Changes in CVD Risk Factors with Immediate and Deferred ART in the START Trial

Jason V. Baker[1,2], Shweta Sharma[3], Amit Achhra[4], Jose Ignacio Bernardino[5], Johannes R Bogner[6], Daniel Duprez[1], Sean Emery[4], Brian Gazzard[7], Jonathan Gordin[8], Greg Grandits[3], Andrew Phillips[9], Siegfried Schwarze[10], Elsayed Z. Soliman[11], Stephen A. Spector[12], Giuseppe Tambussi[13], and Jens Lundgren[14] for the INSIGHT START (Strategic Timing of AntiRetroviral Treatment) Study Group

[1]Department of Medicine, University of Minnesota, USA; [2]Division of Infectious Diseases, Hennepin County Medical Center, USA; [3]Division of Biostatistics, University of Minnesota, USA; [4]Kirby Institute, University of New South Wales, Australia; [5]Department of Medicine. Hospital La Paz. IdiPAZ, Spain; [6]Division of Infectious Diseases, MedIV, University Hospital of Munich, Germany; [7]Chelsea and Westminster Hospital, UK; [8]Division of Cardiology, David Geffen School of Medicine at University of California, USA; [9]HIV Epidemiology & Biostatistics Group, University College London, UK; [10]European AIDS Treatment Group, Germany; [11]Epidemiological Cardiology Research Center, Wake Forest School of Medicine, USA; [12]Division of Pediatric Infectious Diseases, University of California San Diego and Rady Children's Hospital, USA; [13]San Raffaele Scientifi Institute, Italy;[14]CHIP, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Denmark

Jason V. Baker
baker@umn.edu

Background

- HIV infection and certain antiretroviral medications both appear to contribute to cardiovascular disease (CVD) risk [1, 2].
- CVD events in START were similar between participants starting immediate antiretroviral therapy (ART), when compared to deferring ART, with 12 and 14 CVD events, respectively [3].

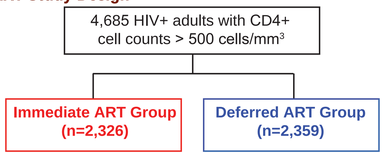
Study Aim

To understand the potential influence of immediate versus deferred ART on CVD risk by studying individual CVD risk factor changes over time in the START study.

The START Trial

START (**Figure 1**) randomly assigned HIV+ adults with a CD4+ count of >500 cells/mm^3 to start ART ('Immediate ART' group) or defer ART until the CD4+ count decreased to 350 cells/mm^3 or until the development of AIDS ('Deferred ART' group); 4,685 participants were randomized across 215 sites in 35 countries, mean follow-up was 3.0 years; immediate and deferred groups spent 94% and 28% of follow-up time on ART, respectively [3].

Figure 1: START Study Design



Data Collection and Analyses

Clinical and laboratory measures were ascertained annually in START. CVD and CHD (coronary heart disease) risk scores were calculated using published equations [4-7]. Mean change from baseline in risk factors between the immediate and deferred ART arms were compared using longitudinal mixed models. Differences between groups in prevalence of dyslipidemia (LDL >160mg/dL or use of lipid lowering drug), diabetes (diagnosis or on diabetes drug, or a fasting blood glucose ≥126 mg/dL) and hypertension (diagnosis or use of blood pressure [BP] drug or systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) over follow-up were compared using binomial regression.

Results

Table 1. Baseline Characteristics in START (n=4,685)

Demographics	Med [IQR], % (N)
Age (years)	36 [29, 44]
Gender (female)	26.8 (1,257)
Race	
Asian	8.3 (388)
Black	30.1 (1,410)
Latino/Hispanic	13.6 (638)
White	44.5 (2,086)
Other	3.5 (163)
HIV History and Laboratory	
Time known to be HIV+ (years)	1.0 [0.4, 3.1]
CD4+ [a](cells/mm^3)	651 [584, 765]
Nadir CD4+ [b](cells/mm^3)	553 [488, 654]
HIV RNA (copies/mL)	13,000 [3,128, 43,837]
Initial ART (after baseline)	
Started ART during follow-up	73.0 (3,421)
First Regimen[c]	
Tenofovir	88.8 (3,038)
NNRTI	72.5 (2,481)
PI	19.8 (676)
INSTI	7.6 (260)

[a] Average of two screening values; [b] Documented in participant record; [c] Percent of those who started ART Antiretroviral Treatment; NNRTI=Non-Nucleoside Reverse Transcriptase Inhibitor; PI=Protease Inhibitor; INSTI=Integrase Strand Transfer Inhibitor

Results Continued

Table 2: Baseline CVD Characteristics in START (n=4,685)

Clinical Measures	Med [IQR], % (N)
BMI (kg/m^2)	24.6 [22.1, 27.9]
Systolic BP (mmHg)	120 [111, 130]
Diastolic BP (mmHg)	76 [70, 83]
Risk Factors	
Current smoker	31.9 (1,496)
Diabetes	3.3 (156)
Prior CVD diagnosis [a]	0.8 (36)
Hypertension	19.2 (898)
BP-lowering drugs	*8.1 (281)*
Dyslipidemia	8.2 (386)
Lipid-lowering drugs	*3.5 (163)*
Glucose and Lipids	
Glucose (mg/dL)	85 [79, 92]
Total cholesterol (mg/dL)	168 [144, 195]
LDL cholesterol (mg/dL)	102 [82, 124]
HDL cholesterol (mg/dL)	41 [35, 50]
Triglycerides (mg/dL)	97 [71, 142]
Total: HDL cholesterol ratio	4.0 [3.2, 5.0]
Total - HDL cholesterol (mg/dL)	124 [102, 150]
10 Year Risk Scores	
CVD FRS (%)[b]	2.3 [0.7, 6.5]
CHD FRS (%)[b]	1.9 [0.5, 5.0]
CVD D:A:D (%)[c]	1.8 [0.9, 3.5]
CHD D:A:D (%)[c]	1.4 [0.7, 2.9]
Pooled Cohort ASCVD (%)[d]	1.3 [0.3, 3.7]
Favorable CVD Risk	
Optimized CVD Risk Factor Profile (%)[e]	25.6 (1,191)

BMI = Body Mass Index; BP=Blood Pressure; HDL=High-Density Lipoprotein, LDL=Low-Density Lipoprotein CVD=Cardiovascular Disease; CHD=Coronary Heart Disease; FRS=Framingham Risk Score; D:A:D=Data collection on Adverse events of Anti-HIV Drugs Cohort; ASCVD= Atherosclerotic Cardiovascular Disease [a] Diagnosis of any of the following prior to randomization: myocardial infarction, stroke, coronary heart disease requiring drug treatment, coronary revascularization, congestive heart failure, peripheral arterial disease; [b] FRS equations in Anderson et al. [4]. [c] D:A:D score equations in Friis-Møller et. al. [5]. Risk equations in Goff et. al. [6]. Risk equations previously published.

Figure 2: Changes in Blood Cholesterol Levels

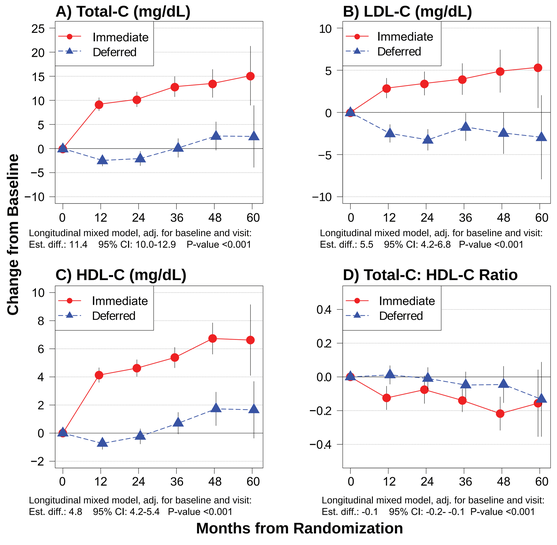


Figure 3: Changes in Blood Pressure, Body Mass Index, and Glucose

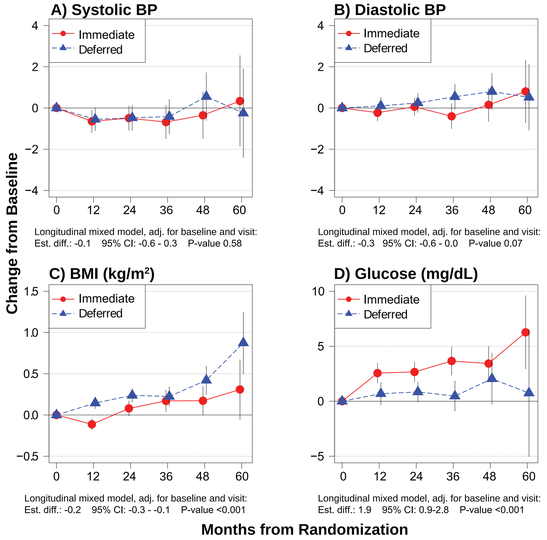


Table 3: Differences (Immediate-Deferred) in Prevalence of CVD Co-morbidities over Follow-up

CVD Co-Morbidity	1 Yr (n=4412)	2 Yr (n=3711)	3 Yr (n=2177)	4 Yr (n=1141)	All Visits
	Diff.[a] ± SE	Diff.[a] ±SE	Diff.[a] ±SE	Diff.[a] ±SE	Diff.[b] (p-value)
Dyslipidemia (%)	2.7 (0.9)	4.8 (1.0)	4.6 (1.4)	4.3 (2.1)	3.9 (<0.001)
Lipid lowering therapy (%)	0.5 (0.5)	1.9 (0.7)	1.5 (0.9)	1.1 (1.5)	1.2 (0.028)
Hypertension (%)	-2.8 (1.1)	-1.4 (1.3)	-2.8 (1.7)	0.0 (2.4)	-2.1 (0.040)
BP lowering therapy (%)	-2.1 (0.6)	-1.7 (0.8)	-3.5 (1.2)	-2.9 (1.8)	-2.2 (<0.001)
Diabetes (%)	-0.3 (0.4)	-0.5 (0.5)	-1.4 (0.7)	0.3 (1.1)	-0.5 (0.22)
Optimized Risk Factor Profile (%)	-4.0 (1.4)	-4.7 (1.5)	-4.6 (2.0)	-7.5 (2.6)	-4.9 (<0.001)

[a]Immediate minus deferred prevalence (± standard error) estimates at each visit using binomial regression models adjusting for baseline levels. [b]Differences over all follow-up estimated from binomial generalized estimating equations adjusting for baseline levels. SE=Standard Error; BP=Blood Pressure.

Table 4: Mean Difference (Immediate-Deferred) in CVD Risk Scores over Follow-up.

CVD Risk Scores	1 Yr (n=4412)	2 Yr (n=3711)	3 Yr (n=2177)	4 Yr (n=1141)	All Visits
	Diff.[a] ± SE	Diff.[a] ±SE	Diff.[a] ±SE	Diff.[a] ±SE	Diff.[b] (p-value)
FRS 10yr CVD (mean %)	-0.2 (0.1)	-0.1 (0.1)	-0.2 (0.2)	-0.4 (0.2)	-0.1 (0.07)
FRS 10yr CHD (mean %)	-0.1 (0.1)	-0.1 (0.1)	-0.2 (0.1)	-0.3 (0.2)	-0.1 (0.07)
D:A:D 10yr CVD (mean %)	0.2 (0.05)	0.2 (0.1)	0.2 (0.1)	-0.1 (0.2)	0.2 (<0.001)
D:A:D 10yr CHD (mean %)	0.2 (0.04)	0.2 (0.1)	0.2 (0.1)	0.05 (0.1)	0.1 (<0.001)
Pooled Cohort 10yr ASCVD (mean %)	-0.04 (0.1)	-0.01 (0.1)	-0.001 (0.2)	-0.2 (0.2)	0.0 (0.71)

[a]Immediate minus deferred mean change from baseline (± standard error) estimates at each visit using linear models adjusting for baseline levels. [b]Differences over all follow-up estimated from longitudinal mixed models adjusting for baseline levels. SE=Standard Error; CVD=Cardiovascular Disease; CHD=Coronary Heart Disease; FRS=Framingham Risk Score; D:A:D=Data collection on Adverse events of Anti-HIV Drugs Cohort; ASCVD= Atherosclerotic Cardiovascular Disease

Summary of Results

When compared to the deferred ART group, in the immediate ART group we observed:

- Increased Total-C, LDL-C, use of lipid-lowering therapy, and ultimately, the prevalence of dyslipidemia.
- Increased HDL-C, resulting in a corresponding decline in Total: HDL-C.
- Marginally lower prevalence of hypertension and BP-lowering therapy, but no difference in systolic or diastolic BP.
- Marginally increased fasting glucose (~2mg/dL), with no difference in the prevalence of diabetes.
- Lower prevalence of an optimal CVD risk factor profile (~5% less), with a clinically insignificant and inconsistent net effect on CVD and CHD risk scores.

Conclusions

- Immediate ART led to significant changes in individual CVD risk factors, likely attributable to both ART exposure (e.g., increases in Total-C and LDL-C) along with reduced inflammation (e.g., reflected in HDL-C increases).
- Among HIV+ adults with relative immune preservation, the net-difference in overall CVD risk between immediate and deferred ART may be clinically insignificant.
- Given that clinical manifestations take years to develop, longer follow-up is needed to determine if immediate ART alters the pattern of CVD event rates over time.

Acknowledgement

We thank the participants and investigators of the START study. The START study was funded by NIH grants UM1-AI068641 and UM1-AI120197.

Citations

1. Strategies for Management of Antiretroviral Therapy Study Group, CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med, 2006. 355(22): p. 2283-96.*
2. Friis-Moller, N., et al., Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med, 2007. 356(17): p.1723-35.*
3. INSIGHT Start Study Group, Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med, 2015. 373: p. 795-807.*
4. Anderson, K.M., et al., Cardiovascular disease risk profiles. *Am Heart J, 1991. 121(1 Pt 2): p. 293-8.*
5. Friis-Moller, N., et al., Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. European journal of cardiovascular prevention and rehabilitation: *Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 2010. 17(5): p.491-501.*
6. Goff, D.C., Jr., et al., 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation, 2014. 129(25 Suppl 2): p. S49-73.*
7. Stamler, J., et al., Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA, 1999. 282(21): p. 2012-8.*