Virologic and Immunologic Responses in Treatment-Naive Patients to Ritonavir-Boosted Atazanavir or Efavirenz With a Common Backbone

Qing Wang,[1] Jim Young,[1] Enos Bernasconi,[2] Pietro Vernazza,[3] Alexandra Calmy,[4] Matthias Cavassini,[5] Hansjakob Furrer,[6] Jan Fehr,[7] Heiner C. Bucher,[1] Manuel Battegay,[8] and the Swiss HIV Cohort Study*

[1]Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland; [2]Division of Infectious Diseases, Regional Hospital of Lugano, Switzerland; [3]Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, Switzerland; [4]Division of Infectious Diseases, University Hospital Geneva, Switzerland; [5]Division of Infectious Diseases, University Hospital Lausanne, Switzerland; [6]Department of Infectious Diseases, Bern University Hospital and University of Bern, Switzerland; [7]Division of Infectious Diseases and Hospital Epidemiology, University Hospital and University of Zürich, Switzerland; [8]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Switzerland

Background: Atazanavir boosted with ritonavir (ATV/r) and efavirenz (EFV) are both recommended as first-line therapies for HIV-infected patients. We compared the 2 therapies for virologic efficacy and immune recovery. **Methods:** We included all treatment-naïve patients in the Swiss HIV Cohort Study starting therapy after May 2003 with either ATV/r or EFV and a backbone of tenofovir and either emtricitabine or lamivudine. We used Cox models to assess time to virologic failure and repeated measures models to assess the change in CD4 cell counts over time. All models were fit as marginal structural models using both point of treatment and censoring weights. Intent-to-treat and various as-treated analyses were carried out: In the latter, patients were censored at their last recorded measurement if they changed therapy or if they were no longer adherent to therapy. **Results:** Patients starting EFV (n = 1,097) and ATV/r (n = 384) were followed for a median of 35 and 37 months, respectively. During follow-up, 51% patients on EFV and 33% patients on ATV/r remained adherent and made no change to their first-line therapy. Although intent-to-treat analyses suggest virologic failure was more likely with ATV/r, there was no evidence for this disadvantage in patients who adhered to first-line therapy. Patients starting ATV/r had a greater increase in CD4 cell count during the first year of therapy, but this advantage disappeared after one year. **Conclusions:** In this observational study, there was no good evidence of any intrinsic advantage for one therapy over the other, consistent with earlier clinical trials. Differences between therapies may arise in a clinical setting because of differences in adherence to therapy. **Key words:** *antiretroviral therapy, CD4, epidemiology, protease inhibitors, reverse transcriptase inhibitors, viral load*

Atazanavir boosted with ritonavir (ATV/r) and efavirenz (EFV) are both recommended as once-daily first-line therapies for HIV-infected patients when combined with 2 nucleoside reverse transcriptase inhibitors (NRTIs).[1,2]

AIDS Clinical Trials Group (ACTG) A5202 was the first adequately powered randomized trial comparing EFV and ATV/r.[3] Trial results suggest that there are no important clinical differences between these 2 drugs when both are used in combination with the preferred NRTI backbone of tenofovir (TDF) and emtricitabine (FTC). Slightly greater increases in CD4 cell count were reported at both 48 and 96 weeks with ATV/r, albeit of unknown clinical relevance. The results were

*Members of the Swiss HIV Cohort Study are listed in the Acknowledgments.

Address for correspondence: Jim Young, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, CH-4031 Basel, Switzerland; phone: +41 61 265 3100; fax: +41 61 265 3109; e-mail: james.young@usb.ch

HIV Clin Trials 2014;15(3):92–103

www.hivclinicaltrials.com

doi: 10.1310/hct1503-92

broadly in line with earlier smaller studies; typically patients in these studies were followed for only 48 weeks.[4-6]

ACTG 5202 has 2 important limitations. First, the trial was open-label. Second, around one-third of the patients in each arm modified or discontinued treatment during this trial. These limitations complicate claims of equivalence between the 2 therapies. As more patients switch from their randomized therapy to the other therapy, any differences between therapies are reduced in an intent-to-treat analysis so that the 2 therapies are more likely to be seen as equivalent.[7]

We aim to mimic ACTG 5202 using data from the Swiss HIV Cohort Study (SHCS), comparing the 2 therapies for virologic efficacy and immunologic recovery in a clinical practice setting. Our study builds on an earlier intent-to-treat analysis of SHCS data where treatment-naïve patients starting different first therapies, including EFV and ATV/r both with TDF and FTC, were compared after one year of follow-up.[4] We consider similar outcomes but extend the period of follow-up. We also report as-treated analyses using inverse probability weights to adjust for the informative censoring that could arise when patients stop taking a first therapy.

METHODS

Patients

The SHCS is a prospective cohort study with continuing enrollment of HIV-infected adults.[8] Our population of interest includes all treatment-naïve patients starting first-line therapy with either ATV/r or EFV and a backbone of TDF and either FTC or lamivudine (3TC) after May 2003, when questions on adherence became part of routine follow-up in the SHCS. Pregnant women were excluded from our population, because for most of this period EFV was not recommended for use in pregnancy. Our sample included all patients from this population with at least one HIV RNA viral load measurement within 6 months before starting therapy and at least one CD4 cell count measurement between 6 months before and 3 months after starting therapy. Hence the baseline CD4 cell count was measured up to 3 months after starting therapy for some patients; without this compromise, such patients would be excluded from our analyses.

Both intent-to-treat and as-treated analyses were carried out. In intent-to-treat analyses, we followed patients from the start of therapy until their last recorded laboratory measurement to date (administrative censoring). In 3 different as-treated analyses, we censored measurements (1) after a patient started or stopped any protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI); (2) after a patient started or stopped any component of antiretroviral therapy; or (3) after either a patient's last report of adherence to first-line therapy or any change to the patient's therapy, whichever came first.

Adherence to treatment was evaluated through patient self-report. A patient was considered non-adherent if he or she missed more than one dose in the last month. If adherence was not recorded, nonadherence was assumed as missing adherence data have been shown to be informative with an effect similar to that of nonadherence.[9]

Outcomes

We defined virologic failure as in ACTG 5202: a viral load ≥1,000 copies/mL at or after 16 weeks from the start of therapy or ≥200 copies/mL at or after 24 weeks. In the trial, these measurements had to be confirmed; in our study, we required failure due to a viral load ≥200 copies/mL to be the first of 2 consecutive measurements ≥200 copies/mL regardless of the time between these 2 measurements. We did not require confirmation of failure if it was due to a viral load ≥1,000 copies/mL, because such a high viral load was unlikely to be an artifactual measurement.[10] We also estimated the difference between the 2 therapies in the proportion of patients with a viral load below 50 copies/mL at both 48 and 96 weeks, as in ACTG 5202.

Immunologic recovery was assessed by estimating the difference over time between the 2 therapies in mean CD4 cell count. We modelled this difference between therapies as a linear increase per year but with a change in slope at one year, because an earlier comparison between EFV and lopinavir suggested that differences between therapies may vary over time.[11] The model we fit implies that the mean CD4 cell count for a patient on ATV/r at a given point in time increases linearly with cumulative treatment at a certain slope until one year of cumulative treatment and at another slope after one year of cumulative treatment, relative to the

mean CD4 cell count for a patient on EFV at the same point in time.[12,13]

Viral load and CD4 cell count were measured at routine follow-up visits scheduled every 6 months, but measurements were also made between cohort visits and both routine and nonroutine measurements were used in our analyses.

Statistical Analyses

We used a discrete time version of the Cox proportional hazards model to assess time to virologic failure, a logistic regression model to estimate the difference between the 2 therapies in the proportion of patients with a viral load below 50 copies/mL at both 48 and 96 weeks, and a repeated measures model for the difference between therapies in CD4 cell count over time. Note that this discrete time version of the Cox model included an offset to adjust for variation in the time between consecutive measurements.[14] All models were fit as marginal structural models using inverse probability weights for confounder control[12,13,15]: Point of treatment weights were used to adjust for differences in the characteristics of patients starting each therapy, and censoring weights were used to adjust for differences in the characteristics of patients remaining on each therapy over time. Time-dependent intercepts were fit using cubic splines: For the Cox model, this provided the nonparametric baseline hazard function[15]; for the repeated measures model, this provided a flexible model of the mean CD4 cell count over time under the reference therapy.[12] In the logistic regression model, censoring weights were used to adjust for differences in the characteristics of patients with and without a measurement within a window of plus or minus 3 months from the index date (48 or 96 weeks).

The inverse probability weights were estimated using logistic regression with covariates that potentially influence outcome as well as determine the choice of first-line therapy, the decision to change therapy, or adherence to therapy. The covariates were (1) female gender, Caucasian ethnicity, intravenous drug use (IDU) as the likely mode of HIV transmission; (2) age, time since diagnosis, cohort center (categorized as private clinics, small hospitals, large hospitals in the French-speaking part of Switzerland, large hospitals in the German-speaking part), and the number of years since 2003 all at baseline; and (3) advanced HIV infection (CDC group C), IDU or methadone substitution, depression or psychiatric illness, diabetes, hypertension, chronic hepatitis B or hepatitis C infection, estimated glomerular filtration rate (eGFR, based on the Chronic Kidney Disease Epidemiology Collaboration formula[16]), viral load, and CD4 cell count both at baseline and time updated. Time-invariant covariates and covariates measured at baseline were used to construct point of treatment weights; an indicator for therapy and all covariates, except the number of years since 2003 and cohort center, were used to construct censoring weights (even for intent-to-treat analyses). Although first-line therapy seems to vary between cohort centers,[4] we assumed that common reasons for changing therapy – such as adverse events, the failure of therapy, or patient preferences – would be independent of time and place.

We report 3 sets of results for each analysis. The first set of results uses unstabilized weights; extreme weights were excluded by truncating these at the value of the 1st or 99th percentile if below or above this value, respectively.[17] Regression models were then fit without baseline covariates, so that the effects of therapy estimated by Cox or logistic models were equivalent to the effects typically estimated in a randomized controlled trial[18] and, in addition, were not subject to a small sample bias that can arise when many parameters are estimated from relatively few events.[19] The second set of results uses unstabilized weights without truncation. The third set of results uses stabilized weights with truncation; however weights were found from a reduced set of variables thought to strongly influence censoring: female gender, IDU, depression, diabetes, hepatitis B, eGFR, viral load, and CD4 cell count. Of the 3 sets of results, the second set is likely to be the least biased but the most variable, whereas the third set is likely to be the most biased but the least variable.[15,17-19]

We also carried out 3 additional sensitivity analyses. First, we excluded censoring weights from intent-to-treat analyses where patients were administratively censored – a process that was probably independent of the therapy received. Second, we analyzed a square root transformation of CD4 cell count, because the transformed CD4 cell count should more closely approximate a normal distribution as required by our model.[20] Finally, we considered whether CD4 cell count when starting therapy was an effect modifier by adding an interaction term between therapy and an indicator of whether patients had a CD4 cell count above or

below 200 cells/mm^3 when starting therapy. This seems an important threshold below which lasting damage to the immune system may occur such that immunologic recovery is impeded.[21-24]

For each analysis, we report estimates and their 95% confidence intervals (CI) with EFV as the reference therapy. We use SAS version 9.2 (SAS Institute Inc., Cary, NC) for analyses and R version 2.15.2 (R Foundation for Statistical Computing, www.r-project.org) for graphics.

RESULTS

Patient Characteristics

As of January 2013, 1,681 patients in the SHCS started first-line therapy with either EFV or ATV/r and a backbone of TDF and either FTC or 3TC. We excluded 10 women who were pregnant when starting therapy and 26 women who became pregnant during follow-up. Of the remaining 1,645 patients, 1,481 (90%) had at least one viral load measurement within 6 months before starting therapy and at least one measurement of CD4 cell counts between 6 months before and 3 months after starting therapy. Compared with patients starting EFV (n = 1,097), those starting ATV/r (n = 384) were more likely to have been infected with HIV through IDU, suffered from depression or psychiatric illness, or were co-infected with chronic hepatitis B or hepatitis C (**Table 1**).

These 1,481 patients were followed for a total of 4,881 person-years, with a median follow-up of 35 and 37 months for patients starting EFV and ATV/r, respectively. During this time, 17,361 viral load measurements were made, with a median time between measurements of 3.0 months (interquartile range [IQR], 2.5 to 4.0) and 2.9 months (IQR, 2.3 to 3.8) for patients starting EFV and ATV/r, respectively.

During the study, 637 (58%) patients on EFV and 172 (45%) patients on ATV/r stayed on the main component of their therapy until the end of follow-up; median times on this main component were 21 and 20 months for patients starting EFV and ATV/r, respectively. At the end of follow-up, 612 (56%) patients on EFV and 150 (39%) patients on ATV/r were still on their first-line therapy; median times on first-line therapy were 20 and 17 months for patients starting EFV and ATV/r, respectively. Furthermore, 558 (51%) patients on EFV and 127 (33%) patients on ATV/r remained adherent to their first-line therapy until the end of follow-up; median times on first-line therapy while reporting adherence to that therapy were 19 and 16 months for patients starting EFV and ATV/r, respectively.

Table 1. Patient characteristics when starting first-line therapy with either efavirenz (EFV) or ritonavir-boosted atazanavir (ATV/r) and a backbone of tenofovir and either emtricitabine (FTC) or lamivudine

Characteristic	EFV (n = 1,097)	ATV/r (n = 384)
FTC as second nucleoside reverse transcriptase inhibitor, %	85	90
Median HIV RNA, $\log_{10}$ copies/mL	4.7	4.8
HIV RNA <100,000 copies/mL, %	67	63
Median CD4 cell count, cells/mm^3	268	248
CD4 cell count ≥200 cells/mm^3, %	70	65
Median age, years	40	41
Female gender, %	18	22
Caucasian ethnicity, %	76	82
Intravenous drug use as the likely mode of transmission, %	6	17
Median time since HIV diagnosis, years	1.4	1.8
Advanced HIV infection, %	12	12
Chronic hepatitis B or hepatitis C infection, %	13	25
Diabetes, %	4	2
Hypertension, %	22	21
Depression or psychiatric problem, %	13	19
Median estimated glomerular filtration rate, mL/min/1.73 m^2	104	104
Year therapy started, %		
2003-2007	34	33
2008-2013	66	67
Center, %		
Large hospitals, German-speaking part of Switzerland	42	57
Large hospitals, French-speaking part of Switzerland	22	12
Small hospitals	4	4
Private clinics	32	27

Among the 485 (44%) patients on EFV and 234 (61%) patients on ATV/r who changed their first-line therapy, changes often took place quickly with a median time to a first change of 10 and 12 months, respectively. Treatment was interrupted in 155 (14%) patients on EFV and 79 (21%) patients on ATV/r. Among those who switched to other regimens, patients starting EFV typically switched to a PI (143; 13%), to another NNRTI (75; 7%) or to an integrase inhibitor (23; 2%), whereas patients starting ATV/r typically switched to another PI (42; 11%), to an NNRTI (45; 12%), or replaced tenofovir with abacavir (22; 6%).

Virologic Failure

In an intent-to-treat analysis, 109 (10%) of 1,097 patients starting EFV experienced virologic failure with a median time to failure of 17 months; 56 (15%) of 384 patients starting ATV/r experienced virologic failure with a median time to failure of 17 months. There was a tendency for patients starting ATV/r to have a higher risk of virologic failure (hazards ratio [HR], 1.34; 95% CI, 0.93 to 1.93) (**Table 2**, **Figure 1**). However, this possible difference between the 2 therapies was not apparent in as-treated analyses (HR, 0.96; 95% CI, 0.47 to 1.94) when patients were censored after last reporting adherence to first-line therapy.

Around 48 weeks, viral load measurements were available in 949 (87%) and 322 (84%) patients starting EFV and ATV/r, respectively; values for 96 weeks were 763 (70%) and 282 (73%), respectively. Data were missing largely due to early administrative censoring (75% and 89% of patients with missing measurements at 48 and 96 weeks, respectively). Among patients with available viral load measurements, 865 (91%) and 283 (88%) patients starting EFV and ATV/r, respectively, had a viral load below 50 copies/mL at 48 weeks; values at 96 weeks were 702 (92%) and 251 (89%), respectively. In intent-to-treat analyses, the proportion of patients with a viral load below 50 copies/mL at 48 weeks was lower for patients starting ATV/r (odds ratio [OR], 0.67; 95% CI, 0.46 to 0.99) and perhaps lower at 96 weeks as well (OR, 0.71; 95% CI, 0.46 to 1.10) (**Table 3**). In as-treated analyses, differences between therapies at weeks 48 and 96 were similar, but estimates became less precise (with wider confidence intervals) as more patients were censored in these analyses.

Immunologic Response

In intent-to-treat analyses, patients starting ATV/r had an estimated difference in CD4 cell count of 44 (95% CI, 3 to 85) cells/mm^3 during the first year of therapy, which was followed by a difference of -18 (95% CI ,-31 to -4) cells/mm^3 for each additional year of therapy (**Table 4**).

Table 2. Estimates of the relative effect of therapy on time to virologic failure when patients start first-line therapy with either efavirenz or ritonavir-boosted atazanavir and a backbone of tenofovir and either emtricitabine or lamivudine

	HR (95% CI)		
Censoring type	Truncated unstabilized weights	Full unstabilized weights	Truncated stabilized weights
Administrative censoring (intent-to-treat) [a]	1.34 (0.93, 1.93)	1.44 (0.96, 2.16)	1.36 (0.97, 1.90)
Censored after change to main component	1.37 (0.75, 2.48)	1.33 (0.73, 2.42)	1.48 (0.80, 2.69)
Censored after change to any component	1.42 (0.78, 2.59)	1.36 (0.74, 2.49)	1.57 (0.85, 2.92)
Censored after last report of adherence to first-line therapy	0.96 (0.47, 1.94)	0.92 (0.45, 1.87)	0.97 (0.47, 2.03)

Note: Each estimate is a hazard ratio (HR) and its 95% confidence interval (CI) with efavirenz as the reference therapy.

[a] Intent-to-treat estimates: without censoring weights, 1.26 (0.89-1.77); no weights but adjusted for baseline covariates, 1.41 (1.01-1.97); no weights and no baseline covariates, 1.52 (1.10-2.10).

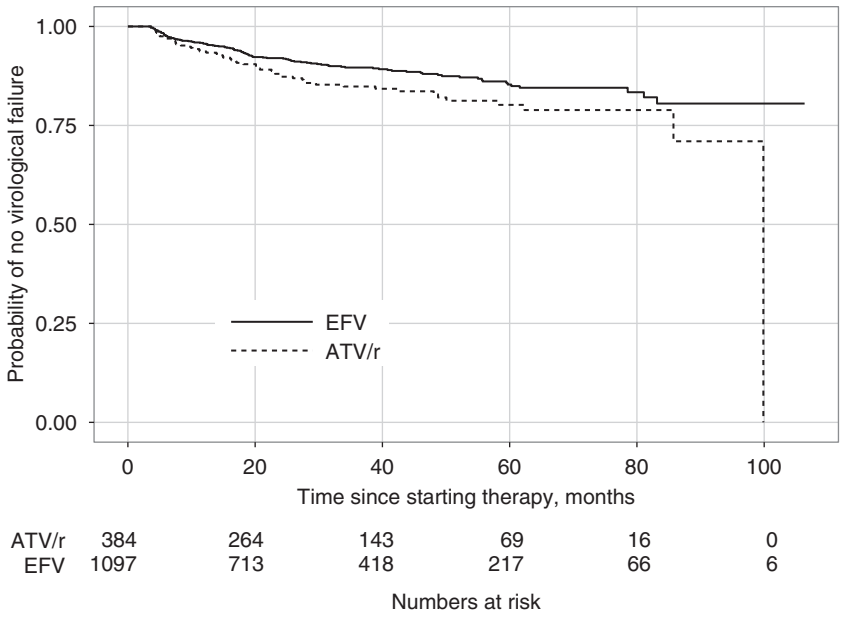

Figure 1. Intent-to-treat Kaplan Meier curves of virologic failure for patients starting first-line therapy with either efavirenz (EFV) or ritonavir-boosted atazanavir (ATV/r) and a backbone of tenofovir and either emtricitabine or lamivudine.

These estimates of the relative effect of therapy suggested that patients starting ATV/r had greater early increase in CD4 cell count, but this advantage then disappeared. **Figure 2** suggests that any differences between EFV and ATV/r in CD4 cell count over time are not clinically important.

As-treated analyses and analyses with different weights showed the same pattern, which was a greater increase in CD4 cell count with ATV/r in the first year of therapy that was then attenuated beyond one year.

Sensitivity Analyses

In sensitivity analyses, if censoring weights were excluded from intent-to-treat analyses, differences between therapies were slightly reduced for both virologic efficacy and immunologic recovery (see footnotes to **Tables 2**, **3** and **4**). We did not have sufficient power to draw conclusions from our interaction model about whether differences in CD4 cell count between therapies depend on the CD4 cell count when starting therapy. Modelling square root transformed CD4 cell count gave results that again suggested greater early increases in CD4 cell count with ATV/r. With square root transformed CD4 cell counts, the difference between therapies must be calculated from model parameters but that calculation implied an additional increase after one year on ATV/r of 31, 53, or 7 cells/mm^3 above an expected CD4 cell count of 459, 447, or 461 cells/mm^3 for patients on EFV (using truncated unstabilized, full unstabilized, or truncated stabilized weights, respectively).

DISCUSSION

We compared EFV and ATV/r with a common backbone of TDF and either FTC or 3TC, 2 of the most frequently used first-line therapies in the SHCS. While intent-to-treat analyses suggested that virologic failure was more likely with ATV/r, there was no evidence for this disadvantage in patients who adhered to therapy. Our data were consistent with greater early increases in CD4 cell count for patients on ATV/r, but there was no good evidence of any long-term advantage for one therapy or the other.

Table 3. Estimate of the relative effect of therapy on proportion of patients with a viral load below 50 copies/mL at 48 and 96 weeks when patients start first-line therapy with either efavirenz (EFV) or ritonavir-boosted atazanavir (ATV/r) and a backbone of tenofovir and either emtricitabine or lamivudine.

	OR (95% CI)		
Censoring type, patients remaining in the analysis	Truncated unstabilized weights	Full unstabilized weights	Truncated stabilized weights
48 weeks			
Administrative censoring (intent-to-treat) [a], EFV (*n* = 949), ATV/r (*n* = 322)	0.67 (0.46, 0.99)	0.67 (0.46, 0.97)	0.71 (0.48, 1.05)
Censored after change to main component, EFV (*n* = 755), ATV/r (*n* =255)	0.61 (0.39, 0.95)	0.96 (0.63, 1.45)	0.59 (0.37, 0.94)
Censored after change to any component, EFV (*n* = 738), ATV/r (*n* = 242)	0.51 (0.33, 0.80)	0.80 (0.53, 1.22)	0.52 (0.33, 0.83)
Censored after last report of adherence to first-line therapy, EFV (*n* = 712), ATV/r (*n* = 227)	0.74 (0.45, 1.22)	1.17 (0.74, 1.87)	0.72 (0.43, 1.20)
96 weeks			
Administrative censoring (intent-to-treat) [b], EFV (*n* = 763), ATV/r (*n* = 282)	0.71 (0.46, 1.10)	0.79 (0.51, 1.21)	0.71 (0.45, 1.12)
Censored after change to main component, EFV (*n* = 557), ATV/r (*n* = 179)	0.82 (0.35, 1.90)	0.99 (0.43-2.27)	0.78 (0.33-1.87)
Censored after change to any component, EFV (*n* = 535), ATV/r (*n* = 168)	0.71 (0.30, 1.69)	0.97 (0.42, 2.25)	0.70 (0.29, 1.71)
Censored after last report of adherence to first-line therapy, EFV (*n* = 497), ATV/r (*n* = 150)	0.66 (0.28, 1.56)	0.85 (0.36, 1.99)	0.59 (0.24, 1.46)

Note: Each estimate is an odds ratio (OR) and its 95% confidence interval (CI) with efavirenz as the reference therapy.

[a] Intent-to-treat estimates: without censoring weights, 0.76 (0.50-1.14); no weights but adjusted for baseline covariates, 0.75 (0.49-1.14); no weights and no baseline covariates, 0.70 (0.47-1.05).

[b] Intent-to-treat estimates: without censoring weights, 0.74 (0.47-1.17); no weights but adjusted for baseline covariates, 0.72 (0.45-1.16); no weights and no baseline covariates, 0.70 (0.45-1.11).

In ACTG 5202, the rate of virologic failure for both EFV and ATV/r was 52 per 1,000 person-years during a median follow-up of 2.6 years. In our study, the rate of virologic failure was lower: 33 and 49 per 1,000 patient-years during a median follow-up of 3.0 and 3.2 years for patients starting EFV and ATV/r, respectively. Hence, in ACTG 5202, the risk of virologic failure did not differ between therapies (HR, 1.01; 95% CI, 0.70 to 1.46); in our study, intent-to-treat analyses suggest a difference between therapies (HR, 1.34; 95% CI, 0.93 to 1.93), although no difference was apparent in patients who adhered to therapy (HR, 0.96; 95% CI, 0.47 to 1.94). In ACTG 5202, 90% and 84% of those starting EFV and ATV/r, respectively, had a suppressed viral load at 48 weeks; values at 96 weeks were 91% and 90%, respectively. In our study, 91% and 88% of those starting EFV and ATV/r, respectively, had a suppressed viral load at 48 weeks; values at 96 weeks were 92% and 89%, respectively. Hence in both our study and ACTG 5202, early virologic suppression was more likely with EFV than with ATV/r.

In the SHCS, ATV/r is often given to patients at risk of nonadherence (patients using injection drugs or with psychiatric illness), because of its

Table 4. Estimates of the relative effect of therapy over time on CD4 cell count when patients start first-line therapy with either efavirenz or ritonavir-boosted atazanavir and a backbone of tenofovir and either emtricitabine or lamivudine

	Difference in CD4 cell count, cells/mm^3 per year (95% CI)					
	Truncated unstabilized weights		Full unstabilized weights		Truncated stabilized weights	
Censoring type	≤1 year	>1 year	≤1 year	>1 year	≤1 year	>1 year
Administrative censoring (intent-to-treat) [a]	44 (3, 85)	-18 (-31, -4)	72 (25, 119)	-27 (-47, -7)	14 (-8, 36)	-5 (-18, 7)
Censored after change to main component	60 (12, 109)	-26 (-46, -6)	73 (18, 128)	-18 (-57, 21)	26 (4, 48)	-14 (-27, -1)
Censored after change to any component	73 (25, 122)	-26 (-48, 5)	82 (25, 139)	-5 (-60, 50)	37 (13, 58)	-15 (-27, -3)
Censored after last report of adherence to first-line therapy	64 (15, 113)	-21 (-44, 3)	67 (10, 123)	5 (-51, 61)	37 (13, 61)	-17 (-29, -4)

Note: Each estimate is the difference between therapies in CD4 cell count per year and its 95% confidence interval (CI) with efavirenz as the reference therapy.

[a] Intent-to-treat estimates: without censoring weights, ≤1 year 26 (-10, 62), >1 year -12 (-25, 1); no weights but adjusted for baseline covariates, ≤1 year 12 (-10, 33), >1 year -4 (-16, 7); no weights and no baseline covariates, ≤1 year 9 (-24, 42), >1 year -7 (-20, 6).

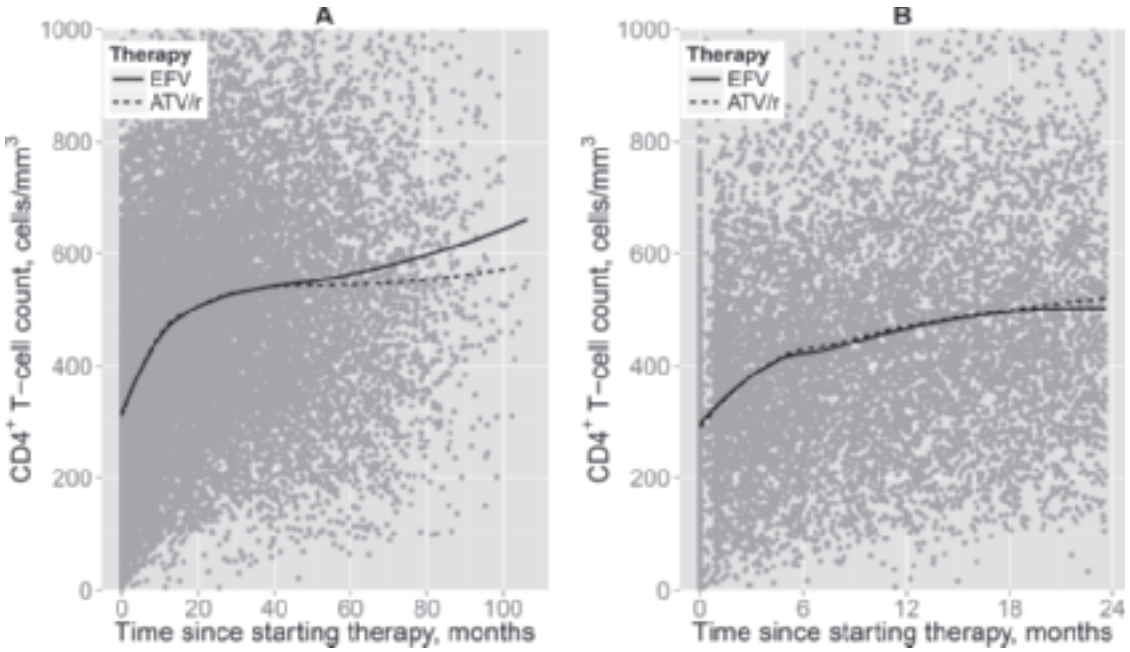

Figure 2. CD4 cell count over time for patients starting first-line therapy with either efavirenz (EFV) or ritonavir-boosted atazanavir (ATV/r) and a backbone of tenofovir and either emtricitabine or lamivudine. The average response curves shown are calculated by the default LOESS function in R version 2.15.2. Response curves are shown (**A**) for the whole study period, and (**B**) for the first 2 years.

relatively high barrier to resistance.[4] Injection drug users receiving treatment for opioid addiction may also be given ATV/r, because of an interaction between EFV and methadone.[2] As expected, patients on ATV/r in our study reported lower adherence than those on EFV. In our study, 92% and 88% of patients on EFV and ATV/r, respectively, reported perfect adherence at 48 weeks (ie, no missed doses in the last month); values at 96 weeks were 90% and 88%, respectively. In ACTG 5202, there was no difference in reported adherence between therapies: At 48 weeks, 92% and 93% of patients on EFV and ATV/r, respectively, reported no missed doses in the last week; values at 96 weeks were 92% and 91%, respectively. This is to be expected unless one therapy is much harder to take than the other; randomization ensures similar patients receive each therapy.

Taken together, our efficacy and adherence data suggest that virologic failure was more likely for patients on ATV/r in our study, because these patients were less adherent to therapy. Poor adherence on ATV/r is more likely to lead to virologic failure than poor adherence on EFV, because EFV has the longer elimination half-life.[25] Patients reporting poor adherence in the SHCS are at greater risk of virologic failure.[9] It is still appropriate to give such patients ATV/r, even though virologic suppression can probably be maintained with a lower degree of adherence on EFV; resistance mutations are less likely to emerge in patients who fail on ATV/r, so future treatment options are preserved.[3]

Studies comparing the efficacy of EFV and ATV/r have shown conflicting results. Clinical trials other than ACTG 5202, with either the same[6] or different backbones,[26-28] have in general shown no difference in virologic and immunologic outcomes between the 2 therapies, although these trials have lacked the power of ACTG 5202. On the other hand, some short-term observational studies showed lower rates of virologic suppression at 48 weeks with ATV/r.[4,5] In another observational study, patients on ATV/r had better adherence than those on EFV, and virologic suppression at 6 months was more likely with ATV/r than with EFV.[29] None of these studies estimates the relative effect of therapy in adherent patients by censoring the nonadherent and then re-weighting data, as we do here. Our results reconcile these differences between studies; our results are consistent with differences in efficacy arising because of different degrees of adherence in patients on these therapies rather than differences between therapies in intrinsic potency.

With respect to immunologic recovery, patients on ATV/r in our study had a greater increase in CD4 cell count during the first year of therapy, but this advantage was not sustained. In ACTG 5202, patients on ATV/r also had a greater early increase in CD4 cell count, with a difference of 12 cells/mm^3 at 48 weeks. This difference is similar to the 14 cells/mm^3 difference estimated in the first year of our study using stabilized weights; of the 3 estimates in **Table 4**, this estimate is the most precise. Our sensitivity analyses of square root transformed CD4 cell counts suggest that estimated differences between therapies are exaggerated in analyses of untransformed CD4 cell counts.

There are other factors to consider when choosing between these 2 first-line therapies. An EFV-based regimen is simpler to take, as it requires fewer pills and it can be taken once daily without dietary restrictions. Hence the lower adherence we saw in patients on ATV/r could partly be due to the fact that this therapy was more difficult to take. This is consistent with the higher rate (61%) at which patients on ATV/r discontinued their first-line therapy in this study relative to patients on EFV (44%). Compared to EFV, ATV/r is associated with a greater increase in body fat[30] and a greater decrease in eGFR when used in combination with TDF.[31,32] However, patients on EFV show greater increases in total cholesterol and low-density lipoprotein cholesterol but also in high-density lipoprotein cholesterol.[3,33] EFV may cause neurotoxic side effects and so is not recommended for women planning a pregnancy or who are sexually active without effective contraception.[2]

We acknowledge that our study has some limitations. Causality is inherently difficult to establish from observational data, and our estimate of the causal effect of one therapy relative to another requires correctly specified models for the 2 sets of weights and for the differences between therapies. There were fewer patients on ATV/r than in ACTG 5202; as a consequence, we did not have the power to adequately estimate any interaction between the effects of therapy and CD4 cell count when starting therapy. We did not look at differences in adverse events, because the reporting of these events and reasons for treatment discontinuation is neither as detailed nor as conscientious in the SHCS as in

a typical clinical trial. Our limited data show that among patients who stopped taking EFV, 27% did so because of neurotoxicity. However 24% and 41% of patients who stopped taking EFV and ATV/r, respectively, did so without any reason being recorded. Data on genetic markers in genes associated with toxicity or pharmacokinetics of the 2 therapies were only available for a limited number of patients and were therefore not included in our study, but patients with relevant genetic risk markers are more likely to discontinue therapy.[34]

On the other hand, our study has several strengths. We include patients with hepatitis B or C and substance abuse so that our patients represent a more typical clinical population than the patients usually recruited into clinical trials. Our use of marginal structural models allows us to mimic a clinical trial by adjusting for differences both between patients starting each therapy and between patients remaining on each therapy. This approach combined with our data on adherence allows us to better appreciate the consequences of prescribing one therapy or the other in a clinical setting.

In conclusion, our observational study confirms results from the only large randomized trial to date (ACTG 5202). Differences between therapies in observational studies appear to arise because of differences in adherence to therapy. In this study, there were no important clinical differences in adherent patients between first-line therapy with either EFV or ATV/r when combined with a backbone of TDF and either FTC or 3TC. The statistical methods we use allow us to replicate a clinical trial in a routine clinical care setting and, along with adherence data, to develop a clearer picture of the practical consequences of prescribing each therapy.

ACKNOWLEDGMENTS

Financial support/disclosures: This study (SHCS 695) has been financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant 33CS30_134277). The Basel Institute for Clinical Epidemiology and Biostatistics is supported by grants from Santésuisse and from the Gottfried and Julia Bangerter-Rhyner-Foundation.

Conflicts of interest: E.B. is a member of the advisory boards of Gilead, ViiV, MSD, Boehringer Ingelheim, Pfizer, and Janssen; he is consultant for AbbVie; his institution has received unrestricted research grants from Gilead, Abbott, Roche, and MSD; he has also received travel grants from Gilead, MSD, Boehringer Ingelheim, Bristol-Meyers Squibb (BMS), and Janssen. P.V. participated as speaker in symposia and/or advisor for BMS, MSD, ViiV, Pfizer, Gilead, and Janssen. The institution of A.C. received unrestricted research grants from AbbVie, MSD, Gilead, and Janssen-Cilag. The institution of M.C. has received advisory board honorarium from BMS, Gilead, MSD, and Janssen-Cilag and received unrestricted research grant from BMS, Gilead, and MSD; he has also received travel grants from BMS, Boehringer-Ingelheim, and Gilead. The institution of H.F. has received payments for participation in advisory boards and/or unrestricted research grants and/or travel grants from ViiV, BMS, Gilead, Abbott, MSD, Boehringer-Ingelheim, Janssen, and Roche. J.F. is consultant for BMS, Gilead, MSD, Janssen, ViiV, and Astellas; his institution received unrestricted research grants and travel grants from all mentioned pharmaceutical companies. H.C.B. is consultant for Abbott, BMS, Gilead, Janssen, Tibotec, MSD, GSK, and ViiV; his institution received unrestricted research grants and travel grants from all mentioned pharmaceutical companies. M.B. has participated in the advisory boards of BMS, Gilead, Janssen, MSD, and ViiV and has received research grants and unrestricted educational grants to his Division by BMS, Gilead, Jannsen, ViiV, and Boeheringer Ingelheim. All other authors declare no competing interests.

The **members of the Swiss HIV Cohort Study** are Barth J, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Cellerai C, Egger M, Elzi L, Fehr J, Fellay J, Flepp M, Francioli P (President of the SHCS), Furrer H (Chairman of the Clinical and Laboratory Committee), Fischer M*, Fux CA, Gorgievski M, Günthard H (Chairman of the Scientific Board), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Rauch A, Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

*Deceased December 13, 2010.

REFERENCES

1. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA.* 2012;308(4):387-402.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed July 24, 2013.
3. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med.* 2011;154(7):445-456.
4. Elzi L, Erb S, Furrer H, et al. Choice of initial combination antiretroviral therapy in individuals with HIV infection: Determinants and outcomes. *Arch Intern Med.* 2012;172(17):1313-1321.
5. Taniguchi T, Grubb JR, Nurutdinova D, et al. Efavirenz outperforms boosted atazanavir among treatment-naive HIV-1-infected persons in routine clinical care. *J Int Assoc Provid AIDS Care.* 2013;12(2):138-141.
6. Puls RL, Srasuebkul P, Petoumenos K, et al. Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: Week 48 data from the Altair study. *Clin Infect Dis.* 2010;51(7):855-864.
7. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: The importance of rigorous methods. *BMJ.* 1996;313(7048):36-39.
8. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: The Swiss HIV Cohort study. *Int J Epidemiol.* 2010;39(5):1179-1189.
9. Glass TR, De Geest S, Hirschel B, et al. Self-reported nonadherence to antiretroviral therapy repeatedly assessed by two questions predicts treatment failure in virologically suppressed patients. *Antivir Ther.* 2008;13(1):77-85.
10. Gallant JE. Making sense of blips. *J Infect Dis.* 2007;196(12):1729-1731.
11. Young J, Bucher HC, Guenthard HF, et al. Virological and immunological responses to efavirenz or boosted lopinavir as first-line therapy for patients with HIV. *Antivir Ther.* 2009;14(6):771-779.
12. Hernan MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med.* 2002;21(12):1689-1709.
13. Cole SR, Hernan MA, Margolick JB, Cohen MH, Robins JM. Marginal structural models for estimating the effect of highly active antiretroviral therapy initiation on CD4 cell count. *Am J Epidemiol.* 2005;162(5):471-478.
14. Carlin JB, Wolfe R, Coffey C, Patton GC. Analysis of binary outcomes in longitudinal studies using weighted estimating equations and discrete-time survival methods: Prevalence and incidence of smoking in an adolescent cohort. *Stat Med.* 1999;18(19):2655-2679.
15. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology.* 2000;11(5):561-570.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.
17. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol.* 2008;168(6):656-664.
18. Hauck WW, Anderson S, Marcus SM. Should we adjust for covariates in nonlinear regression analyses of randomized trials ? *Control Clin Trials.* 1998;19(3):249-256.
19. Greenland S, Schwartzbaum JA, Finkle WD. Problems due to small samples and sparse data in conditional logistic regression analysis. *Am J Epidemiol.* 2000;151(5):531-539.
20. Lipsitz SR, Ibrahim J, Molenberghs G. Using a Box–Cox transformation in the analysis of longitudinal data with incomplete responses. *J R Stat Soc Ser C Appl Stat.* 2000;49(3):287-296.
21. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA.* 2001;286(20):2568-2577.
22. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: A collaborative analysis of prospective studies. *Lancet.* 2002;360(9327):119-129.
23. Phillips AN, Lundgren JD. The CD4 lymphocyte count and risk of clinical progression. *Curr Opin HIV AIDS.* 2006;1(1):43-49.
24. Young J, Psichogiou M, Meyer L, et al. CD4 cell count and the risk of AIDS or death in HIV-Infected adults on combination antiretroviral therapy with a suppressed viral load: A longitudinal cohort study from COHERE. *PLoS Med.* 2012;9(3):e1001194.
25. Maggiolo F, Ravasio L, Ripamonti D, et al. Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. *Clin Infect Dis.* 2005;40(1):158-163.
26. Andersson LM, Vesterbacka J, Blaxhult A, et al. Lopinavir/ritonavir, atazanavir/ritonavir, and efavirenz in antiretroviral-naive HIV-1-infected individuals over 144 weeks: An open-label randomized controlled trial. *Scand J Infect Dis.* 2013;45(7):543-551.
27. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr.* 2004;36(5):1011-1019.
28. Honda M, Ishisaka M, Ishizuka N, Kimura S, Oka S. Open-label randomized multicenter selection study of once daily antiretroviral treatment regimen comparing ritonavir-boosted atazanavir to efavirenz with fixed-dose abacavir and lamivudine. *Intern Med.* 2011;50(7):699-705.
29. Lima VD, Nosyk B, Wood E, et al. Assessing the effectiveness of antiretroviral regimens in cohort studies involving HIV-positive injection drug users. *AIDS.* 2012;26(12):1491-1500.
30. McComsey GA, Kitch D, Sax PE, et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. *Clin Infect Dis.* 2011;53(2):185-196.
31. Young J, Schäfer J, Fux CA, et al. Renal function in patients with HIV starting therapy with tenofovir and

either efavirenz, lopinavir or atazanavir. *AIDS.* 2012;26(5): 567-575.
32. Gupta S, Kitch D, Tierney C, et al. Long-term changes in renal parameters in ART-naive subjects randomized to abacavir/lamivudine or tenofovir/emtricitabine with atazanavir/ritonavir or efavirenz: ACTG A5224s, a sub-study of A5202. Presented at: 20th Conference on Retroviruses and Opportunistic Infections; March 3-6, 2013; Atlanta, GA. Abstract 811.
33. Gotti D, Cesana BM, Albini L, et al. Increase in standard cholesterol and large HDL particle subclasses in antiretroviral-naive patients prescribed efavirenz compared to atazanavir/ritonavir. *HIV Clin Trials.* 2012;13(5):245-255.
34. Lubomirov R, Colombo S, di Lulio J, et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: An observational cohort study. *J Infect Dis.* 2011;203(2):246-257.