Title: The effect of interrupted/deferred antiretroviral therapy on disease risk: a SMART & START combined analysis

Authors: Álvaro H Borges[1], Jacqueline Neuhaus[2], Shweta Sharma[2], James D Neaton[2], Keith Henry[3], Olga Anagnostou[4], Teresa Staub[5], Sean Emery[6] and Jens D Lundgren[1] for the INSIGHT SMART & START Study Groups.

Affiliations:

1. Center of Excellence for Health, Infections & Immunity (CHIP), Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
2. Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA
3. Hennepin County Medical Center, Minneapolis, Minnesota, USA
4. University of Athens, Greece
5. Centre Hospitalier de Luxembourg, Service des Maladies Infectieuses, Luxembourg
6. Faculty of Medicine, University of Queensland, Brisbane, Australia

Corresponding author: Álvaro H. Borges MD MSc PhD at CHIP, Department of Infectious Diseases, section 2100, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark. Fax: +45 3545 5758. Tel: +45 3545 5785. Email: alvaro.borges@regionh.dk

Alternate corresponding author: Jens D Lundgren MD DMSc, Department of Infectious Diseases, section 2100, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark. Email: jens.lundgren@regionh.dk

Summary: By pooling SMART/START data, we found that a randomized strategy of interrupted/deferred ART increases the hazard of AIDS by 3.6, SNA by 1.6, and the composite of AIDS, SNA or death by 2.1.

Abstract:

Background: Pooled data from SMART and START were used to compare deferred/intermittent versus immediate/continuous antiretroviral therapy (ART) on disease risk.

Methods: Endpoints assessed were AIDS, serious non-AIDS (SNA), cardiovascular disease (CVD), cancer, and death. Pooled (stratified by study) hazard ratios (HRs) from Cox models were obtained for deferred/intermittent ART vs immediate/continuous ART; analyses were conducted to assess consistency of HRs across baseline-defined subgroups.

Results: Among 10156 participants, there were 124 AIDS, 247 SNA, 117 cancers, 103 CVD and 120 deaths. Interventions in each trial led to similar differences in CD4 count and viral suppression Pooled HRs (95% CI) of deferred/intermittent ART vs immediate/continuous ART were for AIDS 3.63 (2.37, 5.56); SNA 1.62 (1.25-2.09); CVD 1.59 (1.07-2.37); cancer 1.93 (1.32-2.83); and death 1.80 (1.24-2.61). Underlying risk was greater in SMART than START. Given the similar HRs for each study, absolute risk differences between treatment groups were greater in SMART than START. Pooled HRs were similar across subgroups.

Conclusions: Treatment group differences in CD4 count and viral suppression were similar in SMART and START. Likely as a consequence, relative differences in risk of AIDS and SNA between immediate/continuous ART and deferred/intermittent ART were similar.

Key words: antiretroviral therapy, AIDS, cardiovascular disease, cancer, HIV

Introduction

The Strategies for Management of Antiretroviral Therapy (SMART) [1] and Strategic Timing of AntiRetroviral Treatment (START) [2] studies were the seminal trials to assess the effect of antiretroviral therapy (ART) treatment strategies on risk of both AIDS- and non-AIDS-defining events. These two studies, together with other trials [3,4], established continuous/immediate ART as the standard of care for HIV+ persons.

SMART and START were halted prematurely, by the respective data safety monitoring boards for each trial, before the target numbers of primary endpoints were reached. Therefore, each trial had a limited ability to quantify variation in risk of some outcomes such as cardiovascular disease (CVD) and cancer. To address this, we conducted a pooled analysis of the two trials in which we compared the drug conservation arm in SMART and the deferred ART arm in START(the "deferred/intermittent ART group") with the viral suppression arm in SMART and the immediate ART arm in START (the "immediate/continuous ART group"). We hypothesized that treatment hazard ratios would be similar in each study and that the pooled analysis would better quantify the relative difference between interrupted/deferred ART and continuous/immediate ART on risk of AIDS- and non-AIDS-defining events.

Methods

SMART (NCT00027352) was a randomized controlled trial of 5,472 HIV+ persons with $CD4^+$ > 350 cells/μL at baseline that compared continuous use of ART (viral suppression arm-VS) with structured treatment interruptions until the $CD4^+$ cell count declined to less than 250 cells/μL (drug conservation arm-DC) [1] (Figure 1). Recruitment occurred from January 2002 to January 2006, and the study was unblinded in January 2006 before the

planned enrolment was achieved. START (NCT00867048) was a randomized trial of 4,684 HIV+ ART naive persons with $CD4^+$ > 500 cells/μL at baseline that compared immediate ART initiation (immediate ART arm-IMM) with deferred ART initiation until $CD4^+$ cell counts dropped below 350 cells/μL or development of AIDS (deferred ART arm-DEF) [2] (Figure 1). The study enrolled from April 2009 to December 2013 and was unblinded in May 2015.

SMART and START were conducted in compliance with the Declaration of Helsinki Guidelines, were registered on clinical trial databases and reviewed by independent data and safety interim monitoring boards. An institutional review board/ethics committee at each study site approved the study protocol, and written informed consent was obtained from all participants.

A design schematic for the comparison of the "deferred/intermittent ART group" with the "immediate/continuous ART group" is illustrated in Figure 1. Follow-up was censored at the last known alive date or study unblinding (11 January 2006 for SMART and 25 May 2015 for START), whichever occurred first. Definitions of AIDS and serious non-AIDS (SNA) were harmonized in SMART and START to match those in START [2,5]. Individual events comprising these composite outcomes were defined similarly [6-8]. The adjudicated clinical outcomes considered in this report were: a) AIDS or AIDS death; b) serious non-AIDS (SNA) including CVD, non-AIDS cancer, end stage renal disease, decompensated liver disease and non-AIDS death; c) CVD including myocardial infarction, stroke, coronary revascularization and CVD death; d) AIDS and non-AIDS, infection-related and -unrelated cancer and cancer death; and e) all-cause death. Causes of death were coded using CoDe [9]. Cancer classification as infection-related or infection-unrelated was on the basis of individual review of case report forms and source documentation. Infection-related

cancer was defined as cancer driven by the following infectious agents: human herpesvirus 8 (HHV-8) (Kaposi sarcoma), Epstein-Barr virus (EBV) (non-Hodgkin lymphoma, Hodgkin lymphoma), human papilloma virus (HPV) (anal cancer, cervical cancer) [10-12]. All other malignancies were classified as infection-unrelated cancer.

Hazards ratios (HRs) for deferred/intermittent ART vs immediate/continuous ART were obtained from Cox models with a single indicator for treatment group for each trial separately. Pooled HRs were estimated from Cox models, stratified by study (SMART vs. START), that included a single indicator variable for deferred/intermittent ART vs immediate/continuous ART. Heterogeneity of HRs between SMART and START were assessed from models that included an interaction term between the pooled treatment group (deferred/intermittent ART vs immediate/continuous ART) and an indicator for study. HRs for deferred/intermittent ART vs immediate/continuous ART were estimated for each cancer grouping (infection-related or infection-unrelated) in a Cox model that considered multiple events per participant [13]. To assess consistency of results across baseline-defined subgroups defined by age, gender, race, $CD4^+$ count, CD4:CD8 ratio, income region, smoking status, body mass index, hepatitis B/C co-infection, D-dimer, and IL-6 levels, expanded Cox models that included interaction terms for the baseline subgrouping variable and the pooled treatment indicator were used.

In the analyses that compare HRs for SMART and START and in the subgroup analyses of the pooled HRs by baseline subgroups, the interaction p-values should be viewed cautiously. Multiple endpoints are considered in the comparisons of SMART with START and multiple baseline subgroups were considered for the pooled HR. This increases the risk of a type 1 error. Also, the interaction test lacks power, and for many outcomes the number of events is small so there is a risk of a type 2 error.

Changes in CD4 cell count from baseline through follow-up between the deferred/intermittent ART and immediate/continuous ART groups (within each trial and pooled) were compared using longitudinal mixed models with random intercepts. Viral suppression, defined as HIV RNA ≤ 400 copies/mL, was plotted over time, and the percent of follow-up time with viral suppression was estimated

Analyses were performed with SAS, version 9.3 (SAS Institute, Cary, NC). P-values are 2-sided and values ≤0.05 were considered significant. No adjustments were made for multiple comparisons.

Results

10,156 participants, 4,684 from START and 5,472 from SMART, were included (median age 40y; 27% female; 51% MSM; median baseline $CD4^+$ 634 cells/μL; 37% smokers) (Table 1). Except for gender distribution, SMART and START participants differed markedly in terms of demographics, HIV-specific variables, hepatitis co-infection, smoking and ART (Table 1). Median nadir $CD4^+$ count was 250 cells/μL in SMART and 553 cells/μL in START. SMART participants were also older and the majority (84%) were receiving ART at baseline (Table 1). Median (interquartile range) follow-up was 1.0 (0.4, 2.1) years in SMART and 3.0 (2.2, 4.1) years in START.

During follow-up, the mean (95% CI) $CD4^+$ cell count was 194 (187-200) cells/μL higher in the immediate/continuous ART group than the deferred/intermittent ART group (Figure 2). The average CD4+ count difference between treatment groups in SMART and START

were identical, each was194 cells/μL The treatment differences in CD4 counts between deferred/intermittent ART group and immediate/continuous ART group became clear 8 months after randomization and remained so throughout follow up (Figure 2).

Compared to the deferred/intermittent ART group, the immediate/continuous ART group had a great proportion of participants with an HIV RNA level ≤ 400 copies/mL for more of the follow up period (Figure 3). The percent of follow-up time spent with a viral load < 400 copies/mL was 84.2% in the immediate/continuous ART group compared to 33.3% in the deferred/intermittent ART group. Similar differences were seen in each study (30.6% vs. 89.2% in the DEF vs IMM arms of START; 38.7% vs. 74.1% in the DC vs. VS arms of SMART).

During 22,103 person-years of follow up, there were 124 AIDS events (fatal or non-fatal), 247 SNA or non-AIDS deaths, and 363 AIDS, SNA or death events. Pooled HRs (95% CI) of deferred/intermittent ART group vs immediate/continuous ART group were 3.63 (2.37-5.56) for AIDS, 1.62 (1.25-2.09) for SNA, and 2.06 (1.65-2.56) for the composite of AIDS, SNA or death (Figure 4). The SMART and START HRs for these outcomes were very similar, 3.63 and 3.62 for AIDS (p=0.99 for interaction), 1.74 and 1.56 for SNA (p=0.71), and 2.40 and 1.87 (p=0.28) for the composite of AIDS, SNA or death.

For both AIDS and SNA, event rates were much higher in SMART than START. Coupled with the similar HRs, that resulted in absolute risk differences much larger for SMART than START (0.92 versus 0.50 per 100 person years for AIDS and 1.03 versus 0.28 per 100 person years for SNA). There is greater heterogeneity between the SMART and START HRs for CVD and cancer (p-values for interaction are 0.37 and 0.046, respectively). In both trials, the pooled HRs are significantly greater than 1.0: 1.59 (1.07-

2.37) for CVD and 1.93 (1.32-2.83) for cancer. The pooled HR for death was 1.79 (1.24-2.61).

The HR (95%CI) of deferred/intermittent ART group vs immediate/continuous ART group for infection-related cancer was 2.3 (1.3-4.3), p=0.006, compared to 1.7 (1.0-2.8), p=0.04, for infection-unrelated cancer. P-value comparing the HRs for infection-related versus infection-unrelated cancer was 0.43.

.

Discussion

We pooled data from two landmark global HIV trials and found that a randomized strategy consisting of deferred/intermittent ART, increases the hazard of AIDS by 3.6, SNA by 1.6, and for the composite outcome of AIDS, SNA or death by 2.1 compared to immediate/continuous ART. Pooled treatment differences were similar across the subgroups investigated. The present study is the best randomized evidence that a strategy of deferred/intermittent ARTleads to an increased risk of AIDS-defining and serious non-AIDS-defining conditions.

Compared with START participants, SMART participants were older, had lower nadir CD4 counts, lower follow-up CD4+ counts, and had been diagnosed with HIV for a much longer period of time. As a consequence of these and other, as yet unknown differences, event rates were much higher in SMART as compared to START. The similar relative differences in risk for the two studies coupled with the higher event in SMART resulted in much greater absolute risk differences in SMART compared to SMART.

Our findings indicate that the relative vulnerability to develop immunodeficiency-related phenotypes is not affected by the degree of prior immunodeficiency. It appears that the relative effect of ART on disease risk is determined by the same factors irrespective of when ART is initiated. Interventions in SMART and START led to similar differences in $CD4^+$ cell count and viral suppression, and these differences likely led to the similar HRs for the two studies. With respect to $CD4^+$ cell counts, shifting the distribution from a mean of about 650 to 450 cells/μL during follow-up had the same impact on relative risk of AIDS and SNA as shifting it from 850 to 650 cells/μL (Figure 2).

Differences between SMART and START regarding cardiovascular outcomes have attracted interest from HIV researchers [14,15]. ART interruptions in SMART led to a 70% increased CVD risk [1]; whereas in START no significant differences in CVD risk [2] or surrogate markers of atherosclerosis [16,17] were observed. Hunt et al hypothesized that the much lower nadir $CD4^+$ counts of SMART participants, resulting from later ART initiation, were associated with a deeper perturbation of inflammatory-related pathways which, in turn, could drive a spectrum of end-organ diseases and cancers differently from that observed among START participants with higher nadir $CD4^+$ counts [14]. It is also possible, as the p-value for interaction suggests, that the difference in HRs between the two trials for CVD is due to chance.

We have observed that the increased CVD risk for the deferred/intermittent ART group compared to the immediate/continuous ART group was consistent, without evidence of heterogeneity between SMART and START, despite a difference in nadir $CD4^+$ counts of 300 cells/μL. However, observed HRs for CVD were numerically different in each trial (1.18 for START versus 1.77 in SMART). Lower HRs for START may have reflected the

small number of CVD events and insufficient power to detect significant differences in risk. Follow up was short in START and participants had an inherent low cardiovascular risk at study entry. Efforts are underway to extend follow up among START participants until 2021. This will allow us to determine with accuracy HRs for CVD events in the future. Higher levels of inflammation and coagulation markers measured at study entry were significantly associated with subsequent CVD risk both among SMART [18] and START participants [17]. The definition of CVD, as a part of the composite endpoint for each trial, was virtually the same. Hence, we believe that the variation in absolute CVD risk between SMART and START likely reflects differences in prevalent risk factors between the two study populations. For instance, SMART participants were older, had a higher prevalence of traditional CVD risk factors and received more toxic and old-fashioned ART regimens than START participants.

The impact of continuous ART in SMART [19] and immediate ART in START [12] in reducing the risk of infection-related cancer was significant and comparable between the two studies. As for infection-unrelated cancer, it remained unclear whether the non-significant reduction in risk in both studies [12,19] reflected limited power. The present pooled analysis combining START and SMART had enough statistical power to better estimate the impact of ART strategies on the risk of infection-unrelated cancer than each study separately. The significant increase in risk associated with deferred/intermittent ART did not vary by type of cancer, and was consistently observed for infection-related and -unrelated cancer (P=0.43).

In a previous report, we showed that the benefit of ART in reducing cancer risk was not entirely attributable to HIV RNA suppression [12]. Possible mediators of ART benefit could

have been a curb on oncogenic virus coinfection and/or reduction of inflammation [12,20]. Enhanced inflammation and coagulation, as demonstrated by higher levels of IL-6 and D-dimer, was associated with higher risk of cancer (both infection-related and -unrelated) among SMART participants [11]. In START, however, these biomarkers did not predict cancer risk [18]. The interplay between ART, inflammation and cancer risk is therefore complex; further research is needed to identify mediators of the benefit of immediate/continuous ART in reducing cancer risk.

Our study has limitations to be acknowledged. First, SMART and START were distinct clinical experiments testing different ART strategies in study populations with dissimilar underlying risk profiles. Still, a pooled analysis of SMART and START seemed to us justified given the similar outcomes in deferred/intermittent ART vs immediate/continuous ART (Figure 4) and the larger number of individual endpoints for a better risk estimation. Second, the number of rare but very clinically relevant outcomes such as end-stage renal and liver diseases was too small to allow risk estimation. As a result, these heterogeneous outcomes had to be combined as SNA. With respect to cancer and CVD, however, our analyses had more power. Third, START recruited participants from low-resource settings with limited the diagnostic capacity. It is possible that some outcomes, such as myocardial infarction, might have been under-diagnosed. Fourth, we did not present pooled data on ART-related complications because events were collected differently in each trial. In SMART, there were more grade 4 events in DC than VS arm (173 vs 148; p=0.13). Similarly, there were more events for a composite of grade 4 or death in DC than VS a (205 vs 164; p=0.03) [1]. In START, we collected and reported grade 4 events and unscheduled hospitalizations as separate item [2,5]. Like SMART, there were fewer of these events in the immediate ART arm. For the composite of grade 4, unscheduled

hospitalization or death there 283 participants with at least one event in the immediate group and 311 in the deferred group (p=0.25). On the basis of these results, one can infer that no increased toxicity should be expected from immediate/continuous ART compared to deferred/intermittent ART.

To conclude, compared to a strategy of immediate/continuous ART, a strategy of deferred/intermittent ART, increased the risk of AIDS and SNA events among HIV+ persons consistently in SMART and START. Interventions in SMART and START led to similar absolute differences in mean $CD4^+$ cell count and percentage with viral suppression which in turn led to similar relative risk estimates for AIDS and SNA in each study. Pooled treatment differences for the composite outcome of AIDS, SNA, or death were similar across a number of subgroups.

Acknowledgments

This study was funded by NIH [grant numbers: U01AI068641, U01AI042170 and U01AI46362 (SMART); UM1-AI068641 and UM1-AI120197 (START)]. START was supported by the National Institute of Allergy and Infectious Diseases (United States), Agence Nationale de Recherches sur le SIDA et les Hipatites Virales (France), National Health and Medical Research Council (Australia), Danish National Research Foundation (Denmark), Bundes ministerium 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 the University of Minnesota. Antiretroviral drugs were donated to the central drug repository by AbbVie,

Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, Janssen Scientific Affairs, and Merck.

The present study was also supported by the Research Council at Rigshospitalet and by the Danish National Research Foundation (grant DNRF126). AHB is supported by Lundbeckfonden (R219-2016-762).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript.

We would like to thank the SMART and START investigators and participants. See N Engl J Med 2006; 355:2283-96 for the complete list of SMART investigators and N Engl J Med 2015; 373:795-807 (supplementary material) for the complete list of START investigators.

AHB, JN, SS, JDN and JDL conceived the study. JN and SS performed the statistical analyses. AHB drafted the manuscript. All authors contributed to data interpretation, critically revised the manuscript and approved the final version.

This study was presented in part at the 24th Conference on Retroviruses and Opportunistic Infections, 13-16 February 2017, Seattle. Abstract 474

Conflicts of interest

The authors have no conflicts of interest to declare.

List of Tables and Figures

Table1: Baseline characteristics

Figures

Figure 1: Study Design

ART=antiretroviral therapy; DC: drug conservation; DEF=deferred; deferred/intermittent ART group; IMM=immediate; immediate/continuous ART group; SMART: Strategies for Management of Antiretroviral Therapy; START=Strategic Timing of Antiretroviral Treatment; VS=viral suppression

Figure 2: Mean CD4 cell counts over follow-up by treatment group for START, SMART, and the pooled deferred/intermittent and immediate/continuous ART groups.

Figure 2 legend: The vertical lines around the data points represent the 95% confidence interval (CI). Figure is truncated at 48 months. The table within the figure presents the mean CD4 cell count difference (with 95% CI) over follow-up between the immediate and deferred groups in START, the viral suppression and drug conservation groups in SMART, and the pooled immediate/continuous and deferred/intermittent ART groups.

DC: drug conservation; DEF=deferred; deferred/intermittent ART group; IMM=immediate; immediate/continuous ART group; SMART: Strategies for Management of Antiretroviral Therapy; START=Strategic Timing of Antiretroviral Treatment; VS=viral suppression

Figure 3: Percent of participants with HIV RNA ≤ 400 copies/mL over follow-up, by treatment group for START, SMART, and the pooled deferred/intermittent and

immediate/continuous ART groups. Figure 3 Legend: Figure is truncated at 48 months. DC: drug conservation; DEF=deferred; IMM=immediate; immediate/continuous ART group; START=Strategic Timing of Antiretroviral Treatment; VS=viral suppression

Figure 4: HRs (95% CI) comparing event risk by treatment group within START and SMART separately, and between the pooled deferred/intermittent and immediate/continuous ART groups.

Figure 4 legend: The p-value for interaction is comparing the HR for each event between the deferred vs. immediate group within START to the HR for the same event between the viral suppression vs. drug conservation group within SMART.

CI: confidence interval, CVD: cardiovascular disease; HR: hazard ratio; SMART: Strategies for Management of Antiretroviral Therapy; SNA: serious non-AIDS; START=Strategic Timing of Antiretroviral Treatment

Figure 5: Subgroup analyses for the composite endpoint of AIDS, SNA or death events; HRs (95% CI) comparing the deferred/intermittent ART group vs. immediate/continuous ART group within the pooled cohort.

Figure 5 Legend: For subgroups of age, CD4 cell count, CD4:CD8 ratio, body mass index, D-dimer, and IL-6, the continuous variables were used for the interaction tests. . Baseline CD4:CD8 ratio, hepatitis B/C co-infection, D-dimer and IL-6 were not available for all participants; HRs within subgroups for these measures were computed using participants with available baseline data.

CI: confidence interval, HR: hazard ratio; deferred/intermittent ART group; immediate/continuous ART group

References

1. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med **2006**; 355:2283-96.
2. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med **2015**; 373:795-807.
3. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med **2015**; 373:808-22.
4. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med **2016**; 375:830-9.
5. Babiker AG, Emery S, Fätkenheuer G, et al. Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. Clin Trials **2013**; 10(1 Suppl):S5-S36.
6. Lifson AR, Rhame FS, Belloso WH, et al. Reporting and evaluation of HIV-related clinical endpoints in two multicenter international clinical trials. HIV Clin Trials **2006**; 7: 125-141.
7. Lifson AR; INSIGHT Cause of Death Writing Group, Belloso WH, et al. Determination of the underlying cause of death in three multicenter international HIV clinical trials. HIV Clin Trials **2009**; 9: 177-185.

8. Lifson AR; INSIGHT Endpoint Review Committee Writing Group, Belloso WH, et al. Development of diagnostic criteria for serious non-AIDS events in HIV clinical trials. HIV Clin Trials **2010**; 11:205-219.
9. Kowalska JD, Friis-Møller N, Kirk O, et al. The Coding Causes of Death in HIV (CoDe) Project: initial results and evaluation of methodology. Epidemiology **2011**; 22:516-23.
10. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol **2009**; 10:321-2.
11. Borges ÁH, Silverberg MJ, Wentworth D, et al. Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers. AIDS **2013**; 27:1433-41.
12. Borges ÁH, Neuhaus J, Babiker AG, et al. Immediate Antiretroviral Therapy Reduces Risk of Infection-Related Cancer During Early HIV Infection. Clin Infect Dis **2016**; 63:1668-1676.
13. Wei L J, Lin D Y, Weissfeld L. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distribution. J Am Stat Assoc **1989**; 84:1065–1073.
14. Hunt PW, Lee SA, Siedner MJ. Immunologic Biomarkers, Morbidity, and Mortality in Treated HIV Infection. J Infect Dis **2016**; 214(Suppl 2):S44-50.
15. Siedner MJ. START or SMART? Timing of Antiretroviral Therapy Initiation and Cardiovascular Risk for People With Human Immunodeficiency Virus Infection. Open Forum Infect Dis **2016**; 3:ofw032.
16. Baker JV, Sharma S, Achhra AC, et al. Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among

HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial. J Am Heart Assoc **2017**; 6(5): e004987.

17. Baker JV, Hullsiek KH, Engen NW, et al. Early Antiretroviral Therapy at High CD4 Counts Does Not Improve Arterial Elasticity: A Substudy of the Strategic Timing of AntiRetroviral Treatment (START) Trial. Open Forum Infect Dis **2016**; 3:ofw213.
18. Baker JV, Sharma S, Grund B, et al. Systemic Inflammation, Coagulation, and Clinical Risk in the START Trial. Open Forum Infect Dis **2017**; 4:ofx262.
19. Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. AIDS **2007**; 21:1957-1963.
20. Borges ÁH. Combination antiretroviral therapy and cancer risk. Curr Opin HIV AIDS **2017**; 12:12-19.

Table 1: Baseline characteristics

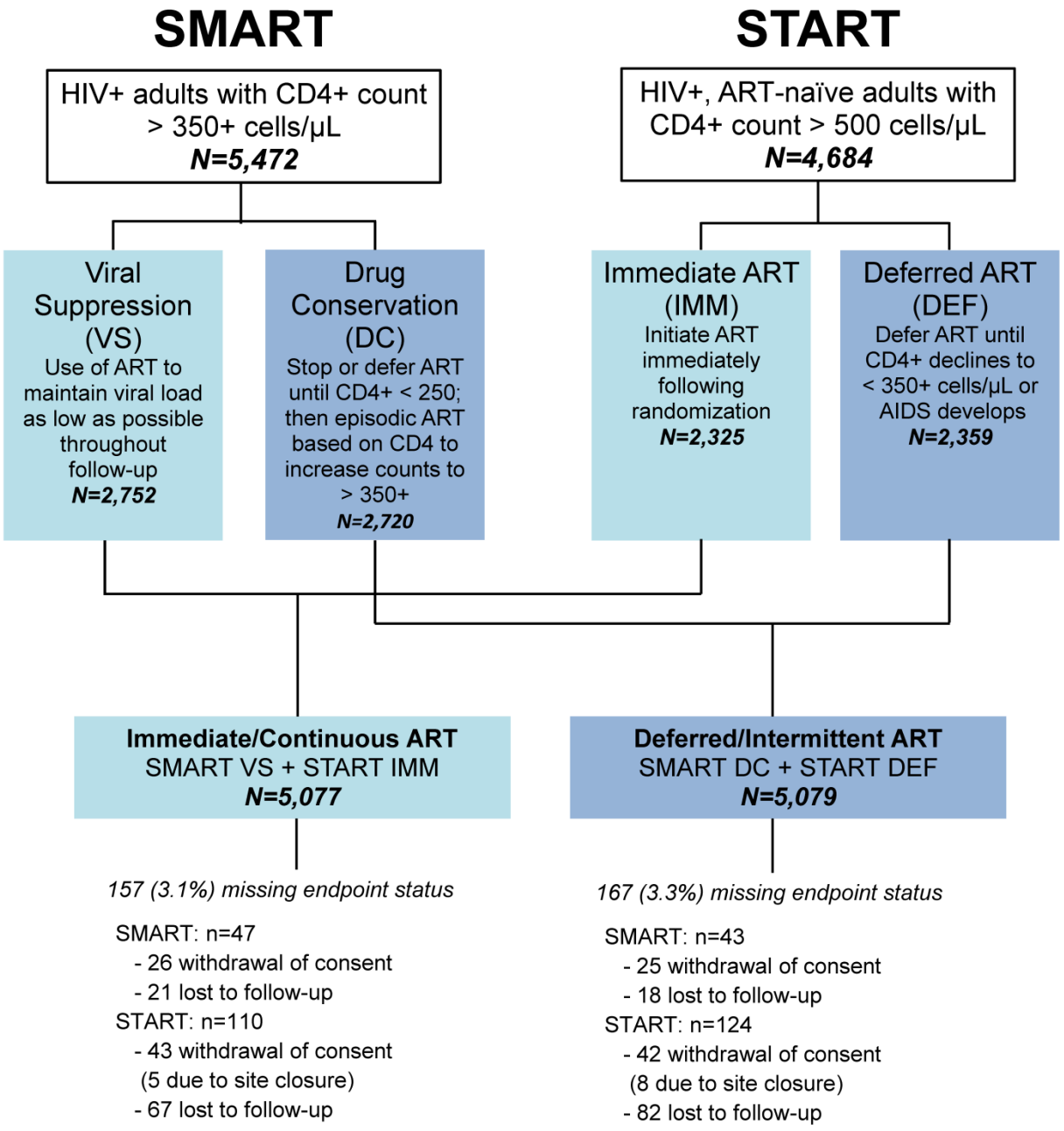
	START (n=4684)	SMART (n=5472)	P-value* (START vs SMART)	Overall (n=10156)
Median age (IQR)	36 (29 - 44)	43 (38 - 50)	<0.001	40 (33 - 48)
Female (%)	26.8	27.2	0.72	27.0
Race or ethnic group (%)				
Black	30.1	29.1		29.6
Latino or Hispanic	13.6	21.1		17.6
Asian	8.3	4.1		6.0
White	44.6	43.6		44.0
Other	3.5	2.1		2.8
Geographical region (%)				
Africa	21.3	1.2		10.5
Asia	7.6	3.2		5.2
Australia	2.3	3.2		2.8
Europe	32.9	25.8		29.1
North America	10.8	56.5		35.4
Latin America	25.1	10.0		17.0
% from high income country	46.0	85.6		67.3
Median years since HIV diagnosis (IQR)	1 (0 - 3)	8 (5 - 12)	<0.001	4 (1 - 9)
Median CD4 (IQR)	651 (584 - 765)	597 (466 - 790)	<0.001	634 (539 - 776)
Median CD4:CD8 ratio (IQR)**	0.66 (0.48 - 0.89)	0.69 (0.48 - 0.97)	<0.001	0.67 (0.48 - 0.93)
Median nadir CD4 (IQR)	553 (488 - 654)	250 (154 - 358)	<0.001	418 (237 - 558)
Median HIV RNA (IQR)**	12761 (3025 - 43482)	80 (50 - 793)	<0.001	1568 (50 - 19274)
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
Hepatitis coinfection (%)**	6.4	17.0	<0.001	12.2
Current smoker (%)	32.0	40.5	<0.001	36.6
Median BMI (IQR)**	24.6 (22.1 - 27.9)	24.9 (22.4 - 28.1)	<0.001	24.8 (22.3 - 28.0)
Median IL-6 (IQR)**	1.39 (0.97 - 2.12)	1.77 (1.09 - 3.01)	<0.001	1.57 (1.03 - 2.57)
Median D-dimer (IQR)**	0.33 (0.23 - 0.50)	0.22 (0.13 - 0.38)	<0.001	0.27 (0.17 - 0.45)

*p-value comparing SMART and START for selected baseline characteristics that did not reflect differences due to study design/conduct. Chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables

**Missing baseline data for the following: CD4/CD8 ratio – START=56, SMART=2637; HIV RNA – START=9, SMART=15; hepatitis B/C coinfection – START=54, SMART=8; BMI – SMART=21; IL-6 – START=388, SMART=435; D-dimer – START=410, SMART=403.

ART= antiretroviral therapy; BMI=body mass index; IQR=interquartile range; SMART: Strategies for Management of Antiretroviral Therapy; START=Strategic Timing of Antiretroviral Treatment

Figure 1.



All participants have been included in the analysis with follow-up censored at the last known alive date or study specific unblinding date, whichever came first.

Figure 2.

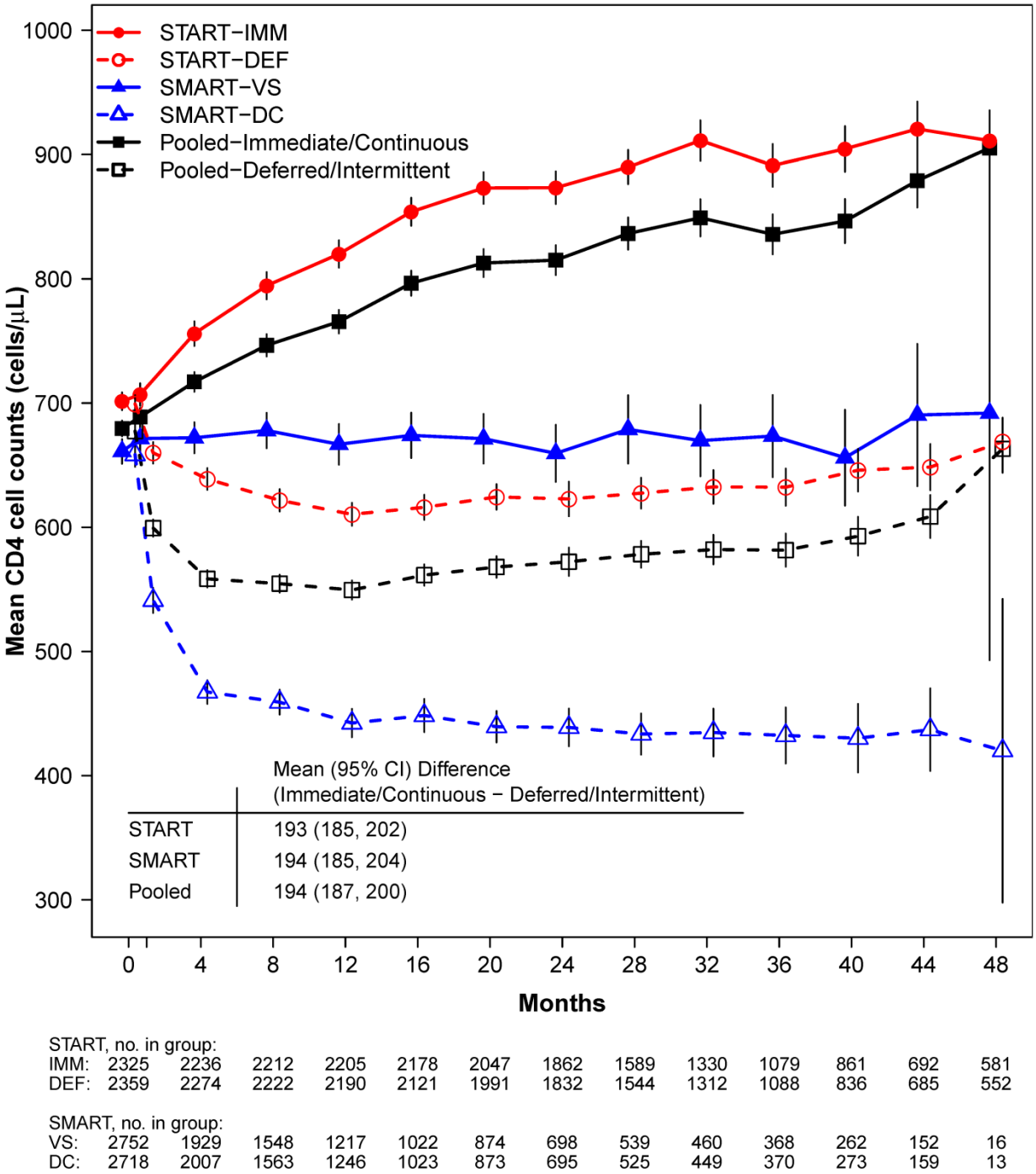
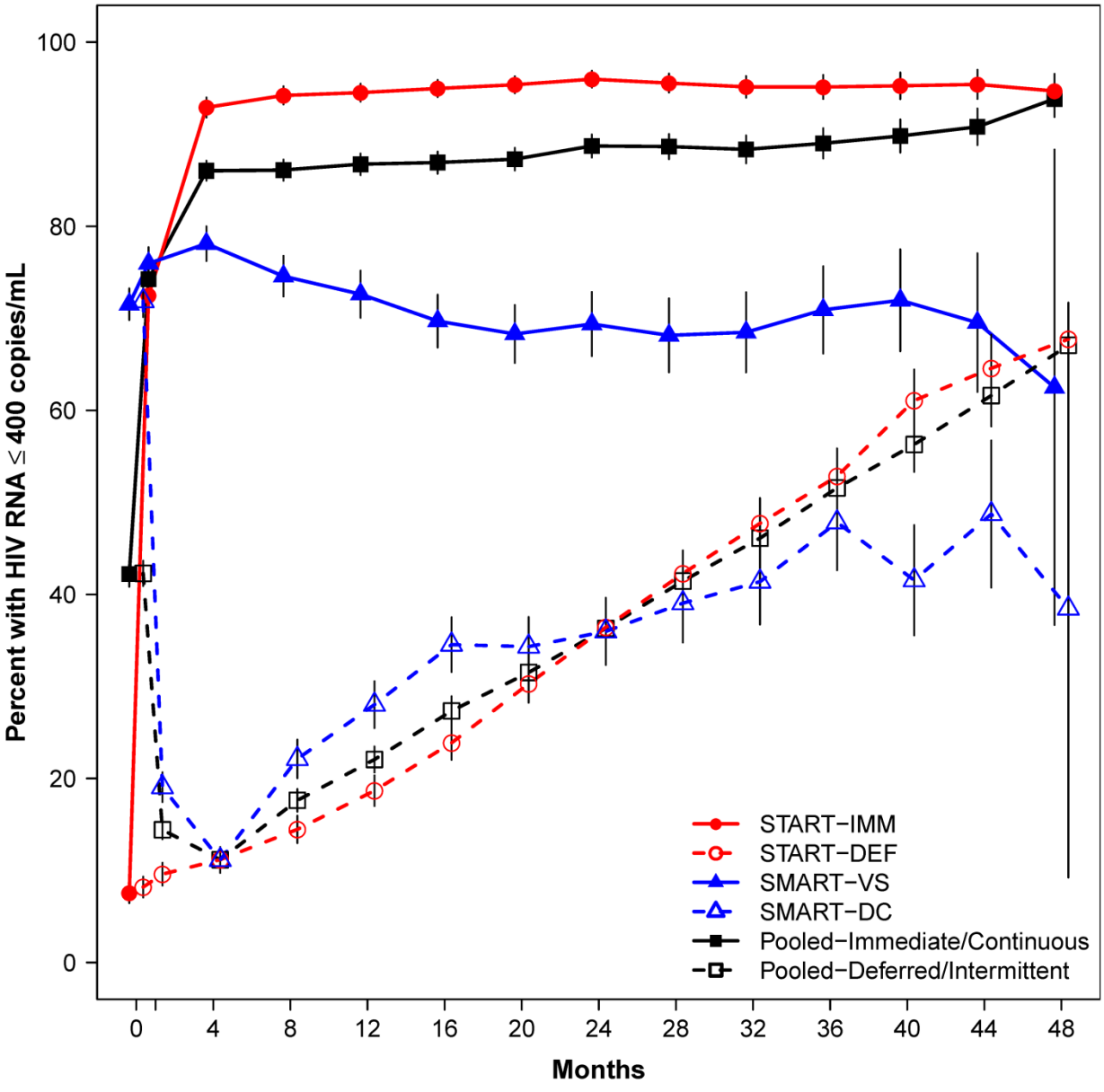


Figure 3.



START, no. in group:

IMM:	2320	2223	2208	2202	2181	2049	1861	1594	1335	1086	863	696	583
DEF:	2355	2263	2219	2185	2120	1994	1831	1552	1316	1090	840	686	555

SMART, no. in group:

VS:	2744	1929	1554	1213	1020	874	699	537	457	368	264	151	16
DC:	2713	2001	1555	1242	1022	871	692	525	447	370	272	158	13

Figure 4.

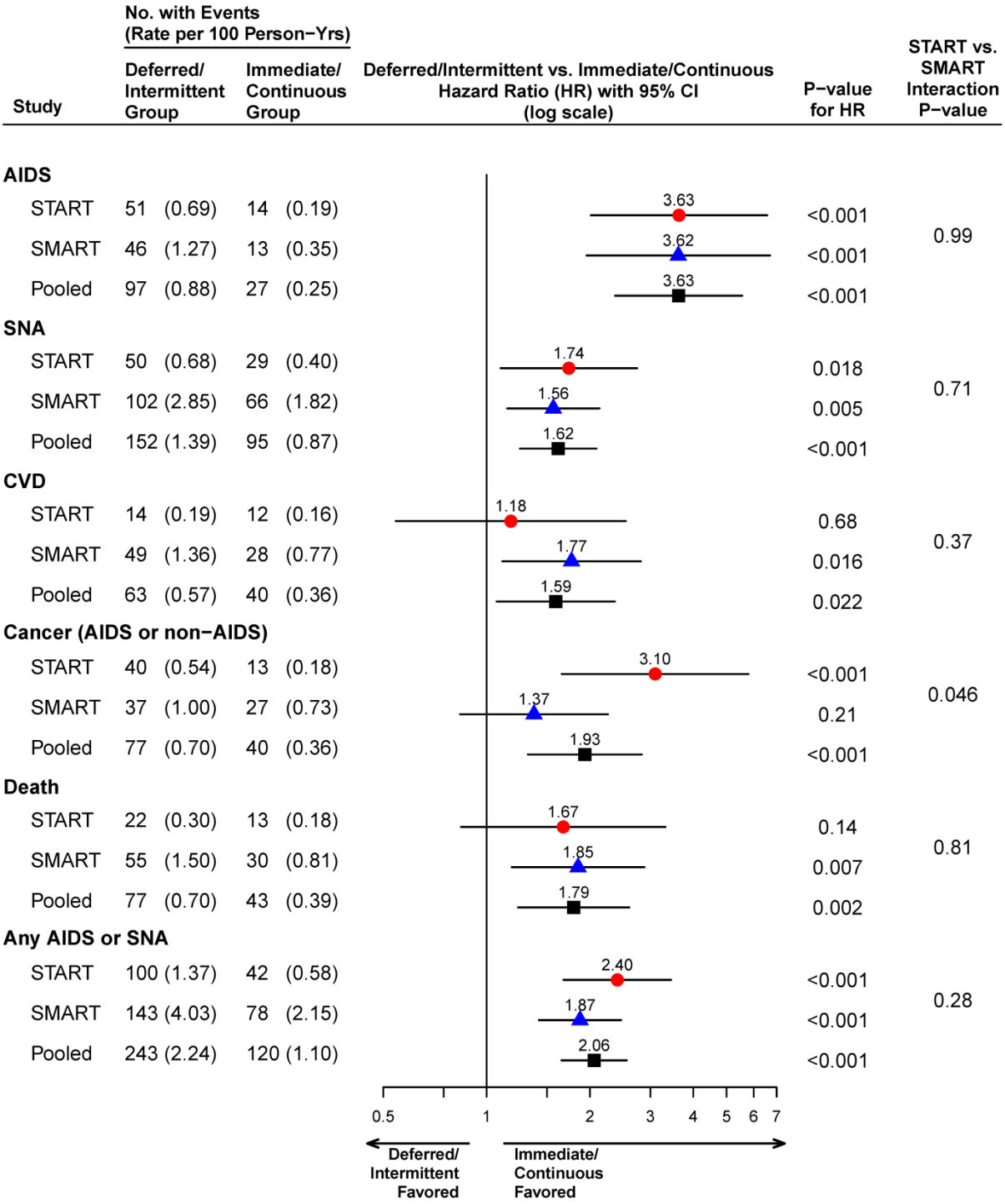


Figure 5.