Effect of Delayed ART Initiation on Anti-CD4 Autoantibodies in ART-Naïve People With HIV

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BACKGROUND

- We previously identified autoantibodies to the CD4 molecule (anti-CD4 AAb) in antiretroviral therapy (ART)-naïve people with HIV (PWH) with CD4 counts <100 cells/μL, and found that the presence of anti-CD4 AAb was associated with lower CD4 cell counts and slower CD4 recovery after ART initiation.[1]

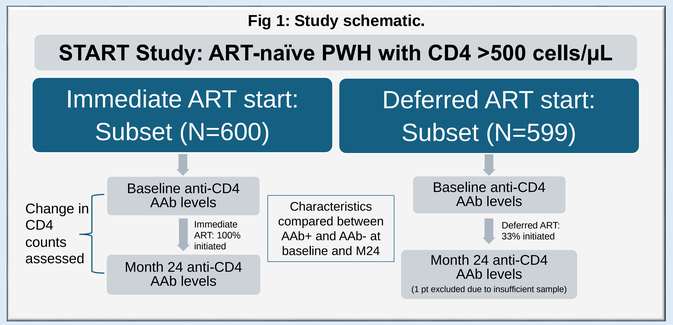
AIMS

- Estimate the prevalence of anti-CD4 AAb over a range of CD4 cell counts >500 cells/μL.
- Estimate the effect of suppressive ART on the prevalence of anti-CD4 AAb in a randomized comparison.
- Assess the effect of anti-CD4 AAb on CD4 recovery in PWH initiating ART with high CD4 cell counts.

METHODS

- In the Strategic Timing of Antiretroviral Treatment (START) trial, ART-naïve PWH with CD4 >500 cells/μL were randomized to immediate ART initiation or deferred (until CD4 <350 cells/μL or AIDS).[2]
- In **a subset of participants (N=1199)**, we measured **anti-CD4 AAb at baseline and month 24 (M24) by luciferase immunoprecipitation systems (LIPS)**[3], defining anti-CD4 seropositivity (**AAb+**) as >25K RLU (*Figs 1&2*). Assays were run in two batches.
- We used multivariate logistic regression models to assess predictors of baseline **AAb+ prevalence and to compare treatment groups for AAb+ at M24**.
- To assess the **effect of AAb+ on CD4 recovery with ART use, we compared the mean change in CD4 count at M24 between baseline AAb+ vs AAb- participants within the immediate arm**.

Fig 1: Study schematic.



Immediate ART initiation decreased the prevalence of anti-CD4 autoantibodies at 24 months compared to deferring ART.

RESULTS

Baseline (ART-naïve)

- **Baseline characteristics were similar between arms:** 1199 participants (600 immediate, 599 deferred); median age 36 yrs, median CD4 count 648 cells/μL; **41% AAb+ at baseline.**
- No difference in AAb+ prevalence by baseline CD4 cell count (p=0.39) (*Fig 2*).
- **Baseline AAb+** was independently **associated with global region and recent (≤6 months) HIV infection**, but not with age, sex, CD4 count, or HIV RNA level (*Fig 3*).

Fig 2: Baseline AAb levels by baseline CD4 count, n=1199. Cut-off of > 25,000 RLU defines AAb+.

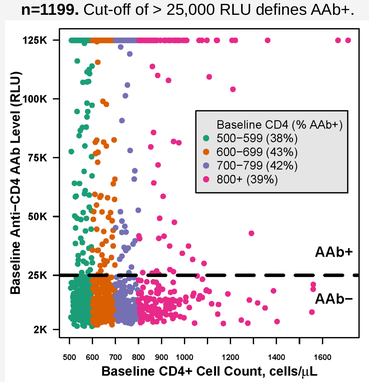


Fig 3: Associations* of baseline factors with AAb+ at baseline.

Factor	N. Grp	N(%) AAb+	Odds Ratio (95% CI)	Pvalue
Female	298	138 (46.3)	1.16	0.36
Male (ref)	901	347 (38.5)		
Africa	212	114 (53.8)	1.88	
Asia	111	50 (45.0)	1.13	
Europe/Israel/Australia (ref)	441	170 (38.5)		0.001
USA	146	43 (29.5)	0.68	
Latin America	289	108 (37.4)	0.89	
HIV infection ≤ 6M	92	60 (65.2)	3.24	<0.001
HIV infection > 6M (ref)	1107	425 (38.4)		
CD4+, per 100 cells/μL incr.	1199		1.01	0.72
HIV RNA, per $\log_{10}$incr.	1199		1.07	0.48

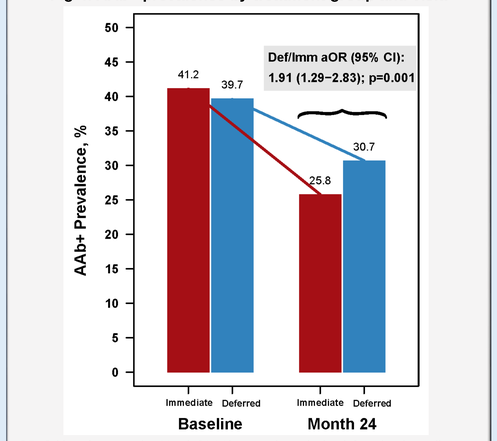
lower prevalence / higher prevalence
0.075 0.25 0.5 1 2 3

*: Multivariate regression model adjusted for all factors listed in Fig 3, plus baseline age (not shown, OR=0.97 per 5 years, p=0.31) and assay batch.

Month 24

- By M24, all participants in the immediate and 33% in the deferred arm had initiated ART.
- Prevalence of **AAb+ at baseline and M24** in the **immediate and deferred arms** are shown in *Fig 4*.

Fig 4: AAb+ prevalence by treatment group and visit.



aOR: Odds ratio comparing Month 24 AAb+ prevalence in the deferred vs immediate treatments groups after adjustment for baseline AAb+, sex, age, HIV subtype, time since HIV diagnosis, baseline CD4 and HIV RNA, and recent HIV infection (within 6 months).

- In those who were **AAb+ at baseline**, **38% (immediate arm) and 29% (deferred) became AAb- at M24 (*Tbl 1*)**.
- In those who were **AAb- at baseline, 0.3% (immediate arm) and 4.4% (deferred) became AAb+ at M24 (*Tbl 1*).**

Tbl 1: Baseline vs. Month 24 cross-tabulation for AAb positivity by treatment group.

		Immediate			Deferred	
		Month 24			Month 24	
Baseline	N	AAb+ N (%)	AAb- N (%)	N	AAb+ N (%)	AAb- N (%)
AAb+	247	154 (62.3)	93 (37.7)	238	168 (70.6)	70 (29.4)
AAb-	353	1 (0.3)	352 (99.7)	361	16 (4.4)	345 (95.6)
Total	600	155	445	599	184	415

- In the immediate arm, **AAb+ decreased from 59% at baseline to 15% at M24 in those with recent HIV infection**, versus from 40% to 27% in other participants (p<0.001 for difference).
- In the immediate arm, *there was* ***no difference in CD4 recovery*** *from baseline to M24* between AAb+ and AAb- participants (mean increase of 203 vs 202 cells/μL, respectively).

CONCLUSIONS

- **Immediate ART initiation decreased the prevalence of anti-CD4 autoantibodies at month 24 compared with deferred ART.**
- When compared to persons with longer duration of HIV infection, **those with recent HIV infection (within 6 months) had an increased prevalence of anti-CD4 autoantibodies at baseline, but a higher proportion reverted to negative** compared to those with longer duration of untreated HIV.
- **Anti-CD4 autoantibody status at baseline was not associated with the rate of CD4 recovery with ART.**
- These findings indicate that **early ART initiation results in reductions in anti-CD4 autoantibodies**, but their potential pathogenic role in people with high CD4 counts remains uncertain.

ACKNOWLEDGEMENTS

We thank the START study participants, investigators, and staff. Funding for START includes NIH Grants UM1-AI068641, UM1-AI120197 and 1U01-AI36780. ClinicalTrials.gov ID: NCT00867048. The START study was supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health Clinical Center, National Cancer Institute, National Heart, Lung, and Blood Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (France), National Health and Medical Research Council (Australia), National Research Foundation (Denmark), Bundesministerium für Bildung und Forschung (Germany), European AIDS Treatment Network, Medical Research Council (United Kingdom), National Institute for Health Research, National Health Service (United Kingdom), and University of Minnesota. Antiretroviral drugs were donated to the START central drug repository by AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, Janssen Scientific Affairs, and Merck. Funding for this analysis was provided in part by the Division of Intramural Research programs of the National Institute of Allergy and Infectious Diseases and the National Institute of Dental and Craniofacial Research.

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