause mortality. We identified three such trials: HPTN 052, which enrolled 1763 participants in nine countries in South America, Asia, and Africa, of whom 134 had the primary endpoint; the TEMPRANO ANRS 12 136 study, which enrolled 2056 participants in Côte d'Ivoire, of whom 204 had the primary endpoint; and the INSIGHT START study, which enrolled 4684 HIV-infected participants in 35 countries, of whom 142 had the primary endpoint. In these studies, the overall risk of developing serious AIDS or non-AIDS conditions or death was 44–57% lower with immediate initiation of ART than with delayed initiation of treatment. In all three studies, relative risk reductions did not differ according to baseline CD4 cell counts. In the START trial, the risk of the primary endpoint was lower with immediate than with deferred ART across various subgroups based on baseline characteristics. Moreover, hazard ratios were homogenous across subgroups. None of these studies compared absolute risk reduction with immediate treatment across subgroups to identify patients who might benefit most from early intervention.

Added value of this study

The START study showed that immediate initiation of ART was associated with similar reductions in relative risk across all baseline characteristics. Therefore, we hypothesised that patients at higher absolute risk would benefit more from immediate initiation of ART because they would have larger absolute risk reductions. In this subgroup analysis of the START trial, the net benefit of immediate initiation of ART was highest among those aged 50 years or older, those with low CD4 to CD8 ratios (<0·5), and those with high plasma HIV RNA viral loads (>50 000 copies per mL) at baseline. These participants had the largest absolute risk reductions, corresponding to the lowest numbers needed to treat for 1 year with immediate ART to prevent one event (AIDS, serious non-AIDS, or death).

Implications of all the available evidence

We identified subgroups of people with HIV who will benefit most from immediate initiation of ART. These subgroups included people who were aged 50 years or older, those with low CD4 to CD8 ratios, and those with high plasma HIV RNA viral loads. These people should be prioritised for immediate treatment by policy makers and health-care workers, particularly in low-resource settings.

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risk because they would have larger absolute risk reductions, which is particularly relevant for clinical practice.

Provision of immediate access to ART for all people with HIV is challenging, and identification of patients who might benefit most from immediate ART would help policy makers and health-care providers to prioritise treatment. In this study, we identified baseline characteristics of participants in the START study associated with high absolute risk reductions, low numbers needed to treat to prevent one clinical event, and, therefore, increased net benefit with immediate initiation of ART.

Methods

Study design and participants

The START study[1] was an international, open-label, randomised trial done by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) and designed to assess the risks and benefits of immediate versus deferred initiation of ART in adults with early asymptomatic HIV. Eligible participants had CD4 counts greater than 500 cells per μL, were ART naive, and had no previous AIDS. Participants assigned to the deferred-initiation group did not receive ART until CD4 counts were lower than 350 cells per μL or until AIDS or other conditions that required ART had developed. ART regimens were selected by the participants and their providers.

The primary endpoint of the study was a composite outcome with two major components: serious AIDS-defining illnesses or death from AIDS and serious non-AIDS illnesses (including cardiovascular disease, end-stage renal and liver diseases, and non-AIDS defining cancers) or non-AIDS-related death. The specific conditions included in the serious AIDS and serious non-AIDS endpoints were described previously.[1] All reported events were reviewed by an endpoint review committee masked to treatment assignment with pre-established criteria.[1] Events adjudicated as confirmed or probable were included. Deaths were classified according to the CoDe system.[1] Details of the design and data collection plans have been published elsewhere.[1]

Participants were enrolled in the START trial between April 15, 2009, and Dec 23, 2013, from 35 countries across five continents. This post-hoc analysis includes data accrued until May 26, 2015, when the results of the START study were unblinded and participants in the deferred ART group were offered ART after recommendation by the data and safety monitoring board because immediate ART initiation decreased the risk of the primary endpoint by 57%.[1]

The study was approved by the institutional review board or ethics committee at each participating site, and

written informed consent was obtained from all participants.

Procedures

To assess which participants benefited most from immediate initiation of ART, we considered subgroups formed according to participants' baseline characteristics. The eight subgroups specified a priori in the protocol were age, sex and route of infection, race, geographical region (high-income regions were Australia, Europe, Israel, and North America, and low-income or moderate-income regions were Africa, Asia, Mexico, and South America), baseline CD4 cell count, baseline plasma HIV RNA viral load, smoking status (currently smoking or not), and Framingham 10-year coronary heart disease risk.[8] Additionally, we investigated several subgroups formed post hoc on the basis of their association with morbidity and mortality in people with HIV:[9–14] baseline CD8 cell count, baseline CD4 to CD8 ratio, co-infection with hepatitis B virus (defined as HBsAg-positive within 1 year before enrolment) and hepatitis C virus (defined as a positive hepatitis C antibody test), anaemia (haemoglobin concentration <12 g/dL in women and <13 g/dL in men), nadir CD4 cell count, hypertension, hyperlipidaemia, and baseline concentrations of interleukin 6 and D-dimer. We also assessed subgroups by prespecified ART regimen. To form subgroups based on continuous characteristics, approximate terciles were chosen as cutoff points, unless different cutoffs were clinically meaningful (eg, age ≥50 years). Concentrations of interleukin 6 and D-dimer were measured in centrally stored plasma samples collected at baseline. Interleukin 6 was measured with QuantiGlo chemiluminescent ELISA (R&D Systems, Minneapolis, MN, USA) and D-dimer with the VIDAS system (bioMérieux, Durham, NC, USA).

Statistical analysis

Study follow-up was censored on May 26, 2015, the day before the results of the START trial were unblinded. Four additional primary events (all in the deferred-initiation group) that occurred before May 26, 2015, have been reported since publication of the original article.[1] Thus, event counts in this paper differ slightly from those previously reported.[1] We considered three endpoints: the START primary endpoint and its two components of serious AIDS (non-fatal and fatal) and serious non-AIDS conditions (non-fatal and death by causes other than AIDS). We estimated event rates per 100 person-years in the immediate and deferred ART groups, overall and by subgroup, through dividing event counts by the person-years accrued and multiplying by 100. Absolute risks reductions, calculated as the difference in event rates between the deferred group and the immediate group, were estimated for each subgroup, and 95% CIs were calculated with Wilson's score method.[15] Heterogeneity in absolute risk reductions between subgroups was tested with Q-statistics and bootstrap estimates of p values.[16] We used bootstrap because Poisson models for absolute risk reductions did not converge for several subgroups. The numbers needed to treat for 1 year in the immediate-initiation group to prevent one event relative to the deferred-treatment group were calculated as 100 divided by the absolute risk reduction. Upper and lower limits of 95% CIs for the numbers needed to treat were calculated as inverses of the lower and upper CI limits for absolute risk reductions, respectively, multiplied by 100.[17]

To assess how the primary endpoint differed between subgroups, we calculated Kaplan-Meier estimates of the cumulative proportion of participants with an event for subgroups according to age, CD4 to CD8 ratio, and HIV RNA viral load.

All analyses were done by intention to treat. Because the statistical analyses might have been unstable for very low numbers of events, only subgroup categories with at least ten primary events were considered. We did not adjust for multiple comparisons; therefore, because of inflation of type I error, significant effects should be interpreted with caution. Also, the method used to test for heterogeneity in the absolute risk reductions might have been sensitive to subgroup cutoff points.

We used SAS software version 9.3 and R version 3 for statistical analyses. All p values are two-sided, and a p value of less than or equal to 0·05 was considered to be significant.

This trial is registered with ClinicalTrials.gov, number NCT00867048.

Role of the funding source

The funders of the study 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 the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 15, 2009, and Dec 23, 2013, 4684 people with asymptomatic HIV previously untreated with ART were enrolled from 35 countries across five continents. At study entry, 2325 of the 4684 participants were assigned to the immediate ART group and 2359 were assigned to the deferred ART group. Baseline characteristics are summarised in the table and by CD4 to CD8 ratio subgroups in the appendix (p 1).

In the immediate ART group, 2250 (97%) of 2325 participants had started ART by month 4 after trial enrolment, and ART was used for 96·8% of follow-up time accrued.[1] In the deferred ART group, median time to ART initiation was 3·0 years (IQR 1·6–5·2), and ART was used for 29·1% of follow-up time accrued. Almost all participants who reported ART use had suppressed viral loads, suggesting high treatment adherence.[1]

In the immediate ART group, 42 primary events occurred over a mean follow-up of 3·1 years (SD 1·2;

See Online for appendix

event rate 0·58 per 100 person-years), compared with 100 events over the same follow-up period in the deferred ART group (1·37 per 100 person-years; figure 1). Thus, the absolute risk reduction with immediate initiation versus deferred initiation was 0·80 (95% CI 0·48–1·13) per 100 person-years, favouring immediate ART (figure 1). As a result, 126 patients (95% CI 89–208) would need to initiate treatment immediately to prevent one primary event per year (figure 1).

For all subgroups, the estimated absolute risk reduction was above zero, favouring the immediate-initiation group. Absolute risk reductions varied significantly by age, baseline CD4 to CD8 ratio, and baseline HIV RNA viral load (figure 2). Across these subgroups, absolute risk reductions were largest and numbers needed to treat were smallest for the 11·8% of participants aged 50 years or older (number needed to treat 42, 95% CI 24–125), for the 29·2% of participants with a baseline CD4 to CD8 ratio below 0·5 (58, 40–93), and for the 21·8% of participants with plasma HIV RNA viral loads of 50 000 copies per mL or higher (68, 42–149). For these three subgroup categories, there was a clear risk gradient in the deferred ART group, with increased event rates among those who were older, had lower CD4 to CD8 ratios, and higher HIV RNA viral loads (figure 2). Only 63 (1·4%) of 4619 participants were in all the subgroup categories with the highest absolute risk reductions (age ≥50 years, CD4 to CD8 ratio <0·5, and HIV RNA ≥50 000 copies per mL). For the 607 (13·1%) participants who were in two or more of these three subgroup categories, the absolute risk reduction was 2·59 (95% CI 1·28–4·07) and the number needed to treat was 39 (95% CI 25–78; appendix p 3).

There was no evidence of differences in absolute risk reduction (and numbers needed to treat) across subgroups according to sex and likely route of HIV infection, race, geographical region, CD4 and CD8 cell counts, Framingham 10-year risk of coronary heart disease, and interleukin 6 and D-dimer concentrations (figure 2). Additionally, absolute risk reduction did not differ across subgroups according to baseline nadir CD4 count, smoking status, hepatitis B or C status, anaemia, hyperlipidaemia, hypertension, or prespecified ART regimen (appendix p 4).

At 36 months, the difference in the estimated cumulative proportions of participants with a primary event between the immediate and deferred ART groups (figure 3) was largest (and the absolute benefit of immediate ART was highest) among those aged 50 years or older (2·8% *vs* 11·3%), those with CD4 to CD8 ratios of less than 0·5 (0·7% *vs* 6·7%), and those with plasma HIV RNA viral loads of 50 000 copies per mL or higher (2·0% *vs* 6·7%).

When considering the major components of the primary endpoint separately, event counts were lower, resulting in reduced power to detect heterogeneity in absolute risk reductions across subgroups. Similar to the primary endpoint, estimated rates of serious AIDS events were consistently lower with immediate versus deferred ART across all subgroups, although absolute risk reduction varied significantly between the subgroups according to baseline CD4 to CD8 ratios (p=0·0005) and CD8 cell counts (p=0·019; appendix p 5). For serious non-AIDS events, older age was associated with larger absolute risk reduction with immediate ART (p=0·0008), with an absolute risk reduction of 1·60 (95% CI 0·23–3·07) per 100 person-years in those aged 50 years or older (appendix p 6). Additionally, the absolute risk

	Immediate ART (n=2325)	Deferred ART (n=2359)	All (n=4684)
Age (years)	36 (29–44)	36 (29–44)	36 (29–44)
Sex			
Female	624 (26·8%)	633 (26·8%)	1257 (26·8%)
Male	1701 (73·2%)	1726 (73·2%)	3427 (73·2%)
Race or ethnicity			
Asian	198 (8·5%)	190 (8·1%)	388 (8·3%)
Black	701 (30·2%)	707 (30·0%)	1408 (30·1%)
Latino or Hispanic	319 (13·7%)	318 (13·5%)	637 (13·6%)
White	1016 (43·7%)	1071 (45·4%)	2087 (44·6%)
Other	91 (3·9%)	73 (3·1%)	164 (3·5%)
Geographical region			
High income	1067 (45·9%)	1088 (46·1%)	2155 (46·0%)
Low or moderate income	1258 (54·1%)	1271 (53·9%)	2529 (54·0%)
Route of infection with HIV			
MSM	1300 (55·9%)	1287 (54·6%)	2587 (55·2%)
Heterosexual	871 (37·5%)	917 (38·9%)	1788 (38·2%)
Injectable drug use	37 (1·6%)	27 (1·1%)	64 (1·4%)
Blood products, other, or unknown	117 (5·0%)	128 (5·4%)	245 (5·2%)
Time since HIV diagnosis (years)	1·0 (0·4–3·0)	1·1 (0·4–3·1)	1·0 (0·4–3·1)
CD4 count* (cells per μL)	652 (585–765)	651 (582–764)	651 (584–765)
Nadir CD4 count (cells per μL)	552 (485–660)	553 (490–650)	553 (488–654)
CD8 count (cells per μL)	1039 (774–1383)	1049 (780–1422)	1041 (777–1402)
CD4 to CD8 ratio	0·65 (0·47–0·86)	0·64 (0·47–0·88)	0·64 (0·47–0·87)
HIV RNA (copies per mL)	13 000 (3128–43 837)	12 550 (2976–42 567)	12 761 (3025–43 482)
Interleukin 6 (pg/mL)	1·4 (1·0–2·2)	1·4 (1·0–2·1)	1·4 (1·0–2·1)
D-dimer (μg/mL)	0·3 (0·2–0·5)	0·3 (0·2–0·5)	0·3 (0·2–0·5)
Framingham 10-year risk of coronary heart disease (%)	1·9% (0·5–5·0)	1·9% (0·5–5·3)	1·9% (0·5–5·1)
Current smoker	732 (31·5%)	767 (32·5%)	1499 (32·0%)
Hepatitis B positive	64 (2·8%)	65 (2·8%)	129 (2·8%)
Hepatitis C positive	89 (3·8%)	82 (3·5%)	171 (3·7%)
Anaemia	321 (13·8%)	348 (14·8%)	669 (14·3%)
Prespecified ART regimen			
NNRTI plus two NRTIs	1845 (79·4%)	1841 (78·0%)	3686 (78·7%)
Protease inhibitor plus two NRTIs	386 (16·6%)	429 (18·2%)	815 (17·4%)
INSTI plus two NRTIs	94 (4·0%)	89 (3·8%)	183 (3·9%)

Data are n (%) or median (IQR). ART=antiretroviral therapy. MSM=men who have sex with men. NNRTI=non-nucleoside reverse-transcriptase inhibitor. NRTI=nucleoside reverse-transcriptase inhibitor. INSTI=integrase strand-transfer inhibitor. *The median CD4 cell count was based on the mean of two CD4 cell counts obtained at screening for each participant.

Table: **Baseline characteristics of the trial participants**

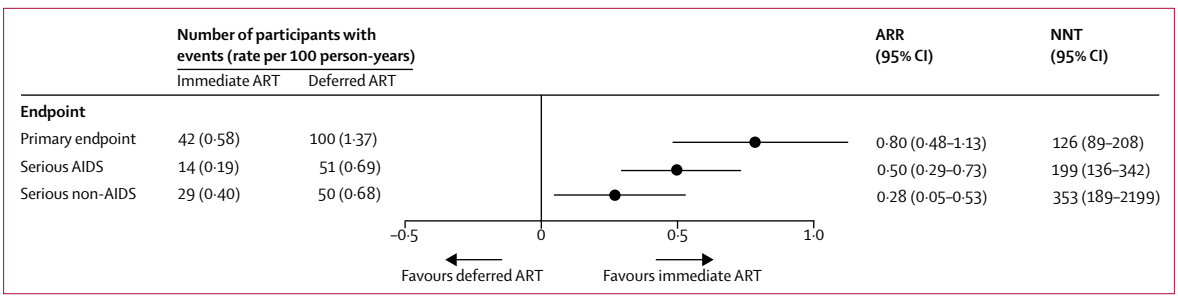

Figure 1: **Event rates, ARRs, and NNTs to prevent one event in the immediate versus deferred ART groups**
ARRs are per 100 person-years and were calculated as the difference in event rates between the deferred group and the immediate group. ART=antiretroviral therapy. ARR=absolute risk reduction. NNT=numbers needed to treat.

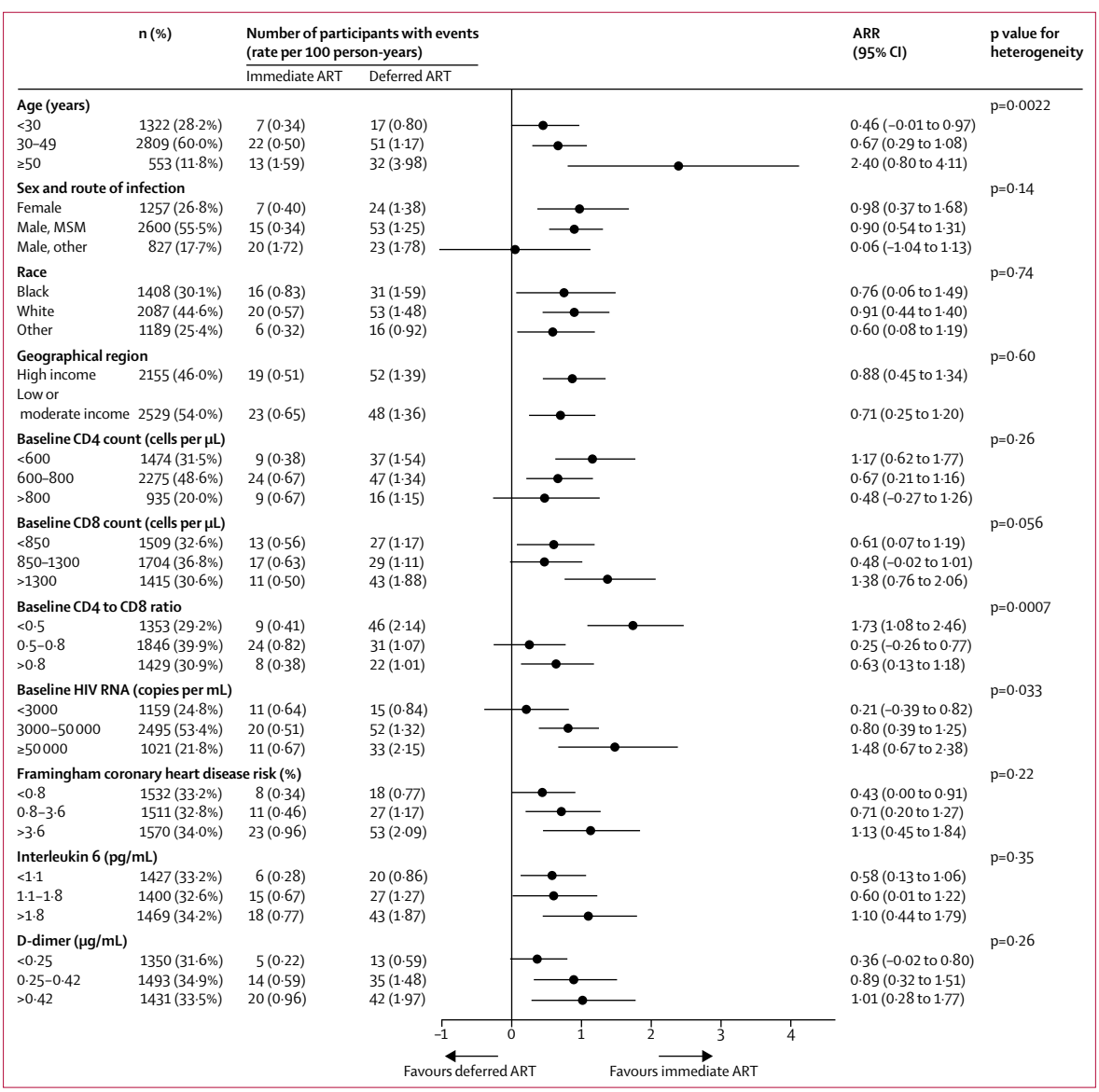

Figure 2: **Rates of the primary endpoint and ARRs in the immediate versus deferred ART groups, by subgroup**
ARRs are per 100 person-years and were calculated as the difference in event rates between the deferred group and the immediate group. ART=antiretroviral therapy. ARR=absolute risk reduction. MSM=men having sex with men.

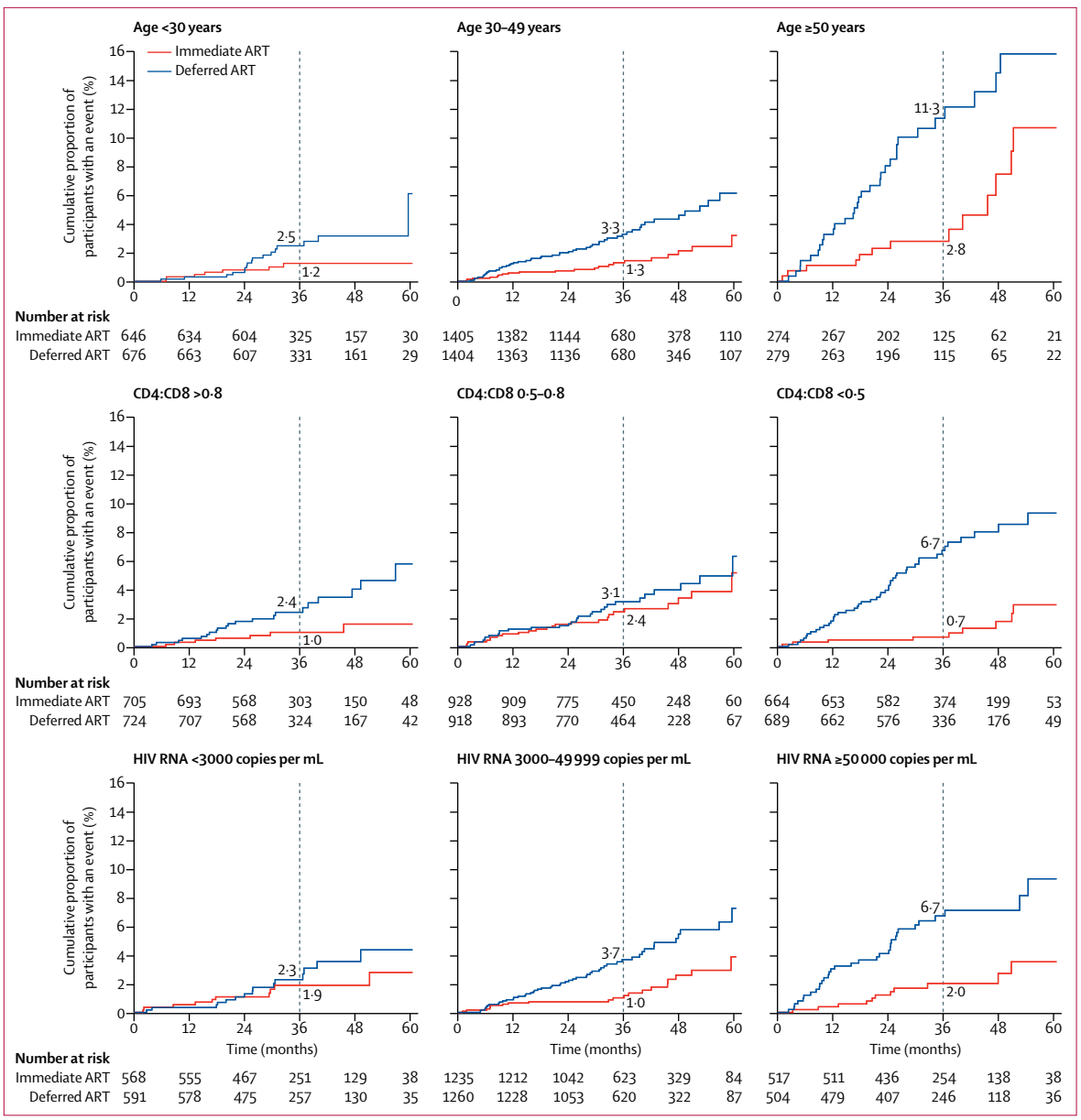

Figure 3: **Kaplan-Meier estimates of the proportions of participants who had a primary event in the immediate and deferred ART groups, by subgroup**
Cumulative proportions at month 36 are shown. ART=antiretroviral therapy.

reduction for serious non-AIDS events differed between the subgroups according to sex and route of infection (p=0·024; appendix p 6).

Discussion

In the START trial, immediate initiation of ART in asymptomatic adults with CD4 counts higher than 500 cells per µL decreased the risk of the primary composite endpoint of serious AIDS, serious non-AIDS illnesses, and all-cause death by 57% compared with deferred ART initiation. This relative risk reduction was consistent and similar across subgroups defined at baseline, emphasising the main finding of the original study that all asymptomatic HIV-infected individuals with CD4 cell counts above 500 cells per µL will have similar relative benefits from immediate initiation of ART.[1] Guidelines from WHO and the US Department of Health and Human Services now recommend starting ART immediately after HIV diagnosis, irrespective of CD4 cell count. Expanding this recommendation to asymptomatic, HIV-positive people with CD4 cell counts above 500 cells per µL was based, in large part, on the results of the START trial.[3–6]

Although the relative risk reduction was similar across all subgroups of participants, we found that absolute risk

reduction was greatest among older participants, those with low baseline CD4 to CD8 ratios, and those with high plasma HIV RNA viral loads, corresponding to low numbers needed to treat immediately to prevent serious AIDS and non-AIDS events. We assessed absolute risk reduction across subgroups to identify people who might benefit most from immediate ART initiation to inform doctors and policy makers who might have to prioritise ART access in low-resource environments. This analysis alludes to the cost-effectiveness of immediate treatment with regard to prevention of serious clinical events, but does not take into account the beneficial effect of immediate treatment on prevention of HIV transmission, which could substantially increase the overall cost-effectiveness of this strategy. [6]

Advanced age, usually defined as age 50 years or older for people with HIV, has been independently associated with more rapid disease progression and mortality in cohort studies in both untreated patients and in those starting ART.[18–20] The reason for more rapid disease progression with age is likely to be multifactorial, including a role for comorbidities associated with ageing and a direct role for HIV. In their modelling study based on retrospective and observational data, Edwards and colleagues[21] showed that the effect of delaying ART on mortality was age dependent, with the greatest absolute benefit of early ART projected in the oldest age group (>45 years). In our study population, in which all participants had CD4 counts above 500 cells per μL at study entry, people aged 50 years or older (11·8% of the total population) had a greater absolute risk of events, a greater absolute risk reduction with immediate ART, and a lower number needed to treat (n=42) to prevent one primary endpoint than people younger than 50 years. The greatest absolute risk reduction among older participants was seen in serious non-AIDS events. These results suggest that patients entering care at older ages are more susceptible to the effects of delaying ART initiation than younger patients and that initiation of ART in patients aged 50 years or older is urgent. In the USA in 2009, 92% of HIV-infected patients older than 55 years who were in care were prescribed ART, a statistic that should be replicated elsewhere.[22] Finally, our findings emphasise the need for increased HIV testing in older populations, because up to 18% of new HIV diagnoses are in people aged 50 years or older, but only 37% of people aged 45–64 years in the USA in 2010 had ever received an HIV test compared with 57% of those aged 25–44 years.[23]

Participants with low CD4 to CD8 ratios at baseline were at increased risk of events with deferred ART and benefited more from immediate treatment than those with higher CD4 to CD8 ratios at baseline. Among those with ratios of less than 0·5 (29·2% of our study population), the absolute risk reduction for the primary endpoint was 1·73 per 100 person-years (and the number needed to treat was only 58) compared with 0·63 per 100 person-years among participants with baseline ratios above 0·8. Participants with ratios of less than 0·5 had the greatest absolute reduction in serious-AIDS events. Our results are consistent with studies in HIV-infected patients previously untreated with ART showing that low CD4 to CD8 ratios are associated with increased risk of AIDS and death, but differ from studies done among virologically suppressed HIV-infected patients on ART in which a low ratio was also associated with an increased risk of non-AIDS events.[10–13] Thus, ART-naive patients with low CD4 to CD8 ratios tend to progress more rapidly to the composite of serious AIDS, serious non-AIDS events, or death and should be prioritised for immediate treatment. Indeed, earlier initiation of ART has been reported to increase the probability of restoring normal CD4 cell counts and normal CD4 to CD8 ratios and to reduce immune activation and inflammation.[11,24–26] The mechanisms driving down CD4 to CD8 ratios in people with HIV who are untreated are not fully understood, but they are probably associated with innate and adaptive immune dysfunction or activation in the peripheral blood and gut induced by HIV and also cytomegalovirus replication, leading to expansion of CD8 cells.[27] In this study, participants with low CD4 to CD8 ratios tended to have not only lower CD4 cell counts but also higher CD8 cell counts and higher plasma HIV RNA viral loads than participants with high CD4 to CD8 ratios. In patients with untreated HIV, most CD8 cells are HIV-specific T cells. Therefore, it is likely that expansion of CD8 cells is a marker of immune dysfunction predictive of AIDS or non-AIDS events, as previously reported.[28]

In our study, participants with higher baseline plasma HIV RNA viral loads also benefited more from immediate ART than did those with lower baseline viral loads, and participants with plasma HIV RNA viral loads of 50 000 copies per mL or higher (21·8% of the study population) had the greatest absolute risk reduction and the lowest number needed to treat to prevent one primary endpoint. The greater absolute risk reduction for participants with high baseline HIV RNA viral loads can be explained by higher event rates, both serious AIDS and serious non-AIDS, in the deferred ART group, whereas immediate ART resulted in similarly low event rates across all baseline HIV RNA categories. High plasma HIV RNA viral loads have been independently associated with increased probabilities of progression to AIDS and death.[29] Moreover, high viral loads are associated with increased risk of transmission; hence, immediate initiation of ART in patients with high viral loads is urgent because it will reduce viral load and, therefore, HIV transmission, as well as decrease the risk of severe AIDS and non-AIDS events and death.[6,7,30]

We found no evidence of differences in absolute risk reductions with immediate ART across subgroups according to sex and route of HIV infection, race, geographic region, Framingham 10-year coronary heart disease risk, interleukin 6 or D-dimer concentrations, and

CD4 or CD8 cell counts. We do not have a clear explanation for why the CD4 to CD8 ratio seemed to have stronger prognostic capacity than did interleukin 6 and D-dimer, by contrast with previous studies,[14] except that previous studies were done in HIV-infected patients already on ART, and START was done in HIV-infected people previously untreated with ART.

Strengths of our study include the randomised design, large sample size, and uniform reporting and central adjudication of events. The main limitations are that the mean duration of follow-up was only 3·1 years and, consequently, event counts in most subgroups were small, particularly when considering the endpoints of AIDS and serious non-AIDS illnesses separately. Low event numbers in individual subgroups resulted in substantial uncertainty in estimates of absolute risk reduction, reflected by large confidence intervals, and limited power to detect heterogeneity in treatment effect across subgroups. We also considered many subgroups, some of which were not prespecified, without adjustment for type I error, which might have led to chance findings. We have chosen to focus on subgroups for which tests for interaction in absolute risk reduction were significant, but we acknowledge that our heterogeneity tests were also sensitive to the cutoff points used to form subgroups.

In summary, this subgroup analysis of START is consistent with the finding of the main study that immediate initiation of ART is beneficial across all baseline characteristics and supports the recommendation of starting ART in all patients with HIV as soon as possible. Moreover, we have identified subgroups of participants who have the greatest reduction in absolute risk from immediate ART: age of 50 years or older, CD4 to CD8 ratio of less than 0·5, and plasma HIV RNA viral load of 50 000 copies per mL or higher. In such patients, immediate initiation of ART at diagnosis is urgent.

Contributors

J-MM wrote the first draft of the manuscript, with substantial contribution from BG. BG and JDN did the statistical analyses. J-MM, FG, IW, MS, MLo, EE, NM, AS, MJW, LV, TB, and JDL enrolled patients in the study. All authors discussed and reviewed the manuscript. A complete list of members in the Strategic Timing of AntiRetroviral Treatment (START) Study Group is available online.

Declaration of interests

J-MM is an advisory board member of Gilead Sciences, Merck, Janssen, ViiV Healthcare, and Teva, and has received grants from Gilead Sciences and Merck, outside the submitted work. MLa reports grants from Boehringer Ingelheim, Gilead Sciences, MSD, Bristol-Myers Squibb, Janssen-Cilag, and ViiV Healthcare, and personal fees from Gilead Sciences and Sirtex, outside the submitted work. MS has received grants and honoraria for participating in advisory boards and has given lectures for Gilead, GlaxoSmithKline, Janssen, Merck, and ViiV Healthcare. IW reports grants from Medical Research Council UK during the conduct of the study, and from MSD, outside the submitted work. BG and JDN report grants from National Institutes of Health (NIH) and National Institute of Allergy and Infectious Diseases (NIAID), during the conduct of the study. All other authors declare no competing interests.

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For a **complete list of members in the Strategic Timing of AntiRetroviral Treatment (START) study group** see http://www.nejm.org/doi/suppl/10.1056/NEJMoa1506816/suppl_file/nejmoa1506816_appendix.pdf

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