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ORIGINAL RESEARCH

Demographic and HIV-specific characteristics of participants enrolled in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial

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Objectives

The risks and benefits of initiating antiretroviral treatment (ART) at high CD4 cell counts have not been reliably quantified. The Strategic Timing of AntiRetroviral Treatment (START) study is a randomized international clinical trial that compares immediate with deferred initiation of ART for HIV-positive individuals with CD4 cell counts above 500 cells/μL. We describe the demographics, HIV-specific characteristics and medical history of this cohort.

Methods

Data collected at baseline include demographics, HIV-specific laboratory values, prior medical diagnoses and concomitant medications. Baseline characteristics were compared by geographical region, gender and age.

Results

START enrolled 4685 HIV-positive participants from 215 sites in 35 countries. The median age is 36 years [interquartile range (IQR) 29–44 years], 27% are female, and 45% self-identify as white, 30% as black, 14% as Latino/Hispanic, 8% as Asian and 3% as other. The route of HIV acquisition is reported as men who have sex with men in 55% of participants, heterosexual sex in 38%, injecting drug use in 1% and other/unknown in 5%. Median time since HIV diagnosis is 1.0 year (IQR 0.4–3.0 years) and the median CD4 cell count and HIV RNA values at study entry are 651 cells/μL (IQR 584–765 cells/μL) and 12 754 HIV RNA copies/mL (IQR 3014–43 607 copies/mL), respectively.

Conclusions

START has enrolled a diverse group of ART-naïve individuals with high CD4 cell counts who are comparable to the HIV-positive population from the regions in which they were enrolled. The information collected with this robust study design will provide a database with which to evaluate the risks and benefits of early ART use for many important outcomes.

Keywords: clinical trial, HIV, START trial, when to start antiretroviral therapy

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Introduction

The Strategic Timing of AntiRetroviral Treatment (START) study is the first randomized clinical trial designed to evaluate the use of antiretroviral treatment (ART) in asymptomatic HIV-positive individuals with CD4 cell counts above 500 cells/μL in about two decades. Earlier studies included the European-Australian Collaborative Group, which enrolled 984 individuals of whom 72% had CD4 cell counts > 500 cells/μL [1]; the Concorde study, which enrolled 1749 individuals of whom 42% had CD4 cell counts > 500 cells/μL [2]; and the AIDS Clinical Trials Group (ACTG) 019 study, which enrolled 1650 participants with CD4 cell counts > 500 cells/ μL [3]. In each of these trials, zidovudine monotherapy was studied; all included predominantly white, homosexual/bisexual men with an average age between 30 and 35 years at sites in the USA, Europe or Australia.

The demographic characteristics and geographical distribution of HIV-positive individuals has changed dramatically since the early 1990s. Largely as a consequence of improved treatments, mortality has declined substantially, resulting in an increasing number of individuals living with HIV. Most HIV-positive individuals live in developing countries. In developed regions, the epidemic progressively affects nonwhite heterosexual populations [4]. The epidemic in men who have sex with men (MSM) shows no signs of decline and is increasing in some areas [4]. In 1990, approximately 43% of individuals above 15 years of age living with HIV were women, compared with 55% in 2012 [4,5]. Causes of death have dramatically changed, with non-AIDS-related causes becoming increasingly important [6–8]. Unlike earlier when-to-start studies, detailed medical histories collected in trials of HIV-positive individuals now also include serious non-AIDS-related conditions and treatments used for these conditions [9].

To date, START is one of the largest most globally representative clinical trials undertaken in HIV-positive individuals. In this paper, we describe baseline data, specifically demographics, HIV-specific characteristics, and medical history of START participants enrolled from 35 countries.

Methods

The design and data collection plan of START have been previously described [10]. Briefly, HIV-positive ART-naïve participants with CD4 cell counts > 500 cells/μL have been enrolled by 215 sites in 35 countries. Prior to randomization, data collected included demographic characteristics (age, gender and self-identified race), HIV-specific factors (likely mode of infection and time since HIV diagnosis), HIV-specific baseline laboratory values (current CD4 and CD8 cell counts, nadir CD4 cell count, current plasma HIV RNA level and highest recorded plasma HIV RNA level), hepatitis B and C serologies, prior medical diagnoses as reported in clinical records [non-AIDS-related cancer, cardiovascular disease (CVD), liver and kidney diseases, and other medical conditions including alcoholism and psychiatric diagnosis], and specified concomitant medication usage. For this analysis, hepatitis B virus (HBV) coinfection was based on a surface antigen test in the year before randomization, and hepatitis C virus (HCV) coinfection was based on a core antibody test from any time before randomization.

Participants were required to have two CD4 cell counts above 500 cells/μL at least 2 weeks apart within 60 days before randomization. If available, up to three additional most recent CD4 cell counts prior to the two qualifying CD4 cell counts were also reported. All laboratory tests, including CD4 cell count and plasma HIV RNA load, were performed locally at the routine pathology service for participating sites.

Statistical methods

Demographics and HIV-specific factors were assessed by subgroups of geographical region, age at enrolment and gender. For geographical distributions, enrolling countries were grouped into six regions: North America (USA), Europe (plus Israel), South America (plus Mexico), Africa, Asia and Australia.

For each participant, the rate of change (i.e. slope) in CD4 measurements prior to randomization was calculated using all available CD4 cell counts (range of 2–5 measurements) using repeated measures with random intercepts and random slopes. The time span for prior CD4 cell counts varied, with 50% of participants having ≤ 72 days between the first and last measurements [interquartile range (IQR) 23–296 days]. Given this variability in the time span for available prior CD4 count data, a sensitivity analysis was performed by limiting the calculation to data for participants with at least 6 weeks between the first and last measurements (n = 2761). Results were similar, so slopes using all available data are cited. CD4 cell count slopes were compared by geographical region, gender and age group.

Continuous variables are presented as medians with frequency distributions or IQRs, and categorical variables are presented as percentages. SAS software, version 9.3 (SAS Institute Inc., Cary, NC) was used.

Results

Baseline characteristics by geographical region

A total of 4688 participants were enrolled in START. Three participants were later found to be HIV negative and have

Table 1 Demographics and selected other characteristics, by region

Factor	North America	Europe	South America	Australia	Asia	Africa	Overall
Participants	507 (10.8)	1539 (32.8)	1174 (25.1)	109 (2.3)	356 (7.6)	1000 (21.3)	4685
Demographics							
Age (median)	36	38	32	40	33	38	36
< 25 years	78 (15.4)	93 (6.0)	200 (17.0)	3 (2.8)	61 (17.1)	65 (6.5)	500 (10.7)
25–34 years	150 (29.6)	524 (34.0)	468 (39.9)	36 (33.0)	145 (40.7)	292 (29.2)	1615 (34.5)
35–44 years	125 (24.7)	513 (33.3)	306 (26.1)	40 (36.7)	114 (32.0)	391 (39.1)	1489 (31.8)
≥ 45 years	154 (30.4)	409 (26.6)	200 (17.0)	30 (27.5)	36 (10.1)	252 (25.2)	1081 (23.1)
Female	111 (21.9)	140 (9.1)	175 (14.9)	4 (3.7)	136 (38.2)	691 (69.1)	1257 (26.8)
Race and gender							
Black, male	172 (33.9)	51 (3.3)	107 (9.1)	2 (1.8)	0 (0.0)	286 (28.6)	618 (13.2)
Black, female	68 (13.4)	46 (3.0)	26 (2.2)	1 (0.9)	0 (0.0)	651 (65.1)	792 (16.9)
Latino, male	68 (13.4)	62 (4.0)	409 (34.8)	1 (0.9)	0 (0.0)	0 (0.0)	540 (11.5)
Latina, female	23 (4.5)	7 (0.5)	69 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	99 (2.1)
Asian, male	8 (1.6)	20 (1.3)	0 (0.0)	5 (4.6)	216 (60.7)	0 (0.0)	249 (5.3)
Asian, female	1 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)	136 (38.2)	0 (0.0)	139 (3.0)
White, male	144 (28.4)	1241 (80.6)	401 (34.2)	93 (85.3)	2 (0.6)	13 (1.3)	1894 (40.4)
White, female	17 (3.4)	81 (5.3)	59 (5.0)	3 (2.8)	0 (0.0)	32 (3.2)	192 (4.1)
Other, male	4 (0.8)	25 (1.6)	82 (7.0)	4 (3.7)	2 (0.6)	10 (1.0)	127 (2.7)
Other, female	2 (0.4)	4 (0.3)	21 (1.8)	0 (0.0)	0 (0.0)	8 (0.8)	35 (0.7)
Education							
< year 12	71 (14.0)	239 (15.5)	217 (18.5)	17 (15.6)	130 (36.5)	723 (72.3)	1397 (29.8)
Completed year 12	124 (24.5)	315 (20.5)	333 (28.4)	22 (20.2)	55 (15.4)	167 (16.7)	1016 (21.7)
Vocational/some college	192 (37.9)	506 (32.9)	356 (30.3)	19 (17.4)	56 (15.7)	85 (8.5)	1214 (25.9)
Bachelor's or higher	120 (23.7)	479 (31.1)	268 (22.8)	51 (46.8)	115 (32.3)	25 (2.5)	1058 (22.6)
HIV history							
Mode of infection							
IDU	24 (4.7)	32 (2.1)	3 (0.3)	4 (3.7)	1 (0.3)	0 (0.0)	64 (1.4)
MSM	302 (59.6)	1179 (76.6)	829 (70.6)	97 (89.0)	148 (41.6)	24 (2.4)	2579 (55.0)
Heterosexual	145 (28.6)	252 (16.4)	308 (26.2)	5 (4.6)	182 (51.1)	898 (89.8)	1790 (38.2)
Other/unknown*	36 (7.1)	76 (4.9)	34 (2.9)	3 (2.8)	25 (7.0)	78 (7.8)	252 (5.4)
Years since diagnosis (median)	1.4	1.1	0.5	1.1	0.9	1.6	1.0
≤ 0.5 years	140 (27.6)	406 (26.4)	579 (49.3)	24 (22.0)	143 (40.2)	249 (24.9)	1541 (32.9)
0.51–1.0 years	78 (15.4)	309 (20.1)	197 (16.8)	25 (22.9)	38 (10.7)	121 (12.1)	768 (16.4)
1.01–3.0 years	124 (24.5)	436 (28.3)	238 (20.3)	34 (31.2)	89 (25.0)	265 (26.5)	1186 (25.3)
3.01–5.0 years	66 (13.0)	207 (13.5)	80 (6.8)	11 (10.1)	40 (11.2)	125 (12.5)	529 (11.3)
> 5.0 years	99 (19.5)	181 (11.8)	80 (6.8)	15 (13.8)	46 (12.9)	240 (24.0)	661 (14.1)
Hepatitis							
Hepatitis B	4 (0.8)	28 (1.9)	20 (1.7)	2 (1.9)	24 (6.8)	52 (5.2)	130 (2.9)
Hepatitis C	43 (8.6)	81 (5.5)	22 (1.9)	5 (4.7)	9 (2.5)	11 (1.1)	171 (3.7)

Values are *n* (%) unless otherwise stated.
IDU, injecting drug use; MSM, men who have sex with men.
*Other/unknown includes: 0.6% blood products, 1.0% other and 3.8% unknown.

been administratively withdrawn from the study. This report is based on the remaining 4685 HIV-positive participants.

Overall and region-specific demographic characteristics and factors related to HIV history are presented in Table 1. Approximately 33% of participants are from Europe, 25% from South America, 21% from Africa, 11% from North America, 8% from Asia and 2% from Australia. The median age at entry is 36 years (IQR 29–44 years). Overall, 27% are female with the highest region-specific female representation in Africa (69%), Asia (38%) and North America (22%). Forty-five per cent of the cohort are white, 30% black, 14% Latino/Hispanic, 8% Asian and 3% other.

Fifty-two per cent of participants have completed up to 12 years of education, with the remainder having completed education beyond high/secondary school (e.g. vocational training/college degree or higher). Regionally, participants in Africa and Asia had the least amount of education at entry.

The likely mode of HIV infection is reported as MSM in 55% of participants, heterosexual contact in 38% and injecting drug use (IDU) in 1.4%; 5% report other or unknown modes of transmission. Most participants reporting IDU are from North America ($n = 24$) and Europe ($n = 32$). The median documented time since HIV diagnosis is 1.0 year (IQR 0.4–3.0 years). Thirty-three per cent of participants were diagnosed up to 6 months before study entry and 14% were diagnosed at least 5 years before entry. South America and Asia have the highest proportions of recently diagnosed participants (≤ 6 months), with 49%

Table 2 HIV-specific characteristics, by region

Factor	North America	Europe	South America	Australia	Asia	Africa	Overall
Participants	507 (10.8)	1539 (32.8)	1174 (25.1)	109 (2.3)	356 (7.6)	1000 (21.3)	4685
CD4 count slope (cells/μL/year) [median (IQR)]	−31 (−56, −8)	−33 (−60, −12)	−20 (−49, −1)	−49 (−71, −31)	8 (−16, 25)	−10 (−38, 9)	−23 (−51, −1)
Slope ≥ 100 decline	35 (6.9)	133 (8.6)	72 (6.1)	14 (12.8)	9 (2.5)	46 (4.6)	309 (6.6)
CD4 count* (median)	666	645	642	652	632	684	651
500–599 cells/μL	150 (29.6)	497 (32.3)	404 (34.4)	33 (30.3)	134 (37.6)	257 (25.7)	1475 (31.5)
600–699 cells/μL	144 (28.4)	523 (34.0)	359 (30.6)	42 (38.5)	109 (30.6)	283 (28.3)	1460 (31.2)
700–799 cells/μL	110 (21.7)	257 (16.7)	188 (16.0)	15 (13.8)	54 (15.2)	189 (18.9)	813 (17.4)
800–899 cells/μL	46 (9.1)	128 (8.3)	109 (9.3)	11 (10.1)	24 (6.7)	119 (11.9)	437 (9.3)
≥ 900 cells/μL	57 (11.2)	134 (8.7)	114 (9.7)	8 (7.3)	35 (9.8)	152 (15.2)	500 (10.7)
Nadir CD4 count (median)	552	531	558	556	542	595	553
< 400 cells/μL	27 (5.3)	167 (10.9)	70 (6.0)	6 (5.5)	18 (5.1)	45 (4.5)	333 (7.1)
400–499 cells/μL	121 (23.9)	398 (25.9)	211 (18.0)	24 (22.0)	72 (20.2)	131 (13.1)	957 (20.4)
500–599 cells/μL	176 (34.7)	535 (34.8)	451 (38.4)	41 (37.6)	153 (43.0)	339 (33.9)	1695 (36.2)
600–699 cells/μL	95 (18.7)	230 (14.9)	218 (18.6)	27 (24.8)	52 (14.6)	200 (20.0)	822 (17.5)
700–799 cells/μL	39 (7.7)	107 (7.0)	120 (10.2)	4 (3.7)	35 (9.8)	126 (12.6)	431 (9.2)
≥ 800 cells/μL	49 (9.7)	102 (6.6)	104 (8.9)	7 (6.4)	26 (7.3)	159 (15.9)	447 (9.5)
CD8 count (median)	989	1082	1043	1030	1112	968	1040
< 500 cells/μL	29 (5.7)	61 (4.0)	46 (3.9)	3 (2.8)	12 (3.4)	59 (6.2)	210 (4.5)
500–999 cells/μL	231 (45.7)	596 (39.0)	485 (41.3)	48 (44.0)	121 (34.0)	445 (46.5)	1926 (41.6)
1000–1499 cells/μL	152 (30.1)	509 (33.3)	420 (35.8)	35 (32.1)	143 (40.2)	295 (30.9)	1554 (33.6)
1500–1999 cells/μL	65 (12.9)	211 (13.8)	147 (12.5)	14 (12.8)	52 (14.6)	109 (11.4)	598 (12.9)
≥ 2000 cells/μL	28 (5.5)	152 (9.9)	76 (6.5)	9 (8.3)	28 (7.9)	48 (5.0)	341 (7.4)
HIV RNA (median)	8000	19440	12256	15033	20506	7450	12754
≤ 400 copies/mL	42 (8.3)	60 (3.9)	76 (6.5)	4 (3.7)	27 (7.6)	161 (16.1)	370 (7.9)
401–3000 copies/mL	116 (23.0)	214 (13.9)	199 (17.0)	13 (11.9)	49 (13.9)	203 (20.3)	794 (17.0)
3001–10 000 copies/mL	122 (24.2)	286 (18.6)	257 (21.9)	26 (23.9)	55 (15.6)	193 (19.3)	939 (20.1)
10 001–100 000 copies/mL	190 (37.6)	774 (50.4)	557 (47.4)	58 (53.2)	166 (47.0)	354 (35.4)	2099 (44.9)
> 100 000 copies/mL	35 (6.9)	202 (13.2)	85 (7.2)	8 (7.3)	56 (15.9)	88 (8.8)	474 (10.1)
Highest HIV RNA (median)	13544	44000	18413	44700	22726	8307	21842
≤ 400 copies/mL	27 (5.3)	26 (1.7)	47 (4.0)	1 (0.9)	27 (7.6)	156 (15.6)	284 (6.1)
401–3000 copies/mL	81 (16.0)	112 (7.3)	155 (13.2)	9 (8.3)	47 (13.3)	191 (19.1)	595 (12.7)
3001–10 000 copies/mL	109 (21.5)	204 (13.3)	255 (21.7)	12 (11.0)	50 (14.2)	193 (19.3)	823 (17.6)
10 001–100 000 copies/mL	229 (45.2)	740 (48.1)	574 (48.9)	62 (56.9)	170 (48.2)	363 (36.3)	2138 (45.7)
> 100 000 copies/mL	61 (12.0)	457 (29.7)	143 (12.2)	25 (22.9)	59 (16.7)	96 (9.6)	841 (18.0)

Values are *n* (%), unless otherwise stated.
IQR, interquartile range.
*Average of two screening values.

and 40%, respectively. In Africa and North America, 24% and 20%, respectively, are reported as having been diagnosed ≥ 5 years ago. Overall, HBV and HCV coinfections rates at entry are low, at 3% and 4%, respectively.

Distributions of HIV-specific laboratory data, overall and by geographical region, are presented in Table 2. The median and nadir CD4 cell counts are 651 cells/μL (IQR 584–765 cells/μL) and 553 cells/μL (IQR 488–654 cells/μL), respectively. Twenty per cent of baseline CD4 cell counts are ≥ 800 cells/μL. The median plasma HIV RNA level at baseline is 12 754 HIV RNA copies/mL (IQR 3014–43 607 copies/mL). Eight per cent have plasma HIV RNA ≤ 400 copies/mL, and 10% have values > 100 000 copies/mL. By region, participants in Africa, North America and South America have the lowest median HIV RNA values (approximately 7400–12 000 copies/mL) while those in Europe and Asia have higher median values of approximately 20 000 copies/mL. Further analysis of baseline HIV RNA in this cohort is presented elsewhere in this supplement [11].

The median CD4 cell count decline prior to enrolment is −23 cells/μL per year (IQR −51, −1 cells/μL per year), and 7% of participants have a decline of ≥ 100 cells/μL per year. The rates of decline are closer to zero in Asia and Africa and more negative in the other regions.

Baseline characteristics by gender and age

The median age at entry for women is 37 years (IQR 30–45 years) and for men it is 35 years (IQR 28–43 years). Sixty-three per cent of women are black and 15% are white; 18% of men are black and 55% are white. A greater proportion of men than women have at least 12 years of education. Median time from HIV diagnosis is 1.5 years (IQR 0.5–4.4 years) for women and 0.9 years (IQR 0.3–2.5 years) for men.

Table 3 HIV-specific characteristics, by gender and age group

	Gender		Age group			
Factor	**Male**	**Female**	**<25 years**	**25–34 years**	**35–44 years**	**≥ 45 years**
Participants	3428 (73.2)	1257 (26.8)	500 (10.7)	1615 (34.5)	1489 (31.8)	1081 (23.1)
CD4 count slope (cells/μL/year) [median (IQR)]	−25 (−52, −6)	−22 (−52, −1)	−19 (−45, −3)	−29 (−56, −11)	−26 (−55, −6)	−23 (−51, −2)
Slope ≥ 100 decline	231 (6.7)	85 (6.7)	17 (3.4)	118 (7.3)	122 (8.2)	80 (7.4)
CD4 count (median)	646	674	646	649	652	654
500–599 cells/μL	1124 (32.8)	351 (27.9)	160 (32.0)	525 (32.5)	454 (30.5)	336 (31.1)
600–699 cells/μL	1103 (32.2)	357 (28.4)	169 (33.8)	503 (31.1)	464 (31.2)	324 (30.0)
700–799 cells/μL	589 (17.2)	224 (17.8)	80 (16.0)	277 (17.2)	256 (17.2)	200 (18.5)
800–899 cells/μL	312 (9.1)	125 (9.9)	44 (8.8)	157 (9.7)	138 (9.3)	98 (9.1)
≥ 900 cells/μL	300 (8.8)	200 (15.9)	47 (9.4)	153 (9.5)	177 (11.9)	123 (11.4)
HIV RNA (median)	16379	6444	13688	14143	11983	11700
≤ 400 copies/mL	184 (5.4)	186 (14.8)	28 (5.6)	103 (6.4)	141 (9.5)	98 (9.1)
401–3000 copies/mL	502 (14.7)	292 (23.3)	83 (16.6)	270 (16.8)	251 (16.9)	190 (17.6)
3001–10 000 copies/mL	668 (19.5)	271 (21.6)	104 (20.8)	329 (20.4)	296 (19.9)	210 (19.5)
10 001–100 000 copies/mL	1667 (48.7)	432 (34.5)	242 (48.4)	751 (46.6)	641 (43.1)	465 (43.1)
> 100 000 copies/mL	402 (11.7)	72 (5.7)	43 (8.6)	158 (9.8)	157 (10.6)	116 (10.8)

Values are *n* (%), unless otherwise stated.
IQR, interquartile range.

The median CD4 cell counts for men and women are 646 cells/μL (IQR 582–750 cells/μL) and 674 cells/μL (IQR 591–805 cells/μL), respectively (Table 3). There are differences in plasma HIV RNA by gender, with men having a higher median value of 16 379 copies/mL compared with women whose median value is 6444 copies/mL. This difference is consistent across regions, with the exception of North America where the difference is much smaller (8234 versus 6900 copies/mL, respectively). Prior to study entry, the median CD4 cell count, HIV RNA level and rate of CD4 decline per year are similar across age groups (Table 3).

Medical history and concomitant medications

Medical history is summarized in Table 4. A history of non-AIDS-related cancer, including basal or squamous cell skin cancer, is reported for 0.6% of participants. About 0.5% have a prior diagnosis of a clinically significant CVD event (i.e. acute myocardial infarction, stroke or coronary revascularization). Almost 1% have a prior serious non-AIDS-related event of CVD or non-AIDS-related cancer. The most common medical diagnoses at entry are alcoholism or other substance abuse (3%) and psychiatric illness (6%), with these conditions being more prevalent in North America, Europe and Australia.

The most commonly prescribed medications are blood-pressure-lowering drugs (8%), antidepressants (6%), hormonal therapy (4%), lipid-lowering drugs (4%), nonsteroidal anti-inflammatory drugs excluding aspirin (3%), proton pump inhibitors (3%), benzodiazepines (2%), drug treatment for diabetes (2%), > 2 weeks of aspirin use (2%) and anti-*Pneumocystis jirovecii* pneumonia (PjP) agents (2%). All anti-PjP drug use is in Africa as prophylaxis for opportunistic infections.

Table 4 Prior medical history (*n* = 4685)

Diagnosis	***n* (%)**
Non-AIDS-related cancer	
Basal or squamous cell skin cancer	10 (0.2)
Other cancer (excluding above)	19 (0.4)
Cardiovascular disease	
Acute myocardial infarction	12 (0.3)
Stroke	6 (0.1)
Coronary revascularization	10 (0.2)
Coronary artery disease requiring drug treatment	11 (0.2)
Congestive heart failure	9 (0.2)
Myocarditis	5 (0.1)
Pericarditis	3 (0.1)
Deep vein thrombosis	16 (0.3)
Peripheral arterial disease	4 (0.1)
Pulmonary embolism	5 (0.1)
Liver/kidney disease	
Chronic liver disease (excluding infectious hepatitis)	17 (0.4)
Cirrhosis (biopsy/clinical diagnosis; including infectious hepatitis-related)	2 (0.04)
Hepatic steatosis (liver biopsy)	9 (0.2)
Pancreatitis	6 (0.1)
End-stage renal disease	0 (0.0)
Chronic kidney disease	9 (0.2)
Any of the above	*122 (2.6)*
*Any prior cardiovascular disease**	*23 (0.5)*
Any prior serious non-AIDS-related condition†	*41 (0.9)*

*Acute myocardial infarction, stroke or coronary revascularization.
†Prior serious non-AIDS-related condition (SNA) as included in the Strategic Timing of AntiRetroviral Treatment (START) endpoint definition: cardiovascular disease, non-AIDS-related cancer (excluding basal or squamous cell skin cancer), or end-stage renal disease. Note that the START SNA definition also includes decompensated liver disease, which is an exclusionary criterion and not part of prior history.

Discussion

The START cohort is diverse and globally well represented, with over half of the participants enrolled from low- and middle-income countries. This diversity makes the population significantly different from those of earlier when-to-start studies [1–3], which included primarily white male participants in high-income countries. The characteristics of START participants are comparable to the current characteristics of the global untreated HIV-positive population and are similar to those of the populations living with HIV in the regions from which they were enrolled, with the exception of injecting drug users. For example, in the USA, of persons living with HIV in 2010, 52% were MSM, 27% contracted HIV from heterosexual contact, 44% were black, 19% were Hispanic/Latino and 24% were female [12]. The START population in the USA has similar demographic characteristics. In the European Economic Area (EEA), new diagnoses in 2012 occurred in the ratio of 3:2 for male to female individuals: 34% of cases were from heterosexual contact (including cases in individuals who had migrated from sub-Saharan Africa), 40% in MSM, 6% from IDU and 20% from unknown acquisition [13]. START in contrast has a lower participation in Europe for each of these groups except for MSM. In Australia, most new diagnoses in 2012 were primarily in MSM (67%); 25% of cases were attributable to heterosexual contact, with 58% of these cases being in individuals originating from high-prevalence countries [14]. Australian participants in START are primarily MSM, white, and slightly older than the current median incidence age of 36 years in the region [14]. In the Asia/Pacific region, 36% of persons living with HIV in 2012 were women, and MSM and heterosexual contact were the main demographics for new infections [15]; these groups are well represented in the START population recruited in Asia. Enrolment of African women in START (69%) is representative of women in Africa with HIV infection; in 2012, sub-Saharan African women accounted for 57% of infections [4]. In South America, the epidemic as reported in 2012 was stable, with MSM as a growing demographic of new infections in addition to heterosexual contact [4]. Seventy per cent of participants in START in this region are MSM and 15% are women.

The rate of CD4 cell count decline at entry for this population is −23 cells/μL per year. This rate should be interpreted with caution, especially in comparisons to other cohorts not selected based on CD4 cell counts. As a consequence of limited pre-randomization data, the slope for 42% of participants is based on the two qualifying screening CD4 cell counts, both required to be within 60 days before randomization.

Other trials in addition to START have been designed to address the when-to-start question since effective combination ART became available. Three of these trials have been completed, and one is ongoing [16–21]. These trials differ from START in several ways: (1) the CD4 cell count threshold in the deferral strategy for the control group is lower in these trials; (2) the CD4 cell counts at study entry are lower (by approximately 200 cells/μL); (3) the sample sizes are smaller; (4) the primary endpoints differ; and (5) they are not as geographically diverse as START. For example, considering the completed trials, one was carried out in Haiti where participants had a median CD4 cell count of 280 cells/μL [16]; a second, the HIV Prevention Trials Network (HPTN) 052 trial, was conducted primarily in Asia, Africa and two sites in Brazil and at study entry participants had a median CD4 cell count of 436 cells/μL [17,18]; and a third was a post hoc subgroup analysis of the SMART study with only 477 participants [19]. The deferral strategy was to wait for a CD4 cell count of 250 cells/μL in two of these trials [17–19] and 200 cells/μL in the other [16]. The Temprano [Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) 12136] trial [20] is currently ongoing and is being conducted in Côte d'Ivoire; the median CD4 cell count at entry for 1952 of the 2076 randomized participants is 469 cells/μL [21].

In summary, START has enrolled 4685 participants with CD4 cell counts > 500 cells/μL from 215 sites in 35 countries. The broad inclusion criteria, the diversity of sites and study participants, and the careful and extensive characterization of the cohort will enable the study results to be broadly generalized and permit assessment of the consistency of the findings across key demographic, geographical, HIV and other factors assessed at study entry.

The START study is registered at clinicaltrials.gov (NCT00867048).

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