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ART in HIV-positive persons with low pre-treatment viremia: results from the START trial

Irini SERETI, MD, MHSc[1], **Roy M. GULICK, MD, MPH**[2], **Sonya KRISHNAN, MD**[1], **Stephen A. MIGUELES, MD**[1], **Adrian PALFREEMAN, FRCP, FRCPI**[3], **Veronique TOUZEAU-RÖMER, MD**[4], **Waldo H. BELLOSO, MD**[5], **Sean EMERY, MA, MSc, PhD**[6], **Matthew G. LAW, MA, MSc, PhD**[7,*] **on behalf of INSIGHT START Study Group**

[1]NIAID/NIH, USA

[2]Weill Cornell Medicine, USA

[3]Leicester Royal Infirmary, Leicester, UK

[4]University Vienna General Hospital, Austria

[5]CICAL and Hospital Italiano de Buenos Aires Argentina

[6]Faculty of Medicine, University of New South Wales, Australia

[7]Kirby Institute, University of New South Wales, Australia

Abstract

Background: The benefit of immediate antiretroviral therapy (ART) at CD4 >500 cells/μL was established in the Strategic Timing of Antiretroviral Treatment (START) study. The benefits and risks of immediate ART in participants with low pre-treatment viremia, including virologic suppressors, was further assessed.

Setting: Randomized prospective international study

Methods: START participants with enrollment viremia <3000c/mL were included. We compared clinical outcomes (grade 4 adverse events, hospitalisations or death), plasma viremia, CD4 counts and changes in biomarkers in immediate versus deferred ART groups.

Results: Participants (N=1134 including 93 with viremia ≤50 c/mL) had a median age of 37 years, 40% were female and median CD4 was 713 cells/μL. 97% in the immediate and 29% in the deferred arm initiated ART at a median of 6 and 699 days respectively. Clinical outcomes were experienced in 64 vs 61 patients in immediate and deferred arms (hazard ratio 1.10 95% CI 0.77 1.56). The CD4 count difference was 125 cells/μL at 12 and 235 cells/μL at 36 months higher in the immediate vs deferred groups. D-dimer and VCAM levels decreased, and CRP increased, in the immediate arm at month 8. No significant changes in CD4 counts or biomarkers were observed in persons who maintained spontaneous virologic suppression.

*See N Engl J Med 2015; 373:795–807 for the complete list of START investigators.

Correspondence to Prof Matthew Law, The Kirby Institute, Level 6, Wallace Wurth Building, UNSW Sydney, NSW 2052, Australia. mlaw@kirby.unsw.edu.au, telephone number: +61 2 9385 0900, fax number: +61 2 9385 0920.

Conclusions: START participants with low enrollment viremia experienced higher CD4 counts, greater proportion with suppressed viremia, and decreases in D-dimer levels upon immediate ART despite the lack of difference in serious clinical outcomes. These data support immediate ART in people with low viremia although equipose remains for suppressors.

Keywords

antiretroviral therapy; CD4 counts; biomarkers; low viremia; HIV RNA

Introduction

Following the groundbreaking results of the START study [1], global HIV treatment guidelines now recommend that the population of HIV-positive individuals, as a whole, benefit from early antiretroviral therapy (ART) initiation, regardless of baseline CD4 count [2–5]. Hazard ratios for the primary endpoint favored immediate initiation consistently across all studied subgroups [1], however, in the 25% of START participants with baseline HIV RNA less than 3,000 copies (c)/mL, there was a smaller absolute benefit (11 events (0.64 /100pyrs) versus 15 (0.84 /100 pyrs), rate difference 0.21 (95% CI −0.39 to 0.82) / 100pyrs) as a result of the lower overall absolute risk of events in this subgroup [6]. Quality of life has also been shown to be improved in the immediate arm of START [7]. Nevertheless, one group of HIV-positive individuals where there remains potential debate regarding starting ART immediately are those with low pre-treatment HIV RNA levels [2–4,8,9].

Furthermore, within the group of patients with baseline HIV RNA less than or equal to 3,000 c/mL, there existed a population of persons with pVL<50 c/mL which probably included some elite controllers (ECs), a rare subset of HIV-positive individuals who demonstrate durable control of HIV, normal CD4 cell counts, and delayed disease progression in the absence of ART [10,11] despite presence of low levels of HIV viral replication [12]. Some studies have shown that ECs may have higher levels of T cell activation, inflammatory biomarkers, tissue fibrosis [13], and atherosclerosis compared to HIV-negative individuals and in some cases ART-suppressed individuals [14–16]. It is unclear though if these measured factors lead to increased serious non-AIDS-related events as suggested by a retrospective study looking at hospitalizations in a specific cohort [17]. Furthermore, it has yet to be definitively established if ECs would benefit from ART initiation as data are sparse and contradictory and no randomized treatment data are available [18–21].

Given the above, there is potential uncertainty among some physicians and patients about the benefits of immediate ART initiation in HIV-positive people with pre-treatment HIV RNA less than 3000 c/mL. Therefore, the aim of our study was to describe clinical, virologic, immunologic and safety data in people participating in START with low baseline plasma viremia randomized to immediate versus deferred therapy arms. We also evaluated changes in plasma biomarkers to give a complete, in depth summary of the risks and benefits of immediate ART in this group.

Methods

Study Design.

The START Study has been described in detail previously [1]. All study participants signed informed consent. We restricted analyses to the subgroup of participants with HIV-RNA ≤3,000 c/mL at baseline, and without evidence of receiving ART at baseline. We chose this cut-off as this corresponded approximately to the lower quartile of participants by HIV RNA at enrollment in START, is a level that would generally be regarded as low in untreated HIV-positive people, and is consistent with the cut-off used for analyses by HIV RNA strata in previous START reports of the relative and absolute benefits of immediate ART [1,6]. We also did further analyses restricted to the subset of participants with baseline HIV RNA ≤50 c/mL, also included within the reported overall <3000c/mL group, which we elected to refer to as suppressors for the scope of this publication since it was unclear how many would have met the various definitions of elite controllers or long-term nonprogressors upon follow up.

We summarized data on a number of endpoints by treatment arm, including serious clinical outcomes (grade 4 adverse events not attributable to AIDS, unscheduled hospitalisations for reasons other than AIDS, and deaths from any cause), laboratory abnormalities, HIV RNA and CD4 counts, and biomarker data. We limited follow-up to 3 years for laboratory abnormalities, HIV RNA and CD4 count data, as this was the period when the difference between the immediate and deferred arms was largest in terms of ART exposure. Laboratory abnormalities were defined per the Division of AIDS criteria (http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables).

Measurement of biomarkers.

Cryopreserved EDTA plasma, collected at baseline and at the month 8 visit and stored centrally at −70°C, was used to measure 7 plasma biomarkers to assess systemic inflammation (IL-6, high-sensitivity C-reactive protein [hsCRP] and serum amyloid A [SAA]), vascular inflammation (soluble intercellular adhesion molecule-1 [sICAM] and vascular adhesion molecule-1 [sVCAM]), immune activation (interleukin-27 [IL-27]), and coagulation activation (D-dimer). IL-6 was measured using high sensitivity ELISA (R&D Systems), D-dimer using VIDAS system (BioMerieux), and IL-27 using immunoassay (MesoScale). A multiplex platform was used to measure hsCRP, SAA, sICAM and sVCAM (Vascular Injury II Panel, MesoScale)[22].

Statistical methods.

Since the purpose of this analysis was largely exploratory, assessing in depth the risks and benefits of immediate ART in this subgroup of participants with low viral load levels, we did not perform sample size calculations for this analysis. We do accept that for protocol defined clinical events the power of analyses was limited, and have attempted not to overinterpret findings.

Formal statistical comparisons between randomized arms, when performed, were done by a two-sample t-test to compare mean CD4 counts, Cox regression to compare time to first serious adverse clinical event, and the rank-sum test and corresponding Hodges-Lehman

non-parametric confidence intervals [23] to compare biomarker data. All analyses were simple, unadjusted comparisons of treatment arms.

Estimating reduction in risk of HIV transmission due to immediate treatment.

The reduction in risk of HIV transmission was estimated based on the 12 month HIV viral load data in the immediate and deferred arms based on ITT data. The risk of HIV transmission was simulated to be proportional to measured viral load, based on the formula: $\beta 1 = 2.45^{**}(\log 10(V1/V2))^{*} \beta 2$ where $\beta 2$ = average per act transmission probability at average chronic viral load level V2 (taken to be 20,000 c/mL here). This formula assumes each ten-fold (1 log10) lower viral load reduces the risk of transmission by 2.45 fold [24,25]. We assumed that this log-linear relationship held only until a viral load of 1000 c/mL, and that there is no transmission risk below a threshold of 1000 c/mL.

Results

Baseline characteristics.

We identified 1159 participants on the START study out of the 4684 study participants (24.8%) with a pre-treatment HIV RNA level <3000 c/mL, including 94 participants with a level ≤50 c/mL. Out of the 370 patients with HIV RNA ≤400 c/mL at baseline, 333 who had a stored blood sample were tested for ART use, of whom 22 were found to have detectable levels of antiretroviral drugs indicating ART use. After randomization, an additional 3 patients reported prior ART use (an exclusion criterion). These 25 patients have been excluded from all analyses.

The baseline characteristics of all the participants who had plasma HIV RNA ≤3000 c/mL (N=1134, including those with ≤50 c/mL) and the subgroup with HIV RNA ≤50 c/mL (N=93) are shown in Table 1. The ≤50 c/mL subgroup included more women and more Africans, as well as participants who were slightly older, with longer duration of HIV infection, higher CD4 counts and a higher proportion of black race.

Of the 555 participants randomized to immediate ART, 536 (97%) started ART, with a median time to ART of 6 days (inter quartile range (IQR) 1 to 15 days) from randomization. Of 579 participants randomized to deferred ART, 173 (29%) started ART during follow-up with a median time of start of 699 days (IQR 397 to 1054 days).

Serious clinical outcomes.—Grade 4 adverse events not attributable to AIDS, deaths from any cause and unscheduled hospitalisations for reasons other than AIDS are summarised in Table 2 for the ≤3000 c/mL subgroup. These total combined serious clinical outcomes were observed in 64 participants in the immediate and 61 participants in the deferred arms respectively with a hazard ratio (HR) of 1.10, (0.77, 1.56) p=0.595. The observed rates of 4.04 and 3.67 per 100 person years in the immediate and deferred arms respectively were lower than the combined rates seen in the entire trial of 4.56 and 5.52 per 100 person years [1]. There were no treatment related deaths as assessed by the investigators (supplemental table 1).

The ≤50 c/mL subgroup was too small for formal comparisons, there were no deaths and there were 2 participants in the immediate and 5 in the deferred arm respectively with any serious clinical outcome, an overall rate of 3.11 per 100 person years.

Virologic and immunologic responses

Antiretroviral therapy initiation in the immediate arm led to suppression of HIV RNA to ≤200 c/mL that was sustained to month 36 of study follow up whereas participants randomized in the deferred arm had persistent viremia throughout the study duration (Figure 1a). At 12 months 93% in the immediate and 22% of persons in the deferred arms had plasma viremia <200 copies/mL (94 and 27% respectively at 24 months). Mean CD4 counts increased in the immediate arm, and declined over time in the deferred arm (Figure 1b). Mean CD4 counts clearly diverged and the mean difference in CD4 counts at 12 months was 125 cells/μL higher in the immediate arm (95% confidence interval (CI) 93 to 156 cells/μL, $p<0.001$). The mean difference in CD4 counts at 36 months was 235 cells/μL (CI 187 to 283, $p<0.001$), again higher in the immediate arm.

Participants in the subgroup of ≤50 c/mL had overall stably suppressed HIV-RNA, albeit the proportion of those persons with ≤200 c/mL gradually decreased in the deferred ART arm (Figure 1c). Furthermore, of the 51 participants with ≤50 c/mL included in the deferred ART arm, 28 (55%) had HIV RNA measured as >50 c/mL within the first 12 months of follow-up.

Mean CD4 counts were stable over the period of follow up in the ≤50c/mL group regardless of randomization arm with a mean difference at 12 months of 24 cells/μL (CI −106 to 153) (Figure 1d).

Effect of ART initiation on laboratory measurements.—There was little discernable difference in the proportions of patients with grade 4 (severe) abnormal haemoglobin, platelets, creatinine, ALT or Alkaline phosphatase at years 1, 2 and 3. There was a higher proportion of participants with increased total bilirubin in the immediate arm but when censored for those who received atazanavir this difference largely disappeared.

Effect of ART initiation on biomarkers of inflammation, coagulation and immune activation.—Supplemental Tables 2a (overall group of ≤3000 c/mL) and 2b (≤50 c/mL subgroup) show the changes of measured soluble biomarkers at month 8 from baseline, similar to the analyses done in the larger trial [22]. A significant difference between treatment arms was noted in the levels of D-dimer, and sVCAM which decreased and CRP which increased in the Imm arm. Differences in biomarkers in participants with HIV RNA ≤50 c/mL were largely non-significant.

Effect of treatment initiation on potential transmission risk.—To give an idea of the possible magnitude of reduced onward transmission of HIV as a result of immediate ART, we assumed that 40% of participants were men who have sex with men, 40% heterosexual females and 20% heterosexual males, roughly consistent with START baseline demographics.

We further assumed that the per contact transmission probabilities were 0.0075 per act for MSM (average of insertive and receptive unprotected risks), 0.0008 per act for heterosexual females and 0.004 per act for heterosexual males [26]. We assumed an average of 200 acts per year, 10% without condoms and condom use reduced the risk of transmission by 95%.

With these assumptions, and based on the HIV RNA levels seen in at 12 months in our analyses, we estimate that there would be 0.2 transmissions per 100 patients per year in the immediate ART arm, and 3.2 transmissions per 100 patients per year in the deferred treatment arm.

Discussion

Treatment guidelines dictating initiation of antiretroviral therapy in persons with HIV infection have undergone major changes over the years regarding the recommended CD4 count for treatment initiation, and have settled after the results of the START [1], TEMPRANO [27] and HPTN 052 [28] studies into immediate initiation of therapy upon HIV diagnosis at any CD4 count. One subgroup where there remains some potential uncertainty regarding the benefit of immediate ART is in individuals with low pre-treatment HIV RNA levels [2,4,9]. In previous START analyses comparing immediate versus deferred treatment in individuals with HIV RNA <3,000 c/mL, the absolute rate of primary study endpoints (AIDS, serious non-AIDS or death) was low over the 3 years of the analyses at a rate of 0.64 and 0.84 per 100 pyrs in the immediate and deferred arms respectively. The benefits of immediate ART, however, can be seen in our analyses with complete virologic suppression and with significantly higher CD4 counts. Importantly, there was little evidence of harm from immediate ART, with low numbers of, and a lack of difference between arms, in serious clinical outcomes and laboratory adverse events and no treatment related deaths. Furthermore, inflammatory and coagulation biomarkers inluding D-dimer and sVCAM showed a favorable downward change after 8 months of ART in the immediate arm. Finally, simple mathematical modeling, addressing risk of onward HIV transmission suggested that the suppression of HIV viremia would reduce transmission risk by a modest absolute amount, an important public health goal of early ARV therapy.

There are further practical reasons to support immediate ART in individuals with low HIV RNA levels. First, of the 581 START individuals with <3,000 c/mL randomized to deferred ART, the proportion with either a HIV RNA >3,000 c/mL or a CD4 < 500 cells/μL was 63% by 12 months and 72% by 24 months, suggesting that a delay in ART initiation is accompanied by disease progression as reflected by these markers. Second, a few encouraging trends were noted in inflammatory and coagulation biomarkers namely decreased D-dimer and VCAM which although not as impressive as typically seen in patients with higher viremia, were consistent with the overall strategy of decreasing inflammation with virologic suppression. It is unclear why levels of other important biomarkers, especially IL-6, did not change significantly but it is possible that people with low viremia do not have levels that can quickly decrease with therapy as was already noted in the biomarker study by Baker et al, which showed that differences in changes in IL-6 levels differed by baseline levels of viremia [22].

Among the group of low yet detectable viremia of START participants there was a subgroup of suppressors that could fit, based on some definitions, the category of elite controllers, i.e. HIV infected persons maintaining spontaneously a plasma viral load below 50 copies/mL, since they remained suppressed throughout the study duration in the deferred arm and maintained high CD4 counts. It is known that 1–2% of people with HIV infection, more enriched in HLA-B57 or 27 genetic background, have this unusual course of natural suppression of plasma viremia. Some studies have found evidence of higher immune activation in elite controllers, cardiovascular disease and occasional HIV disease progression [15,17,29,30, 31]. It is thus unclear if and when these HIV infected persons should be treated with ART.

Our subgroup analysis of those with enrollment HIV RNA <50 c/mL was based on relatively low numbers of patients, and high variability in the biomarkers means that differences in these variables would have had to be very large to be detected as statistically significant. However, we found that the clinical event rate and number of events over an average of 3 years follow-up were low, and a longer time period likely would be required to draw firm conclusions. In addition, in participants with baseline HIV RNA <50c/mL we saw mostly suppressed viremia, albeit at higher levels in the immediate arm, and stable CD4 cell counts in both the immediate and the deferred arms.

The case of suppressors brings into light how clinicians are occasionally faced with the challenge on making decisions for persons with rare disease phenotypes that may be underrepresented in large clinical trials that dictate treatment guidelines. Although no clear clinical benefit could be observed in START, which included the largest randomized number of people with pVL≤50c/mL reported to date, there was little evidence of harm, as assessed by serious clinical outcomes and laboratory adverse events. In the dawn of individualized medicine, it is prudent to think beyond treatment guidelines at times and also to create decision partnerships with the persons who are affected by these treatment decisions. As the number needed to treat to show clinical benefit in suppressed individuals who maintain pVL<50c/L may well exceed the number of EC in the world, the decision may be tailored to the specific course of each person that may include co-morbidities, plasma viremia and CD4 trajectory, and importantly willingness (or lack thereof) to be treated as suggested by previous retrospective studies [29]. An international registry of EC capturing longitudinal data may provide further necessary data for their unusual course of disease and potential benefit of antiretroviral treatment.

The limitations of our study include the limited power of a subgroup analysis, and the mean 3 years duration of follow up, though it should be noted that START participants will eventually be followed-up for an average of 10 years. The mathematical models we used to estimate potential reduction of onward transmission due to immediate ART are simple, and only intended to give an indication of likely HIV transmission risk and did not include the potential risk of noncompliance with onward transmission of resistant viruses. These models are subject to unverifiable assumptions, and should not be over-interpreted. In addition, our group demographics with high proportion of women and blacks (including suppressors) and low proportion of hepatitis co-infection may not be fully representative of other populations. Finally, adverse events were only collected if characterized as grade 4 (severe) and the

occurrence of lower grade adverse events, which were not collected, also may be relevant. Despite these limitations, our data represent the best comparative data among people with low viremia and high CD4 counts for a detailed analysis of the effects of immediate versus deferred treatment initiation.

In conclusion, for most HIV-positive people with HIV RNA ≤3000 c/mL although there are low numbers of clinical events, our analyses show that immediate ART results in suppressed HIV RNA, CD4 count increases, little evidence of increased serious clinical outcomes, and an estimated modest decreased risk of onward HIV transmission.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Group ISS, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 2015; 373(9): 795–807. [PubMed: 26192873]
2. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA 2016; 316(2): 191–210. [PubMed: 27404187]
3. Churchill D, Waters L, Ahmed N, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 HIV Med 2016; 17 Suppl 4: s2–s104.
4. U.S. Department of Health and Human Services. Adult and adolescent treatment guidelines. AIDSinfo https://aidsinfo.nih.gov/guidelines/. Published October 25th 2018 Accessed 28th February 2019.
5. World Health Organization. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations 2016 update. World Health Organization https://apps.who.int/iris/bitstream/handle/10665/246200/9789241511124-eng.pdf;jsessionid=CE7EDD654B0B5FCEB1A736F0457485B8?sequence=1. Published 2016 Accessed 28th February 2019.

6. Molina JM, Grund B, Gordin F, et al. 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. Lancet HIV 2018; 5(4): e172–e80. [PubMed: 29352723]
7. Lifson AR, Grund B, Gardner EM, et al. Improved quality of life with immediate versus deferred initiation of antiretroviral therapy in early asymptomatic HIV infection. AIDS 2017; 31(7): 953–63. [PubMed: 28121710]
8. World Health Organization Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV September 2015. World Health Organization https://www.ncbi.nlm.nih.gov/books/NBK327115/pdf/Bookshelf_NBK327115.pdf. Published September 2015 Accessed 28th February 2019.
9. Ryom L, Boesecke C, Gisler V, et al. Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons. HIV Med 2016; 17(2): 83–8. [PubMed: 26548563]
10. Gurdasani D, Iles L, Dillon DG, et al. A systematic review of definitions of extreme phenotypes of HIV control and progression. AIDS 2014; 28(2): 149–62. [PubMed: 24149086]
11. Migueles SA, Connors M. Success and failure of the cellular immune response against HIV-1. Nat Immunol 2015; 16(6): 563–70. [PubMed: 25988888]
12. Dahl V, Peterson J, Spudich S, et al. Single-copy assay quantification of HIV-1 RNA in paired cerebrospinal fluid and plasma samples from elite controllers. AIDS 2013; 27(7): 1145–9. [PubMed: 23211774]
13. Sanchez JL, Hunt PW, Reilly CS, et al. Lymphoid fibrosis occurs in long-term nonprogressors and persists with antiretroviral therapy but may be reversible with curative interventions. J Infect Dis 2015; 211(7): 1068–75. [PubMed: 25344521]
14. Hsue PY, Hunt PW, Sinclair E, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. AIDS 2006; 20(18): 2275–83. [PubMed: 17117013]
15. Krishnan S, Wilson EM, Sheikh V, et al. Evidence for innate immune system activation in HIV type 1-infected elite controllers. J Infect Dis 2014; 209(6): 931–9. [PubMed: 24185941]
16. Pereyra F, Lo J, Triant VA, et al. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. AIDS 2012; 26(18): 2409–12. [PubMed: 23032411]
17. Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization Rates and Reasons Among HIV Elite Controllers and Persons With Medically Controlled HIV Infection. J Infect Dis 2015; 211(11): 1692–702. [PubMed: 25512624]
18. Chun TW, Shawn Justement J, Murray D, et al. Effect of antiretroviral therapy on HIV reservoirs in elite controllers. J Infect Dis 2013; 208(9): 1443–7. [PubMed: 23847057]
19. Hatano H, Yukl SA, Ferre AL, et al. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. PLoS Pathog 2013; 9(10): e1003691. [PubMed: 24130489]
20. Okulicz JF, Marconi VC, Landrum ML, et al. Clinical outcomes of elite controllers, viremic controllers, and long-term nonprogressors in the US Department of Defense HIV natural history study. J Infect Dis 2009; 200(11): 1714–23. [PubMed: 19852669]
21. Sedaghat AR, Rastegar DA, O'Connell KA, Dinoso JB, Wilke CO, Blankson JN. T cell dynamics and the response to HAART in a cohort of HIV-1-infected elite suppressors. Clin Infect Dis 2009; 49(11): 1763–6. [PubMed: 19857162]
22. Baker JV, Sharma S, Grund B, et al. Systemic Inflammation, Coagulation, and Clinical Risk in the START Trial. Open Forum Infect Dis 2017; 4(4): ofx262. [PubMed: 29308409]
23. Law MG, Achhra A, Deeks SG, et al. Clinical and demographic factors associated with low viral load in early untreated HIV infection in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med 2015; 16 Suppl 1: 37–45. [PubMed: 25711322]
24. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. Lancet 2008; 372(9635): 314–20. [PubMed: 18657710]
25. Smith RJ, Blower SM. Could disease-modifying HIV vaccines cause population-level perversity? Lancet Infect Dis 2004; 4(10): 636–9. [PubMed: 15451492]
26. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS 2014; 28(10): 1509–19. [PubMed: 24809629]

27. Group TAS, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med 2015; 373(9): 808–22. [PubMed: 26193126]

28. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011; 365(6): 493–505. [PubMed: 21767103]

29. Okulicz JF, Boufassa F, Costagliola D, Ganesan A, Lambotte O. Cancers in elite controllers: appropriate follow-up is essential. AIDS 2016; 30(11): 1852–5. [PubMed: 27177315]

30. Okulicz JF, Lambotte O. Epidemiology and clinical characteristics of elite controllers. Curr Opin HIV AIDS 2011; 6(3): 163–8. [PubMed: 21502920]

31. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T Cell Activation and CD4 T Cell Count in HIV-Seropositive Individuals with Undetectable Plasma HIV RNA Levels in the Absence of Therapy. J. Infect Dis.2008197 (January 1):126–33. [PubMed: 18171295]

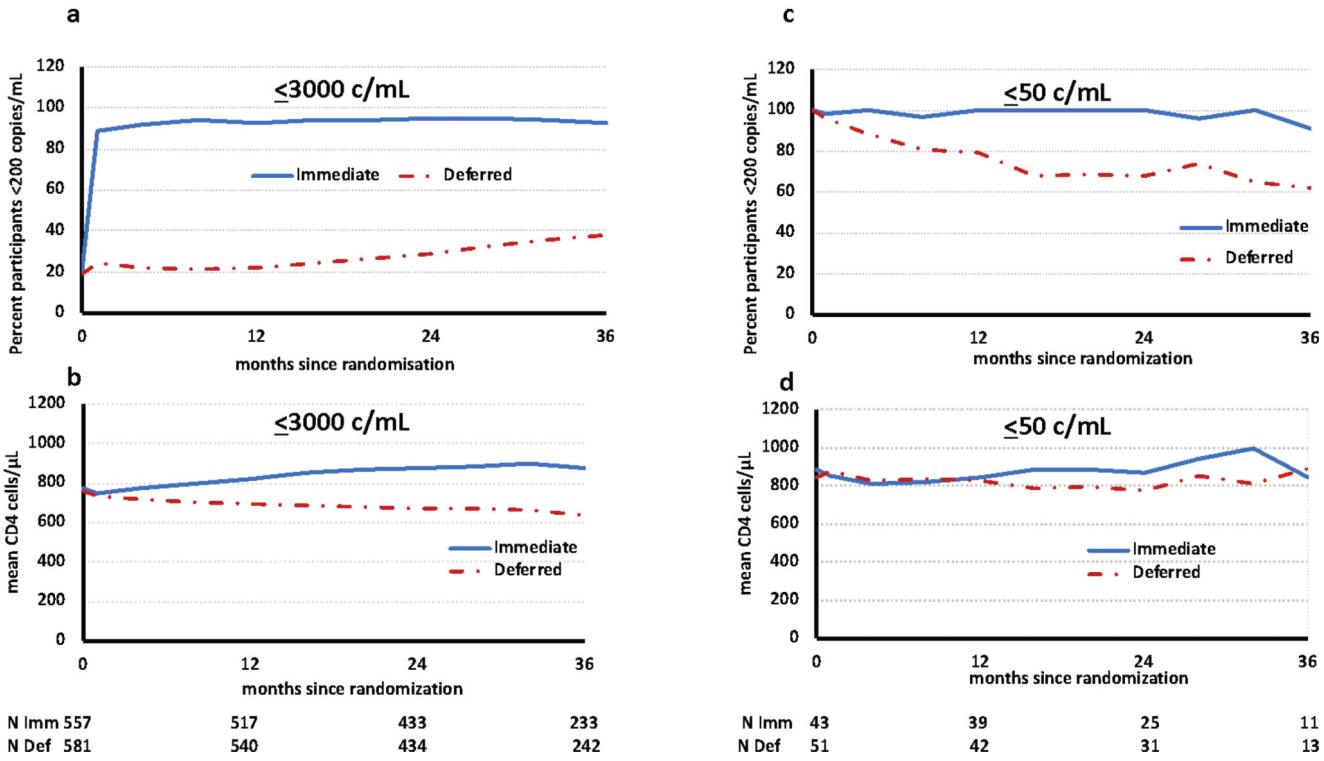

Figure 1.

HIV RNA and CD4 counts over time in immediate versus deferred groups based on pre-treatment HIV RNA

Table 1.

Participant characteristics by enrollment HIV RNA and randomized treatment (<3000 and ≤50 c/mL) (cont)

				Baseline HIV RNA (c/mL)				
				<3,000		≤50		
				Imm N=555	Def N=579	Imm N=42	Def N=51	Both Imm and Def arms N=1134
Age (years)		Median		37	37	41	40	37
		(IQR)		(29, 44)	(29, 45)	(34, 48)	(31, 50)	(29, 44)
Sex		Male	N (%)	327 (59%)	349 (60%)	16 (38%)	23 (45%)	676 (60%)
		Female		228 (41%)	230 (40%)	26 (62%)	28 (55%)	458 (40%)
HIV Mode of exposure		IDU	N (%)	12 (2%)	9 (2%)	0 (0%)	2 (4%)	21 (2%)
		MSM		225 (41%)	229 (40%)	10 (24%)	8 (16%)	454 (40%)
		Heterosexual		274 (49%)	300 (52%)	27 (64%)	37 (73%)	574 (51%)
		Other		44 (8%)	41 (7%)	5 (12%)	4 (8%)	85 (8%)
Years since		Median		1.2	1.2	2.5	1.7	1.2
HIV diagnosis		(IQR)		(0.4, 3.8)	(0.3, 3.7)	(1.1, 7.8)	(0.4, 6.2)	(0.4, 3.7)
Current CD4		Median		721	700	837	806	715
(cells/μL)		(IQR)		(623, 865)	(615, 845)	(712, 1022)	(667, 972)	(619, 855)
Current CD8		Median		933	921	794	699	927
(cells/μL)		(IQR)		(707, 1233)	(687, 1233)	(578,1024)	(527, 970)	(698, 1233)
				Missing =11		Missing=3		
Race	Black		N (%)	249 (45%)	241 (42%)	26 (62%)	30 (59%)	490 (43%)
	Hispanic			53 (10%)	72 (12%)	2 (5%)	8 (16%)	125 (11%)
	Asian			40 (7%)	39 (7%)	2 (5%)	2 (4%)	79 (7%)
	White			189 (34%)	212 (37%)	11 (26%)	9 (18%)	401 (35%)
	Other			24 (4%)	15 (3%)	1 (2%)	2 (4%)	39 (3%)
Region	NA		N (%)	75 (13%)	83 (14%)	4 (10%)	9 (18%)	158 (14%)
	Europe			133 (24%)	139 (24%)	4 (10%)	8 (16%)	272 (24%)
	SA			129 (23%)	141 (24%)	6 (14%)	9 (18%)	270 (23%)
	Oceania			11 (2%)	6 (1%)	0 (0%)	0 (0%)	17 (2%)
	Asia			36 (6%)	37 (6%)	2 (5%)	2 (4%)	73 (6%)
	Africa			171 (31%)	173 (30%)	26 (62%)	23 (45%)	345 (30%)

		Baseline HIV RNA (c/mL)				
		<3,000		≤50		
		Imm N=555	Def N=579	Imm N=42	Def N=51	Both Imm and Def arms N=1134
HCV	Negative N (%)	521 (95%)	551 (96%)	40 (98%) 4	6 (90%)	1072 (96%)
Antibody	Positive	26 (5%)	24 (4%)	1 (2%)	5 (10%)	50 (4%)
		Missing = 12		Missing=1		
HBsAg	Negative N (%)	528 (97%)	560 (97%)	40 (95%)	48 (94%)	1088 (97%)
	Positive	14 (3%)	15 (3%)	2 (5%)	3 (6%)	29 (3%)
		Missing = 17		Missing = 0		

Percentages are column percent, <50 group is included in the larger ≤3,000 group.

Table 2.

Serious adverse outcomes occuring in participants with enrollment HIV-RNA <3000 c/mL

		N	N patients with event	Total events	Rate	Hazard ratio (95% CI)	p
Grade 4 adverse events	Def	579	17	17	0.97	1.0	
	Imm	555	16	18	0.95	0.97 (0.49, 1.92)	00.935
Death*	Def	579	3	3	0.17	1.0	
	Imm	555	5	5	0.29	1.74 (0.41, 7.25)	0.576
Any hospitalisation	Def	579	56	65	3.34	1.0	
	Imm	555	58	82	3.65	1.09 (0.75, 1.57)	0.648
Any of above combined	Def	579	61	72	3.67	1.0	
	Imm	555	64	90	4.04	1.10, (0.77, 1.56)	0.595

Rate = rate of first events per 100 person years

Hazard ratio is for time to first event