



# Severe Anaemia and Associated Risk Factors following Initiation of ZDV-containing Regimens in Adults with HIV Infection in Africa within the DART Trial

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on behalf of the **DART** Trial Team



# Background



- Anaemia is common in advanced HIV disease
  - associated with poor survival in untreated patients, independent of CD4 and viral load
- 1% incidence of grade 4 anaemia during ZDV-based therapy in industrialised countries
  - peak 4-12 weeks after initiating ART
  - baseline CD4 an important risk factor
- Few data in resource-limited settings



# DART trial: Uganda & Zimbabwe



3315 previously untreated HIV-infected patients  
stage WHO 2, 3 or 4 and  $CD4 < 200$  cells/mm<sup>3</sup>

randomise to  
initiate triple  
drug ART with

Clinical and  
Laboratory Monitoring  
(including FBC  
at weeks 4 & 12,  
and then every 12 weeks)

Clinical Monitoring  
Only  
(FBC results available  
if requested for clinical  
reason, or Grade 4 toxicity)

• First line regimens: Combivir (ZDV/3TC) plus

- tenofovir DF (TDF) 2468 (74%)
- nevirapine (NVP) 247 (7%)
- blinded NVP or abacavir 600 (18%) [substudy]



# Objectives



- To estimate the prevalence and incidence of anaemia over time in DART:
  - grade 1: 8.0 to <9.5 g/dl
  - grade 2: 7.0 to <8.0 g/dl
  - grade 3: 6.5 to <7.0 g/dl
  - grade 4: <6.5 g/dl**
- To describe episodes of grade 4 anaemia, including concurrent clinical events
  - “episode” defined as the period between the first grade 4 measurement and first return to baseline grade or better
- To investigate predictors of developing grade 4 anaemia using multivariable logistic regression
  - age, sex, WHO stage, CD4, weight and BMI at baseline
  - haematological parameters at baseline and week 4



# Baseline characteristics



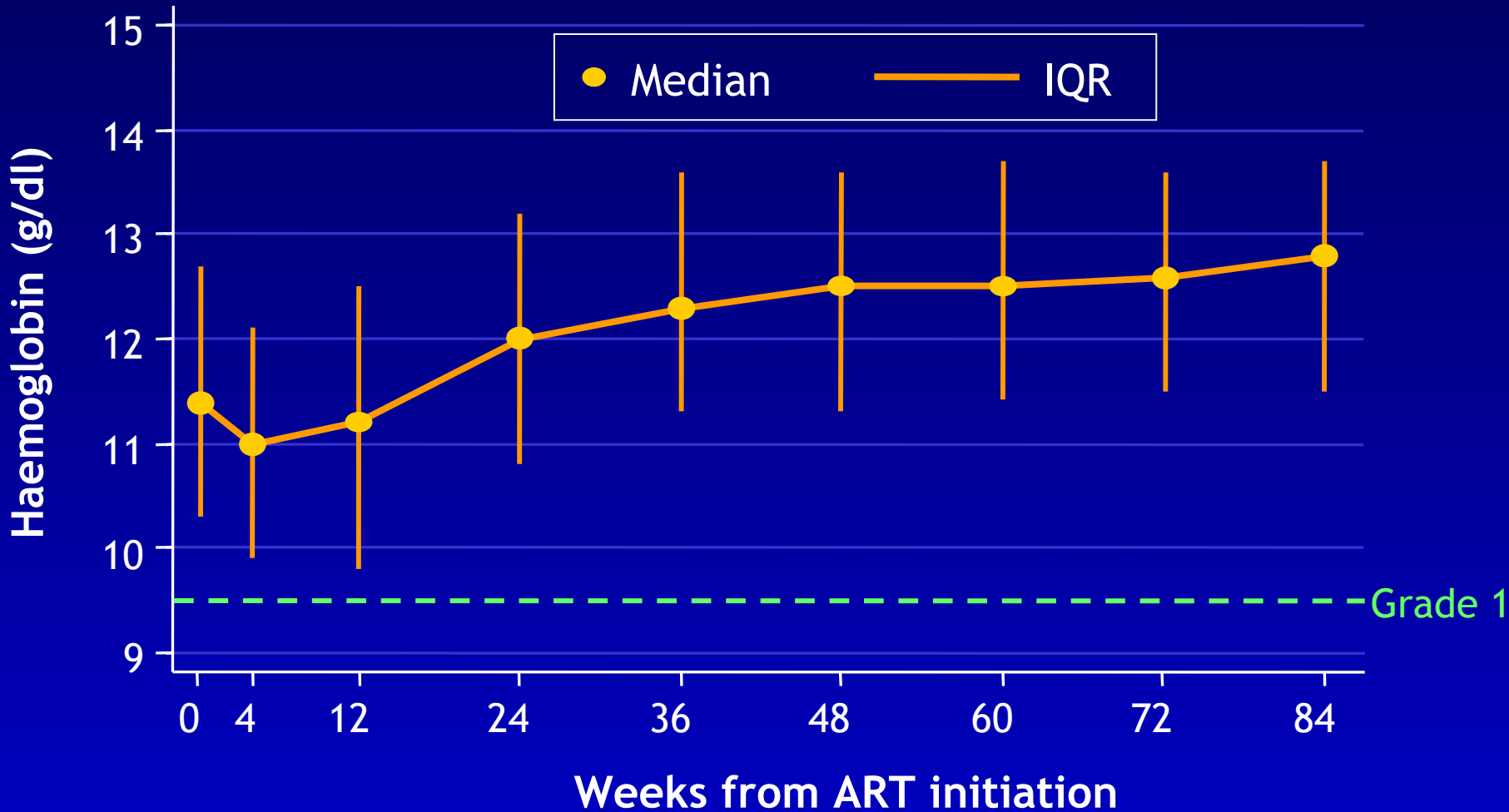
3315 participants (accrual completed Oct 2004)

- Sex 65% women
- Median age 37 years (IQR: 32-42)
- Median CD4 86 cells/mm<sup>3</sup> (IQR: 31-140)
- WHO stage 23% WHO 4 56% WHO 3
- Median Hb 11.4 g/dl (IQR: 10.3-12.7)
- Anaemia 12% <9.5g/dl (grade 1)
- Median BMI 21.2 (IQR: 19.2-23.6)
- Median follow-up 48 weeks (IQR: 25-60, max: 96)

Data to 15 January 2005 (trial ongoing)



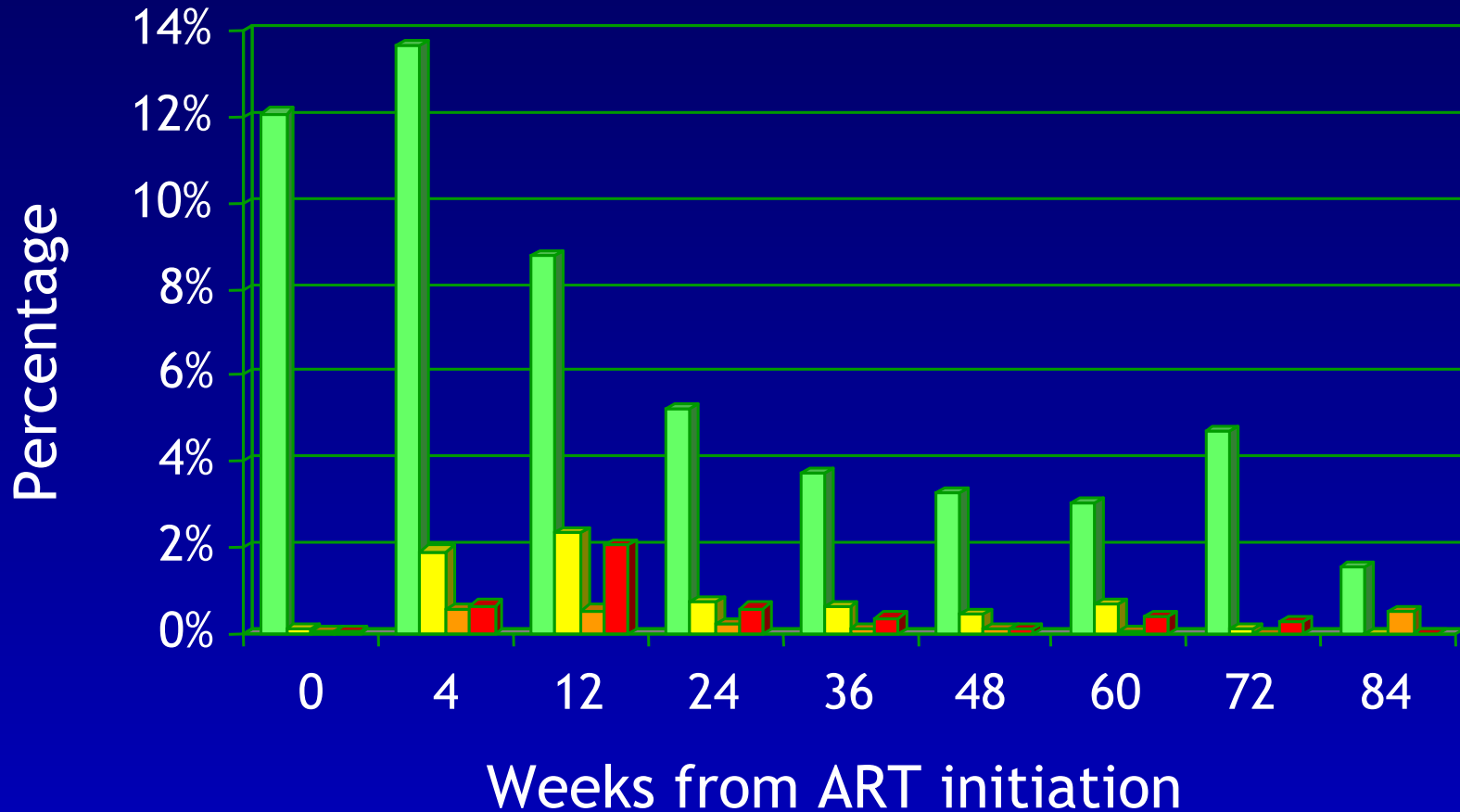
# Haemoglobin at scheduled assessments after initiation of ART



Number 3302 3149 2830 2407 1932 1439 767 196



# Prevalence of anaemia at scheduled assessments





# Incidence of anaemia



- Most severe new episode:

|                     | n   | %      | cumulative |
|---------------------|-----|--------|------------|
| Grade 4 (<6.5 g/dl) | 220 | 6.6 %  | 6.6 %      |
| Grade 3             | 38  | 1.2 %  | 7.8 %      |
| Grade 2             | 136 | 4.1 %  | 11.9 %     |
| Grade 1             | 407 | 12.3 % | 24.2 %     |

- 14 patients had >1 grade 4 episode



# First new Grade 4 anaemia



220 of 3315 patients had a new grade 4 anaemia episode

- first episode occurred median 12 weeks after ART initiation (IQR: 8-20, range: 2-88)
- median episode duration 26 days (IQR 6-45)
- 101 (46%) presented at a scheduled DART doctor visit (4 and 12 weeks, then every 12 weeks)
- 119 (54%) presented at 4-weekly nurse visit or other time (additional FBC performed)
- 171 (78%) had baseline haemoglobin  $\geq 9.5$  g/dl
- 38% microcytic, 26% normocytic, 27% macrocytic, 9% unknown



# ART following grade 4 anaemia



After start of first new grade 4 anaemia episode

|  | n  | %    |
|--|----|------|
| Substituted d4T for ZDV                                  | 88 | 40 % |
| Stopped ART (median 9 days)                              | 79 | 36 % |
| - subsequently substituted d4T for ZDV                   | 69 | 31 % |
| - subsequently restarted ZDV                             | 7  | 3 %  |
| Died before stopping/substituting                        | 9  | 4 %  |
| No substitution or interruption recorded (trial ongoing) | 44 | 20 % |

- case note review to identify transfusions and other specific anaemia-related therapy ongoing



# Concomitant events during first new Grade 4 anaemia episode



|  |              |              |
|--|--------------|--------------|
| <b>Clinical events</b>                     | <b>n=51</b>  | <b>(23%)</b> |
| - bacterial infection                      | n=13         | (6%)         |
| - WHO 4 event                              | n=24         | (11%)        |
| • mainly cryptococcosis, extrapulmonary TB |              |              |
| - malaria                                  | n=22         | (10%)        |
| <b>Laboratory events</b>                   | <b>n=93</b>  | <b>(42%)</b> |
| - Neutropenia (grade 3/4)                  | n=89         | (40%)        |
| - Thrombocytopenia (grade 3/4)             | n=20         | (9%)         |
| • neutropenia & thrombocytopenia           | n=16         | (7%)         |
| <b>None of the above</b>                   | <b>n=101</b> | <b>(46%)</b> |



# Mortality



42 (19%) of 220 patients with new grade 4 anaemia have subsequently died

- 14 patients died before resolution of grade 4 anaemia
  - 11 probable sepsis/pneumonia (6 with pancytopenia)
  - 3 other (transverse myelitis, TB, cryptococcal meningitis)
  - 1 death considered directly attributable to ZDV-related anaemia in DART by Endpoint Review Committee
- 28 died after resolution of grade 4 anaemia
  - 15 deaths were considered primarily HIV-related
  - 2 lactic acidosis after substituting d4T for ZDV



# Risk factors for developing grade 4 anaemia



- a higher risk of developing grade 4 anaemia was independently associated with being female; low BMI, haemoglobin or CD4 at baseline; and low neutrophils at week 4

| Independent* factors                          | OR   | p value |
|---|------|---------|
| female  | 1.59 | 0.010   |
| baseline BMI (per unit)                       | 0.92 | 0.001   |
| baseline haemoglobin (per g/dl)               | 0.81 | <0.001  |
| baseline CD4 (per 100 cells/mm <sup>3</sup> ) | 0.63 | 0.001   |
| week 4 neutrophils (per 10 <sup>9</sup> /l)   | 0.81 | 0.043   |

- baseline neutrophils, WHO stage, cotrimoxazole and age did not predict development of grade 4 anaemia



# Summary



- The vast majority of patients have substantial increases in haemoglobin by 24 weeks after ART initiation
- However, the incidence of grade 4 anaemia in DART is higher than in studies in industrialised countries
  - patients who died all had other (mainly HIV-related) conditions
  - 1 death considered directly attributable to anaemia in DART
- DART population has a higher level of baseline risk
  - advanced disease (low CD4, haemoglobin and BMI)
  - high proportion of women (65%)
- Other possible explanations for higher incidence
  - poor/inadequate nutritional status
  - ? more concomitant clinical events
  - malaria, helminthiasis



# Conclusions



- Clinicians initiating patients on ZDV-containing regimens in resource-limited settings need to be alert to clinical signs of anaemia in the minority of patients who will develop it
  - education/counselling of patients about symptoms
  - clinical vigilance of Health Care Workers
- Haemoglobin between 4-12 weeks
- Anaemia is a clinically detectable and reversible toxicity of an otherwise successful initial therapy



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- DART Data and Safety Monitoring Committee
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