

Using causal models to determine optimal dynamic treatment regimes with a time-to-event outcome

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Background and objectives

- Growing literature on causal modelling
- Marginal structural models
- Optimal dynamic treatment regimes
 - Hernán *et al.* 2006, Robins *et al.* 2008

Objectives:

- Apply MSMs to optimal dynamic treatment regimes with a time-to-event outcome
- Explore interactions with patient characteristics

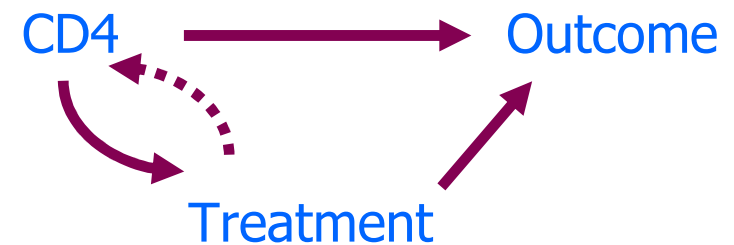
Motivating example: when should HIV-infected persons start treatment?

Early: potentially minimise long-term immunosuppressive damage of HIV

Late: minimise side effects and risk of developing drug resistance

Key biomarker: CD4 cell count

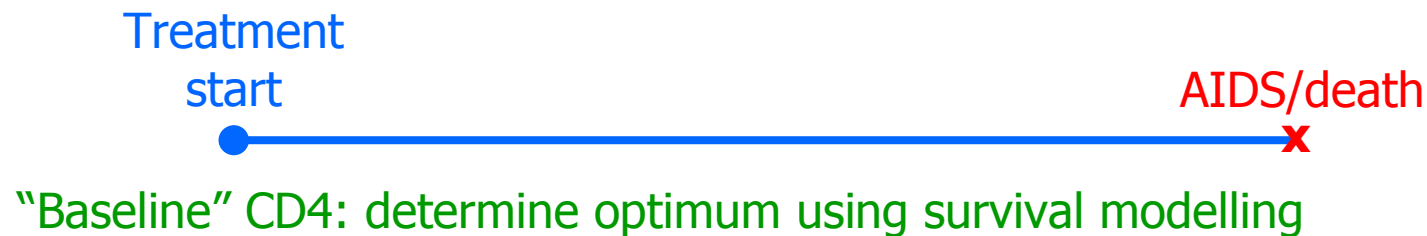
- Typically declines after initial infection
- Low values predict poor outcome
- Used to decide when to start treatment
 - Dynamic treatment regimes



Optimal CD4 at which to start treatment is unknown
-> Optimal dynamic treatment regimes

A naïve analysis

In the absence of a randomised trial, turn to observational data



Reasons why patients chose to start treatment when they did?

A potential randomised trial: protocol

HIV-infected persons

Hernán *et al.* 2008



Treatment naïve
CD4 ≥ 500 cells/mm³

Randomise to start treatment when confirmed CD4 first $< x$ cells/mm³



x in $\{200, 210, 220, \dots, 490, 500\}$

Patients should start treatment ≤ 1 month after the confirmed CD4

Follow up until AIDS/death

Visits every 3 months

CD4 at least every 12 months

Attempt to mimic this randomised trial
using causal methods with observational data

A causal approach

- T_x , time to AIDS/death under regime x

- Marginal structural model:

$$\lambda_{T_x}(t/x, V_0, \beta, \gamma) = \lambda_0(t) \exp\{\beta'V_0 + \gamma'g(x)\}$$

V_0 =baseline covariates

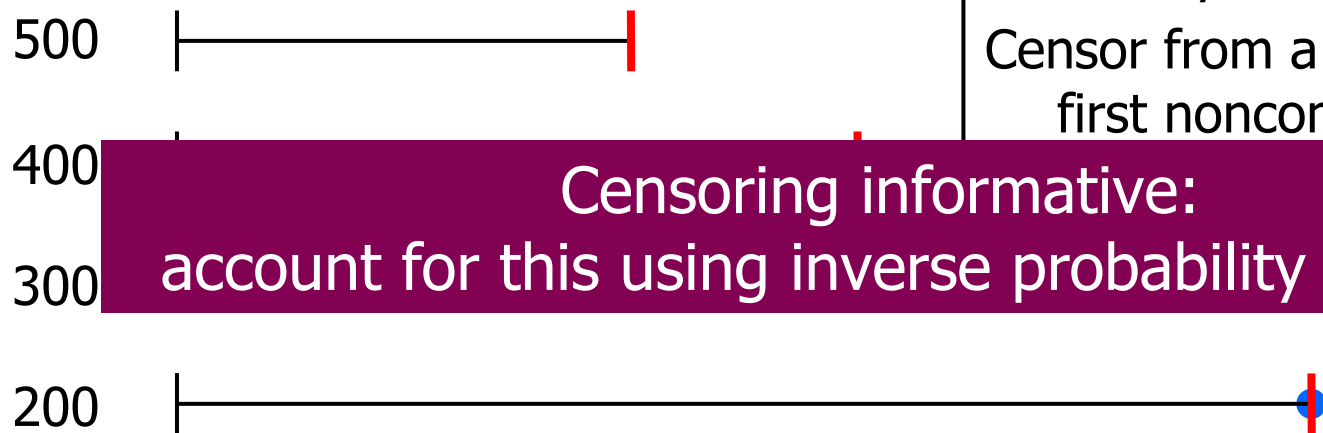
- Optimal x is that which minimises the risk of AIDS/death
- Even in the absence of any other censoring, T_x only observed for the regime(s) a patient follows
- The causal parameters of interest γ can be estimated using inverse probability weighting

Step 1. All patients follow all regimes

Example patient, observed data:



Simple scenario:
"Randomisation", $x =$



Consider all patients to be compliant with all regimes initially

Censor from a regime when first noncompliant

**Censoring informative:
account for this using inverse probability weighting**

Step 2. Estimate inverse probability weights

- At a given time t , and given baseline and time-updated covariates, and treatment history:
 - Weights: inverse probability of remaining uncensored to t
 - $P(\text{remaining uncensored to } t) = P(\text{observed treatment to } t)$
- Model for treatment initiation with discrete time
 - Estimate probability of observed treatment in each interval
 - Multiply across intervals to obtain the probability of observed treatment to that time
- **Key assumption:** no unmeasured confounders for treatment initiation and outcome
- Stabilised weights: narrower CIs

Step 3. Weighted discrete-time survival regression

- Pooled logistic regression

$$\text{logit}\{P(\Delta = 1/x, V_0, \beta, \gamma, \delta)\} = \exp\{\beta'V_0 + \delta'f(t) + \gamma'g(x)\}$$

$\Delta = I(\text{AIDS/death uncensored})$

- Parameters estimated using weighted maximum likelihood
 - (Conservative) robust standard errors
- The parameters γ of this model can be interpreted as the causal parameters of the MSM
- As previously, **optimal x** is that which minimises the risk of AIDS/death

Example: CASCADE

- Collaboration of 22 cohorts of HIV-infected persons with well-estimated dates of infection across 15 countries
- Match the trial protocol
 - Include patients from first CD4 ≥ 500 cells/mm³
 - Censor patients if no CD4 measurement for over 12 months
 - Second set of weights
 - Multiply by treatment weights to get overall weights
- N = 4803
 - Median first CD4 = 660 cells/mm³ (IQR 567-826)
 - 234 AIDS/death events

Construction of inverse probability weights

- Selection, transformation and interaction of covariates performed using a multivariable fractional polynomial procedure

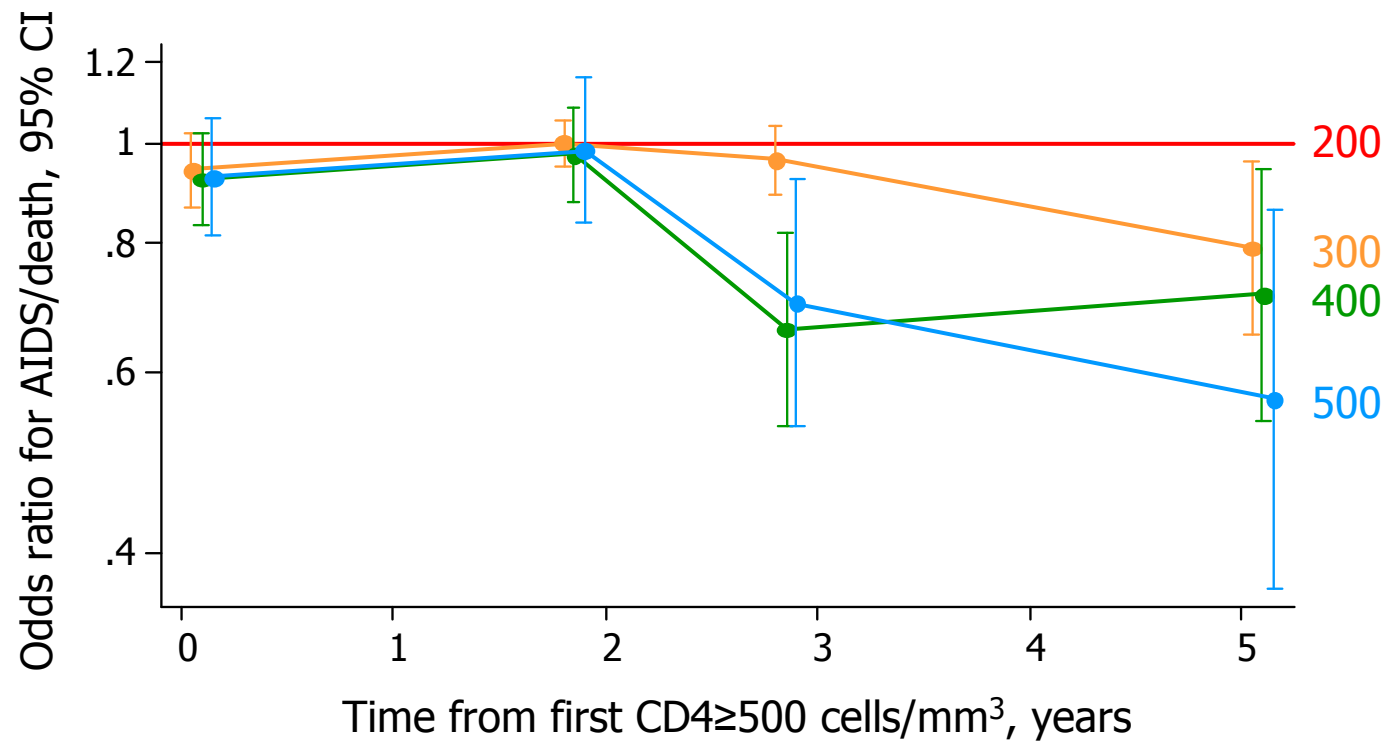
	Treatment model	Censoring model
Period, 3 monthly	Linear	Two frac poly powers selected (-2, -0.5)
Baseline covariates	Age, year of infection, route of transmission, cohort; no transformations	
Time-updated covariates		
CD4*	Two frac poly powers selected (3, 3*ln)	Linear
Decrease in ICD4 over last period	Linear	Linear
Treatment	N/A	Binary
Interactions	ICD4*period CD4 decrease*period	CD4 decrease*period CD4 decrease*treatment

* CD4 = $\ln(\text{current confirmed CD4})$; if no recent CD4, then LOCF for up to one year

- Sensitivity analyses: also considered HIV RNA
 - Outcome results very similar, but wider confidence intervals due to smaller numbers of patients

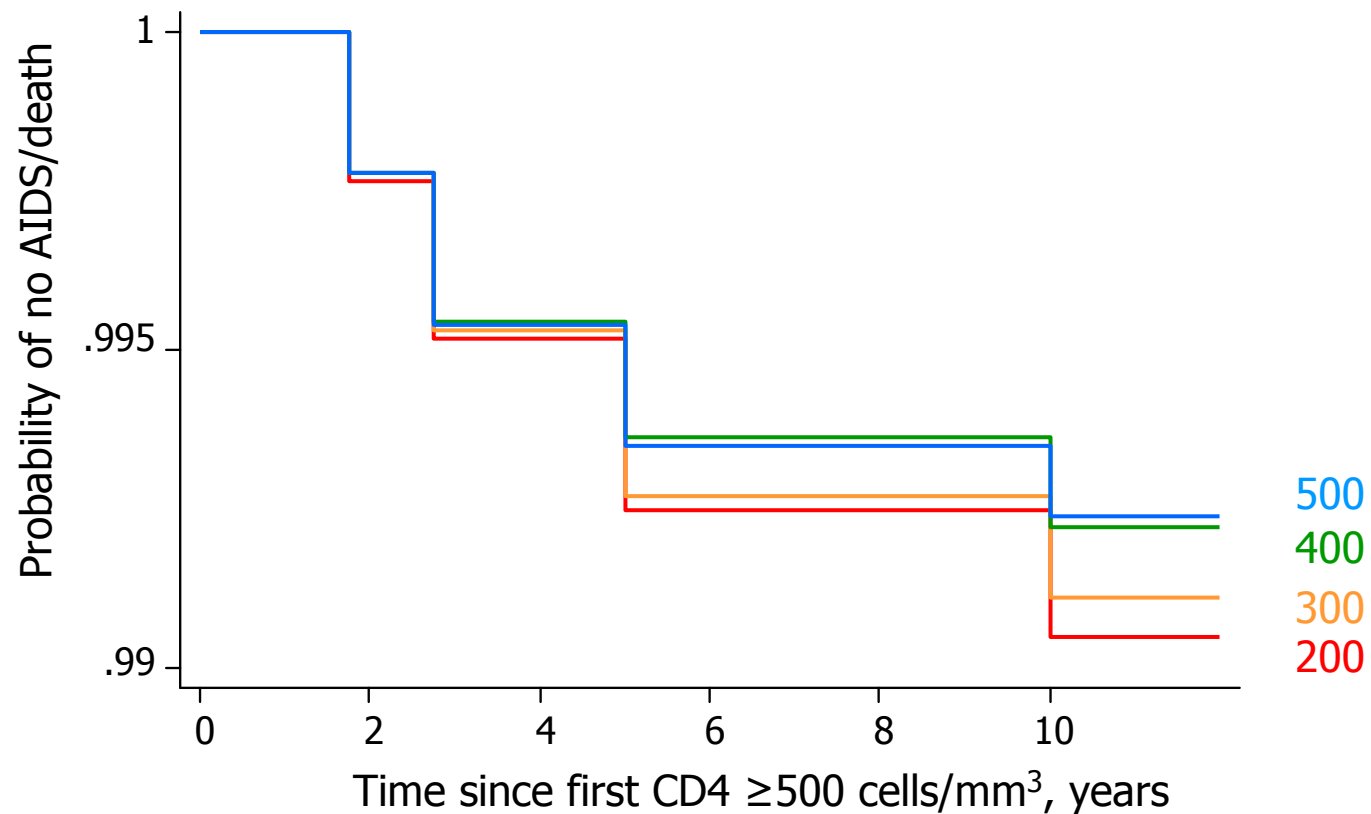
Results: "randomisation" $x = 200, 300, 400, 500$

- Period as a categorical variable (quartiles)
- Period * x interaction
- Same baseline covariates as in treatment model



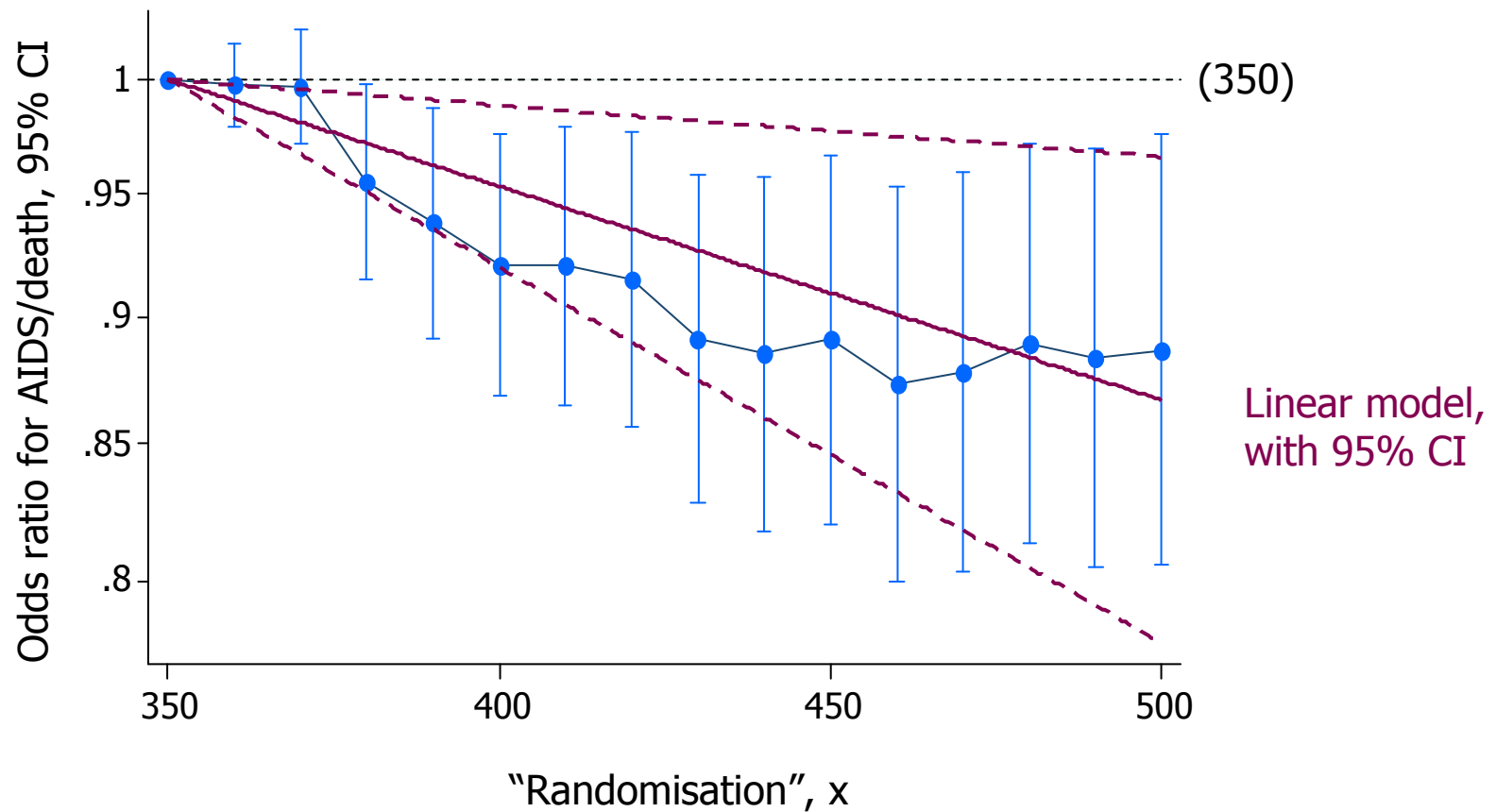
Results: "randomisation" $x = 200, 300, 400, 500$ (2)

- Cumulative survival, for a typical patient:



Results: "randomisation" x in {350, 360, ..., 500}

- No evidence of interaction between x and period



Tailoring the regime to the patient

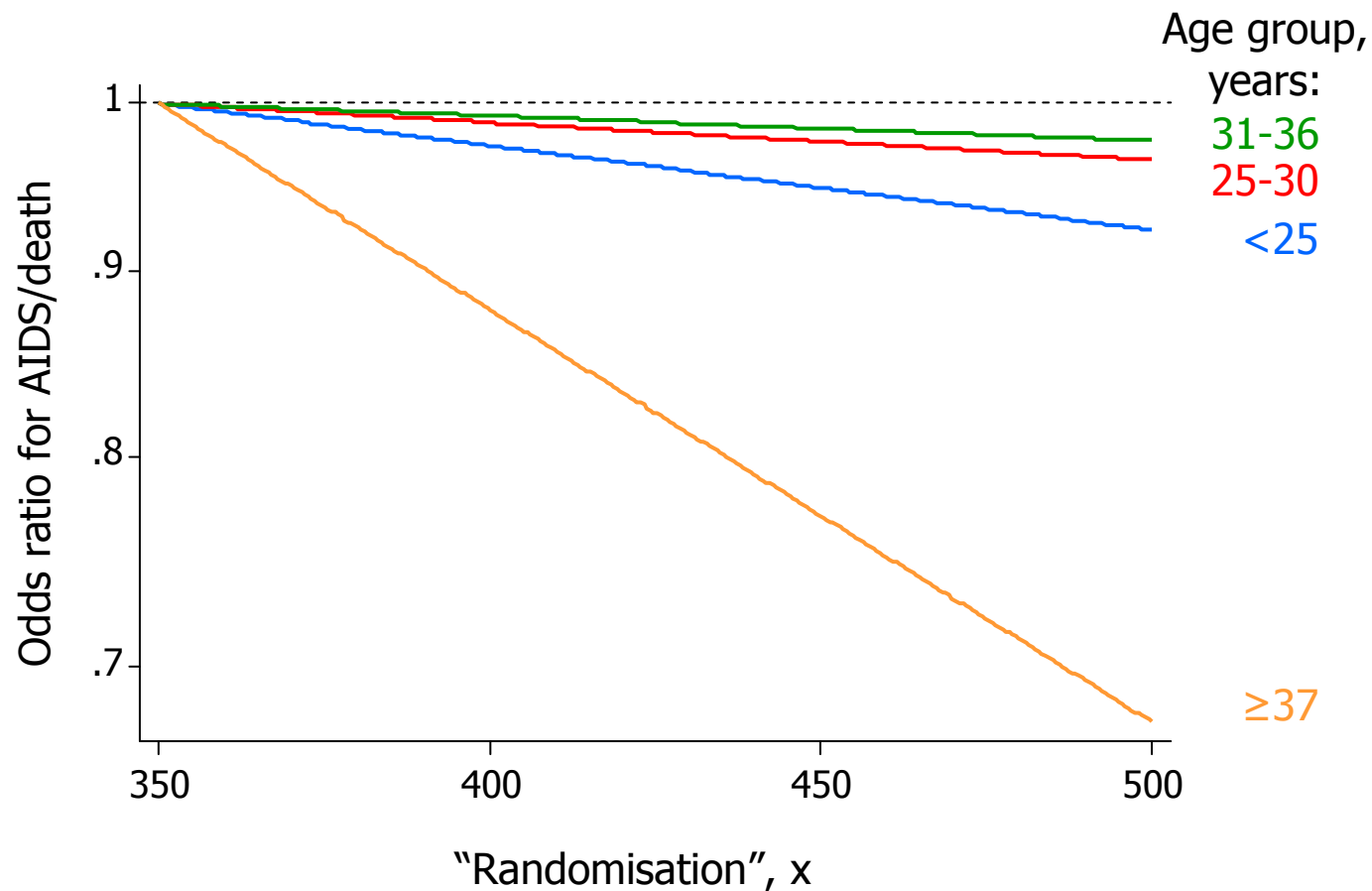
- Optimal regime x may vary by patient characteristics such as age or year of infection
 - Interactions
 - Replace function $g(x)$ in the outcome model with, for example:

$$g(x, V_0) = \sum_j (\gamma_j + \eta_j V_0) x^{p_j}$$

- **CASCADE:**
 - No evidence of randomisation interaction with year of infection, route of transmission or cohort
 - Interaction with age at infection (linear, $p=0.02$)

Results: "randomisation" x by age group

- For illustration, age group defined roughly by quartiles



Summary

- Illustrated how MSMs can be used in the context of optimal dynamic treatment regimes with a time-to-event outcome
- Demonstrated how optimal regimes may depend on patient characteristics
 - How these may be incorporated using MSMs
- Initiating treatment at $CD4 \geq 380$ cells/mm³ may be beneficial
- Patient characteristics such as age may be important in these decisions
- These findings need to be confirmed in larger datasets

Limitations and further work

- This is not a randomised trial
- Key assumptions
 - For any causal model: no misspecification of the models, no unmeasured confounders
 - In addition for MSM: positivity assumption
- Perform further sensitivity analyses to assess the impact of possible residual unmeasured confounders
- In principle more complicated regimes, eg
 - If recent drop in CD4 $>z$ cells/mm³, then initiate when CD4 first $<x$ cells/mm³
 - Otherwise initiate when CD4 first $<y$ cells/mm³

Thank you

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