Early Treatment is Likely More Important Than Previously Thought

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Background

- The Strategic Timing of Antiretroviral Treatment (START) trial randomized 4,685 HIV+ adults with CD4+ >500 cells/μL to immediate or deferred (CD4+ <350 cells/μl or development of AIDS) antiretroviral treatment (ART) initiation.[1]
- START demonstrated that early ART for HIV is more beneficial than waiting until CD4+ count drops below 350 cells/μL.[1]
- We examined whether CD4+ count response differed between those recently infected and those infected for a longer duration within the START trial.

Methods

Study Population

- START participants were classified into groups by duration of HIV infection (self-report) or time since HIV diagnosis (documented) at study entry:
  - **Group 1:** recently infected (≤6 months) by self-report or recently infected using a multi-assay algorithm (MAA) based on serologic markers of early infection (n=373)[2]
  - **Group 2:** diagnosis date ≤6 months but recent infection not confirmed by MAA or diagnosis date 6-24 months (n=2,635)
  - **Group 3:** diagnosis date ≥2 years (n=1,605)

MAA Testing

- Stored plasma samples collected at baseline from individuals diagnosed within 6 months prior to study entry were tested by a MAA where subjects had to have a low titer and weak avidity antibodies to HIV, and detectable viral load to be classified as recently infected.[2,3]

Statistical Analysis

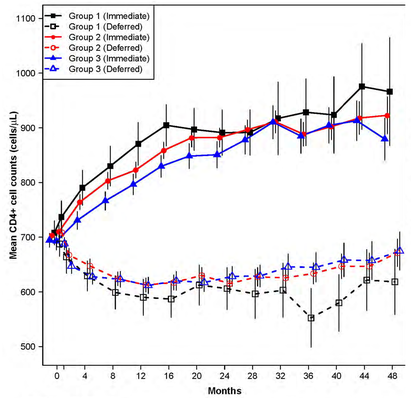
- Baseline characteristics compared between groups using χ^2 test for proportions and Wilcoxon rank sum tests for medians (unadjusted).
- Longitudinal regression was used to compare changes in CD4+ count, CD8+ count, and CD4:CD8 ratio levels during follow-up between the immediate and deferred ART arms by duration of infection (Groups 1-3), adjusting for baseline levels.
- In the deferred arm, time to CD4+ <350 cells/μL or AIDS (threshold for initiating ART) was compared by duration of infection, with and without censoring for ART initiation.

Results

Table 1. Baseline characteristics of individuals within each duration of HIV infection group.

	Group 1 Med[IQR], N(%)	Group 2 Med[IQR], N(%)	Group 3 Med[IQR], N(%)	Overall Med[IQR], N(%)	p-Value
No. Pts	***373***	***2635***	***1605***	***4613***	
Demographics					
Age (years)	31 [25, 40]	34 [28, 42]	40 [33, 46]	36 [29, 44]	<0.001
Gender (female)	41 (11.0)	637 (24.2)	562 (35.0)	1240 (26.9)	<0.001
Race					<0.001
Asian	52 (13.9)	201 (7.6)	130 (8.1)	383 (8.3)	
Black	54 (14.5)	686 (26.0)	647 (40.3)	1387 (30.1)	
Latino/Hispanic	58 (15.5)	396 (15.0)	170 (10.6)	624 (13.5)	
White	191 (51.2)	1253 (47.6)	618 (38.5)	2062 (44.7)	
Other	18 (4.8)	99 (3.8)	40 (2.5)	157 (3.4)	
Geographic Location					0.019
US/Europe/Australia (High)	167 (44.8)	1179 (44.7)	788 (49.1)	2134 (46.3)	
S America/Africa/Asia (Low-Mid)	206 (55.2)	1456 (55.3)	817 (50.9)	2479 (53.7)	
HIV History					
Likely mode of HIV infection					<0.001
Men who have sex with men	281 (75.3)	1556 (59.1)	709 (44.2)	2546 (55.2)	
Heterosexual	69 (18.5)	941 (35.7)	752 (46.9)	1762 (38.2)	
Injection drug use	4 (1.1)	23 (0.9)	36 (2.2)	63 (1.4)	
Blood products/other/unknown	19 (5.1)	115 (4.4)	108 (6.7)	242 (5.2)	
Laboratory Results					
CD4 (cells/μl)	660 [585, 780]	654 [587, 773]	644 [579, 747]	651 [584, 764]	0.008
CD8 (cells/μl)	1018 [764, 1358]	1030 [767, 1368]	1070 [795, 1457]	1040 [776, 1400]	0.004
CD4:CD8 ratio	0.7 [0.5, 0.9]	0.7 [0.5, 0.9]	0.6 [0.4, 0.9]	0.7 [0.5, 0.9]	<0.001
HIV RNA (copies/mL)	27199 [8140, 75431]	13550 [3330, 44103]	9744 [2176, 35769]	12673 [3023, 43053]	<0.001

Results



Group 1, no of participants:
Imm.: 198 194 189 192 191 181 169 131 101 77 62 49 36
Def.: 175 171 163 157 157 145 142 116 98 80 62 49 33

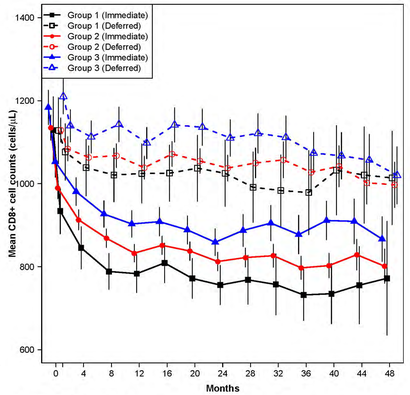
Group 2, no. of participants:
Imm.: 1319 1264 1254 1254 1233 1164 1072 912 780 628 508 398 326
Def.: 1316 1267 1245 1233 1189 1113 1030 851 728 603 477 405 327

Group 3, no. of participants:
Imm.: 777 749 740 731 723 672 588 519 433 357 280 238 208
Def.: 828 798 779 765 742 696 624 544 461 383 281 218 184

Within Group		Between Groups	
	Mean [95% CI] CD4+ difference (Imm-Def) over follow-up, cells/μL		Mean [95% CI] CD4+ difference (Imm-Def) over follow-up, cells/μL
Group 1	230 [198, 263]	Group 1 – Group 2	28 [-6, 63]
Group 2	202 [190, 214]	Group 1 – Group 3	59 [23, 95]
Group 3	171 [156, 187]	Group 2 – Group 3	31 [11, 50]
P-value for treatment arm x HIV infection group interaction (2df): <0.001			

CI: confidence interval

Figure 1. Mean CD4+ cell counts (95% CI) over follow-up for the immediate and deferred ART groups by recent infection group.



Group 1, no of participants:
Imm.: 197 194 188 192 191 180 169 128 101 77 61 49 35
Def.: 174 171 163 158 155 145 143 116 98 80 63 50 33

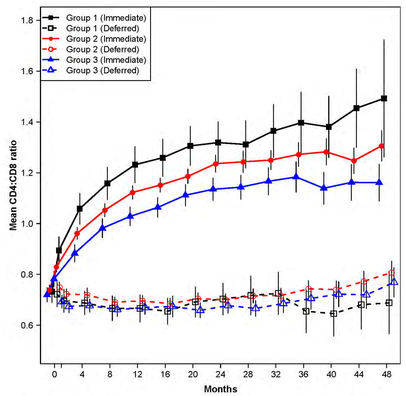
Group 2, no. of participants:
Imm.: 1304 1254 1250 1250 1229 1162 1070 910 779 625 505 397 325
Def.: 1300 1258 1241 1230 1185 1108 1027 849 727 601 476 401 327

Group 3, no. of participants:
Imm.: 765 739 740 731 716 670 587 511 433 356 278 237 207
Def.: 817 789 778 763 738 692 623 538 458 381 279 215 183

Within Group		Between Groups	
	Mean [95% CI] CD8+ difference (Imm-Def) over follow-up, cells/μL		Mean [95% CI] CD8+ difference (Imm-Def) over follow-up, cells/μL
Group 1	-223 [-279, -167]	Group 1 – Group 2	-35 [-94, 25]
Group 2	-188 [-209, -167]	Group 1 – Group 3	-46 [-107,16]
Group 3	-177 [-204, -150]	Group 2 – Group 3	-11 [-45, 23]
P-value for treatment arm x HIV infection group interaction (2df): <0.001			

CI: confidence interval

Figure 2. Mean CD8+ cell counts (95% CI) over follow-up for the immediate and deferred ART groups by recent infection group.



Group 1, no of participants:
Imm.: 197 194 188 192 191 180 169 128 101 77 61 49 35
Def.: 174 171 163 158 154 145 142 116 98 80 62 49 33

Group 2, no. of participants:
Imm.: 1304 1254 1250 1250 1229 1162 1070 909 779 624 505 397 324
Def.: 1300 1258 1241 1230 1185 1108 1027 849 727 601 478 401 326

Group 3, no. of participants:
Imm.: 765 739 740 731 716 670 587 511 433 356 278 237 207
Def.: 817 789 778 762 738 692 621 538 458 381 279 215 183

Within Group		Between Groups	
	Mean [95% CI] CD4:CD8 ratio difference (Imm-Def) over follow-up		Mean [95% CI] CD4:CD8 ratio difference (Imm-Def) over follow-up
Group 1	0.52 [0.46, 0.58]	Group 1 – Group 2	0.12 [0.06, 0.18]
Group 2	0.40 [0.38, 0.42]	Group 1 – Group 3	0.18 [0.12, 0.24]
Group 3	0.34 [0.31, 0.36]	Group 2 – Group 3	0.06 [0.03, 0.10]
P-value for treatment arm x HIV infection group interaction (2df): <0.001			

CI: confidence interval

Figure 3. Mean CD4:CD8 ratio (95% CI) over follow-up for the immediate and deferred ART groups by recent infection group.

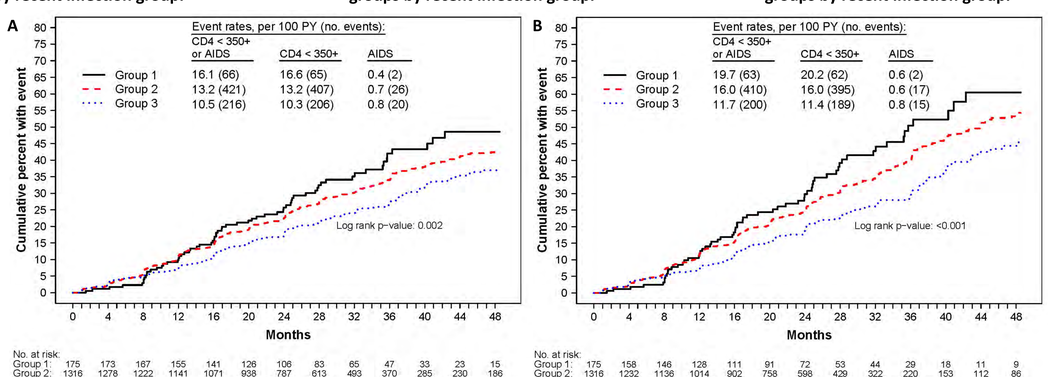


Figure 5. A) Kaplan-Meier plot for time to CD4+ < 350 cells/μl or the development of AIDS in the deferred arm by duration of infection group. The threshold for initiating ART in the deferred arm was reaching a CD4+ < 350 cells/μl or developing AIDS. B) Kaplan-Meier plot for time to CD4+ < 350 cells/μl or AIDS in the deferred arm by duration of infection group, censored when participants initiated ART.

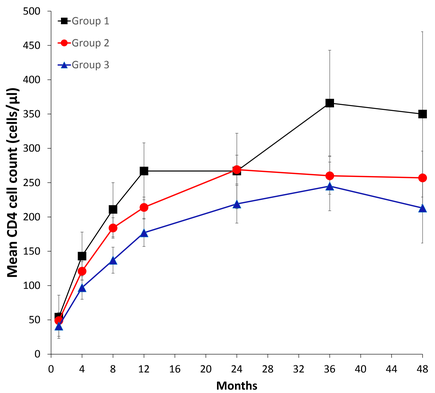


Figure 4. Mean (95% CI) CD4+ cell count difference (immediate minus deferred) over follow-up.

Results

- At entry, individuals in the recently infected (Group 1) were younger than those in Groups 2 and 3 (31 vs 34 vs 40 (years), p<0.001); more likely to be MSM (75% vs 59% vs 44%, p<0.001); and had a higher median baseline HIV RNA than the other two groups (27199 vs 13550 vs 9744 (copies/mL), p<0.001) (Table 1).
- The mean CD4+ difference (immediate minus deferred) over follow-up was significantly greater for those in the recent infection group compared to the two other groups (230 vs 202 and 171 cells/μL; p<0.001) (Figure 2).
- In the deferred arm, time to CD4+ decline to 350 cells/μL or AIDS was faster among those recently infected compared to those who were not (Figure 5).

Summary & Conclusions

- Our results demonstrate that the CD4+ count difference over follow up between the immediate and deferred ART arms was greater among those recently infected. This START subgroup represents the largest trial to date on the effect of early versus deferred ART among recently infected participants.
- Immediate treatment after HIV infection likely has a greater impact than originally observed by the START trial, as selection into the trial required individuals to have two CD4s > 500 cell/μL and those enrolled were less likely to be recently infected and more likely to be individuals with decreased pathogenic progression as measured by CD4+ decline. Long-term follow-up is needed to confirm this.

Acknowledgments

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References

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[3] Konikoff J et al. *Plos One*. Dec 27 2013;8(12):e82772.