Forum for Collaborative HIV Research

DART Trial Overview

The Development of AntiRetroviral Therapy in Africa

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Washington DC

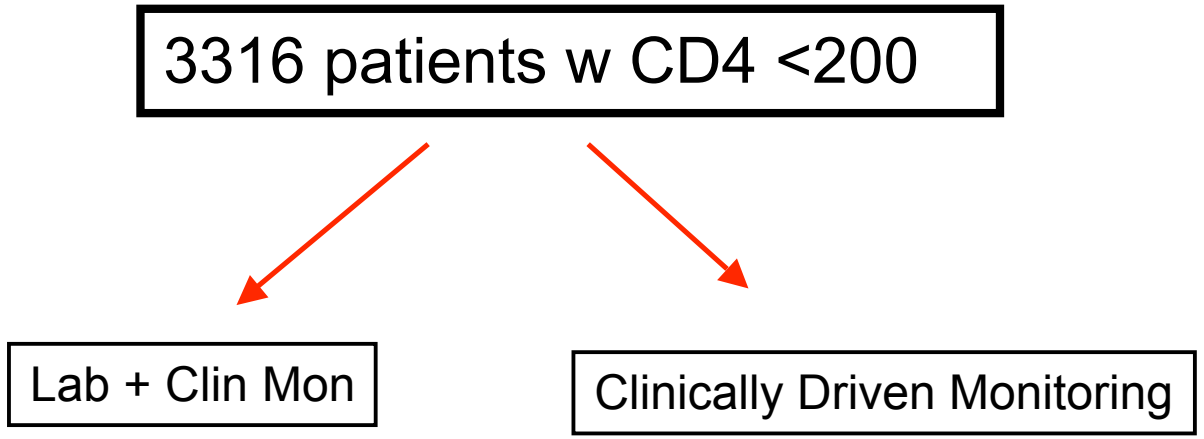
Comparison of Routine vs clinically driven laboratory monitoring in HIV-infected African adults over 5 years on ART

Question: can ART be given safely with clinically driven, rather than routine, laboratory monitoring?

"Routine Laboratory Monitoring"

- 12 weekly biochemistry, FBC and CD4
- Switch to 2nd line if CD <100 or new recurrent WHO 4 (multiple 3)

Study Design



- Primary endpoints
  - ***Efficacy***: new WHO stage 4 HIV event (AIDS) or death
  - ***Safety***: any Serious Adverse Event which is not only HIV-related
- Final data to 31 December 2008 (max 6, median 4.9 years

Study Design

enhancing & facilitating HIV research

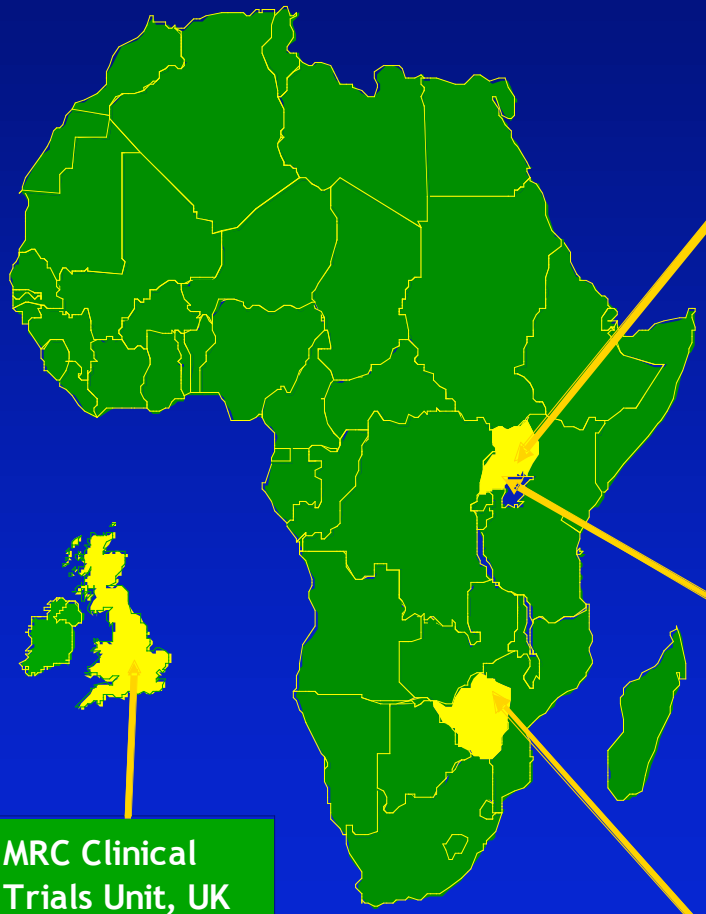
**Designed with sufficient power to determine whether CDM was non-inferior to LCM defined as no more than a very small increase in event rate from 10/100 PY in LCM to 11.8/100 PY in CDM

**this small difference was considered acceptable, given potential benefits of CDM in terms of costs, access to and ease of decentralised ART delivery and hence wider rollout

DART partners

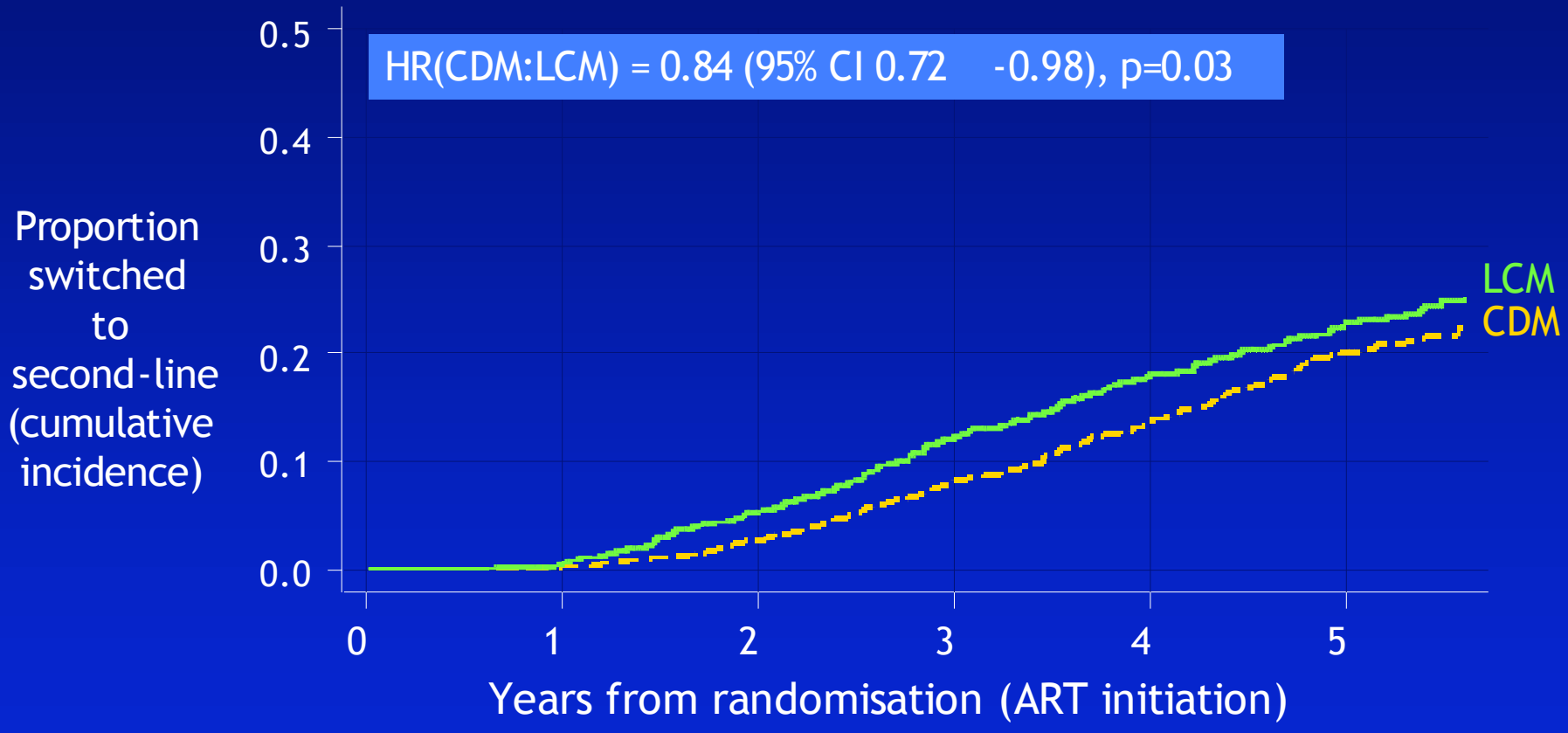
Support:

- MRC, UK
- DFID, UK
- Rockefeller Foundation
- GlaxoSmithKline
  Gilead Sciences
  Boehringer -Ingelheim
  Abbott



- Joint Clinical Research Centre, Kampala, Uganda
- Infectious Diseases Institute, Makerere University, Uganda
- MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda
- TASO, Uganda
- University of Zimbabwe, Harare, Zimbabwe
- MRC Clinical Trials Unit, UK
- Imperial College, UK

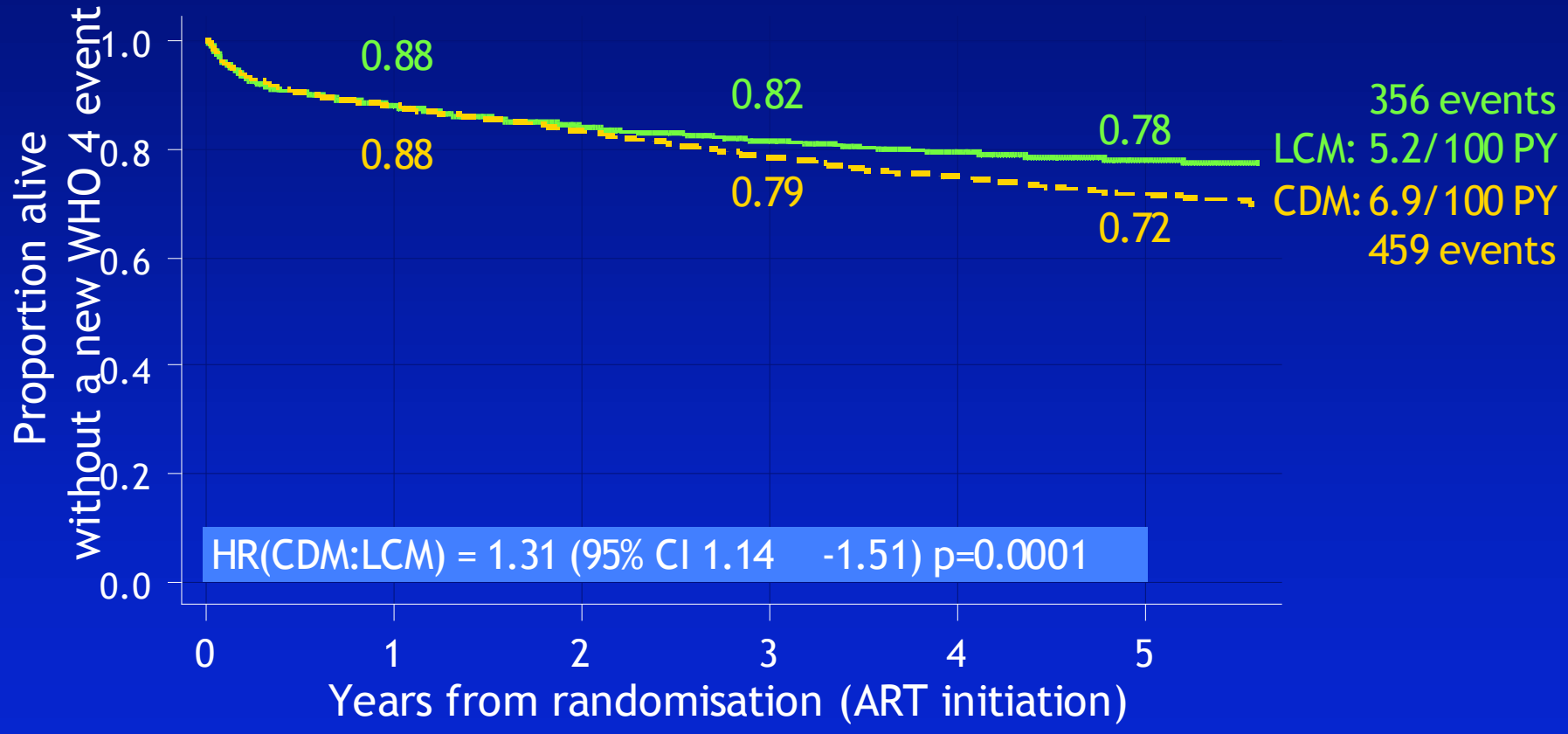
Switch to second-line



HR(CDM:LCM)	**0.48**	**0.77**	0.90	**1.35**	1.10

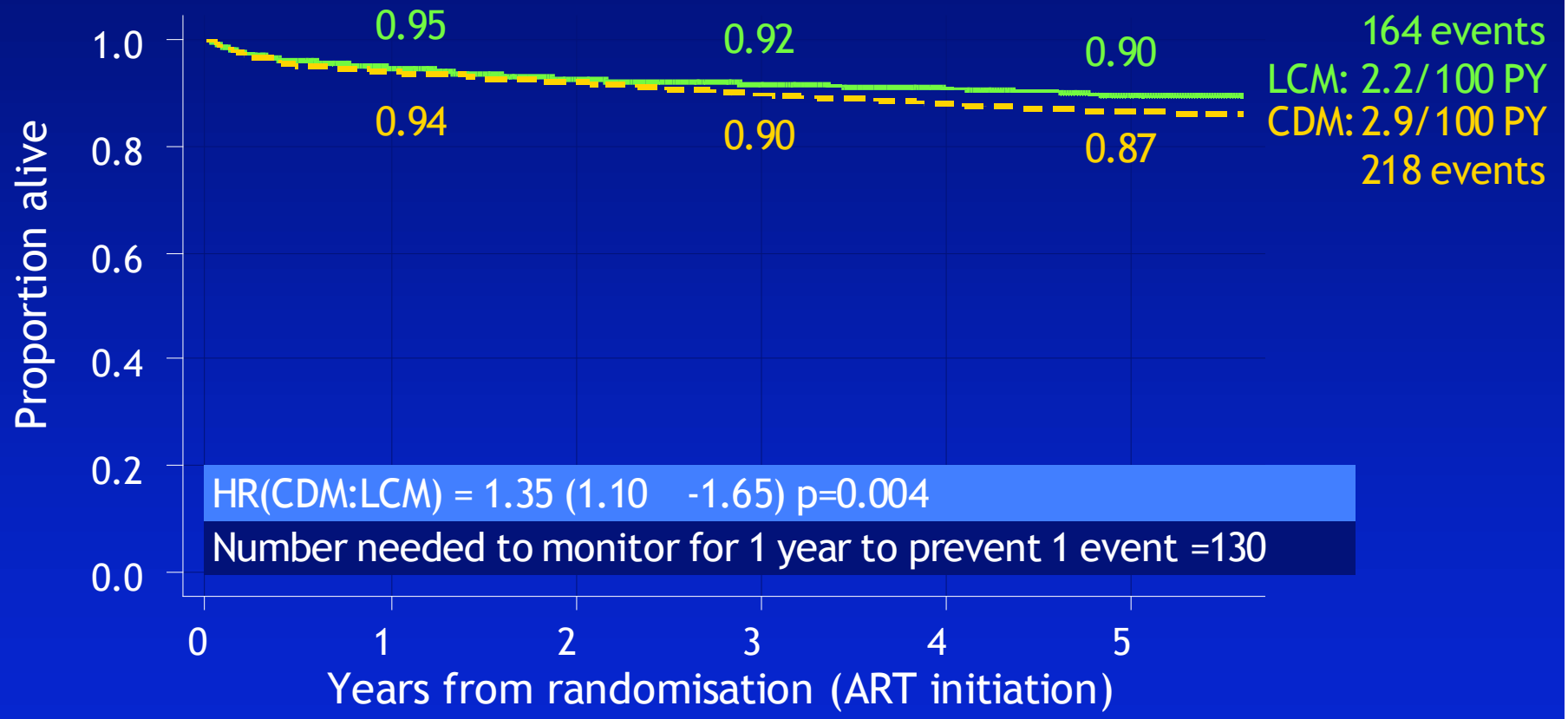
heterogeneity p=0.001

Progression to new WHO 4 event or death (primary endpoint)



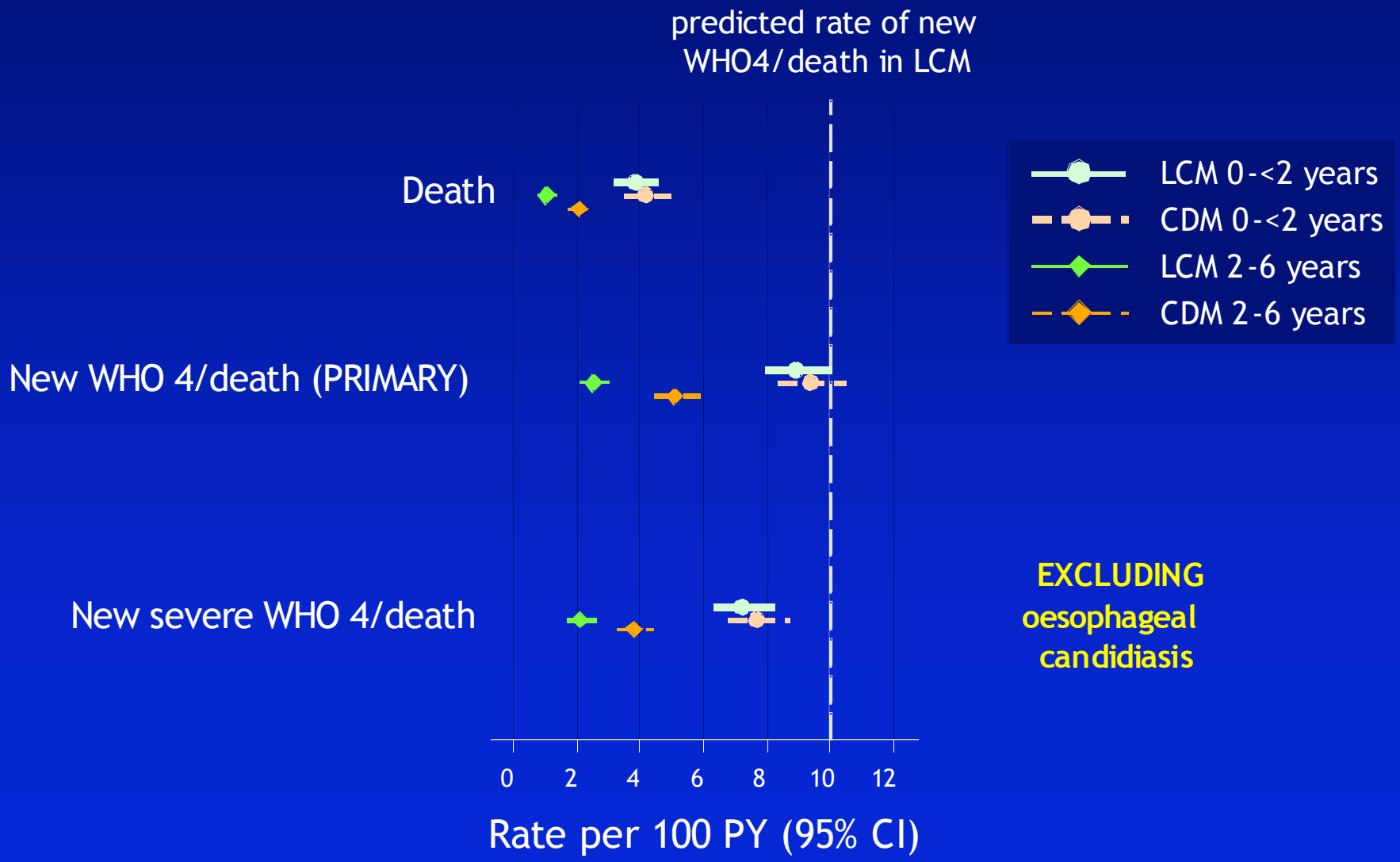
LCM: n=	1656	1438	1364	1306	1255	682
CDM: n=	1660	1443	1354	1262	1184	613

Survival



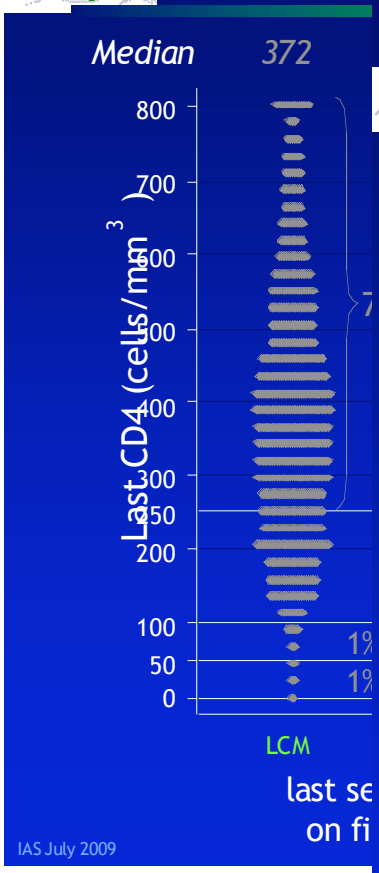
LCM	1656	1552	1501	1468	1436	796
CDM	1660	1542	1494	1445	1395	749

Absolute event rates over time on ART



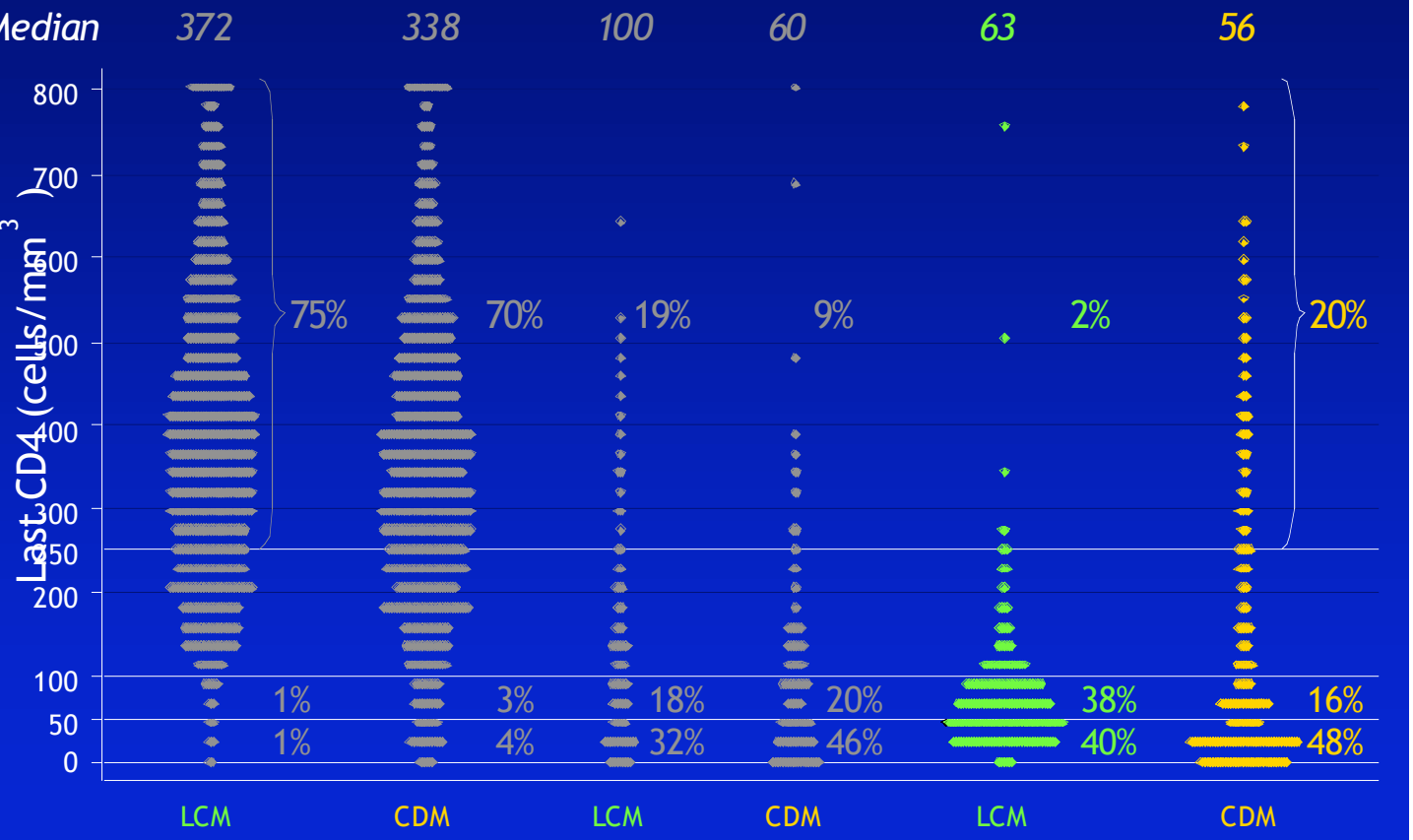
EXCLUDING oesophageal candidiasis

Most recent CD4 on first -line



IAS July 2009

Most recent CD4 on first -line or at switch



Conclusions

- 5-year survival in 3316 participants with advanced HIV disease pre-ART was excellent (CDM 87%, LCM 90%)
- Loss to follow-up was very low
- Routine laboratory monitoring for toxicity did not impact adverse events or substitutions in first-line
- 12-weekly CD4 monitoring had no impact on disease progression during the first 2 years on ART
  - after 2 years, a small but significant impact on clinical disease progression favouring LCM appeared to be driven by later switch to second-line ART in CDM
  - there may be a role for targeted, as opposed to routine, CD4 monitoring from the second year on ART

Sensitivity analysis: CD4 count costs

- At current costs ($7.1 - $8.8), CD4 testing is not cost effective

- We sought to establish the cost per test at which CD4 monitoring would be cost effective

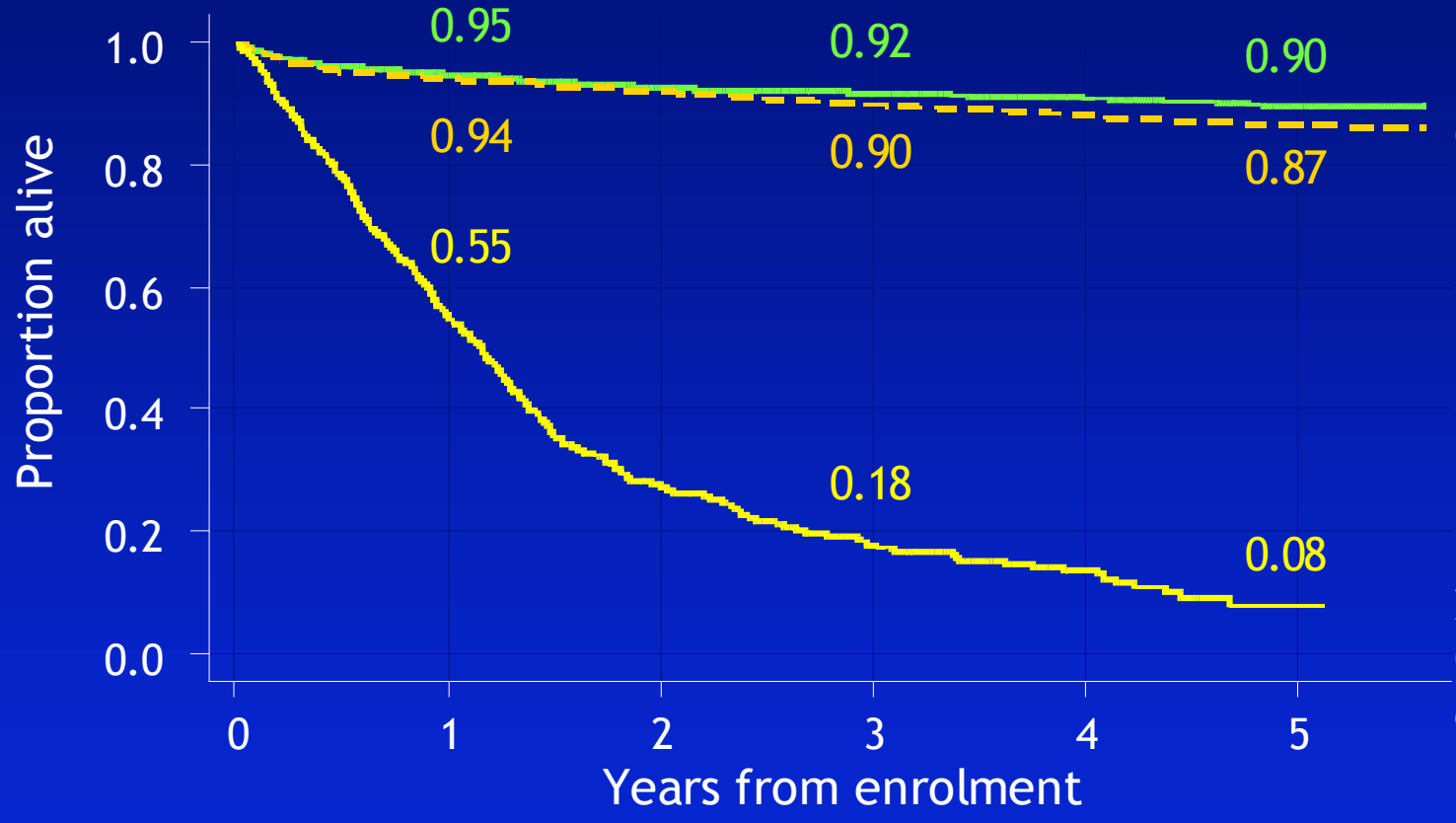
  (ICER of $1200 ~3 times GDP per capita; WHO Commission on Macroeconomics and Health)

  CD4 count would have to cost $3.8 or less for ART management with 12 -weekly CD4 monitoring from the 2nd year to be cost effective

Discussion Points

- Outcome based on survival and new AIDS diagnoses
  - No viral load, no resistance testing
    - Impact on transmission to others?
- Patients randomized at advanced stage of disease (<200)

Survival



164 events
LCM: 2.2/100 PY
CDM: 2.9/100 PY
218 events

Entebbe Cohort (Uganda): pre-ART 1996-2000, median CD4 75 at enrolment: 57.7/100 PY