The Development of AntiRetroviral Therapy in Africa (DART) trial

Comparison of routine vs clinically driven laboratory monitoring in HIV-infected African adults over 5 years on ART: Final results of the DART trial

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on behalf of the **DART** *Trial Team*

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Main objective of DART

- To evaluate the need for routine laboratory monitoring of ART
  - in African adults who fulfilled clinical and CD4 criteria for ART initiation
  - in terms of clinical effectiveness, safety and costs

- Primary endpoints
  - *Efficacy:* new WHO stage 4 HIV event (AIDS) or death
  - *Safety:* any Serious Adverse Event which is not only HIV-related

Trial design

3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease, CD4<200 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 & 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

Trial status

- 6578 patients screened
- 3316 patients randomised to CDM or LCM
  - between 15 January 2003 and 28 October 2004

- Final data to 31 December 2008 (max 6, median 4.9 years)
  - during Jan 2009, all laboratory tests returned to CDM participants
  - participants transitioned care into Ugandan and Zimbabwean national ART programmes (except those in second-line studies)
  - results of second-line studies expected early 2010

Characteristics at baseline (ART initiation)

		LCM N=1656		CDM N=1660	
Women		1092	*66%*	1064	*64%*
Age (years)	median (range)	36	(18-67)	36	(18-73)
CD4 count (cells/mm^3)	median	86	(0-199)	86	(1-199)
	<50 cells/mm^3	**554**	*33%*	**555**	*33%*
HIV-1 RNA (log_{10} copies/ml)	mean (SD)*	5.4	(0.7)	5.4	(0.7)
WHO stage	2	363	*22%*	310	*19%*
	3	916	*55%*	948	*57%*
	4	377	*23%*	402	*24%*
On cotrimoxazole before/at ART initiation		1014	*61%*	1034	*62%*
ART: ZDV+3TC plus	TDF	1232	*74%*	1237	*75%*
	ABC	150	*9%*	123	*9%*
	NVP	274	*16%*	273	*16%*
Identified at any time (including post-baseline) as having previously received ART		65	*4%*	65	*4%*
Previous ART for MTCT (% of women)		23	*2%*	38	*4%*

* assayed in a subset (N=968) at baseline only

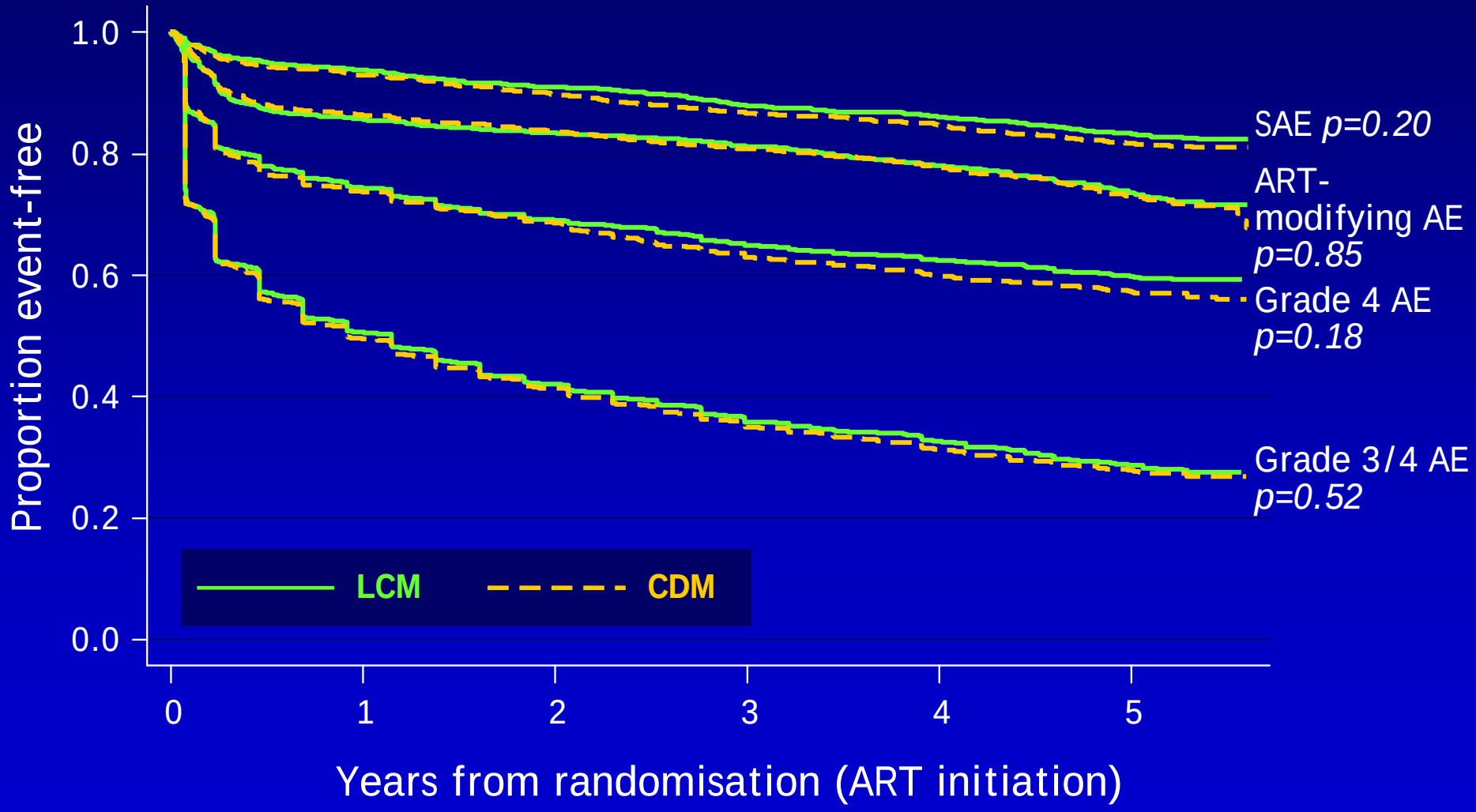
Follow-up

- Median follow-up to 31 December 2008 4.9 years (IQR 4.5-5.3)
  - 14,937 person-years
  - 236 (7%) lost to follow-up
  - 98% and 99% of expected nurse and doctor visits attended
  - high patient-reported adherence

Blinding of laboratory test results in the CDM arm

- Few CDM participants sought external CD4 counts
  - clinicians remained blinded
  - at DART exit, 81/1281 (6%) reported having CD4s done privately
    - 43/81 had 1 CD4 test only
    - 3/81 had 6 or more

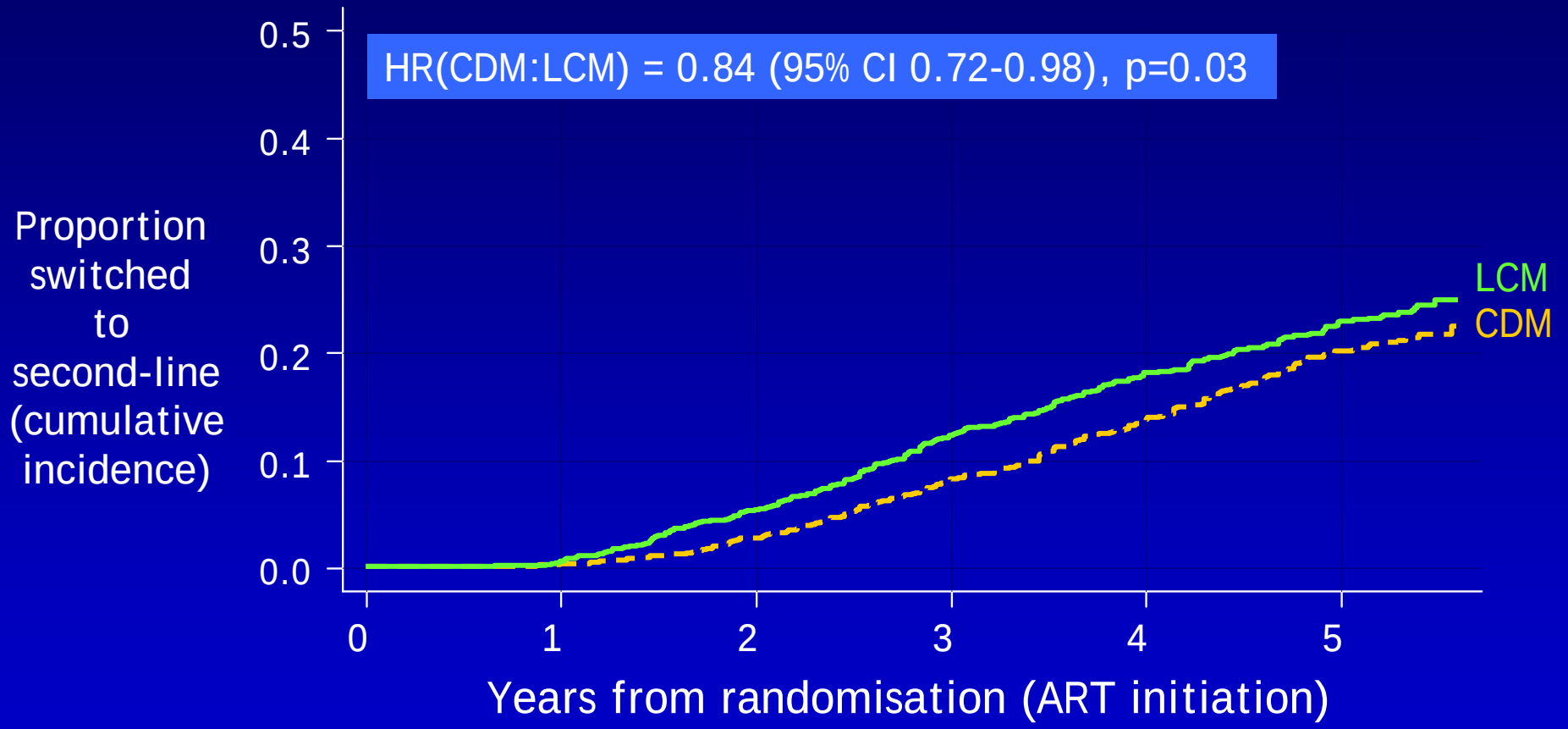
Adverse events



Antiretroviral therapy

At last follow-up/31 December 2008	LCM N=1656		CDM N=1660	
Remained on first-line	1295	*78%*	1346	*81%*
- still taking original first-line regimen	1014	*61%*	1059	*64%*
- substituted CBV only	113	*7%*	98	*6%*
- substituted third drug (±CBV)	162	*10%*	179	*11%*
- off ART for >90 days	6	*0.4%*	10	*0.6%*
Had switched to second-line	361	*22%*	314	*19%*

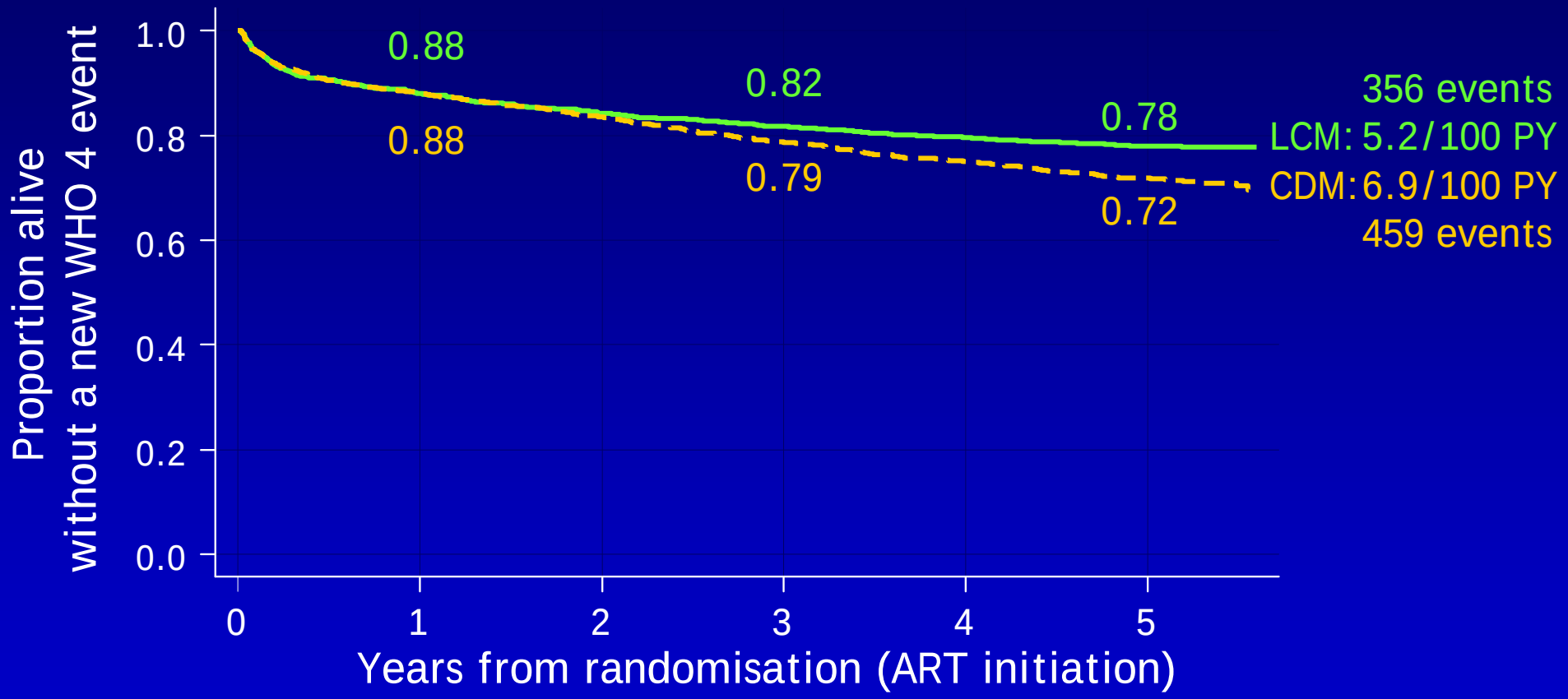
Switch to second-line



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

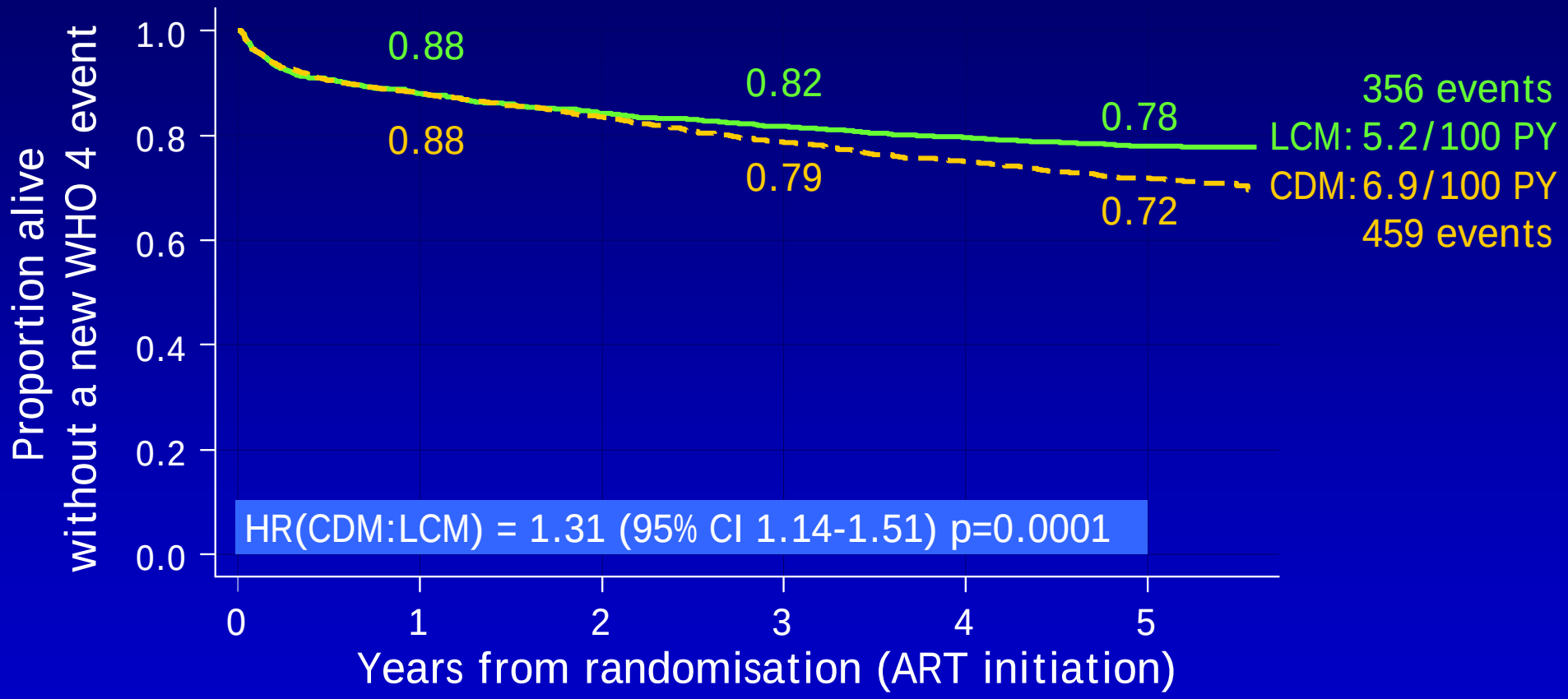
heterogeneity p=0.001

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

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



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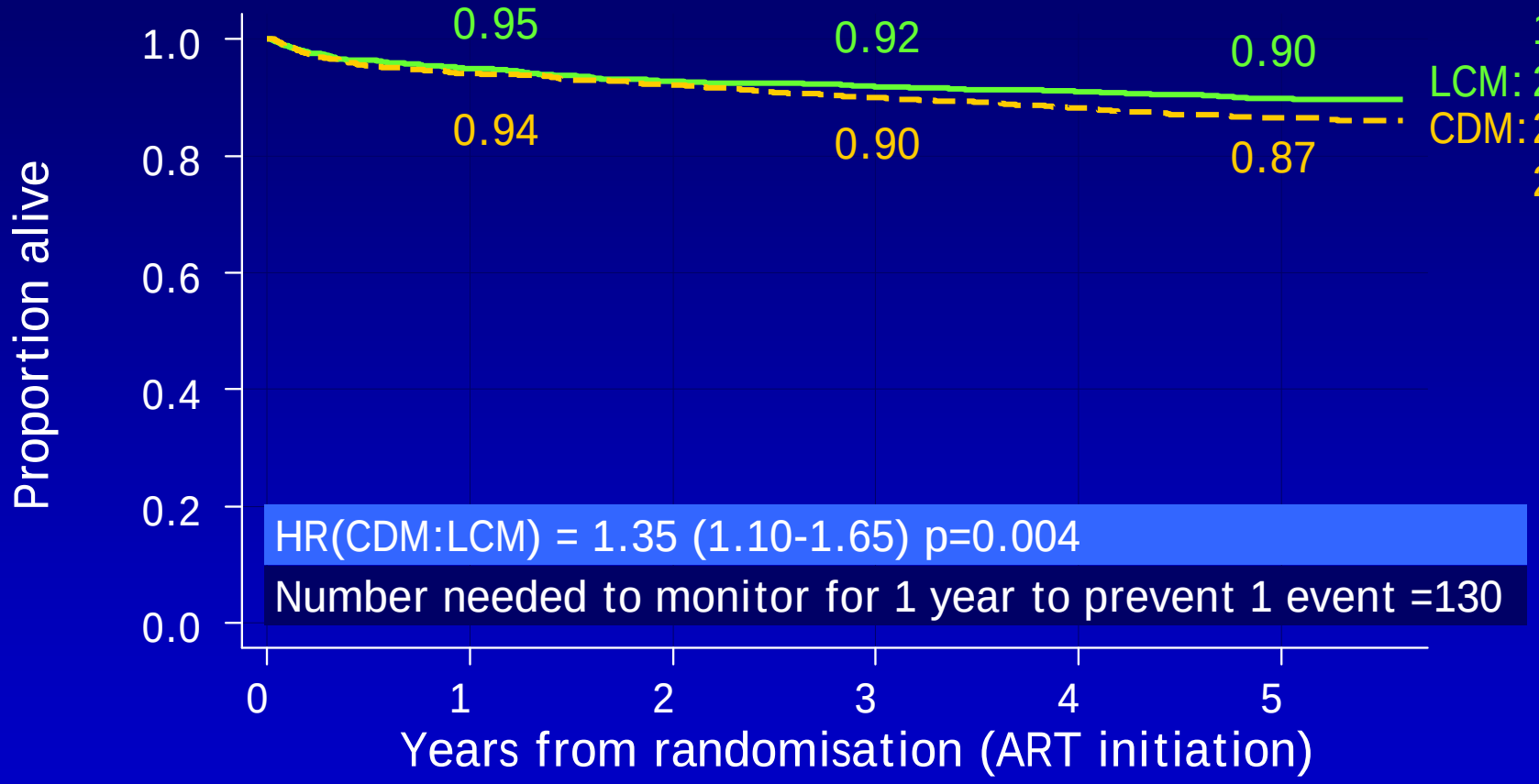
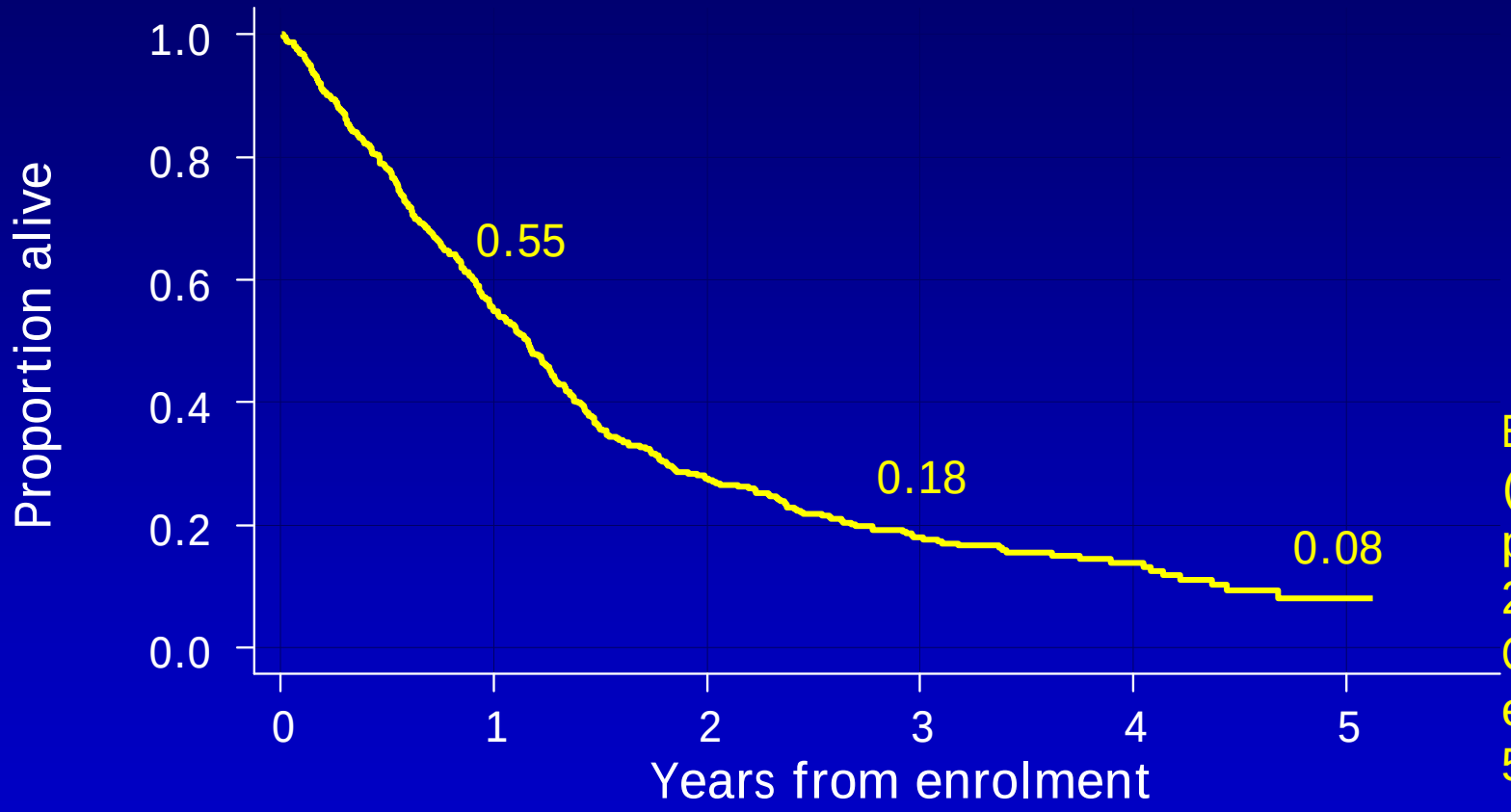
Survival



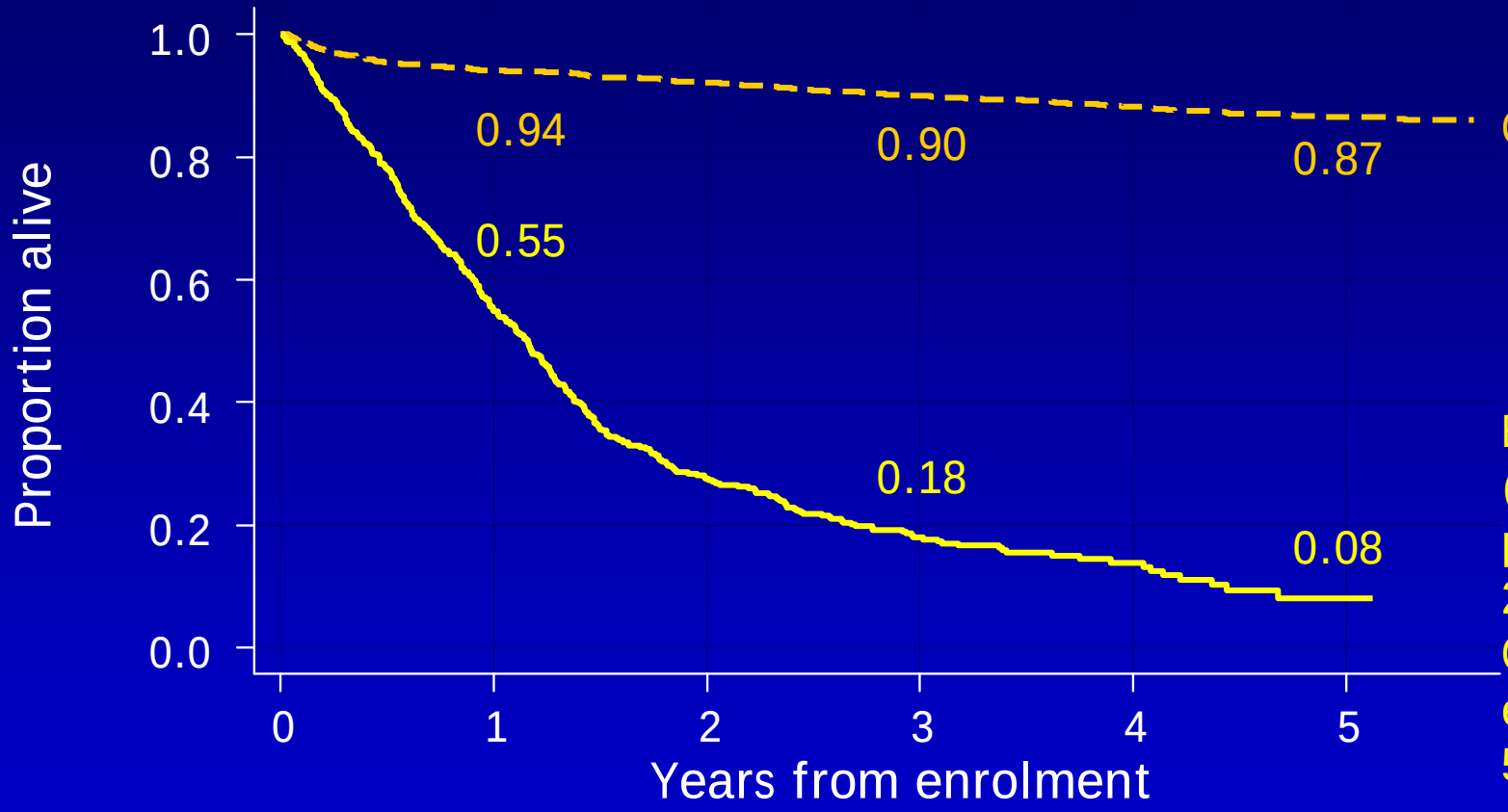
LCM	1656	1552	1501	1468	1436	796
CDM	1660	1542	1494	1445	1395	749

Survival



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

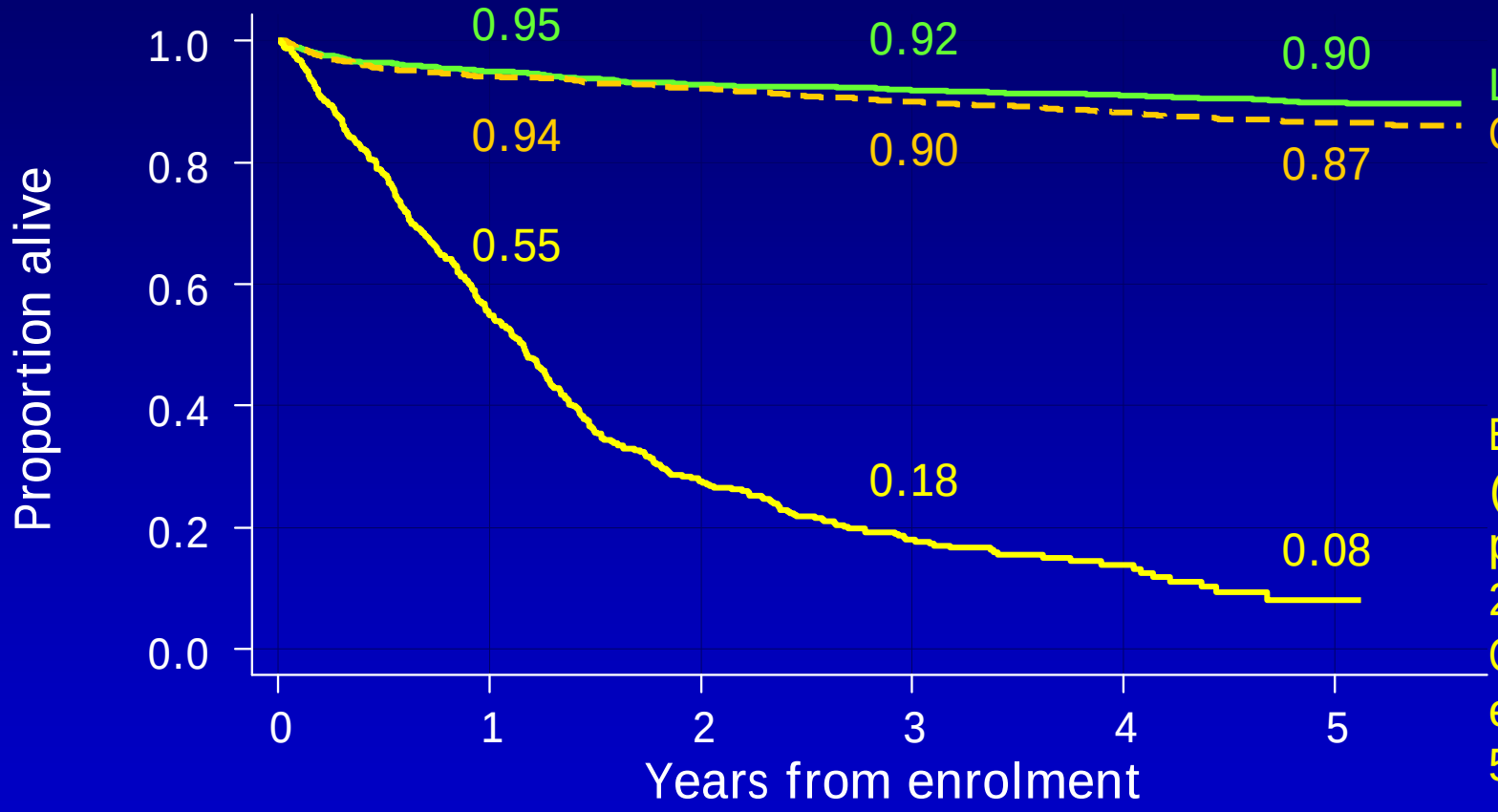
Survival



CDM: 2.9/100 PY
218 events

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

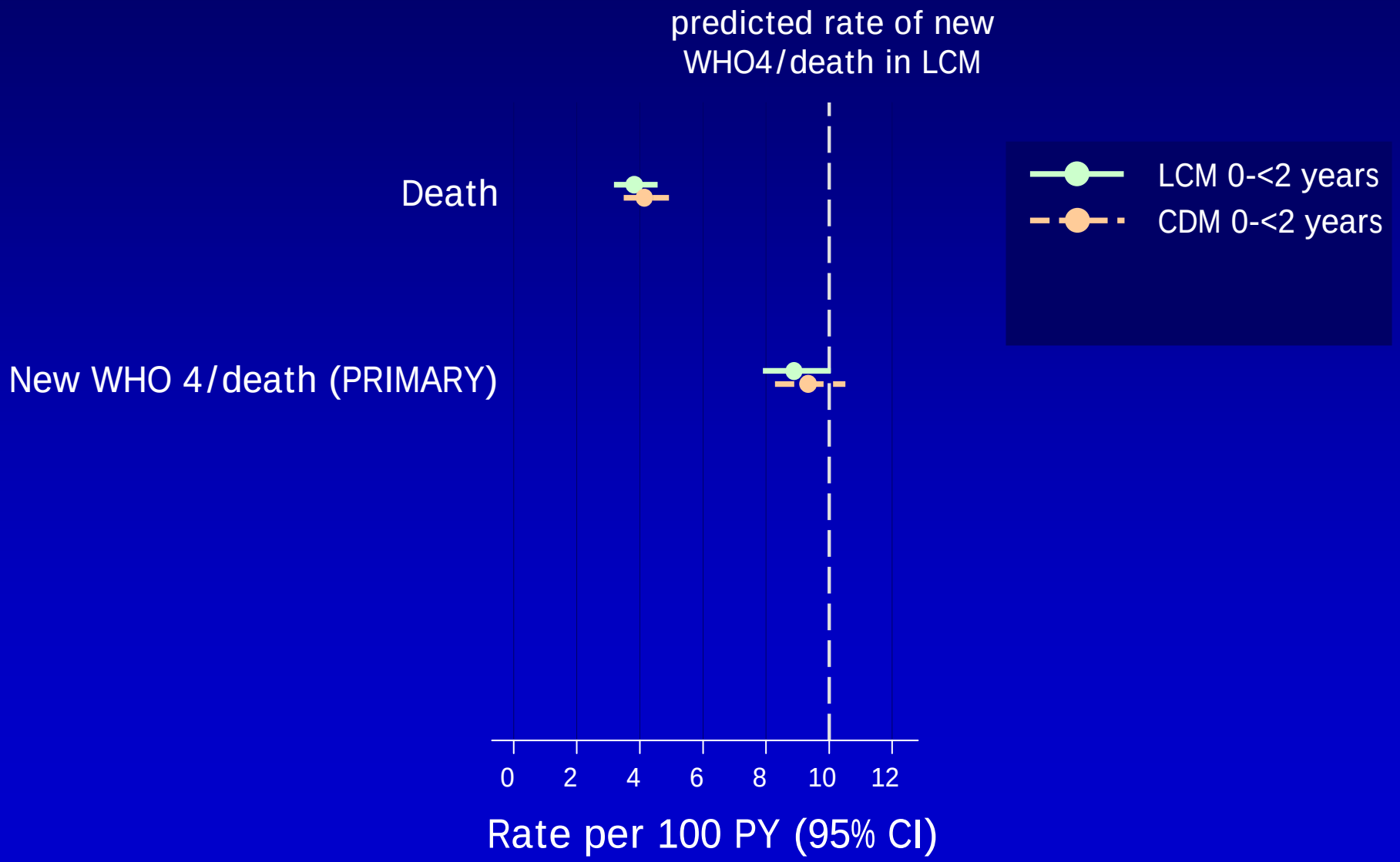
Survival



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

Absolute event rates over time on ART



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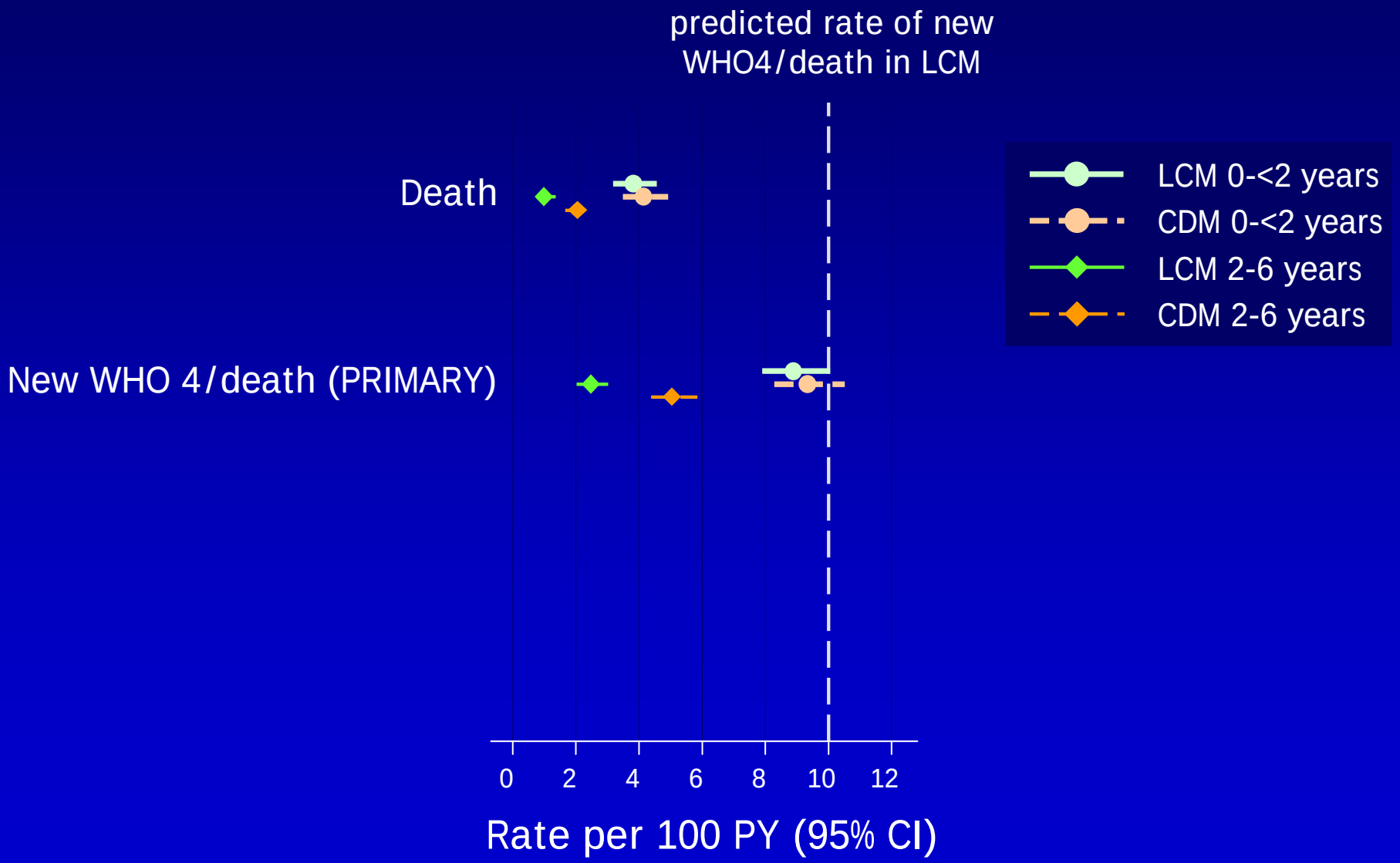

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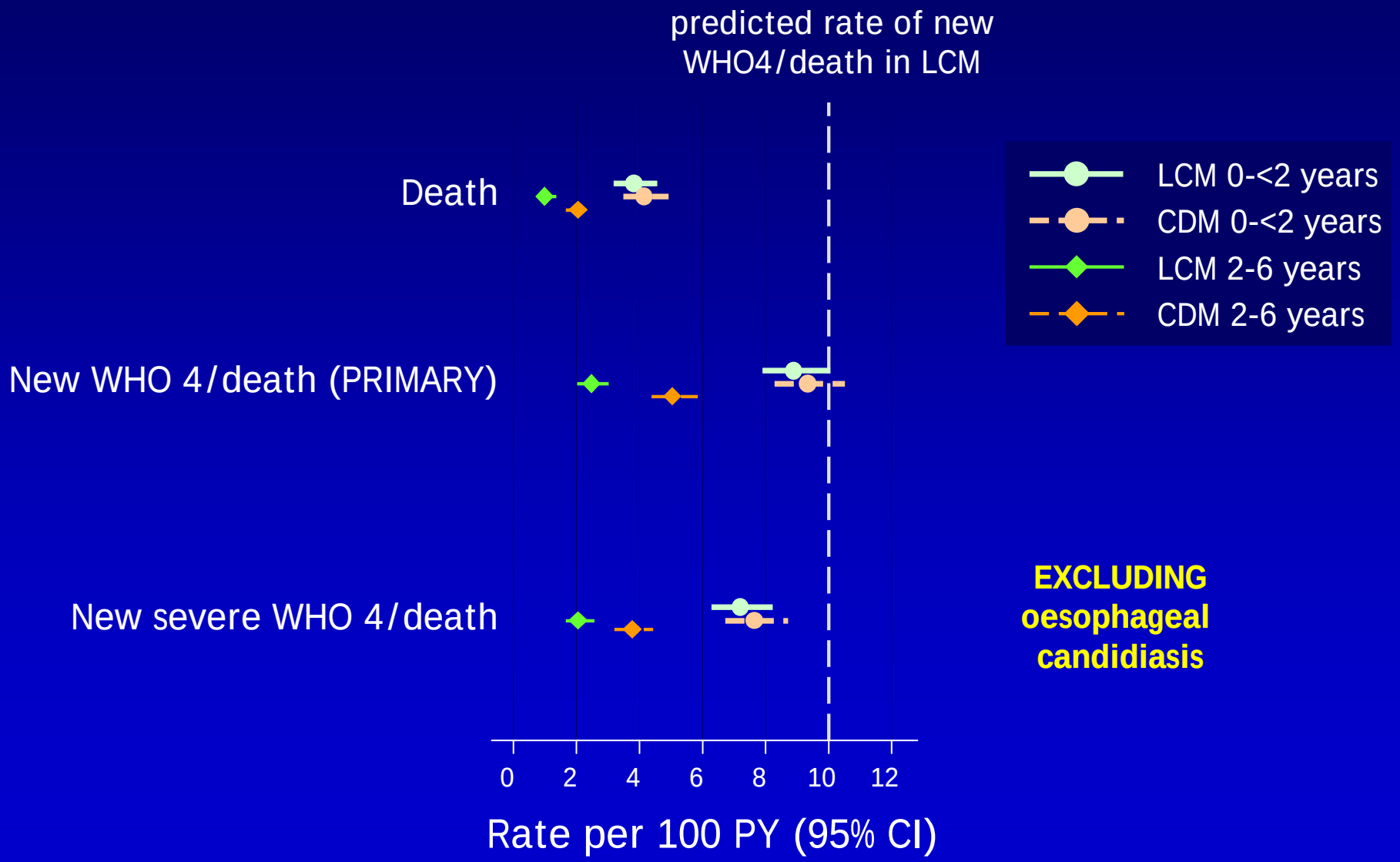


EXCLUDING oesophageal candidiasis

Main Finding

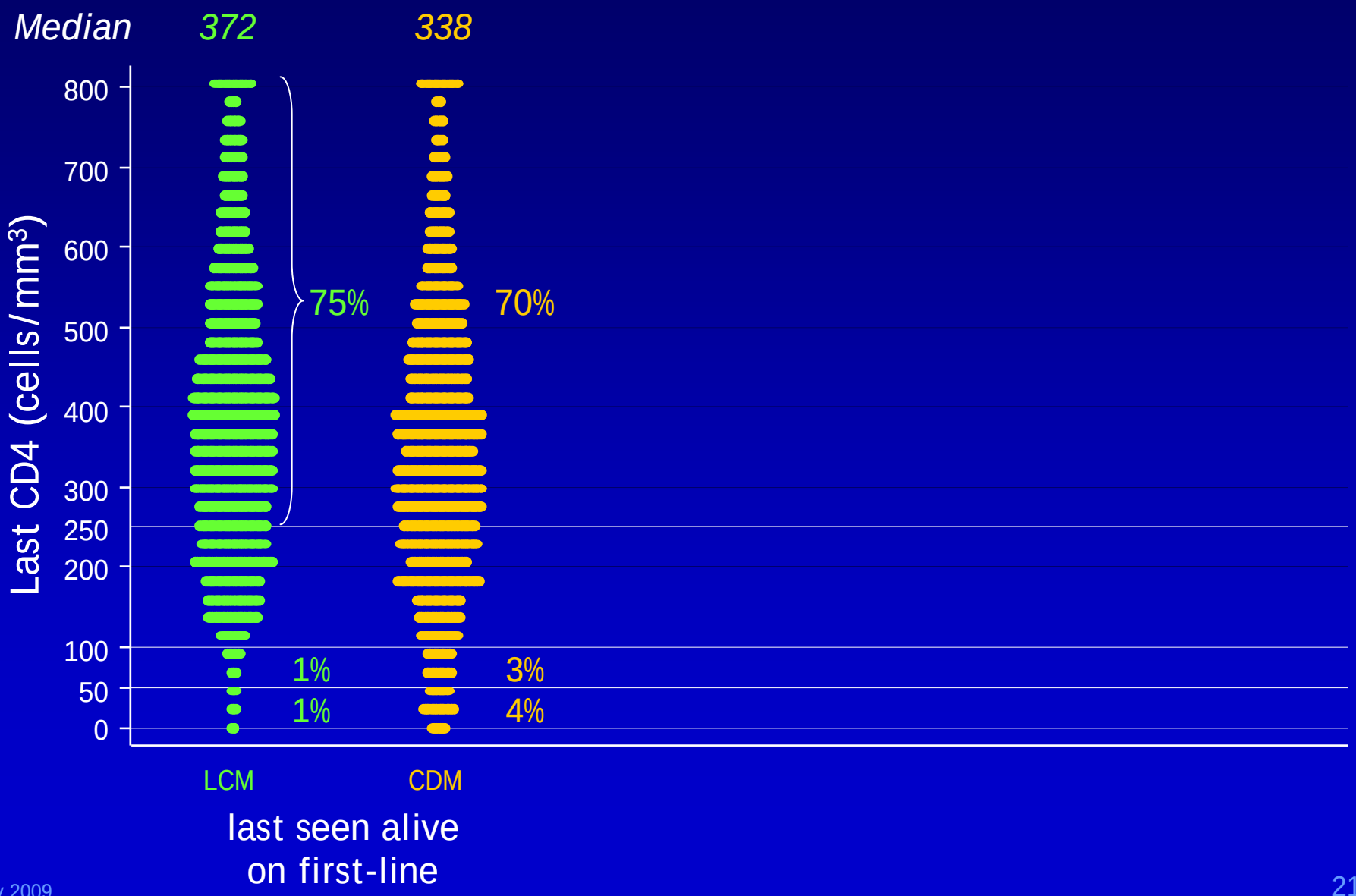
- There is a small but statistically significant difference in mortality and disease progression between the two arms only from the third year on ART

- What causes this?

Explanation

- There is a small but statistically significant difference in mortality and disease progression between the two arms only from the third year on ART
- What causes this?
- Slightly later switching to second-line therapy in CDM leading to a few more patients in CDM living with lower CD4 counts on first-line and at increased risk of clinical events

Most recent CD4 on first-line



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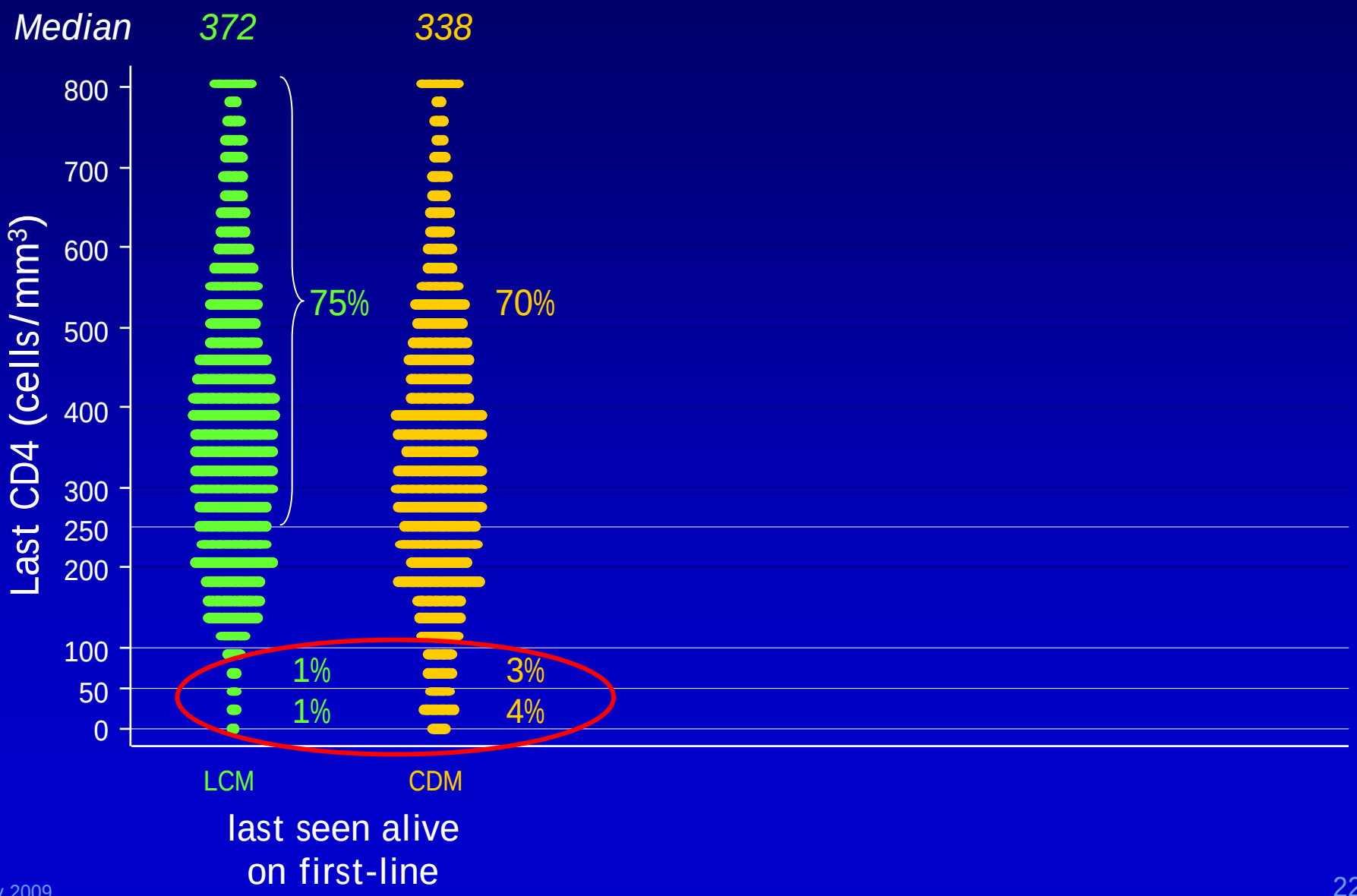
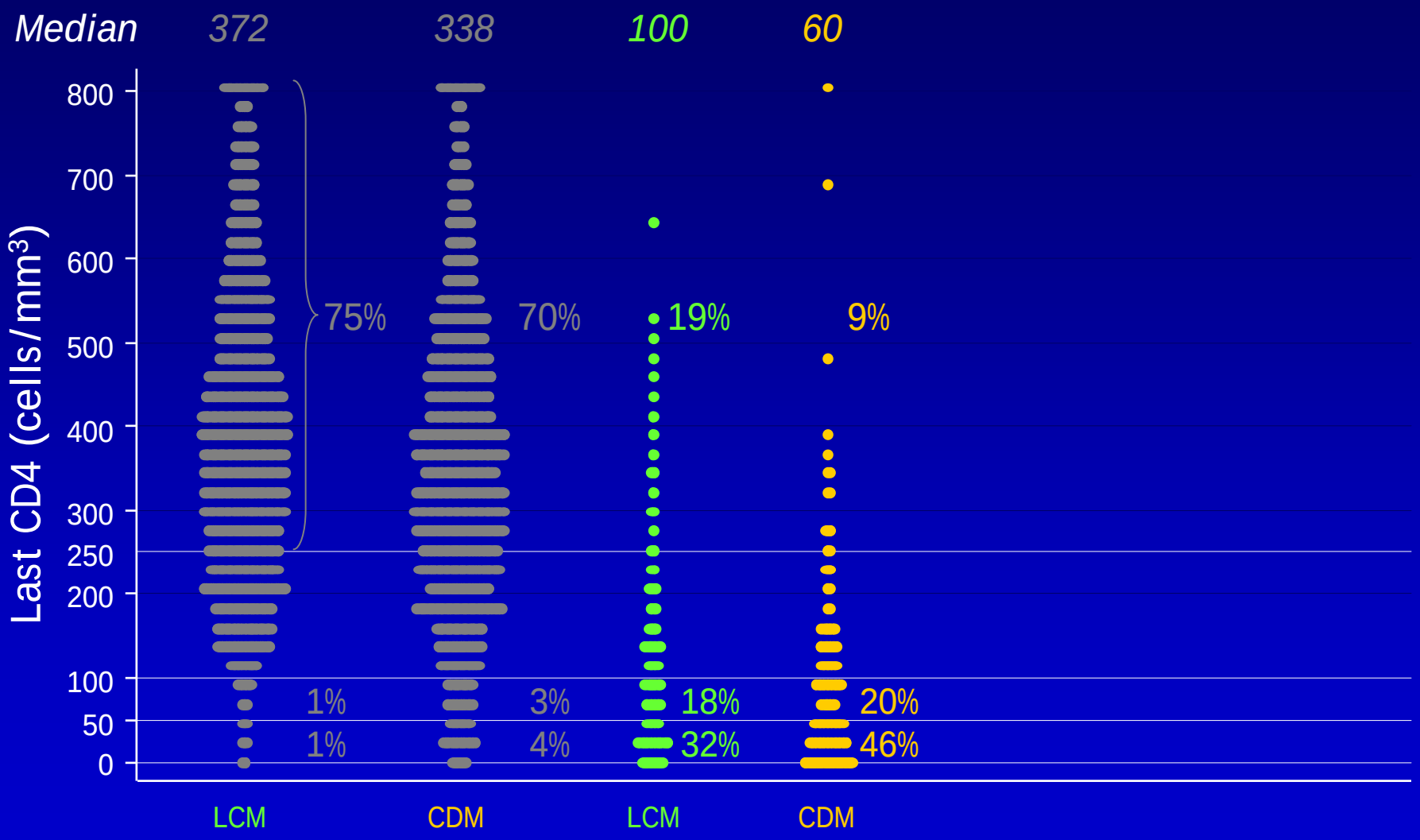
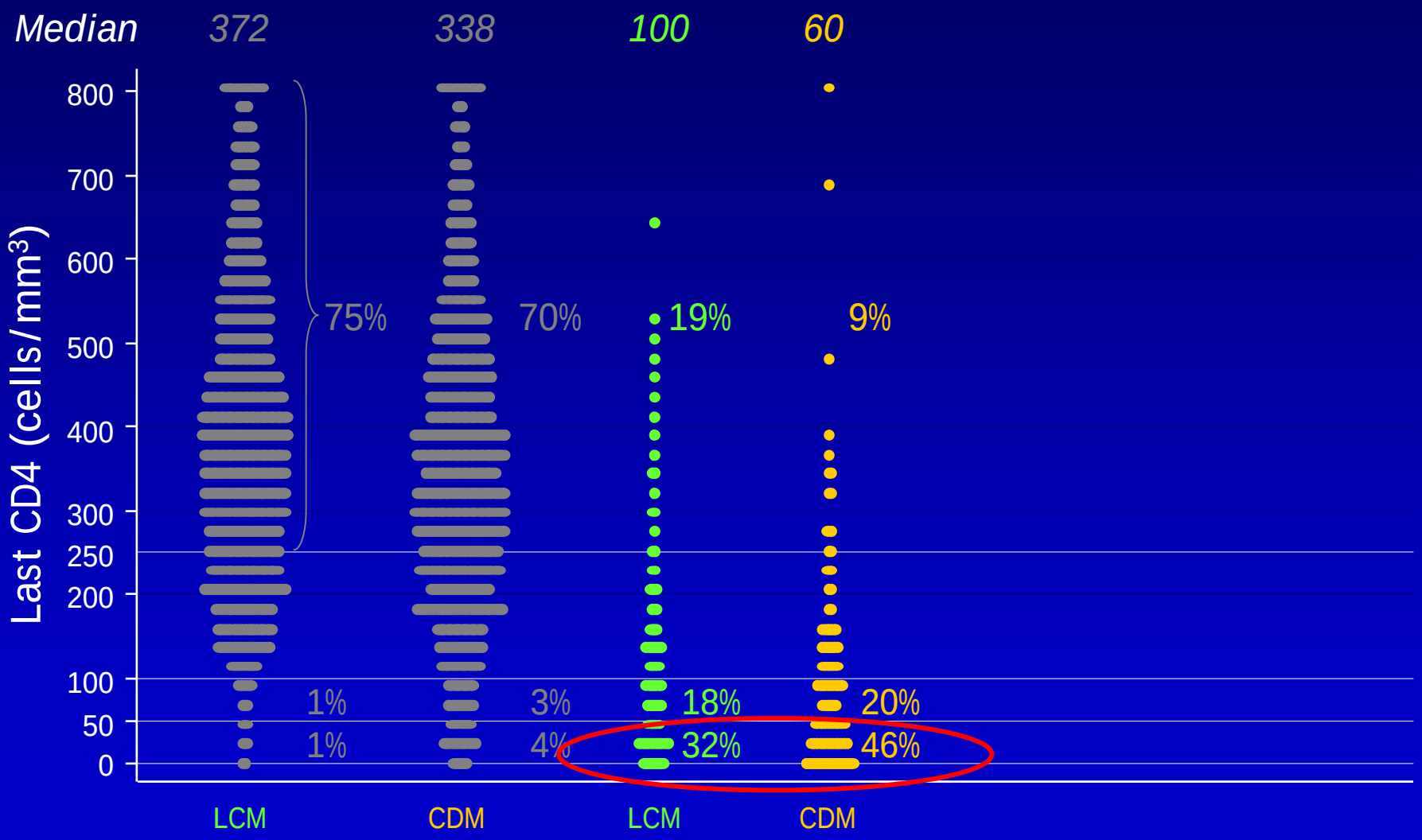


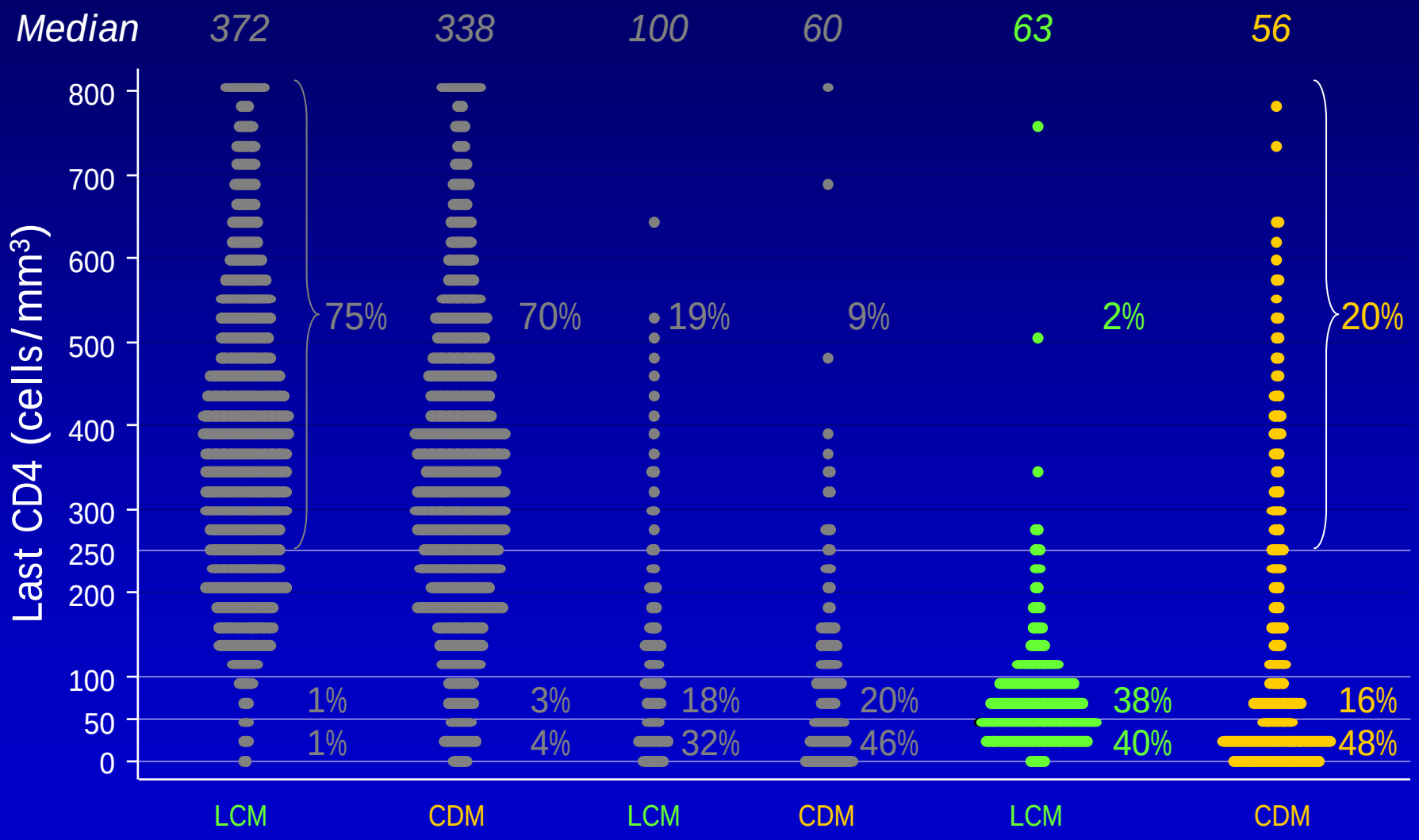
Most recent CD4 on first-line



Most recent CD4 on first-line



Most recent CD4 on first-line or at switch



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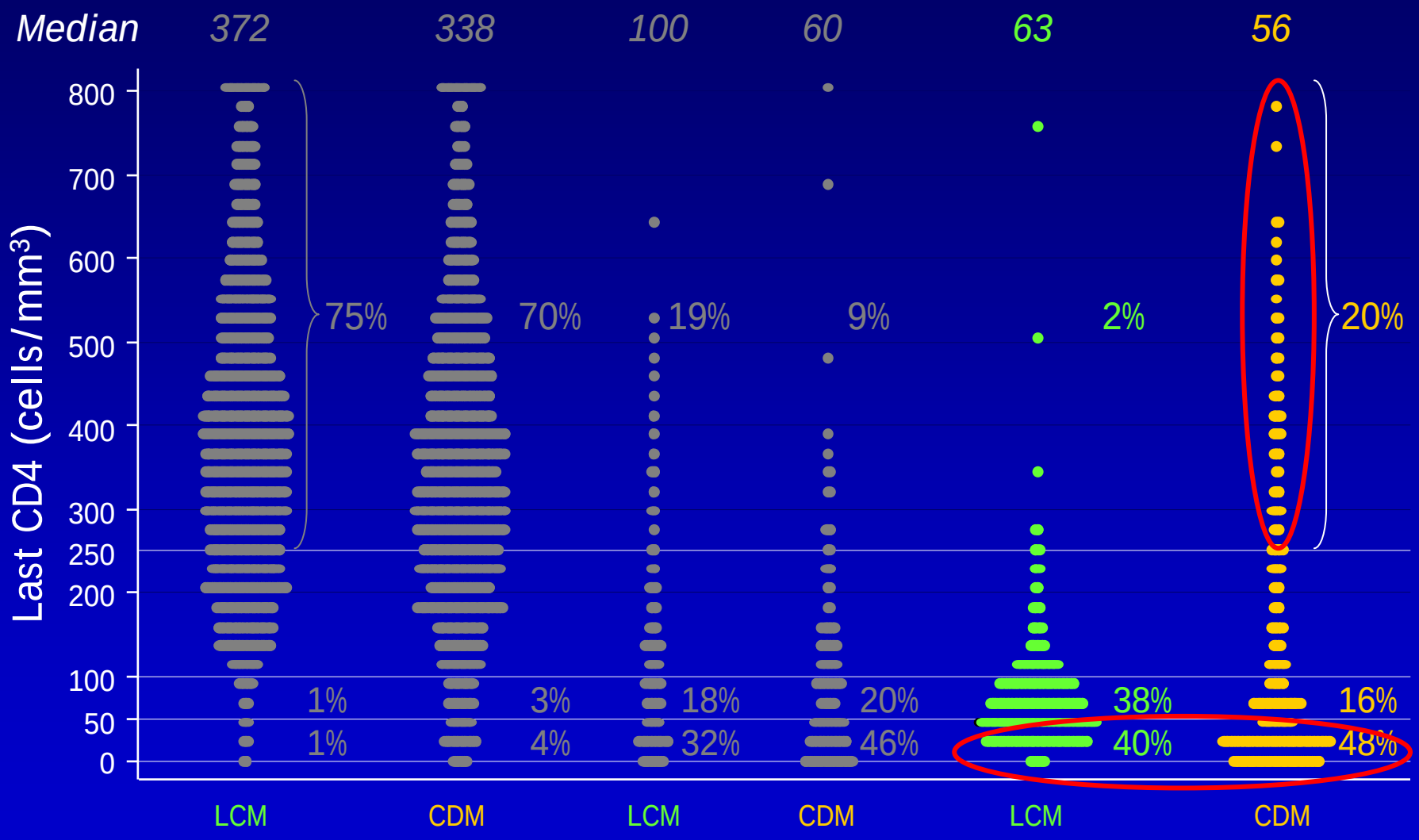
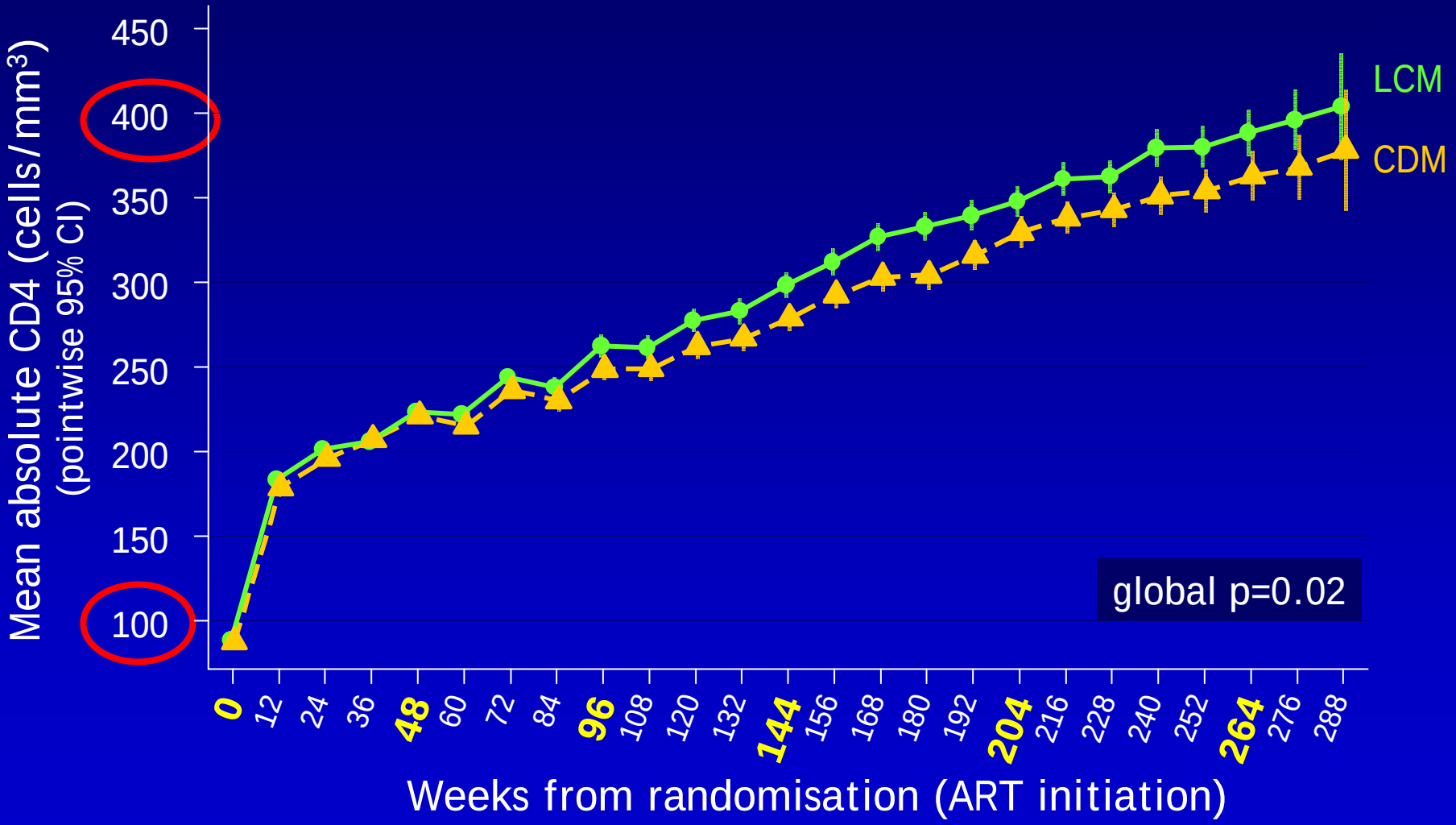


Absolute change in CD4 over 5 years



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

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