Association between modifiable and non-modifiable risk factors and specific causes of death in the HAART era:

Results from the D:A:D study

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on behalf of D:A:D Study Group

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Background

- Although dramatic reductions in death rates have been seen amongst HIV-infected individuals in recent years, they remain higher than those observed in the general population
- Additionally, there is still limited evidence on the extent to which modification of some risk factors could further reduce death rates in this population
- Thus, we investigated the specific causes of death, and aimed to identify potentially modifiable risk factors associated with these

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Methods (1)

- All participants in the D:A:D study, a collaboration of 11 cohorts from Europe, USA and Australia, were included
- Individuals were prospectively followed from study entry until last follow-up or date of death
- Database used for analysis closed February 2007
- Causes of death were assigned according to the underlying cause determined by CoDe system (http://www.cphiv.dk)

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Methods (2)

- Factors associated with specific causes of death were identified using Poisson regression:
  - Non-modifiable risk factors: Age, gender
  - Modifiable non-HIV-specific risk factors: Smoking status, BMI, diabetes, HBV status, HCV status, hypertension*
  - Modifiable HIV-specific risk factors: Current CD4 and HIV-RNA
- All results presented are adjusted for above risk factors, as well as race, HIV risk, calendar year and ART use
- Hypertension, current CD4 and current HIV-RNA lagged by 3 months

* Receipt of anti-hypertensives, SBP>140 mmHg or DBP>90 mmHg

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Study Entry Characteristics (1)

		Number (%)
Number of participants		33,347 (100)
Gender	Male	24,692 (74)
Race	White Black African Prohibited/Other	14,890 (45) 3,470 (10) 14,987 (45)
Risk for HIV Transmission	MSM Heterosexual IDU Other	14,376 (43) 10,047 (30) 5,951 (18) 2,973 (9)
Smoking status	Current Ex Never Unknown	11,316 (34) 5,617 (17) 8,754 (26) 7,660 (23)
HCV antibody HBV surface antigen	Positive Positive	6,606 (20) 4,755 (14)
Diabetes	Yes	952 (3)

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Study Entry Characteristics (2)

	% with measurement	Median (IQR)
Age (years)	100	39 (34-45)
BMI (kg/m^2)	86	23 (21-25)
Systolic BP (mmHg)	55	120 (110-130)
HIV-RNA viral load (log copies/ml)	96	2.7 (1.7-4.2)
CD4 cell count (cells/mm^3)	97	408 (248-600)
	Number exposed (%)	**Median (IQR)**
Cumulative ART exposure (years)	24,391 (73)	3.1 (1.6-4.8)
Cumulative HAART exposure (years)	22,562 (68)	2.4 (1.2-3.4)
Cumulative PI exposure (years)	19,332 (58)	2.3 (1.2-3.2)
Cumulative NNRTI exposure (years)	11,063 (33)	0.9 (0.4-1.6)
Cumulative NRTI exposure (years)	24,299 (73)	3.1 (1.6-4.8)

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Deaths

- There were 2,192 deaths over 158,959 person-years

Death Rate = 13.8 per 1000 person-years
(95% CI 13.2-14.4)

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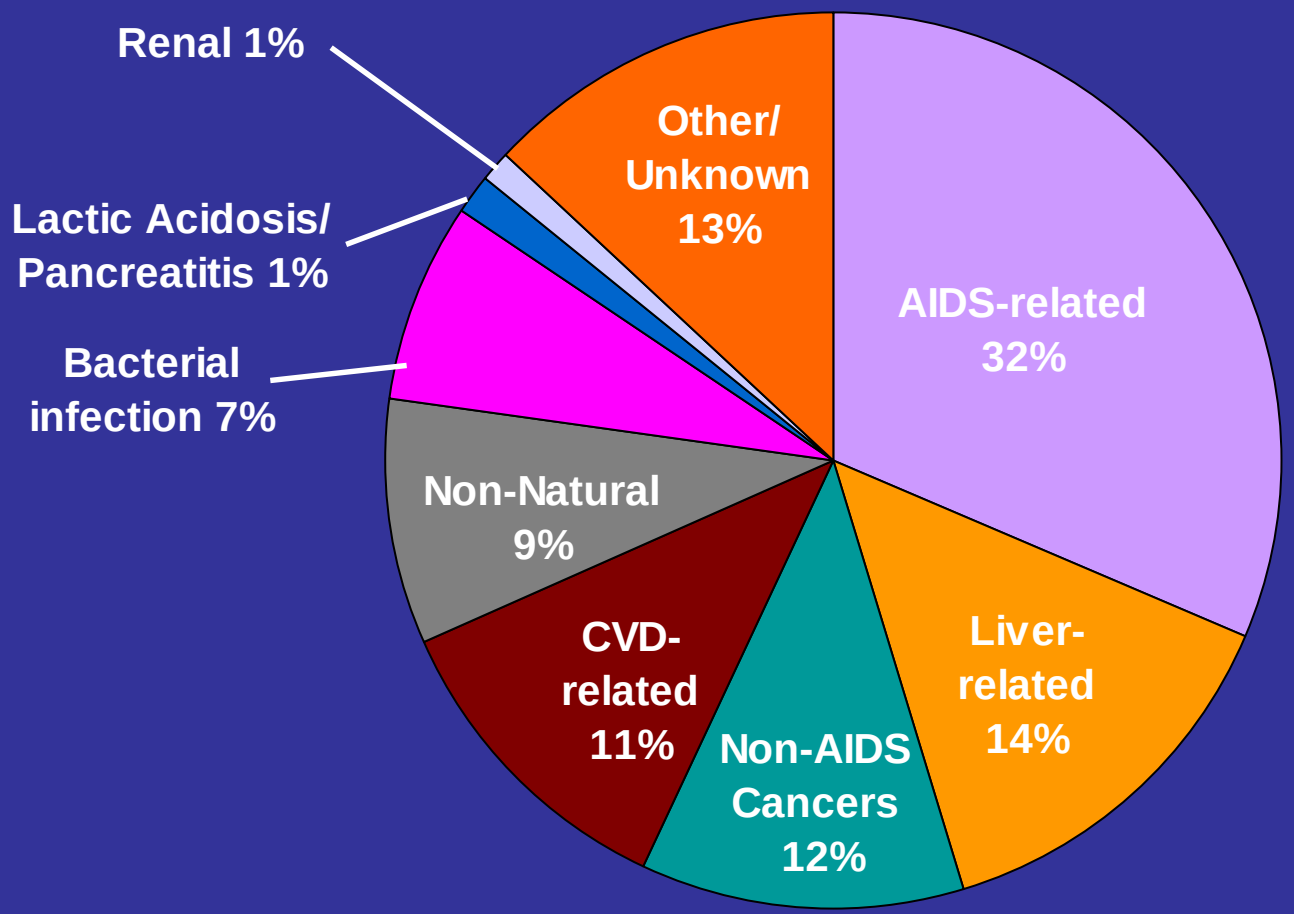
Causes of death



Non-modifiable risk factors

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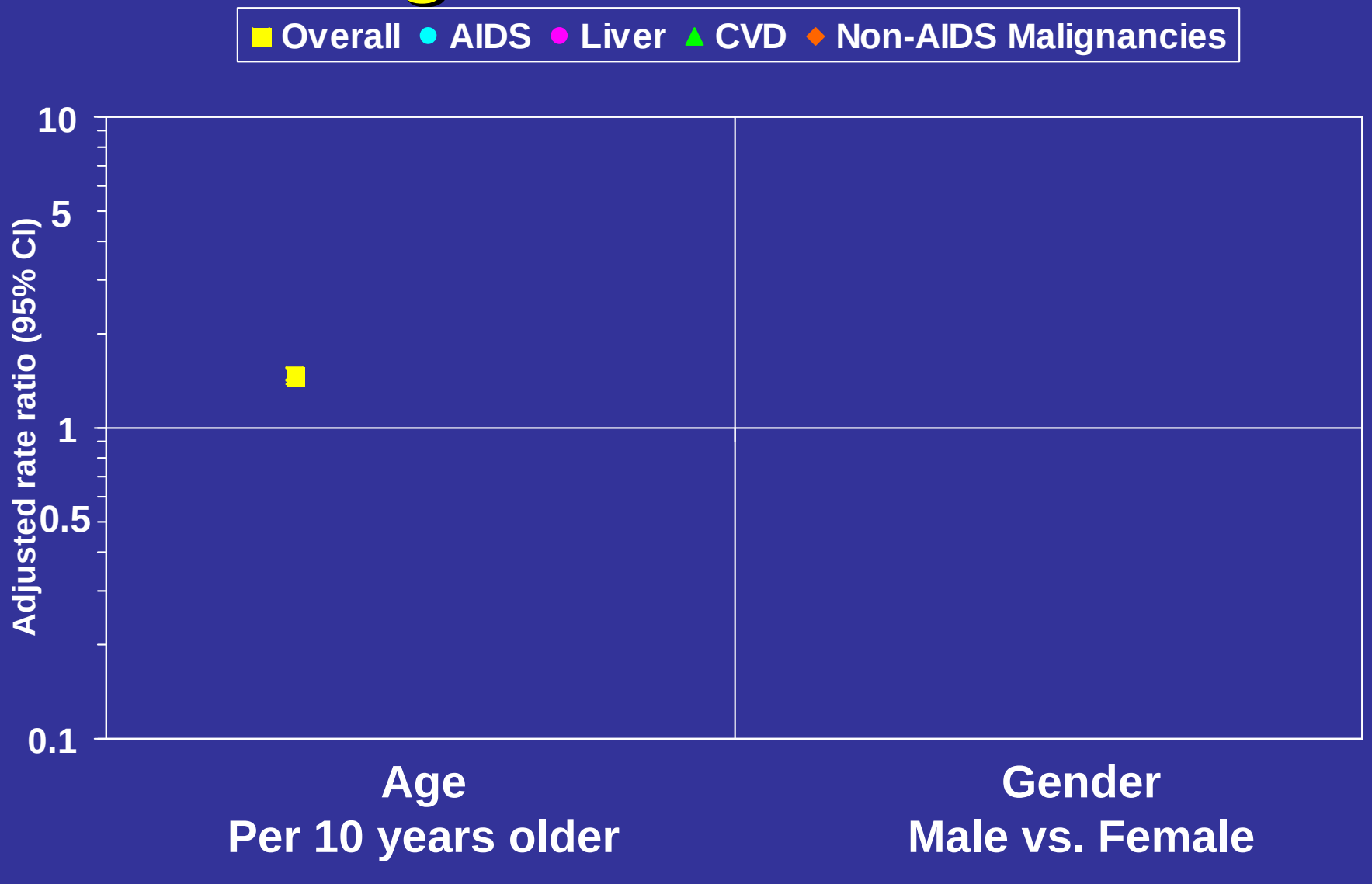
Age and Gender



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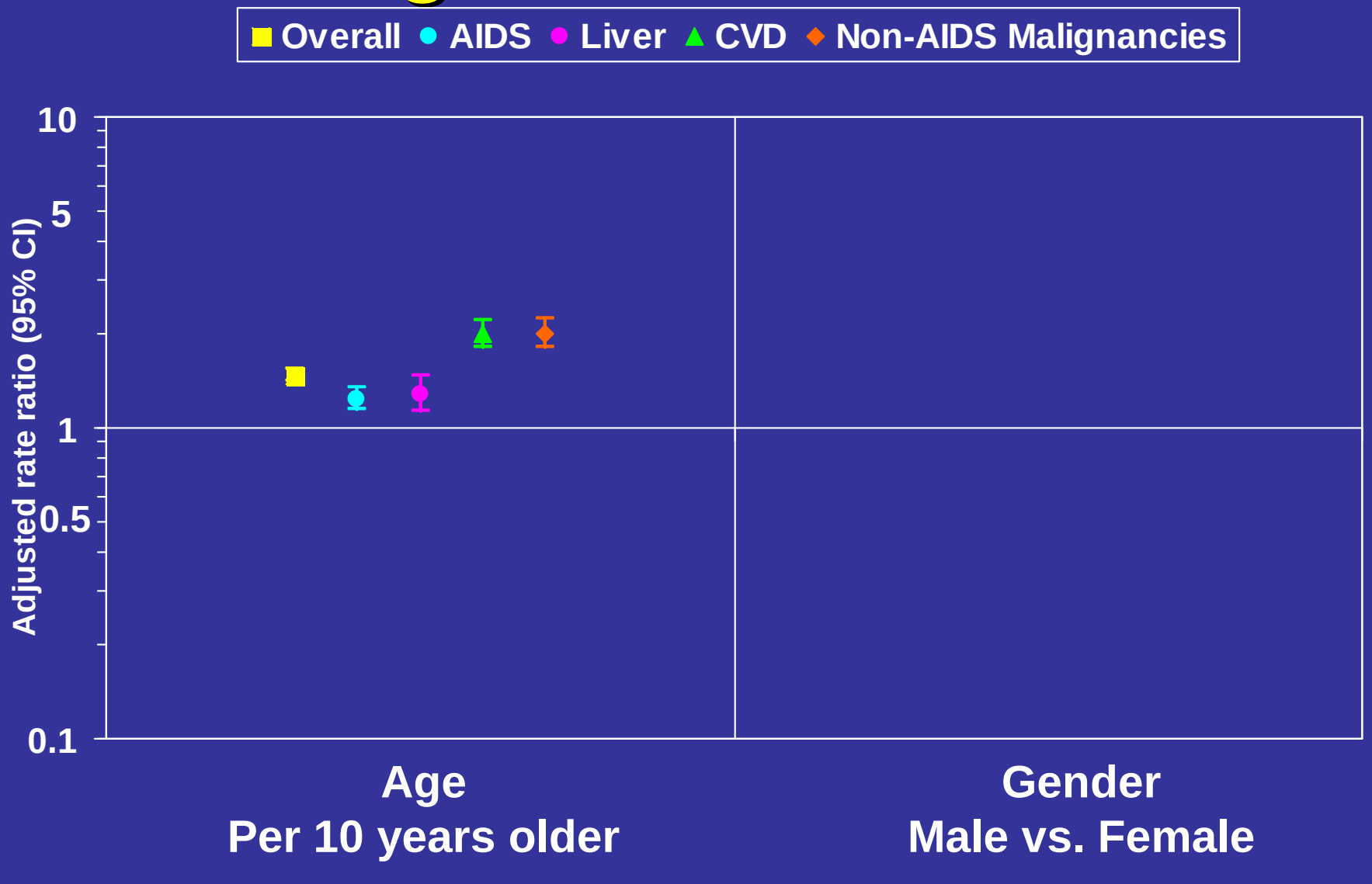
Age and Gender



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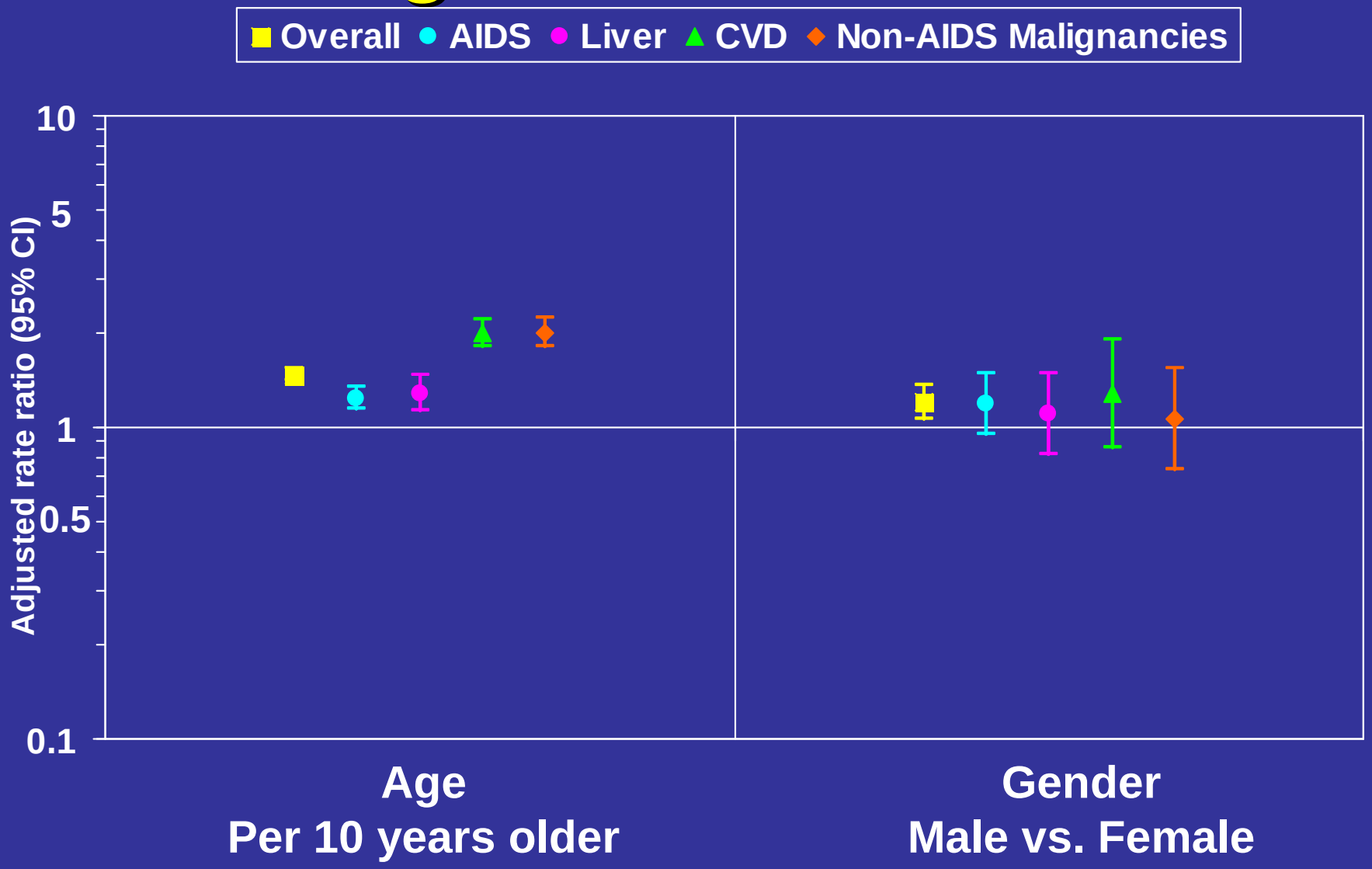

Modifiable non-HIV-specific factors

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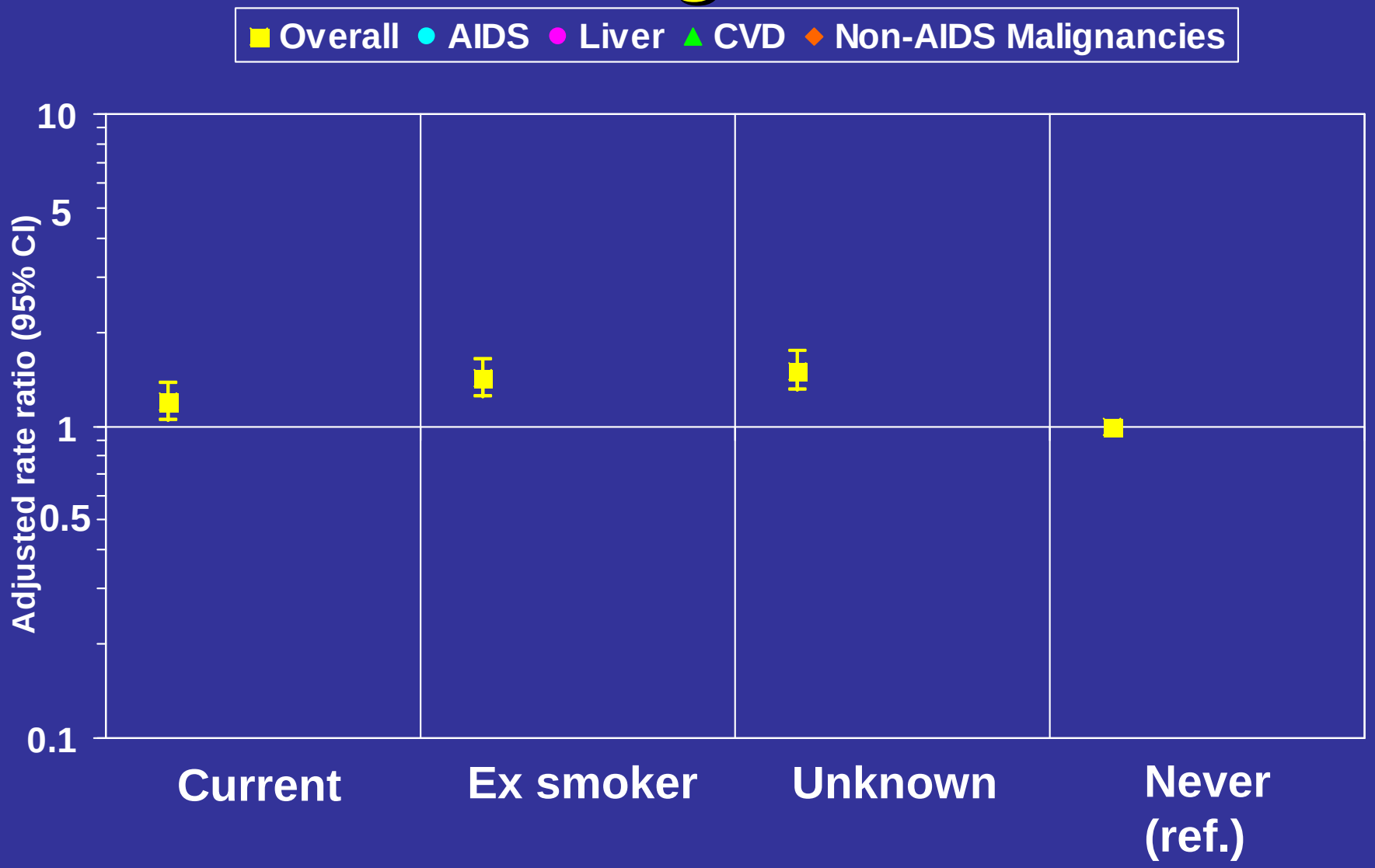
Smoking Status



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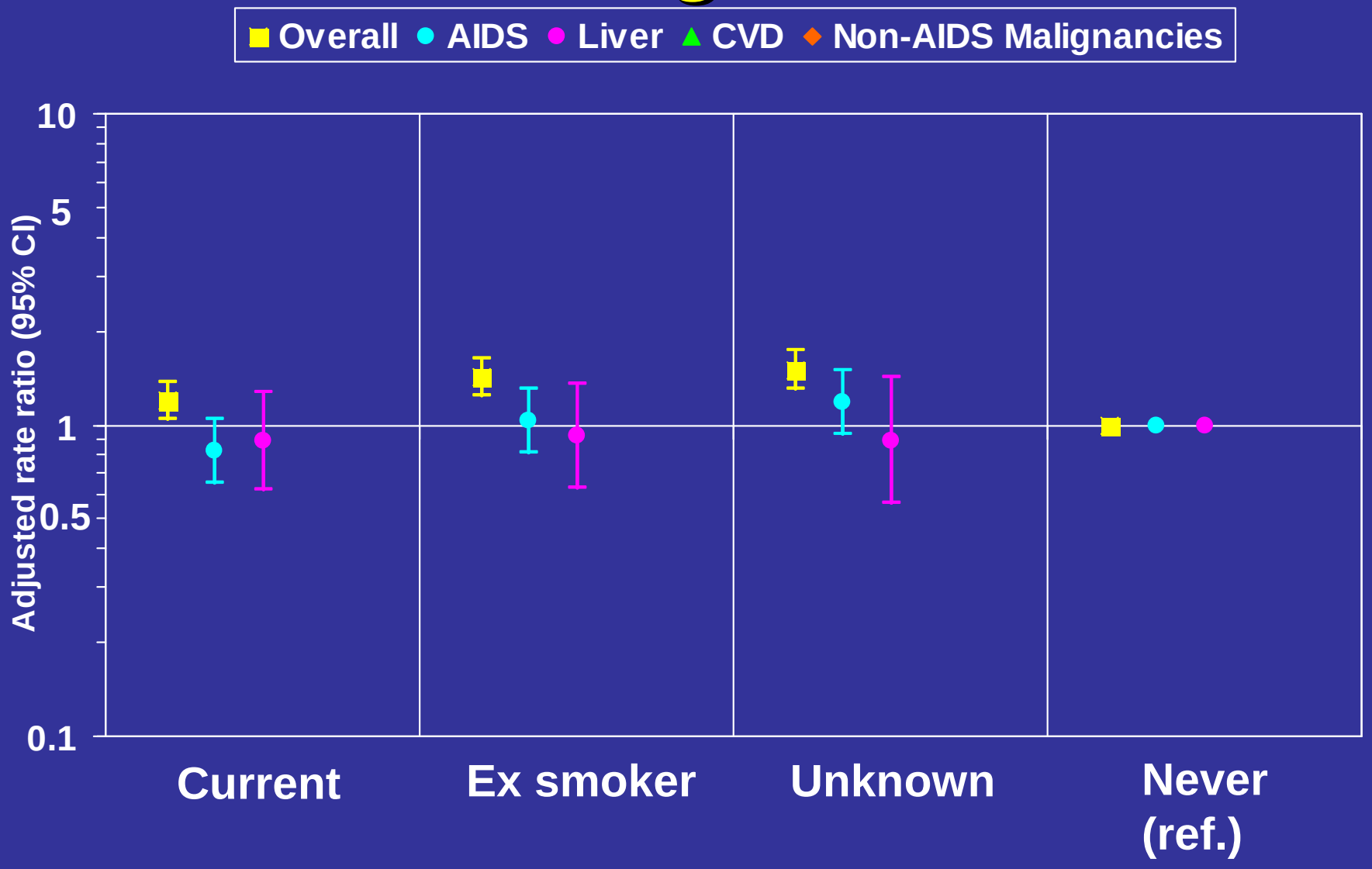

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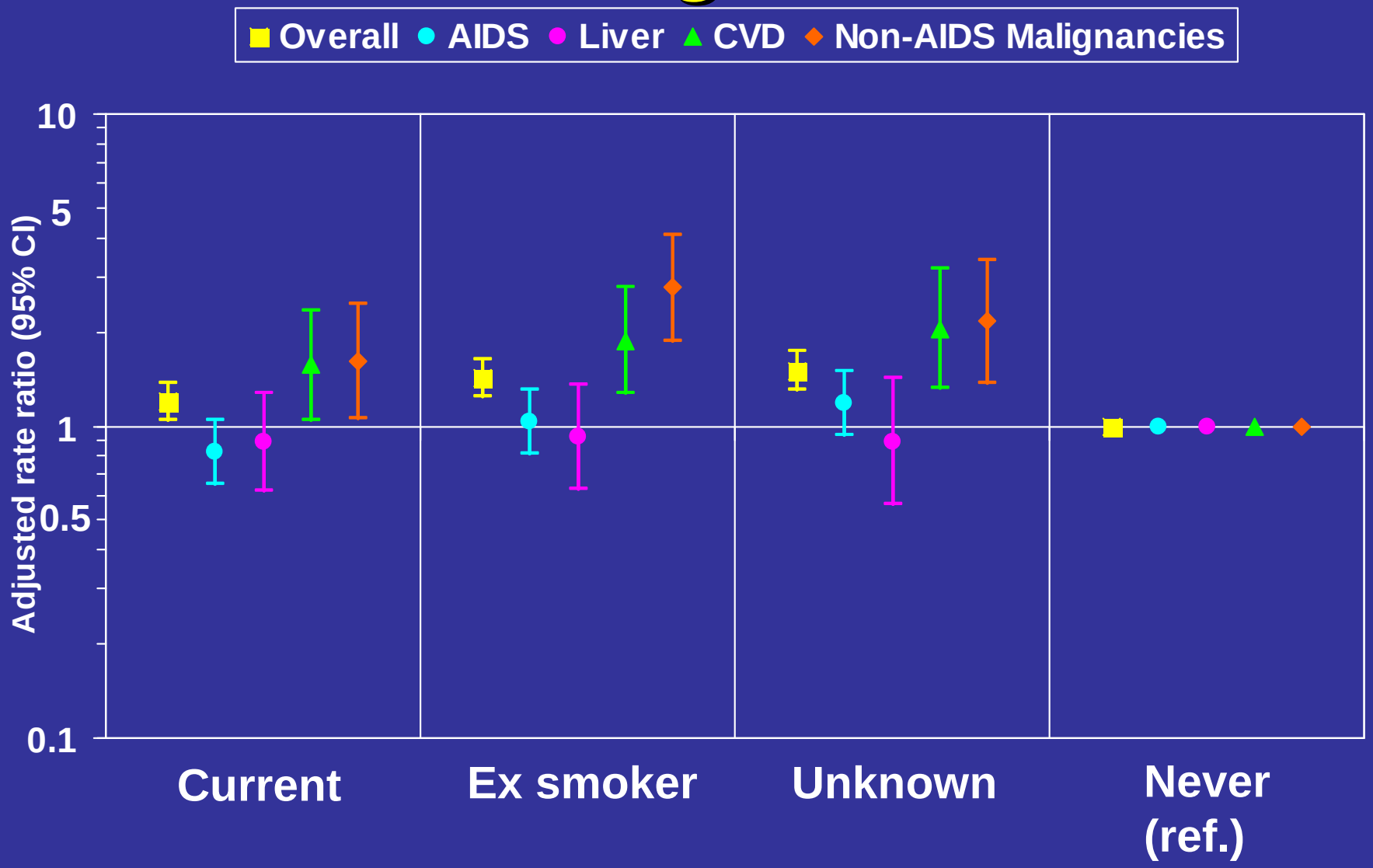

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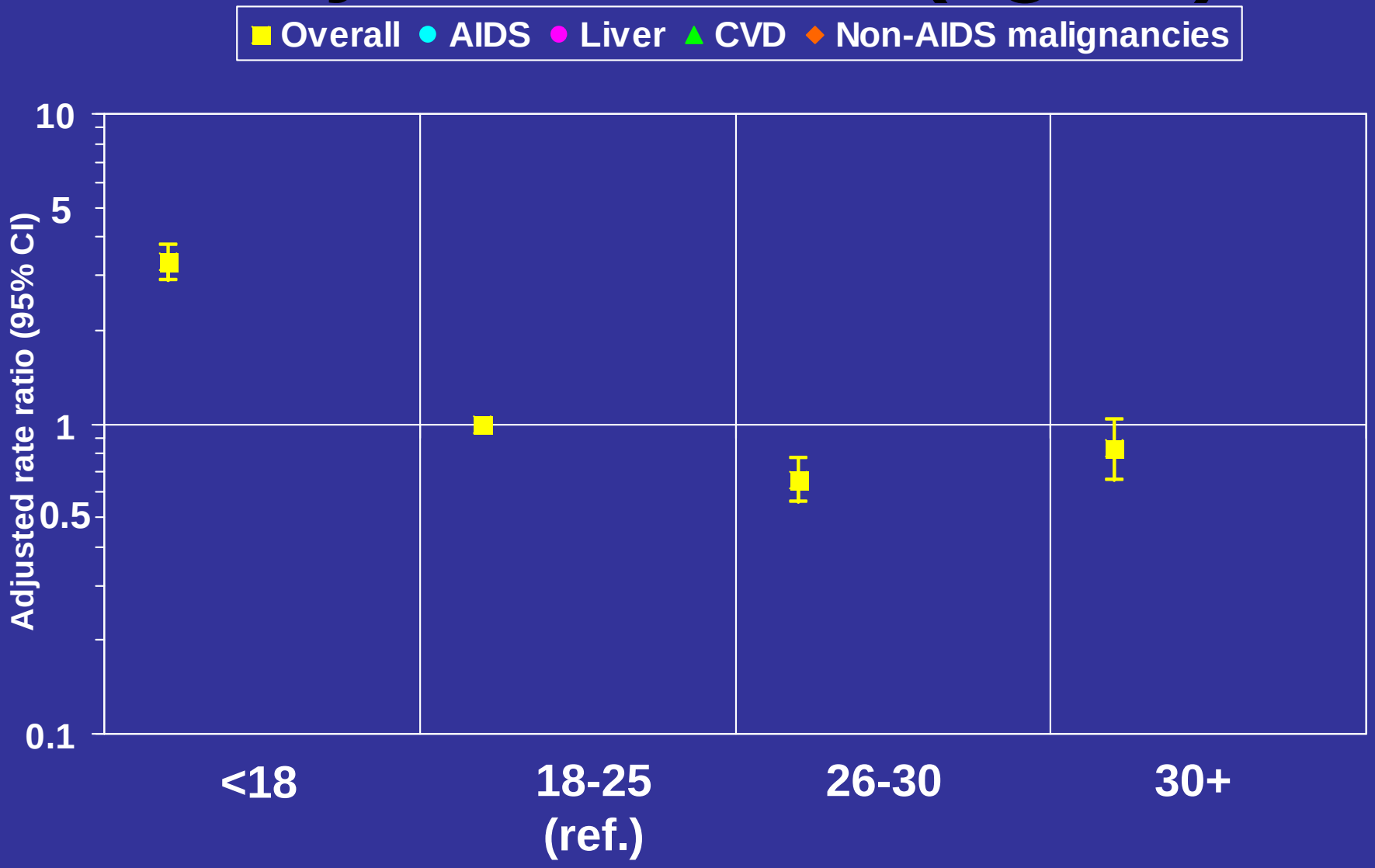
Body Mass Index (kg/m^2)



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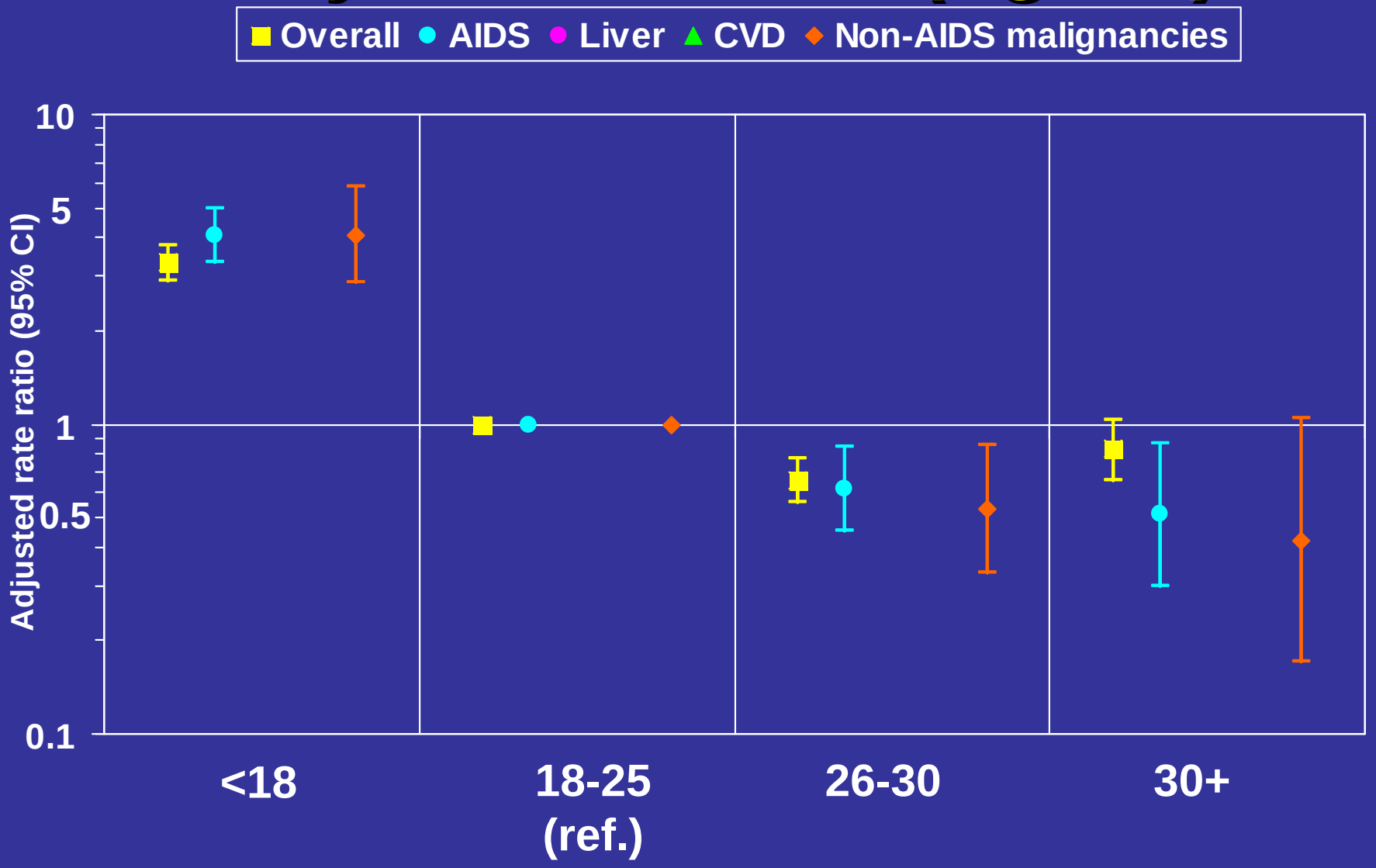

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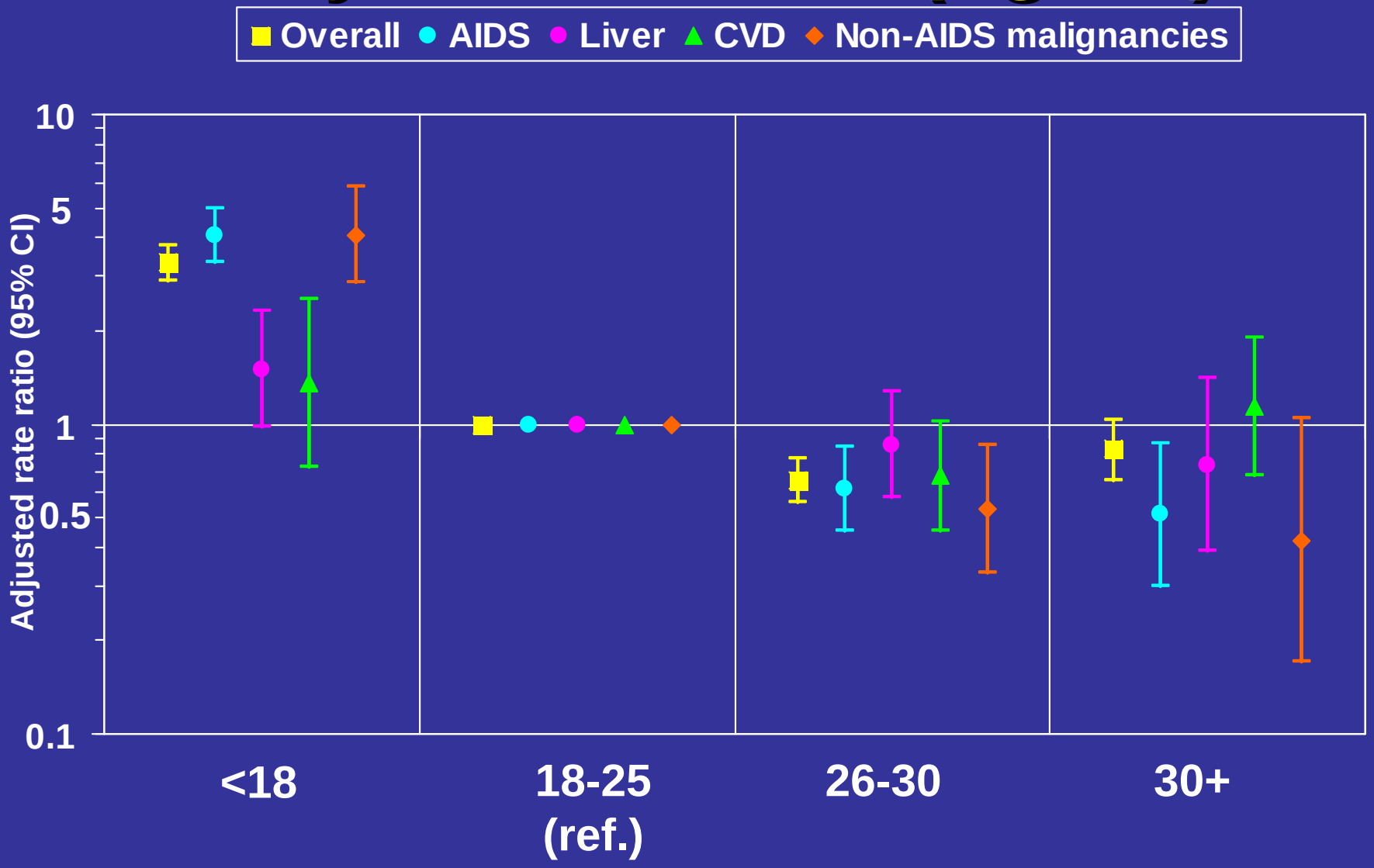

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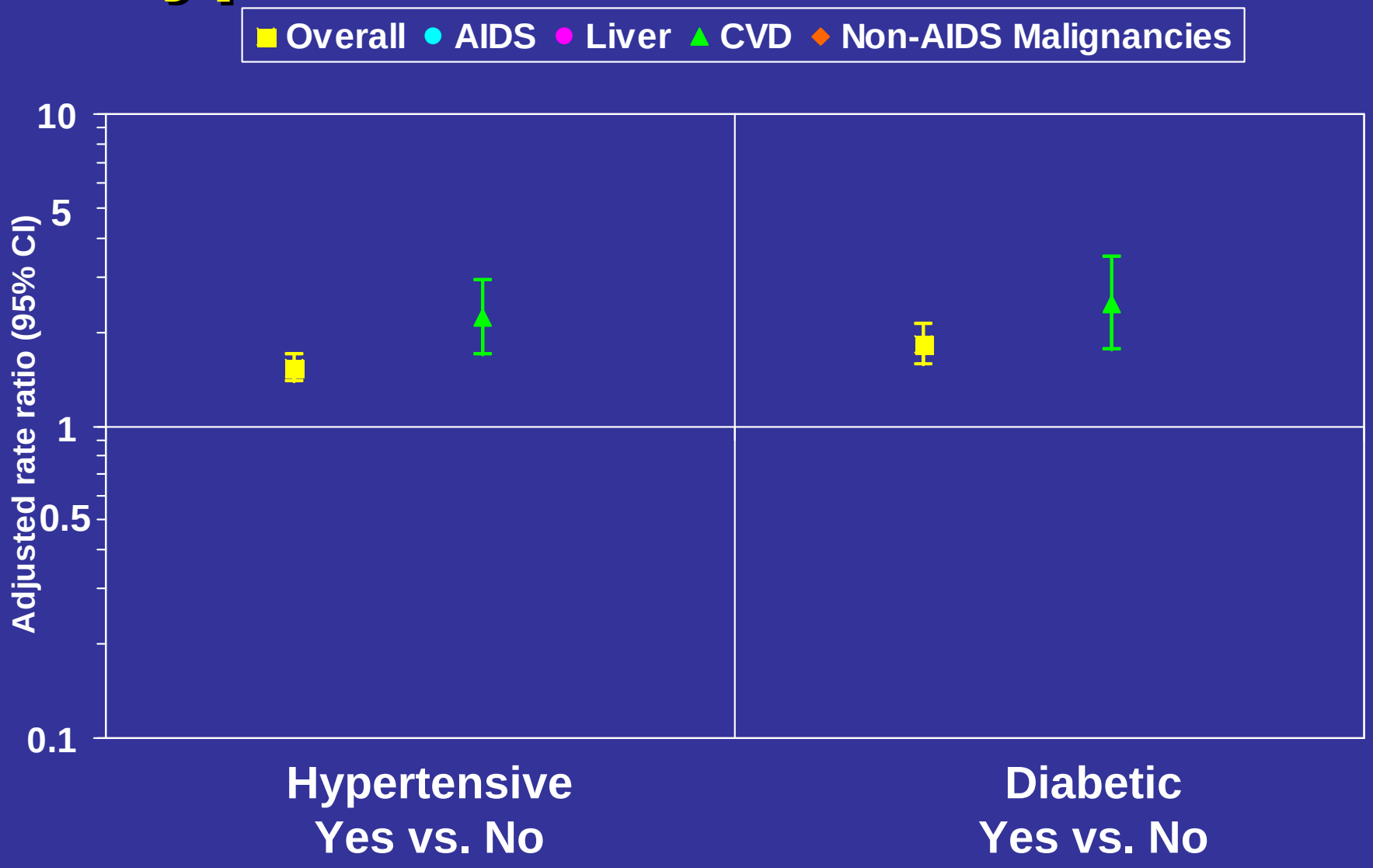
Hypertension and Diabetes



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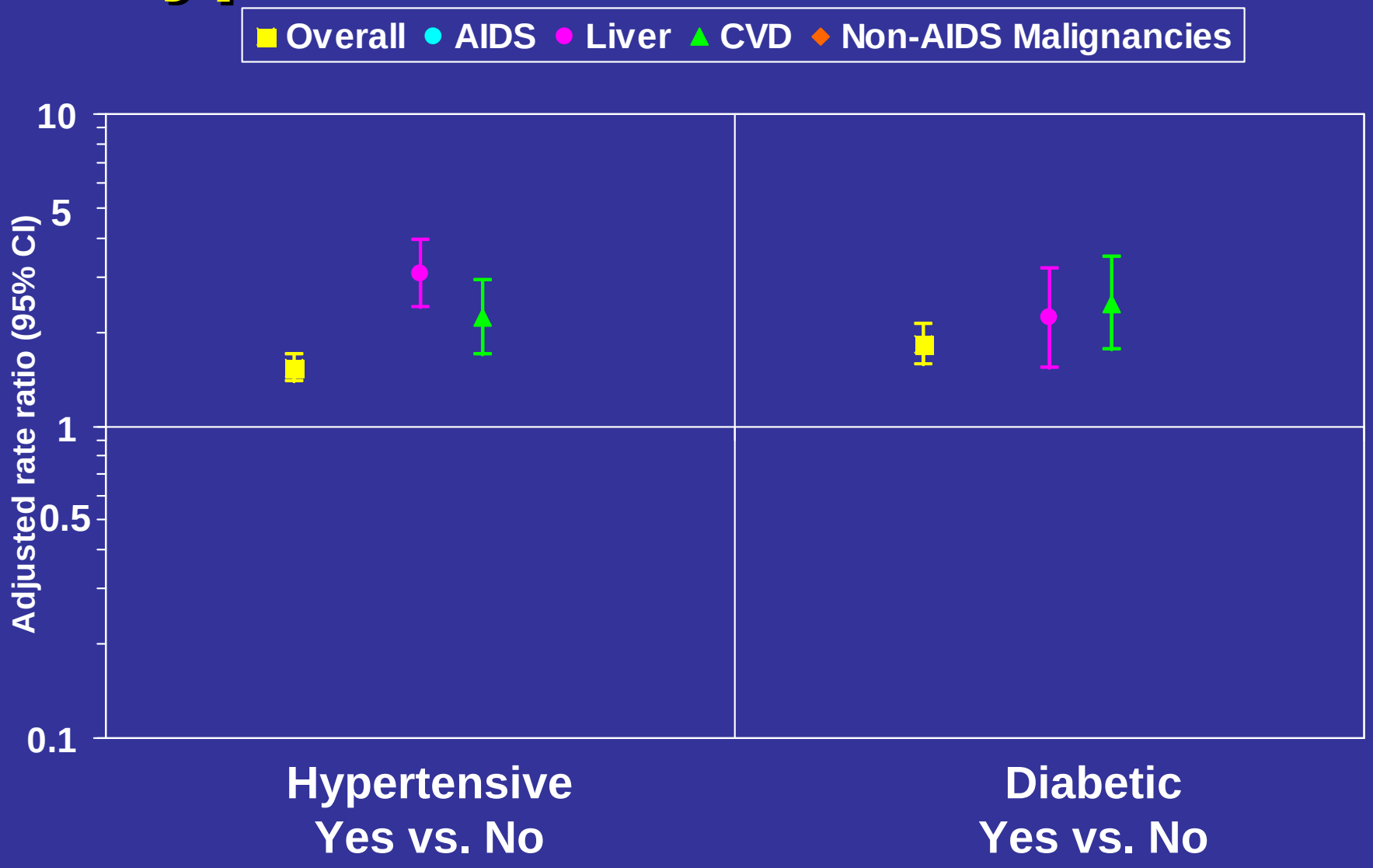

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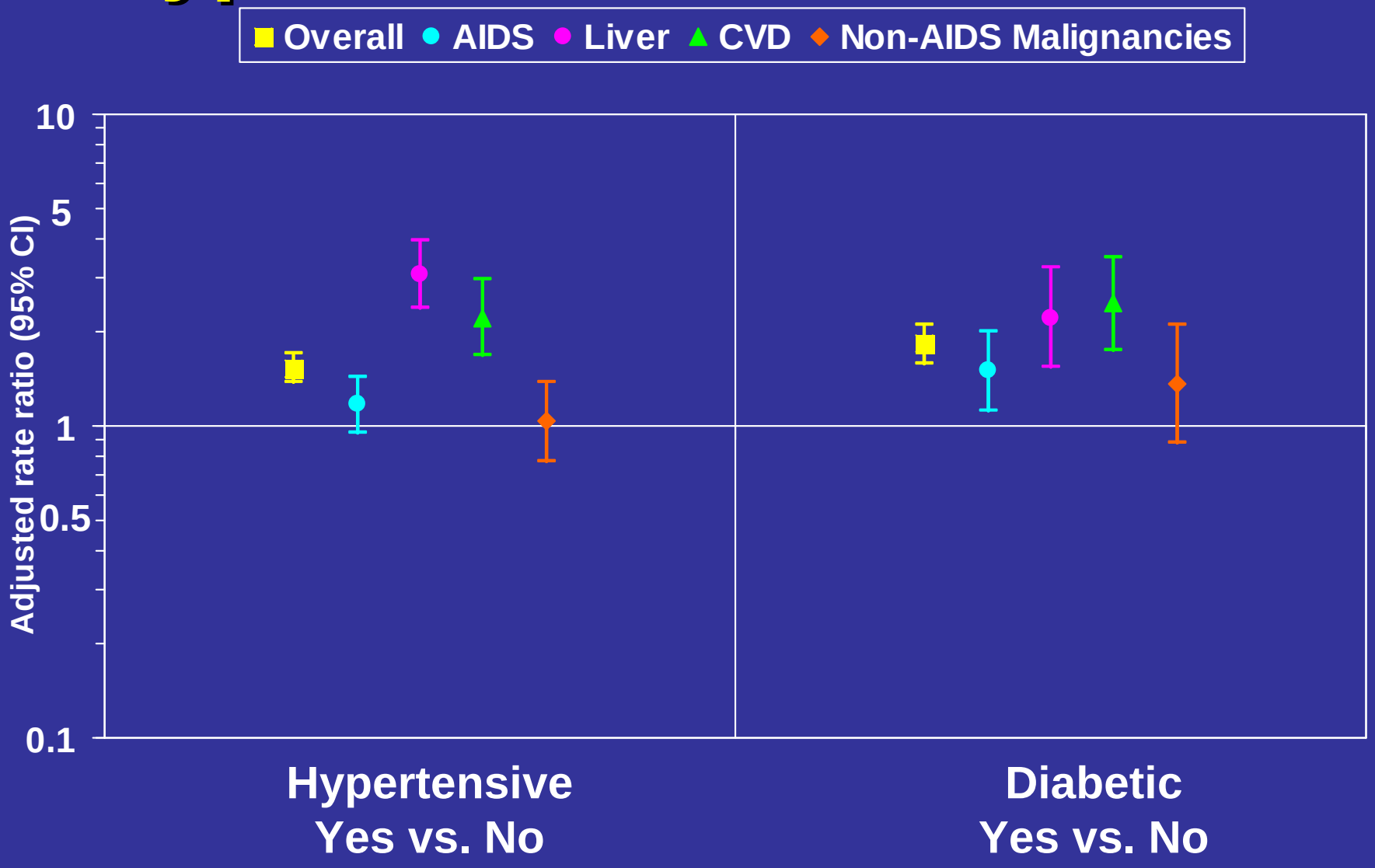

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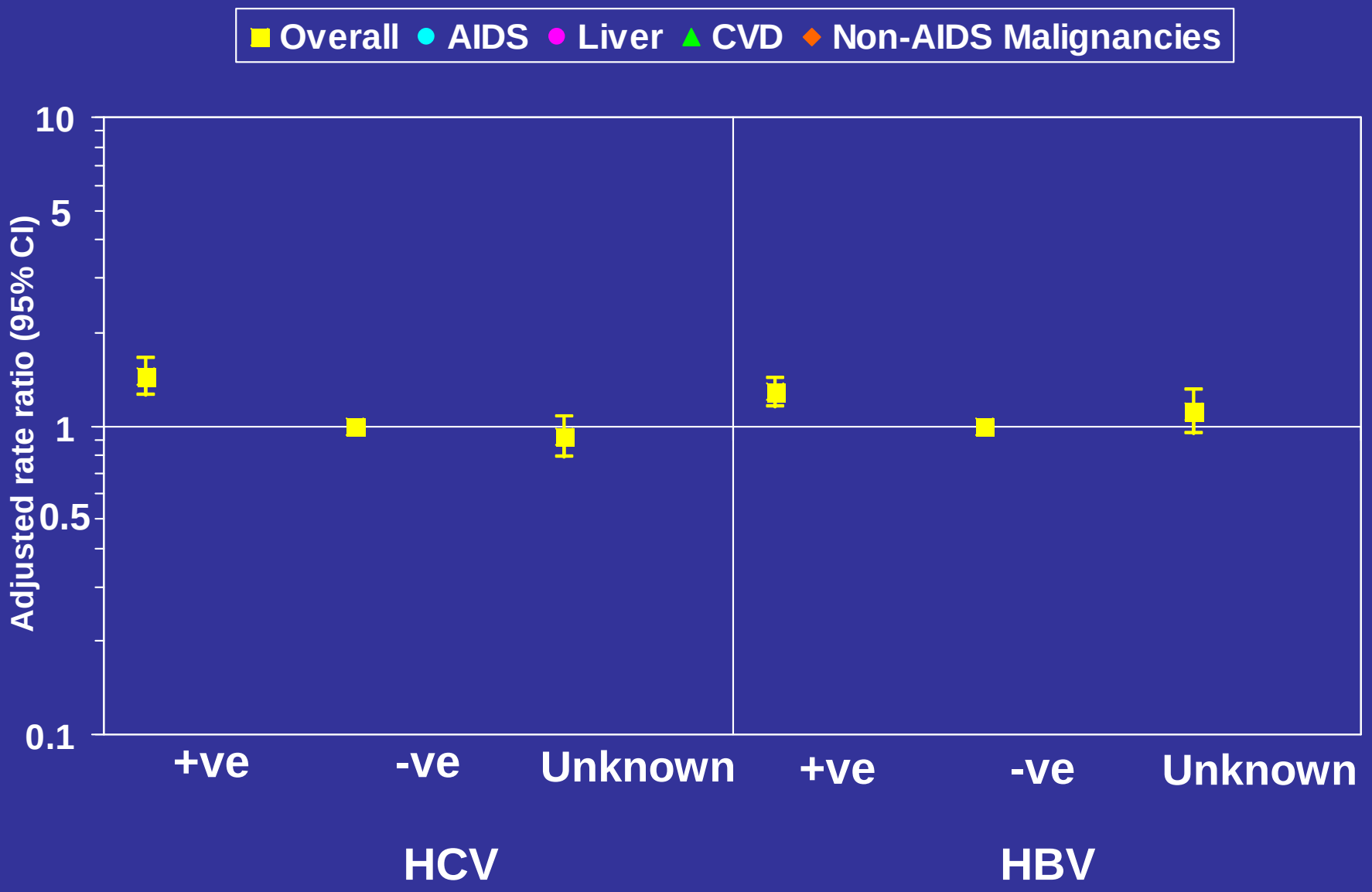
HCV and HBV Status



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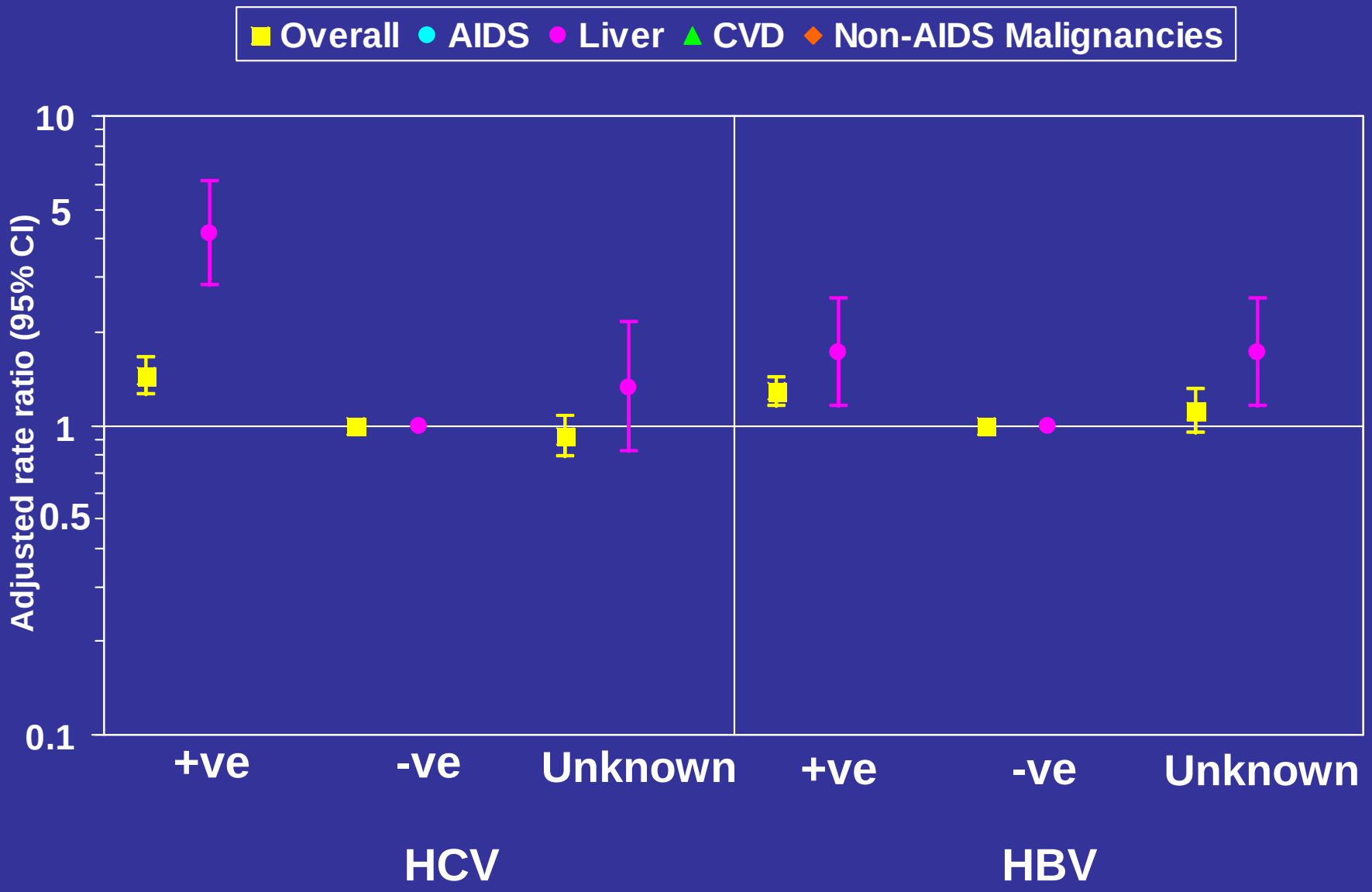

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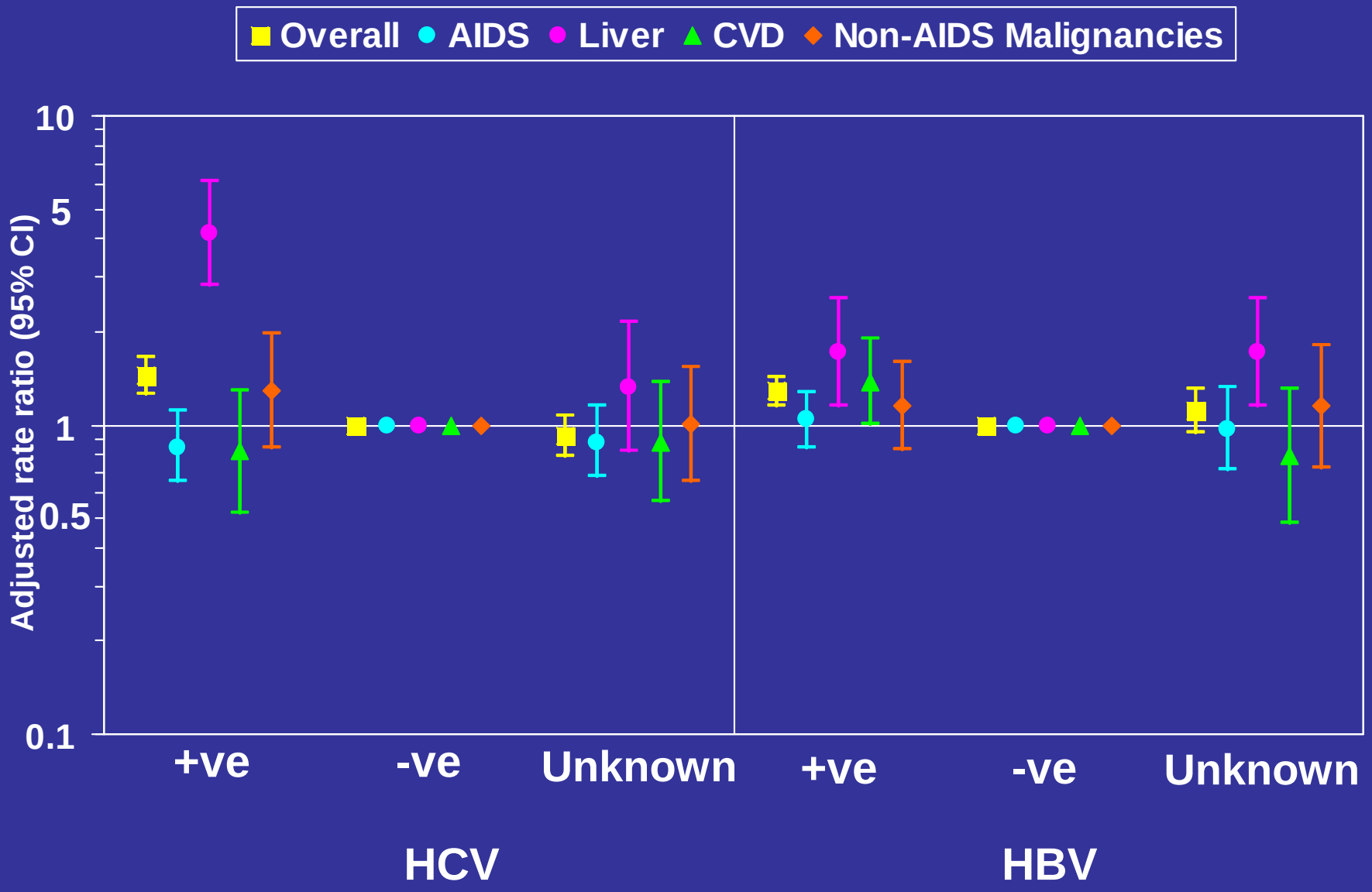
HCV and HBV Status



Modifiable HIV-specific risk factors

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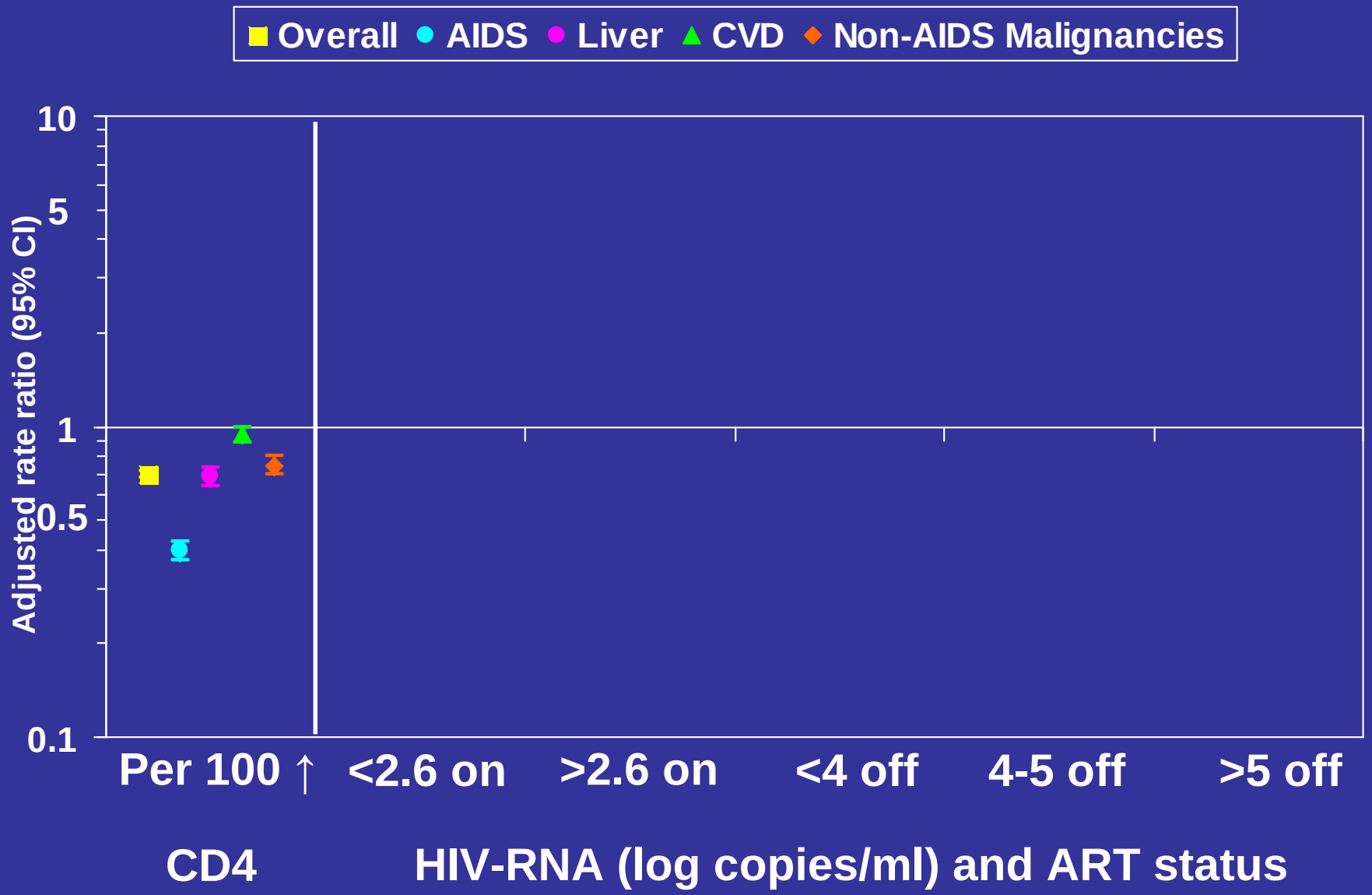
CD4 and HIV-RNA status



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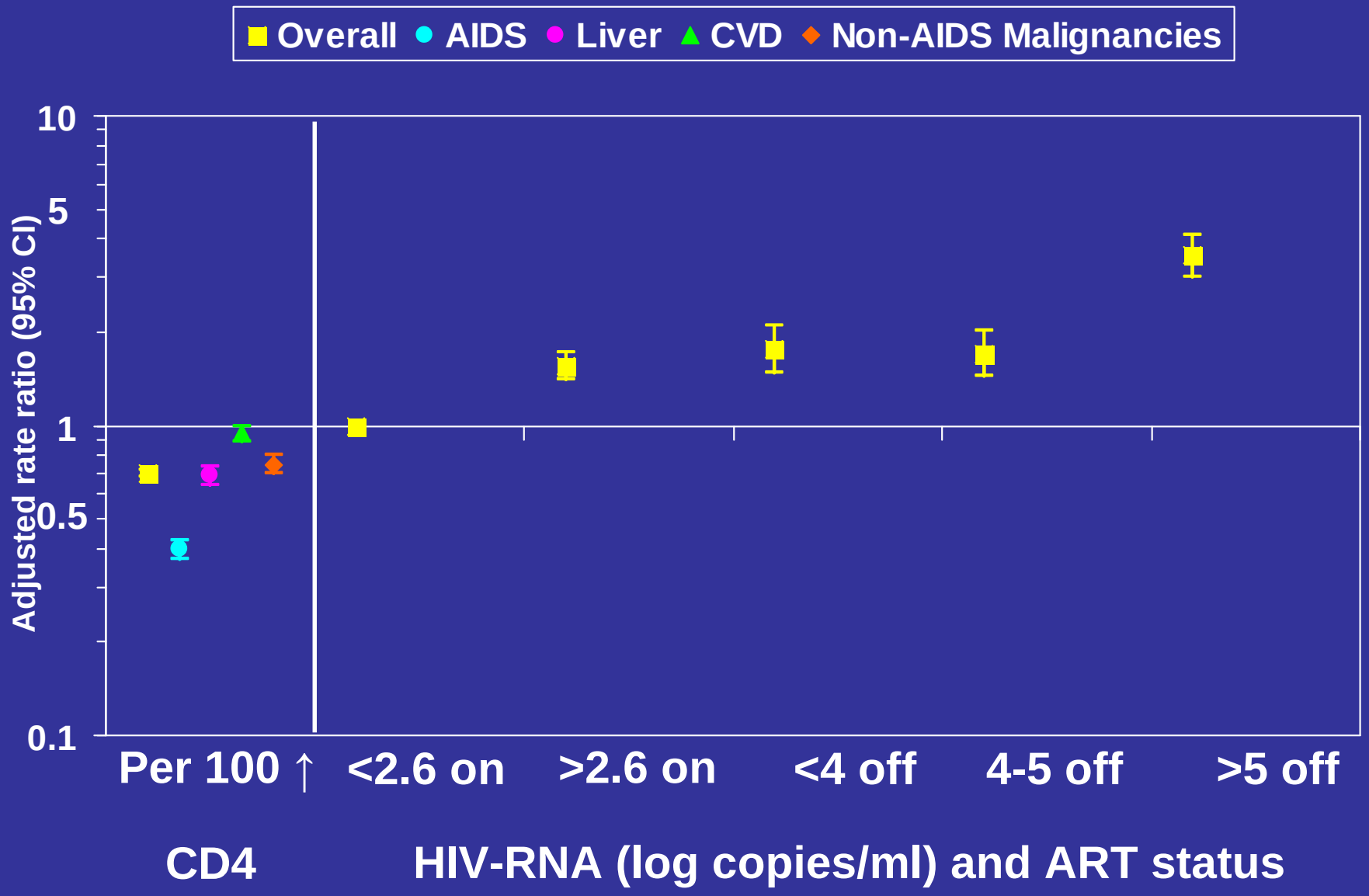
CD4 and HIV-RNA status



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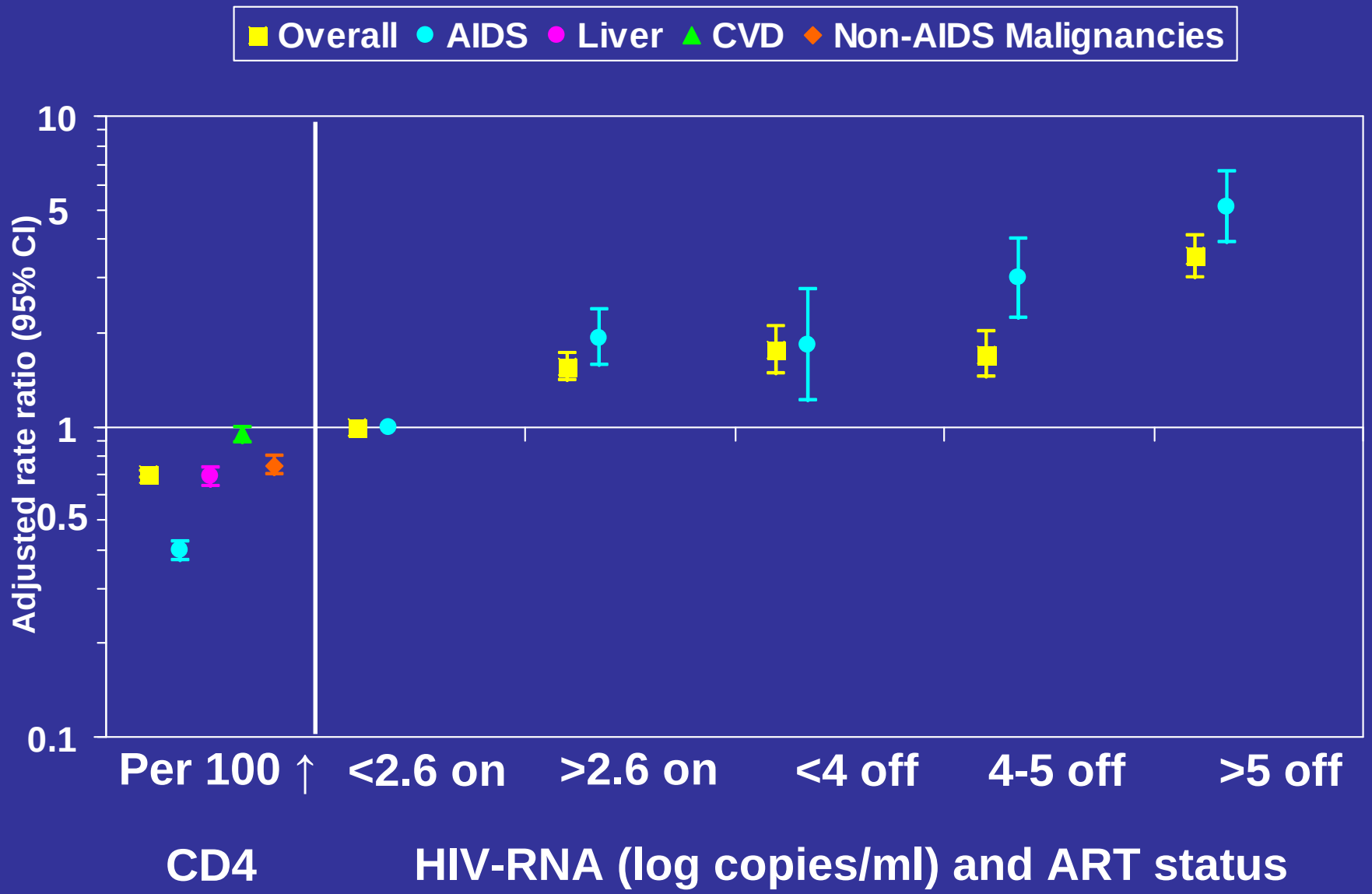
CD4 and HIV-RNA status



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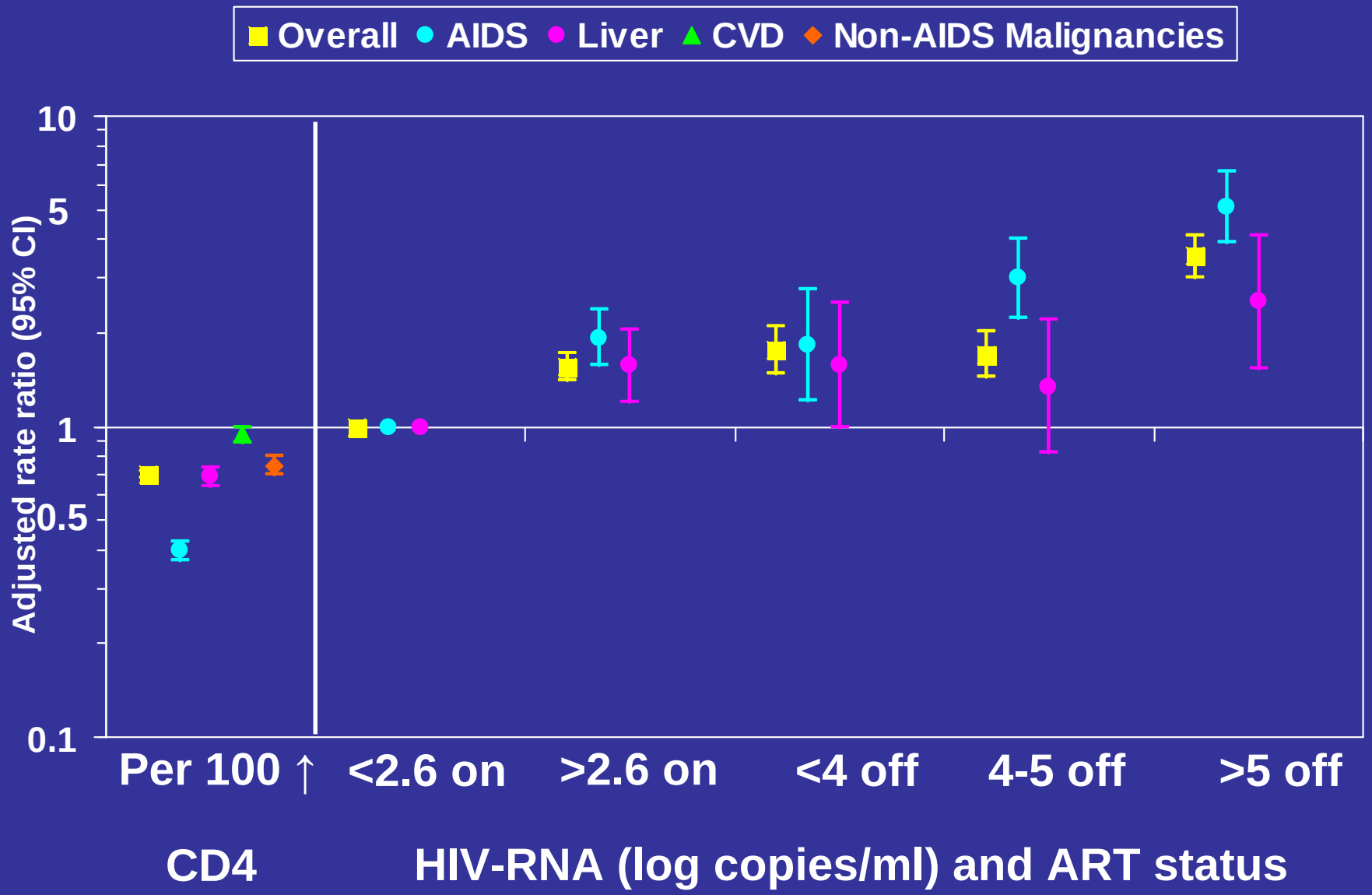
CD4 and HIV-RNA status



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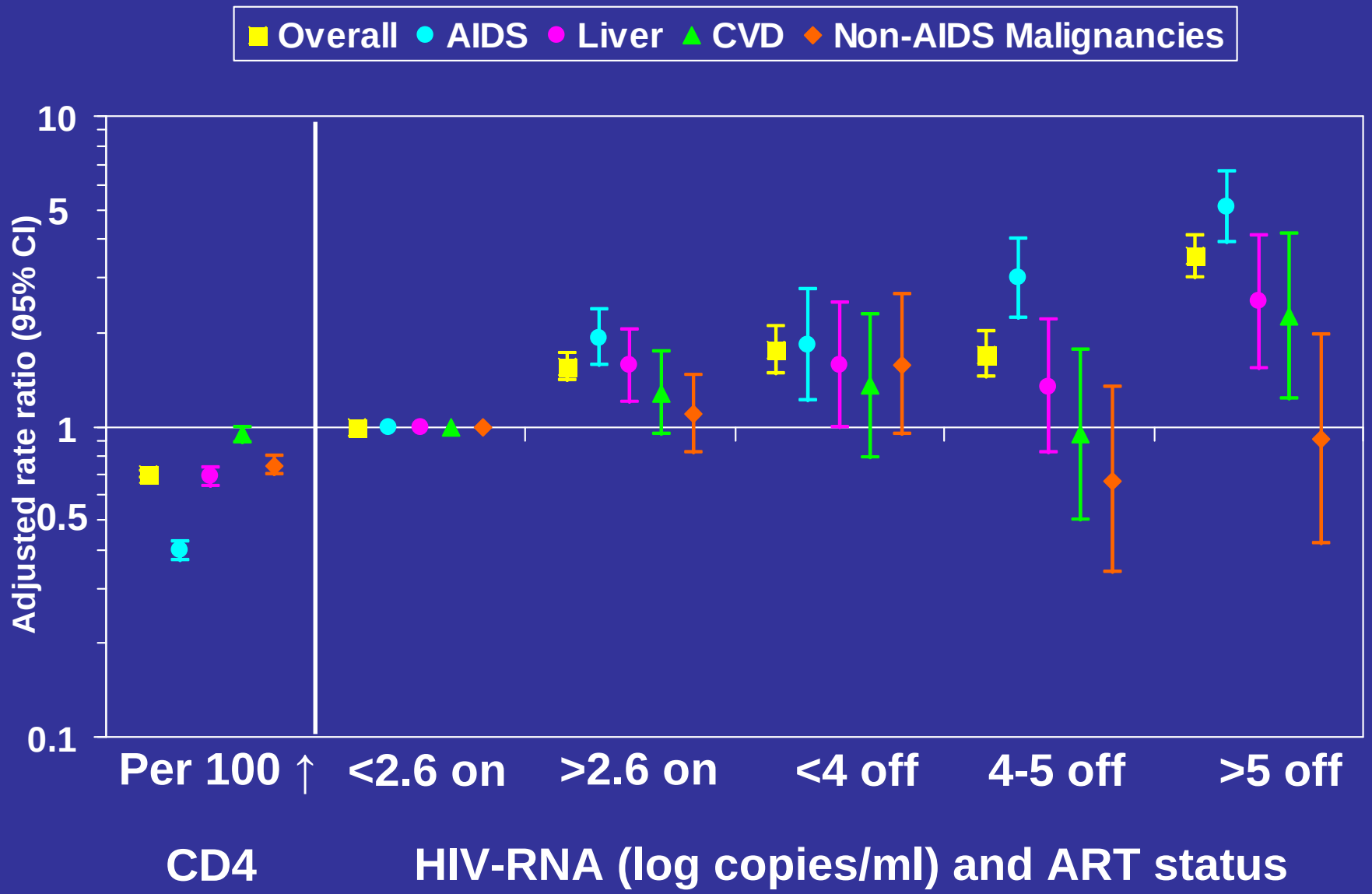
CD4 and HIV-RNA status



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Summary (1)

- This study reiterates the importance of addressing traditional, non-HIV specific, risk factors in order to further reduce death rates in HIV-positive populations
- Additionally, high CD4 cell counts and control of HIV replication is associated with reduced risk of death for some specific non-AIDS related causes
- Further reductions in mortality in HIV-infected populations may only be possible if these factors are appropriately addressed

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Summary (2)

- Large cohort collaborations with systematic ascertainment enable us to investigate factors associated with specific causes of death
- However, even in this study with 160,000 person-years, there is still limited power for some specific causes (e.g. renal disease)
- Although we see an association between the CD4 count/HIV-RNA level and non-AIDS mortality, there is currently no evidence that modifying these markers will reduce the risk of non-AIDS mortality

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D:A:D Study Group

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- **Statisticians:** C Sabin*, A Phillips*, A Kamara, C Smith
- **Community representative:** S Collins*
- **DAD coordinating office:** SW Worm, N Friis-Møller, A Sawitz, J Lundgren*¢
- **Steering Committee:** Members indicated with *; ¢ chair; Additional members: S Storfer*, D Pizzuti*, I Weller*
- **Funding:** 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMEA and a consortium of Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Roche and Tibotec