Excess Inflammation Associated with AIDS and Non-AIDS Complications in Adults on ART

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BACKGROUND

- Inflammation and dysregulated coagulation are associated with increased morbidity and mortality among persons living with HIV.[1,2]
- Although antiretroviral treatment (ART) reduces inflammation, it is unclear to what extent prolonged inflammation that accumulated prior to starting treatment (e.g., due to delays in diagnosis) contributes to clinical risk after ART is initiated.

Aims

We studied longitudinal trajectories of interleukin-6 (IL-6) and D-dimer in the START clinical trial in order to:

1. Quantify the duration and amount of excess inflammation due to delaying ART in the deferred group.
2. Investigate the influence of excess inflammation on clinical event risk during viral suppression following delayed or immediate ART initiation.

METHODS

Study Design

- The Strategic Timing of AntiRetroviral Treatment (START) trial (2009-2021) randomized (1:1) persons with HIV who were ART-naïve with CD4>500 cells/μL to either immediate or deferred ART initiation; those in the deferred arm were recommended to initiate ART when their CD4 cell count fell below <350 cells/μL or at disease progression, whichever occurred first.[3]
- On May 26, 2015, the trial results were unblinded; participants in the immediate arm had a reduced risk of the composite of AIDS, serious-non AIDS (SNA), and death events, and all participants were advised to start treatment.[3,4]
- Current analyses include 2209 START participants in the Genomics substudy who had serial biomarker assessments **(Figure 1)**.

Outcome Measures

- IL-6 (ELISA, R&D Systems) and D-dimer (VIDAS, BioMerieux) levels were determined centrally from stored plasma collected at enrollment (baseline), month 8 and annually through 2017.
- The primary clinical outcome was a composite of AIDS events, SNA events, and all-cause deaths, assessed from 2016 to 2021.

Statistical Methods

- IL-6 and D-dimer were summarized as geometric means over two periods:
  1. ***Prior to study unblinding:*** Enrollment (2009-2013) through May 26, 2015.
  2. ***After study unblinding:*** A two-year calendar period (2016-2017) during which both arms were recommended to take ART.
- Longitudinal averages of biomarker levels from enrollment through 2015 were compared between treatment arms using rank-sum tests.
- Quartiles of biomarker levels (averaged within each participant from enrollment through 2015) were determined (pooled across treatment arms).
- Kaplan-Meier curves for time to the composite outcome during 2016-2021 were estimated for the upper quartile (Q4) versus the lower 3 quartiles (Q1-Q3).
- Associations between pre-2016 averaged biomarker levels (Q4 vs Q1-Q3) and the composite clinical outcome during 2016-2021 were estimated using Cox proportional hazards regression models stratified by geographic region.

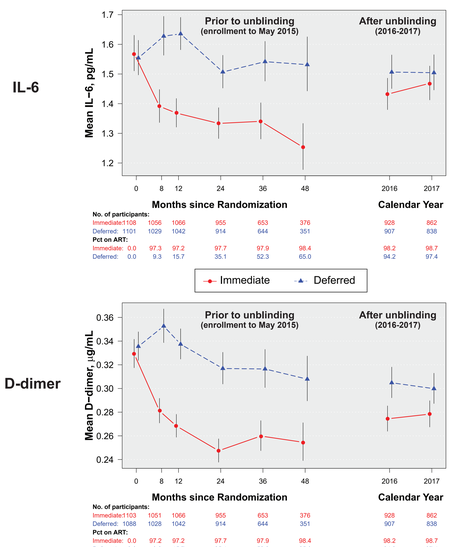
RESULTS

Participant Characteristics, ART Use, and Viral Suppression

- Participant characteristics at study entry are summarized in **Table 1**.
- In the immediate arm, 94-97% were taking ART at each of the annual visits.
- ART use increased in the deferred arm over time (median time to ART start was 2.5 years before unblinding). By January 1, 2016, 87% in the deferred vs. 99% in the immediate arm had started ART, and 79% in the deferred arm had suppressed HIV RNA (≤ 200cp/mL) vs 94% in the immediate arm.

RESULTS, continued

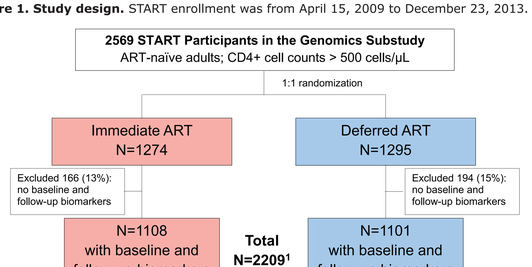
Figure 2. IL-6 and D-dimer levels for time periods before and after study unblinding. Geometric means of IL-6 and D-dimer levels measured from study enrollment through unblinding ("Months since randomization") and after study unblinding (years 2016-2017); vertical lines show +/- 2 SE. Percent of participants on ART (Pct on ART) at each timepoint are also provided.



IL-6 and D-dimer Through Follow-up

- *Prior to study unblinding*: Over a median follow-up of 3.2 years, the deferred compared to the immediate arm had higher averaged biomarker levels **(Figure 2);** median averaged IL-6 1.7 vs 1.5 pg/mL in the immediate vs. deferred arms, respectively; D-dimer 0.33 vs 0.27 mg/mL (both p<0.001).
- *After study unblinding (2016-2017)*: IL-6 and D-dimer levels remained relatively higher in the deferred vs the immediate arms, although this difference diminished from 2016 to 2017 **(Figure 2)**.

Figure 1. Study design. START enrollment was from April 15, 2009 to December 23, 2013.



[1]*Of the 2209 participants, 2114 and 2096 had available IL-6 and D-dimer measures, respectively, prior to 2016, and had follow-up during 2016-2021 to assess associations with clinical events.*

Figure 3. Time to first clinical event. Kaplan-Meier estimates for the cumulative percentage of participants experiencing the composite of AIDS, SNA, or death during 2016-2021 for 4 subgroups: participants in the immediate (red) and deferred arms (blue) with averaged pre-2016 biomarker levels in the upper quartile (Q4, solid) versus combined lower quartiles (Q1-Q3, dashed). Event rates are summarized in Table 2.

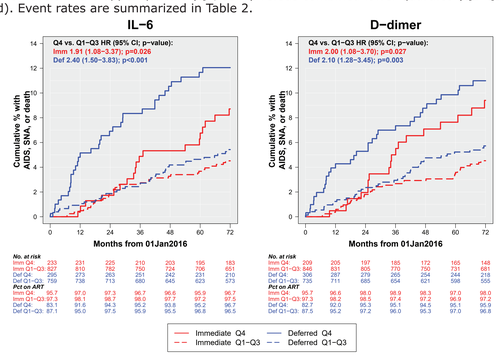


Table 2. Event rates for the composite outcome of AIDS, SNA, or death during 2016-2021 according to averaged biomarker level pre-2016.

	Quartile of pre-2016 average biomarker level	Immediate N	Immediate No. Events (Rate/100PY)	Deferred N	Deferred No. Events (Rate/100PY)
IL-6, pg/mL	Q4 (upper), ≥ 0.444	233	19 (1.49)	295	34 (2.24)
	Q1-Q3, < 0.444	827	35 (0.77)	759	38 (0.93)
D-dimer[1], μg/mL	Q4 (upper), ≥ 2.144	209	18 (1.63)	306	32 (2.01)
	Q1-Q3, <2.144	846	36 (0.77)	735	39 (0.99)

[1]One participant in the deferred arm who experienced an AIDS event did not have D-dimer measures.

AIDS, Serious Non-AIDS, and Death Events

- There were 126 AIDS, SNA, or death events from 2016-2021. The estimated treatment difference in the composite clinical outcome did not reach statistical significance during this period: HR (immediate/deferred) = 0.72 (95% CI 0.51-1.03; p=0.07).
- Higher averaged longitudinal IL-6 and D-dimer levels through 2015 were associated with higher risk of the composite outcome during 2016-2021 in each treatment arm (**Figure 3**, event rates are summarized in **Table 2**):
  - Pooled across treatment arms: HR(Q4 vs Q1-Q3)=2.19 (95% CI 1.53-3.14) for IL-6 (p<0.001) and 2.05 (95% CI 1.39-3.01) for D-dimer (p<0.001).

Table 1. Participant characteristics at study enrollment, N=2209.

Characteristic	Median [IQR] or N(%)
Age (years)	36 [29, 45]
Female sex	443 (20.1)
Race	
Black	494 (22.4)
White	1227 (55.5)
Other (Latino, Asian, Other)	488 (22.1)
Geographic Location	
High income (US, Europe, Australia)	1477 (66.9)
Mid-Low income (Africa, Latin America)	732 (33.1)
Time known to be HIV-positive (years)	1.1 [0.4, 2.9]
CD4+ cell count (cells/μL)	649 [584, 761]
HIV RNA (copies/mL)	14884 [3460, 45100]
IL-6 (pg/mL)	1.47 [1.02, 2.24]
D-dimer (μg/mL)	0.31 [0.22, 0.47]

LIMITATIONS

- Longitudinal trajectories of IL-6 and D-dimer levels may be confounded with assay drift over time; the comparison between the immediate and deferred arms is protected by randomizaion.
- Due to staggered enrollment from 2009-2013, the number of participants with annual biomarker levels prior to unblinding decreased after month 24, which may result in a cohort effect in the longitudinal trajectories in Figure 2.
- Given the modest number of events over 6 years of follow-up (2016-2021), power was limited to assess the impact of preceding inflammation on events that take longer to manifest (e.g., cardiovascular disease, cancer).
- Not all participants in the deferred arm started ART after study unblinding.

CONCLUSIONS

- In START, higher levels of inflammation averaged over follow-up until study unblinding (in 2015) were associated with a subsequent higher risk of AIDS, serious non-AIDS, or death events during a period of 6 years of continuous ART, within both the immediate and the deferred treatment arms.
- Compared to immediate ART initiation, ART deferral resulted in higher levels of systemic inflammation during follow-up in START.
- Our findings emphasize the need to diagnose HIV earlier, which can facilitate earlier initiation of ART, and thus shorten the duration of viremia that may contribute to future inflammation-associated adverse clinical events.

In START, ART deferral resulted in higher levels of inflammation, which may have contributed to higher events rates in the deferred arm that extended after ART-induced viral suppression.

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