Michael Schomaker

Growth & mortality outcomes for different antiretroviral therapy initiation criteria in children aged 1-5 years:

– a causal modelling analysis from West and Southern Africa –

Background
Methodology
Results
Conclusions
Limitations

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The IeDEA West & Southern Africa Paediatric Group

Background

- Limited evidence from RCTs on when to start ART in children aged 1-5 years
- CHER study: Early ART initiation reduces mortality in infants (enrolled at $<$ 3 months of age)

  Violari (2008), NEJM
- PREDICT study, children aged 1-12 years:
  - No difference between starting ART immediately and deferring ART with respect to mortality and morbidity outcomes
  - However, better height gain for children who started ART immediately

  Phutanakit (2012), Lancet Infectious Diseases

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Background: PREDICT results

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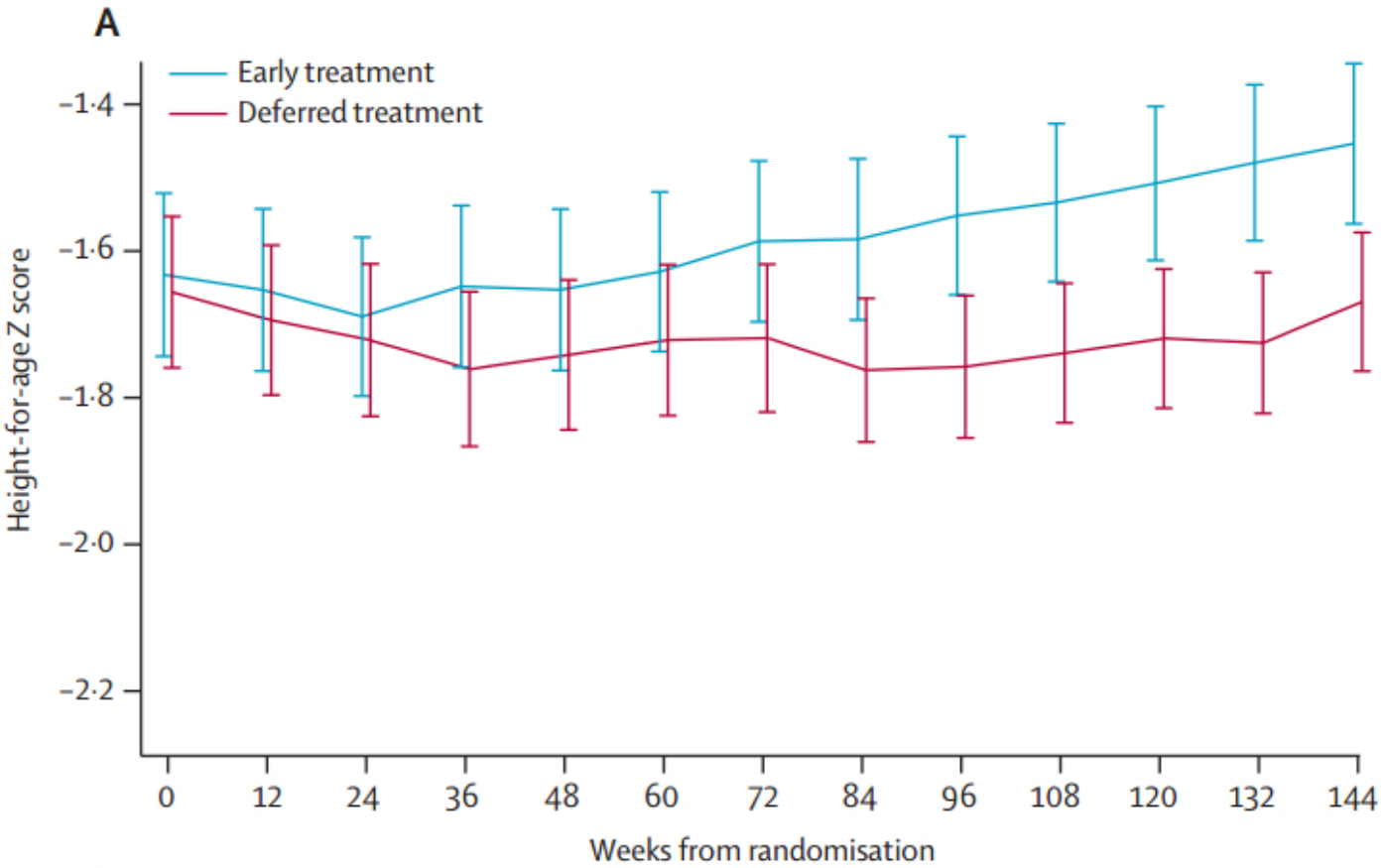

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Objectives

To use observational data from children aged 1-5 years in the IeDEA-WA and IeDEA-SA collaborations to compare

- cumulative mortality
- growth

up to 3 years between 4 initiation strategies

i) starting ART immediately, irrespective of CD4 criteria $\approx$ WHO 2013

ii) starting ART when CD4 drops below 750 cells/mm^3 or 25% $\approx$ WHO 2010

iii) starting ART when CD4 drops below 350 cells/mm^3 or 15% $\approx$ WHO 2006

iv) starting ART not at all

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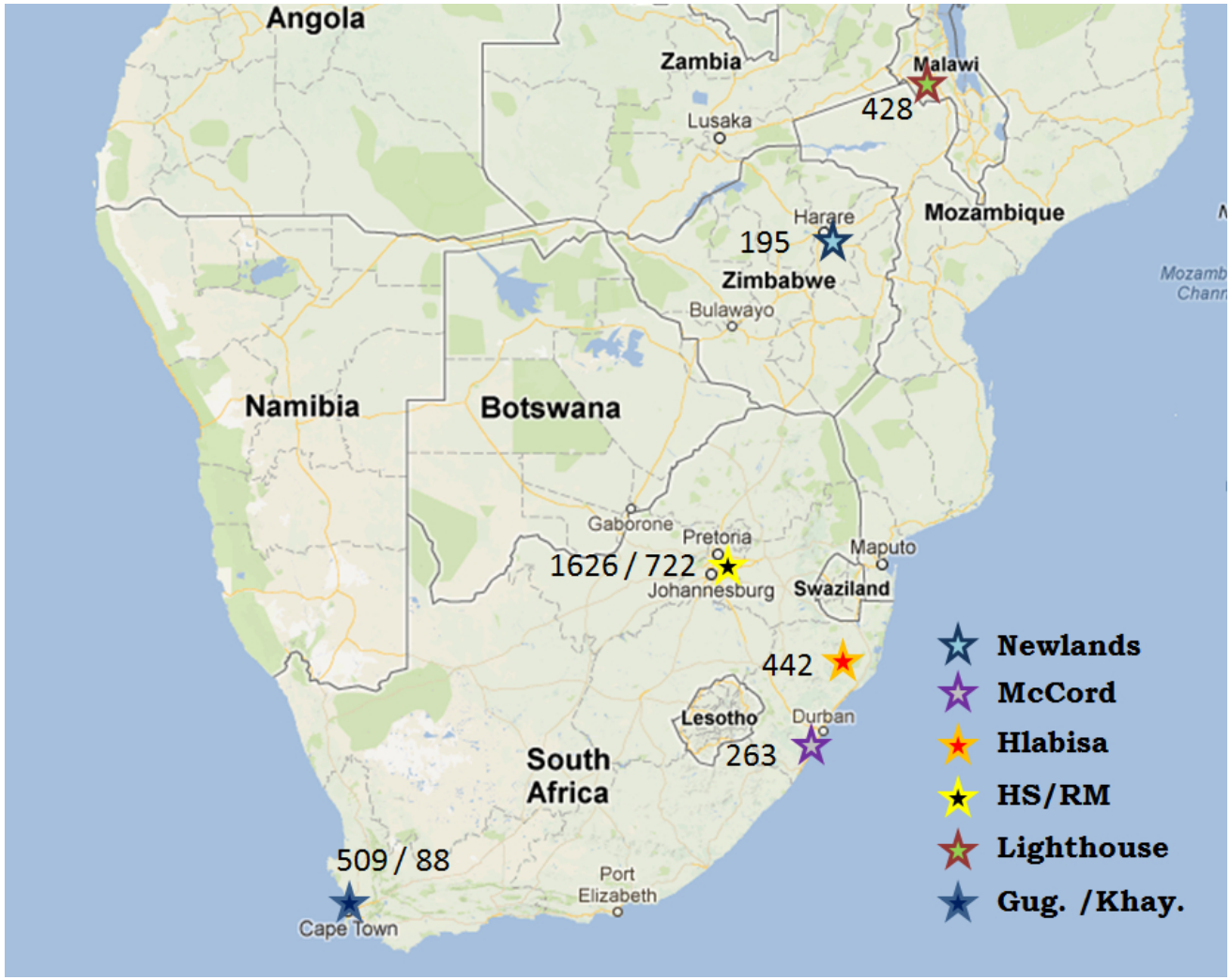
Inclusion criteria

We included 5826 ART naive children, with at least one follow-up visit, from 16 cohorts from West and Southern Africa



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Data from West Africa

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Methods

- The primary analysis used *g-computation* to estimate cumulative mortality and growth (mean HAZ of children who are alive) for different interventions strategies.
- We adjusted for time dependent confounding affected by prior treatment of CD4 count, CD4%, and Weight for age z-score (WAZ, proxy for WHO stage)
- missing baseline data was multiply imputed

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Methods

This analysis emulates the following clinical trial:

- HIV positive and ART-naive children, aged 1-5 years, presenting at a health care facility for the first time, are randomly assigned one of the four treatment strategies.
- Each of the four arms is therefore differing by the CD4 thresholds used to determine the timing of ART initiation.
- Assuming full adherence to the regime, no administrative censoring, no loss to follow-up, and regular CD4 monitoring we can estimate mortality/growth at time t ($t = 1, ..., 36$ months after first visit).

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Descriptives – Characteristics at first visit

	Southern Africa	West Africa
	Median (1^{st}; 3^{rd} quartile)	
Age	2.6 (1.7; 3.7)	2.7 (1.8; 3.8)
CD4 count	646 (380; 984)	719 (433; 1081)
CD4%	16 (11; 23)	16 (10; 22)
WAZ	-1.5 (-2.6; -0.6)	-1.9 (-3.2; -0.9)
HAZ	-2.6 (-3.6; -1.6)	-2.1 (-3.1; -1.0)
started ART	75.6%	72.5%

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Mortality

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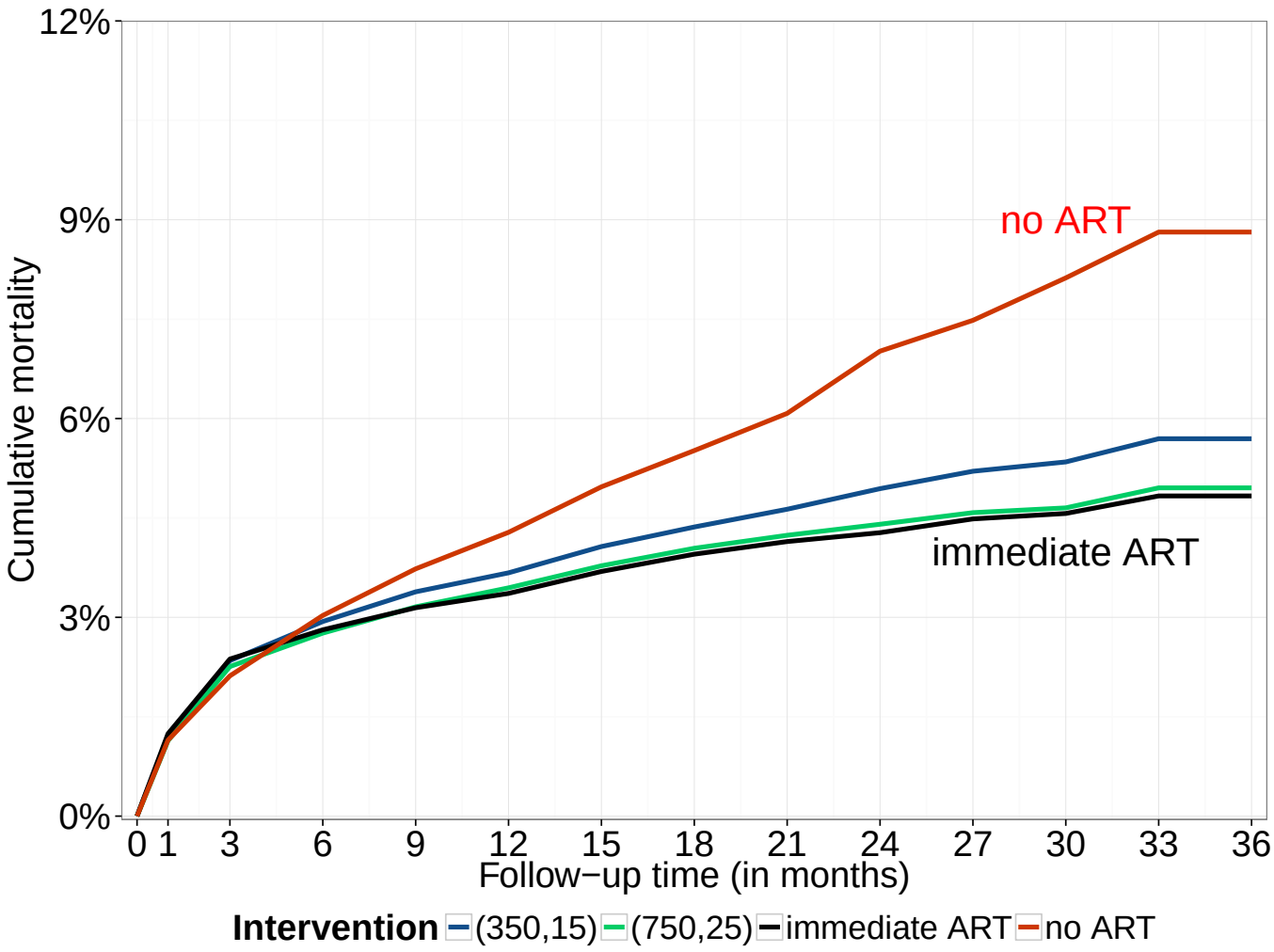

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Growth

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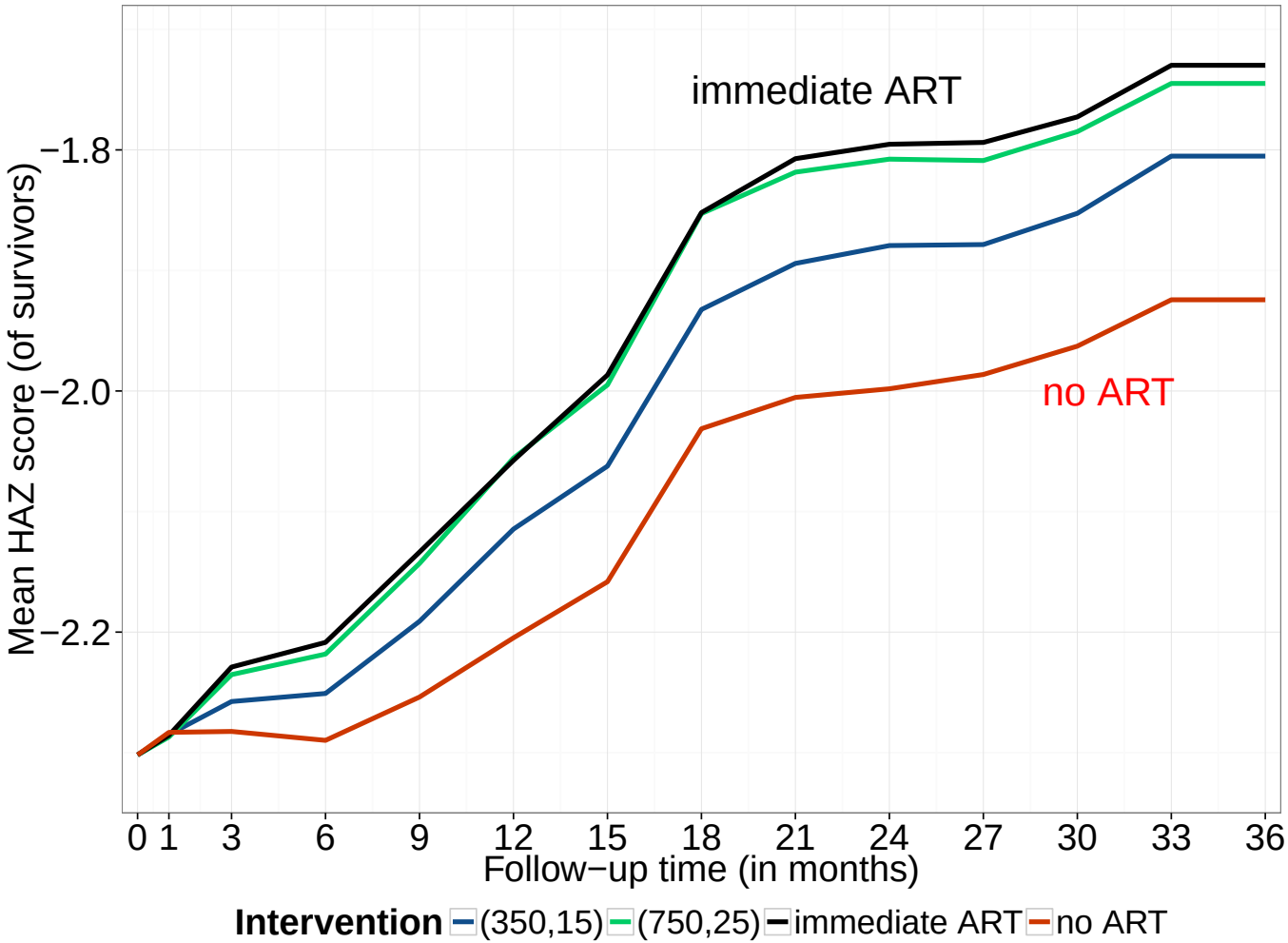

Difference immediate ART to 750/25% at 3ys: -0.02 (-0.04; 0.01)
Difference immediate ART to 350/15% at 3ys: -0.08 (-0.10; -0.05)

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Conclusions

- Lower mortality and better growth when starting ART earlier in children aged 1-5.
- These differences were small when comparing immediate ART initiation with deferring ART until the CD4 threshold of 750/25% is reached, but clearer when comparing it with the CD4 threshold of 350/15%.
- Our findings were consistent over age groups and regions, but mortality was estimated to be lower, and growth to be faster, in children aged 2-5 [data not shown].

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Limitations

- Missing HAZ data
  [but sensitivity analyses reassuring]
- Competing event: death
  [but sensitivity analyses reassuring]
- Other: Long term outcomes (toxicity, drug resistance), WAZ as proxy for stage, ...

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Writing team: Michael Schomaker, Mary-Ann Davies, Karen Malateste, Lorna Renner, Shobna Sawry, Sylvie N'Gbeche, Karl-Günter Technau, François Eboua, Frank Tanser, Haby Sygnatè-Sy, Sam Phiri, Madeleine Amorissani-Folquet, Vivian Cox, Fla Koueta, Cleophas Chimbete, Annette Lawson-Evi, Janet Giddy, Clarisse Amani-Bosse, Robin Wood, Matthias Egger, Valeriane Leroy

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