# Discordance between virological/immunological and clinical outcomes at 48 weeks, in a randomised comparison of ZDV/3TC/NVP and ZDV/3TC/ABC in patients with low CD4 counts in Africa

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on behalf of the **DART** Trial Team

# Background - NORA

- A randomised, double-blind, 24 week, phase II trial
- 600 ARV-naïve adults, symptomatic HIV infection, CD4<200 cells/$mm^3$ and no contraindications to ART randomised in a 1:1 ratio to receive:

  zidovudine/lamivudine (Combivir) twice daily, plus
  - 300 mg ABC and nevirapine placebo twice daily, or
  - 200 mg NVP and abacavir placebo twice daily

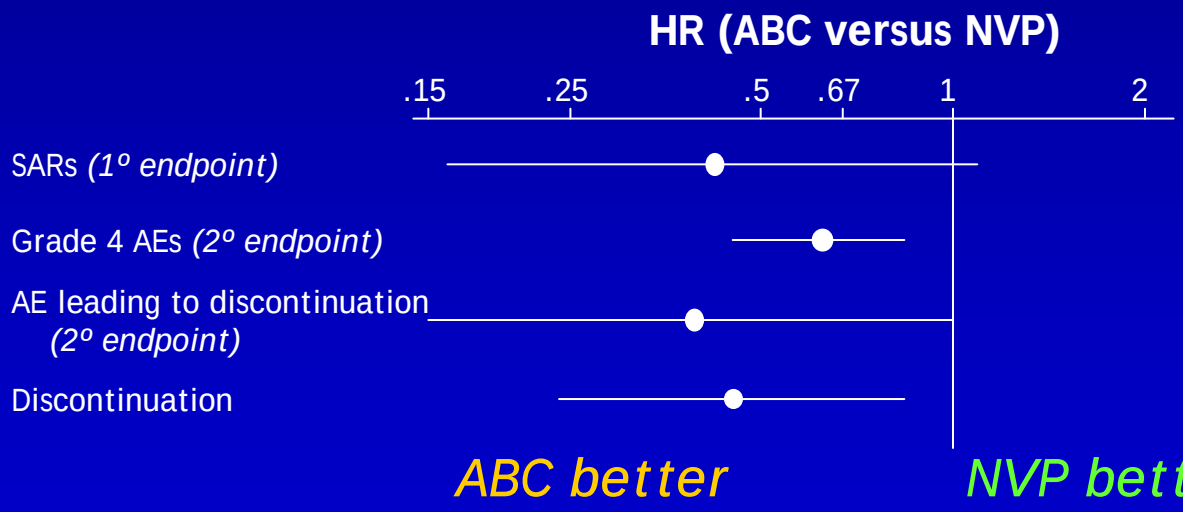
- switch to open-label active drug at 24 weeks, then follow-up
- 1º endpoint: Safety

# Baseline Characteristics

| | | ABC | NVP |
|---|---|---|---|
| Total patients | | 300 | 300 |
| Women | | 72% | 71% |
| Prior ART to prevent MTCT (% of women) | | 2% | 5% |
| Age | median | 37 | 36 |
| CD4 at randomisation (cells/mm$^3$) | 0-99 | 50% | 50% |
| | 100-199 | 50% | 50% |
| | median | 99 | 100 |
| HIV-1 RNA at randomisation (copies/ml) | median | 292,300 | 283,100 |
| WHO stage at randomisation | 2 | 28% | 25% |
| | 3 | 58% | 52% |
| | 4 | 15% | 22% |

# Safety Outcomes – 24 weeks

- 289 ABC 280 NVP completed 24 weeks
  - 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



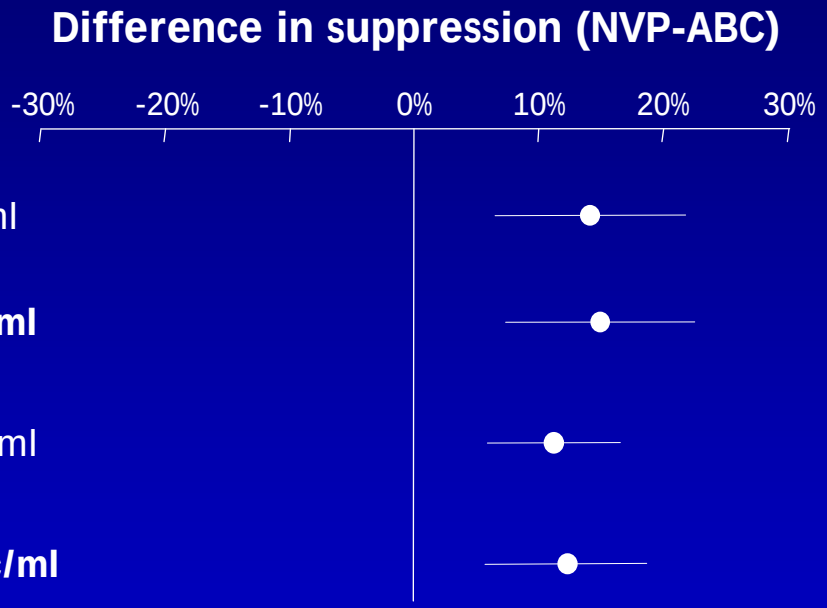

| | ABC Events | NVP Events | HR | LR p |
|---|---|---|---|---|
| SARs *(1º endpoint)* | 6 | 14 | 0.42 | 0.07 |
| Grade 4 AEs *(2º endpoint)* | 65 | 98 | 0.62 | 0.002 |
| AE leading to discontinuation *(2º endpoint)* | 6 | 15 | 0.39 | 0.05 |
| Discontinuation | 14 | 30 | 0.45 | 0.01 |

# Efficacy Outcomes

- **Efficacy analysis was not planned as part of NORA protocol**
- Patients continued to be seen in DART study clinic every 4 weeks
- Exploratory ITT analysis of efficacy outcomes to 48 weeks
  - clinical events (WHO 3 and 4 events) and death documented and independently reviewed
  - CD4 cell count (measured in real-time at 0, 12, 24, 36, 48 weeks)
  - plasma HIV-1 RNA (assayed retrospectively at 0, 4, 12, 24, 48 weeks)
- 12 patients (2%) lost to follow-up before 48 weeks

# Virological Efficacy to 48 Weeks

## (a) virological efficacy: NVP is superior

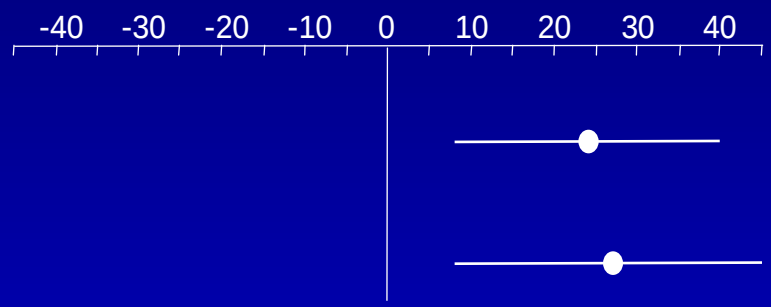



| | ABC % | NVP % | Difference | Exact p |
|---|---|---|---|---|
| 24 weeks: % <50 c/ml | 62% | 76% | +14% | <0.001 |
| **48 weeks: % <50 c/ml** | 62% | 77% | +15% | <0.001 |
| 24 weeks: % <400 c/ml | 82% | 93% | +11% | <0.001 |
| **48 weeks: % <400 c/ml** | 75% | 87% | +12% | <0.001 |

# Immunological Efficacy to 48 Weeks

## (b) immunological efficacy: NVP is superior

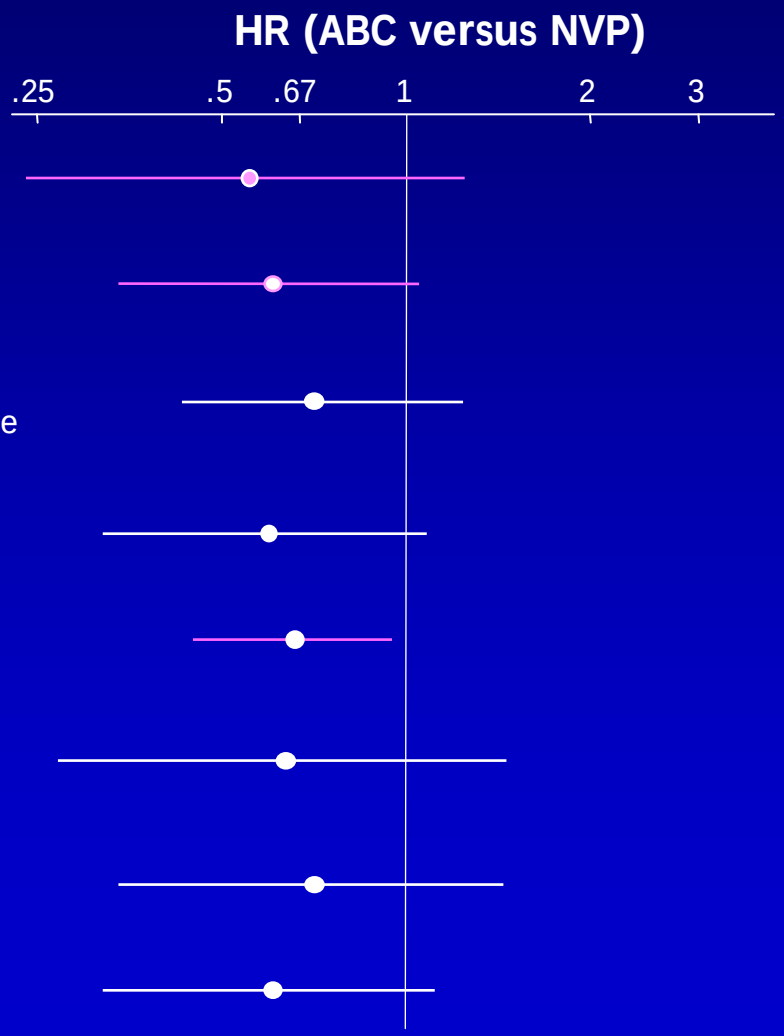
**Difference in mean cells/mm$^3$ increase (NVP-ABC)**




| | ABC mean | NVP mean | Difference | T-test p |
|---|---|---|---|---|
| 0-24 weeks | +111 | +134 | +24 | 0.003 |
| **0-48 weeks** | +147 | +173 | +27 | 0.006 |

# Clinical Efficacy to 48 Weeks

## (c) clinical efficacy: trend towards superiority of ABC




| | ABC Events | NVP Events | HR | LR p |
|---|---|---|---|---|
| Death | 9 | 16 | 0.55 | 0.15 |
| WHO 4/death | 20 | 32 | 0.60 | 0.07 |
| WHO 4/death or severe brain/lung disease | 24 | 32 | 0.73 | 0.24 |
| WHO 4 excl candida/death | 17 | 28 | 0.59 | 0.08 |
| WHO 3 or 4/death | 48 | 68 | 0.65 | 0.02 |
| TB | 9 | 14 | 0.63 | 0.28 |
| WHO 3 bacterial infection | 13 | 18 | 0.70 | 0.33 |
| Candida (oral or oesophageal) | 16 | 26 | 0.60 | 0.10 |

# Discussion

## Possible explanations for these results

- Increased toxicity of NVP led to more clinical events on NVP - unlikely
  - most clinical events not related to ARV toxicity (HIV related)
- Was there a difference in rate of 'switching' to alternative regimens (with altered potency) ? - No
  - more ART substitutions in NVP arm (34 vs 21)
- These differences between outcomes are a chance finding (Type I error)
  - cannot be ruled out

# Discussion cont ..

No evidence that excess events in NVP arm were due to IRIS

- Events were not classified as IRIS or not IRIS
- Surrogate markers for IRIS e.g. early vs late events

| Number of new or recurrent WHO 4 events or death | ABC | NVP | HR |
|---|---|---|---|
| Before 12 weeks | 15 | 25 | 0.58 |
| After 12 weeks | 5 | 7 | 0.67 |
| *test for heterogeneity p=0.84* | | | |

- Similar results for CD4 or WHO stage at ART initiation
- Similar changes in HIV-1 RNA at week 4 in both groups

# Conclusion

- NVP has superior virological/immunological efficacy compared to ABC over 48 weeks
- Trend towards clinical superiority of the ABC arm to 48 weeks

- No clear explanation so far for this apparent discordance
  - it may be a chance finding
  - if real, it suggests a disconnect between early clinical and virological/immunological outcomes which may influence the way surrogate markers are interpreted

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# Dame Anne McLaren

Chair of DART DSMC

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