



**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<sup>3</sup> 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
- 1° endpoint: Safety



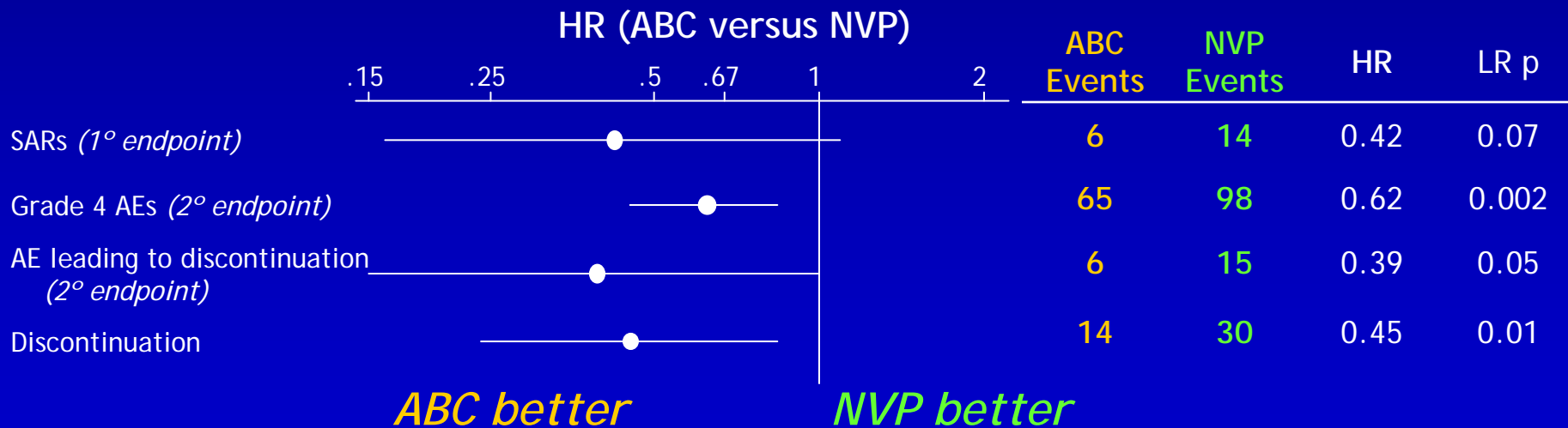
# Baseline Characteristics

		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 <sup>3</sup> )	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





# Efficacy Outcomes



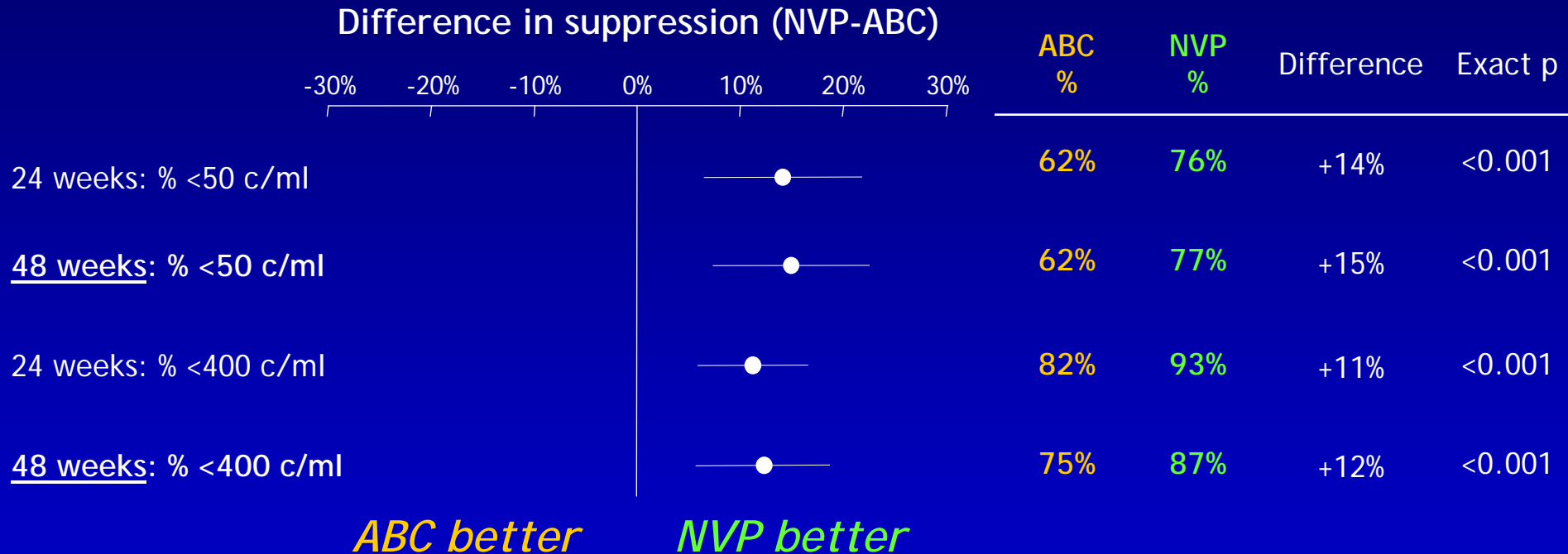
- **Efficacy analysis was not planned as part of NORA protocol**
- Patients continued to be seen in DART study clinic every 4 weeks
- Exploratory ITT analysis of efficacy outcomes to 48 weeks
  - clinical events (WHO 3 and 4 events) and death documented and independently reviewed
  - CD4 cell count (measured 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

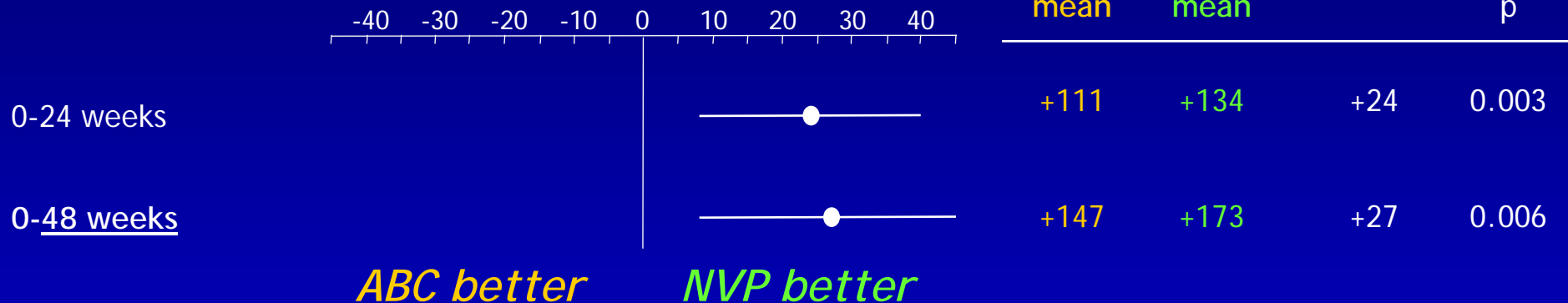


(a) virological efficacy: NVP is superior



(b) immunological efficacy: NVP is superior

Difference in mean cells/mm<sup>3</sup> increase (NVP-ABC)

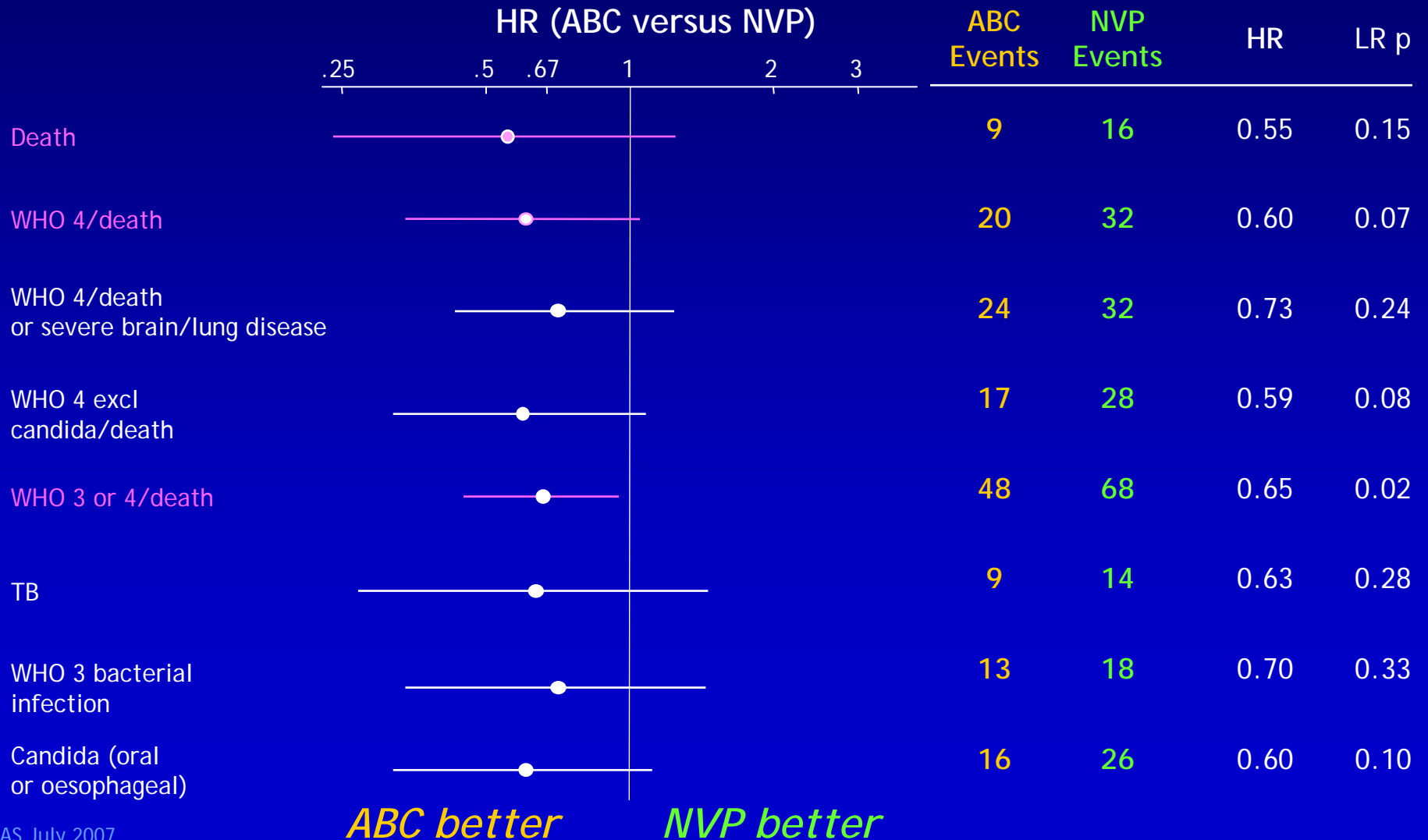




# Clinical Efficacy to 48 Weeks



(c) clinical efficacy: trend towards superiority of ABC





# 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
<i>test for heterogeneity p=0.84</i>			

- 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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- **Trial Steering Committee:** I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Darbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, C Mapuchere, O Mugurungi, P Mugenyi; Observers C Burke, S Jones, C Newland, J Rooney, W Snowden, J-M Steens.
- **Data and Safety Monitoring Committee:** A McLaren (Chair), C Hill, J Matenga, A Pozniak, D Serwadda
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# Dame Anne McLaren



Chair of DART DSMC

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