Safety of Nevirapine Compared to Abacavir on a Background of Zidovudine/Lamivudine as First-line Antiretroviral Therapy: a Randomised Double-Blind Trial conducted in Uganda

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on behalf of the **DART** Trial Team

Background

- Standard 1st line regimen in Africa is 2NRTI/NNRTI
  - Nevirapine (NVP) is the most frequently used NNRTI
- Consideration of an Abacavir-based regimen in Africa remains warranted
  - High rates of TB co-infection
  - Initiation of treatment in women
- High rates of **HSR** may limit use of Abacavir (ABC)
  - In Africa HSR may be difficult to distinguish from intercurrent infections, for example malaria
- No randomised trials have reported on toxicity of nevirapine and abacavir in Africa

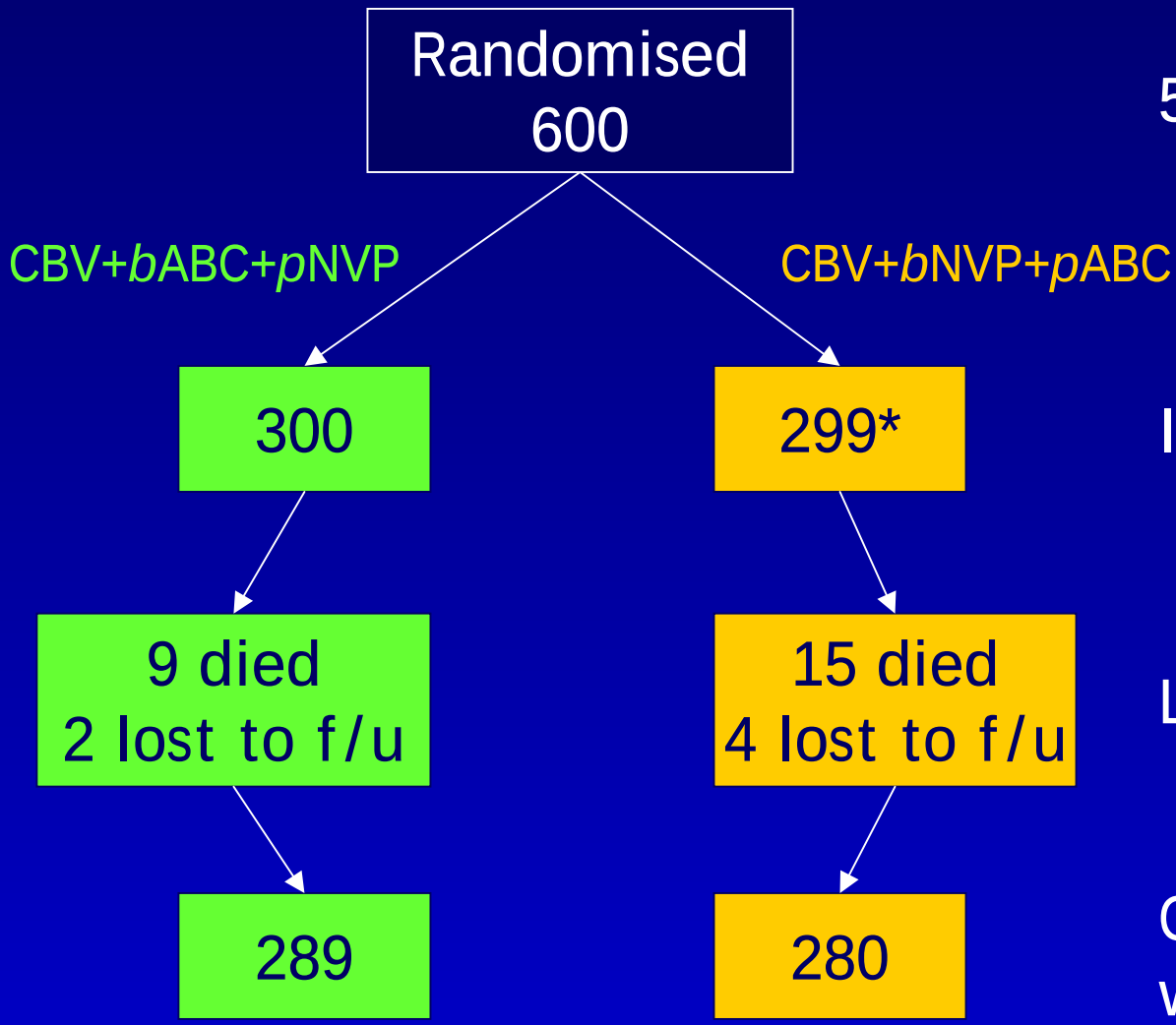
NORA Trial Design

- A randomised, double-blind, 24 week, phase II trial at 2 centres in Uganda
- Evaluating the safety of Nevirapine OR Abacavir [NORA]
- A substudy of the DART Trial
- 600 ARV naïve adults with symptomatic HIV infection CD4<200 cells/mm3 and no contraindications to ARTwere randomised in a 1:1 ratio, to receive: zidovudine/lamivudine (Combivir) twice daily, plus
  - 300 mg ABC and nevirapine placebo twice daily
  - 200 mg NVP and abacavir placebo twice daily

Endpoints

- Primary: SAE as defined by ICH-GCP definitely/probably or uncertainly related to blinded nevirapine/abacavir (SAR)
  - Independently adjudicated by clinicians blind to randomised allocation
  - Secondary: AE of any grade leading to permanent discontinuation of blinded nevirapine/abacavir
  - Secondary: Grade 4 events irrespective of whether or not they resulted in nevirapine/abacavir discontinuation

Follow-up



5 Jan to 28 Oct 2004

Initiated allocated ART

Lost before 24 weeks

Completed 24 weeks, went onto open label

* 1 patient excluded due to previous ART

Baseline Characteristics

		ABC	NVP
Total patients		300	299
Women		72%	71%
Prior ART to prevent MTCT		2%	5%
Age	mean	37.6	36.3
CD4 at randomisation (cells/mm^3)	0-49	25%	29%
	50-99	25%	21%
	100-149	25%	28%
	150-199	25%	22%
WHO stage at randomisation	2	28%	25%
	3	58%	53%
	4	18%	22%

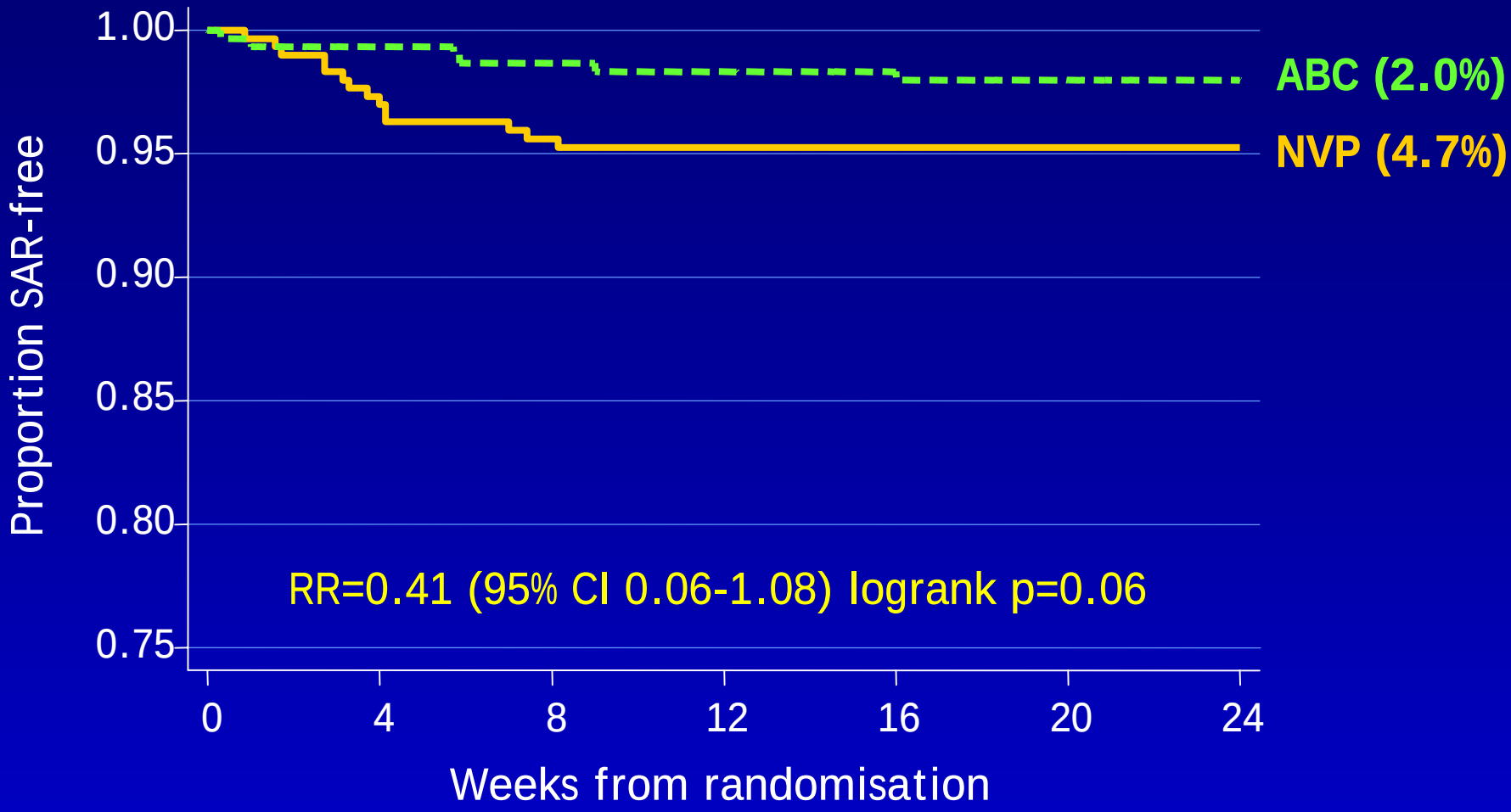
Outcome

- 34 SAEs occurred on blinded drug in 33 patients
- Primary endpoint: 20 SAEs in 20 patients were definitely/possibly related to blinded abacavir/nevirapine and classified as Serious Adverse Reactions (SAR)
  - 6 (2.0%) on ABC
  - 14 (4.7%) on NVP p=0.06
- 14 SAEs considered unlikely to be related to blinded drug were anaemia (n=7), pancytopenia, death from unknown cause, head trauma, DVT, duodenal ulcer/haematemesis, fever*, rash**

** rabies vaccination*

*** open label NVP following discontinuation of blinded ABC for HSR*

Time to first SAR



SAR & HSR

- 19/20 SAR were considered consistent with diagnosis of hypersensitivity reaction (HSR)

	ABC (N=6)	NVP (N=13)	Total (N=19)
Respiratory symptoms	4	7	11
Constitutional symptoms	3	7	10
Gastrointestinal symptoms	2	5	7
Rash	6	10	16
Fever	6	9	15
Hepatic involvement	0	3	3
Oral/mucosal involvement	2	5	7

  - 1 SAR was asymptomatic elevation of ALT/AST (NVP)

Discontinuation of blinded trial drug

	ABC (N=300)	NVP (N=299)	Total (N=599)
Discontinuation of blinded drug	**14**	**30**	**44**
percent (%)	**(5%)**	**(10%)**	**(7%)**
for adverse events (secondary endpoint) (%)	**6* (2%)**	**15* (5%)**	**21* (4%)**
for anti-TB treatment	6	13	19
for pregnancy	0	1*	1*
for patient decision	2	1	3
Proportion of time at risk to 24 weeks on allocated treatment	96.8%	92.2%	94.5%

* patients and clinicians were unblinded

exact p=0.05

exact p=0.05

Secondary endpoint: Grade 4 AE

- 187 (78 ABC, 109 NVP) Grade 4 AEs in 155 patients (64 ABC, 91 NVP) on blinded drug
  - 59 per 100 PY at risk in ABC
  - 88 per 100 PY at risk in NVP p=0.008
- Majority were haematological
  - greatest difference in neutropenia: 46 ABC, 71 NVP
  - anaemia: 17 ABC, 16 NVP
    - d4T substituted for ZDV in 45 patients, (22 ABC, 23 NVP)
- 30 (19%) adverse reactions to blinded trial drugs
- 8 patients (all NVP) had Grade 4 elevations in LFTs

Conclusions

- In Ugandan patients with low CD4 counts initiating ART with CBV/NVP or CBV/ABC
  - A trend towards a lower rate of SARs with ABC
  - A lower discontinuation rate with ABC
  - A lower rate of any grade 4 AE with ABC
- Considerable overlap in clinical manifestations of NVP and ABC reactions
- Rate of ABC HSR in this population is 2%
- Ongoing assessment of
  - Genetic polymorphisms
  - Virological and immunological efficacy

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