Superior Virological Suppression with Nevirapine/Zidovudine/Lamivudine versus Abacavir/Zidovudine/Lamivudine Without Evidence of Clinical Benefit to 48 Weeks: a Randomised Comparison in Patients with Low CD4 Counts in Africa

AS Walker[1], C Kityo[2], P Kaleebu[3], F Ssali[2], F Lyagoba[3], A Reid[4], D Gibb[1], C Gilks[5], P Mugyenyi[2], P Munderi[3] and the DART Trial Team

1Med Res Council Clin Trials Unit, London, UK; 2Joint Clin Res Ctr, Kampala, Uganda; 3Med Res Council/Uganda Virus Res Inst Prgm on AIDS, Entebbe; 4Univ of Zimbabwe, Harare; and 5Imperial Coll, London, UK

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www.ctu.mrc.ac.uk/dart

Email: asw@ctu.mrc.ac.uk

ABSTRACT

Background: Abacavir(ABC)-based 3NRTI regimens have potential advantages over standard nevirapine(NVP)-based 1st-line in Africa, as they avoid interactions with TB therapy, spare 2 classes for 2nd-line and have low pill burden. We have previously shown a trend towards lower toxicity and discontinuation with ABC vs NVP, but their clinical, immunological and virological efficacy have not been compared in Africa.

Methods: A randomised trial comparing the safety of NVP vs ABC was conducted in 2 Ugandan centres within the DART trial. 600 ARV-naive adults with CD4 <200 cells/mm3 were allocated to Combivir plus ABC (n=300) or NVP (placebo-controlled for the 1st 24 weeks to the 1° toxicity endpoint). Plasma HIV-1 RNA was retrospectively assayed at 0, 24, 48 weeks using Roche Amplicor. CD4 was measured in real-time 12 weekly, and clinical events documented and independently reviewed. All analyses are ITT.

Results: 430 patients were women (72%); at baseline, 111 (19%) had WHO stage 4 disease, median age was 36 years (range 18-66), CD4 99 cells/mm3 (1-199) and HIV-1 RNA 284600 c/ml (mean 5.4 log10, SD 0.7). 563 (94%) patients completed 48 weeks: 25 (4%) died and 1 (2%) were lost. In total 21 (7%) ABC vs 34 (11%) NVP patients were off randomised drug at 48 weeks/last alive (most had substituted TDF). 62% ABC vs 76% NVP had HIV RNA <50 c/ml at week 24, and 62% ABC vs 77% NVP at week 48 (both n=551, p<0.001): 74% vs 87% were <400 c/ml at week 48 (p<0.001). Mean CD4 increases from baseline in ABC vs NVP were +111 vs +134 cells/mm3 at week 24 (p=0.003) and +147 vs +173 at week 48 (p=0.006). In contrast, 17 (6%) ABC vs 29 (10%) NVP patients developed new WHO 4 events or died by 48 weeks (HR=0.57 [95% CI 0.31-1.03] p=0.06, similar inc WHO 3 events p=0.06). First events were oesophageal candida (4A,3N), extra-pulmonary TB (2A,5N), cryptococcus (3N), other WHO 4 (4A,5N) or death (7A,11N): most (13A,23N) occurred in the 1st 12 weeks. Nine (3%) ABC vs 16 (5%) NVP patients died (HR=0.55 [0.24-1.25] p=0.15), all but 1 (N) in the 1st 24 weeks and most (7A,12N) in the 1st 12 weeks.

Conclusions: NVP has superior virological and immunological efficacy compared to ABC over 48 weeks, although viral load suppression and CD4 gains were substantial in both groups. Further follow-up will be important to monitor the observed trend towards clinical superiority of the ABC arm during this period. The potential contribution of IRIS to these results also requires further study.

RATIONALE

The standard first-line therapy recommended by WHO in resource-limited settings is 2NRTI/NNRTI

- options for second-line therapy may be limited at clinical or immunological failure following the WHO public health approach, as extensive resistance to NNRTI and NRTI is likely
- development of TB may necessitate change of NNRTI
- efavirenz (EFV): contraindicated in women wishing to become pregnant
- nevirapine (NVP): treatment-limiting side-effects in 5-10%

Triple NRTI regimens are more widely advocated by WHO for simplification. In Ugandan adults with low CD4 counts initiating ART within the DART trial, the randomised NORA study *[CROI 2006, LB109]* demonstrated

- a trend towards a lower rate of serious adverse reactions with abacavir (ABC) versus NVP to 24 weeks
- a lower discontinuation rate of ABC versus NVP to 24 weeks

suggesting that ABC could be used more widely in resource-limited settings. **However, the clinical, immunological and virological efficacy of NVP and ABC have not been compared in Africa: here, we report efficacy data to 48 weeks from the NORA trial.**

NORA TRIAL DESIGN

NORA was a 24 week randomised double-blind Phase II toxicity trial conducted in two clinical centres in Uganda (JCRC, Kampala and the MRC/UVRI Uganda Research Unit on AIDS, Entebbe), as a nested substudy within the DART trial.

600 previously untreated symptomatic HIV-infected adults initiating ART with CD4<200 cells/mm³ were randomly allocated to combivir plus

- 300 mg **abacavir** and nevirapine placebo twice daily
- abacavir placebo and 200 mg **nevirapine** twice daily

for 24 weeks (double dummy design). After 24 weeks, participants were unblinded and continued their allocated regimen open-label.

The primary endpoint of the 24 week study was SAE judged definitely/probably or uncertain whether related to blinded trial drug.

Results presented here are exploratory analyses of efficacy outcomes to 48 weeks. All analyses are ITT.

- Plasma HIV-1 RNA was retrospectively assayed on stored plasma samples at 0, 4, 24, and 48 weeks using Roche Amplicor at JCRC
- CD4 was measured in real-time 12 weekly at each site
- All WHO 3 or 4 clinical events were documented in real-time and independently reviewed

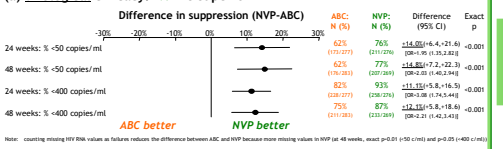
BASELINE CHARACTERISTICS

		ABC	NVP
Total patients		300	300*
Women		72%	71%
Prior ART to prevent MTCT (most sdNVP) (% of women)		2%	5%
Age	median	37.6	36.3
CD4 at randomisation (cells/mm³)	median (IQR)	99 (49-199)	100 (45-145)
HIV RNA at randomisation (copies/ml) (N=586)	median mean $\log_{10}$ (SD)	292,300 5.4 (0.7)	283,000 5.4 (0.7)
WHO stage at randomisation	2 3 4	28% 58% 15%	25% 52% 22%

* including 1 participant who disclosed (a year after entering DART) that they had taken 3 months of Triomune prior to enrolment: this participant is not excluded because the number of other participants with concealed prior exposure is unknown.

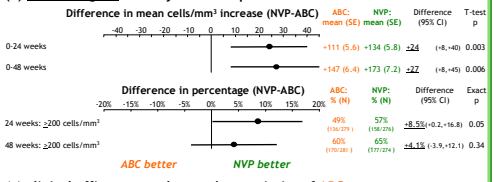
OUTCOMES to 48 WEEKS

(a) virological efficacy: NVP is superior

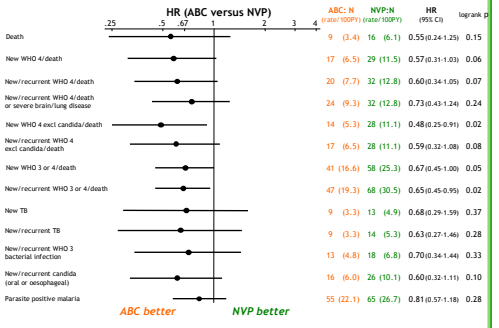


Note: counting missing HIV RNA values as failures reduces the difference between ABC and NVP because more missing values in NVP (at 48 weeks, exact p=0.01 (<50 c/ml) and p=0.05 (<400 c/ml))

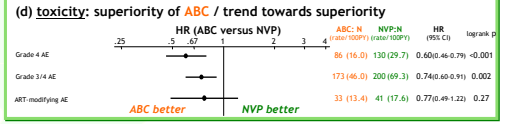
(b) immunological efficacy: NVP is superior



(c) clinical efficacy: trend towards superiority of ABC



(d) toxicity: superiority of ABC / trend towards superiority



FOLLOW-UP to 48 WEEKS

	ABC		NVP	
Initiated allocated ART regimen	300	(100%)	300	(100%)
Died before 48 weeks	9	(3%)	16	(5%)
Lost to follow-up before 48 weeks	5	(2%)	7	(2%)
Alive and in follow-up at 48 weeks	286	(95%)	277	(92%)
At last alive or 48 weeks				
still on randomised drug+2NRTI*	279	(93%)	266	(89%)
substituted ABC/NVP for another drug	21	(7%)	34	(11%)
Percentage of person-time at risk to 48 weeks spent				
on randomised drug+2NRTI*	95%		91%	
off ART	1%		1%	
on other ART	5%		8%	

* allowing substitution of ZDV to d4T

POSSIBLE EXPLANATIONS

We observed a highly significant benefit to NVP in terms of virological and immunological response without clinical benefit to 48 weeks, similar to results recently reported by the ART-CC *[JID 2006]*. If real, this finding suggests a disconnect between virological/immunological and clinical outcomes which may have major implications for the way surrogate markers are used *[Hughes JID 2006]*. However, other possible explanations for these results should also be considered, namely

- (I) increased toxicity of NVP led to more clinical events on NVP
- (II) more switching to clinically superior drug regimens occurred in ABC
- (III) differences between outcomes are a chance finding (Type I error)
- (IV) improved immune response led to increased IRIS on NVP
- (V) timescale for virological/immunological & clinical response differs
- (VI) current CD4 and viral load mean something different in ABC and NVP groups in terms of risk of clinical events

(I): TOXICITY?

Hypothesis: More toxicity in the NVP group (as observed with 1° and 2° toxicity outcomes to 24 weeks) could have led to more clinical events

➪ ***POSSIBLE** if led to lower adherence or increased risk of infection (neutropenia)*

- to 48 weeks, there was an excess in the NVP arm of Grade 4 AE and Grade 3/4 AE, but no statistically significant difference in ART-modifying AEs (see Figure)
  - mostly by differences in neutropenia: eg 54 ABC versus 94 NVP patients had Grade 4 neutropenia, whereas 0 ABC versus 10 NVP patients had Grade 4 LFTs
  - many AEs were laboratory toxicity only
- however, there was no clear relationship between toxicity (ART-related or relating to other drugs or drug-drug interactions) and cause of death
  - cryptosporidia (1N), cryptococcal meningitis (1N), other meningitis (2A), presumed septicaemia/bacteraemia or neutropenia (3A,5N), visceral abscess (1N), pneumonia (3N), pulmonary TB (1A,1N), haematemesis (1N), fits/convulsions (1A), HIV-related indeterminate cerebral disease (1A,1N), uncertain (1A,2N)

(II): ART SWITCHES?

Hypothesis: patients with poor immunological/virological response in ABC substituted ABC with another drug and thus avoided clinical events ➪ ***UNLIKELY***

- all viral loads were performed retrospectively: half the patients did not receive CD4 results (following the main randomisation in DART)
- in total 21 (7%) ABC versus 34 (11%) NVP participants were off randomised drug at 48 weeks
  - most (12A,29N) had substituted blinded ABC/NVP with TDF for AEs or to start TB treatment following the protocol: the remainder stopped ART permanently or temporarily (3A,4N) or switched to the opposite drug (6A,1N: incorrect unblinding/switch for pregnancy)
  - very few discontinuations occurred before clinical events: 2 (2N) before death, 1 (N) before 1st of new/recurrent WHO 4 or death, 2 (1A,1N) before 1st of new/recurrent WHO 3, 4 or death

(III): CHANCE FINDING?

Hypothesis: inconsistent results were observed by chance ➪ ***POSSIBLE***

- The blinded Endpoint Review Committee judged more reported WHO 4 events did not meet protocol criteria for trial endpoints in ABC. In particular 5 events (4A,1N) were judged to be severe brain or lung disease which did not meet criteria for diagnosis of toxoplasmosis or PCP
  - including these severe brain/lung events (occurring at weeks 3, 5, 6, 46, 2 (patient died week 3)) did reduce statistical significance, but there was still no evidence of clinical benefit to NVP (Figure)

(IV): IRIS?

Hypothesis: Viral suppression and CD4 increases were greater in the NVP arm. This could have led to more IRIS ➪ ***POSSIBLE, but not strongly supported***

- most events were early: all but 1 (N) death occurred in the 1st 24 weeks, and most (7A,12N) were in 12 weeks. Most new WHO 4/death (13/17A, 23/29N) were also in the 1st 12 weeks.
  - however, there was no evidence of heterogeneity in the relative difference between ABC and NVP before and after 12 weeks for death (HR=0.57, 0.48 respectively, het p=0.86), new WHO 4/death (HR=0.55, 0.62 respectively het p=0.87), or other outcomes
- first new WHO 4/death events were oesophageal candida (4A,3N), extra-pulmonary TB (2A,5N), cryptococcus (3N), PCP (2A,1N), Herpes simplex (1A,1N), toxoplasmosis (1A,1N), KS (2N), wasting (1N), cryptosporidia (1N) or death (7A,11N).
  - no clear relationship in occurrence of specific events by time on ART
- CD4 at ART initiation has previously been reported as a predictor of IRIS
  - however, there was no evidence of significant heterogeneity in the relative difference between ABC and NVP in those with pre-ART CD4 0-49, 50-100 or 100-199 cells/mm³ for death (HR=0.82, 0.25, 0.75 respectively, het p=0.47), new WHO 4/death (HR=0.50, 0.34, 0.99* respectively het p=0.40), or other outcomes (*non-significant attenuation of difference in highest CD4 group not seen including WHO 3 events)
  - also no evidence of significant heterogeneity by baseline WHO stage (p=0.73)
- the first post-ART CD4 count in DART is at week 12: it is not possible to compare early CD4 changes in those with and without events because many events were before week 12
- The first post-ART HIV RNA is at week 4:
  - the overall mean decrease in HIV-1 RNA was similar (-2.80 ABC, -2.76 NVP, p=0.52)
  - there were no large or significant differences in HIV-1 RNA decrease in those who died (-0.16 lower, p=0.39) or had new WHO 4 events/death (+0.02, p=0.88)

(V): CHANGING EFFECTS OVER TIME?

Hypothesis: inferior 48 week immunological/virological response in ABC may attenuate difference in clinical outcome later in time ➪ ***POSSIBLE***

- no evidence for heterogeneity over time for death or WHO 4 events (see above)
  - for new WHO 3, 4 or death there was a suggestion that the relative difference between ABC and NVP might be attenuating (HR=0.55 0-12 weeks, 0.76 12-24 weeks, 1.62 24-48 weeks, het p=0.21)
  - however, overall to 48 weeks there was a statistically significant benefit to ABC in terms of development of new WHO 3 or 4 events or death (HR=0.67,p=0.05: see Figure): 14% ABC and 19% NVP had developed new WHO 3 or 4 events or died by 48 weeks
  - therefore, even if the difference between groups is attenuating, it may not lead to overall clinical benefit to NVP even in the medium term

(VI): PROGNOSTIC VALUE OF CD4 & VL?

Hypothesis: inconsistent results observed because absolute levels of CD4 and HIV RNA have different prognostic value for clinical outcomes in the NVP and ABC groups ➪ ***UNLIKELY because trend towards clinical benefit to ABC remains after adjustment***

- averaging effects across treatment groups, the most important predictors of new WHO 4/death before 48 weeks were **low most recent CD4** (HR=0.57 per 50 cell/mm³ higher [95% CI 0.40-0.84]) and **low most recent haemoglobin** (HR=0.69 per 1 g/dl higher [0.59-0.81])
  - there was a suggestion that higher CD4 counts reduced the risk of new WHO 4/death less in ABC than NVP (HR=0.71 and 0.50 per 50 cell/mm³ higher respectively, het p=0.13)
- adjusting for these factors did not alter the relative risk of clinical events between randomised groups (HR(ABC:NVP)=0.58 [0.32,1.07], virtually identical to unadjusted results, see Figure)
- similar results for predictors of new WHO 3, 4 or death

SUMMARY

- NVP has superior virological/immunological efficacy compared to ABC over 48 weeks
  - although viral load suppression was good and CD4 gains substantial in both groups
- Further follow-up will be important to monitor the trend towards clinical superiority of the ABC arm observed during this period
- As well as the possible contribution of IRIS to these results, other potential mechanisms could be explored
  - quality as well as quantity of immune restoration
  - the relative fitness cost of NNRTI and NRTI mutations
- At 52 and 76 weeks, NORA patients with CD4 ≥300 cells/mm3 were randomised to 12 week on/off STIs or continuous ART in the DART STI study: further results from this randomised comparison will therefore require careful analysis and interpretation, because more NVP patients achieved this threshold and were randomised
- Patients receiving triple NRTI in DART do not appear to have been disadvantaged clinically. Further, these patients have two new classes (NNRTI+PI) available at immunological/clinical failure of first-line therapy (following the WHO public health approach to ART) when extensive NRTI resistance is likely to have developed in both 3NRTI and NNRTI+2NRTI groups

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