HIV Infection, HIV Treatment and Risk for Cardiovascular Disease

Issues in study design and analysis

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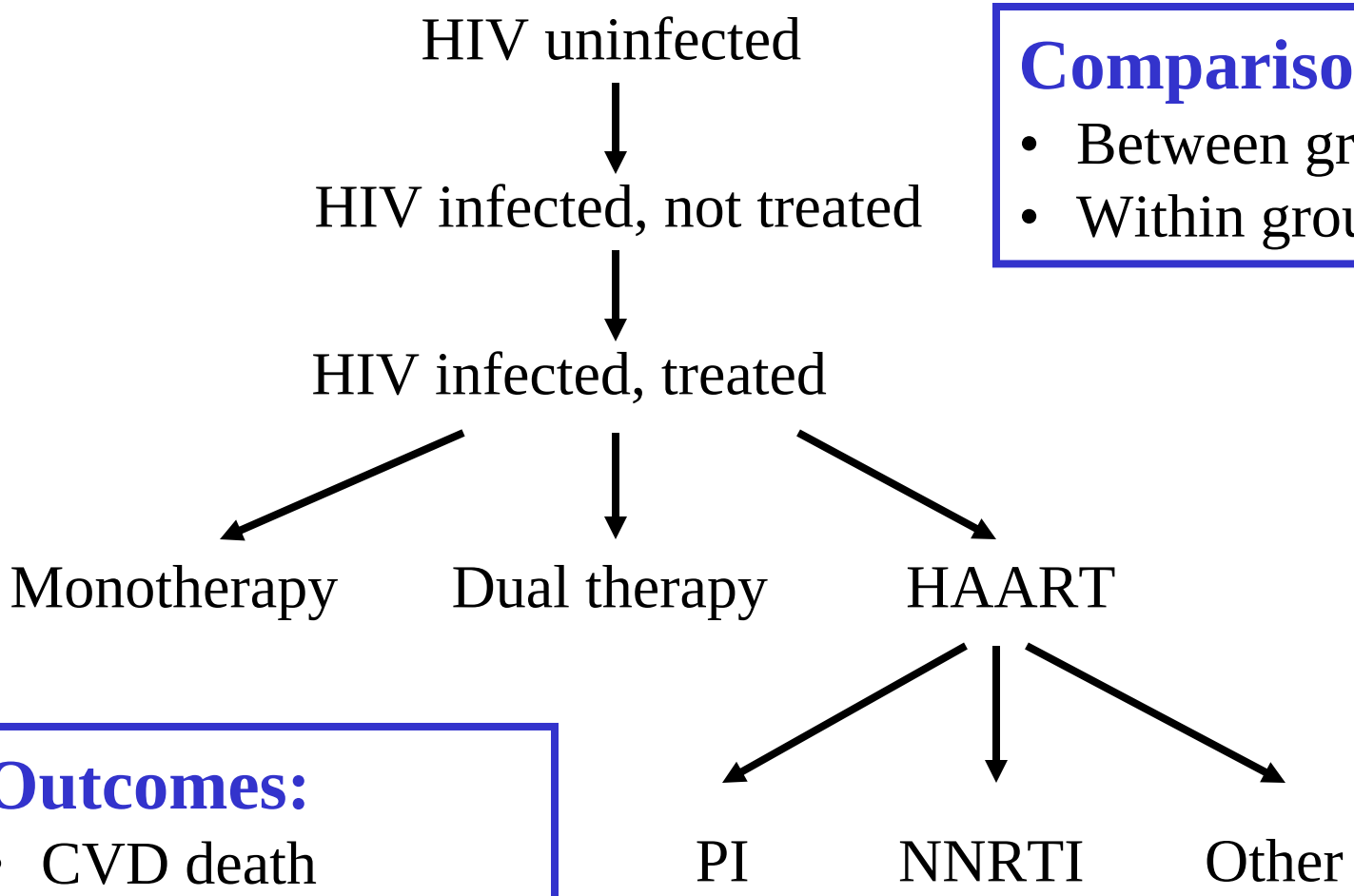
Outline

- Questions being addressed
- Estimating associations with CVD
  - Direct
  - Indirect
- Methodological issues
- Issues in modelling cardiovascular risk from multiple cohorts

What's the question?

- Does HIV infection affect the risk of CVD?
- Does ART, or some types of ART, affect CVD risk in HIV-infected individuals?
  - Overall?
  - Excluding direct effects of HIV infection on cardiovascular risk?
- By how much does ART, or some types of ART, affect CVD risk in HIV-infected individuals?
- Is the increase in CVD risk associated with ART sufficient to:
  - Offset beneficial effects of ART on progression of HIV infection?
  - Justify special efforts to counsel HIV-infected individuals?
  - Justify (e.g.) automatic use of lipid-lowering therapy?
- Might the ART-associated increase in CVD risk become sufficient to justify some of these in the future, as HIV-infected individuals age and/or the effectiveness of therapy declines?

Study design



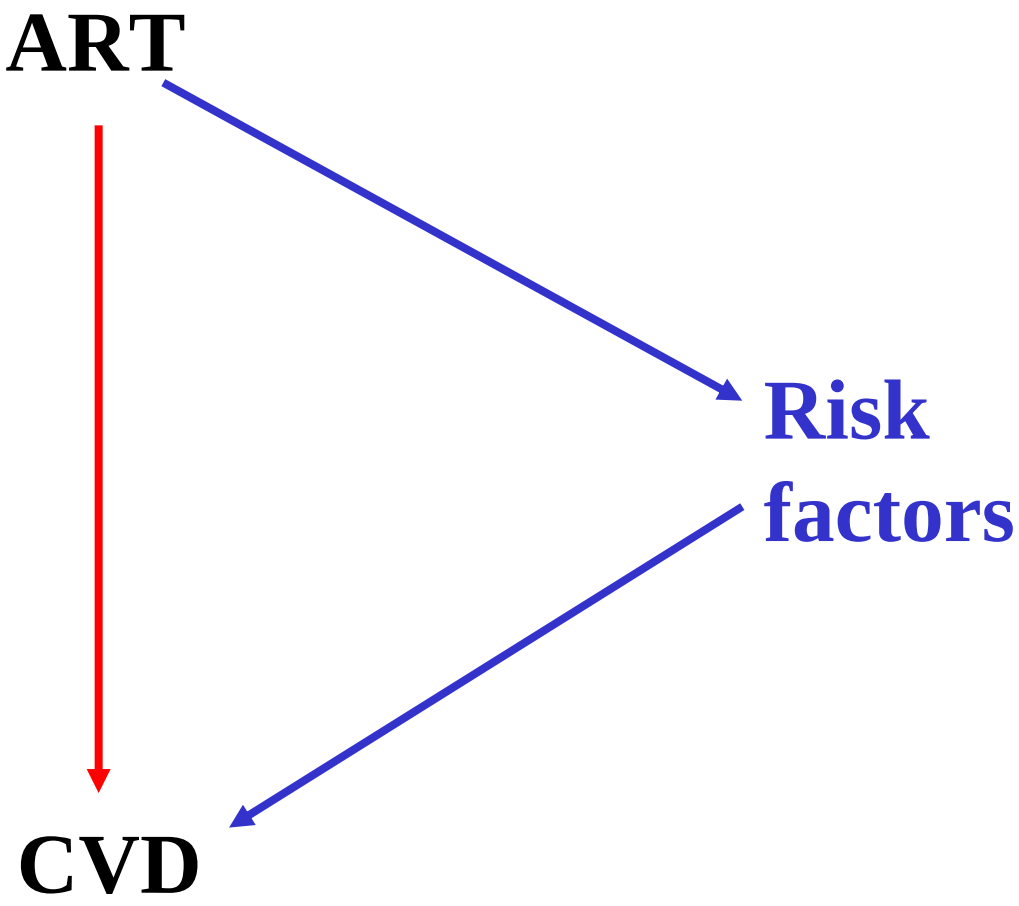
Comparisons:

- Between groups
- Within groups, over time

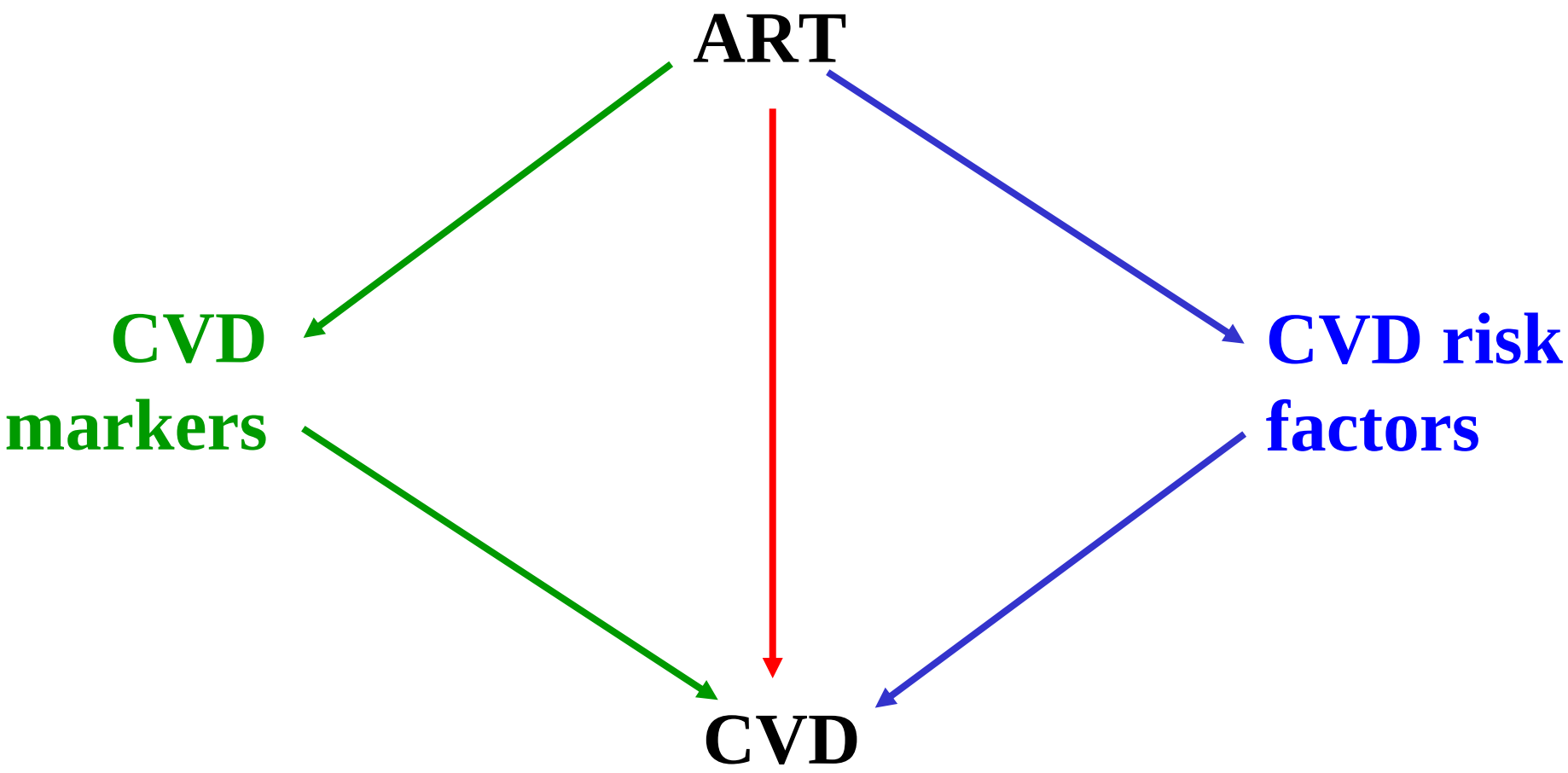
Outcomes:

- CVD death
- Markers (e.g. IMT)
- Risk factors

Triangulation of direct and indirect evidence will be necessary



We will need to compare results from three lines of evidence



Strategies to estimate the association between HAART and CVD risk

- Direct
  - Compare CVD (in large studies!), or markers of CVD, within or between populations
  - Methodological issues
    - What comparison groups, what confounders?
    - How to compare/separate the (adverse) effect of HAART on CVD risk with the beneficial effects of HAART on progression?
    - Are associations consistent in different patient groups, of between populations?
    - If physicians are already allocating treatments on the basis of CVD risk then RCTs may be the only way to assess the implications of particular HAART regime for CVD risk

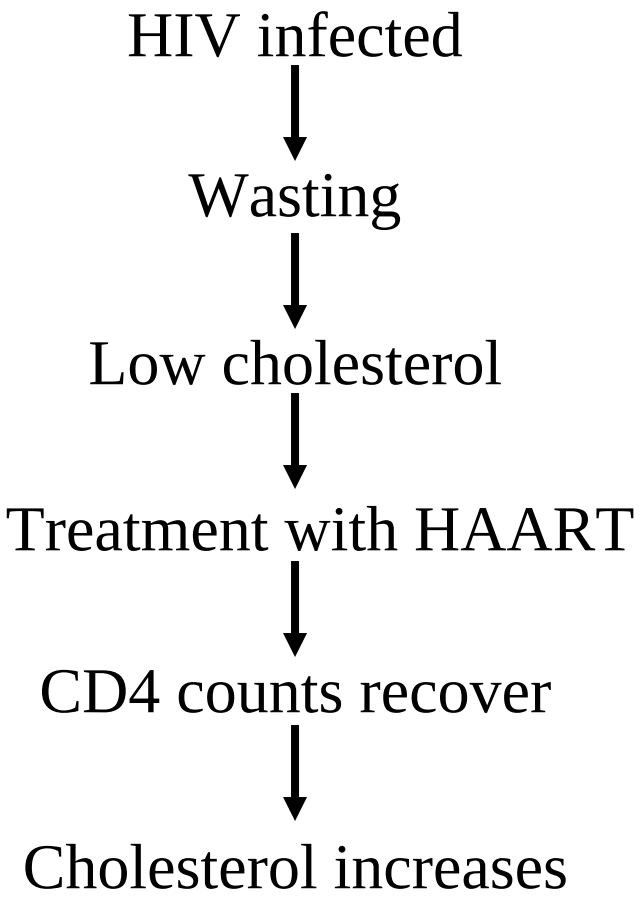
Strategies to estimate the association between HAART and CVD risk

- Indirect
  1. Estimate the effect of ART on risk factors for CVD
  2. Model the effects of changes in risk factors on the risk of CVD

  Methodological issues:
  - Are there consistent effects of ART on CVD risk factors?
  - Do ART-induced differences in risk factors have the same effect as population differences?
  - How to model the effects of risk factors on CVD risk?
    - Are existing models applicable to existing patient populations (time, place)?
    - Do we need to develop new models?

Direct evidence – methodological issues

- **Are comparisons with HIV-uninfected groups useful?**
  - Arguably the "effect" of HAART can only be examined meaningfully in HIV-infected individuals
- **What do we mean by the effect of HAART on MI risk?**



Similarly, behaviours that increase the risk of CVD are/were a rational response to low life expectancy before HAART.

If effective treatments lead to reduced smoking/cholesterol intake, does that count as a protective effect of treatment on CVD risk?

Choice of "confounders" in these analyses will require careful thought!

Direct evidence – which study design?

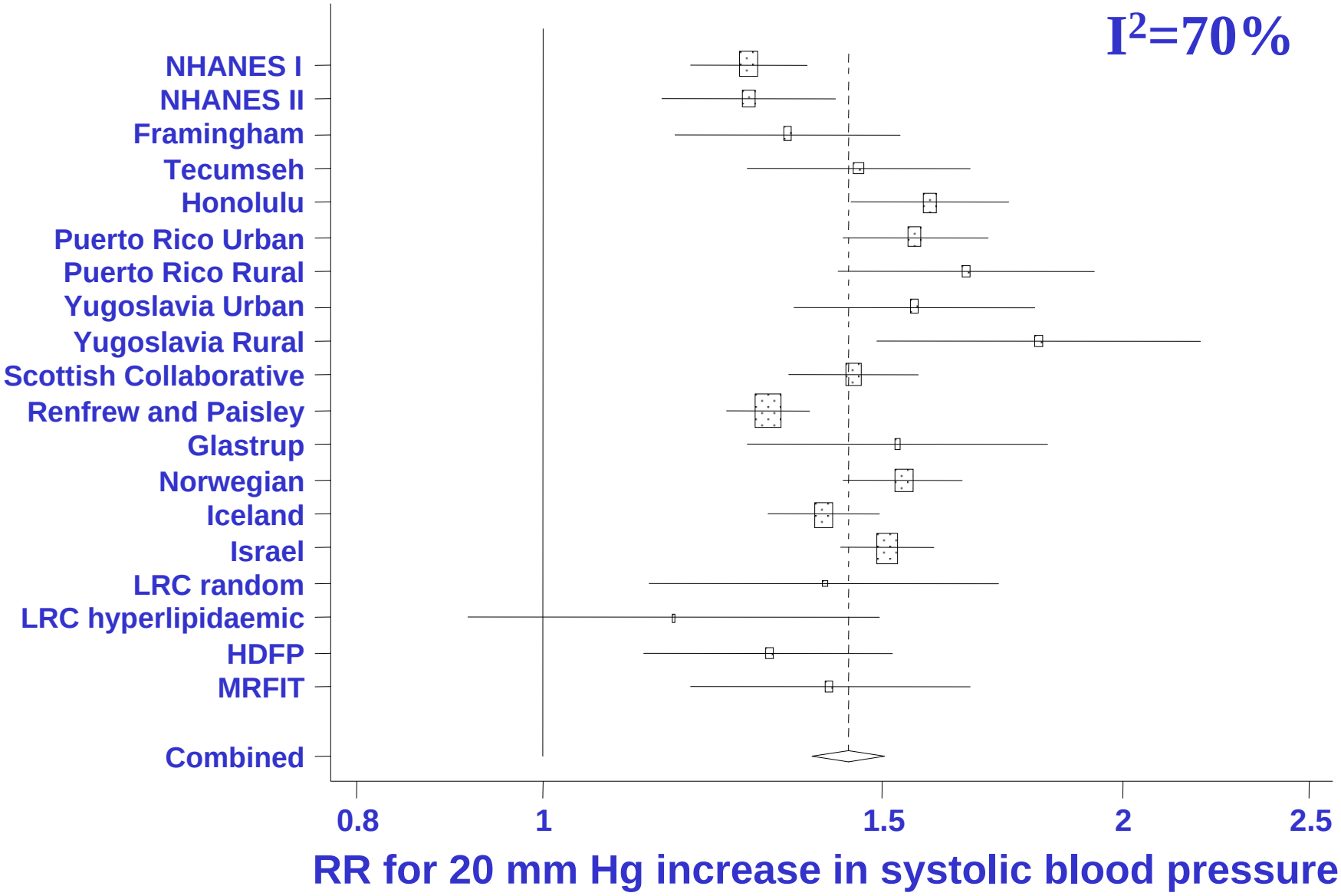
- Confounding by indication can make observational studies of the effect of treatment uninterpretable
  - Time for simple trials?
    - In patients starting HAART
    - In patients with CD4 counts above the usual threshold?
- Cohort studies have provided the best direct evidence so far:
  - Very large studies needed, difficult to decide on comparison groups, difficult to measure all confounders
- Case control studies?
  - Potential for nesting within existing cohorts, but then would there be any advantage?
  - Nested case control studies useful if we want to measure confounders in detail, and can do this retrospectively

Indirect evidence – methodological issues

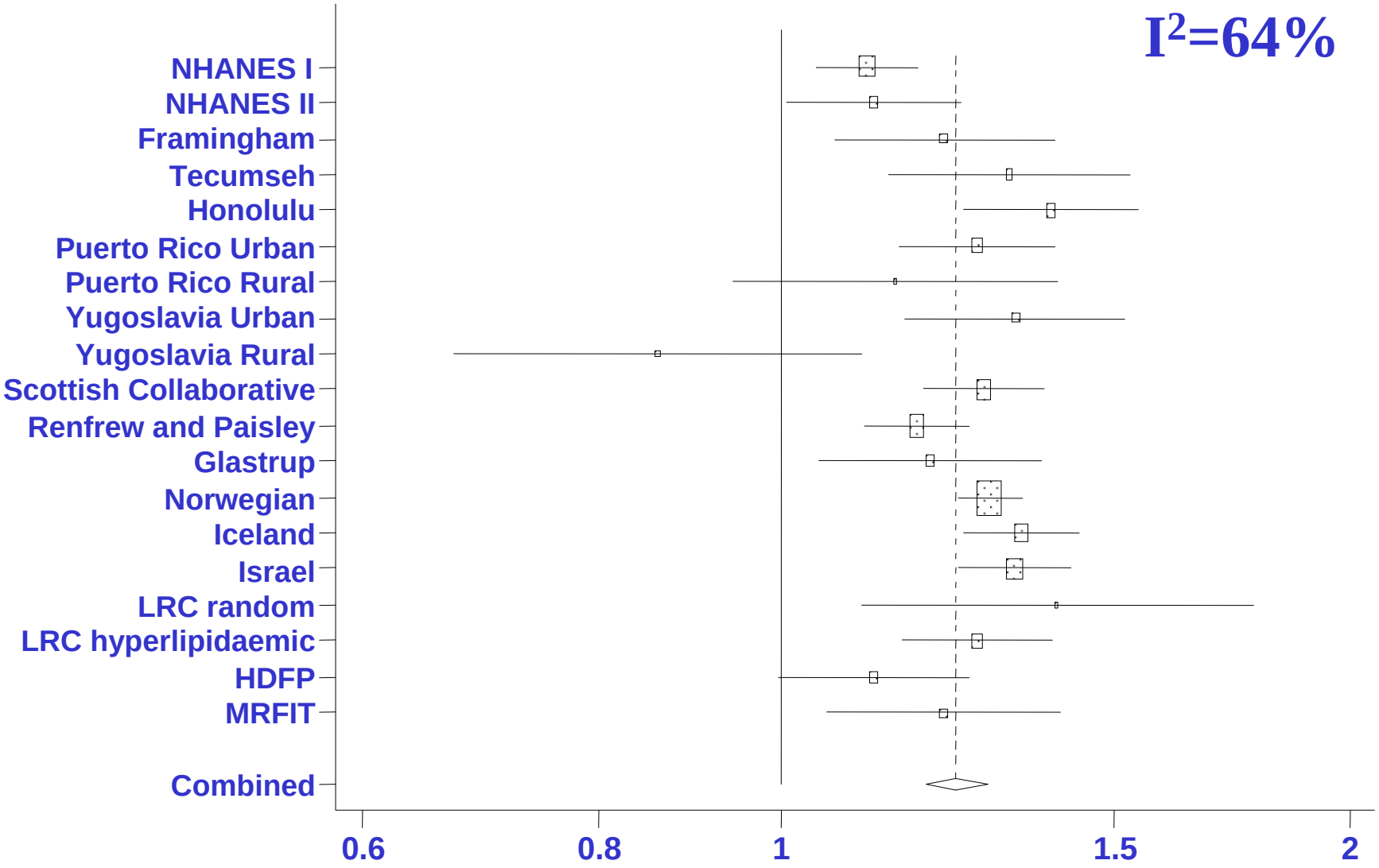
- We will need to compare **absolute** increases in the risk of CVD with absolute reductions in the risk of progression to AIDS/HIV-related death
- So we will have to combine:
  - Estimated levels of CVD risk factors in patients treated with particular HAART combinations for particular lengths of time, with
  - Estimated increases in CVD risk associated with the difference between these values and those expected in the absence of treatment
- Existing models for the risk of CVD (in particular the Framingham equations) are known to require recalibration to estimate absolute CVD risks in different populations

Development of models for the effect of HAART-associated changes in CVD risk factors on the risk of CVD in HIV-infected patients

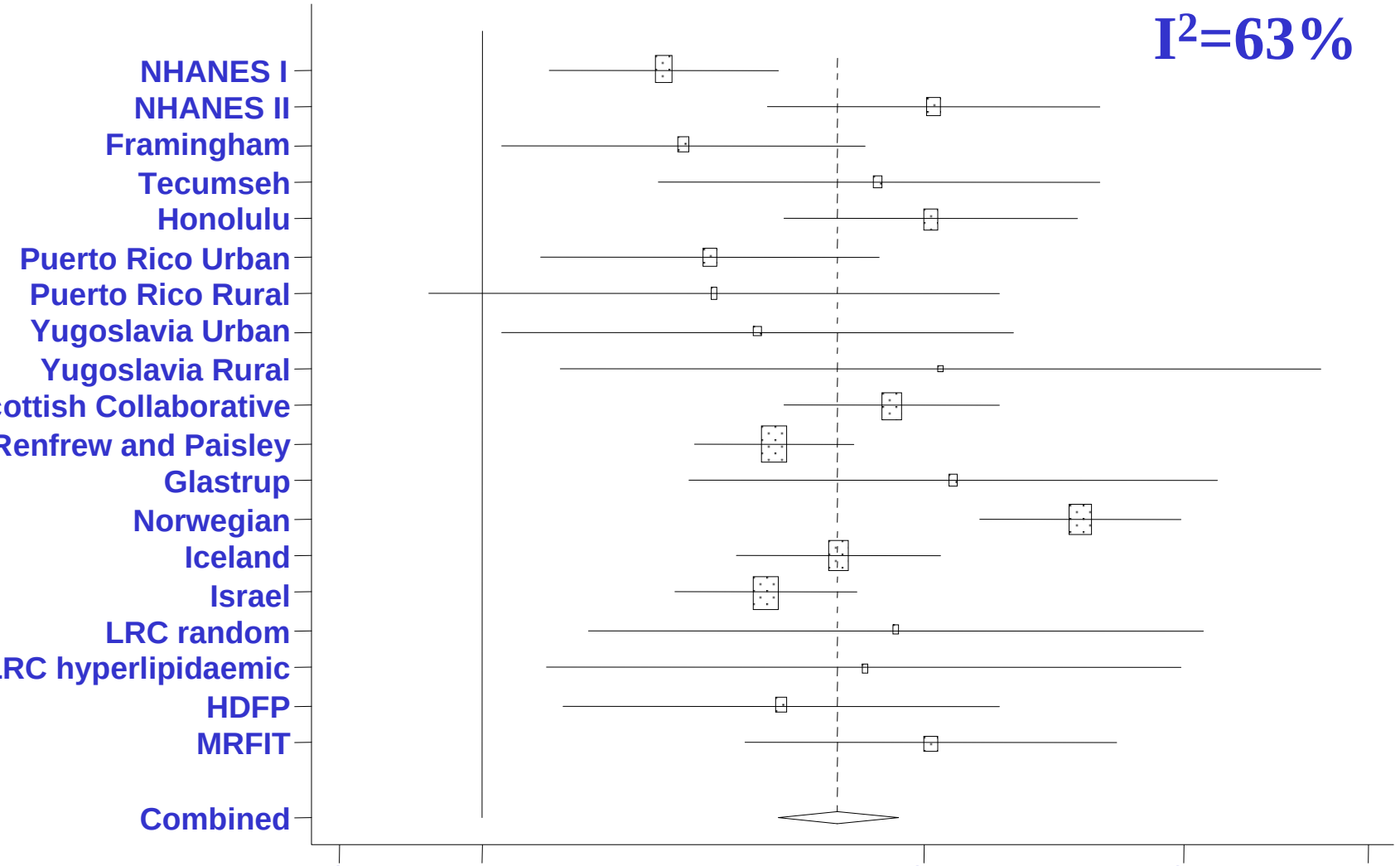
Diverse Populations collaboration

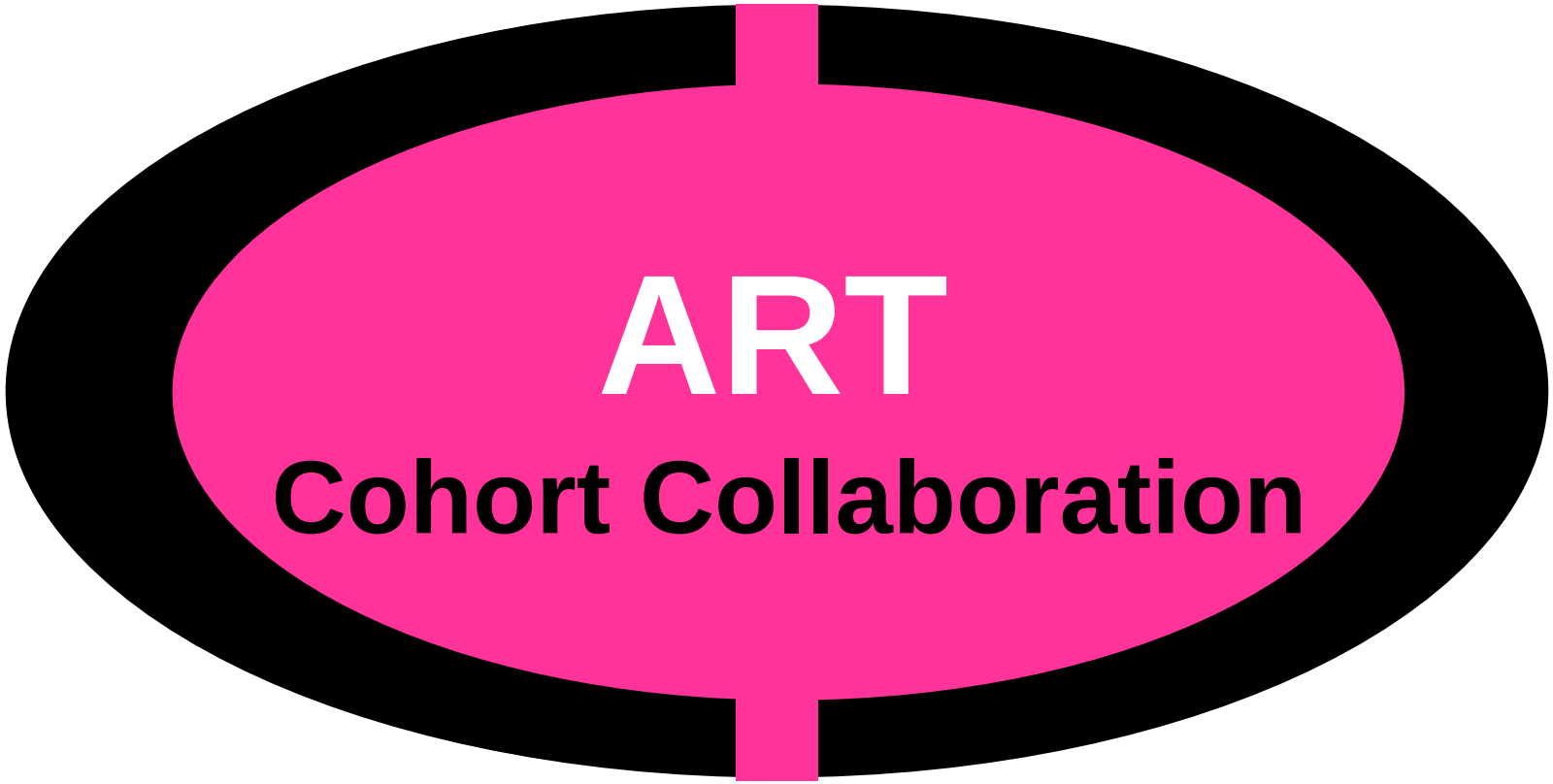


Diverse Populations collaboration



Diverse Populations collaboration





Defining prognosis in the era of potent antiretroviral therapy

Contributing Cohorts

ROCO (AntiPROtéases Cohorte): cohort of patients who started protease inhibitor containing regimens at 47 centers in France

uitaine: Bordeaux University Hospital and four other public hospitals in the Aquitaine region, France

HENA (AIDS Therapy Evaluation project Netherlands): All 22 hospitals specialising in HIV medicine in The Netherlands

IORUS: 4 clinics in the United States (Nashville, New York, San Francisco and Los Angeles)

ROSIDA: 60 centres in 20 countries across Europe

ankfurt: Klinikum der JW Goethe-Universität Frankfurt

DH (French Hospital Database on HIV): National cohort study based on 68 hospitals in France

DNA (Italian Cohort of Antiretroviral-Naive Patients): cohort of treatment-naïve patients based in 65 clinics in Italy

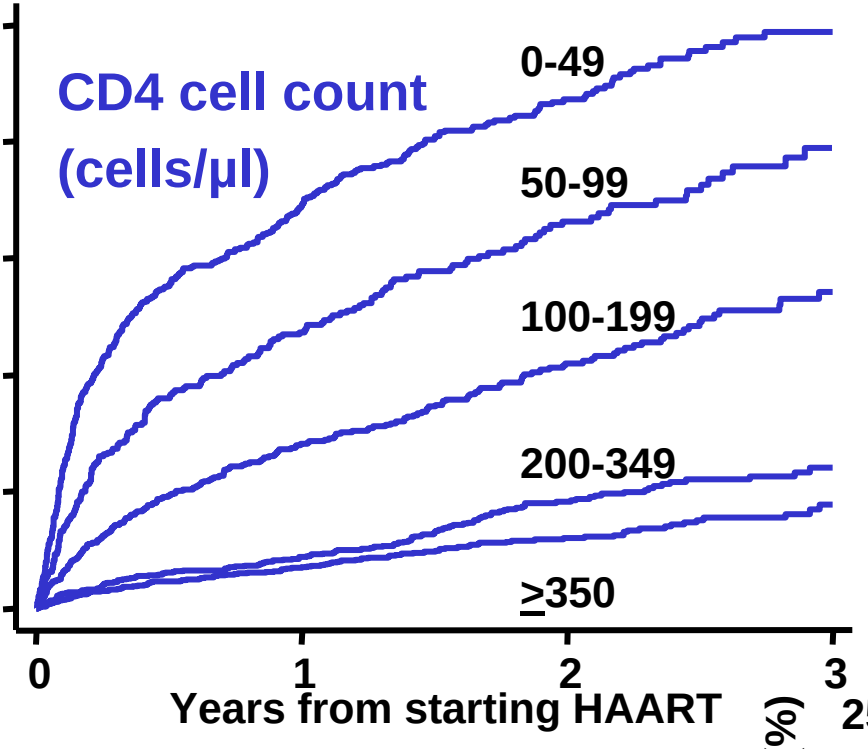
ln/Bonn: Departments of Internal Medicine at University of Cologne and Bonn, Germany

yal Free: Ian Charleson Centre at the Royal Free Hospital London, UK

uth Alberta: Southern Alberta Clinic, Canada

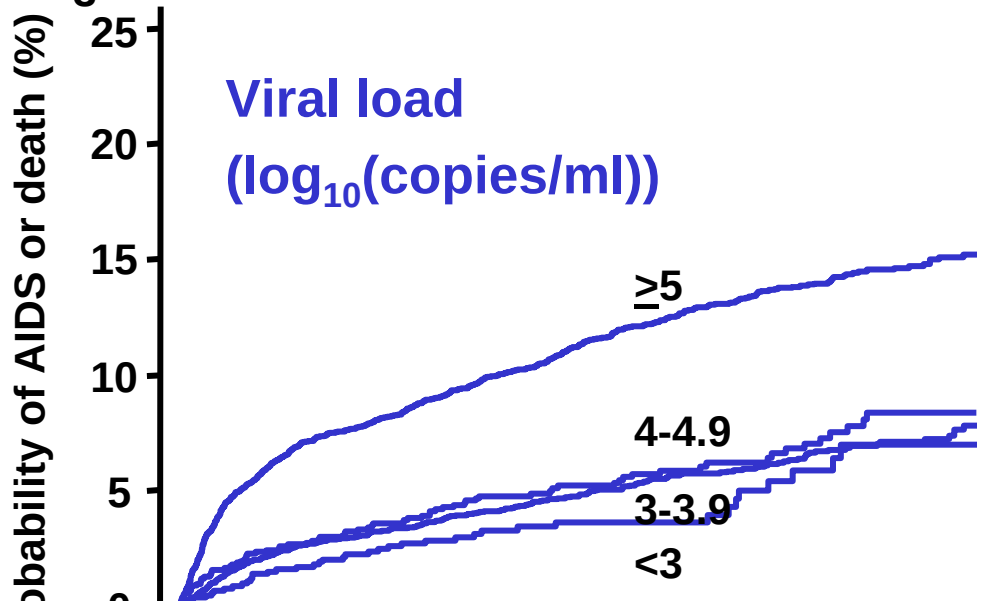
Prognosis from starting HAART

(Egger *et al.*, *Lancet* 2002; **360**: 119-129)



ther prognostic factors

- Risk group (IDU v other)
- Age (≥50 v <50)
- CDC stage C v A/B



Development of model for estimating progression probabilities in HIV-infected patients treated with HAART

Fit candidate parametric survival models on data pooled from all but one of the cohorts

Test on omitted cohort

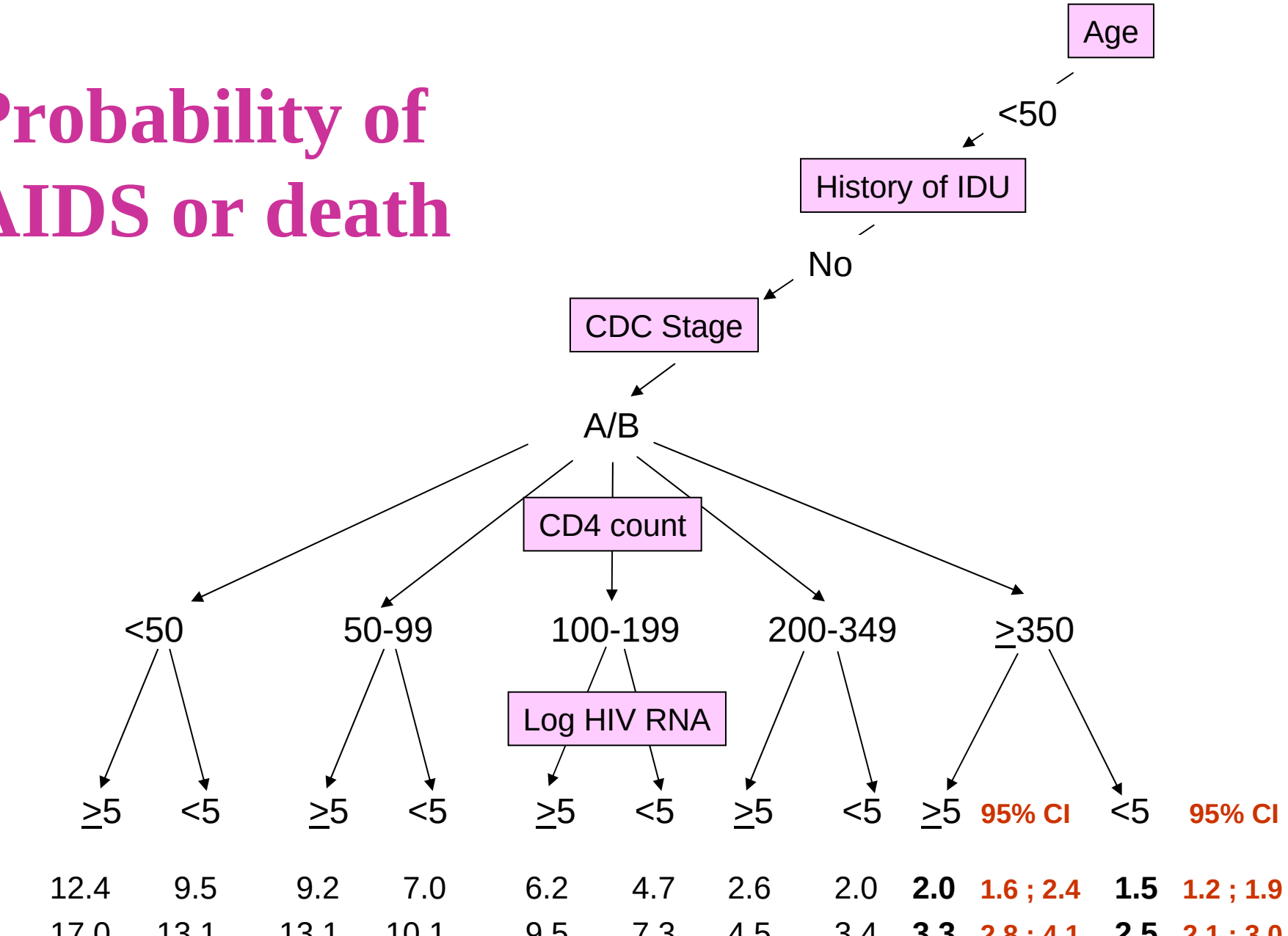
Repeat, rotating the omitted cohort

Choose **best-generalizing** model

- Use deviance differences to quantify the additional lack-of-fit when a model is fitted on one data set and predictions are made on another data set

Final model: Weibull model with stratification on CD4

Probability of AIDS or death



Summary

- Need for clarification of questions
  - Can we move on from “Does HAART affect CVD risk?”?
- Results from a range of study designs will contribute
- In the short and medium term, we know that HAART leads to dramatic reductions in rates of progression to AIDS/death
  - Interpretation and reporting must bear this in mind
- Need for RCTs?