Long-term randomised comparison of clinical outcomes following ART initiation with triple-nucleoside (Combivir/Abacavir) or NNRTI-based (Combivir/Nevirapine) therapy in Africa: the NORA substudy of the DART trial

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Background: NORA trial design

- **Nevirapine OR Abacavir (NORA) substudy**
- 600 patients within the DART trial randomised to initiate ART with ZDV+3TC (combivir, CBV) plus
  - **Abacavir (ABC)**
  - **Nevirapine (NVP)**
- Primary and secondary endpoints: toxicity at 24 weeks (placebo-blinded)
- Continued open-label follow-up after 24 weeks for up to 5 years in DART

The question

- To 48 weeks, we observed
  - clear superiority of **NVP** over **ABC** in terms of VL <50 copies/ml (**77%** vs **62%**) and CD4 increases (**+173** vs **+147** cells/mm³)
  - trend towards superiority or superiority of **ABC** over **NVP** in terms of clinical outcomes, for example
    - Death: HR(**ABC**:**NVP**) = 0.55 (95% CI 0.24-1.25) p=0.15
    - Death/WHO 4: HR(**ABC**:**NVP**) = 0.60 (95% CI 0.34-1.05) p=0.07
    - Death/WHO 3/4: HR(**ABC**:**NVP**) = 0.67 (95% CI 0.46-0.96) p=0.03

➢ **QUESTION: How does clinical disease progression in ABC compare to that in NVP over the longer-term?**

The challenge: Structured Treatment Interruptions

- 813 (25%) DART patients with a good early response to ART (achieving CD4>300 cells/mm3 at 48 or 72 weeks) were randomised in a **conditional factorial (non-inferiority) design** between
  - continuous therapy (CT)
  - structured treatment interruptions (STIs)
    - 12 weeks on ART, 12 weeks off ART, etc
- **CT/STI randomisation stopped early in March 2006 showing inferiority of STIs on disease progression**
  - 2.6 fold increased rate of disease progression
  - CD4 count dropped by mean 150-200 cells/mm³ during STI

PROBLEM 1

- CD4 response was better in **NVP**, so more patients achieved the CD4>300 cells/mm³ threshold and were randomised in the CT/STI substudy in **NVP** than **ABC**

PROBLEM 2

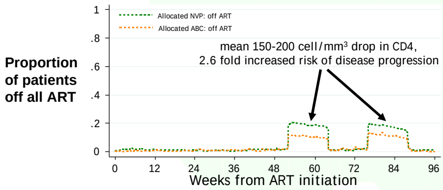
- There was a **chance imbalance** in CT/STI randomisation between **NVP** and **ABC**, with even more **NVP** patients randomised to STI
  - CT/STI randomisation stratified by original allocation to LCM/CMO (factorial), centre and weeks of first-line ART (48/72) with variable block size (8,12); all other factors well balanced across CT/STI groups; no evidence of tampering with randomisation procedure integrated into trial database

Table 1: NORA patient characteristics

	ABC		NVP		Total	
Total NORA patients	**300**	**(100%)**	**300**	**(100%)**	**600**	**(100%)**
Women	217	(72%)	213	(71%)	430	(72%)
Previously received sdNVP	4	(1%)	11	(4%)	15	(3%)
Median (IQR) pre-ART CD4	99(49-149)		99(40-145)		99(44-147)	
Mean (SD) pre-ART log_{10} VL	5.4	(0.7)	5.4	(0.7)	5.4	(0.7)
Not randomised to CT/STI	211	(70%)	183	(61%)	394	(66%)
Randomised to CT/STI	**89**	**(30%)**	**117**	**(39%)**	**206**	**(34%)**
Randomised to CT	*53*	*(18%)*	*47*	*(16%)*	*100*	*(17%)*
*Randomised to STI**	*36*	*(12%)*	*70*	*(23%)*	*106*	*(18%)*

* stopped all ART for 12 weeks out of every 24 weeks from 52 or 76 weeks after starting ART: mean 150-200 cell/mm³ drop in CD4, 2.6 fold increased risk of disease progression

Twice as many NVP NORA participants underwent STIs compared with ABC



Statistical methods

- We adjusted Cox models for time-to-event outcomes for differential recruitment to STI/CT by **weighting**: specifically we excluded all follow-up after participants were randomised to STI, and probability up-weighted equivalent post-randomisation follow-up from participants randomised to CT. This effectively
  - treats the 53 **ABC** patients randomised to CT (Table 1) as if they were really the 89 **ABC** patients randomised to STI/CT in the statistical model
  - treats the 47 **NVP** patients randomised to CT (Table 1) as if they were really the 117 **NVP** patients randomised to STI/CT in the statistical model
  - randomisation ensures those randomised to CT are representative of the whole group randomised to STI/CT
- Simply including "randomised to STI", "randomised to CT", "not randomised" as a time-updated explanatory factor in the Cox model can produce biased estimates, because of **time-depending confounding**
  - estimates from models adjusted using time-updated explanatory factors were actually very similar to the unadjusted estimates

LIMITATION:

- **The unequal randomisation to STI between NVP and ABC happened: whilst statistical methods can be used to adjust for the imbalance, these rely on modelling assumptions**
  - the approach used here was validated in numerous simulations studies

Cotrimoxazole prophylaxis and mortality

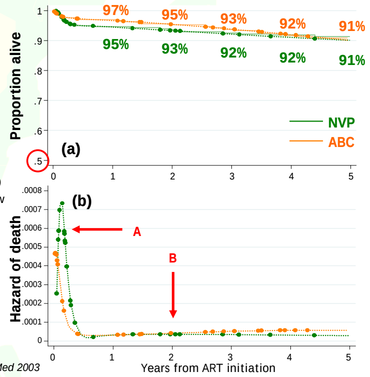
- 2458 person-years (2103 excluding follow-up after randomisation to STI) accrued from ART initiation to 31/12/2008 (end of CMO/LCM follow-up)
  - ➢ median 4.5 years follow-up (IQR 4.3-4.7, maximum 5 years)

	Death		New/recurrent WHO4/death	
Not adjusted for STIs				
Events	**25 ABC, 31 NVP**		**54 ABC, 65 NVP**	
Rate/100 PY	**2.0 vs 2.5**		**4.6 vs 5.8**	
HR(**ABC**:**NVP**) (95% CI)	0.80 (0.47-1.36) p=0.42		0.80 (0.56-1.15) p=0.24	
% event-free at 4.5 years	**91% vs 89%**		**81% vs 77%**	
HR(**ABC**:**NVP**) by time on ART	heterogeneity p=0.78		heterogeneity p=0.08	
0-90 days	0.58	(0.23-1.48)	0.62	(0.32-1.18)
91 days – 1 year	0.49	(0.09-2.65)	0.82	(0.28-2.43)
1-2 years	1.22	(0.33-4.54)	0.45	(0.19-1.03)
2-3 years	0.59	(0.14-2.48)	0.62	(0.22-1.75)
3-4 years	1.66	(0.40-6.95)	3.59	(1.19-10.8)
4-5 years	1.05	(0.22-5.15)	1.04	(0.26-4.14)
Adjusted for STIs by weighting*				
Events*	**26 ABC, 25 NVP**		**53 ABC, 54 NVP**	
Rate/100 PY*	**2.1 vs 2.0**		**4.6 vs 4.8**	
HR(**ABC**:**NVP**) (95% CI)	1.04 (0.59-1.84) p=0.89		0.95 (0.64-1.42) p=0.82	
% event-free at 4.5 years	**91% vs 91%**		**81% vs 81%**	
HR(**ABC**:**NVP**) by time on ART	heterogeneity p=0.47		heterogeneity p=0.10	
0-90 days	0.58	(0.23-1.48)	0.62	(0.32-1.18)
91 days – 1 year	0.49	(0.09-2.65)	0.82	(0.28-2.43)
1-2 years	1.63	(0.39-6.82)	0.67	(0.25-1.77)
2-3 years	1.45	(0.29-7.32)	0.83	(0.26-2.64)
3-4 years	2.89	(0.55-15.1)	5.20	(1.49-18.1)
4-5 years	2.18	(0.20-23.3)	1.11	(0.16-7.84)

* excluding all follow-up after participants were randomised to STI, and probability up-weighting equivalent post-randomisation follow-up from participants randomised to CT

Death

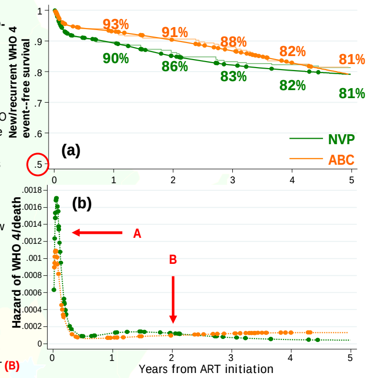
- Solid lines in (a) are the Kaplan-Meier **survival** estimate
- Dotted lines in (a) show the fit from a model[1] estimating the instantaneous risk of death over time (the **hazard**; in (b))
- Estimated survival percentages from the model are shown in (a)
- Points in (a) & (b) show the actual death times
- The risk of death is higher in **NVP** shortly after starting ART **(A)**
- After 2 years the hazards cross, and the risk of death is higher in **ABC**: but rates are far lower than after starting ART **(B)**



[1] Royston & Parmar Stat Med 2003

New/recurrent WHO 4 or death

- Solid lines in (a) are the Kaplan-Meier **WHO-4-free survival** estimate
- Dotted lines in (a) show the fit from a model[1] estimating the instantaneous risk of WHO 4/death over time (the **hazard**; in (b))
- Estimated percentages alive & WHO 4-free from the model are shown in (a)
- Points in (a) & (b) show the actual even times
- The risk is higher in **NVP** shortly after starting ART **(A)**
- After 2 years the hazards cross, and the risk is higher in **ABC**: but rates are far lower than after starting ART **(B)**



Conclusions

- **There was no statistically significant difference in the rate of new WHO 4 events/death or death between participants initiating ART with Combivir plus nevirapine versus abacavir through 5 years follow-up**
  - as a consequence of the large early differences and low long-term event rates, at 4.5 years 91% participants were estimated to be alive in both groups
  - those taking only NRTIs 1st-line have two new classes (bPI+NNRTI) for 2nd-line
  - nevirapine had clear superiority in terms of CD4 (and VL supression to 96 weeks): the unexpected failure of laboratory markers to predict clinical outcomes is unexplained and requires further evaluation
- **Including time-dependent factors in multivariable models is the standard method for adjustment in observational analyses, but provides incomplete adjustment for time-dependent confounders**
  - these may occur more frequently than is recognised, as here, so using weighting to adjust for post-baseline changes should be considered more

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