Poster 783

ART Cohort Collaboration

Outcomes of Abacavir and Efavirenz-based HAART: Comparison of ACTG 5095 Trial Results with Observational Cohort Studies

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on behalf of the Adult AIDS Clinical Trial Group (ACTG) and the Antiretroviral Therapy Cohort Collaboration (ART-CC)

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Abstract

Background

RCTs are the study design of choice for evaluating the effects of ART, but trials often focus on virologic suppression, rather than clinical endpoints. Large observational cohort studies have the power to examine clinical outcomes, but results may be affected by confounding by indication. We compared the ACTG 5095 trial (A5095) with data from the ART Cohort Collaboration (ART-CC), 15 cohort studies in Europe and North America.

Methods

We compared EFV vs. ABC (combined with ZDV/3TC) stratifying by study design, and A5095 vs. ART-CC stratifying by 3rd drug in ARV-naïve patients starting ART. A5095 data and ART-CC data were analyzed using identical logistic regression models to evaluate 24-wk virologic failure (VF) (>400 c/mL), and Cox models to compare 48-wk progression to AIDS or death, adjusting for age, sex, baseline CD4 count and viral load.

Results

5796 patients met inclusion criteria; 753 from A5095 (ABC=377, EFV=376) and 5043 from ART-CC (ABC=2009, EFV=3034). Overall, VF was observed in 13.8% of A5095 patients (89/643) and 18.6% of ART-CC patients (813/4368) with available 24-wk VL measures (P<0.01) and 3.1% (23/753) and 6.9% (350/5043) progressed to AIDS or death (P<0.01). Prognostic factors were well balanced in A5095. In ART-CC patients starting with ABC had higher mean CD4 counts than patients starting with EFV (251 vs. 209 cells).

VF and clinical progression in pts. starting ABC and EFV-based regimens in ACTG 5095 and ART-CC

	Odds Ratio (95%CI) for VF		Hazard Ratio (95%CI) for AIDS/death	
EFV vs. ABC	Crude	Adj.	Crude	Adj.
A5095	0.64 (0.41-1.01)	0.57 (0.36-0.90)	0.77 (0.34-1.75)	0.66 (0.28-1.53)
ART-CC	0.47 (0.40-0.55)	0.45 (0.38-0.53)	1.42 (1.13-1.77)	0.99 (0.78-1.25)
A5095 vs. ART-CC				
ABC	0.58 (0.42-0.81)	0.45 (0.32-0.64)	0.60 (0.34-1.06)	0.40 (0.22-0.73)
EFV	0.80 (0.57-1.13)	0.78 (0.54-1.13)	0.33 (0.17-0.62)	0.37 (0.19-0.72)

Conclusions

Patients on EFV were less likely to experience VF in both A5095 and ART-CC. Of note, EFV-based regimens performed similarly in ART-CC and A5095, while virologic responses to ABC-regimens were considerably better in A5095 compared to ART-CC. There was no clear evidence of differences in clinical progression between EFV and ABC, but the attenuation of the hazard ratio for AIDS/death after adjustment for covariates in the ART-CC suggests residual confounding by indication in the observational data. Clinical progression rates were higher in ART-CC than A5095, independently of the regimen used.

Background

- Randomized controlled trials (RCTs) are the preferred method to evaluate the 'efficacy' of antiretroviral regimens as they provide the highest standard of evidence[1]
  - However, RCT findings may not be generalizable to practice settings due to volunteer and selection bias
- Observational cohort studies are a complementary methodology that evaluates the 'effectiveness' of ARV regimens in clinical practice settings
  - However, the non-random selection of ARVs in practice may lead to differential regimen selection based on patient or clinical factors; "confounding by indication"[2-4]
  - Statistical methods may be employed to adjust for such confounding, but the possibility that unmeasured confounders not included in statistical models impact observational study results can never be excluded[5]

Objective

- To compare the 'efficacy' and 'effectiveness' of abacavir (ABC) and efavirenz (EFV) when given in combination with zidovudine (ZDV) and lamivudine (3TC) in ARV-naïve pts.

Methods

- ARV-naïve patients initiating therapy with ABC or EFV in combination with ZDV and 3TC were identified from:
  - A5095 – an Adult ACTG-sponsored RCT[6]
  - ART-CC – an observational cohort study of 15 cohorts in Europe and North America[7]
- Outcome measures
  - 24-week VF (unconfirmed HIV RNA>400 copies/mL)
  - AIDS defining event (ADE) or death at 48 weeks
- Statistical analysis
  - EFV vs. ABC were compared stratifying by study design
  - A5095 vs. ART-CC ('efficacy' vs. 'effectiveness') were compared stratifying by 3rd drug
  - 24-week virologic failure – Logistic regression
  - 48-week AIDS or death – Survival analysis
  - Multivariable analyses adjusted for age, sex, baseline CD4 count and HIV RNA, AIDS before initiation of therapy, and year starting ARV therapy

Results

Table 1. Baseline characteristics of 5,796 study participants by 3rd drug and study design

	ABC		EFV	
Characteristic	A5095	ART-CC	A5095	ART-CC
N (%) or Median (IQR)	N=377	N=2,009	N=376	N=3,034
Male	305 (81)	1,440 (72)	310 (82)	2,426 (80)
Age years	38 (33-43)	38 (32-46)	37 (31-43)	40 (33-48)
HIV-1 RNA log copies/ml	4.7 (4.2-5.1)	4.8 (4.4-5.4)	4.8 (4.5-5.5)	4.9 (4.5-5.4)
CD4 cell count	197 (79-343)	251 (160-355)	201 (86-319)	209 (77-331)

Table 2. Crude and adjusted odds ratios for 24-week virologic failure (>400 copies/mL) by 3rd drug (EFV vs. ABC) and study design (A5095 vs. ART-CC)

	N		Odds Ratio (95%CI) for VF	
EFV vs. ABC	Patients	Failed (%)	Crude	Adjusted
A5095	643	89 (13.8)	0.64 (0.41-1.01)	0.57 (0.36-0.90)
ART-CC	4368	813 (18.6)	0.47 (0.40-0.55)	0.45 (0.38-0.53)
A5095 vs. ART-CC	Patients	Failed (%)	Crude	Adjusted
ABC	2065	502 (24.3)	0.58 (0.42-0.81)	0.45 (0.32-0.64)
EFV	2946	400 (13.6)	0.80 (0.57-1.13)	0.78 (0.54-1.13)

Adjusted analyses control for age, sex, baseline CD4 count, baseline plasma HIV RNA, AIDS before initiation of therapy, and year of starting ARV therapy

Table 3. Crude and adjusted hazard ratios for 48-week clinical events (AIDS or death) by 3rd drug (EFV vs. ABC) and study design (A5095 vs. ART-CC)

	N		Hazard Ratio (95%CI) for AIDS or Death	
EFV vs. ABC	Patients	AIDS/Death (%)	Crude	Adjusted
A5095	753	23 (3.1%)	0.77 (0.34-1.75)	0.66 (0.28-1.53)
ART-CC	5043	350 (6.9%)	1.42 (1.13-1.77)	0.99 (0.78-1.25)
A5095 vs. ART-CC	Patients	AIDS/Death (%)	Crude	Adjusted
ABC	2386	126 (5.3%)	0.60 (0.34-1.06)	0.40 (0.22-0.73)
EFV	3410	247 (7.2%)	0.33 (0.17-0.62)	0.37 (0.19-0.72)

Adjusted analyses control for age, sex, baseline CD4 count, baseline plasma HIV RNA, AIDS before initiation of therapy, and year of starting ARV therapy

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Results

- Evidence of "confounding by indication" was observed in the ART-CC: EFV was used more commonly in men, and median CD4 counts were higher for patients starting ABC vs. EFV (251 vs. 209 cells/mm^3) (Table 1)
- 24-week VF was observed in 13.8% of patients in A5095 and 18.6% in ART-CC (P<0.01) (Table 2)
- However, different 'efficacy' vs. 'effectiveness' relationships were observed for ABC vs. EFV (Table 2)
  - For EFV, 24-week VF was similar between A5095 vs. ART-CC (OR=0.78, 95%CI=0.54-1.13)
  - For ABC, 24-week VF was significantly lower for A5095 vs. ART-CC (OR=0.45, 95%CI=0.32-0.64)
  - The differential 'efficacy' vs. 'effectiveness' relationships for ABC vs. EFV were statistically significant; ratio of OR=0.58, 95%CI=0.35-0.97
- 48-week AIDS or death was observed in 3.1% of patients in A5095 and 6.9% in ART-CC (P<0.01), and was seen independently of 3rd drug (Table 3)

Conclusions

- 24-week virologic failure for EFV-based ARV therapy was similar in clinical trial (A5095) and cohort (ART-CC) studies, while ABC-based therapy performed significantly worse in a clinical practice setting
- Possible explanations for differential 'efficacy' vs. 'effectiveness' relationships for ABC and EFV include:
  - Unmeasured confounders not included in adjusted statistical models; factors that impact both selection of ABC vs. EFV as well as 24-week virologic failure
  - Intrinsic 'efficacy' vs. 'effectiveness' differences between ARVs, perhaps related to differential adherence/resistance relationships[8]
- 48-week clinical events were more common in ART-CC vs. A5095, independent of ABC or EFV as 3rd drugs
  - This may relate to volunteer bias, selection bias, and closer follow-up through clinical trials relative to the clinical practice setting of cohort studies

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