When should HIV-1 infected persons initiate antiretroviral therapy? Collaborative analysis of HIV cohort studies

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When To Start Consortium of HIV Cohort Studies

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Background

- The CD4 count at which combination antiretroviral therapy (cART) should be initiated is a central, unresolved issue in the care of HIV-1 infected patients
- Recently published guidelines recommend that cART is started in individuals with CD4<350 cells/mm^3
- We analyzed data from a collaboration of HIV cohort studies, employing novel methods to estimate the effect of initiating cART at different CD4 thresholds.

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Antiretroviral Therapy (ART) Cohort Collaboration

University of Alabama: 1917 Clinic Cohort, Birmingham Alabama USA
Aquitaine: Bordeaux University Hospital and four other public hospitals in the Aquitaine region, France
ATHENA (AIDS Therapy Evaluation project Netherlands): All 22 hospitals specialising in HIV medicine in The Netherlands
CHORUS: 4 clinics in the USA (Nashville, New York, San Francisco and LA)
EUROSIDA: 60 centres in 20 countries across Europe
Frankfurt: Klinikum der JW Goethe-Universität Frankfurt
FHDH (French Hospital Database on HIV): National cohort study based on 68 hospitals in France
ICONA (Italian Cohort of Antiretroviral-Naive Patients): cohort based in 65 clinics in Italy
Köln/Bonn: Departments of Internal Medicine at University of Cologne and Bonn, Germany
PISCIS: Catalonia and Balearic islands, Spain
Royal Free: Ian Charleson Centre at the Royal Free Hospital London, UK
South Alberta: Southern Alberta Clinic, Canada
Swiss HIV Cohort Study (7 centres in Switzerland)
Vancouver: St. Paul's Hospital in Vancouver, Canada
VACS: observational cohort study of HIV-positive and matched HIV-negative veterans based on the Veterans Health Administration, USA

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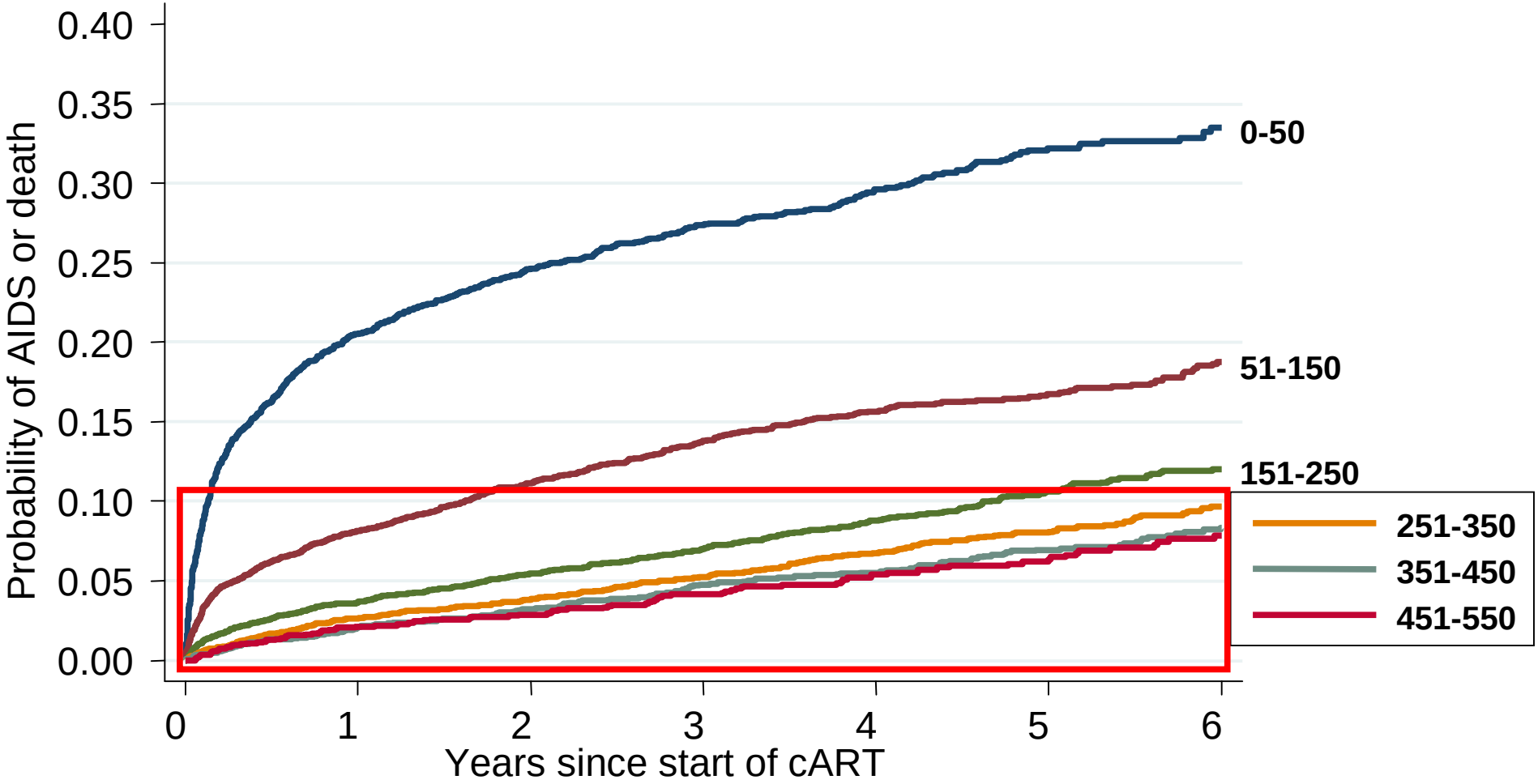
Probability of AIDS or death in ART-naïve AIDS-free non-IDU patients starting cART after 1998



Based on 24,444 patients from 15 cohort studies, 2,366 events in 81,071 person-years of follow up

ART Cohort Collaboration

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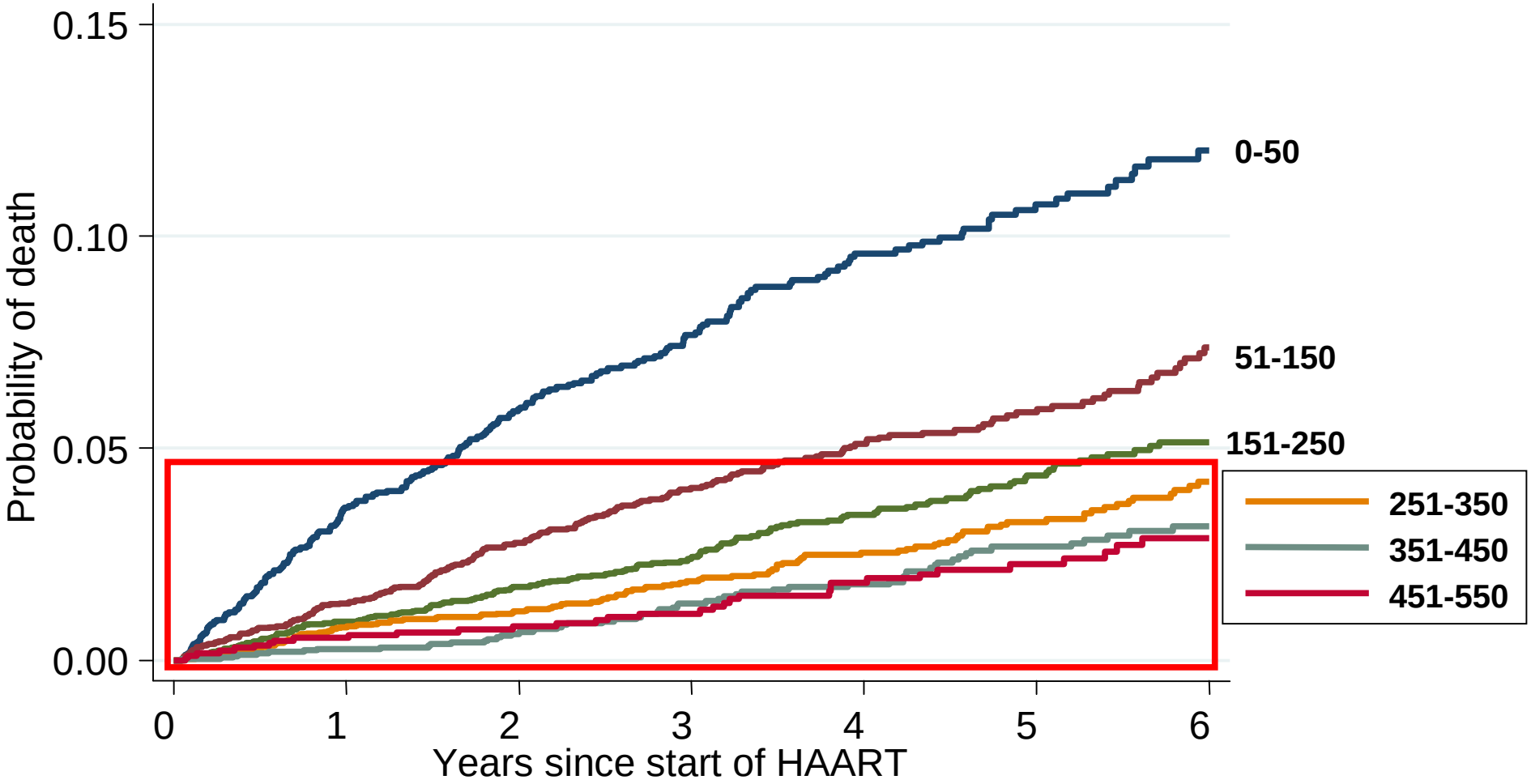

Based on 24,444 patients from 15 cohort studies, 808 deaths in 81,071 person-years of follow up

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Prognosis according to CD4 count at initiation of cART

- Consistent, strong, graded association between CD4 at initiation of cART and subsequent rates of AIDS and death
- **However, analyses of prognosis from the time of starting cART do not tell us the effect of deferring initiation of therapy**

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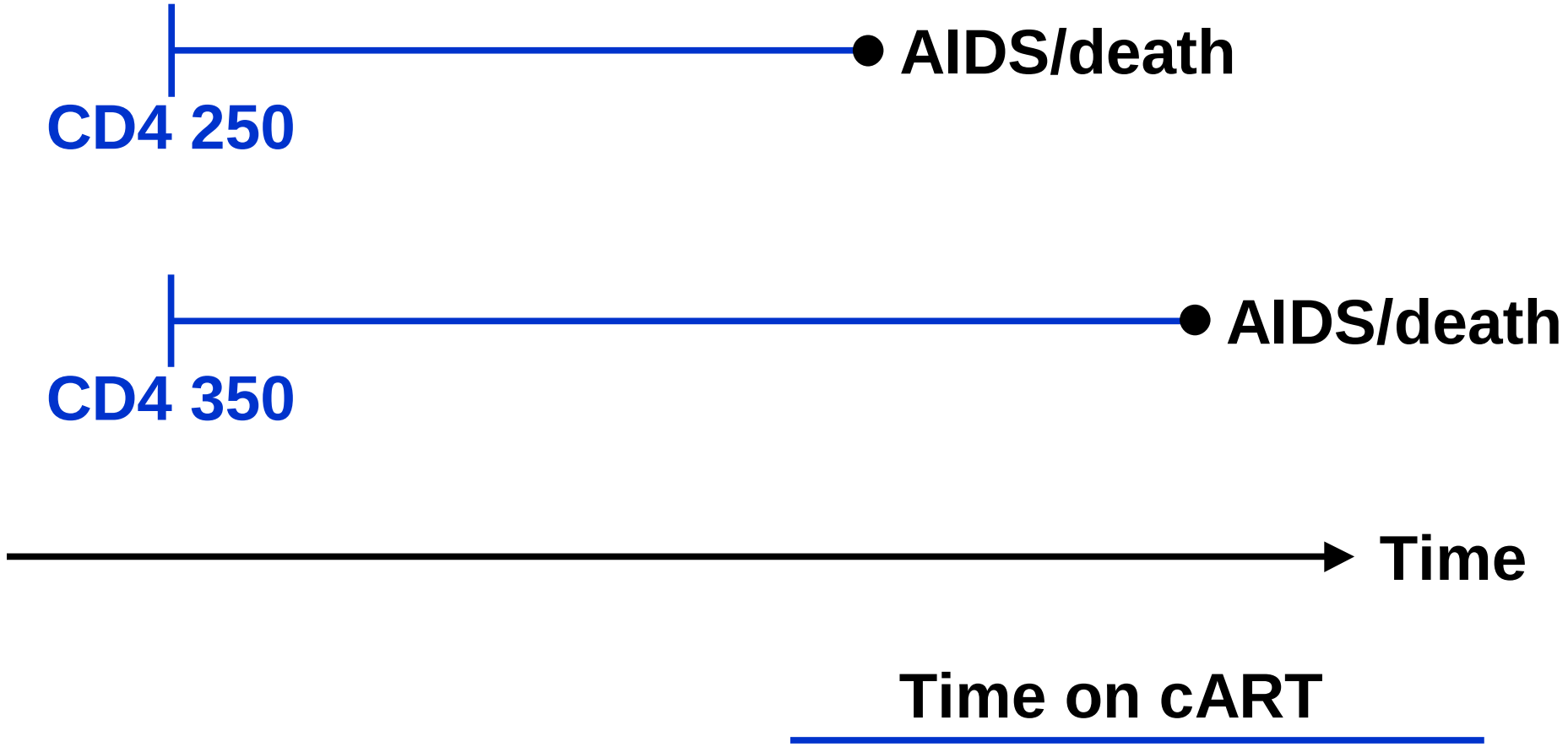

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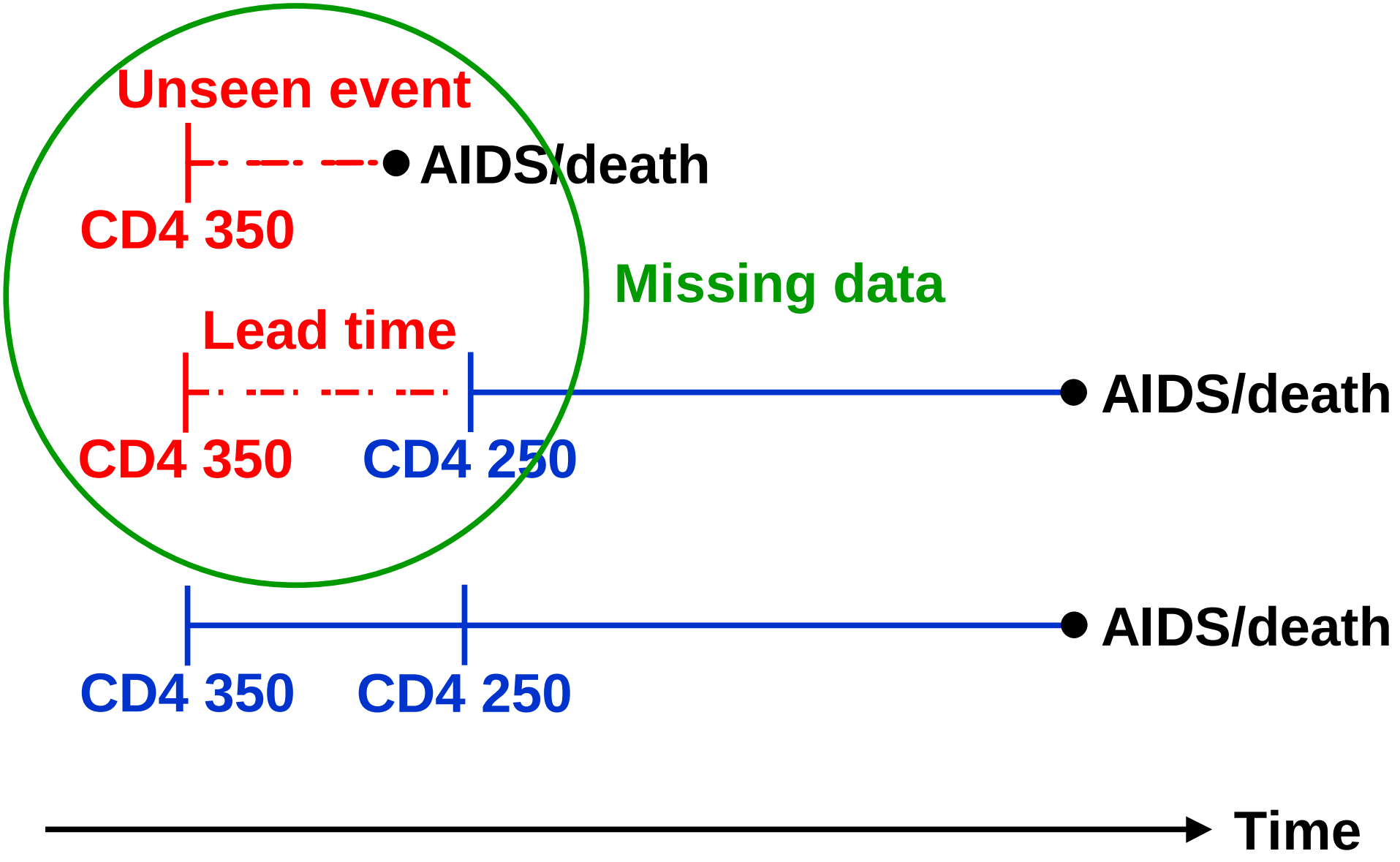

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Accounting for lead times and unseen events

- Aim is to mimic an RCT comparing a strategy of delay to a lower CD4 range with initiation of cART in a higher CD4 range
- Method proposed by Cole et al. (*Stat Med* 2004; **23**: 3351–3363)
  - Use data from the pre-cART era to estimate distributions of lead times and unseen events
  - Impute the (unobserved) lead time for each individual who started in a lower CD4 range, and the unseen events
  - Use multiple imputation to allow for the fact that lead times and unseen events are estimated with error

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Pre-cART data

- Data were combined from 7 cohort studies with patients followed up between July 1989 and December 1995
  - Multicenter AIDS Cohort Study (MACS)
  - Swiss HIV Cohort Study
  - French Hospital Database on HIV ANRS CO4
  - Aquitaine Cohort ANRS CO3
  - Amsterdam Cohort Studies
  - South Alberta Clinic
  - Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) collaboration
- Patients whose presumed HIV transmission was via injection drug use were excluded
- Data were available on 21,247 patients (68,253 person-years of follow up, 5356 AIDS events, 3630 deaths)

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Hazard ratios for deferred compared with immediate treatment

- We compared deferred with immediate initiation of cART in adjacent ranges of width 100 cells/mm^3
  - "defer to 0-100" compared with "initiate at 101-200"
  - "defer to 25-125" compared with "initiate at 126-225"
  - and so on, with increments of 25 cells/mm^3, until…
  - "defer to 351-450" compared with "initiate at 451-550"

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Comparison	% progressing before lower limit	Hazard ratio (95% CI) for AIDS or death	
		Naïve	**Adjusted for lead times and unseen events**
351-450 vs 451-550	0.5 (0.3 to 0.7)	1.04 (0.81 to 1.34)	**0.99 (0.76 to 1.29)**
0-100 vs 101-200	3.7 (3.0 to 4.4)	2.25 (2.01 to 2.51)	**3.35 (2.99 to 3.75)**

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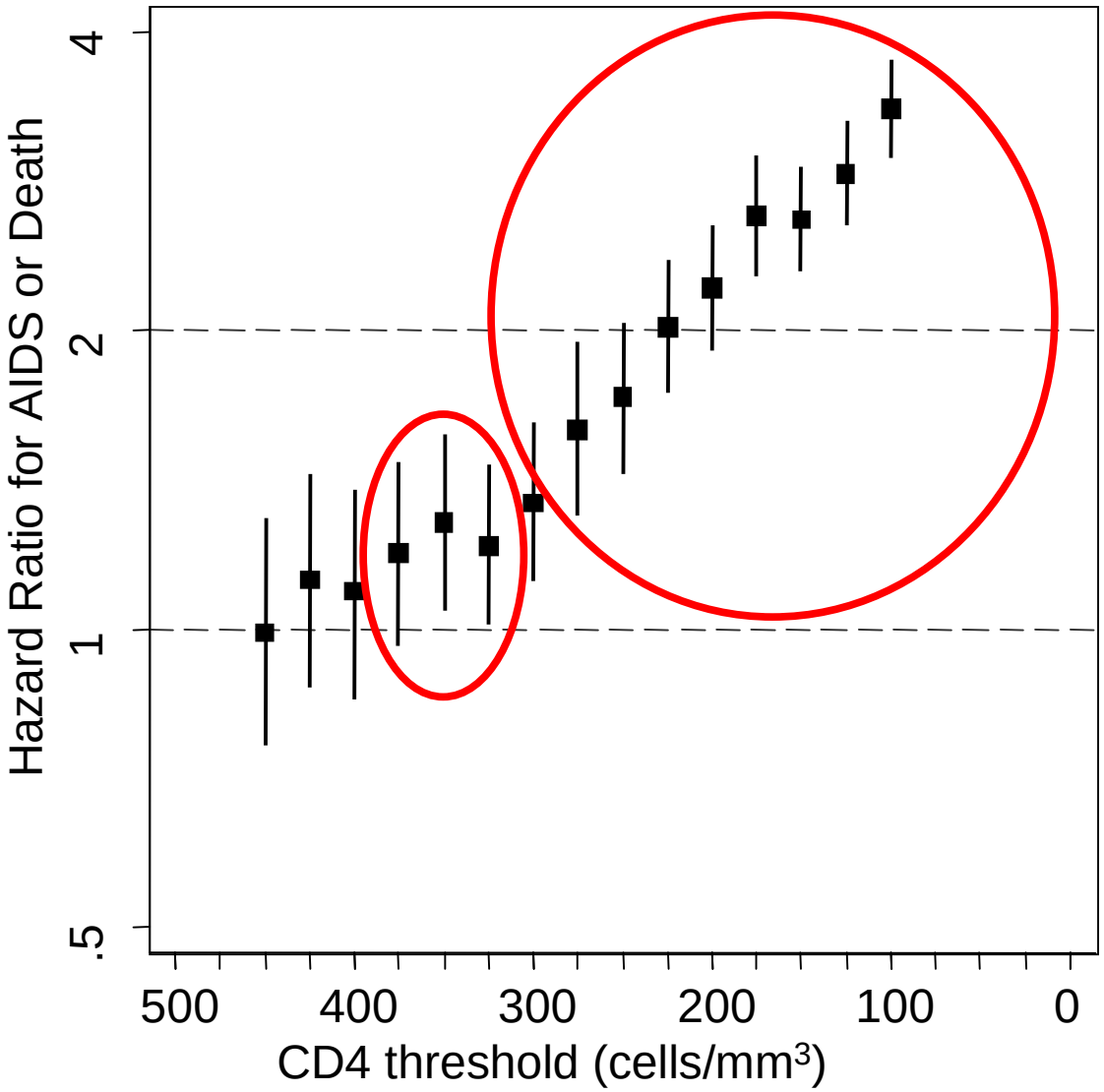
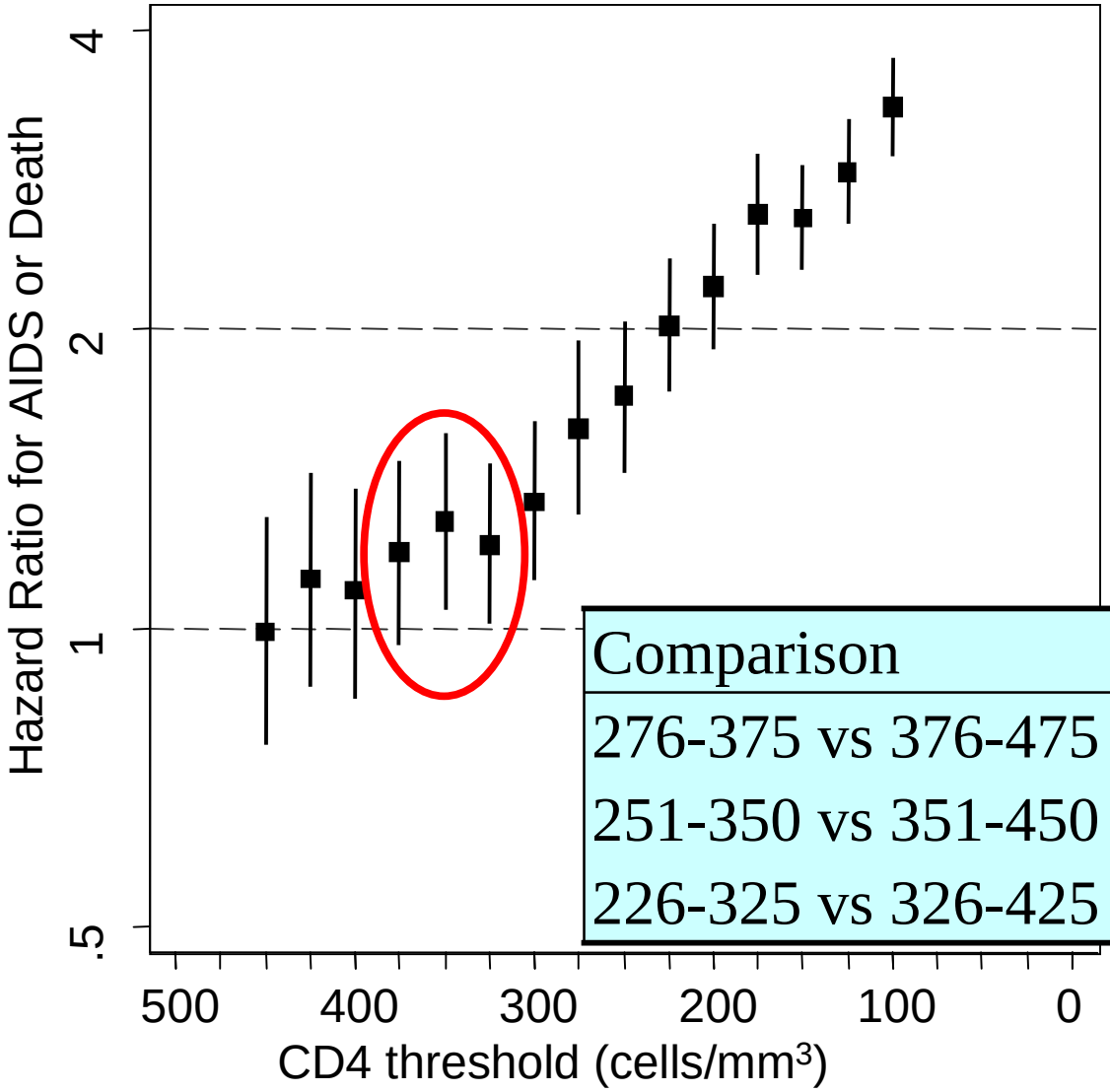
Hazard ratios for AIDS or death, adjusted for lead times and unseen events



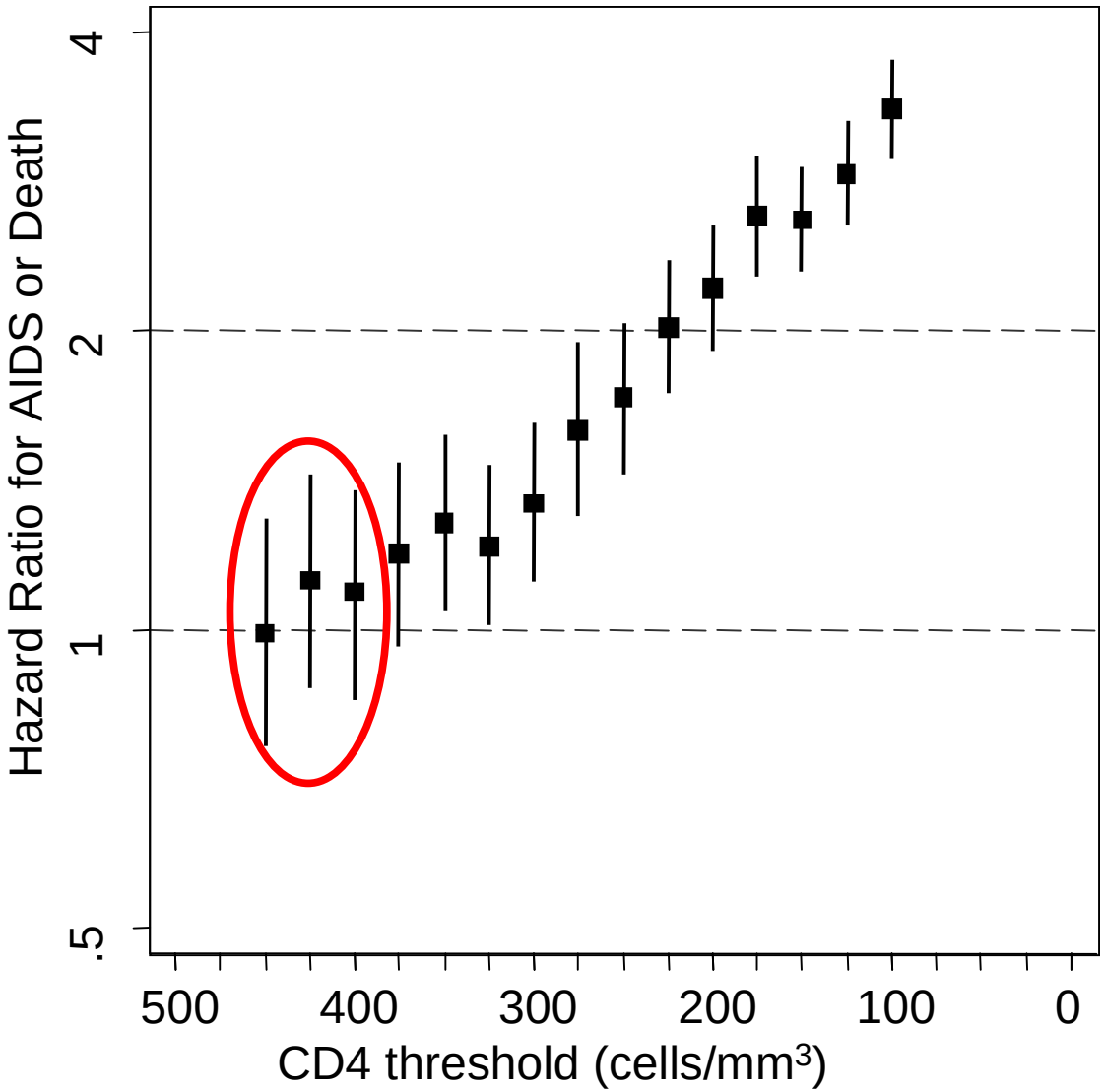
Note that successive comparisons are not statistically independent

Hazard ratios for AIDS or death, adjusted for lead times and unseen events



Comparison	Hazard ratio (95% CI)
276-375 vs 376-475	1.19 (0.96 to 1.47)
251-350 vs 351-450	1.28 (1.04 to 1.57)
226-325 vs 326-425	1.21 (1.01 to 1.46)

Hazard ratios for AIDS or death, adjusted for lead times and unseen events



Estimated effects on mortality

- We repeated all comparisons using death alone as the endpoint, assuming that:
  - cART does not prevent death within two weeks of initiation
  - an AIDS diagnosis will lead to immediate initiation of cART

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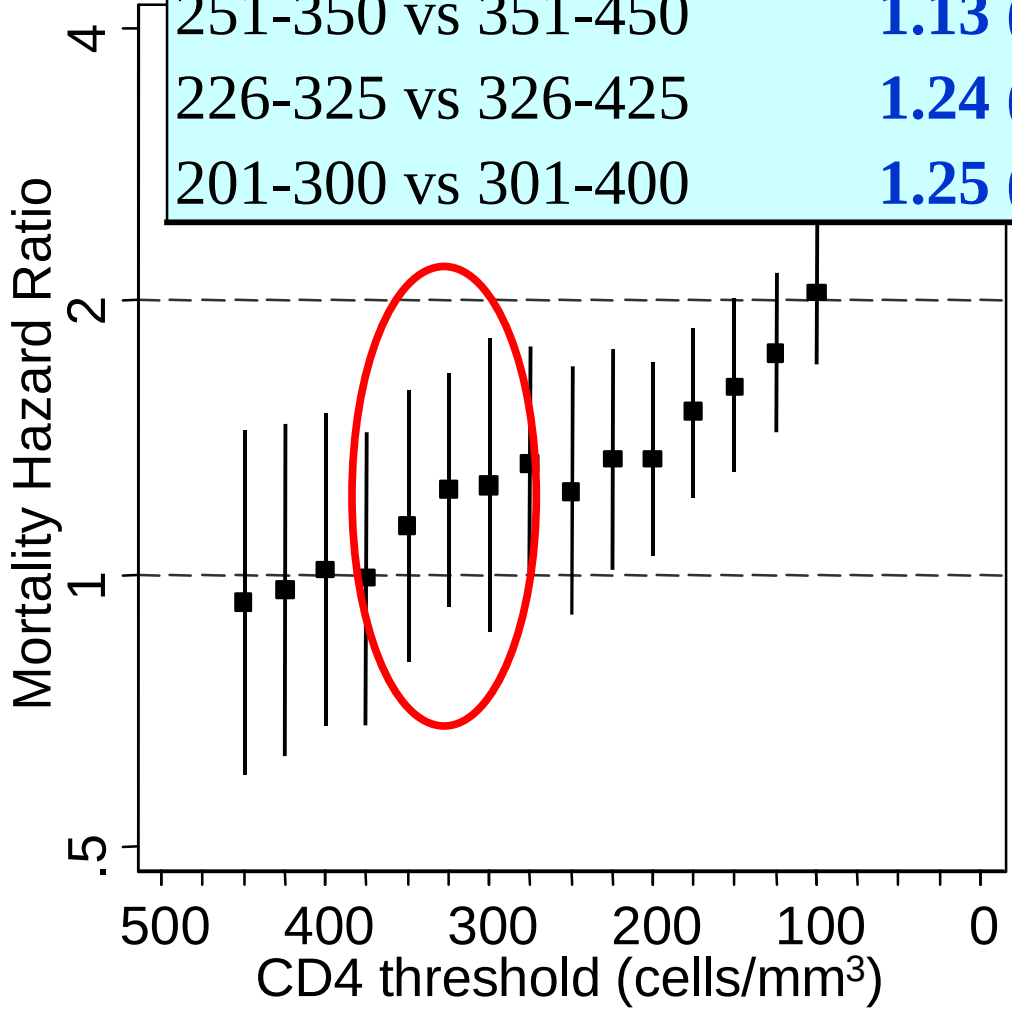
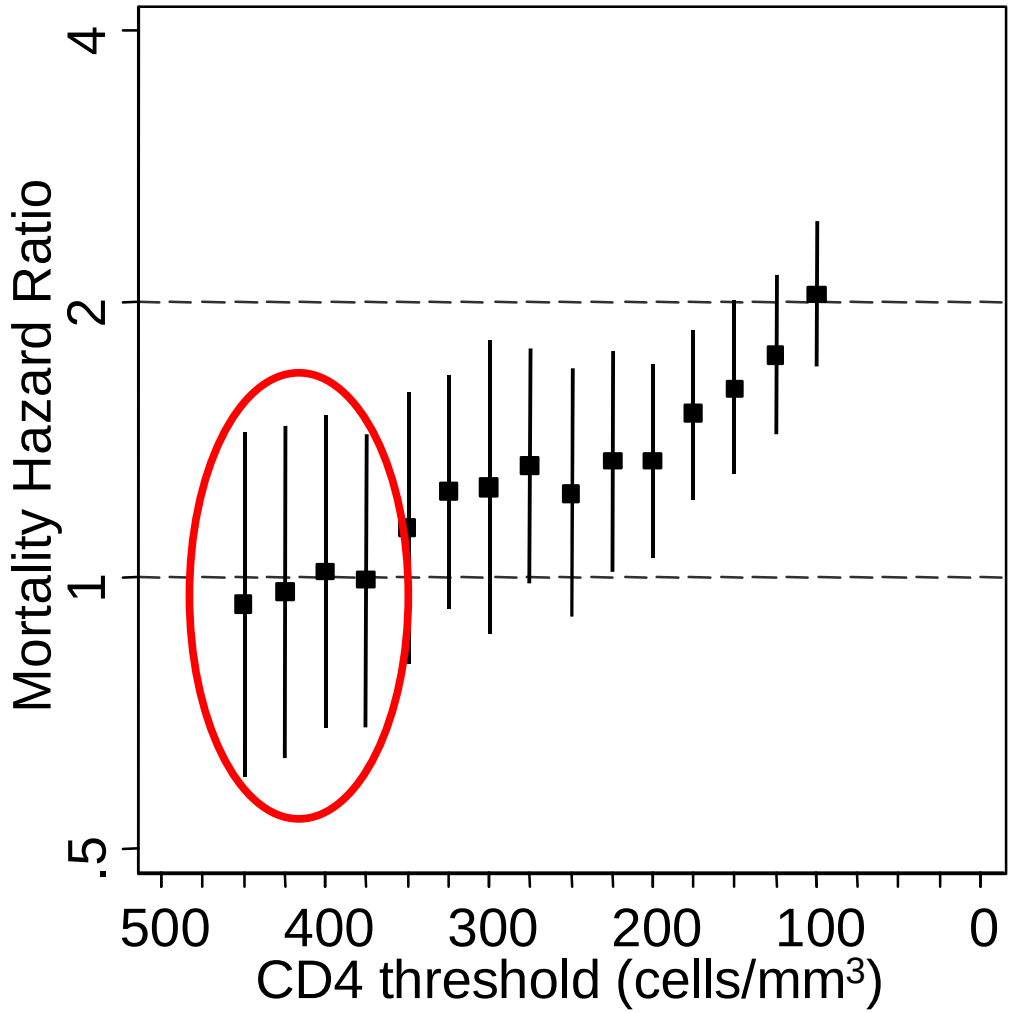
Mortality hazard ratios, adjusted for lead times and unseen events

Comparison	Hazard ratio (95% CI)
251-350 vs 351-450	**1.13 (0.80 to 1.60)**
226-325 vs 326-425	**1.24 (0.92 to 1.67)**
201-300 vs 301-400	**1.25 (0.86 to 1.82)**



Mortality hazard ratios, adjusted for lead times and unseen events



Further analyses, and limitations

- We restricted analyses to non-IDU AIDS-free individuals, but did not otherwise control for confounding factors
  - Results in patients with presumed transmission via IDU were broadly consistent, though with wider CIs
- We could not examine effects on serious non-AIDS events
- The magnitude of estimated differences between higher thresholds could arise from confounding
  - Individuals selected to defer ART may have worse prognosis, for example because they are less likely to adhere to therapy
  - **Only an RCT can deal with both measured and unmeasured confounding factors**
- Additionally, we assumed that pre-cART-era progression rates were representative of rates in untreated individuals

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Conclusions

- Delaying treatment to below 250 cells/mm^3 is clearly associated with an increased risk of AIDS and death
  - Supports efforts to identify undiagnosed HIV infection
- Delaying treatment to below 350 cells/mm^3 also appears associated with an increased risk of AIDS and death
- These are observational analyses: we cannot exclude confounding
- For higher CD4 thresholds, differences in absolute risk were relatively small
- We hope that these findings help guide physicians and patients balance treatment benefits and toxicities in deciding when to initiate ART

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