Virologic Response to Efavirenz vs Nevirapine-containing ART in the ARROW Trial

Poster 895

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ABSTRACT (updated)

Background: Poorer virologic response to NVP vs EFV-based ART has recently been reported. We compared VL response in ARROW trial children aged ≥3 years initiating ART with NVP vs EFV.

Methods: 836 ART-naïve children age ≥3 years from Uganda/Zimbabwe were randomized to 3-drug NNRTI+3TC+ABC (Arm A) vs 4-drug NNRTI+3TC+ABC+ZDV induction, decreasing at week 36 to 3-drug NNRTI+3TC+ABC (Arm B) or 3TC+ABC+ZDV (Arm C). NNRTI was chosen by clinicians. VL was assayed using Abbott Taqman or Roche Amplicor, with lower detection limit 80 c/ml. Predictors of suppression <80 c/ml at 36wk (all children) and 144wk (Arm A/B only) after ART initiation were identified using backwards elimination (p=0.1) from pre-ART WHO stage, CD4, CD4%, weight/height-for-age, VL, sex, centre, ART randomization, CD4 monitoring, and reported missed ART doses in the last 4wk, forcing EFV vs NVP and age at ART initiation into the model, and categorizing age to reflect non-linear effects.

Results: 445 (53%) children received EFV and 391 (47%) NVP. Children on EFV were more likely to be male (54%, p=0.007), older (median 8.6 year EFV vs 7.5 NVP, p<0.001), less underweight (weight-for-age -1.7 vs -2.4, p<0.001) and had higher CD4% (12% vs 10%, p=0.05) and lower pre-ART VL (160022 vs 203763c/ml, p=0.10), but similar pre-ART CD4 (p=0.9). 689 (82%) had ≥1 post-baseline VL. Overall there was a trend to better suppression <80 c/ml with EFV (global unadjusted p=0.08, particularly ≤36wk). After adjustment, at wk 36 (n=293), EFV was superior to NVP in those with pre-ART VL>50000 (p=0.002; interaction p=0.009); suppression <80 c/ml was poorer in the youngest and oldest children (aOR(3-4 vs 5-9yr olds)=0.62 p=0.18; aOR(10+ vs 5-9yr olds)=0.34 p=0.008). Differences at wk144 were smaller (74% EFV vs 72% NVP <80 c/ml p=0.06 (n=210)), with a relationship between older age and poorer VL suppression in those on EFV (aOR per year older=0.78 [0.68-0.89] p<0.001) but no relationship in NVP (aOR=0.94 [0.78-1.13] p=0.51) (age interaction p=0.10).

Conclusions: In a non-randomized NNRTI comparison, although short-term VL suppression favoured EFV, long-term suppression depended on age: children <10 years at ART initiation had better long-term VL suppression with EFV than NVP; whereas those >10 years had better long-term suppression with NVP than EFV. The relative performance of EFV vs NVP therefore varies over time on ART, by baseline VL and by age at ART initiation, the latter possibly due to CNS side-effects of EFV.

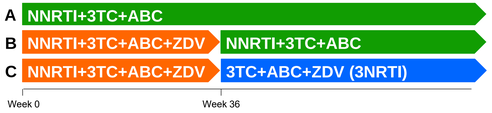
BACKGROUND

- Poorer virologic response to NVP vs EFV-based ART has recently been reported:
  - Lack of suppression to <400 c/ml by 6 months or confirmed ≥400 c/ml after suppression: NVP 26% vs. EFV 14% (p<0.001 (n=804 Botswanan children aged 3-16)) [1]
  - Lower risk of virological failure with EFV vs NVP in the CHIPS cohort (IAS 2013; median 8 years at ART); differences were modest after 2 years
- Meta-analysis associates NVP with greater frequency of severe adverse events, in particular treatment discontinuation (OR=2.2 [1.9-2.6] in adults ≥15 years; limited data in children) [2]
- We compared VL response in ARROW trial children aged ≥3 years initiating ART with NVP vs EFV

METHODS

- Analyses included the 836 ART-naïve Ugandan/Zimbabwean children aged ≥3 years in the ARROW trial (ISCRTN24791884)

Randomisation:



- NNRTI (EFV or NVP) chosen by clinicians depending on local availability (not supplied by the trial)
- VL was assayed using Abbott RealTime and Roche Amplicor 1.5, with lower detection limit 80 c/ml (many samples diluted due to low volumes)
- Predictors of suppression<80c/ml at 36wk (all children) and 144wk (Arm A/B only) identified using backwards elimination (p=0.1) from pre-ART WHO stage, CD4, CD4%, weight/height-for-age, VL, sex, centre, ART randomization, CD4 monitoring and reported missed doses in last 4wk, forcing EFV vs NVP and age at ART initiation into model, categorizing age to reflect non-linear effects

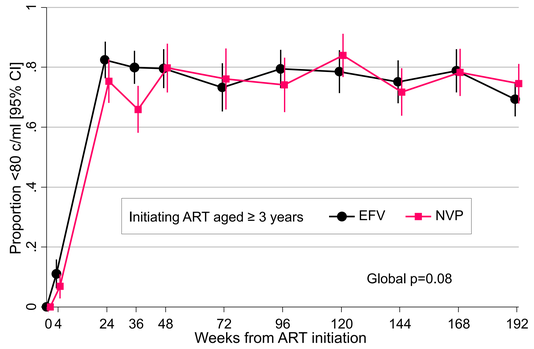
Table 1: Pre-ART characteristics of children receiving EFV vs NVP

	EFV (n=445)	NVP (n=391)	p
Boys	242 (54%)	176 (45%)	0.007
Age (years)	8.6 (6.4-11.0)	7.5 (4.9-10.1)	<0.001
Pre-ART CD4 (cells/ul)	277 (115-436)	261 (102-476)	0.9
Pre-ART CD4%	12 (6-18)	10 (5-17)	0.05
Weight-for-age Z-score	-1.7 (-2.6 to -1.0)	-2.4 (-3.6 to -1.5)	<0.001
Height-for-age Z-score	-1.9 (-2.8 to -1.1)	-2.6 (-3.5 to -1.6)	<0.001
Pre-ART VL (c/ml)	160022 (187000-1385000)*	203763 (178000-1212000)**	0.10
WHO stage 3/4	269 (60%)	322 (82%)	<0.001
Initial ART Arm A (3TC/ABC/NNRTI throughout) Arm B (36 weeks ZDV) Arm C (long-term ZDV)	 141 (32%) 153 (34%) 151 (34%)	 135 (35%) 134 (34%) 122 (31%)	0.61
CD4 monitoring***	225 (51%)	202 (52%)	0.75
Country/centre Uganda/Entebbe Uganda/JCRC Uganda/PIDC Zimbabwe/Harare	 52 (12%) 205 (46%) 98 (22%) 90 (20%)	 94 (24%) 25 (6%) 45 (12%) 227 (58%)	<0.001

* n=255 ** n=217. *** Randomised to CD4 monitoring or no CD4 monitoring as part of ARROW.
Note: values are n (%) or median (IQR)

RESULTS

Figure 1:Suppression <80 c/ml (n=660 with one or more VL measurement*)



<80 c/ml	Week 36 (n=341 with VL measurement)	Week 144 (n=265*)
NVP	93/141 (66.0%)	89/124 (71.8%)
EFV	160/200 (80.0%)	106/141 (75.2%)
Difference (95% CI)	14.0% (4.5% to 23.6%)	3.4% (-7.3% to 14.1%)

Note: unadjusted. *Only including Arm A/B from week 48 onwards

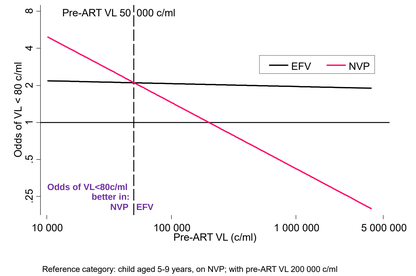
- 445 (53%) children received EFV and 391 (47%) NVP
- Children on EFV were more likely to be male (p=0.007) (Table 1) and were also older (p<0.001)
- **Children on EFV tended to have less severe HIV disease pre-ART**, being less underweight (p<0.001), higher CD4% (p=0.05) and lower pre-ART VL (p=0.10)
  - however pre-ART CD4 was similar (p=0.9)
- Centre was a strong predictor of EFV vs NVP, reflecting local availability
- Overall there was a trend to better suppression <80 c/ml with EFV (global unadjusted p=0.08) driven by effects before 36 weeks (Figure 1)
- Performance of EFV vs NVP varied over time on ART, by baseline VL and by age at ART initiation

Multivariate analysis for suppression <80 c/ml

Week 36 (n=293 complete cases)

- EFV was superior to NVP in those with pre-ART VL>50000 (p=0.002; interaction p=0.009) (Figure 2):

Figure 2: Odds of VL < 80 c/ml (Week 36)



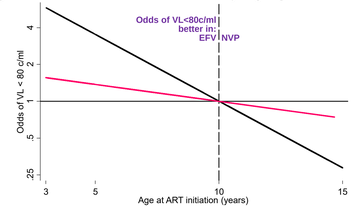
Reference category: child aged 5-9 years, on NVP; with pre-ART VL 200 000 c/ml

- Suppression <80 c/ml was poorer in the youngest and oldest children
  - aOR(3-4 vs 5-9yr olds)=0.62 [0.31-1.25] p=0.18
  - aOR(10+ vs 5-9yr olds)=0.34 [0.15-0.76] p=0.008

Week 144 (n=210 complete cases)

- **EFV** 74% <80 c/ml
  - Poorer VL suppression with older age (Figure 3) *(relationship now linear as pre-ART 3-4yr olds 5-9 yrs at w144)*
  - aOR per year older=0.78 [0.68-0.89] p<0.001
- **NVP** 72% < 80 c/ml (p=0.06 EFV vs NVP)
  - No association with age (interaction p=0.10)
  - aOR per year older =0.94 [0.78-1.13] p=0.51

Figure 3: Odds of VL < 80 c/ml by age (Week 144)



Reference category: child aged 10 at ART initiation, on NVP in Arm A (NNRTI+3TC+ABC); with pre-ART VL 200 000 c/ml and no reported missed ART doses in the last 4wk

- Suppression lower in those:
  - with **higher pre-ART VL** (aOR=0.53 per $\log_{10}$ higher [95% CI 0.31-0.92] p=0.02)
  - in **Arm A** vs **B** (aOR=0.49 [0.25-0.96] p=0.04)
  - **missing doses** (aOR=0.41 [0.15-1.12] p=0.08)
- No evidence of interaction between NNRTI and **ART strategy** (**A/B**; p=0.2) or pre-ART VL (p=0.9)

References
[1] Lowenthal E, et al. JAMA 2013; 17: 1803-1809
[2] Shubber Z et al. AIDS 2013; 27(9):1403 - 12

CONCLUSIONS

- **In a non-randomized comparison, short-term VL suppression favoured EFV**
- **Long-term suppression depended on age (possibly due to CNS side-effects of EFV):**
  - **Children aged 3-9 years at ART initiation had better long-term VL suppression with EFV than NVP**
  - **Those 10 years or older at ART initiation had better long-term suppression with NVP than EFV**
- **Short-term performance of EFV vs NVP also varied by baseline VL, with EFV being better early on in those with higher pre-ART VL**

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