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Insurability and Survival of Lives Living with HIV and Other Chronic Disease

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Agenda

- Context
  - Insurability of HIV
  - Why Type 2 Diabetes (DM2)
  - HIV timeline
  - South African context
- Disease progression
  - Definitions
  - HIV and DM2
- Data and methodology
- Results
- Limitations
- Conclusions

Insurability of HIV in South Africa

- Mortality at longer-term durations on ART remains uncertain in South Africa
  - Short follow up periods used to extrapolate 10-30 years
  - In developed countries, life cover for HIV+ lives is often restricted to term cover
  - Limitations of life expectancy estimates for insurance
- Further research is required to assess subgroup mortality differences
- Comparisons of subgroups of HIV-infected lives and subgroups of lives with other chronic conditions requiring lifelong treatment, e.g. Diabetes
  - However…no published South African study has compared the mortality of HIV-infected lives with insured-lives or lives with other chronic conditions
- ***Study Design:*** *Estimate and compare the mortality of HIV-infected South African adults initiating ART with that of South African adults initiating therapy for Type II Diabetes and a control group in a large cohort of privately insured South Africans with long follow-up time to assess the hypothesis that there exist insurable subgroups of HIV-infected South African adults on ART*

Why Type 2 Diabetes (DM2)

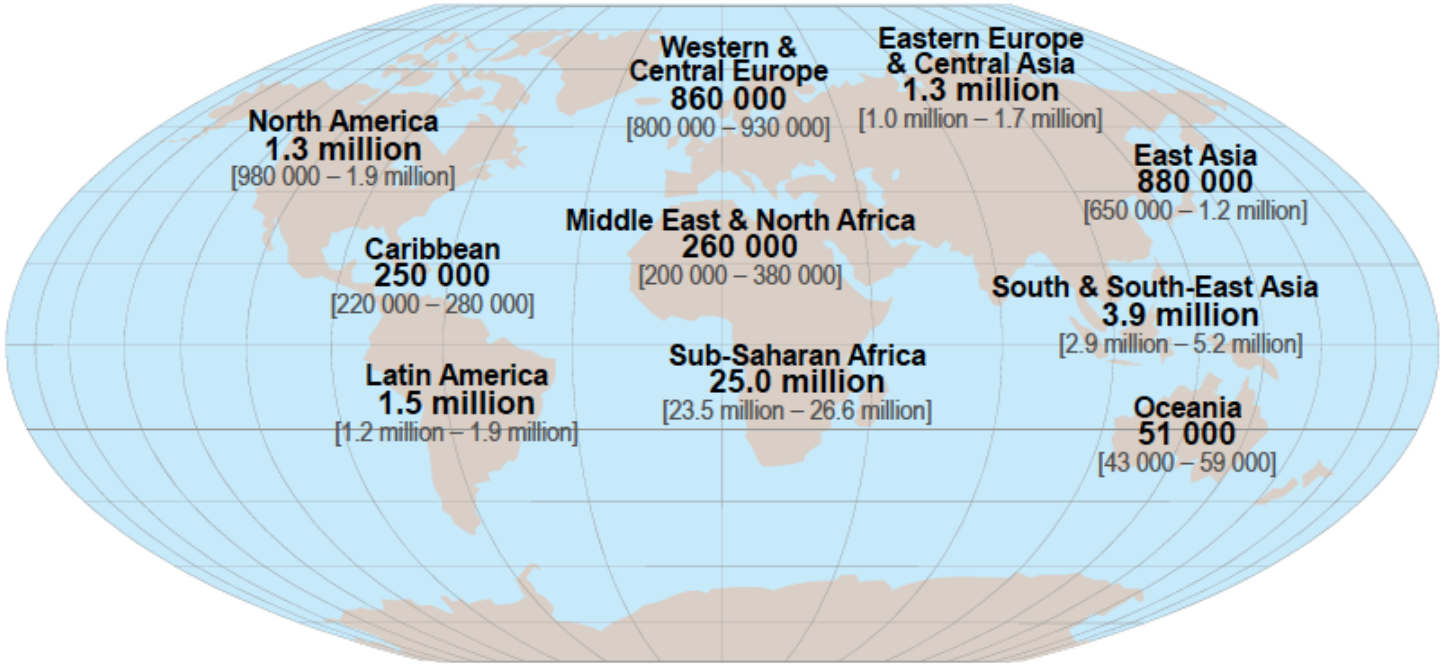
- Insurability is often defined by a threshold of extra mortality
  - Further context given by comparing to other chronic manageable diseases that are already covered
- Similarities to HIV:
  - Laboratory marker of treatment success - HbA1c is analogous to HIV viral load
  - Control of either is associated with better short- and long-term prognoses
  - Requires life-long treatment
- One of the most common non-communicable diseases
  - International Diabetes Federation: in 2011, 8.3% global prevalence (adults aged 20-79) and by 2030 9.9%
  - 2011: 8.2% of global all-cause mortality (adults aged 20-79)
- Low- and middle-income countries bear 80% of the global DM2 burden
  - Africa: largest expected percentage increase (90%) in adult DM2 numbers by 2030, outstripping population growth

Timeline of HIV

- **HIV thought to have spread to humans from chimpanzees (bush meat trade in central africa)**
- **First identified HIV infection in Congo**
- **Zidovudine (AZT) first active antiretroviral therapy (ART)**
- **The syndrome of AIDS was described**
- **HIV identified as the cause of AIDS**
- **First treatment for patients with AIDS: AZT**
- **Combination ART suppresses HIV replication completely with the advent newer classes of therapy**
- **First actuarial AIDS and demographic model**
- **Access to ART in low- and middle-income countries**
- **Safer and more effective ART**

South African context

- People (all ages) with HIV in 2012 (UNAIDS, 2013):



Total: 35.3 million [32.2 million – 38.8 million]

- South Africa: 6.1m living with HIV out of 50.7m (UNAIDS,2013)
- South Africa: 17.9% adult HIV prevalence (2012)
- Globally, 17% of adult deaths attributed to HIV & TB
- South Africa: 70% of adult deaths attributed to HIV & TB (WHO, GBoD 2010)

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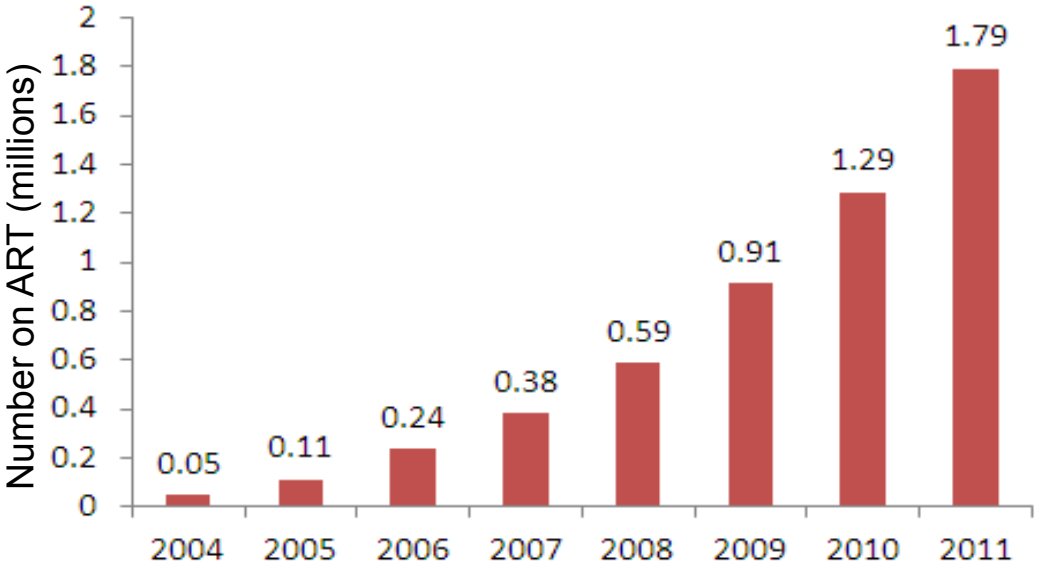
South African context



Dr Aaron Motsoaledi (South African Minister of Health since 2009) with the first “one pill per day” regimen in South Africa

- Exponential growth in numbers receiving ART
- One of the largest pharmacological interventions in history
- >2 million lives on ART by mid-2012 (HSRC, 2013)
- Coverage <50% in 2011 assuming eligibility at CD4 <350 cells/μl (Johnson, 2012)
- 8.7m medical scheme/insurance beneficiaries (3.82m principal), CMS, 2012/2013

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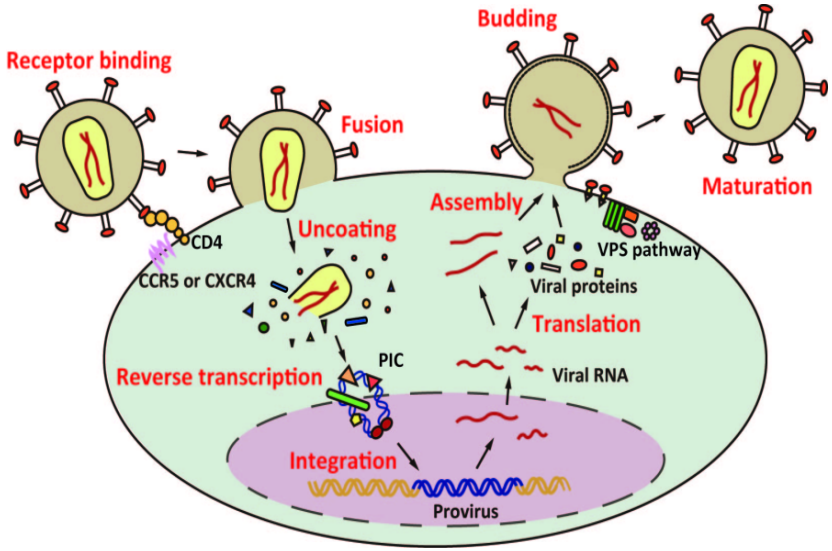
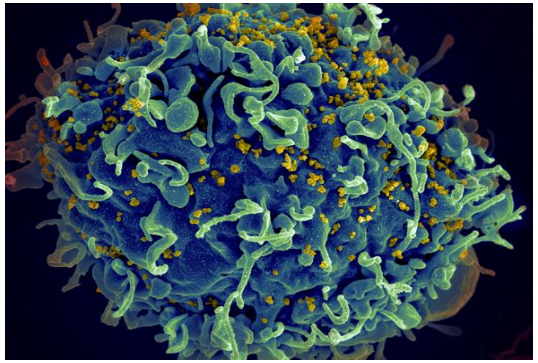
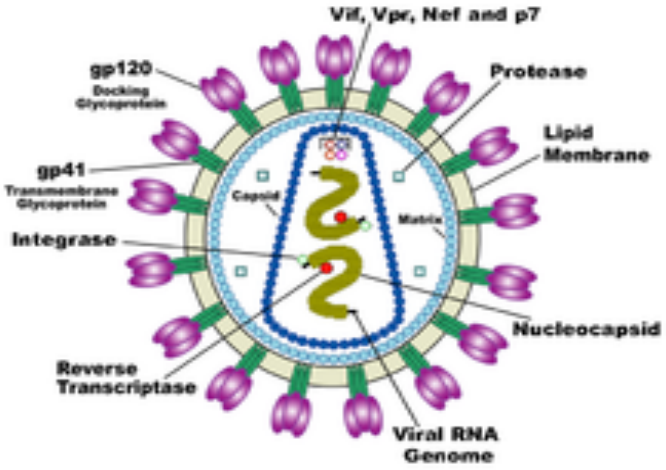
Definitions

- **CD4 count:**
  - CD4 cells infected by HIV
  - CD4 prognostic marker
  - Monitoring state of immune system

- **Viral load (VL):**
  - amount of virus in the blood stream in copies/ml of blood
  - Monitoring effectiveness of ART







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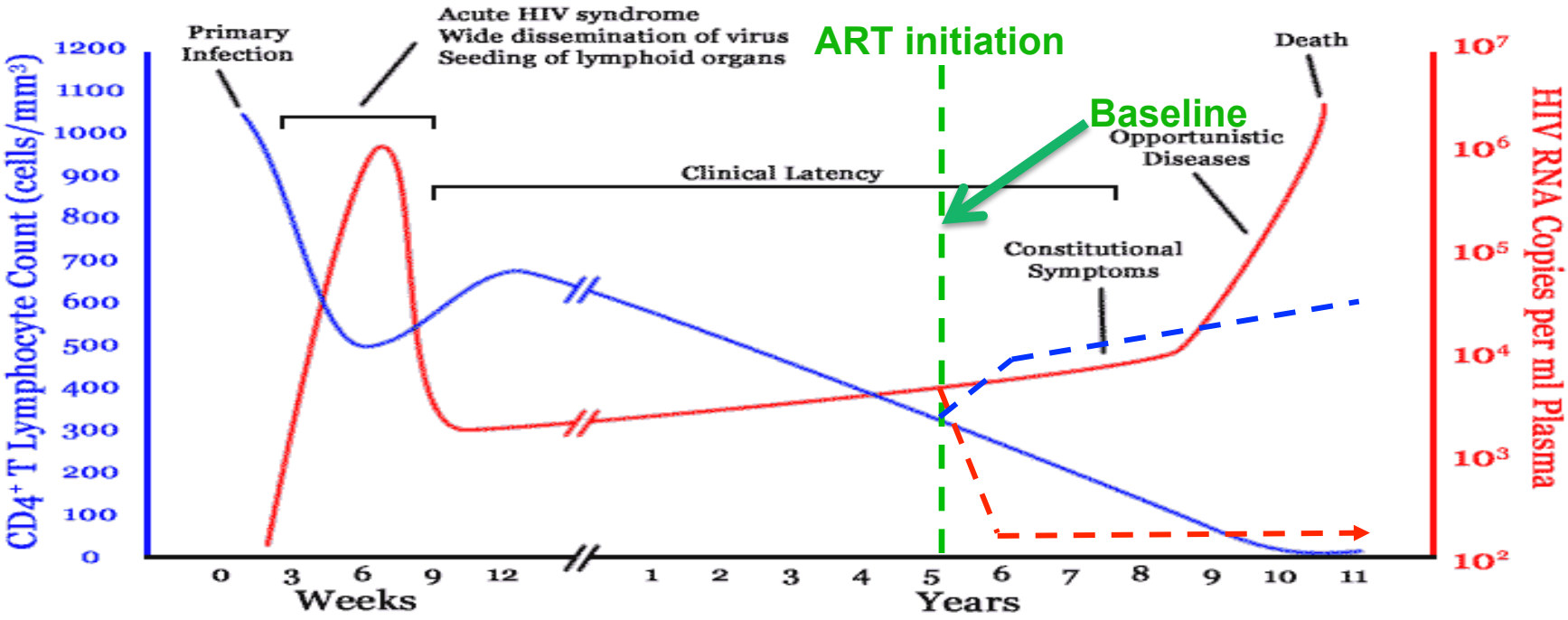
HIV disease progression and response to ART

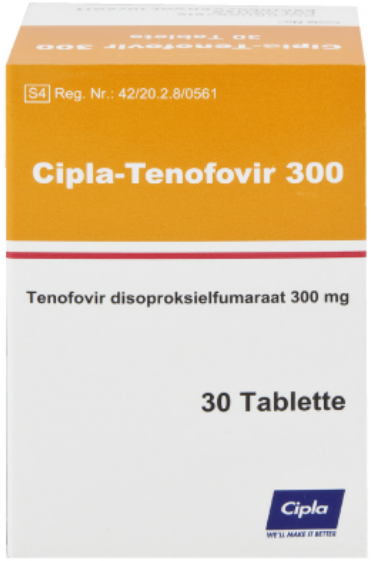


- CD4 count declines
- The higher the VL, the faster the CD4 declines, the greater the risk of developing AIDS
- **With ART, CD4 recovers and VL falls to undetectable levels**

Pantaleo, G et al. 1993. New concepts in the immunopathogenesis of human immunodeficiency virus infection". New England Journal of Medicine 328 (5): 327-335.

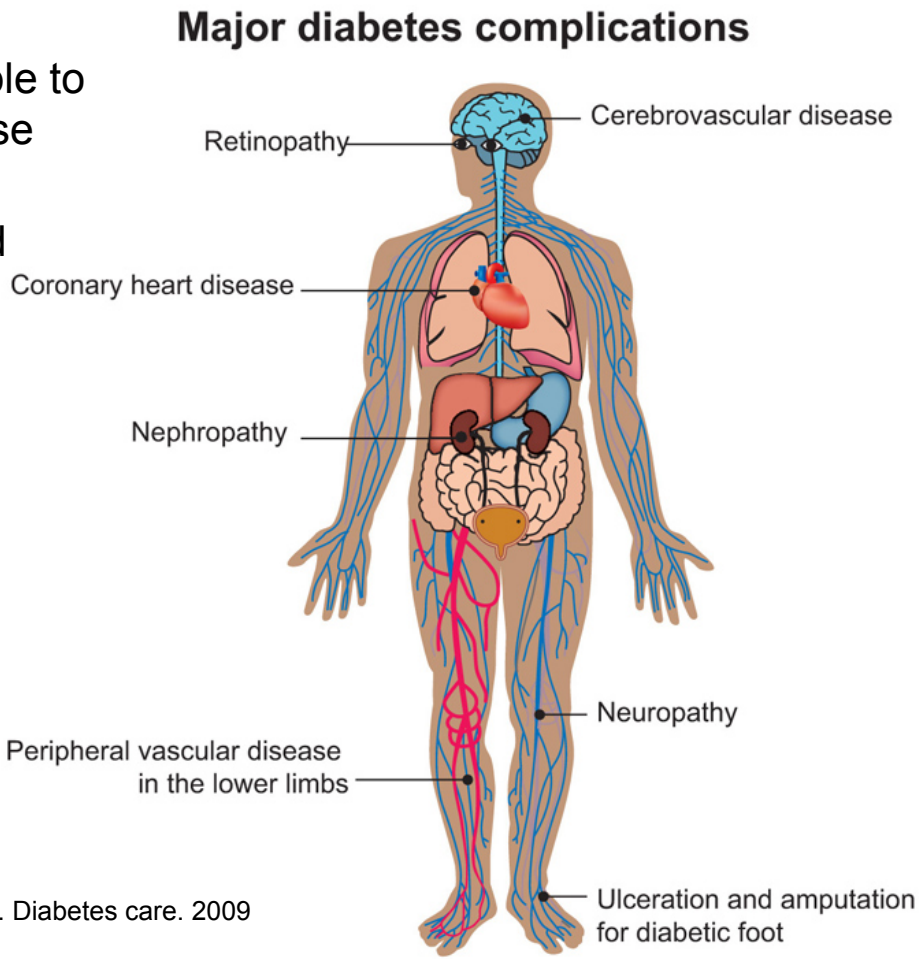
ART management

- When to start ART?
  - CD4 count or symptoms
- LMICs:
  - Standardised ART regimens
- VL:
  - Monitoring informs changes in regimen
  - Measure of ART success
  - Drug resistance develops if VL unsuppressed on ART
- Change in regimen



DM2 disease progression

- Characterized by
  - Slow development of insulin resistance
  - Insulin-producing cells in pancreas unable to fully cope with a sugar – impaired glucose tolerance
  - Full-blown diabetes – uncontrolled blood sugar levels
- Complications
- HbA_{1c}



- Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes care. 2009 Nov;32 Suppl 2:S151-6.
- Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels:a systematic review and meta-analysis. Diabetes care. 2010 Aug;33(8): 1859-64.

Management of DM2

- Non-medication:
  - Lifestyle – physical activity, diet
  - Foot and eye screening
  - Monitoring HbA_{1c}
- Medication:
  - Therapy recommended: HbA_{1c} >7 mmol/L
  - "Line" of therapy:
    - Oral
    - Injectable insulin

- Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels:a systematic review and meta-analysis. Diabetes care. 2010 Aug;33(8):1859-64.

Data and Methodology

- A large private-sector cohort (>1 million) of South African adults, from which three cohorts are observed over the period 1998-2013:
  - **HIV cohort**: Aid for Aids (AfA) – HIV managed care provider in Southern Africa
    - Authorised for ongoing ART and medicine claim data available
    - Identity numbers available
    - Medical scheme/insurance beneficiaries and generally employed
    - Largest study of HIV-infected patients managed in a private healthcare setting globally: >340,000 person years of observation (PYO) and >10,000 deaths
    - Large patient volumes surviving 5-13 years on ART
    - Baseline and updated patient characteristics
  - **Type II Diabetes cohort**: patients initiating therapy
  - **Control cohort**: assumed HIV-negative and without Diabetes due to no history of CD4 or viral load tests; no ART claimed, no AHT claimed
- Deaths matched to national death registry (80-90% complete*) to improve death ascertainment
- Generalized mixed-effects Poisson model and standardized mortality ratios

*Van Cutsem, G., et al. 2011. and Yiannoutsos, C.T., et al. 2012.

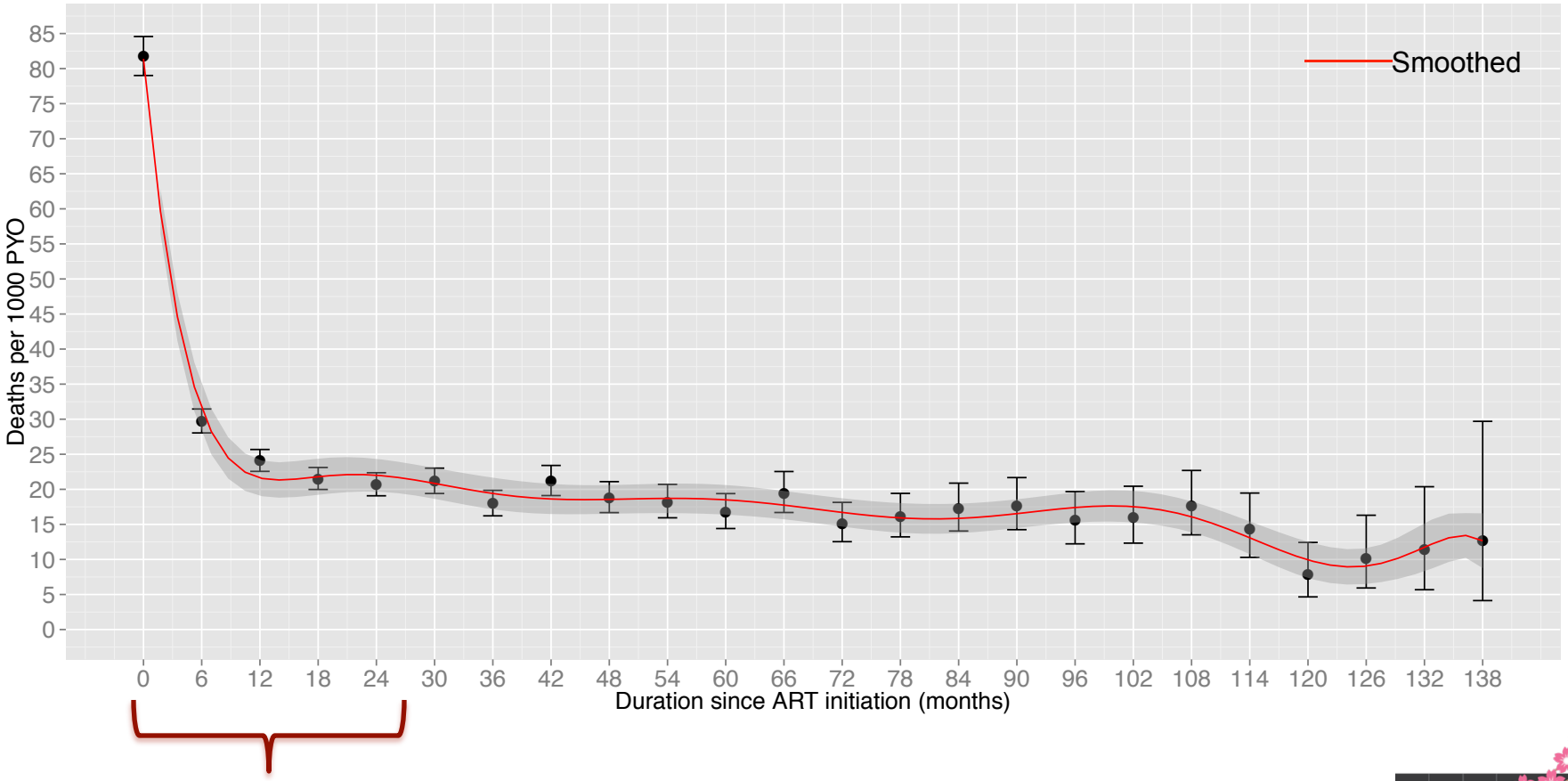
Descriptive Statistics

Description	Units	HIV	Diabetes	Control
Patient numbers: • Overall • >5 years follow-up • >8 years follow-up	Number of patients	 83,994 23,451 9,807	 67,806 41,954 23,837	 552,364 389,667 247,011
Person years of observation	PYO	342,698	366,029	3,455,510
Deaths		9,719	8,006	25,459
Median [IQR] follow up	Years	3.3 [2.1,5.3]	6.2 [3.9,9.5]	7.2 [4.6,11.2]
Median [IQR] baseline age	Years	38 [33,45]	48 [40,56]	34 [27,44]
Gender	Female	63%	49%	48%
Population group	Black	96%	62%	61%
Crude mortality incidence	Deaths per 1000 PYO	28.4	21.9	7.4
Median [IQR] baseline CD4	(cells/µl)	159 [73,241]	-	-

Results

- HIV survival
  - Crude
- Relative risk
  - Modelled

Time since ART initiation



Most published studies in low and middle-income countries often report outcomes only within the first two years of ART

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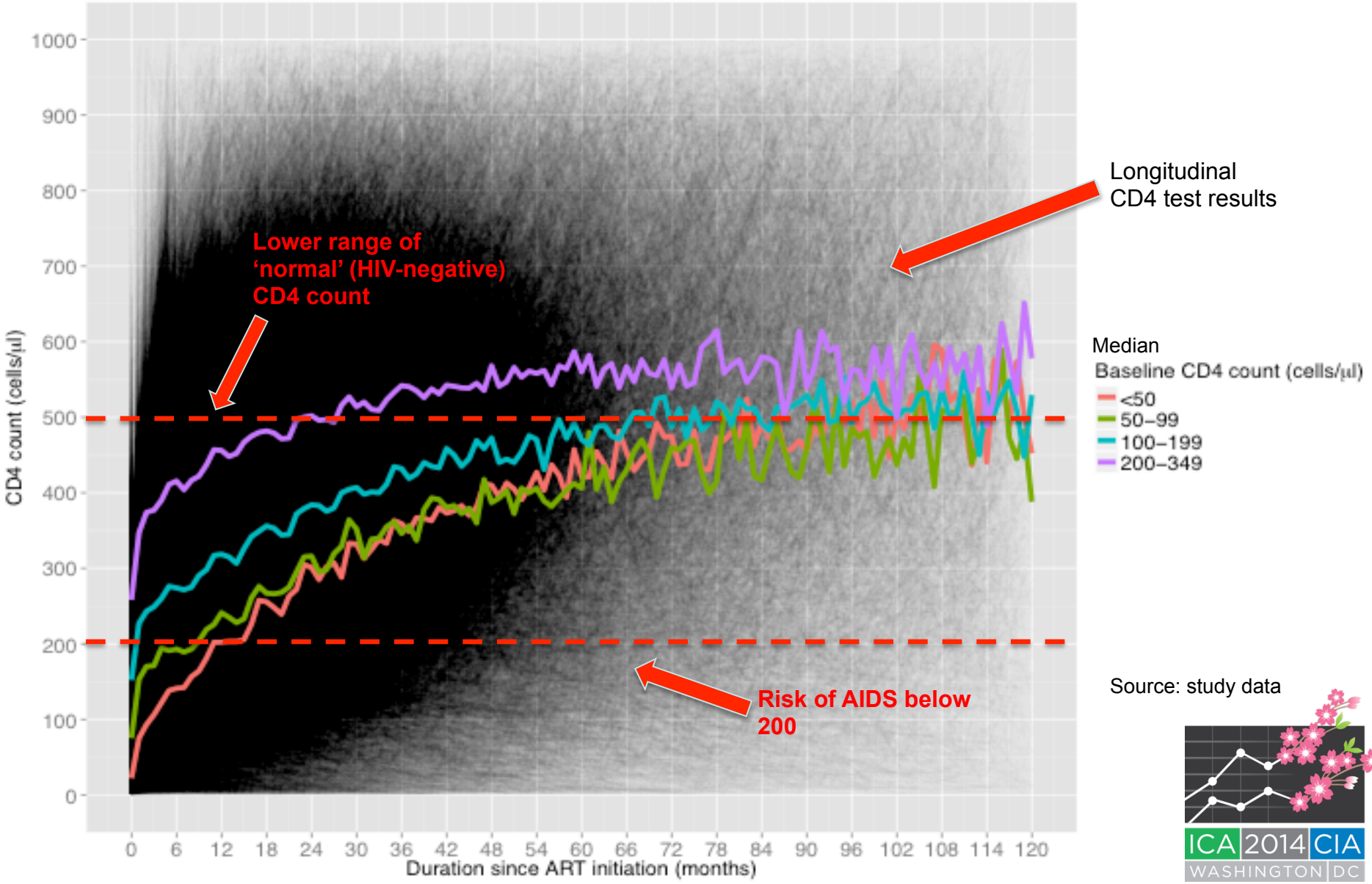
CD4 response to ART



Source: study data

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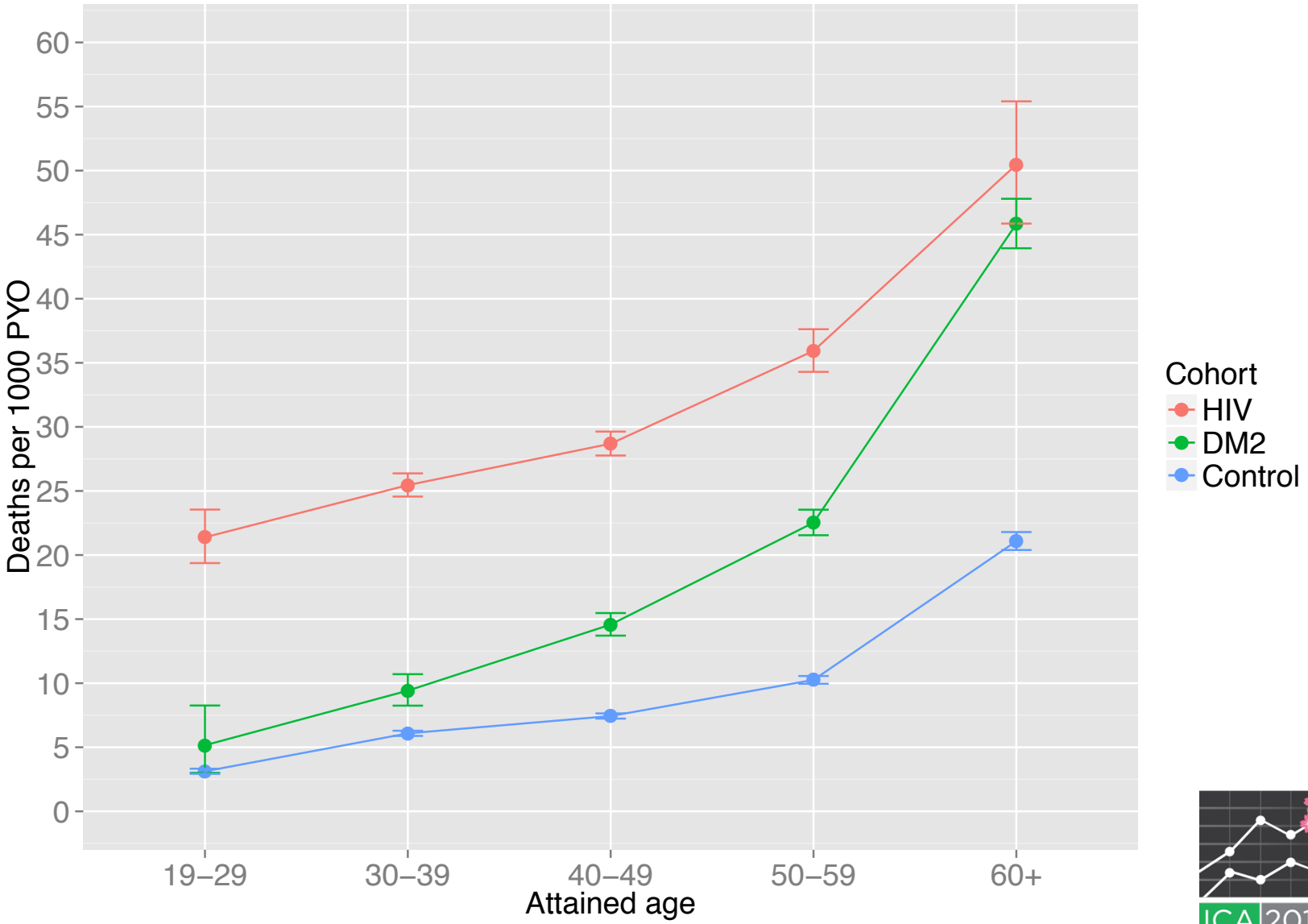
Crude mortality incidence



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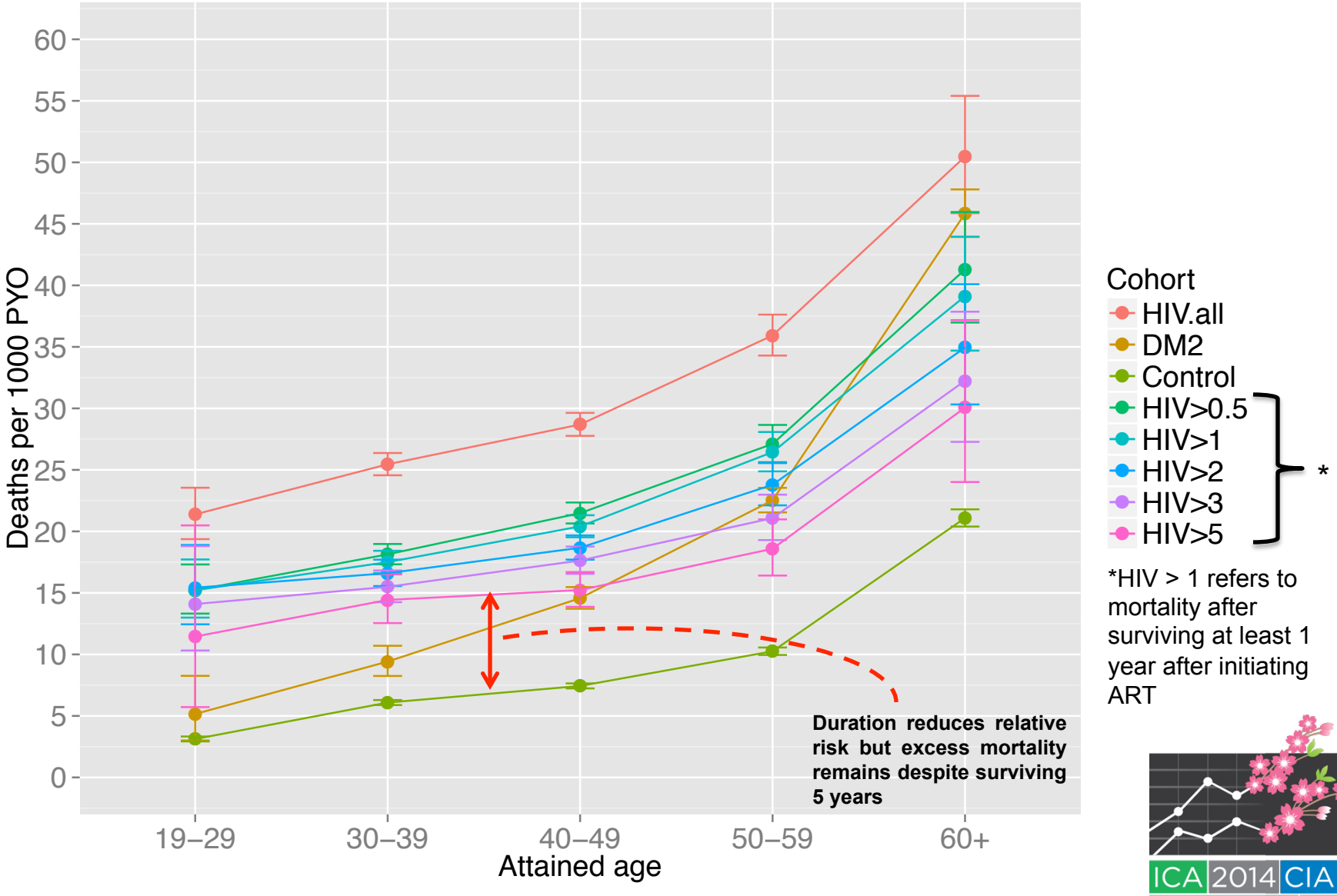
Mortality incidence (ART duration)



*HIV > 1 refers to mortality after surviving at least 1 year after initiating ART

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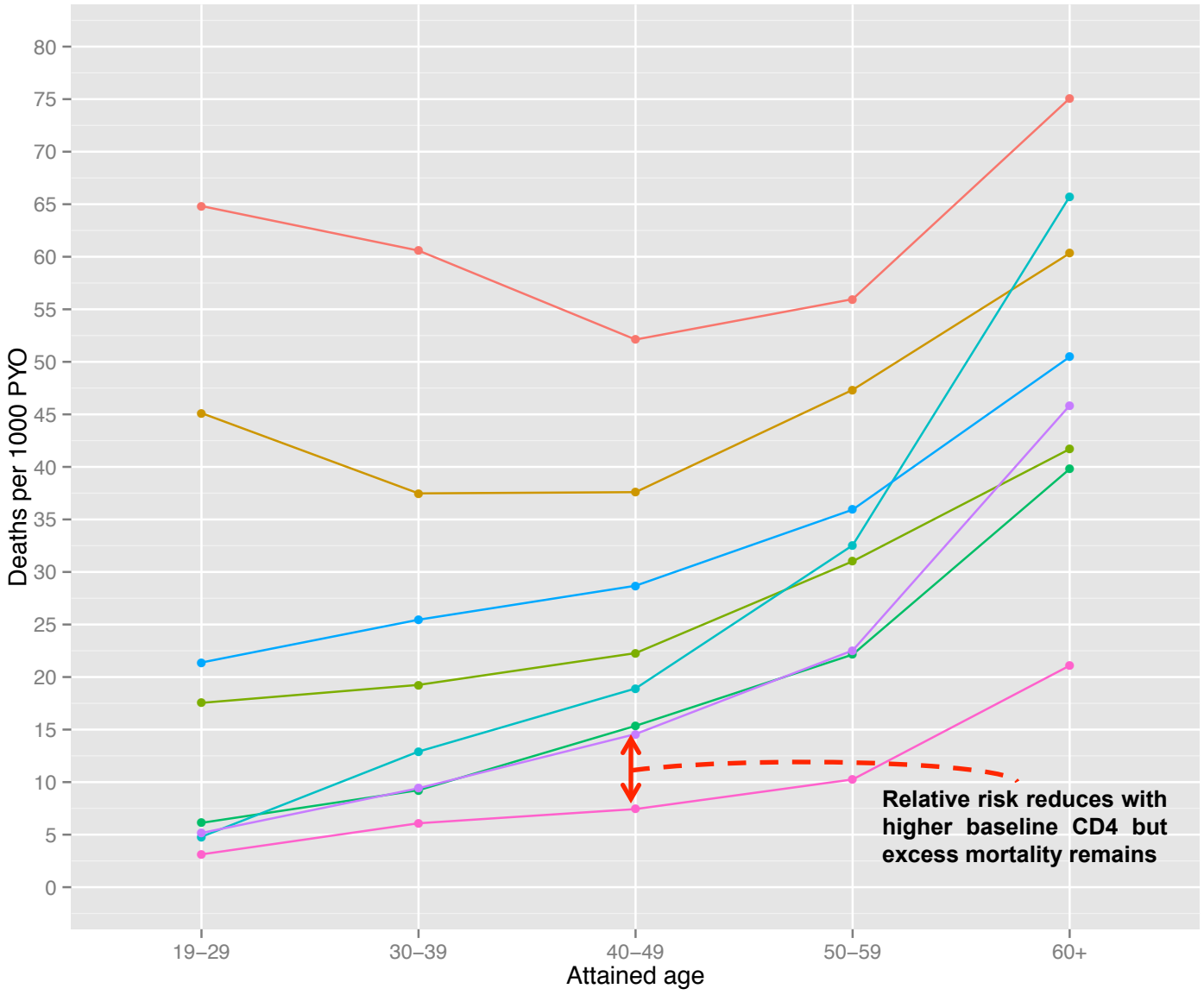
Mortality incidence (baseline CD4)



*350+ represents ART initiation upon advanced clinical (WHO) stage and therefore reflects historic ART eligibility criteria (CD4<350 or AIDS defining illnesses) and not initiation at high CD4 counts

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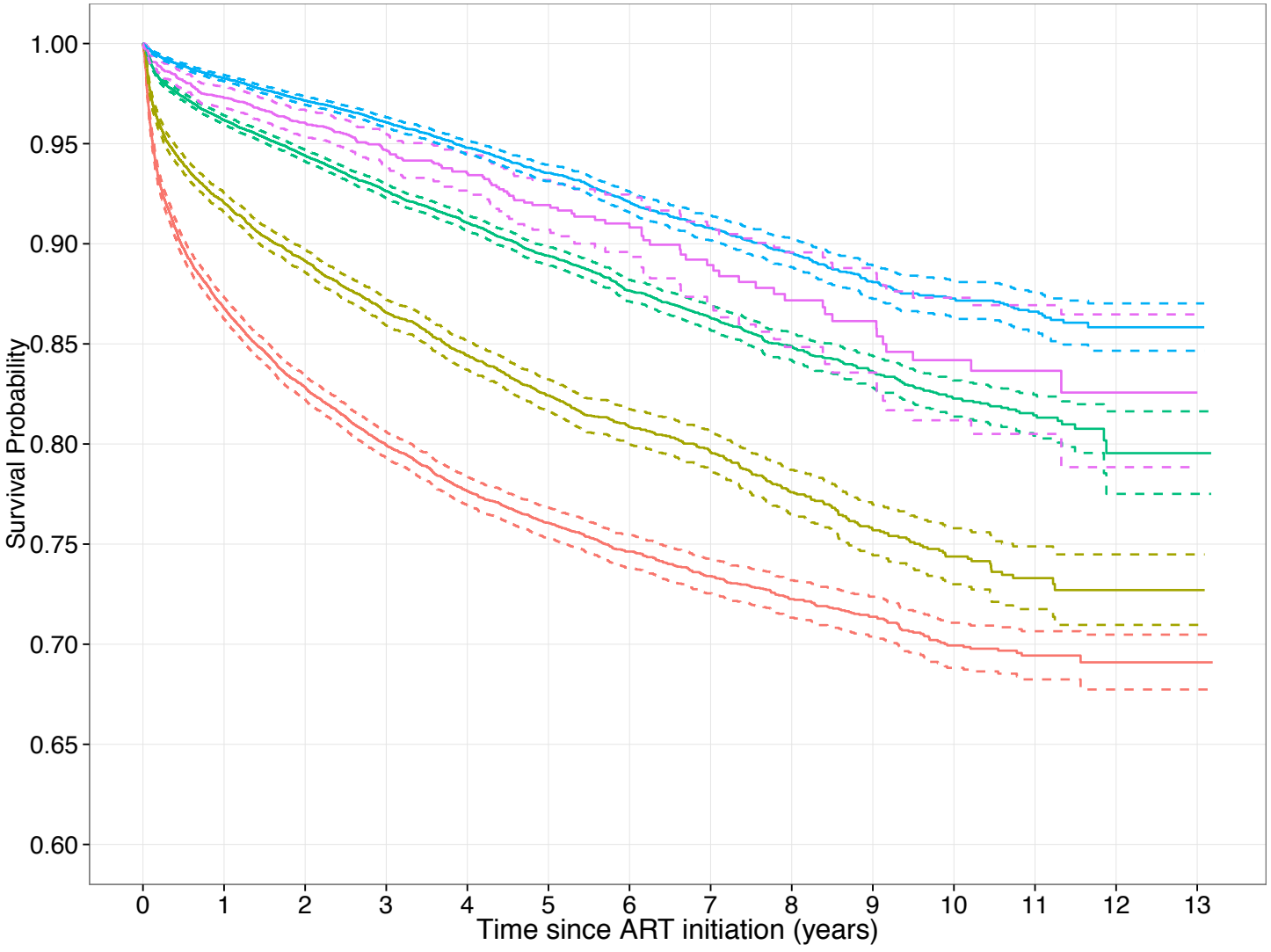
Survival: Kaplan Meier



Baseline CD4 count (cells/μl)

- <50
- 50–99
- 100–199
- 200–349
- 350+ *

*350+ represents ART initiation upon advanced clinical (WHO) stage and therefore reflects historic ART eligibility criteria (CD4<350 or AIDS defining illnesses) and not initiation at high CD4 counts

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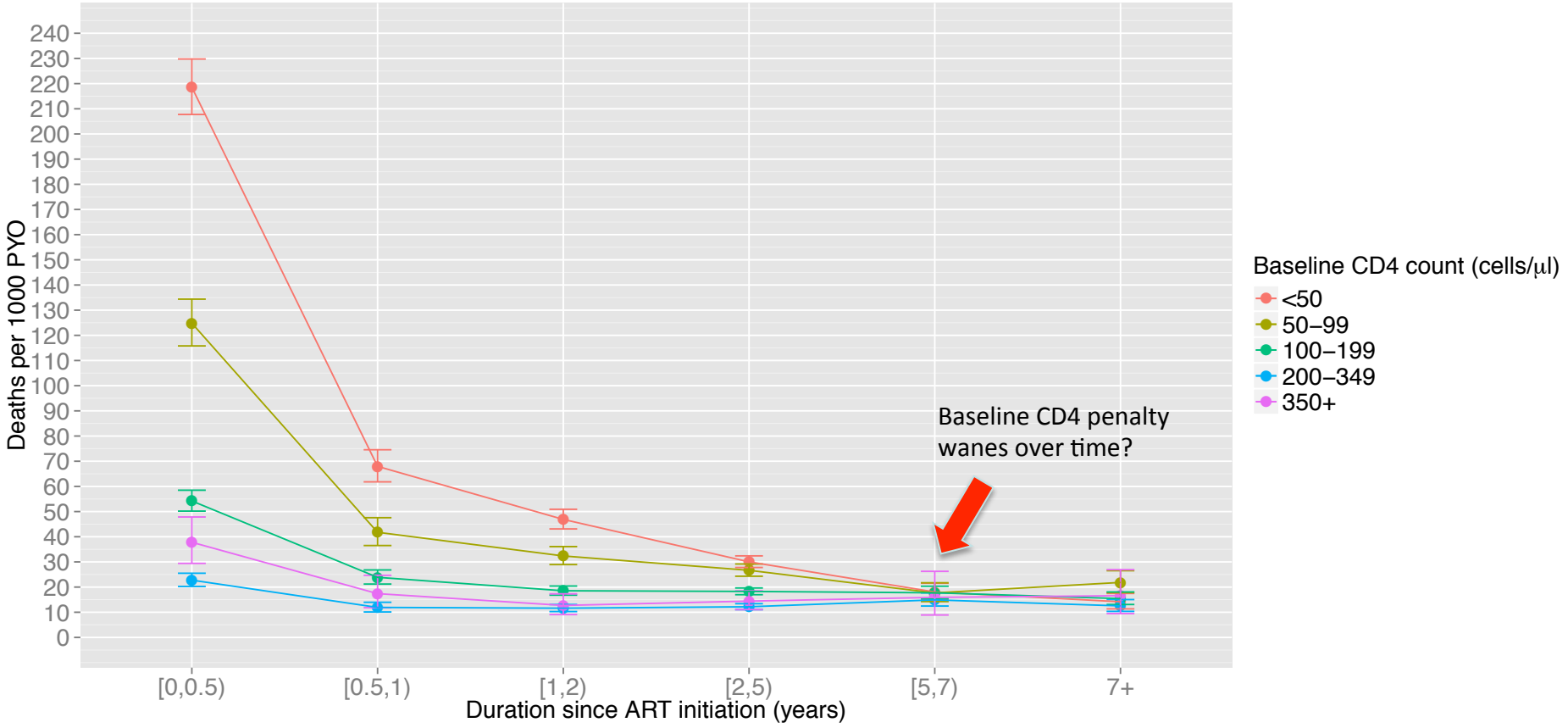
Baseline CD4 count, duration



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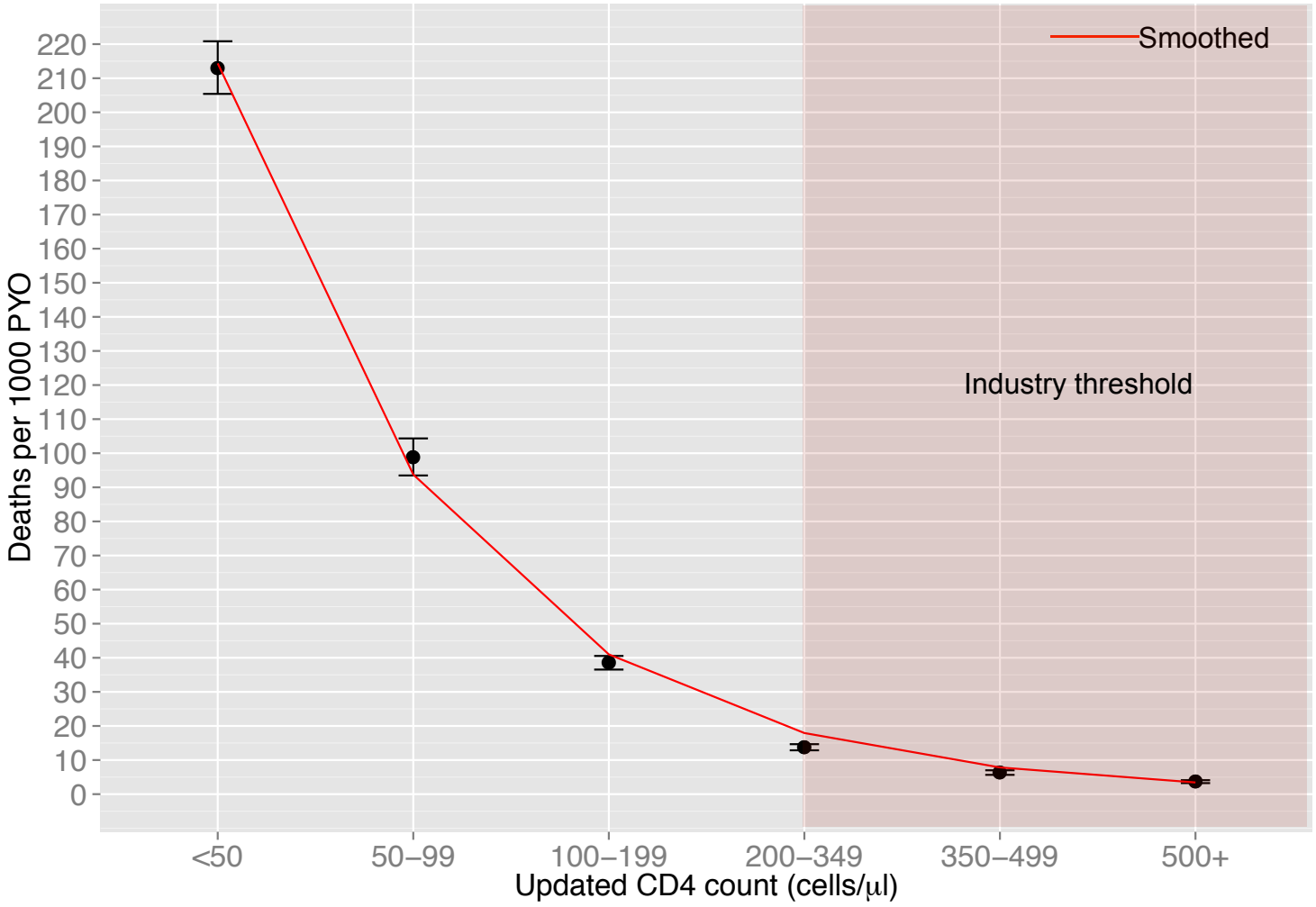
Updated CD4



Updated CD4 refers to CD4 test results observed at future time points after initiating ART. Mortality incidence by updated CD4 count provides an indication of mortality during exposure accrued at CD4 strata

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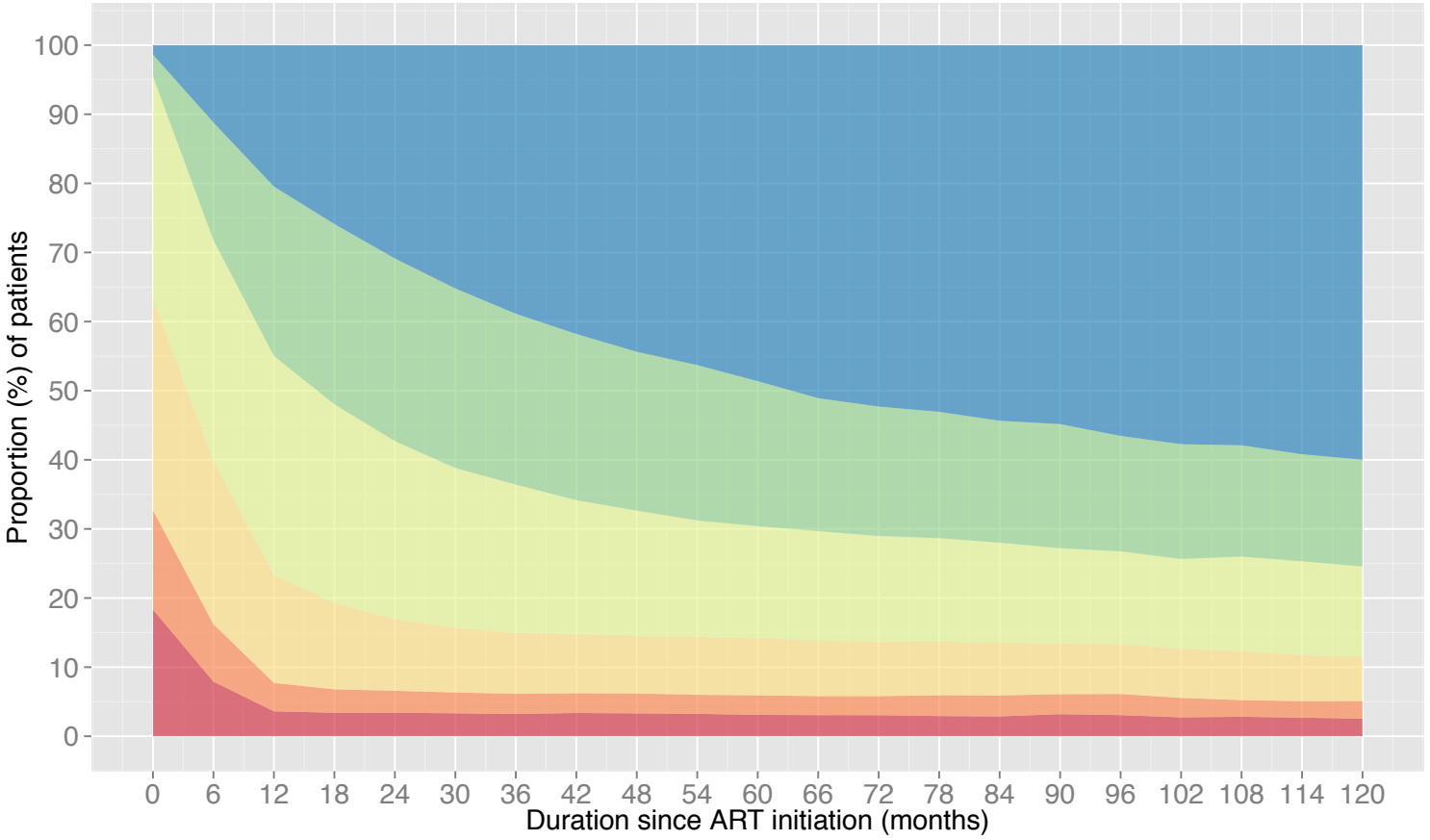
CD4 response to ART



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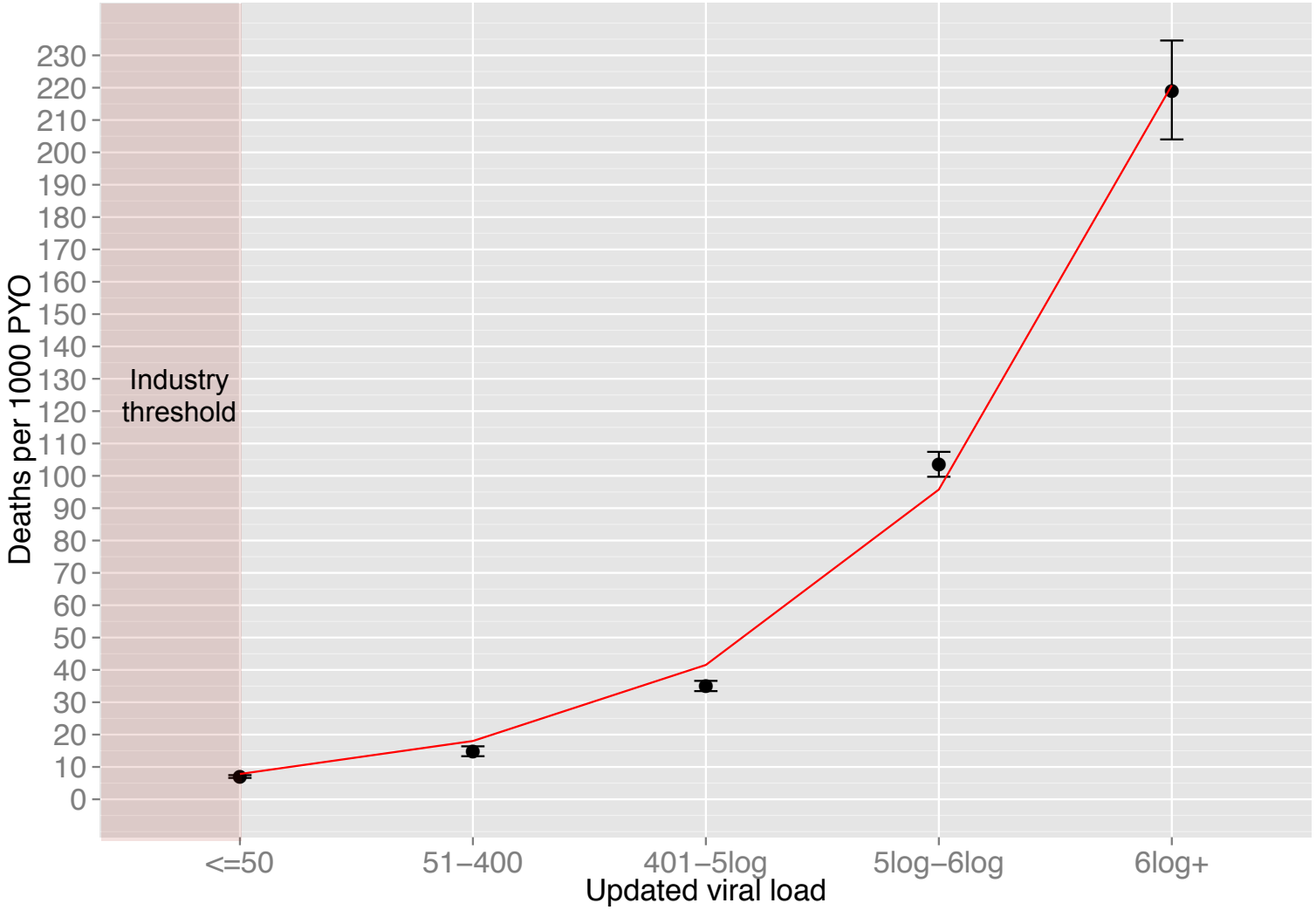
Updated viral load



Updated VL refers to VL test results observed at future time points after initiating ART. Mortality incidence by updated VL provides an indication of mortality during exposure accrued at VL strata

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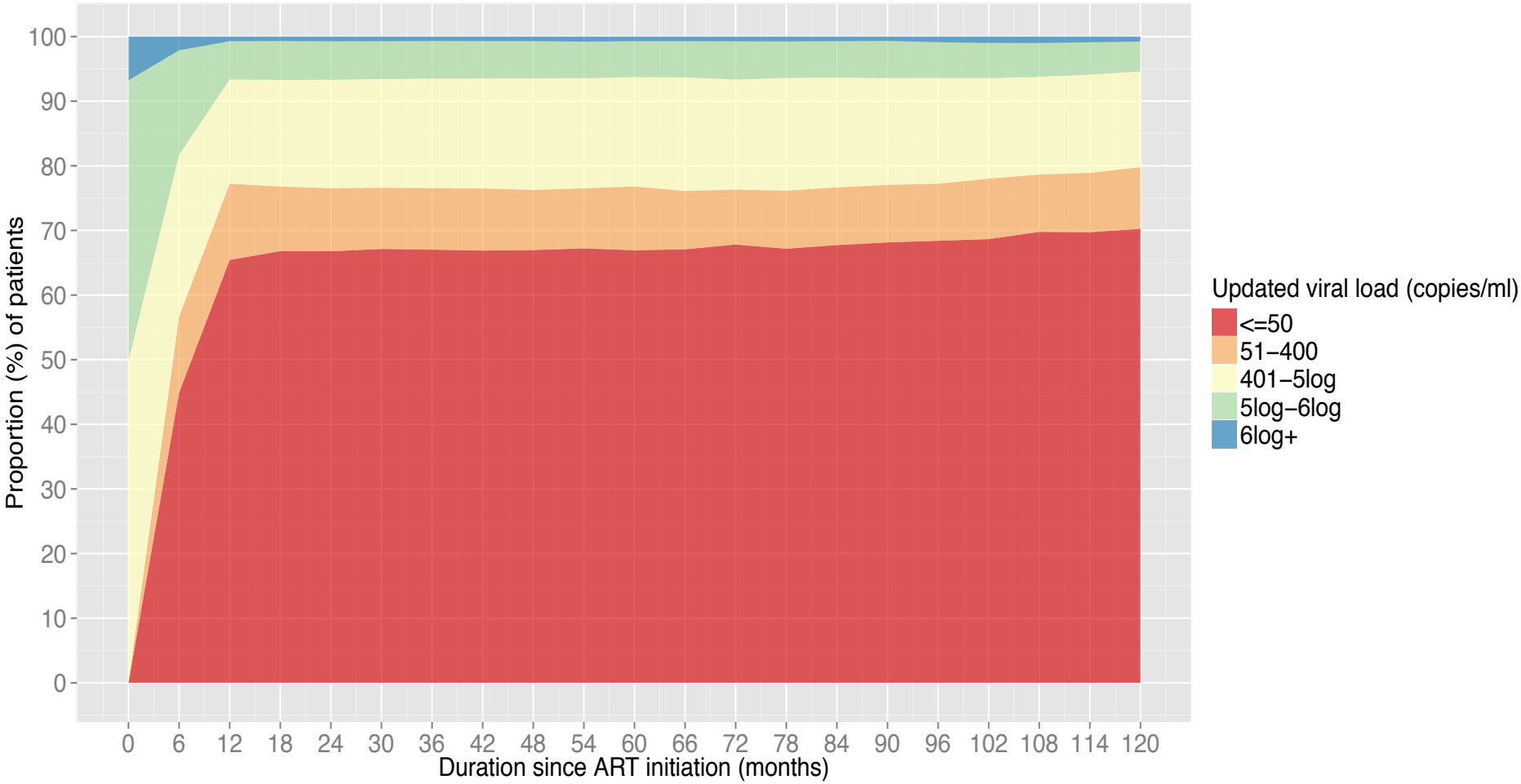
Viral load response to ART



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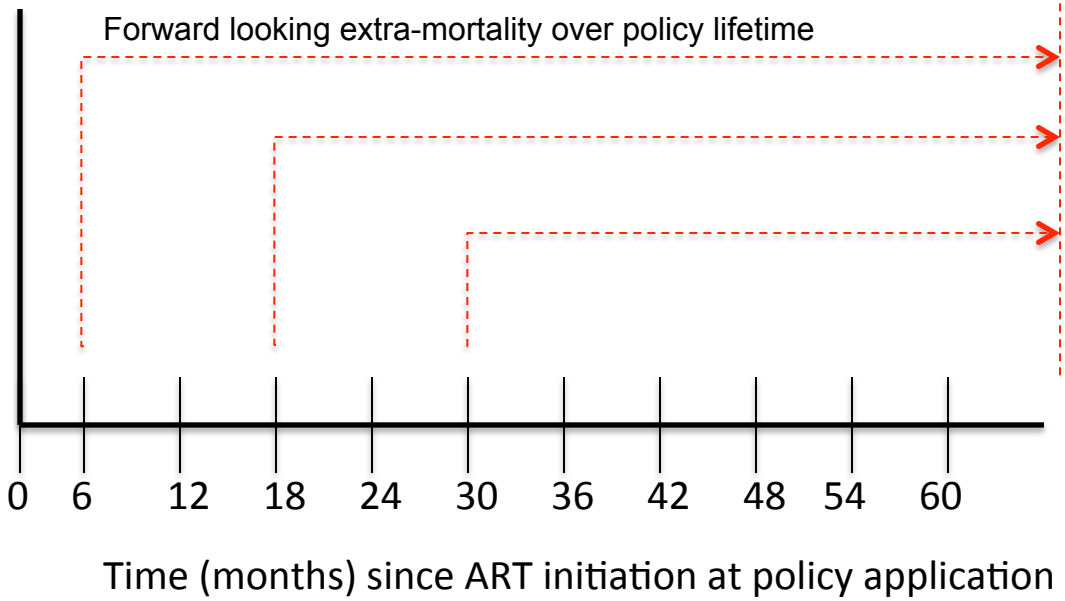
Adjusted relative risk

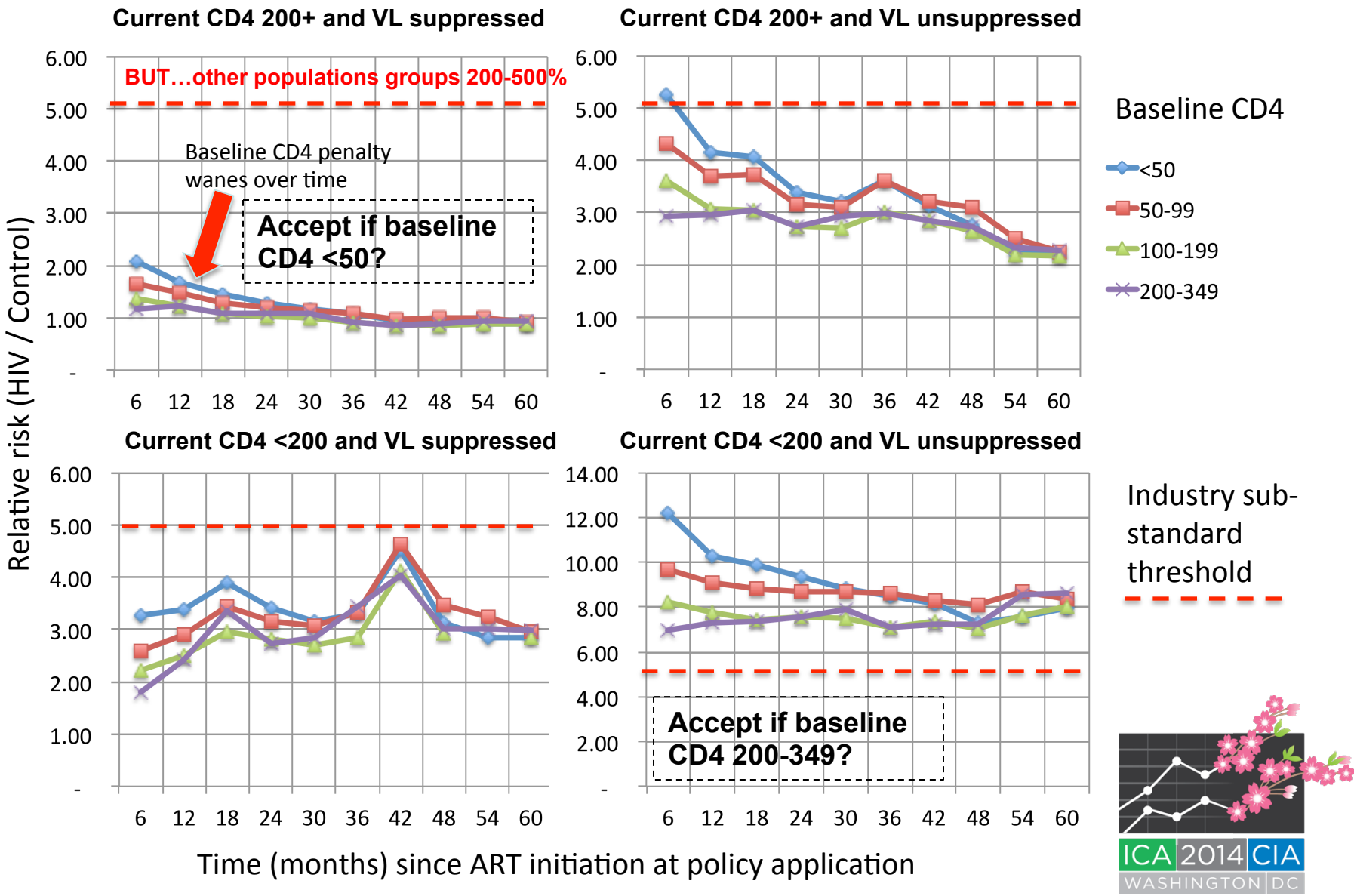
- Subgroups analysed by current CD4 and VL, baseline CD4 and time since ART initiation:

Current CD4 \ Current VL	Suppressed (≤400)	Unsuppressed (>400)
≥200		
<200		



Example policy applicant:
- Baseline variables:
  - CD4: 200-349
  - VL: 5log-6log
  - Demographic
- At policy application:
  - Age
  - Current CD4: 200+
  - Current VL: suppressed
  - On ART
  - Time since ART: 18 months
- Underwriting criteria?
- Extra-mortality?

Adjusted relative risk



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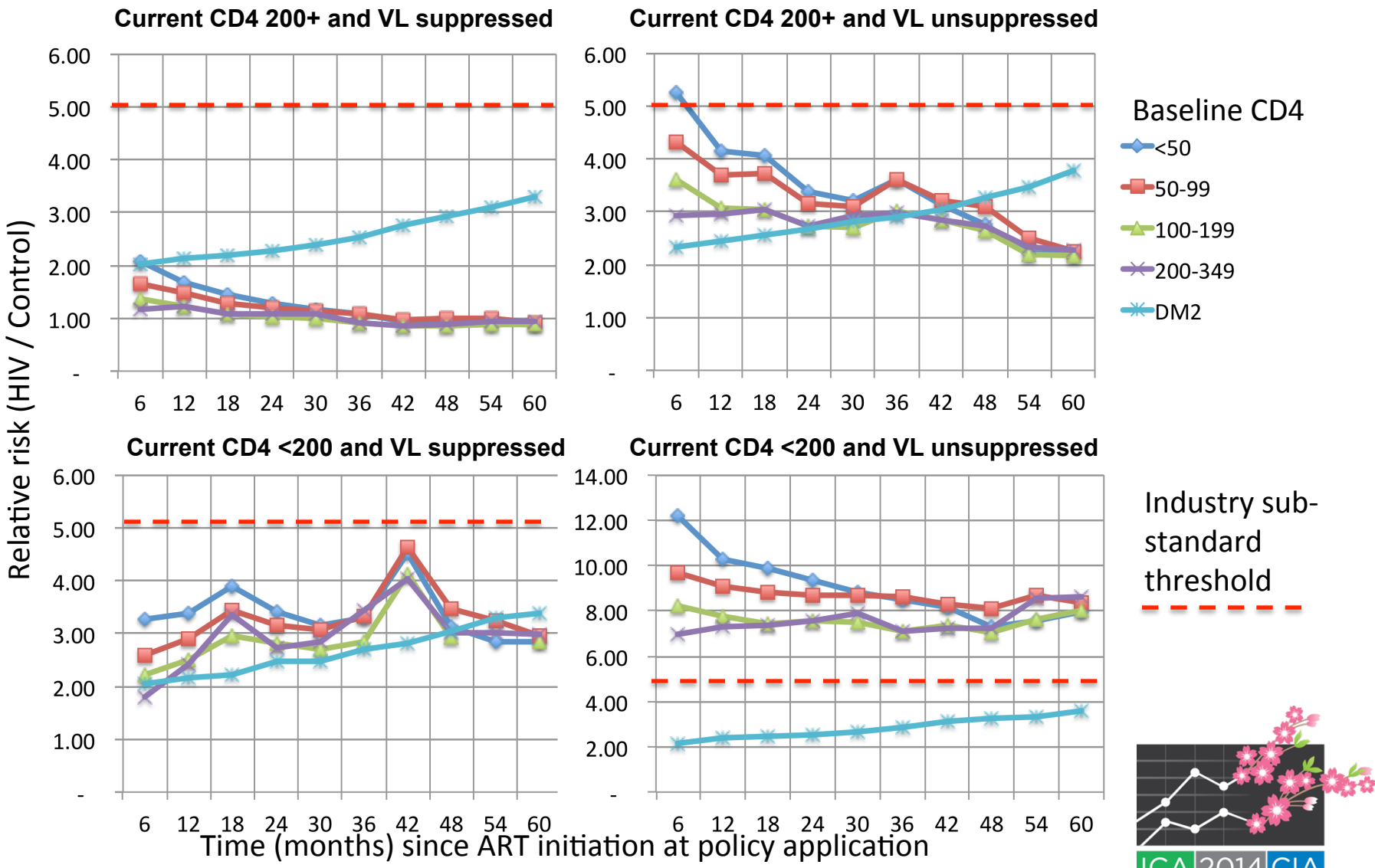
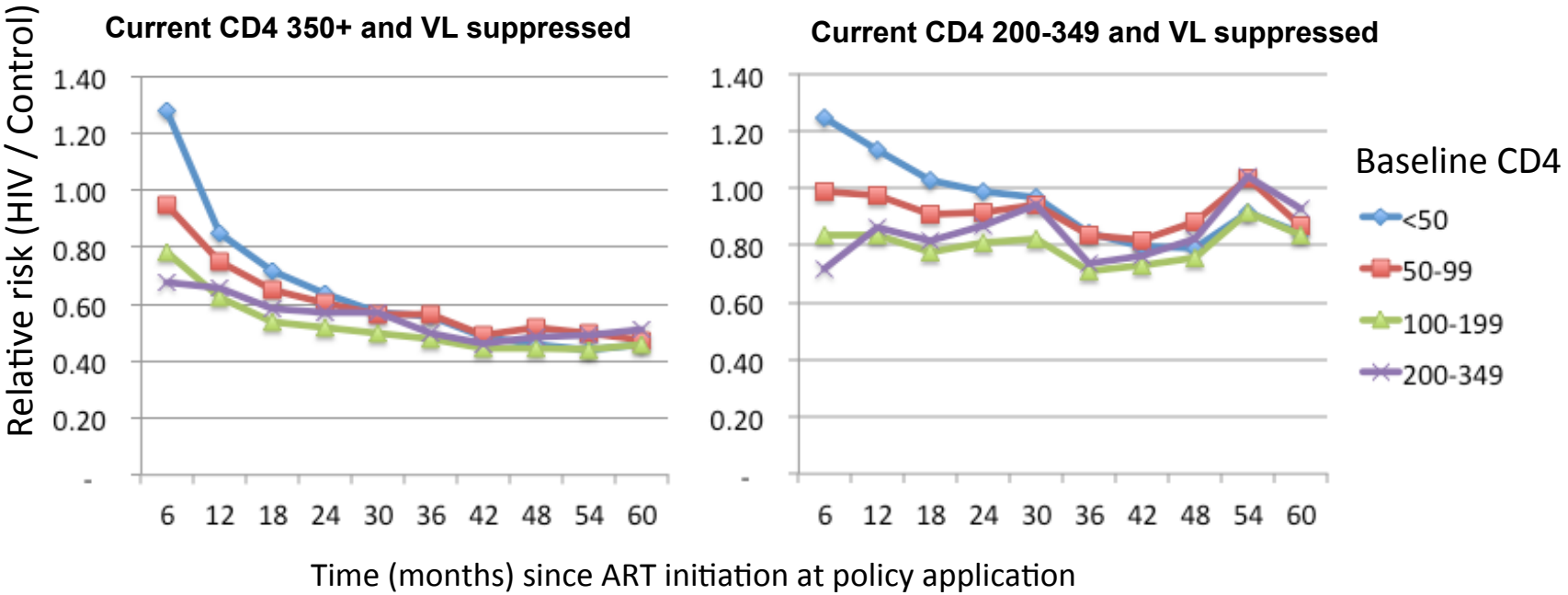
Adjusted relative risk



Adjusted relative risk

- Sensitivity to current CD4



- Other sensitivities observed:
  - Age
  - Gender
  - Population group

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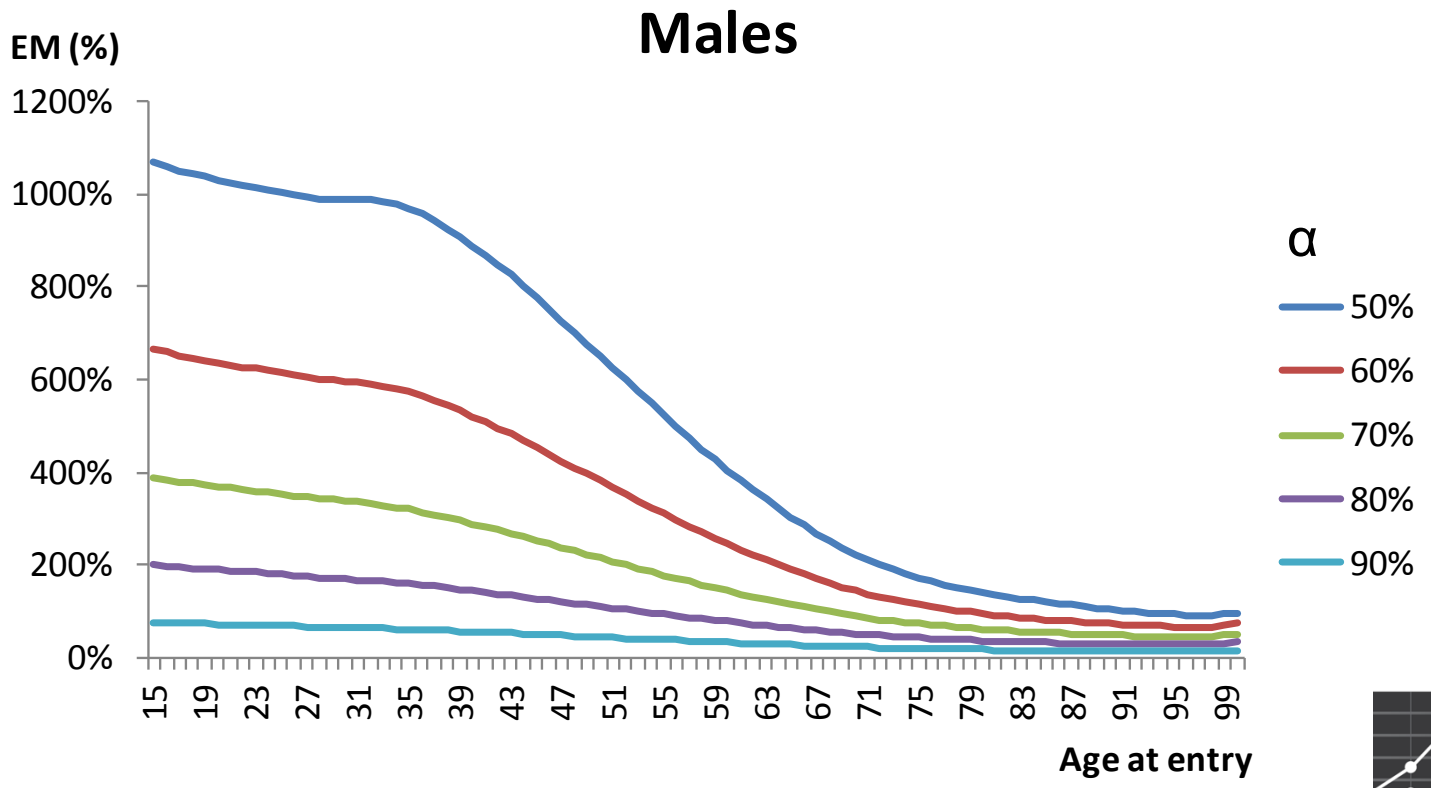
Life expectancy check

- Assumed fully underwritten standard-life risk rates
- Ratio of life expectancy from ART initiation to HIV-negative life expectancy
- Sensitivity to α = HIV+/standard-life life expectancy



Limitations

- Generalizability to other populations
  - Differences in underlying unnatural mortality
  - Co-infection, e.g. Tuberculosis
  - Socio-economic status

- DM2: no measure of control

- Virological suppression rates of treatment programmes using Markov models

Conclusions

- Key underwriting criteria:
  - At policy application:
    - current CD4 count and viral load
    - Age, gender, socio-economic status
    - Time since ART initiation – first 6 months far in excess of 500% relative risk
  - Baseline CD4 count <100 predictive within first three years on ART

- Stratification of relative risk:

		Current VL	
		Suppressed (≤400)	Unsuppressed (>400)
Current CD4	≥200	Approaches HIV-negative mortality after three years on ART **BUT…sensitive to socio-economic status and baseline CD4**	+/- 300-400% Improving over time
	<200	+/- 300-400% Worsening over time	> 700%

Conclusions (ctd)

- Current CD4 >=350 and 200-349 both within the 500% threshold
- Generally stable after 36 months since ART initiation

- Type 2 Diabetes:
  - Relative risk initially 200%, increasing with duration on therapy
  - Further analysis of sub groups required, e.g. by HbA_{1c}

- Findings support most existing market underwriting criteria

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    - Michael Hislop
    - Lourens Walters

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Questions

- Contact: Lsarkin@munichre.com
- Disclaimer:
  - Application of relative risk estimates contained in this presentation should not be applied withtout considering the sensitivity to the:
    - Socio-economic mix of the target market
    - Adherence of the target market to treatment guidelines