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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

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Introduction—HIV infection and certain antiretroviral therapy (ART) medications increase atherosclerotic cardiovascular disease risk, mediated, in part, through traditional cardiovascular disease risk factors.

Methods and Results—We studied cardiovascular disease risk factor changes in the START (Strategic Timing of Antiretroviral Treatment) trial, a randomized study of immediate versus deferred ART initiation among HIV-positive persons with CD4+ cell counts >500 cells/mm³. Mean change from baseline in risk factors and the incidence of comorbid conditions were compared between groups. The characteristics among 4685 HIV-positive START trial participants include a median age of 36 years, a CD4 cell count of 651 cells/mm³, an HIV viral load of 12 759 copies/mL, a current smoking status of 32%, a median systolic/diastolic blood pressure of 120/76 mm Hg, and median levels of total cholesterol of 168 mg/dL, low-density lipoprotein cholesterol of 102 mg/dL, and high-density lipoprotein cholesterol of 41 mg/dL. Mean follow-up was 3.0 years. The immediate and deferred ART groups spent 94% and 28% of follow-up time taking ART, respectively. Compared with patients in the deferral group, patients in the immediate ART group had increased total cholesterol and low-density lipoprotein cholesterol and higher use of lipid-lowering therapy (1.2%; 95% CI, 0.1–2.2). Concurrent increases in high-density lipoprotein cholesterol with immediate ART resulted in a 0.1 lower total cholesterol to high-density lipoprotein cholesterol ratio (95% CI, 0.1–0.2). Immediate ART resulted in 2.3% less BP-lowering therapy use (95% CI, 0.9–3.6), but there were no differences in new-onset hypertension or diabetes mellitus.

Conclusions—Among HIV-positive persons with preserved immunity, immediate ART led to increases in total cholesterol and low-density lipoprotein cholesterol but also concurrent increases in high-density lipoprotein cholesterol and decreased use of blood pressure medications. These opposing effects suggest that, in the short term, the net effect of early ART on traditional cardiovascular disease risk factors may be clinically insignificant.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00867048. (J Am Heart Assoc. 2017;6: e004987. DOI: 10.1161/JAHA.116.004987.)

Key Words: antiretroviral therapy • cholesterol • HIV • risk factor

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Accompanying Table S1, Figure S1, and Appendix S1 are available at http://jaha.ahajournals.org/content/6/5/e004987/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of the INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group members are given in Appendix S1.

Data were presented as a research abstract at the 24th Conference on Retroviruses and Opportunistic Infections, February 22–25, 2016, in Boston, MA.

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IV-positive persons are at increased risk for premature cardiovascular disease (CVD),\(^1\) which is currently a leading cause of morbidity and mortality.\(^2\) Atherosclerotic disease accounts for a substantial proportion of HIV-related CVD among contemporary patients. This atherosclerotic disease manifests as excess risk for coronary heart disease (CHD; eg, myocardial infarction)\(^1\) and stroke,\(^3\) and may also contribute to excess risk for heart failure\(^4\) and sudden cardiac death.\(^5\)

It is well established that features of both HIV infection and certain antiretroviral medications increase the risk for CVD. Some of this excess CVD risk may be caused by long-term systemic inflammation that is mitigated, in part, via antiretroviral therapy (ART)–associated viral suppression,\(^6\)\(^–\)\(^9\) whereas some may be caused by exposure to specific antiretrovirals (eg, certain protease inhibitors [PIs] and abacavir)\(^10\) with potential for adverse changes in blood cholesterol, platelet dysfunction, and/or endothelial dysfunction.\(^10\)\(^–\)\(^13\)

Despite unique features of HIV disease, traditional risk factors are highly predictive for CVD among HIV-positive patients\(^1\)\(^,\)\(^10\)\(^,\)\(^14\) and can be adversely affected by HIV infection and ART treatment (eg, dyslipidemia).\(^15\)

Given the potential for ART to both increase (via drug toxicity and low-density lipoprotein cholesterol [LDL-C] increases) and decrease (via viral suppression and reduced inflammation) atherosclerosis, it is important to study this pathophysiology in the context of randomized comparisons. The START (Strategic Timing of Antiretroviral Treatment) trial is a randomized controlled study of immediate initiation of ART (“immediate” group) versus deferral of ART initiation until CD4\(^+\) cell counts decline to <350 cells/mm\(^3\) or clinical symptoms develop (“deferred” group) among participants naive to ART with CD4\(^+\) cell counts >500 cells/mm\(^3\) at entry.\(^16\) The START trial used an ideal design to compare CVD risk factors between ART-treated and untreated HIV infection in a controlled fashion among persons at low risk for AIDS. CVD events were a component of the composite end point in the START trial, and participants with a recent CVD event (<6 months from entry) were not eligible. The START trial did not have sufficient power to specifically assess CVD event risk (12 and 14 CVD events in the immediate and deferred groups, respectively).\(^16\) In this study, we characterized the influence of immediate versus deferred ART on CVD risk factor changes and incidence of CVD-related comorbidities.

Methods

Study Design and Data Collection

The design and primary findings from the START trial have been described.\(^16\)\(^,\)\(^17\) The START protocol was approved by the human subjects institutional review committee at the University of Minnesota and at all international coordinating centers and participating clinical sites. After informed consent was obtained, data collection occurred at baseline, months 1 and 4, and every 4 months thereafter. Participants were instructed to fast (minimum of 8 hours) for annual blood draws. Laboratory measures were performed using standardized clinical assays at the sites. HIV RNA level, CD4\(^+\) cell count, weight, and blood pressure (BP) were ascertained at every study visit. The BP values used in the analyses were the average of 2 measurements separated by a brief rest. Glucose and serum lipid levels (total cholesterol, high-density lipoprotein cholesterol [HDL-C], LDL-C, and triglycerides) and concomitant medication use were obtained at baseline and annually. At screening, clinicians together with participants prespecified the intended ART regimen a participant would initiate if randomized to the immediate group. This regimen was required to include 2 background nucleoside reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted PI, or an integrase strand transfer inhibitor (INSTI). Defining subgroups by the prespecified ART regimen allowed a randomized comparison between the immediate and deferred groups among those who were designated to start the same antiretroviral medication. Data for this report included visits up to the START trial unblinding date of May 26, 2015.

Clinical Comorbidities and Risk Factor Scores

Dyslipidemia was defined as an LDL-C level ≥160 mg/dL or use of lipid-lowering therapy. Hypertension was defined as a systolic BP ≥140 mm Hg, a diastolic BP ≥90 mm Hg, or use of BP-lowering therapy. Diabetes mellitus was defined as a fasting glucose level >126 mg/dL, use of medication for diabetes mellitus, or a clinical diagnosis of diabetes mellitus (adjudicated as confirmed or probable). Body mass index (BMI) was computed using visit-specific weight and baseline height. Ten-year risk scores were calculated at baseline and updated during follow-up for the following\(^18\)\(^–\)\(^21\): (1) Framingham Risk Score for a CVD or CHD event; (2) D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) risk score for a CVD or CHD event; and (3) the pooled cohort risk assessment for an atherosclerotic CVD event.

Statistical Methods

The mean changes from baseline between the immediate and deferred groups for continuous measures were compared using longitudinal mixed models with random intercepts, including treatment group, visit, and baseline value in the model. The differences between groups for the prevalence of binary measures were compared using generalized estimating equations (binomial regression) with treatment group, visit, and baseline prevalence in the model. Histograms showed
that total cholesterol, LDL-C, HDL-C, and BP were approximately normally distributed and were analyzed untransformed. The proportional hazards assumption was tested using log-time as a covariate in the model. Comparisons within subgroups defined by prespecified ART drug or class (efavirenz [EFV], PI, or INSTI) are reported. EFV-based ART was included as a subgroup in analyses by ART class, given that EFV represented 95% of the NNRTI use in the START trial. Incidence for binary risk factors was determined in participants without that condition at baseline using a single factor for treatment in Cox regression models. To directly compare treated versus untreated HIV infection we repeated the analyses by excluding immediate group participants who never started ART (n=39) and censoring the deferred group at the time of ART initiation. Analyses were performed using SAS software version 9.3 (SAS Institute Inc) and R software version 3.2.3 (R Foundation for Statistical Computing).

Results

Participant Characteristics

A total of 4685 HIV-positive individuals from 215 sites in 35 countries were enrolled into the START trial. The median age of participants was 36 years and 27% were female (Table 1).22 Self-reported race/ethnicity reflected global enrollment from the United States (11%), South America and Mexico (25%), Europe, Israel and Australia (35%), Africa (21%), and Asia (8%). The CD4\(^+\) cell count at entry was 651 cells/mm\(^3\), and the median time since HIV diagnosis was 1 year. Mean (SD) and median [interquartile range] follow-up time was 3.0 (1.2) and 2.8 [2.1–3.9] years, respectively, with no difference in follow-up time between the immediate and deferred groups. Baseline characteristics did not differ between groups (Table 1). In addition to a high smoking prevalence, START trial participants were at low risk for CVD based on the median values for BMI, BP, cholesterol, and CVD/CHD risk scores.

The percentage of participants taking ART during follow-up is presented in Figure 1; 98% of the immediate group and 48% of the deferred group initiated ART, with a median time to initiation of 36 months in the deferred group. The percentage of follow-up time spent taking ART varied between 75% and 80% for the immediate and deferred groups, respectively. The frequency of specific antiretrovirals in the initial ART regimen reflects contemporary clinical practice (Table S1). Among the 2287 immediate group participants who initiated therapy, ART included tenofovir disoproxil fumarate in 89%, an NNRTI in 77% (73% EFV), a ritonavir-boosted PI in 19% (10% atazanavir and 7% darunavir), and an INSTI in 5% (4% raltegravir); corresponding values for the 1134 deferred group participants who initiated therapy included tenofovir disoproxil fumarate in 89%, an NNRTI in 64% (51% EFV), a PI in 22% (11% darunavir), and an INSTI in 14% (8% raltegravir).

Changes in Serum Cholesterol Levels and Lipid-Lowering Therapy

Mean changes in lipid levels (Figure 2) and the incidence of dyslipidemia (Figure 3) are presented for each group. Compared with the ART deferral group, the immediate ART group had 11 mg/dl higher total cholesterol (95% CI, 10–13), 6 mg/dl higher LDL-C (95% CI, 4–7), and 5 mg/dl higher HDL-C (95% CI, 4–5) levels. The rise in total cholesterol and LDL-C in the immediate group was associated with a 1.2% greater use of lipid-lowering therapy (95% CI, 0.2–2.2) and a higher incidence rate of dyslipidemia (hazard ratio, 1.7; 95% CI, 1.4–2.02). Among the 346 participants taking lipid-lowering therapy at entry or during follow-up, 68% were taking a statin. Increases in HDL-C levels resulted in a marginally lower total cholesterol to HDL-C ratio in the immediate versus the deferred group (–0.1; 95% CI, −0.2 to −0.1). When HDL <40 mg/dl was included in the criteria for dyslipidemia, 49% (2283) of participants had dyslipidemia at study entry. When including low HDL in the definition, the incidence rate for dyslipidemia was lower in the immediate ART group compared with the deferred ART group (hazard ratio, 0.7; 95% CI, 0.6–0.8) (Figure 3). Immediate ART also resulted in higher triglyceride (8 mg/dl; 95% CI, 3–12) and non–HDL-C (7 mg/dl; 95% CI, 5–8) levels than deferred ART. Participants were fasting for ≈91% of blood draw visits and the findings were similar when analyses were restricted to fasting specimens. In analyses of treated versus untreated HIV infection, the treatment differences in lipid changes from baseline were of higher magnitude but similar.

Table 2 presents analyses of subgroups defined by prespecified ART, with comparisons for EFV-, PI-, and INSTI-based ART. These data represent the effect of starting a specific antiretroviral when compared with a group randomized to defer ART but who intended to start the same antiretroviral medication or class. Time spent during follow-up taking the prespecified ART varied between 75% and 80% for the immediate group and 15% and 20% for the deferred group. There was a significant interaction between the prespecified ART regimen and the treatment difference for several cholesterol measures. Specifically, participants who prespecified EFV use had a greater difference in both total cholesterol and HDL-C level between the immediate and deferred groups, when compared with those who prespecified PI use. Similarly, when compared with those who prespecified an INSTI, the EFV subgroup had greater differences in total cholesterol, LDL-C, and HDL-C levels between the immediate and deferred.
groups. Notably, there was no difference in any lipid parameters between immediate and deferred ART among the subgroup that prespecified INSTI use. In analyses of treated versus untreated HIV infection, the magnitude of the treatment differences in lipid changes from baseline was higher for EFV- and PI-based ART.

Changes in BP

When compared with patients who underwent ART deferral, those who took immediate ART demonstrated no difference in systolic BP, a lower diastolic BP that was not significant (Figure 2), and a lower prevalence of BP-lowering therapy (−2.2%; 95% CI, −3.6 to −0.93). At entry, 19% of participants had hypertension (per our definition), and when new-onset hypertension rates were compared between the immediate and deferred groups, the hazard ratio for reduced incidence of hypertension did not reach significance (0.87; 95% CI, 0.74–1.02; \(P = 0.10\)) (Figure 3). After analyses of treated versus untreated HIV infection, there remained no difference in use of BP-lowering therapy or incident hypertension between the groups, whereas diastolic BP was significantly lower in the immediate ART group (−0.4; 95% CI, −0.1 to −0.7 \(P=0.02\)).

Changes in Metabolic Parameters

Patients in the immediate group had a higher mean glucose level of 2 mg/dL (95% CI, 1–3) than patients in the deferred group (Figure S1), but there was no difference in the incidence

Table 1. Continued

<table>
<thead>
<tr>
<th>Prespecified ART regimen</th>
<th>Median [IQR] or % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>75.1 (3516)</td>
</tr>
<tr>
<td>PI</td>
<td>17.4 (815)</td>
</tr>
<tr>
<td>INSTI</td>
<td>3.9 (183)</td>
</tr>
<tr>
<td>Non-EFV NNRTI</td>
<td>3.7 (171)</td>
</tr>
</tbody>
</table>

ART indicates antiretroviral therapy; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; EFV, efavirenz; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; START, Strategic Timing of Antiretroviral Treatment.

*Average of 2 screening values.
†Documented in participant record.
‡Diagnosis of any of the following prior to randomization: myocardial infarction, stroke, coronary heart disease requiring drug treatment, coronary revascularization, congestive heart failure, or peripheral arterial disease.
§Framingham Risk Score (FRS) equations in Anderson et al.18
††Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) score equations in Fris-Møller et al.19
‡‡Atherosclerotic cardiovascular disease (ASCVD) risk equation in Goff et al.20
§§Lifetime ASCVD risk score in Berry et al.22

Table 1. Baseline Characteristics of Patients in the START Trial (n=4685)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Median [IQR] or % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36 [29–44]</td>
</tr>
<tr>
<td>Female sex</td>
<td>26.8 (1257)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>8.3 (388)</td>
</tr>
<tr>
<td>Black</td>
<td>30.1 (1410)</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>13.6 (638)</td>
</tr>
<tr>
<td>White</td>
<td>44.5 (2086)</td>
</tr>
<tr>
<td>Other</td>
<td>3.5 (163)</td>
</tr>
<tr>
<td>HIV history and laboratory</td>
<td></td>
</tr>
<tr>
<td>Time known to be HIV positive, y</td>
<td>1.0 [0.4–3.1]</td>
</tr>
<tr>
<td>CD4, cells/mm³†</td>
<td>651 [584–765]</td>
</tr>
<tr>
<td>Nadir CD4, cells/mm³††</td>
<td>553 [488–654]</td>
</tr>
<tr>
<td>HIV RNA, copies/mL</td>
<td>12 759 [3019–43 391]</td>
</tr>
<tr>
<td>Clinical measures</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.6 [22.1–27.9]</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>120 [111–130]</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76 [70–83]</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>31.9 (1496)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.3 (156)</td>
</tr>
<tr>
<td>Prior CVD diagnosis‡</td>
<td>0.8 (36)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19.2 (898)</td>
</tr>
<tr>
<td>BP-lowering drugs</td>
<td>8.1 (281)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>8.2 (386)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>3.5 (163)</td>
</tr>
<tr>
<td>Glucose and lipids</td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>85 [79–92]</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>168 [144–195]</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>102 [82–124]</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>41 [35–50]</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>97 [71–142]</td>
</tr>
<tr>
<td>Total cholesterol to HDL-C ratio</td>
<td>4.0 [3.2–5.0]</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL</td>
<td>124 [102–150]</td>
</tr>
<tr>
<td>10-year predicted risk scores</td>
<td></td>
</tr>
<tr>
<td>CVD FRS, %§</td>
<td>2.3 [0.7–6.5]</td>
</tr>
<tr>
<td>CHD FRS, %§</td>
<td>1.9 [0.5–5.0]</td>
</tr>
<tr>
<td>CVD D:A:D, %‖</td>
<td>1.8 [0.9–3.5]</td>
</tr>
<tr>
<td>CHD D:A:D, %‖</td>
<td>1.4 [0.7–2.9]</td>
</tr>
<tr>
<td>Pooled cohort ASCVD, %‖</td>
<td>2.2 [1.0–4.4]</td>
</tr>
<tr>
<td>Lifetime ASCVD risk score, %‖</td>
<td>31.2 [15.6–39.6]</td>
</tr>
</tbody>
</table>

ART indicates antiretroviral therapy; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; EFV, efavirenz; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; START, Strategic Timing of Antiretroviral Treatment.

*Average of 2 screening values.
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of type 2 diabetes mellitus (Figure 3). In contrast, BMI was significantly lower among patients in the immediate versus deferred groups (−0.2 kg/m²; 95% CI, −0.3 to −0.1), although the magnitude of this effect is of unclear clinical significance (Figure S1). The treatment effect on BMI appeared greatest early after randomization (P<0.001 for interaction of treatment group by follow-up time). When comparing subgroups defined by prespecified ART regimen, BMI showed a significantly greater decline (with immediate versus deferred ART) among patients in the EFV (−0.3 kg/m²; 95% CI, −0.4 to −0.2) versus PI (−0.1 kg/m²; 95% CI, −0.2 to 0.1) subgroups. Finally, there was no evidence of an interaction between prespecified ART regimen and a treatment effect for serum glucose or incident diabetes mellitus.

**Differences in Risk Factor Profile and Predicted Risk Scores**

We studied the effect of immediate ART on CVD and CHD predicted risk scores. Smoking contributed the most to predicted risk, but rates did not differ between treatment groups during follow-up (Figure S1). The mean difference between groups was not significant for the atherosclerotic CVD pooled cohort 10-year risk score (−0.1; 95% CI, −0.2 to −0.1), the Framingham Risk Score 10-year CVD (−0.1; 95% CI, −0.3 to −0.0), or the Framingham Risk Score 10-year CHD (−0.1; 95% CI, −0.3 to −0.0), but was slightly higher in the immediate group for the D:A:D 10-year CVD (0.2; 95% CI, 0.1−0.3) and CHD (0.1; 95% CI, 0.1−0.2) estimates. Differences in the D:A:D scores were caused primarily by the fact that this score considers exposure to certain antiretrovirals (eg, abacavir, lopinavir); there were no differences when censoring participants after initiation of these antiretrovirals. After analyses of patients with treated versus untreated HIV infection, the treatment differences in the Framingham Risk Score estimates were of a similar low magnitude but reached statistical significance.

**Discussion**

The START trial is the first randomized clinical investigation to study the impact of immediate ART initiation, when compared with deferral, on CVD risk factors among a large global HIV-positive cohort with high CD4+ cell counts. It is in this context that understanding and mitigating risk for CVD becomes a high priority in clinical practice. When compared with ART deferral, ART initiation increased total cholesterol and LDL-C levels and use of lipid-lowering therapy, but also increased HDL-C level and resulted in a decline in total cholesterol to HDL-C ratio. Changes in CVD or CHD prediction scores with immediate versus deferred ART were minimal or nonsignificant.

A well-described consequence of untreated HIV infection is a decline in most serum lipids levels (the primary exception being an elevation in triglycerides), with ART initiation then leading to a compensatory increase in total cholesterol and LDL-C levels to a degree that often varies by regimen.15,23,24 We present novel randomized data quantifying the absolute effect of ART initiation on serum lipids, when compared with initially untreated HIV disease. Increases in total cholesterol were greatest among the subgroups that prespecified EFV. Prior studies have lacked a comparison group of untreated persons, but have reported greater within-participant increases in total cholesterol (mean 19 and 55 mg/dL) and LDL-C (mean 4 and 23 mg/dL) levels 1 year after starting NNRTI- (eg, EFV) or PI-based ART, when compared with the changes reported in the START trial.15,25,26 It is unclear whether the greater increases in LDL-C level with EFV-based ART reflects greater CVD risk, given that increases in HDL-C level were also greater with EFV and that epidemiologic data demonstrate that exposure to certain PIs, but not to NNRTIs (eg, EFV), are associated with greater risk for myocardial infarction.10,27

Data from comparative antiretroviral trials have shown the greatest rises in HDL-C level after starting EFV (73% in the START trial) or tenofovir (89% in the START trial), with the effect from INSTIs (5% in the START trial) being
**Figure 2.** Cardiovascular risk factor changes by treatment group. Shown in the first 3 rows are the unadjusted mean changes from baseline at annual visits for participants in the immediate (I) and deferred (D) antiretroviral therapy (ART) groups for the following measures: total cholesterol (A), low-density lipoprotein cholesterol (LDL-C; B), high-density lipoprotein cholesterol (HDL-C; C), total cholesterol to HDL-C ratio (D), systolic blood pressure (BP; E), and diastolic BP (F). Presented within (A through F) are the estimated mean differences (with 95% CIs and \( P \) values) during follow-up between the 2 groups (I minus D), adjusting for the baseline value and visit from longitudinal mixed models. Shown in the last row is the unadjusted prevalence (percentage) at baseline and follow-up annual visits for participants in both ART groups for use of BP-lowering drugs (G) and lipid-lowering drugs (H). Presented within (G and H) are the overall estimated differences in prevalence during follow-up (with 95% CIs and \( P \) values) between the 2 groups (I minus D), adjusting for the baseline prevalence and visit from generalized estimating equations. Figures are truncated at month 48.
Our findings support that ART initiation with EFV-based ART led to the greatest increases in HDL-C level. Furthermore, the degree of HDL-C level increase attributable to initiating EFV-based ART was large enough to result in a concurrent decline in the ratio of total cholesterol to HDL-C, which was not observed for PI- or INSTI-based ART. The differential effect on HDL-C level by ART regimen and lack of significant INSTI effects on any blood lipids suggests that cholesterol changes may, in part, be mediated via effects other than those related to HIV viral suppression.

Multiple factors contribute to dyslipidemia among ART-treated HIV-positive patients, including altered hepatic synthesis, inflammation, oxidative stress, direct drug toxicity (eg, PI binding of the LDL-C receptor protein), and possibly genetic factors. The modest degree of ART-associated increases in total cholesterol and LDL-C levels described in the START trial was surprising, although, as noted, may be caused by the fact that previous estimates cannot isolate the net effect of ART versus no ART. One important caveat to the increase in dyslipidemia with immediate ART in the START trial was that if low HDL level was included as criteria, then dyslipidemia was less with immediate ART. Another important difference between findings from the START trial and most prior ART trials is the health of the study population, raising the question of whether ART-related effects on serum lipids may be decreased when initiating treatment earlier in HIV disease. Still, the effect of ART treatment on blood lipid levels in the START trial emphasizes that cholesterol should remain a key target for CVD risk factor modification within this population.

**Figure 3.** Cumulative incidence of comorbid conditions by treatment group. Shown are Kaplan–Meier estimates of the cumulative incidence of participants with dyslipidemia, excluding high-density lipoprotein (HDL) in the definition (A), dyslipidemia, including HDL <40 mg/dL in the definition* (B), hypertension† (C), and diabetes mellitus (D) during follow-up for participants in the immediate (I) and deferred (D) antiretroviral therapy (ART) groups. Presented within the figures are the estimated hazard ratios (HRs) for the immediate (I) vs deferred (D) groups (with 95% CIs and P values) from Cox proportional hazards regression models. Figures are truncated at month 48. The cumulative incidence plots have jumps annually because measurements were obtained only at annual visits. †A total of 2203 (49%) START (Strategic Timing of Antiretroviral Treatment) trial participants had dyslipidemia at baseline when including the criteria of HDL <40 mg/dL. The incidence computation during follow-up for this definition is limited to the 2402 participants without baseline dyslipidemia. †For the incidence computation, an individual was defined as being hypertensive at the first visit when systolic blood pressure (BP) was ≥140 mm Hg, diastolic BP was ≥90 mm Hg, or BP medication use was reported. In some individuals classified as hypertensive based on BP alone, the BP may be lower at subsequent visits. This definition leads to a higher incidence.

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Original Research

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Table 2. Overall Treatment Difference (I–D) in Metabolic Parameters by Subgroups Defined by Prespecified ART Regimen at Baseline

<table>
<thead>
<tr>
<th>Measure</th>
<th>Prespecified ART</th>
<th></th>
<th></th>
<th>Interaction P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EFV (n=3516)</td>
<td>PI (n=815)</td>
<td>INSTI (n=183)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>13.2 (11.5–14.9)</td>
<td>8.7 (5.2–12.1)</td>
<td>−2.4 (−10.1 to 5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>6.5 (5.0–7.9)</td>
<td>3.7 (0.7–6.7)</td>
<td>−1.1 (−7.8 to 5.7)</td>
<td>0.036</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>5.8 (5.2–6.4)</td>
<td>2.2 (0.9–3.5)</td>
<td>0.4 (−2.5 to 3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol to HDL-C ratio</td>
<td>−0.2 (−0.2 to −0.1)</td>
<td>−0.0 (−0.2 to 0.1)</td>
<td>−0.2 (−0.5 to 0.2)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

EFV indicates efavirenz; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; LDL-C, low-density lipoprotein cholesterol; PI, protease inhibitor.

*Mean differences (immediate [I] minus deferred [D]) during all follow-up using longitudinal mixed models adjusting for baseline level and visit.

†df P value for interaction between treatment group and 3 prespecified antiretroviral therapy (ART) regimens comparing the I–D treatment difference among subgroups.

Although immediate ART initiation did not lead to significant changes in BP or incident hypertension, the use of BP-lowering therapy and the prevalence of hypertension were less with immediate ART. Reasons for this discrepancy are unclear, but incident hypertension does not reflect influences on the use of BP-lowering therapy among patients with known hypertension at entry. Associations between inflammatory cytokines and vascular stiffness provide some biologic prelude for why suppressing HIV replication may reduce the need for BP therapy.36–39 However, if a true ART-treatment effect on absolute BP was present but not detected in this study (eg, type 2 error), it is unlikely to be clinically significant.

ART is well known to be associated with body composition changes, although contemporary ART regimens are less toxic than early-era antiretrovirals.40–42 In the START trial, immediate ART initiation led to a clinically insignificant increase in serum glucose (ie, with no change in incidence of diabetes mellitus), but was also associated with a marginally lower BMI. The BMI findings are counter to prior observations of ART increases in abdominal fat, but, importantly, BMI assessments do not delineate between changes in visceral and subcutaneous fat.41,43 In addition, the relative immune preservation in the START trial may be important in that toxicity from a given antiretroviral medication may be more pronounced among patients with more severe immune depletion. This hypothesis was suggested by notable findings from HOPS (the HIV Outpatient Study), in which starting ART at higher (versus lower) CD4+ cell counts reduced the incidence of peripheral neuropathy, even when using antiretrovirals well known to cause neuropathy.44

Ultimately, the net effect of early ART initiation on traditional risk factors appeared to have a clinically insignificant effect on CVD and CHD risk algorithms. While 10-year CVD/CHD predicted risk remained low in absolute terms, the estimated lifetime atherosclerotic CVD risk at study entry among this younger population was still >30%,22 reinforcing that traditional risk factor management remains an important strategy to mitigate the cumulative effects of HIV, ART, and advancing age over time. However, it does remain unclear how well the atherosclerotic CVD lifetime risk estimation reflects true clinical risk in this context as it has not been validated among HIV-positive persons.

Study Limitations

These analyses have several limitations. We did not directly assess or characterize other potentially important CVD risk mechanisms (eg, HIV-related systemic inflammation) or potential mechanisms of ART toxicity. There was potential for confounding in terms of baseline lipid levels influencing the choice of ART regimen; however, we did not see evidence for this, as the prevalence of prespecified PI (17%) was the same for persons with and without hyperlipidemia at baseline. Also, analyses focused on the INSTI subgroup were limited by small numbers. Finally, we are not able to characterize whether the ART-related changes in CVD risk factors will translate to differences in clinical event risk caused by the limited number of events in the START trial, although findings to date have not detected a significant effect of immediate versus deferred ART on risk for CVD events (HR, 0.84; 95% CI, 0.39–1.81).16

Conclusions

These data, among a diverse global population of HIV-positive persons with high CD4 cell counts, suggest that immediate ART initiation has both positive and negative influences on CVD risk factors. Ultimately, long-term follow-up in the START trial is needed to determine the net effect of ART treatment initiation for CVD event risk among HIV-positive individuals with preserved immunity.
Acknowledgments

The authors would like to specifically thank the participants in the START trial. See supplemental material for the complete listing of the INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) START (Strategic Timing of Antiretroviral Treatment) Study Group (also published in N Engl J Med. 2015;373:795–807).

Sources of Funding

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Disclosures

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44. Lichtenstein KA, Arcon M, Buchacz K, Chmiel JS, Moorman AC, Wood KC, Holmberg SD, Brooks JT; HIV Outpatient Study Investigators. Initiation of antiretroviral therapy at CD4 cell counts >350 cells/mm3 does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency. J Acquir Immune Defic Syndr. 2008;47:27–35.
Table S1. Distribution (number and percent) of specific ART used for the first regimen and total follow-up time spent taking a specific ART (Person Years, percent of follow-up).

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Deferred</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Regimen N(%)†</td>
<td>Cumulative Follow-up Time on Drug PY(% time)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>No. of participants</td>
<td>2326</td>
<td>2359</td>
</tr>
<tr>
<td>Any NRTI</td>
<td>2285 (98.2)</td>
<td>6582 (93.9)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>72 (3.1)</td>
<td>344 (4.9)</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>2025 (87.1)</td>
<td>5794 (82.7)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2026 (87.1)</td>
<td>5821 (83.1)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>260 (11.2)</td>
<td>779 (11.1)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>188 (8.1)</td>
<td>411 (5.9)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Any NNRTI</td>
<td>1759 (75.6)</td>
<td>4524 (64.6)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1661 (71.4)</td>
<td>4097 (58.5)</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>97 (4.2)</td>
<td>360 (5.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.0)</td>
<td>68 (1.0)</td>
</tr>
<tr>
<td>Any PI</td>
<td>424 (18.2)</td>
<td>1653 (23.6)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>230 (9.9)</td>
<td>887 (12.7)</td>
</tr>
<tr>
<td>Darunavir</td>
<td>165 (7.1)</td>
<td>611 (8.7)</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>11 (0.5)</td>
<td>33 (0.5)</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>18 (0.8)</td>
<td>121 (1.7)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>422 (18.1)</td>
<td>1630 (23.3)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Any INSTI</td>
<td>103 (4.4)</td>
<td>448 (6.4)</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>1 (0.0)</td>
<td>10 (0.1)</td>
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<tr>
<td>Elvitegravir</td>
<td>1 (0.0)</td>
<td>25 (0.4)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>101 (4.3)</td>
<td>413 (5.9)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other ART‡</td>
<td>1 (0.0)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Not on any ART</td>
<td>39 (1.7)</td>
<td>400 (5.7)</td>
</tr>
</tbody>
</table>

*N* – number; *PY* – Person years; *ART* – Antiretroviral therapy; *NRTI* – nucleoside reverse transcriptase inhibitor; *NNRTI* – non-nucleoside reverse transcriptase inhibitor; *PI* – protease inhibitor; *INSTI* – integrase strand transfer inhibitor

* Denominator is all participants in the randomization group.
† Person years includes switches and accounts for stops and therefore includes time spent on drug for participant who did not initiate ART with the given drug. Denominator is over all follow-up time accumulated within the randomization group.
‡ 1 participant started a blinded study and the type of ART taken is unknown.
Figure S1. Changes in the Prevalence of Selected CVD Risk Factors by Treatment Group

Shown in panels A-C is the unadjusted prevalence (%) at baseline and follow-up annual visits for participants in the immediate (I, solid line) and deferred (D, dashed line) ART groups for CVD (cardiovascular disease) risk factor, including hypertension (panel A), dyslipidemia (panel B), current smoker (panel C), BMI (kg/m²) (panel D), and glucose (mg/dL) (panel E).
B), and current smoking (panel C). Presented within panels A-C are overall estimated differences in prevalence (with 95% confidence interval and p-value) over follow-up between the two groups (immediate minus deferred), adjusting for the baseline prevalence and visit from generalized estimating equations. Shown in panels D-E are the unadjusted mean changes from baseline at annual visits for participants in both ART groups for the following measures: body mass index (BMI, panel D) and glucose (panel E). Presented within panels D-E is the estimated mean difference (with 95% confidence interval and p-value) over follow-up between the two groups (immediate minus deferred), adjusting for the baseline value and visit from longitudinal mixed models. Figures are truncated at Month 48.
Appendix: The INSIGHT START (Strategic Timing of AntiRetroviral Treatment) Study Group

In addition to writing group, the following committee members contributed to the conduct of the START trial:


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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


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