Mortality risk related to delayed switching of ART, depending on CD4 count at time of virological failure

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Background

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- The effect of delayed switch to second-line treatment on mortality has been quantified by several studies.
- None of these studies have explored the functional relationship between time of switch and mortality.
- However, the effect of delay on mortality

  i) may be nonlinear, and

  ii) may differ between patients of different CD4 count levels at failure.

Objective

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To model the relationship between time of switching and 5-year survival, conditional on CD4 count at failure
(using observational data from IeDEA-SA and causal inference techniques).

Study Setting

- We included 8 HIV treatment facilities in South Africa that take part in the IeDEA-SA collaboration.
- 7255 adult patients ($\geq$ 18 years) that started ART after 2004, failed first-line therapy, and had complete data of CD4 count and WHO stage at failure, were included in the analysis.
- *Viral failure:* two consecutive VL over 1000 copies per/ml, measured at least 4 weeks apart.
- *Switch:* A switch from first-line ART to second-line ART was broadly defined as a switch from 2 NRTIs and 1 NNRTI to 2 NRTIs and 1 PI.

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- We are interested in the effect of (timing of) switch, measured in months since failure, on 5-year survival.
- Measured time-dependent confounders that are affected by prior treatment decisions are: CD4 count, viral load and visit frequency (number of visits in the past 6 months).
- We use longitudinal targeted maximum likelihood estimation[1] to adjust for these measured confounders and estimate 5-year survival that had been observed under different delay strategies:

  i) switch immediately (at month 1) or never,

  ii) switch after 1 month, 3 months, ..., 60 months .

[1] as suggested by Petersen et al., *JCI*, 2014 and implemented in the *R*-package `ltmle`

Methods (II)

For approach ii), we specify marginal structural (working) models to summarize how the counterfactual probability of death varies as a function of follow-up time (t) and assigned switch time (st):

i) independent of CD4 count at failure:

$$logit(P(Death)^{t,st}) = b_0 + b_1 \log(t) + b_2(st - t) + b_3([st - t]^2) + b_4([st - t]^3) + b_5(\log(t) \cdot [st - t]) + b_6(\log(t) \cdot [st - t]^2)$$

ii) conditional on CD4 count at failure:

$$\begin{aligned} logit(P(Death|CD4)^{t,st}) = b_0 + b_1 \log(t) + b_2(st - t) + b_3([st - t]^2) \\ + b_4([st - t]^3) + b_5(\log(t) \cdot [st - t]) + b_6 I(101 < CD4 < 200) + \\ b_7 I(CD4 > 200) + b_8 I(101 < CD4 < 200) \cdot (st - t) + \\ b_9 I(CD4 > 200) \cdot (st - t) + b_{10} I(CD4 < 100) \cdot \sqrt{t} + \\ b_{11} I(101 < CD4 < 200) \cdot \sqrt{t} + b_{12} I(CD4 > 200) \cdot \sqrt{t} \end{aligned}$$

Descriptives

- Median time from ART start to failure was $\approx$ 3.3 (2; 5.2) years.
- Median time from confirmed failure to switch was 121 (49; 288) days.
- 3765 patients (52%) switched, 842 (12%) died.
- The included patients were mostly female (65%), had advanced WHO stage (60%), and achieved suppression prior to failure (75%).

Results (I) – immediate switch versus no switch

The counterfactual probability of death, 5 years after first-line failure, was estimated as

- 10.5% (2.2%; 18.8%) if everyone had been switched immediately,
- 26.6% (20.9%; 32.3%) if everyone had stayed on their failing regimen.

This corresponds to a difference of -16.1% (-26.1%; -6.1%).

Results (II) – graphical summary of the 2 (working) MSM's

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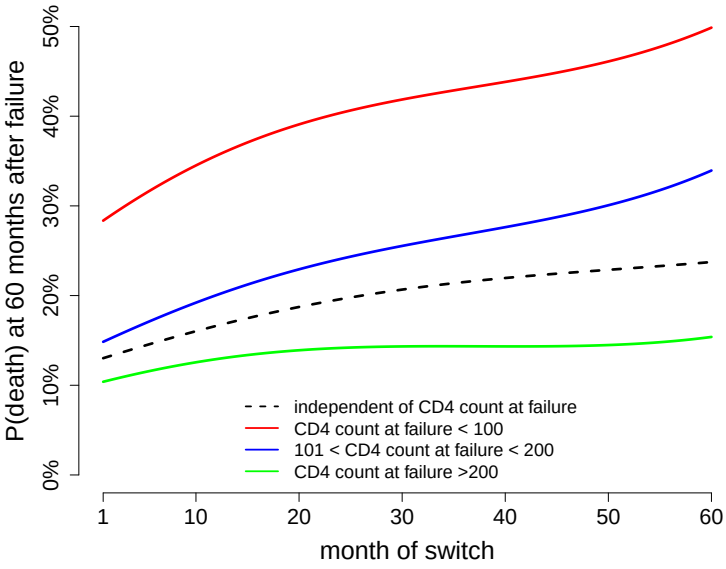

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Conclusions:

- Early switch of regimen is highly beneficial in terms of reduced mortality.
- Patients with low CD4 counts at time of failure are at particularly high risk of increased mortality (whereas a moderate delay in very healthy patients seems reasonably acceptable).

Limitations:

- No availability of adherence data.
- Limited number of patients for particular switching strategies; positivity violations.

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