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Comparative Effectiveness of Initial Antiretroviral Therapy Regimens: ACTG 5095 and 5142 Clinical Trials Relative to ART-CC Cohort Study

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Abstract

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DISCLOSURES

All remaining authors have no conflicts of interest to declare.

Background—The generalizability of antiretroviral therapy (ART) clinical trial efficacy findings to routine care settings is not well studied. We compared the relative effectiveness of initial ART regimens estimated in AIDS Clinical Trial Group (ACTG) randomized controlled trials with that among patients receiving ART at Antiretroviral Therapy Cohort Collaboration (ART-CC) study sites.

Methods—Treatment-naive HIV-infected patients initiating identical ART regimens in ACTG trials (A5095 and A5142) and at 15 ART-CC cohort study sites were included. Virological failure (HIV-1 RNA >200 copies/ml) at 24- and 48-weeks, incident AIDS-defining events and mortality were measured according to study design (ART-CC cohort vs. ACTG trial) and stratified by 3rd drug [Abacavir (ABC), Efavirenz (EFV), and Lopinavir/r (LPV/r)]. We used logistic regression to estimate and compare odds ratios for virological failure between different regimens and study designs, and used Cox models to estimate and compare hazard ratios for AIDS and death.

Results—Compared with patients receiving ABC, those receiving EFV had roughly half the odds of 24-week virologic failure (>200 copies/mL) in both ACTG 5095 (OR=0.53, 95% CI 0.36–0.79) and ART-CC (0.46, 0.37–0.57). Virologic superiority of EFV (vs. ABC) appeared comparable in ART-CC and ACTG 5095 (ratio of ORs 0.86, 95% CI 0.54–1.35). Odds ratios for 48-week virologic failure, comparing EFV with LPV/r, were also comparable in ACTG 5142 and ART-CC (ratio of ORs 0.87, 0.45–1.69).

Conclusions—Between ART regimen virologic efficacy of 3rd drugs ABC, EFV, and LPV/r observed in the ACTG 5095 and 5142 trials appear generalizable to the routine care setting of ART-CC clinical cohorts.

Keywords

HIV; AIDS; Antiretroviral therapy; Comparative effectiveness; Viral load

Introduction

Randomized controlled clinical trials are the cornerstone of evidence based medicine and are essential to inform human immunodeficiency virus (HIV) antiretroviral treatment (ART) guidelines and clinical practice decisions.[1–3] For over two decades, the Adult AIDS Clinical Trial Group (ACTG) has been a leading organization in the conduct of clinical trials, including those comparing the efficacy of initial ART regimens-(https://actgnetwork.org/). Because of the potential for selection bias imposed by trial eligibility criteria and volunteer bias for participation in clinical trials, there is always uncertainty whether clinical trial findings will be generalizable to the broader patient population treated through routine clinical care outside the context of a study.[4, 5] Regardless, randomized controlled trials remain the optimal means to compare the efficacy between treatment strategies and the only study methodology able to directly assess causality.

Observational cohort studies offer a complementary research design that allows for a comparison of the effectiveness of different treatment strategies in routine care settings. Analyses of HIV cohort studies have similarly made important contributions to treatment strategies, particularly in assessing effects on clinical events and mortality, which often cannot be adequately evaluated in clinical trials because of limited duration of RCTs and low event frequency. The Antiretroviral Therapy Cohort Collaboration (ART-CC) has been a leading, international multi-site HIV cohort study for over a decade (http://www.art-cohort-collaboration.org).[6, 7] A notable limitation inherent to cohort studies is the potential for confounding by indication and unmeasured confounding, which may impact outcome interpretation and reliability of study findings.[4, 5, 8, 9] Regardless, well conducted observational cohort studies play an important role in HIV treatment decisions as

they are inclusive and reflective of treatment responses and outcomes of the broader population of HIV-infected persons than typically studied through clinical trials and generally can provide longer follow-up.

In recent years, considerable emphasis has been placed on the importance of comparative effectiveness research (CER) to allow for informed treatment decisions to improve individual and population level health.[10] Inherent to the definition of CER is the direct comparison of alternative treatments in patients typical of those treated in day-to-day clinical care. Among the priority areas in the CER agenda is the development and evaluation of methodologies of clinical research that address limitations of existing study designs to generate novel data elements to augment the traditional evidence base thereby fostering more informed treatment decisions.[10] Here, we compare patient-level virologic and clinical effectiveness of a number of initial ART regimens estimated in ACTG clinical trials with that estimated in patients treated in routine clinical care and enrolled in cohorts participating in the ART-CC. To our knowledge, this is the first large-scale regimen-level comparison of contemporary initial ART regimens among patients receiving treatment through clinical trials v. routine care. These analyses address the pivotal questions of whether ART efficacy findings observed in clinical trials translate to routine care settings, and whether differential ART regimen-level effects are observed across study designs and treatment settings.

Methods

Setting and Participants

AIDS Clinical Trial Group (ACTG) Study 5095—ACTG 5095 is a randomized, double-blind study that compared three ART regimens for the initial treatment of subjects infected with HIV-1 and has been described in detail.[11, 12] We used data from the two arms of the trial that compared three drug regimens: zidovudine (AZT), lamivudine (3TC) and abacavir (ABC) with AZT+3TC plus efavirenz (EFV).

Eligible patients were HIV-1–infected adults who had received no previous ART and who had a plasma HIV-1 RNA level of at least 400 copies/mL and acceptable safety laboratory results across a range of different measures. Patients were excluded if they had received immunomodulator or investigational therapy or vaccines within the previous 30 days, if they weighed less than 40 kg, or if they were pregnant or breast-feeding. Subjects enrolled in the study between March 2001 and November 2002.

ACTG Study 5142—ACTG 5142 is a randomized, open-label trial that compared three ART regimens for the initial treatment of subjects infected with HIV-1 and has been described in detail.[13] We used data from the two arms of the trial that compared EFV with lopinavir boosted with ritonavir (LPV/r) each together with two NRTIs (3TC with either AZT or stavudine (D4T) or tenofovir (TDF)).

The study population consisted of HIV-1–infected patients at least 13 years of age who had not received previous ART. All patients had a plasma HIV-1 RNA level of at least 2000 copies/mL with any CD4 cell count, and acceptable laboratory results across a range of different measures. Patients were enrolled from January 2003 to May 2004.

ART-CC Cohort Collaboration (ART-CC)—ART-CC is an international collaboration between the investigators of cohort studies of HIV-1–infected patients from Europe and North America that was established in 2000 to estimate prognosis of HIV-1 infected, treatment-naïve patients initiating combination ART. The collaboration has been described in detail elsewhere.[6, 7] Prospective cohort studies were eligible for participation if they had enrolled at least 100 HIV-1–infected patients aged 16 years or more who had not previously

received antiretroviral treatment, started ART with a combination of at least three antiretroviral drugs after 1996, and been followed for a median duration of at least 1 year after ART initiation. The dataset analyzed here was assembled during 2009 and included data from 15 cohorts: the AIDS Therapy Evaluation Project, Netherlands (ATHENA),[14] the Agence Nationale de la Recherche sur le SIDA et les hépatites virales (ANRS) CO3 Aquitaine Cohort,[15] the ANRS CO4 French Hospital Database on HIV (FHDH),[16] the Italian Cohort of Antiretroviral-Naive Patients (ICONA),[17] the Köln/Bonn Cohort, Germany,[18] the Proyecto para la Informatización del Seguimiento Clínico-epidemiológico de la Infección por HIV y SIDA (PISCIS) Cohort,[19] Cohorte de la Red de Investigación en Sida (CoRIS Cohort),[20] VIH-Aplicación de Control Hospitalario (VACH) Cohort, Spain, the Royal Free Hospital Cohort, UK,[21] the British Columbia Center for Excellence in HIV (HOMER),[22] the South Alberta Cohort,[23] Canada, the Swiss HIV Cohort Study (SHCS),[24] the 1917 Clinic Cohort from the University of Alabama,[25] the HIV Atlanta VA Cohort Study (HAVACS)[26] and the University of Washington HIV Cohort, US. At all sites, institutional review boards approved the collection of data. All cohorts provided anonymized data on a predefined set of demographic, laboratory, and clinical variables, which were then pooled and analyzed centrally.

Patient selection

All patients enrolled in the specified arms of ACTG 5095 and in ACTG 5142 and who had measurements of CD4 count and HIV-1 RNA at start of ART were included. Patients in ART-CC included in this study initiated ART after 1 January 2000 and had at least one year of follow-up before end of study. Comparator patients in ART-CC started on the same regimens as in the corresponding trial: for ACTG 5095 EFV or ABC together with AZT +3TC, and for ACTG 5142 EFV or LPV/r together with 3TC plus choice of AZT or D4T or TDF. Our analysis included all subjects meeting our eligibility criteria from each study. Formal matching according to ART regimen constituents was not done, as we did not conduct a case-control study. Potential imbalances across study designs with respect to regimen constituents were controlled for in multivariate analyses.”

Statistical analyses

In all analyses, we used an intent-to-continue-treatment approach, and thus ignored changes to treatment regimen, including treatment interruptions and terminations. In ART-CC baseline measurements of CD4 count and viral load were the nearest to date of starting ART within 3 months before start date. Measurements at 24 and 48 weeks were the nearest within a window of +/− 7 weeks. Primary analyses included patients with available HIV RNA measures and patients with missing outcome data were excluded.

Comparison of ACTG 5095 and ART-CC—We defined virologic failure as a single HIV-1 RNA level >200 copies/ml at 24 weeks. Because of early termination of the ABC arm in A5095,[12] 24 week virologic failure was selected over 48-weeks as the primary outcome measure. We used logistic regression to estimate crude and adjusted odds ratios (ORs) for virological failure comparing EFV v. ABC as a third drug in both ACTG 5095 (“trial”) and ART-CC (“cohort”). Models were adjusted for year of starting ART, age, sex, assumed transmission via injection drug use (IDU), prior AIDS diagnosis, CD4 count and HIV RNA at start of ART. We estimated ratios of odds ratios (OR in cohort\OR in trial) to compare relative effects of ART regimens in the cohort and trial settings; formal criteria for these comparisons are not established. We also estimated the OR for virological failure comparing trial with cohort, separately in patients on EFV and on ABC.

We used Cox proportional hazards models to estimate crude and adjusted hazard ratios (HR) comparing the effect of ART regimens on the clinical endpoint of time to AIDS or death, in

both the trial and the cohort. We estimated ratios of HR (HR in cohort\HR in trial) to compare the relative effects of ART regimens in the cohort and trial settings. We estimated HR for AIDS or death comparing the cohort with trial, within strata defined by drug regimens. As there were few deaths in the trial, mortality HRs were only estimated using cohort data (analysis stratified by constituent cohorts).

Comparison of ACTG 5142 and ART-CC—Analyses described above were repeated to compare EFV with LPV/r as a third drug using data from ACTG 5142 and ART-CC. The primary end point for these analyses was 48 week virological failure, defined as a single HIV-1 RNA level >200 copies/ml. We also investigated progression to AIDS and death.

Sensitivity analyses—Analyses were repeated using a higher threshold for virological failure (HIV-1 RNA > 400 copies/ml), which allowed the inclusion of additional patients from ART-CC who had viral load measured using a less sensitive assay. We repeated all analyses stratifying by baseline HIV-1 RNA (<100,000, ≥100,000 copies/mL) and CD4 count (<200, ≥200 cells/μL). Finally, we conducted sensitivity analyses using a 3-month window around the 24- and 48-week endpoints and also conducted analyses carrying the last viral load value forward to evaluate the potential impact of missing viral load measurements using a +/− 7 week window.

Role of the Funding Source

This study was supported by the UK Medical Research Council and the US National Institutes of Health, neither of which played a role in the study's design, conduct, and reporting.

Results

Patient characteristics are presented by third drug (ABC, EFV, and LPV/r) and study design (Table 1); ACTG 5095 (n=753) and identical regimens in ART-CC (n=4610), and ACTG 5142 (n=498) and identical regimens in ART-CC (n=8212). In general, the proportion of female patients was slightly higher for ART-CC than for ACTG, while median age at ART initiation was similar (roughly 38 years) across arms and study designs. Median CD4 counts at ART initiation were approximately 200 cells/μL in all ACTG treatment arms and among those receiving EFV in ART-CC, with notable differences among ABC (median 250 cells/μL) and LPV/r (median 146 cells/μL) treated patients in the ART-CC. Virologic failure (>200 copies/mL) was higher among ABC treated patients in both ACTG 5095 and ART-CC relative to EFV and LPV/r treated patients in A5095, A5142 and ART-CC. AIDS-defining events and deaths were relatively infrequent at 48 weeks following ART initiation, and notably higher among ART-CC patients.

Adjusted estimates of virologic effectiveness stratified by 3rd drug (Table 2), showed that patients receiving EFV had roughly half the odds of 24-week virologic failure (>200 copies/mL) compared with ABC treated patients for both ACTG 5095 (OR=0.53, 95% Confidence Interval=0.36–0.79) and ART-CC (0.46, 0.37–0.57). The ratio of ORs (0.86, 0.54–1.35), (cohort study effectiveness/clinical trial efficacy, or effectiveness/efficacy ratio), indicates the virologic superiority of EFV v. ABC was comparable in ART-CC and ACTG 5095. Adjusted estimates of 48-week virologic effectiveness showed that the odds of failure were similar for EFV compared with LPV/r in ACTG 5142 (0.97, 0.51–1.85), but somewhat lower for EFV compared with LPV/r in ART-CC (0.84, 0.71–1.00). However, the ratio of ORs (0.87, 0.45–1.69) did not provide evidence that cohort effectiveness differed from trial efficacy. Adjusted analyses comparing study design (ACTG 5095 v. ART-CC and A5142 v.

ART-CC, Table 2), found comparable odds of virologic failure in trials compared with the cohort study across all treatment regimens.

When comparing 48-week AIDS defining events or deaths stratified by 3rd drug (Table 3), there was clear evidence of confounding by indication in estimates based on cohort data, suggested by sizeable shifts in parameter estimates in adjusted analyses. Consistent with the patterns of prognostic factors in the cohort data presented in Table 1, the effect of EFV compared with ABC was more beneficial after adjustment, while the effect of EFV compared with LPV was attenuated towards 1. Estimates from trials were imprecise because of the small number of events. In adjusted analyses patients receiving EFV had lower rates of AIDS and death compared with those receiving ABC in both ACTG 5095 (0.60, 0.26–1.41) and ART-CC (0.73, 0.54–0.99). Rates of AIDS and death appeared similar in patients treated with EFV and LPV/r in both ACTG 5142 (0.96, 0.40–2.30) and ART-CC (0.88, 0.73–1.06). Effectiveness estimated in ART-CC appeared similar to efficacy estimated in ACTG trials for each regimen comparison (ratios of ORs EFV v. ABC; 1.21, 0.50–2.95 and EFV v. LPV/r; 0.92, 0.39–2.17).

Adjusted analyses of all-cause 48-week mortality by ART regimen were restricted to patients in ART-CC (because there were insufficient deaths in both ACTG 5095 and ACTG 5142). There was little evidence of between-regimen differences in mortality rates (EFV v. ABC, 0.81, 0.48–1.38; EFV v. LPV/r 0.85, 0.63–1.15), although confidence intervals were wide (Table 4).

Findings from sensitivity analyses using a virologic failure threshold of 400 copies/mL were largely in accordance to those from primary analyses (Supplemental Digital Content appendix 1). Analyses of virological failure stratified by viral load and CD4 count at ART initiation showed that the benefit of EFV over ABC is greater in patients with viral load ≥100,000 (v. <100,000) copies/mL and in those with CD4 count <200 (v. ≥200) cells/μL (Supplemental Digital Content appendix 2). Finally, at viral load ≥100,000 (v. <100,000) copies/mL, more disparate findings in comparisons of EFV v. LPV/r stratified by study design and cohort v. trial stratified by regimen are observed relative to primary analyses, albeit with wide confidence intervals (Supplemental Digital Content appendix 2).

Discussion

Among patients initiating antiretroviral therapy for HIV infection, differences in virologic and clinical effectiveness between ART regimens compared in the ACTG 5095 and ACTG 5142 were similar to observed differences when comparing identical regimens administered in routine care in the ART Cohort Collaboration. The virologic superiority of EFV over ABC observed in ACTG 5095 was similar to that seen in the ART-CC, suggesting the findings of this trial translated well to a routine care setting. The comparable efficacy of EFV and LPV/r as a third drug paired with 2 NRTIs in ACTG 5142 was mirrored by the similar virological and clinical effectiveness of these regimens in ART-CC. To our knowledge, this is the first large scale regimen level evaluation of the comparative effectiveness of initial ART when administered in a clinical trial and routine care settings. Our finding that ART regimen differences in the ACTG clinical trials correlated with the routine care setting of ART-CC suggests the generalizability of the results and provides an important link between clinical trials and their applicability to a broader patient population.

Although comparisons of clinical trial efficacy with routine care effectiveness are well documented for other medical conditions,[27–30] evaluation of ART regimens for the treatment of HIV infection in clinical trials vs. routine clinical care has not been widely studied.[31, 32] A recent study from a single, academic US HIV clinic found similar rates of

virologic suppression among patients receiving ART through clinical trials and routine care, but could only assess treatment strategy (trial v. routine care) as the sample was too small for regimen level comparisons.[32] Because care providers must choose among numerous initial ART regimen options, the ability of the current study to move beyond treatment strategy to the regimen level should provide valuable information to inform HIV treatment decisions in accordance with the goals of comparative effectiveness research.[10] In the current study, the clinical trial efficacy of evaluated regimens (EFV, ABC, and LPV/r paired with 2 NRTIs) was mirrored by the effectiveness in routine care settings.

In the evaluation of virologic effectiveness, the definition of virologic failure and analytic approach to assess failure in the current study differed from the primary analyses in the original ACTG 5095 and 5142 studies.[11–13] This is particularly noteworthy with regards to the comparison of virologic effectiveness between EFV v. LPV/r. In the original ACTG 5142 study, EFV was found to have superior virologic efficacy relative to LPV/r using survival methods and with assessment of virologic failure starting at 32-weeks following ART start.[13] Of note, as seen with the current analyses, similar rates of cross-sectional 48-week virologic failure were observed between the EFV and LPV/r groups in original analyses of the ACTG 5142 study, although at 96-weeks patients receiving EFV were significantly more likely to achieve a viral load <200 c/mL (93% v. 86%, P=0.04).[13] The analytic approach employed for the current study, cross-sectional evaluation of unconfirmed virologic failure (>200 copies/mL) at 48-weeks after ART start, was selected based on availability of plasma HIV RNA measures in the ART-CC. In contrast to the ACTG studies, plasma HIV RNA measures are obtained considerably less frequently in routine care, making the definition and analytic methods employed in clinical trials impractical for cohort data based on the limited availability of outcome measures.

Several strengths of our study are noteworthy. This study represents an initial collaboration between the Adult ACTG and ART-CC to allow for innovative approaches to evaluate ART regimen performance at the patient level. The evaluation of clinical events in additional to virologic failure adds contextual richness to the between ART regimen comparisons and provides important information for patients and providers. Beyond the evaluation of between ART regimen differences in surrogate HIV biomarkers across study design, evaluation of clinical events has important implications for patient health. The conduct of sensitivity analyses, the results of which are largely in accordance with findings from primary analyses (see web appendices), provides additional confidence in the interpretation of study findings.

Our study has limitations. As with all observational studies, there is potential for unmeasured confounding that may bias estimates from cohort data.[4, 5] The imbalances in prognostic factors between cohort patients who received different regimens were reflected in differences between the crude and adjusted hazard ratios for clinical events presented in Table 3. However, we cannot exclude the possibility that further, unmeasured prognostic factors were used by physicians choosing between different ART regimens in routine care settings. Many of the NRTIs evaluated in the current study are not among those recommended in updated HIV treatment guidelines.[1–3] Future analyses should assess more modern ART regimens. ART-CC includes patients in Europe, Canada and the US, whereas with the exception of a handful of individuals in A5142 enrolled in South Africa, ACTG sites in these studies are restricted to the US and Puerto Rico. Analyses were conducted according to intent-to-continue-treatment principles and ignoring missing outcome data as done for the original ACTG clinical trials such that the impact of treatment changes, terminations and missing data were not evaluated in the current analyses. On-going studies in the ART-CC are evaluating ART interruptions, terminations and switches. Since patient follow-up in ACTG studies continues beyond initial treatment change or failure, future

analyses may be possible to evaluate these factors. At 24-weeks, missing viral load data was observed in 7% of ACTG participants and 31% of ART-CC patients, which may impact outcomes interpretation. However, missing viral load data was observed in 7% of ACTG participants and 13% of ART-CC patients in sensitivity analyses using a 3-month window around the 24-week endpoint. Sensitivity analyses using this wider viral load measurement window as well as those using a last viral load carried forward approach yielded findings consistent with primary analyses (Supplemental Digital Content appendix 3). Confidence intervals were fairly wide, particularly for the ratio of odds and hazards ratios, limiting the precision of parameter estimates. Although caution must be exercised when comparing findings across studies and designs, we suggest our analyses have an important role and are particularly germane in light of considerable recent emphasis on comparative effectiveness research and methodology.[10]

In conclusion, our study found ART regimen virologic and clinical efficacy for ABC, EFV, and LPV/r in combination with 2 NRTIs observed in ACTG 5095 and 5142 clinical trials were mirrored when these regimens were administered in the routine care setting at ART-CC clinical sites. The generalizability of findings for these trials to routine care settings suggests ART regimen performance in clinical trials likely translates to routine care settings. Although additional studies are needed to confirm our findings and evaluate other ART regimens, we believe our study provides pivotal new evidence demonstrating the comparative effectiveness of antiretroviral treatments evaluated in clinical trials and a large clinical cohort study; this research will help inform ART treatment decisions for HIV-infected patients in routine clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Citations

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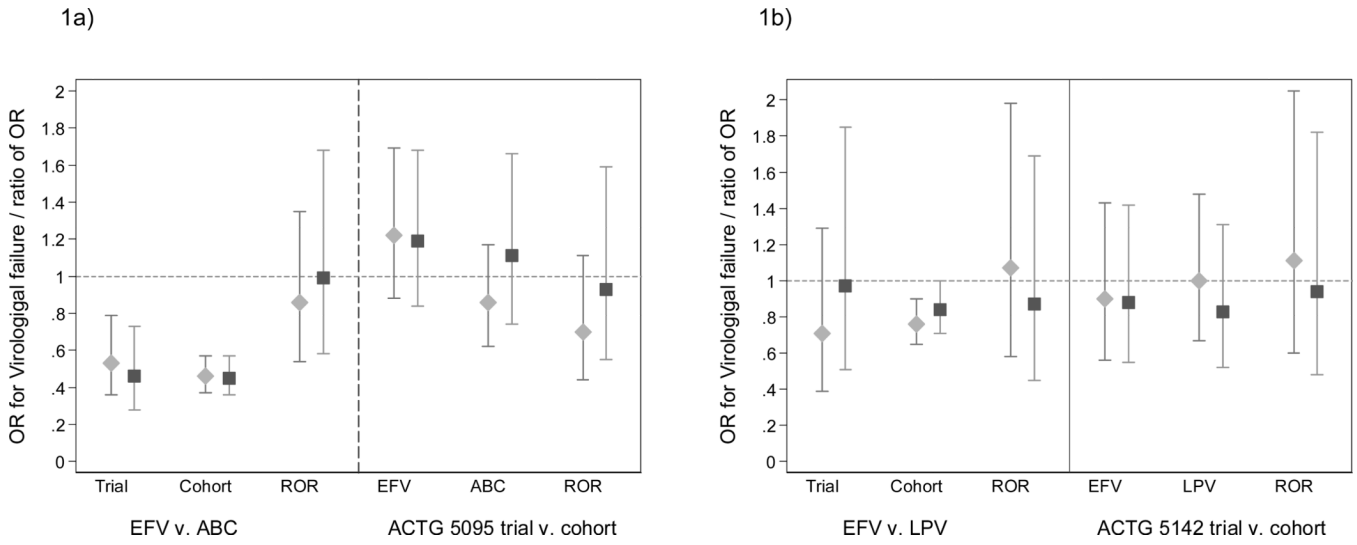

Figure 1.

Adjusted odds ratio (OR) for virological failure (HIV-1 RNA >200 copies/ml) with ratio of odds ratios at 24 and 48 weeks after starting treatment between study design comparison of drug regimen (3rd drug) and between drug regimen comparison of study design (ACTG5095 EFV v. ABC, ACTG5142 EFV v.ABC).

1a) Odds ratio (OR) for virological failure at 24 (diamond) and 48 (square) weeks from start of ART comparing efavirenz (EFV) with abacavir (ABC) within ACTG 5095 trial and ART-CC cohorts (left panel) and comparing trial with cohort separately for patients on EFV and on ABC (right panel) together with ratio of ORs. 1b) Odds ratio (OR) for virological failure at 24 (diamond) and 48 (square) weeks from start of ART comparing efavirenz (EFV) with lopinavir/r (LPV/r) within ACTG 5142 trial and ART-CC cohorts (left panel) and comparing trial with cohort separately for patients on EFV and on LPV/r (right panel) together with ratio of ORs. The comparable ratio of odds ratios suggest the between ART regimen virologic efficacy of 3rd drugs ABC, EFV, and LPV/r observed in the ACTG 5095 and 5142 trials appear generalizable to the routine care setting of ART-CC clinical cohorts.

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Table 1

Baseline characteristics of study subjects and their outcomes at 24 and 48 weeks from starting ART by regimen (3rd drug) and study design for (i) ACTG5095 & ART-CC (N = 5363) (ii) ACTG5142 & ART-CC (N = 8710)

	ABC		EFV		LPV		EFV	
Characteristic	**ACTG5095**	**Cohort**	**ACTG5095**	**Cohort**	**ACTG5142**	**Cohort**	**ACTG5142**	**Cohort**
N (%) or median (IQR)	**N=377**	**N=1694**	**N=376**	**N=2916**	**N=250**	**N=3871**	**N=248**	**N=4341**
Male	305 (81)	1146 (68)	310 (82)	2239 (77)	191 (76)	2827 (73)	201 (81)	3270 (75)
Age years	38 (33–43)	37 (31–44)	38 (31–43)	38 (32–45)	37 (32–44)	38 (32–45)	39 (32–44)	38 (32–45)
16–29	57 (15)	318 (19)	68 (18)	499 (17)	41 (16)	669 (17)	41 (17)	723 (17)
30–39	163 (43)	717 (42)	149 (40)	1202 (41)	106 (42)	1520 (39)	89 (36)	1755 (40)
40–49	114 (30)	444 (26)	123 (33)	773 (27)	80 (32)	1080 (28)	90 (36)	1213 (28)
≥50	43 (11)	215 (13)	36 (10)	442 (15)	23 (9)	602 (16)	28 (11)	650 (15)
IDU	40 (11)	286 (17)	36 (10)	373 (13)	23 (9)	423 (11)	24 (10)	577 (13)
HIV-1 RNA $\log_{10}$ copies/ml	4.8 (4.4–5.3)	4.6 (4.1–5.0)	4.8 (4.4–5.4)	5.0 (4.5–5.4)	4.8 (4.4–5.2)	5.1 (4.7–5.5)	4.8 (4.4–5.2)	5.0 (4.5–5.4)
<4	37 (10)	358 (21)	28 (7)	311 (11)	25 (10)	363 (9)	26 (10)	460 (11)
4–4.99	192 (51)	908 (54)	201 (52)	1200 (41)	137 (55)	1224 (32)	139 (56)	1789 (41)
≥5	148 (39)	428 (25)	147 (41)	1405 (48)	88 (35)	2284 (59)	83 (33)	2092 (48)
CD4 cell count cells/μL	197 (79–343)	250 (170–339)	209 (77–331)	198 (90–291)	190 (70–300)	146 (50–260)	195 (48–314)	191 (84–280)
0–49	63 (17)	104 (6)	79 (21)	489 (17)	47 (19)	950 (25)	65 (26)	741 (17)
50–99	46 (12)	101 (6)	24 (6)	285 (10)	35 (14)	570 (15)	21 (8)	467 (11)
100–199	80 (21)	370 (22)	77 (20)	690 (24)	52 (21)	887 (23)	40 (16)	1061 (24)
200–349	103 (27)	720 (43)	112 (30)	1012 (35)	80 (32)	960 (25)	69 (28)	1503 (35)
≥350	85 (23)	399 (24)	84 (22)	440 (15)	36 (14)	504 (13)	53 (21)	569 (13)
VL>200 copies/mL at 24 wks N /N patients with VL (%)	79/330 (23.9)	245/1043 (23.5)	55/363 (15.2)	231/1831 (12.6)	32/237 (13.5)	416/2926 (14.2)	22/230 (9.6)	340/3059 (11.1)
VL>200 copies/mL at 48 wks N /N patients with VL (%)	51/193 (26.4)	207/970 (21.3)	49/344 (14.2)	204/1789 (11.4)	23/220 (10.5)	369/2762 (13.4)	21/214 (9.8)	333/2966 (11.2)
AIDS or death at 24 wks	10 (2.65)	50 (2.95)	7(1.86)	123 (4.22)	7 (2.8)	238 (6.15)	7 (2.82)	197 (4.54)
AIDS or death at 48 wks	13 (3.45)	82 (4.84)	10 (2.66)	176 (6.04)	11 (4.40)	312 (8.06)	11 (4.44)	279 (6.43)
Deaths at 24 wks	3 (0.80)	13 (0.77)	0(0)	31 (1.06)	0(0)	74 (1.91)	3 (1.21)	57 (1.31)
Deaths at 48 wks	3 (0.80)	26 (1.53)	1 (0.27)	57 (1.95)	2 (0.80)	114 (2.94)	5 (2.02)	97 (2.23)

IQR = inter-quartile range

Table 2

Crude and adjusted odds ratio (OR) for virological failure (HIV-1 RNA >200 copies/ml) with ratio of odds ratios at 24 and 48 weeks after starting treatment (i) between study design comparison of drug regimen (3rd drug) (ii) between drug regimen comparison of study design (white band ACTG5095 EFV v. ABC, grey band ACTG5142 EFV v.ABC).

	Weeks of follow-up	OR (95% CI) VL>200 copies/mL					
		Crude			Adjusted		
Comparison of regimens		**Trial**	**Cohort**	**Ratio of OR (cohort:trial)**	**Trial**	**Cohort**	**Ratio of OR (cohort:trial)**
EFV v. ABC (ACTG 5095)	24	0.57 (0.39, 0.83)	0.47 (0.39, 0.57)	0.83 (0.54,1.28)	0.53 (0.36, 0.79)	0.46 (0.37, 0.57)	0.86 (0.54,1.35)
	48	0.46 (0.30, 0.72)	0.47 (0.38, 0.59)	1.03 (0.63,1.67)	0.46 (0.28, 0.73)	0.45 (0.36, 0.57)	0.99 (0.58,1.68)
EFV v. LPV (ACTG 5142)	24	0.68 (0.38,1.21)	0.75 (0.65,0.88)	1.11 (0.61,2.02)	0.71 (0.39,1.29)	0.76 (0.65,0.90)	1.07 (0.58,1.98)
	48	0.93 (0.50,1.74)	0.82 (0.70,0.96)	0.88 (0.46,1.68)	0.97 (0.51,1.85)	0.84 (0.71,1.00)	0.87 (0.45,1.69)
Comparison of study designs		**Patients on EFV**	**Patients on ABC**		**Patients on EFV**	**Patients on ABC**	
ACTG 5095 v. cohort	24	1.24 (0.90, 1.70)	1.03 (0.77, 1.37)	0.83 (0.54,1.28)	1.22 (0.88, 1.69)	0.86 (0.62, 1.17)	0.70 (0.44,1.11)
	48	1.29 (0.92, 1.81)	1.32 (0.93, 1.89)	1.03 (0.63,1.67)	1.19 (0.84, 1.68)	1.11 (0.74, 1.66)	0.93 (0.55,1.59)
		Patients on EFV	**Patients on LPV**		**Patients on EFV**	**Patients on LPV**	
ACTG 5142 v. cohort	24	0.85 (0.54,1.33)	0.94 (0.64,1.39)	1.11 (0.61,2.02)	0.90 (0.56,1.43)	1.00 (0.67,1.48)	1.11 (0.60,2.05)
	48	0.86 (0.54,1.37)	0.76 (0.48,1.18)	0.88 (0.46,1.68)	0.88 (0.55,1.42)	0.83 (0.52,1.31)	0.94 (0.48,1.82)

Adjusted models control for year of starting ART, age, sex, assumed transmission via injection drug use (IDU), AIDS diagnosis, CD4 count and HIV RNA at start of ART

Table 3

Crude and adjusted hazard ratio (HR) for AIDS or death with ratio of hazard ratios at 24 and 48 weeks after starting treatment (i) between study design comparison of drug regimen (3rd drug) (ii) between drug regimen comparison of study design (white band ACTG5095 EFV v. ABC, grey band ACTG5142 EFV v.ABC).

Comparison of regimens	Weeks of follow-up	HR (95% CI) AIDS or death					
		Crude			Adjusted		
		Trial	Cohort	Ratio of HR (cohort:trial)	Trial	Cohort	Ratio of HR (cohort:trial)
EFV v. ABC (ACTG 5095)	24	0.70 (0.27, 1.84)	1.35 (0.95, 1.92)	1.93 (0.69,5.39)	0.53 (0.20, 1.44)	0.88 (0.61, 1.28)	1.65 (0.58,4.75)
	48	0.77 (0.34, 1.75)	1.10 (0.83, 1.46)	1.43 (0.60,3.43)	0.60 (0.26, 1.41)	0.73 (0.54, 0.99)	1.21 (0.50,2.95)
EFV v. LPV (ACTG 5142)	24	1.00 (0.35,2.86)	0.70 (0.58,0.86)	0.70 (0.24,2.03)	0.87 (0.29,2.59)	0.87 (0.71,1.08)	1.00 (0.34,2.93)
	48	1.00 (0.44,2.32)	0.74 (0.62,0.88)	0.74 (0.31,1.73)	0.96 (0.40,2.30)	0.88 (0.73,1.06)	0.92 (0.39,2.17)
Comparison of study designs		**Patients on EFV**	**Patients on ABC**		**Patients on EFV**	**Patients on ABC**	
ACTG 5095 v. cohort	24	0.43 (0.20, 0.93)	0.88 (0.45, 1.74)	2.03 (0.73,5.63)	0.42 (0.19, 0.90)	0.53 (0.25, 1.08)	1.26 (0.44,3.62)
	48	0.43 (0.22, 0.80)	0.68 (0.38, 1.22)	1.60 (0.68,3.81)	0.41 (0.21, 0.77)	0.40 (0.21, 0.73)	0.98 (0.40,2.38)
		Patients on EFV	**Patients on LPV**		**Patients on EFV**	**Patients on LPV**	
ACTG 5142 v. cohort	24	0.61 (0.29,1.30)	0.45 (0.21,0.95)	0.73 (0.25,2.11)	0.65 (0.30,1.39)	0.54 (0.25,1.15)	0.83 (0.28,2.44)
	48	0.67 (0.37,1.22)	0.53 (0.29,0.96)	0.79 (0.34,1.84)	0.71 (0.38,1.31)	0.63 (0.34,1.15)	0.88 (0.37,2.08)

Adjusted models control for year of starting ART, age, sex, assumed transmission via injection drug use (IDU), AIDS diagnosis, CD4 count and HIV RNA at start of ART