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Benefit of continuous/immediate ART on disease risk: SMART & START combined analysis

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INTRODUCTION

- The Strategies for Management of Antiretroviral Therapy (SMART)[1] and Strategic Timing of AntiRetroviral Treatment (START)[2] studies were the seminal trials to establish continuous/immediate antiretroviral therapy (ART) as the standard of care for HIV+ persons.
- Each trial was halted prematurely before the pre-calculated number of endpoints was reached.

HYPOTHESIS

- Treatment differences (hazard ratios) are similar in each study and the pooled analysis will better quantify immediate/continuous ART use in reducing risk of individual clinical outcomes:
- AIDS or AIDS death
- Serious non-AIDS (SNA) including cardiovascular disease (CVD), non-AIDS cancer, end stange renal disease, decompensated liver disease and non-AIDS death
- CVD including myocardial infarction, stroke, coronary revascularization and CVD death
- AIDS and non-AIDS cancer
- All-cause death

METHODS

- **SMART[1]:** Randomised controlled trial (RCT) of 5,472 HIV+ persons with CD4$^+$ > 350 cells/mm^3 at baseline that compared continuous use of ART (Viral Suppression arm) with structured treatment interruptions guided by CD4$^+$ cell count (Drug Conservation arm) **(Table 1, Figure 1)**.
- **START[2]**: RCT of 4,685 HIV+ ART naive persons with CD4$^+$ > 500 cells/mm^3 at baseline that compared immediate ART initiation (Immediate ART arm) with deferred initiation until CD4$^+$ cell counts dropped below 350 cells/mm^3 or development of AIDS (Deferred ART arm) **(Table 1, Figure 1)**.
- **Pooled treatment groups (Figure 1)**: SMART and START were combined to created two treatment groups:
  - **Immune Impairment group (IIG):** SMART Drug Conservation (DC) + START Deferred ART (DEF) arms
  - **Immune Preservation group (IPG):** SMART Viral Suppression (VS) + START Immediate ART (IMM) arms

STATISTICAL ANALYSES

- Definitions of clinical outcomes were harmonised in SMART and START to match those in START
- Hazards ratios (HRs) for IIG vs IPG were obtained from Cox models for each outcome, stratifying by study; heterogeneity across studies assessed with interaction terms.
- Cancers were grouped by infection-related or infection-unrelated causes and IIG vs IPG HRs were estimated for each cancer grouping in a single Cox model stratified by type of cancer (infection-related or infection-unrelated) and study.
- To assess consistency of results, we performed subgroup analyses based on demographics, CVD and cancer risk factors, CD4 count, CD4:CD8 ratio and geographical location.

Table 1 Baseline Characteristics

	START	SMART	Overall
No. pts	**4685**	**5472**	**10157**
Median age (IQR)	36	43	40 (33 - 48)
Female (%)	26.8	27.2	27.0
High income region[a] (%)	46.0	85.6	67.3
Median years since HIV diagnosis (IQR)	1	8	4 (1 - 9)
Median CD4 (IQR)	651	597	634 (539 - 776)
Median nadir CD4 (IQR)	553	250	418 (237 - 558)
Median CD4:CD8 ratio[b] (IQR)	0.66	0.68	0.67 (0.48 – 0.93)
Median HIV RNA (IQR)	12759	80	1568 (50 - 19270)
HIV RNA ≤ 400 copies/mL (%)	7.9	71.7	42.3
On ART at baseline (%)	0.0	84.0	45.2
ART naive (%)	100.0	4.6	48.6
Current smoker (%)	31.9	40.5	36.5
Hepatitis B/C coinfection (%)	6.3	17.0	12.1

[a] High income region = North America, Europe and Australia; low-middle income = Latin America, Africa, and Asia
[b] CD4:CD8 ratio available for 2835 participants in SMART
Note: Except for female gender, all baseline characteristics significantly different between the two studies.

Figure 1 Study Design

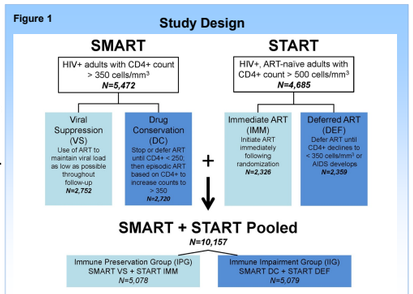
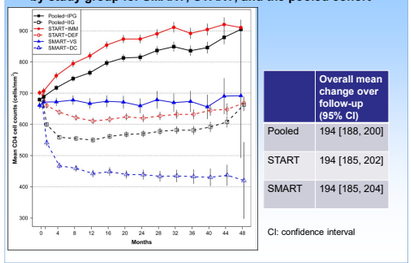


Figure 2 Mean CD4 cell counts (95% CI) over follow-up; by study group for SMART, START, and the pooled cohort



	Overall mean change over follow-up (95% CI)
Pooled	194 [188, 200]
START	194 [185, 202]
SMART	194 [185, 204]

CI: confidence interval

RESULTS

- Among 10,157 participants (median age 40y; 27% female; 51% MSM; median baseline CD4$^+$ 634 cells/mm^3 ; 37% smokers) (Table 1), there were 123 AIDS or AIDS-deaths, 244 SNA or non-AIDS deaths, 117 cancers, 103 CVD, 118 deaths, for a total of 359 AIDS , SNA or death events.
- Nadir median CD4$^+$ counts in SMART and START were 250 and 553 cells/mm^3, respectively (Table 1).
- During follow-up, the overall mean (95% CI) CD4$^+$ cell count was 194 (188-200) cells/mm^3 higher in the IPG group than the IIG group (**Figure 2**).
- When compared to the IIG arm, the IPG arm reached virologic suppression more quickly and remained so during most of the follow up (**Figure 3**).
- HRs for outcomes were similar in both trials (p-value for heterogeneity ≥ 0.08 for all events) (**Figure 4**).
- The HR (95%CI) of IIG/IPG for infection-related cancer was 2.3 (1.3-4.3), p=0.006 compared to 1.6 (1.0-2.6), p=0.06 for infection unrelated cancers. P-value comparing the HRs for infection-related versus infection-unrelated cancer was 0.34.
- Adjustment for time-updated CD4 and HIV RNA attenuated the pooled HRs for SNA and death (not shown).
- IIG was consistently associated with increased risk for AIDS and SNA endpoints across all subgroups investigated (interaction p>0.1) (**Figure 5**), except that the risk of cancer associated with IIG was higher among those ≤ 35 years (p=0.05).

CONCLUSIONS

- A strategy of immune preservation, consisting of immediate and continuous ART use, reduces the risk of AIDS and non-AIDS-defining events during HIV infection.
- Disease risk relative reductions for immune preservation are consistent despite a difference in nadir CD4$^+$ counts of 300 cells/μL
- Risk reduction did not vary by type of cancer.
- Pooled treatment differences are similar across the subgroups investigated.

REFERENCES:
1)SMART Study Group. NEJM 2006 Nov 30;355(22):2283-96;
2)START Study Group. 2015 Aug 27;373(9):795-807

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Figure 3 Percent of participants with HIV RNA ≤ 400 copies/mL over follow-up; by study group for SMART, START, and the pooled cohort

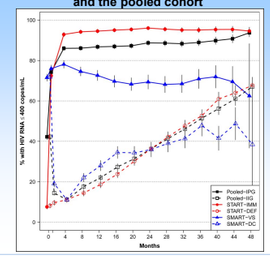
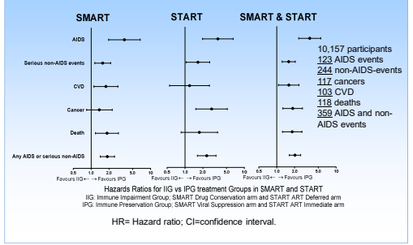
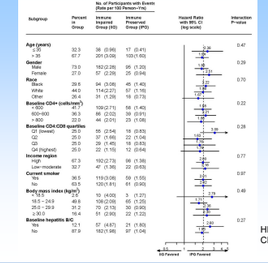


Figure 4 HRs (95% CI) comparing the treatment groups within SMART and START separately and comparing the IIG vs. IPG groups within the pooled cohort



HR= Hazard ratio; CI=confidence interval.

Figure 5 Subgroup analyses for AIDS, SNA or death events; HRs (95% CI) comparing IIG vs. IPG groups within the pooled cohort



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