The Development of AntiRetroviral Therapy in Africa (DART) trial

Risk of WHO 4 events and death by current CD4 on ART in the DART trial: the impact of CD4-dependent reporting bias

AS Walker, AG Babiker, C Kityo, J Hakim, P Munderi, F Ssali, A Reid, H Grosskurth, CF Gilks, TEA Peto
on behalf of the **DART** *Trial Team*

MRC | MRC/UVRI Uganda Research Unit on AIDS
JCRC
IDI Infectious Diseases Institute
Imperial College London
MRC | Clinical Trials Unit

Background

- In resource-rich countries, standard of care on ART includes routine laboratory monitoring for
  - toxicity (haematology, biochemistry)
  - efficacy (CD4 cell count, viral load)
- In Sub-Saharan Africa, laboratory monitoring
  - is not widely available (infrastructure, personnel etc)
  - is costly to maintain (reagents, quality control etc)

- DART Trial objective: to evaluate the need for on-ART routine laboratory monitoring for toxicity and CD4 cell counts in African adults starting ART having fulfilled clinical and CD4 criteria for ART initiation

Trial design (non-inferiority)

3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease, CD4<200 cells/mm^3 (median **86** cells/mm^3) initiating triple drug ART

randomise

Laboratory and Clinical Monitoring (LCM)

12 weekly biochemistry, FBC & CD4

Other investigations & concomitant medications if clinically indicated

Switch to second-line for
- new/recurrent WHO 4 *(or multiple WHO 3)*
- **CD4<100 cells/mm^3**

Clinically Driven Monitoring (CDM)

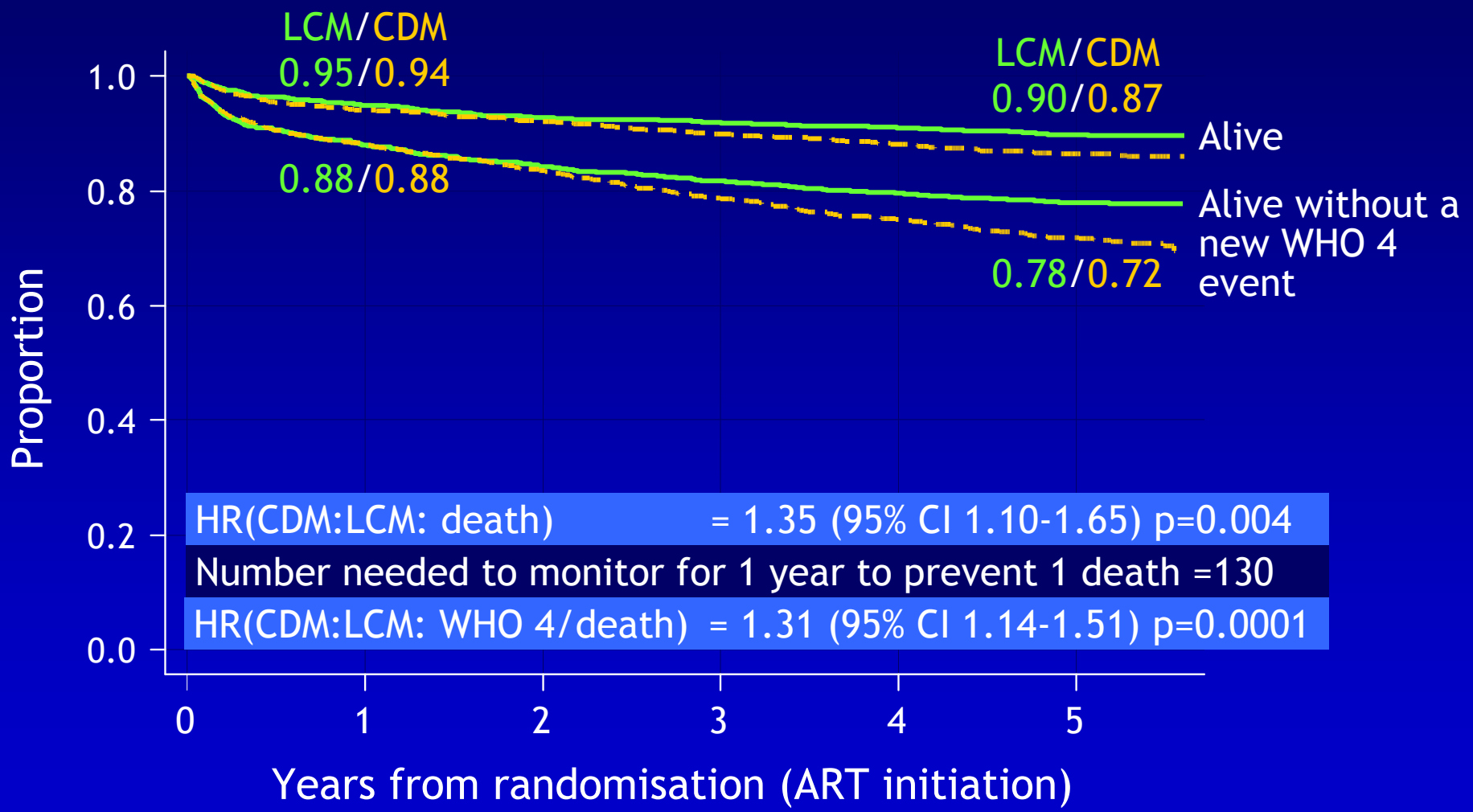
12 weekly biochemistry, FBC & CD4;
FBC & biochemistry only returned if clinically indicated (or grade 4 toxicity);
CD4 never returned

Other investigations (not CD4) & concomitant medications if clinically indicated

Switch to second-line for
- new/recurrent WHO 4 *(or multiple WHO 3)*

As per WHO guidelines, switching before 48 weeks discouraged in both arms

New WHO 4 event or death (co-primary endpoint) and death (secondary endpoint)



LCM: in follow-up	1656	1552	1501	1468	1436	796
CDM: in follow-up	1660	1542	1494	1445	1395	749

DART trial results (*Lancet* 2010;375:123-31)

- 5-year survival in 3316 participants with advanced HIV disease pre-ART (33% < 50 cells/mm^3) was excellent
  - loss to follow-up was very low (7% at 6 years; median 4.9 years FU)
- Routine 12-weekly laboratory monitoring for **toxicity** did not impact any adverse event outcome
- Routine 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

Objective

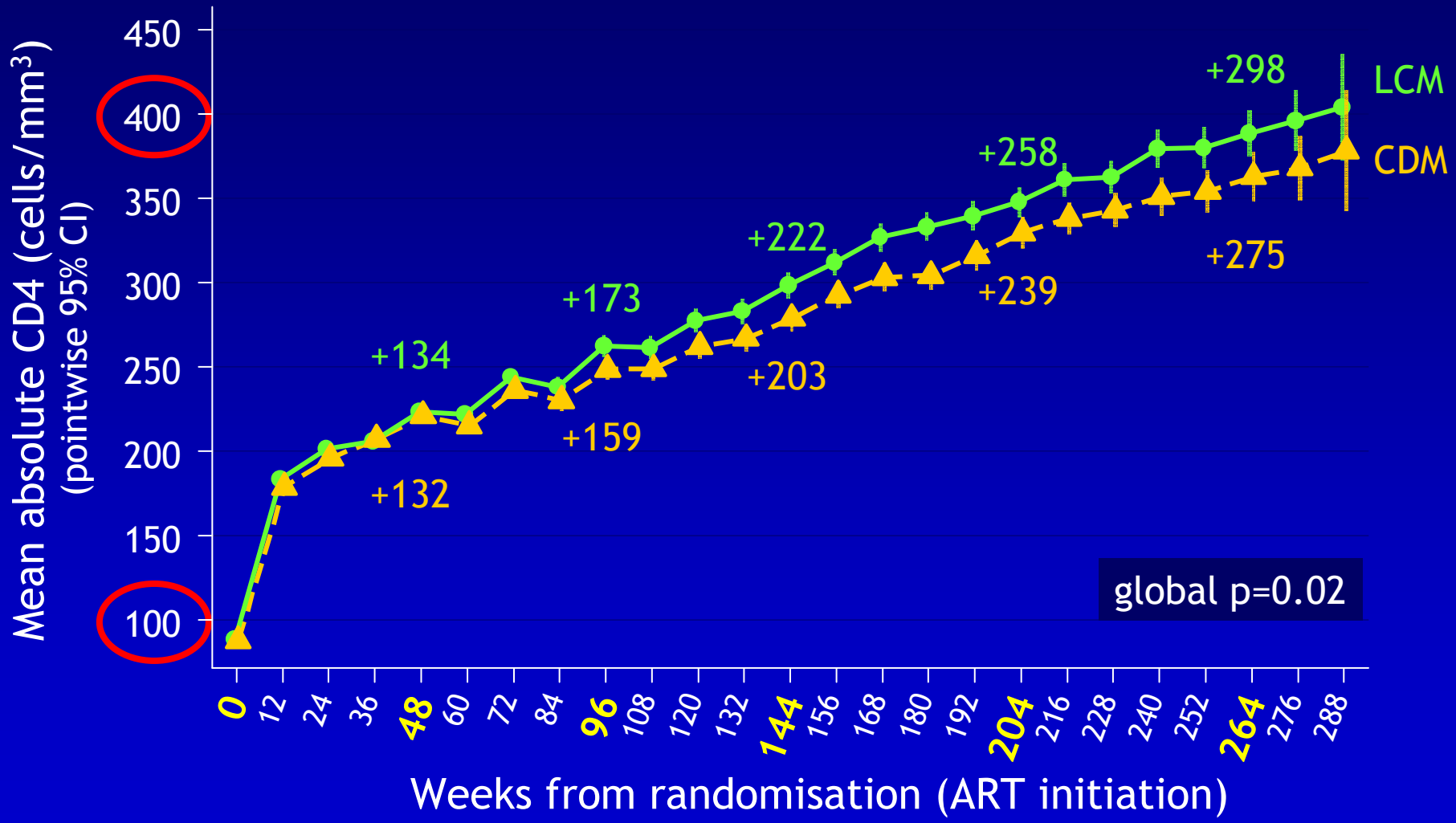
- To compare the risk of death and disease progression events between randomised groups at various CD4 counts
  - Poisson models, including multiple WHO 4 events (ie subsequent events after the first during the trial)

- Hypothesis: low CD4 in CDM may have more serious consequences because of clinicians not knowing this

Outcome ascertainment

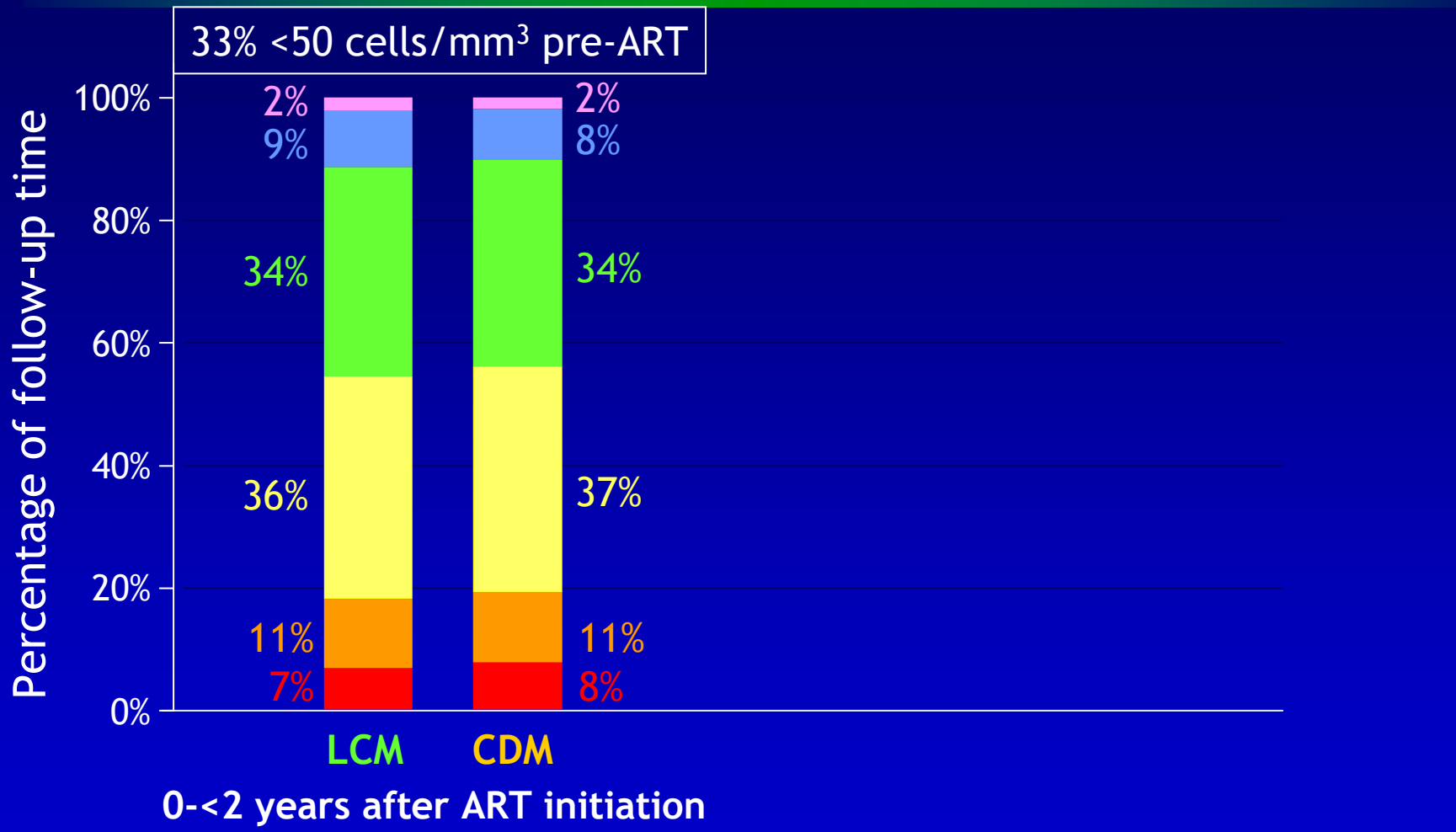
- Clinicians were encouraged to report and investigate all potential WHO 4 events
  - patients not returning to clinic had home visits to ascertain deaths and other outcomes
- However, randomisation was open
  - All reported WHO 4 events (and cause of death) were adjudicated against pre-specified protocol criteria by an Endpoint Review Committee with independent Chair and members, **blinded to randomised group and to CD4 counts**
    - 780/992 (79%) reported WHO 4 events met protocol criteria ("accepted" events)
    - most common reasons for rejecting events as endpoints were missing tests or other plausible diagnoses *(Borok IAS 2009 TUPEB098)*

Absolute change in CD4 over 5 years

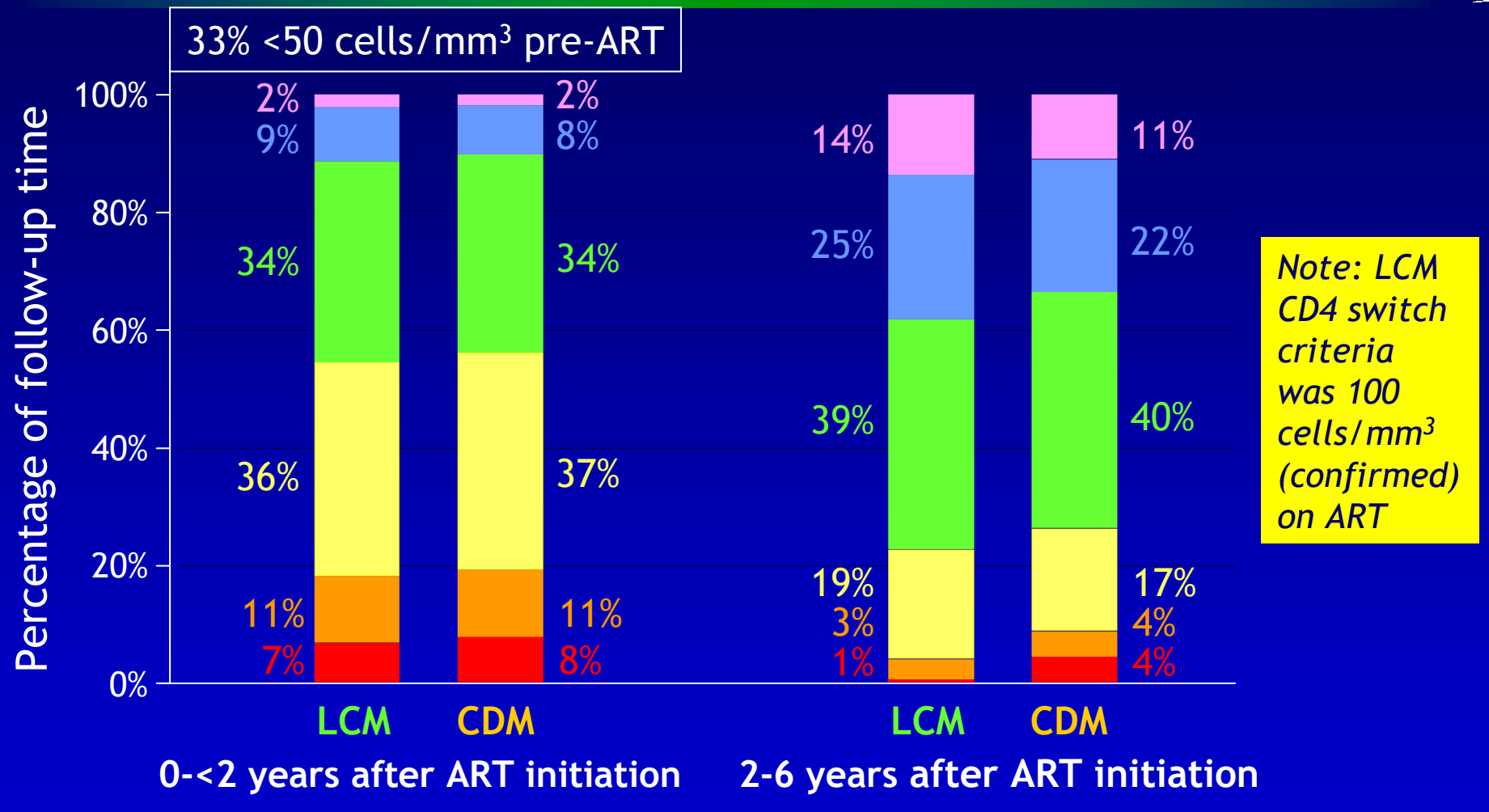


NB: some participants were on STIs at weeks 60, 84 and 108

CD4 over follow-up time

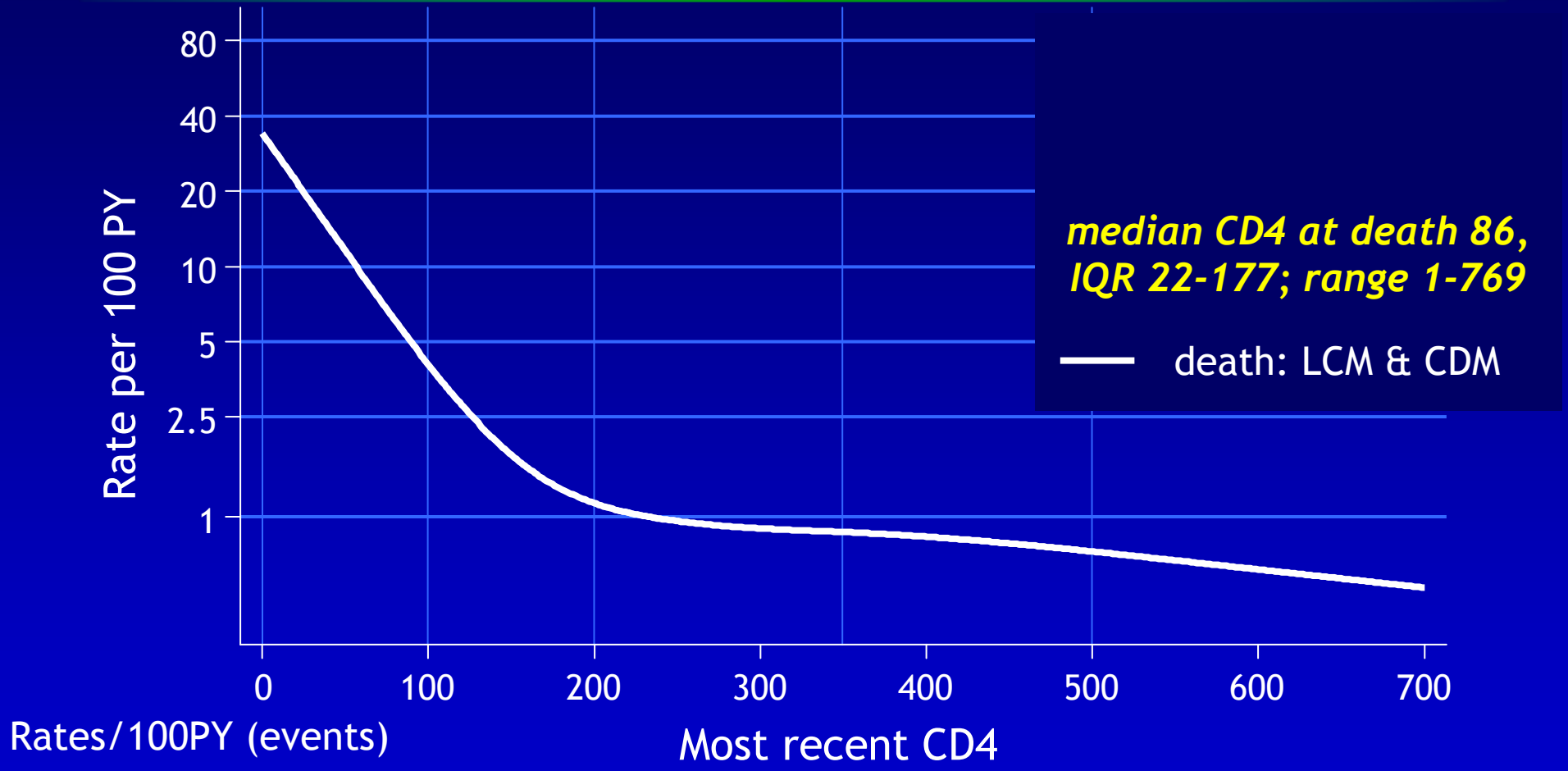


CD4 over follow-up time



Note: LCM CD4 switch criteria was 100 cells/mm³ (confirmed) on ART

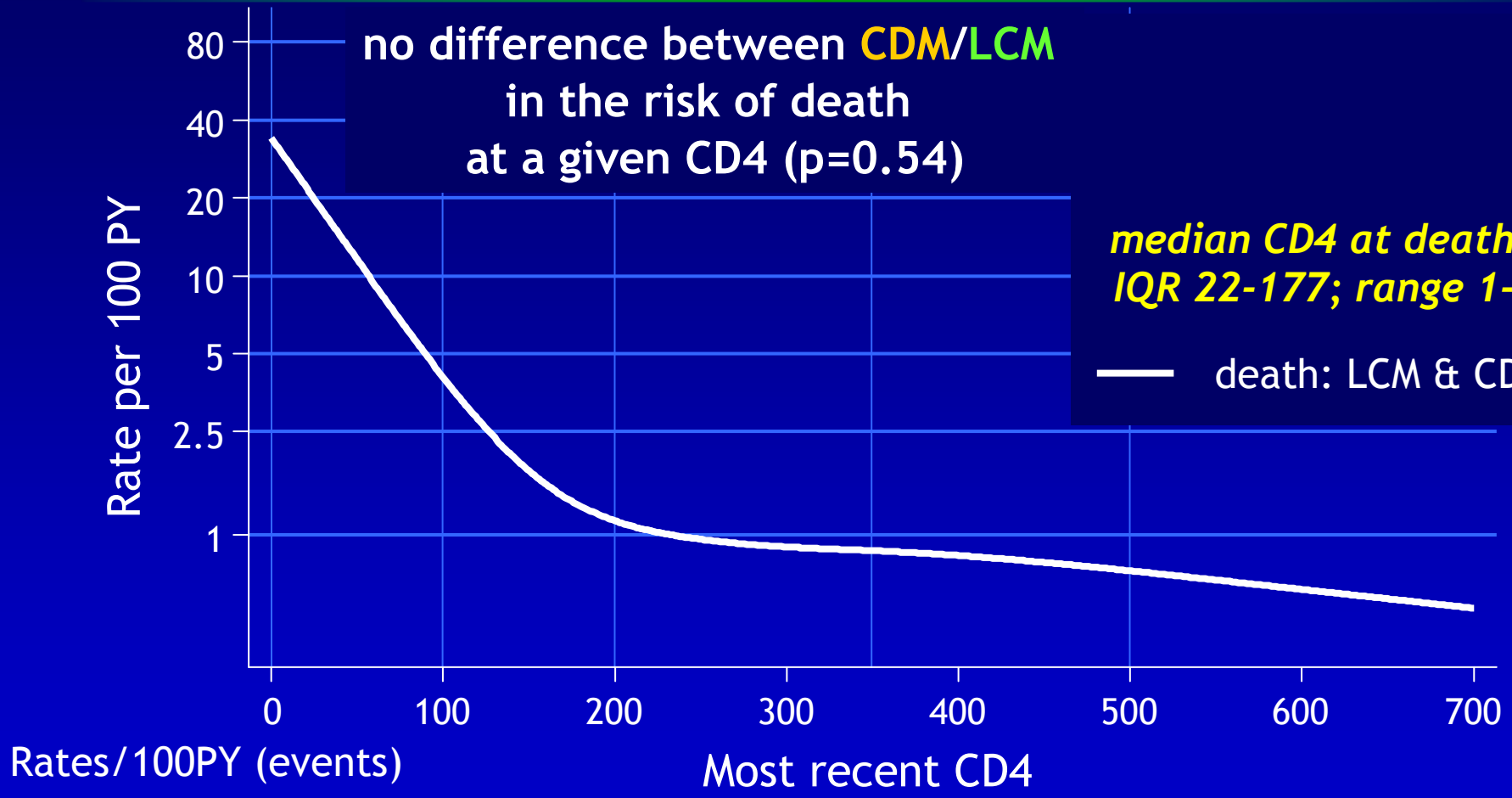
Risk of death by current CD4



Rates/100PY (events)

Death	LCM&CDM	12.6(215)	2.0(75)	1.0(54)	0.9(23)	0.6(7)	(382 deaths)

Risk of death by current CD4



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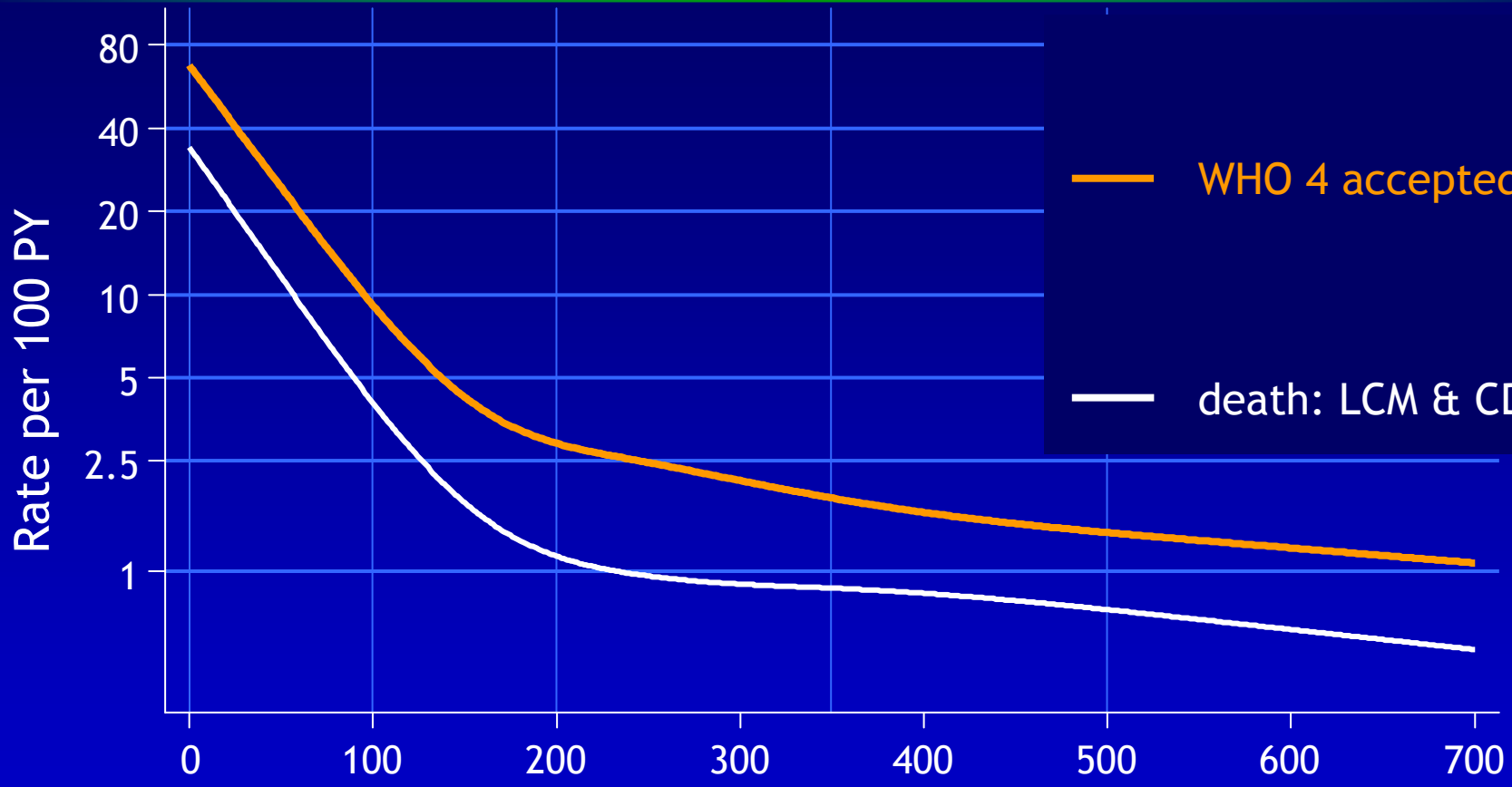

Rates/100PY (events)							
WHO 4							
(acc)	CDM	27.5(268)	4.8(91)	2.3(65)	1.7(21)	1.1(6)	(452 events)
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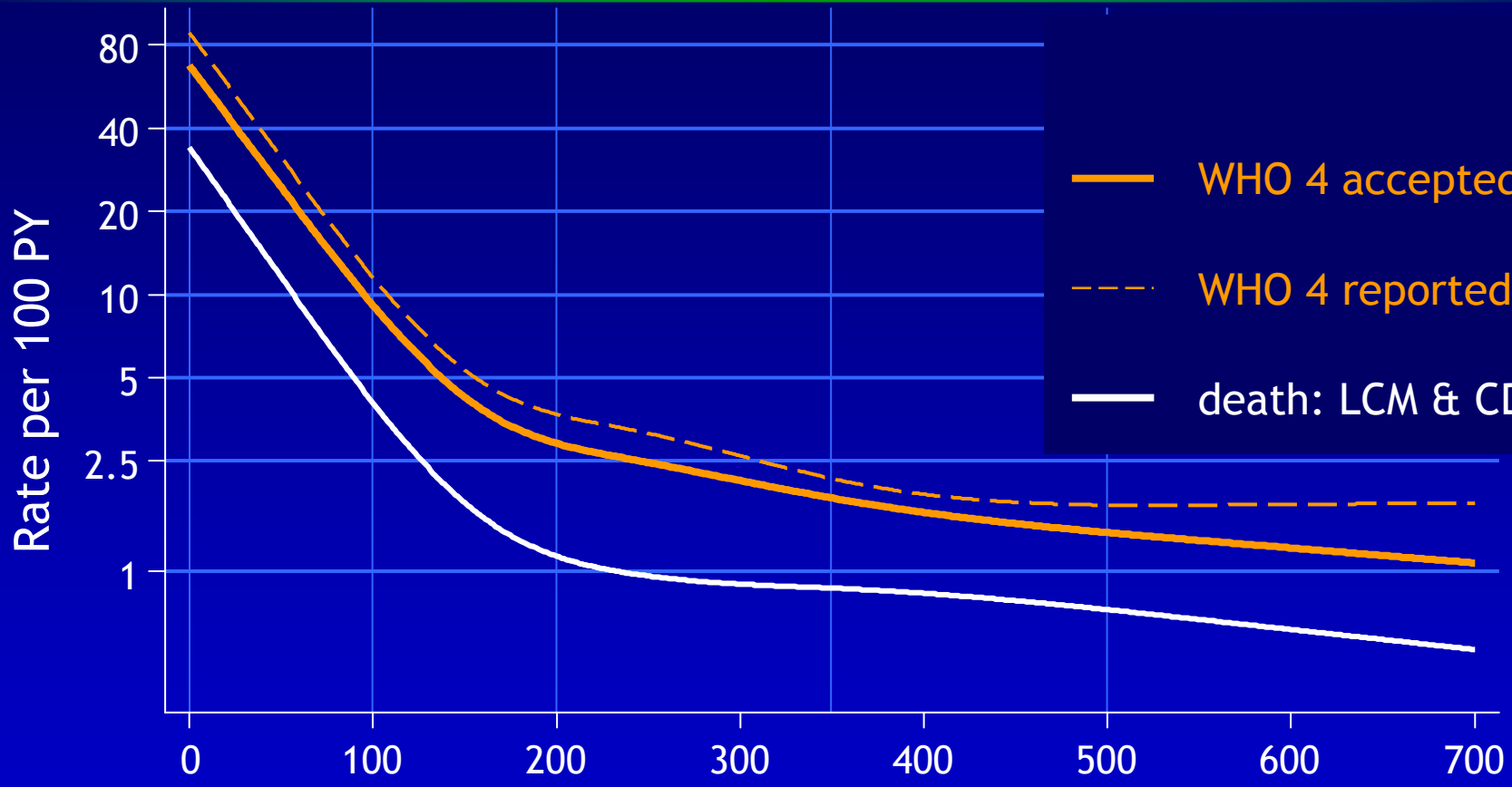

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WHO 4 events at high CD4s

- CD4s at which WHO 4 event reported
  - CDM: 33 (6%) events >350 cells/mm^3 *(max 895, 6 above 540)*
- CD4s at which WHO 4 event accepted
  - CDM: 27 (6%) events >350 cells/mm^3 *(max 895, 4 above 540)*

WHO 4 events at high CD4s

- CD4s at which WHO 4 event reported
  - CDM: 33 (6%) events >350 cells/mm^3 *(max 895, 6 above 540)*
  - LCM: 18 (4%) events >350 cells/mm^3 *(max 540)*
- CD4s at which WHO 4 event accepted
  - CDM: 27 (6%) events >350 cells/mm^3 *(max 895, 4 above 540)*
  - LCM: 16 (5%) events >350 cells/mm^3 *(max 540)*

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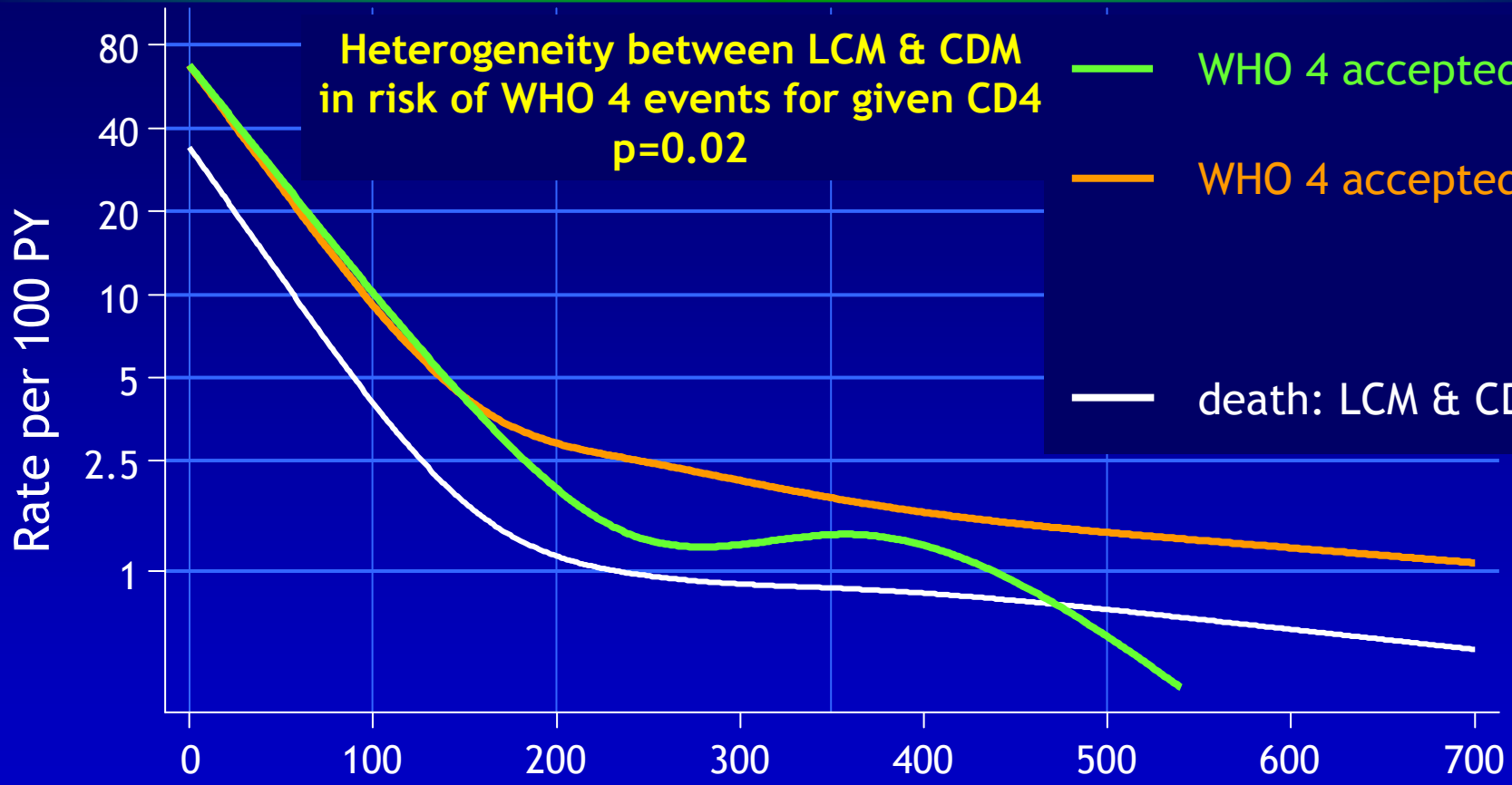
  - LCM: 16 (5%) events >350 cells/mm^3 *(max 540)*

- Risks of both reported and accepted WHO 4 events for a given CD4 differed significantly between CDM vs LCM (p=0.002 and p=0.02 respectively), **being greater in CDM only at higher CD4 where most time was spent**

Risk by current CD4



Rates/100PY (events)							
WHO 4	LCM	24.9(184)	4.4(87)	1.4(40)	0.9(13)	0.4(3)	(328 events)
(acc)	CDM	27.5(268)	4.8(91)	2.3(65)	1.7(21)	1.1(6)	(452 events)
Death	LCM&CDM	12.6(215)	2.0(75)	1.0(54)	0.9(23)	0.6(7)	(382 deaths)

Possible explanation

- In CDM, the clinician does not know the CD4 count
- Any serious clinical episode could be a WHO 4 event because the patient could have a low CD4 count without the clinician knowing
  - full work up, diagnostic tests, event reported on CRFs etc
  - ⇨ identify WHO 4 events which can occur at high CD4 counts (hence interest in "when to start ART" at high CD4 counts)
- In LCM, the clinician "knows" the episode cannot be a WHO 4 event, because the patient has a high CD4 count
  - no work up, event not reported

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  - no work up, event not reported

Predicting the expected number of events given observed CD4s in LCM suggests 40 missed LCM WHO 4 events at CD4>200 cells/mm^3

Conclusions

- Despite numerous strategies to reduce bias (standardised follow-up schedule, home visits, objective criteria, blinded ERC etc), open randomisation likely led nevertheless to **CD4-dependent reporting bias in WHO 4 events**
  - under-reporting and under-investigation of potential WHO 4 events at higher CD4 in LCM
- 356 LCM vs 459 CDM primary endpoints (Δ=103)
  - estimate 40 missed LCM events but as primary endpoint was **first new** WHO 4/death impossible to predict number of missed endpoints
- **True differences between CDM/LCM in time to WHO 4/death, but not death, may be smaller than estimated**
- Implications for open trials with clinical endpoints (let alone observational studies)

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