Comparison of dynamic monitoring strategies based on CD4 cell counts in virally suppressed, HIV-positive individuals on combination antiretroviral therapy in high-income countries: a prospective, observational study

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Background

- Frequency at which CD4 cell count and HIV RNA viral load should be monitored in patients on cART is unknown

- **Guidelines** recommend dynamic strategies CD4 monitoring (decrease of frequency in virologically suppressed individuals on cART with increasing CD4 cell counts):

  → **EACS:** threshold of CD4 > 350 cells/µL (and HIV RNA VL < 50 c/ml)
  → **BHIVA:** threshold of CD4 > 200cells/µL (and HIV RNA VL < 50 c/ml)

  No guidelines on frequency of VL monitoring

- **Evidence** 2 RCTs and several observational studies *(+ Caniglia JAIDS 2016)*:

  → No clinical harm for annual or biannual monitoring

  → No assessment of the effectiveness of the dynamic monitoring strategies with respect to virological and clinical outcomes

Study Aim

- Investigate the effect of dynamic monitoring strategies for CD4 cell count and HIV RNA viral load on clinical, virological, and immunological outcomes in virally suppressed HIV-positive individuals with observational data from two collaborations of prospective cohort studies from high-income countries.

- We aimed to establish whether information about an individual's time-varying CD4 cell count can provide any additional benefit in determining when monitoring frequency can be decreased

Methods: *Study design and participants*

HIV-CAUSAL Collaboration (prospective cohort studies):

- France: FHDH-ANRSC04, ANRS PRIMO, ANRS SEROCO, ANRS CO3-Aquitaine
- UK: UK CHIC, UK register of HIV seroconverters (UK),
- NL: ATHENA (the Netherlands),
- CH: SHCS
- Spain: PISCIS, CoRIS/CoRIS-MD, GEMES
- USA: VACS
- Greece: AMACS
- Brazil IPEC
- Canada: SAC

The Centers for AIDS Research Network of Integrated Clinical Systems(CNICS): 8 US sites:

Case Western Reserve University in Ohio, Fenway, Community Health Clinic in Massachusetts, Johns, Hopkins University in Maryland, University of Alabama at Birmingham, University of California at San Diego, University of California at San Francisco, University of North Carolina, and University of Washington

Inclusion criteria

- ≥ 18 years of age
- non-pregnant
- CDC stage A/B
- cART-naive with cART start in the year 2000 -2015
  (≥ 2 NRTI plus 1PI/NNRTI/INSTI/Fusion inh)
- Confirmed viral suppression
  (2 HIV RNA VL ≤200 c/ml) within 12 months after cART start)

Baseline

Date of confirmed viral suppression after ART initiation.

Methods: 3 Monitoring strategies

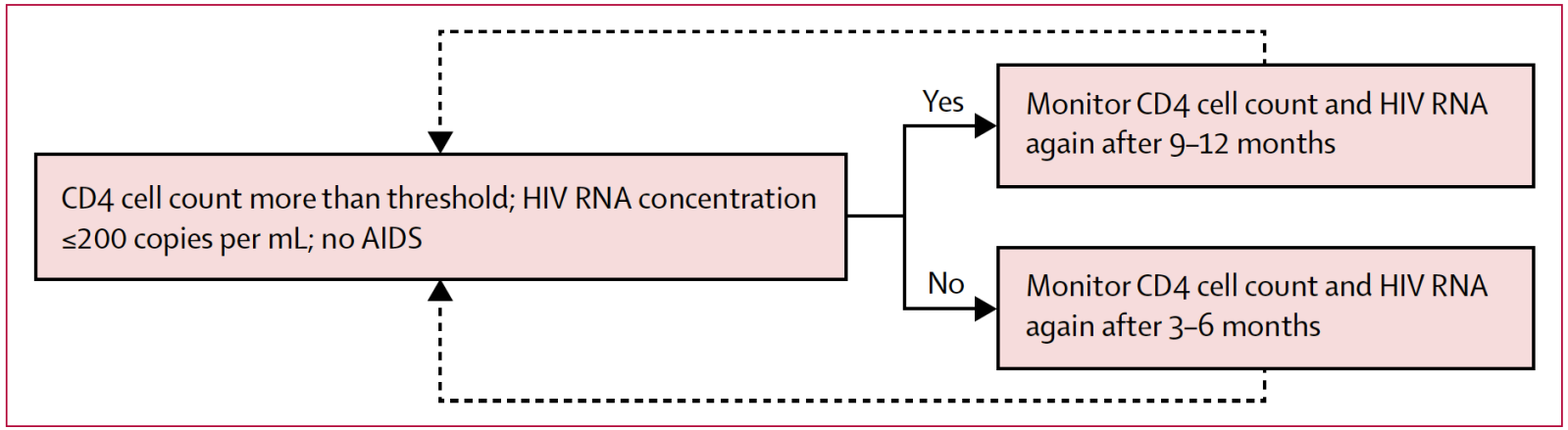

***Figure 1*: Dynamic monitoring strategies with three CD4 cell count thresholds**
The three CD4 count thresholds used in this study were 200 cells per µL, 350 cells per µL, and 500 cells per µL.

- If VL >200 or AIDS defining illness → Monitoring every 3–6 months
- Each strategy allowed an additional 1 month before and after each monitoring window (eg, 3–6 ± 1 month), so the grace period was 5 months.

Creation of an expanded dataset (3 identical replicates for each strategy) in order to emulate a hypothetical RCT with artifical censoring if

→ an individual patient‘s data were no longer consistent with the strategy

→ Earlier or later monitoring than indicated in the strategy

→ CD4 cell measurement without VL testing or vice versa

Outcomes

1. All-cause mortality
2. combined endpoint of AIDS-defining illness or death.

3. virological failure (viral load >200 copies per mL) at 24 months (±2 months)
4. mean CD4 cell count over the first 24 months

Statistical analysis

- pooled logistic regression model (hazard ratio for endpoints 1 and 2 for each strategy
  - Conditional on time of follow-up (1, 6, 12 months)
  - Conditional on baseline covariates (sex, CD4, years since dx, race, geographic origin, acquisition mode, calendar year, age, months from ART initiation to VL supprssion)

- adressing of timevarying selection bias by artificial censoring

Results

- 47 635 individuals met the eligibility criteria (data pooled in November, 2015)

- During follow-up, CD4 cell count was measured on average every 4.0 months and HIV RNA viral load every 3.8 months.

- Viral load was measured in more than 94% of months in which CD4 cell count was measured.

- Of the individuals who had data consistent with at least one monitoring strategy for 1 complete year, those following the **threshold 500 strategy**
  - had higher baseline and current CD4 cell counts,
  - were more likely to be homosexual or bisexual,
  - were less likely to have been diagnosed with HIV infection in the previous year,

  than individuals following the other strategies (table 1).

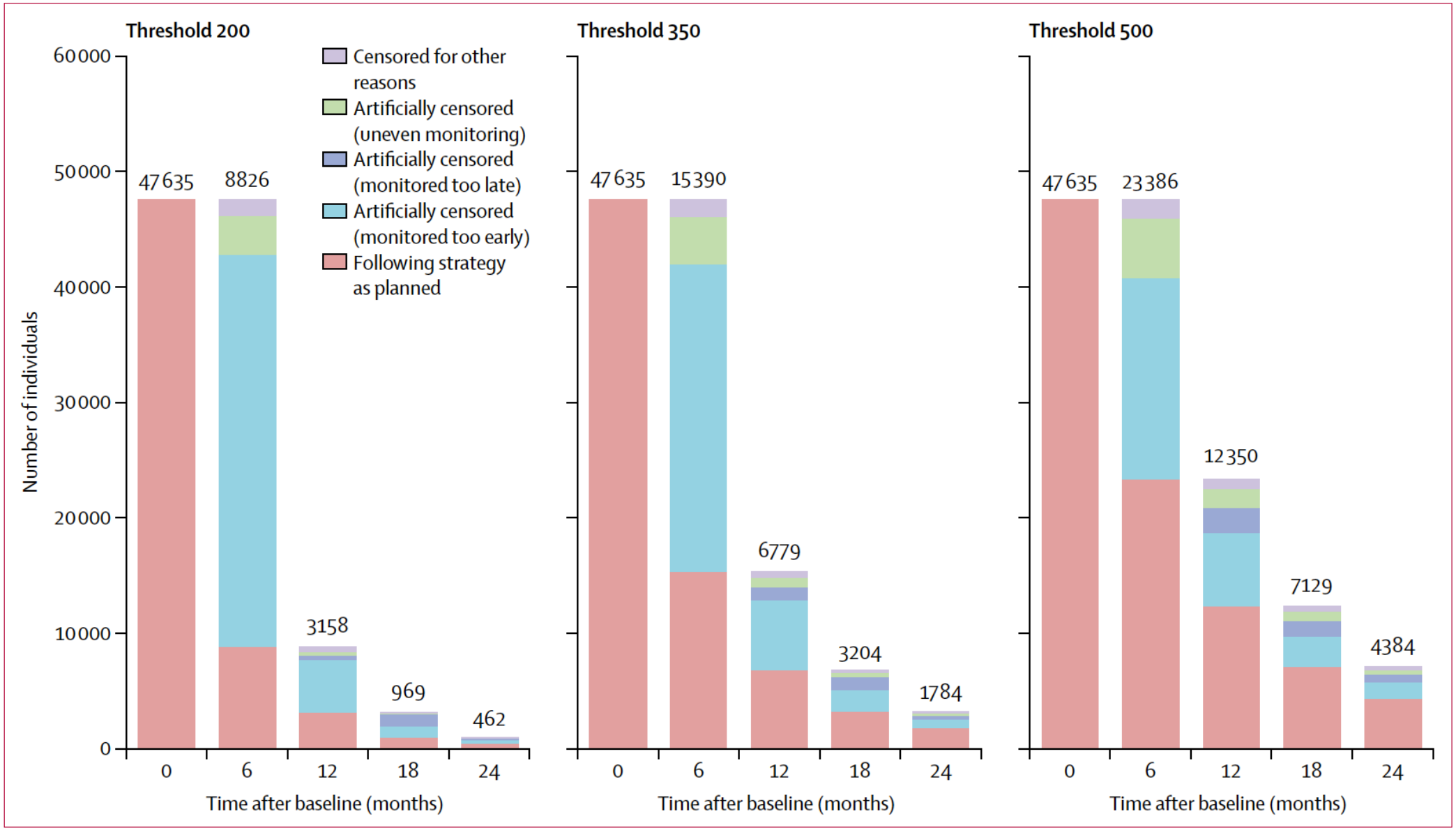

***Figure 2*: Number of individuals following each monitoring strategy and censored during follow-up by monitoring strategy**

Data above bars are numbers of patients following strategy as planned.

464 deaths
1091 AIDS-defining illness or death.

individuals follow more than one monitoring strategy over time
→ each death contributed to 2.2 strategies
→each AIDS-defining illness/death contributed to 2.3 strategies

	Number of events	Person-months	Risk estimate* (95% CI)
All-cause mortality			
Threshold 200	107	249 597	HR 1·05 (0·86–1·29)
Threshold 350	157	340 428	HR 1·02 (0·91–1·14)
Threshold 500	200	490 713	1
AIDS-defining illness or death			
Threshold 200	267	247 816	HR 1·08 (0·95–1·22)
Threshold 350	365	337 823	HR 1·03 (0·96–1·12)
Threshold 500	459	487 232	1
Virological failure (HIV RNA >200 copies per mL) at 24 months†			
Threshold 200	35	..	RR 2·01 (1·17–3·43)
Threshold 350	89	..	RR 1·24 (0·89–1·73)
Threshold 500	171	..	1

HR=hazard ratio. RR=risk ratio. *Adjusted for the baseline covariates (sex, age, race, geographic origin, acquisition group, CD4 cell count, HIV RNA concentration, calendar year, years since HIV diagnosis, cohort, and months from combined antiretroviral therapy initiation to virological suppression). We adjusted for potential selection bias induced by artificial censoring using inverse probability weighting. †Based on 405 individuals (threshold 200), 1610 individuals (threshold 350), and 3962 individuals (threshold 500) with HIV RNA concentration measurements at 24 (±2) months.

***Table 2*: Clinical and virological outcomes by monitoring strategy**

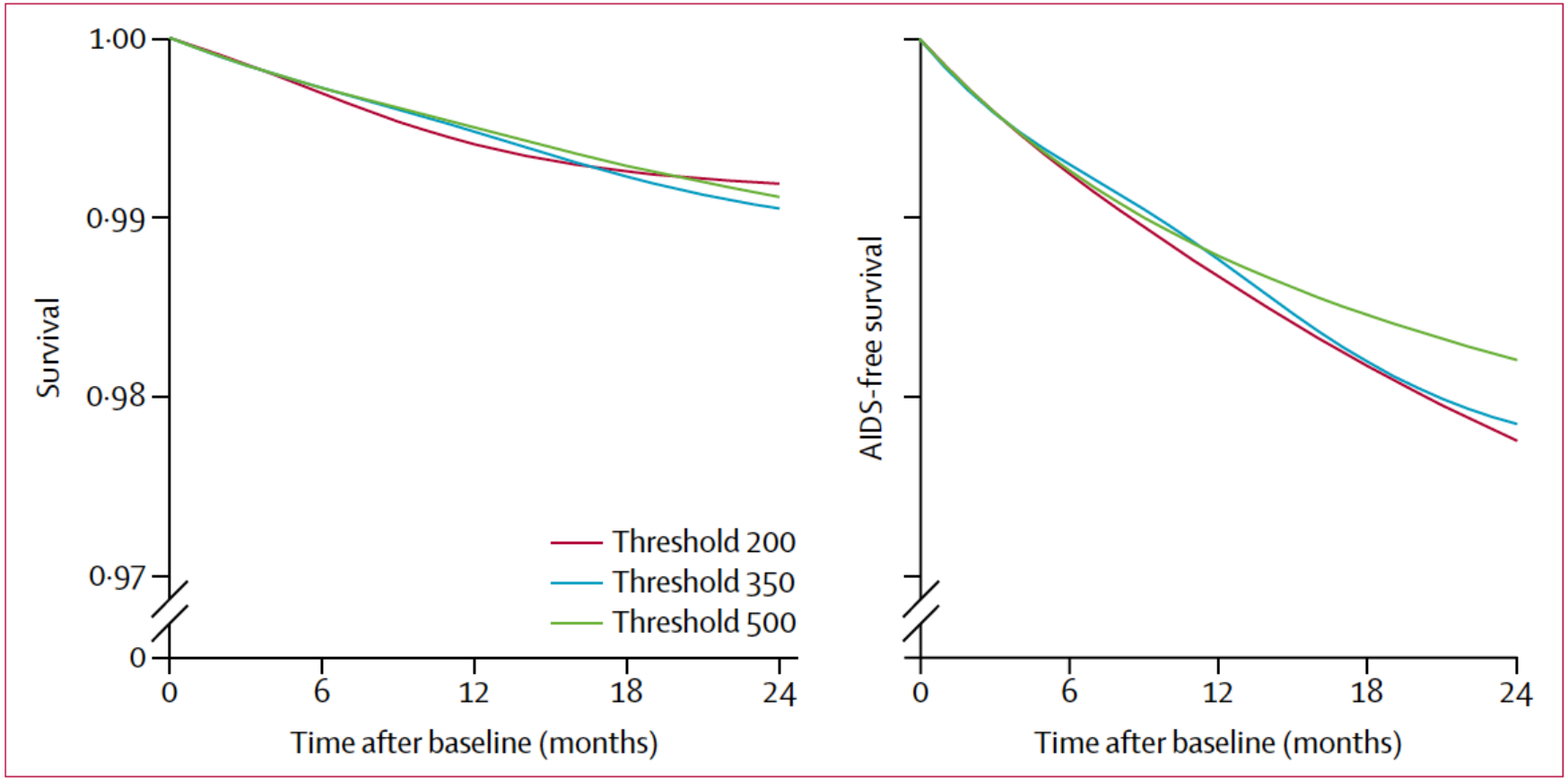

***Figure* 3: 24 month survival and AIDS-free survival curves by monitoring strategy**

The curves are standardised by the baseline covariates: sex, CD4 count (≤200 cells per μL, 201–350 cells per μL, 351–500 cells per μL, ≥501 cells per μL), years since HIV diagnosis (<1 year, 1–4 years, ≥5 years, unknown), race (white, black, other or unknown), geographic origin (North America or western Europe, sub-Saharan Africa, other, unknown), acquisition group (heterosexual, homosexual or bisexual, injection drug use, other or unknown), calendar year (restricted cubic splines with three knots at 2001, 2007, and 2011), age (restricted cubic splines with three knots at 25 years, 39 years, and 60 years), cohort, and months from initiation of combination antiretroviral therapy to virological suppression (2–4 months, 5–8 months, ≥9 months). We adjusted for potential selection bias induced by artificial censoring using inverse probability weighting.

Conclusion

- In individuals with CD4 >200 cells/µL, monitoring of CD4 cells and VL every 9–12 months does worsen 2 year clinical and immunological outcomes (in virally suppressed individuals on ART without AIDS in high-income countries).

- Decreasing monitoring frequency in individuals with a CD4 count > 200 cells/µL compared to > 500 cells/µL leads to an increased risk of virological failure at 24 months of follow-up (wide 95% CIs)

- Because few individuals followed the strategies of interest for extended periods of time, we were not able to assess clinical, immunological, and virological outcomes after 2 years of follow-up.

Limitation

- Unknown whether measured covariates were sufficient to exclude selection bias (observational data)
- Possible imbalance induced by biased testing frequency
- No assessment of non-HIV-associated events (e.g. cancer, Hepatitis C)
- No inclusions of individuals starting ART before 2000

→ Reduction of CD4 monitoring in patients with CD4>200/ul (up to 2 years)

→ More frequent VL monitoring probably neeeded for early detection of VL failure