Monitoring and outcomes of ART– Mathematical model based on IeDEA Southern Africa

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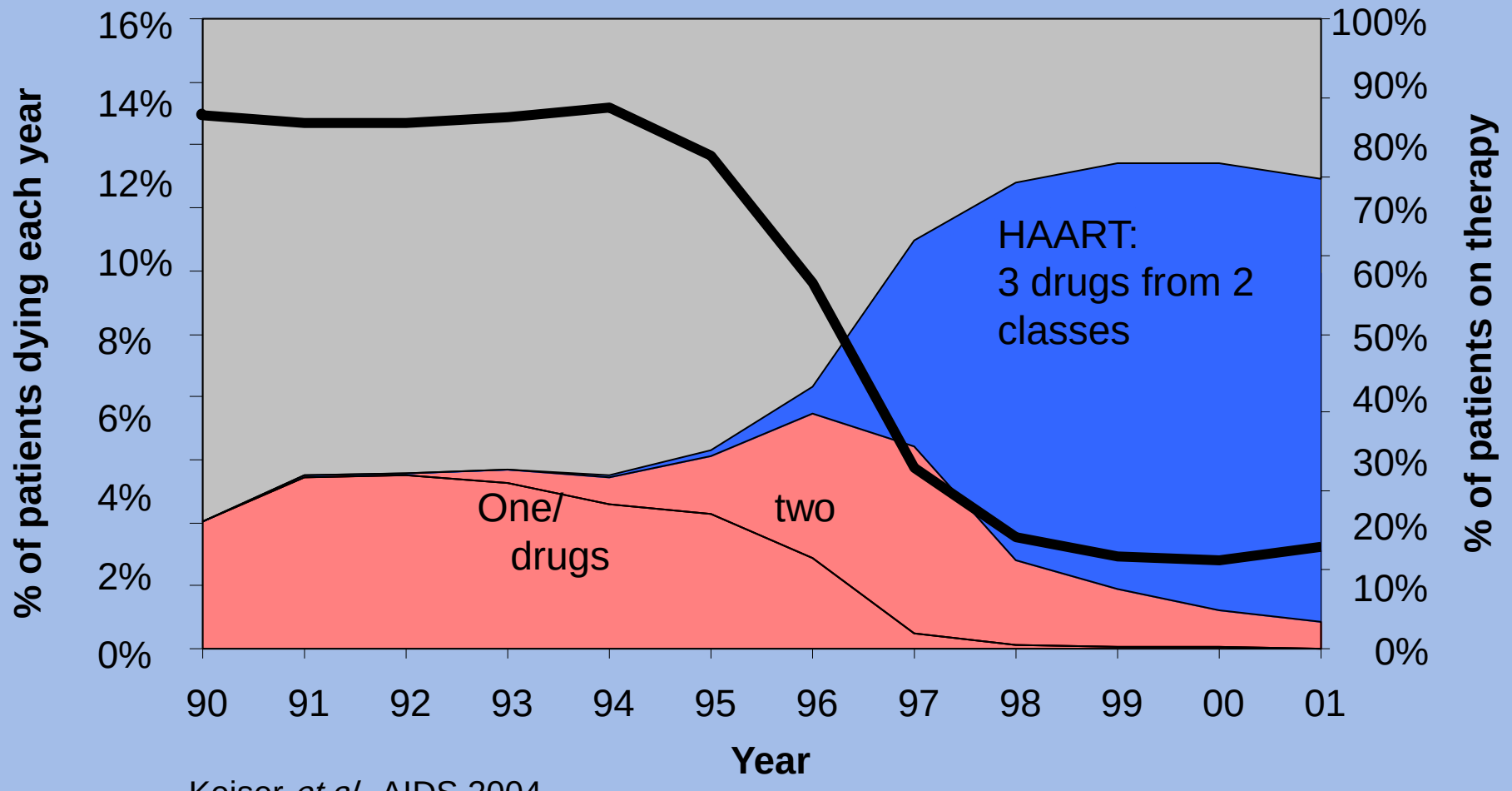
Background: HIV and ART

- HIV is a major global health burden – over 33 million people infected, 22 million of whom in sub-Saharan Africa (WHO, 2009)
- Antiretroviral therapy (ART) has improved the survival of HIV infected patients tremendously

Background: HIV and ART



Keiser *et al.*, AIDS 2004

Background: HIV and ART

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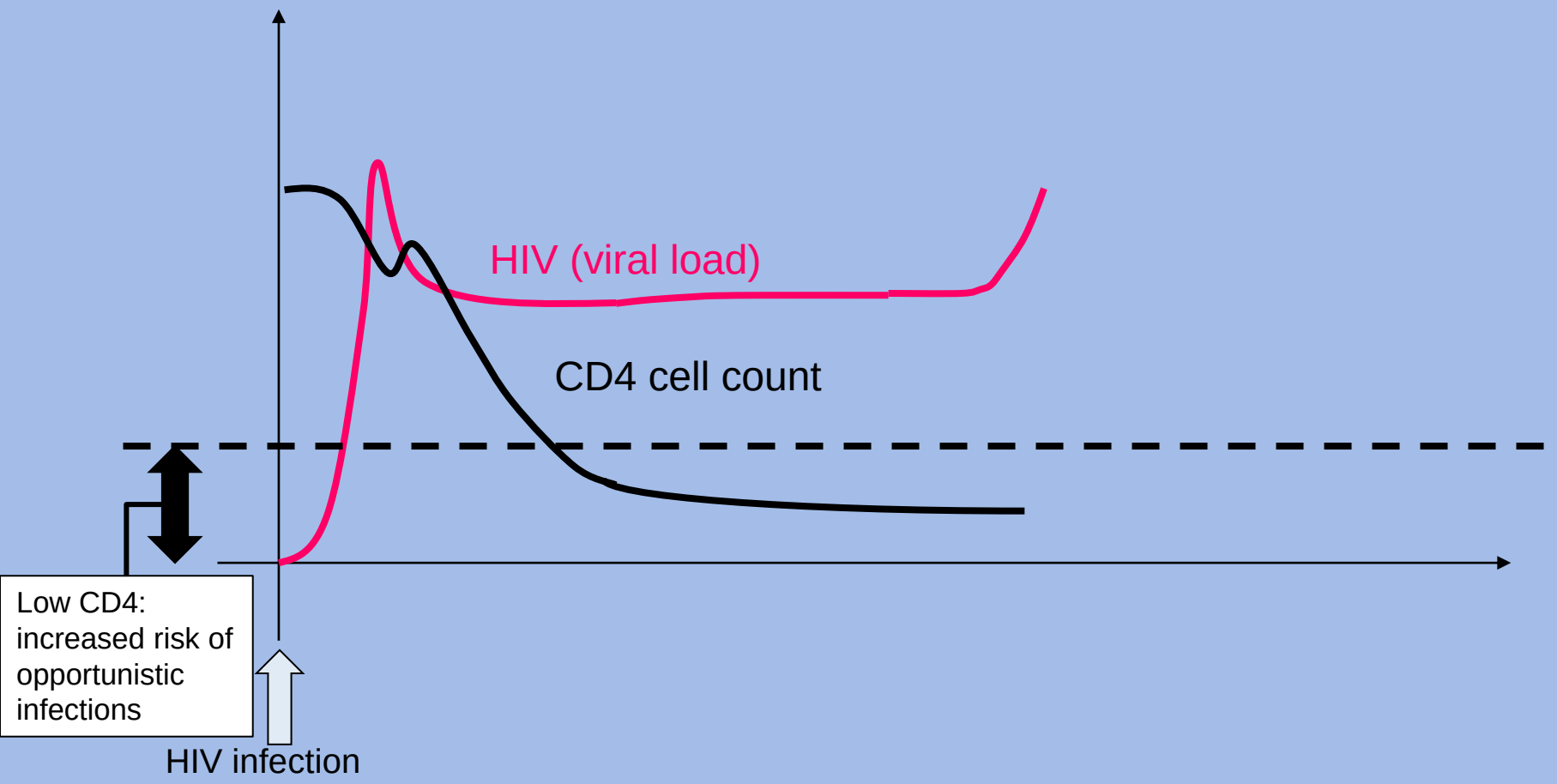
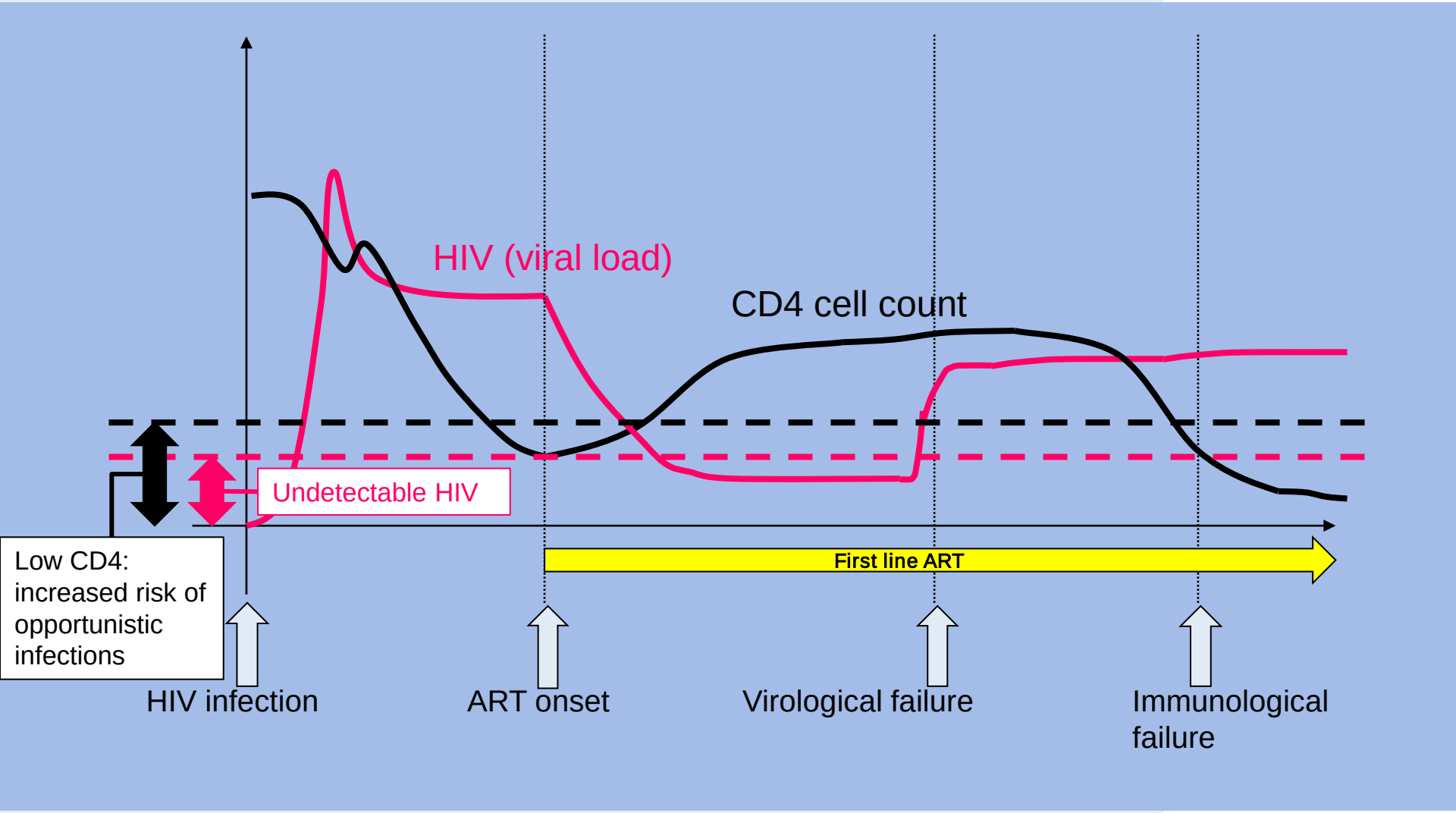
- In low-income countries, ART is provided with a public health approach – often with very restricted drug regimen options and laboratory monitoring facilities

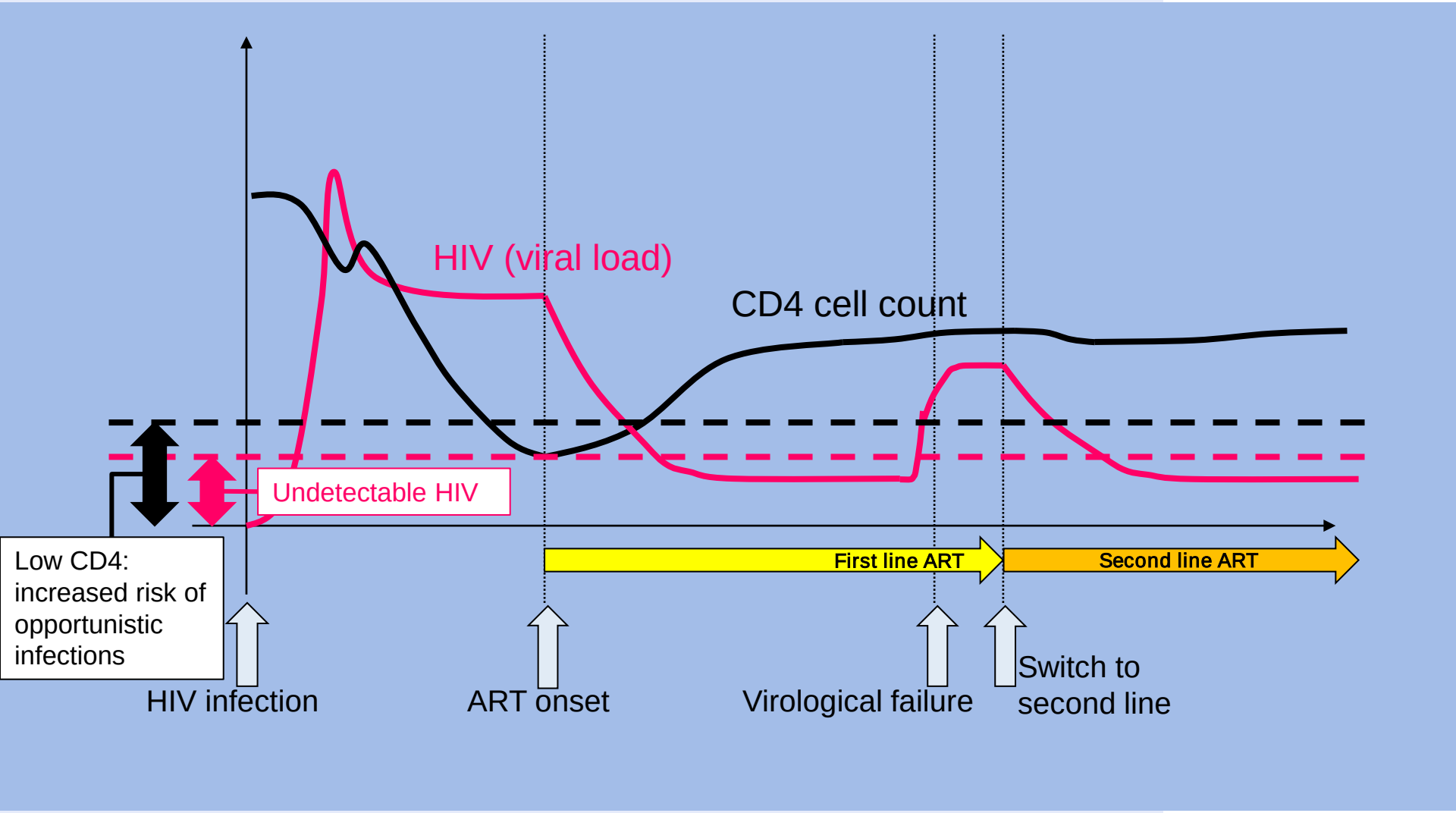
Background: HIV and ART



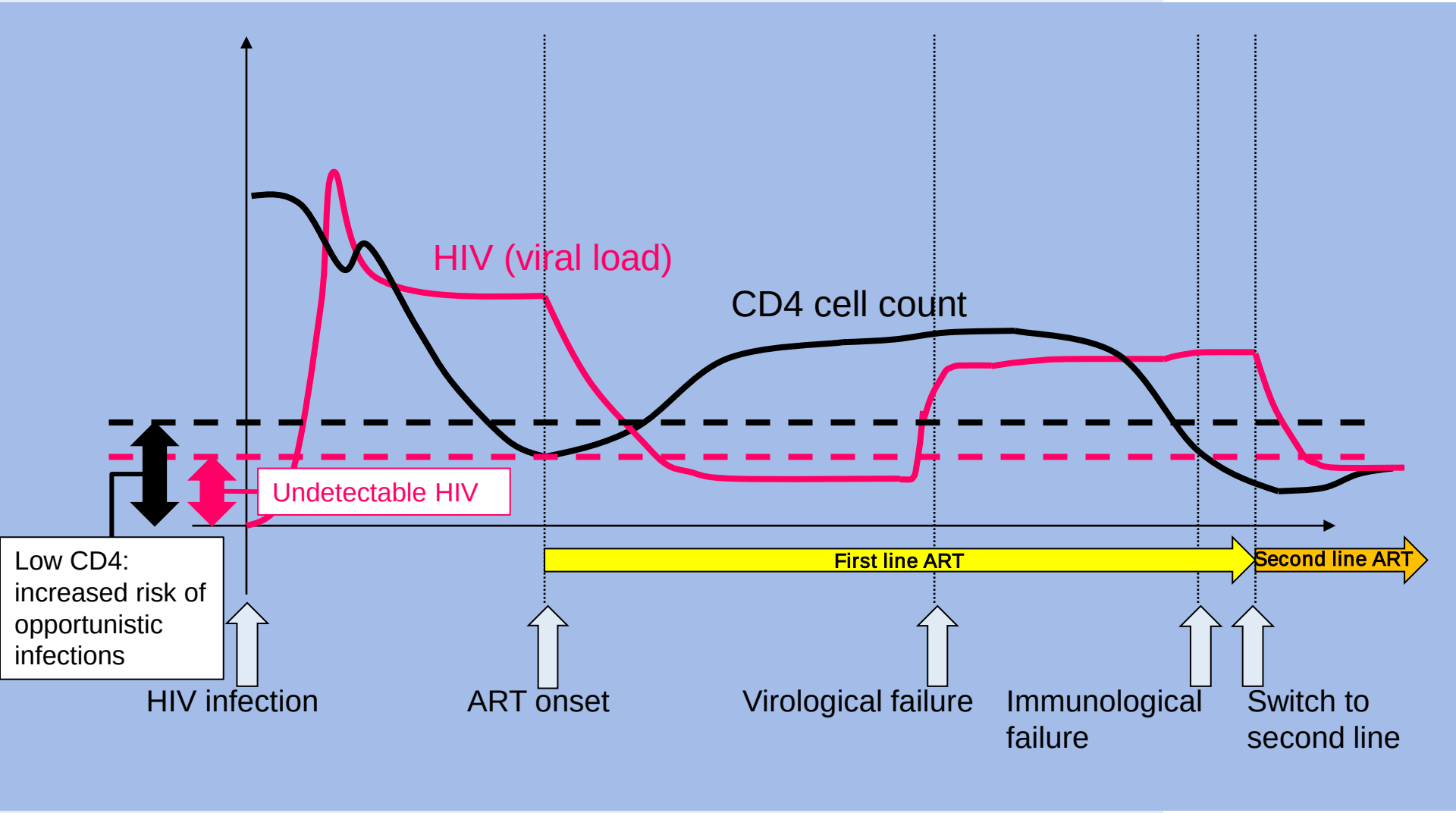
Background: HIV and ART



Background: HIV and ART



Background: HIV and ART



Background:
Routine viral load monitoring

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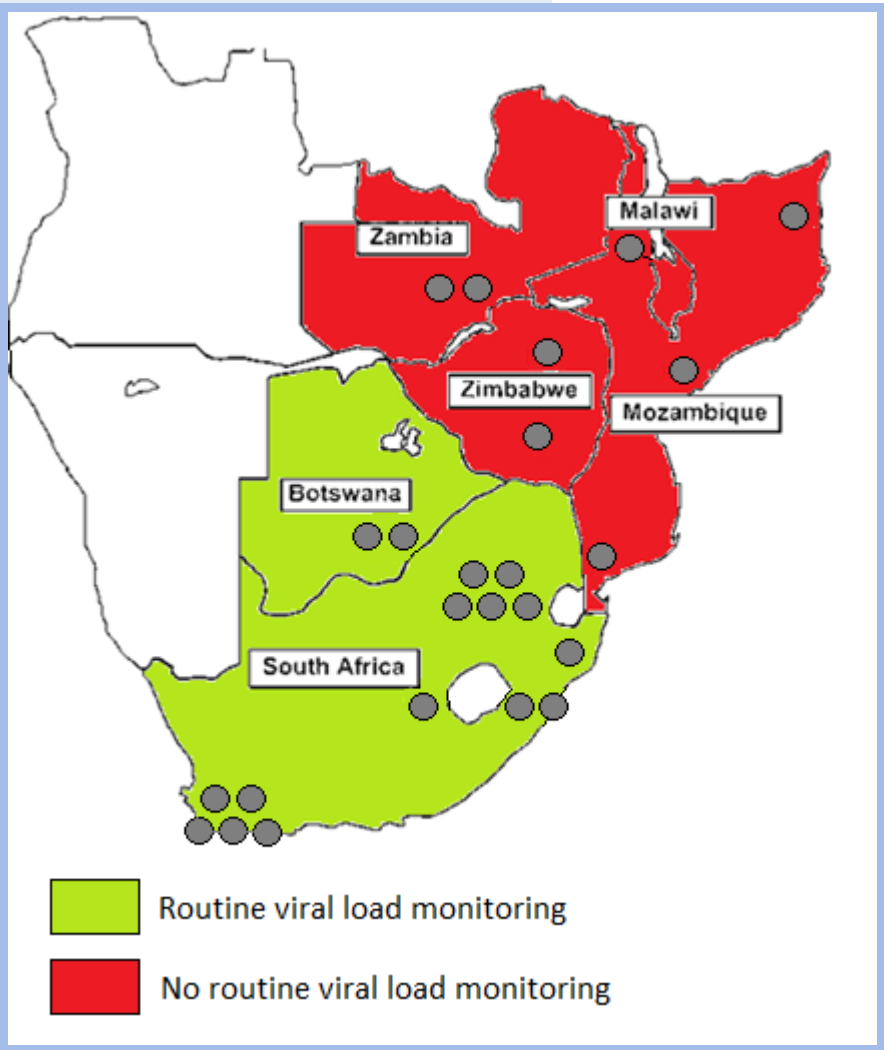
- Routine viral load monitoring: viral load is measured regularly for all patients
- Question: How large are benefits of routine viral load monitoring on the:
  - Individual level (e.g. reducing mortality)
  - Population level (e.g. reducing transmission)

Background: leDEA-SA

- Over 200,000 patients receiving ART
- 24 cohorts in six countries
- Two countries (South Africa, Botswana) have routine viral load measurements as part of the national ART programme



The mathematical model

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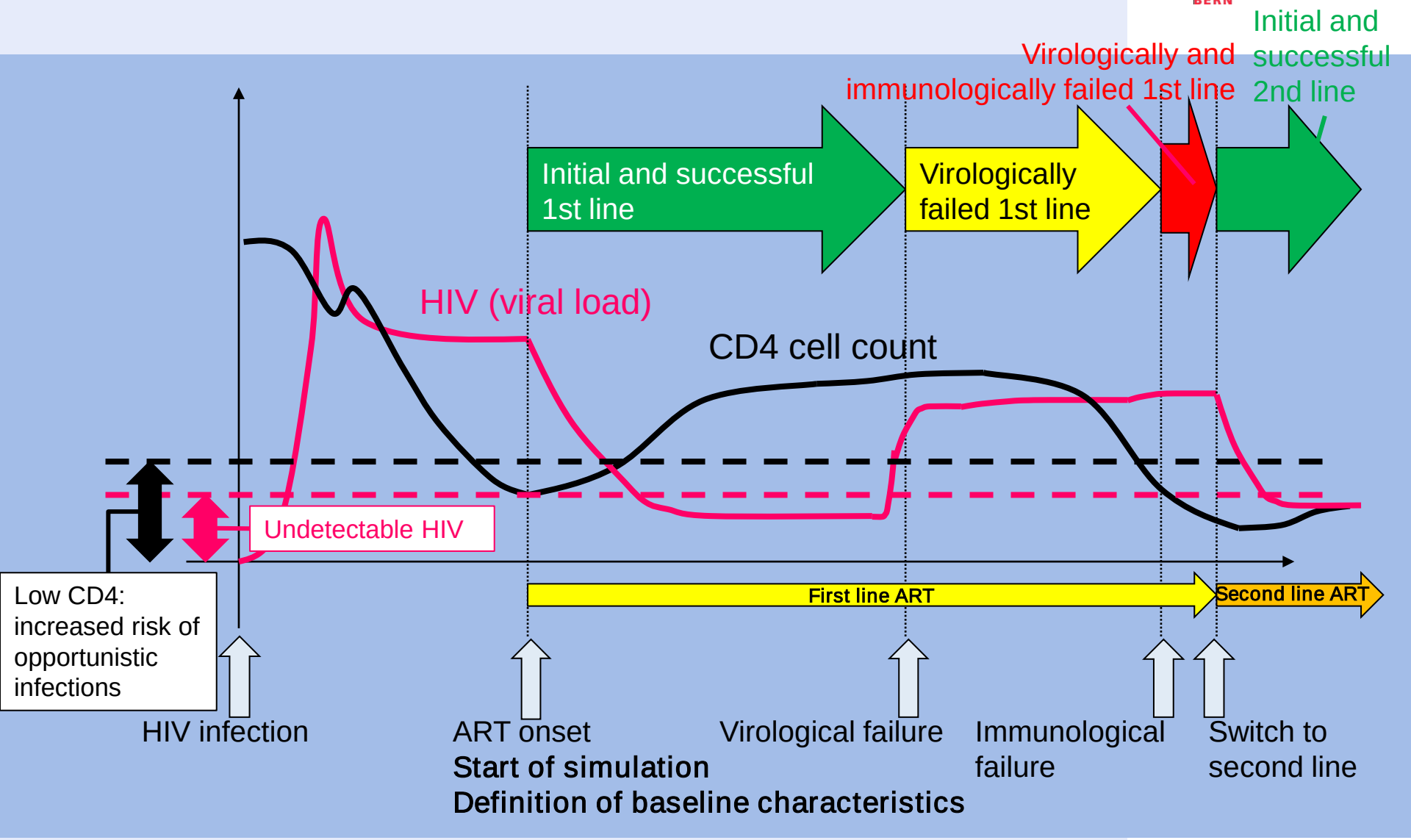
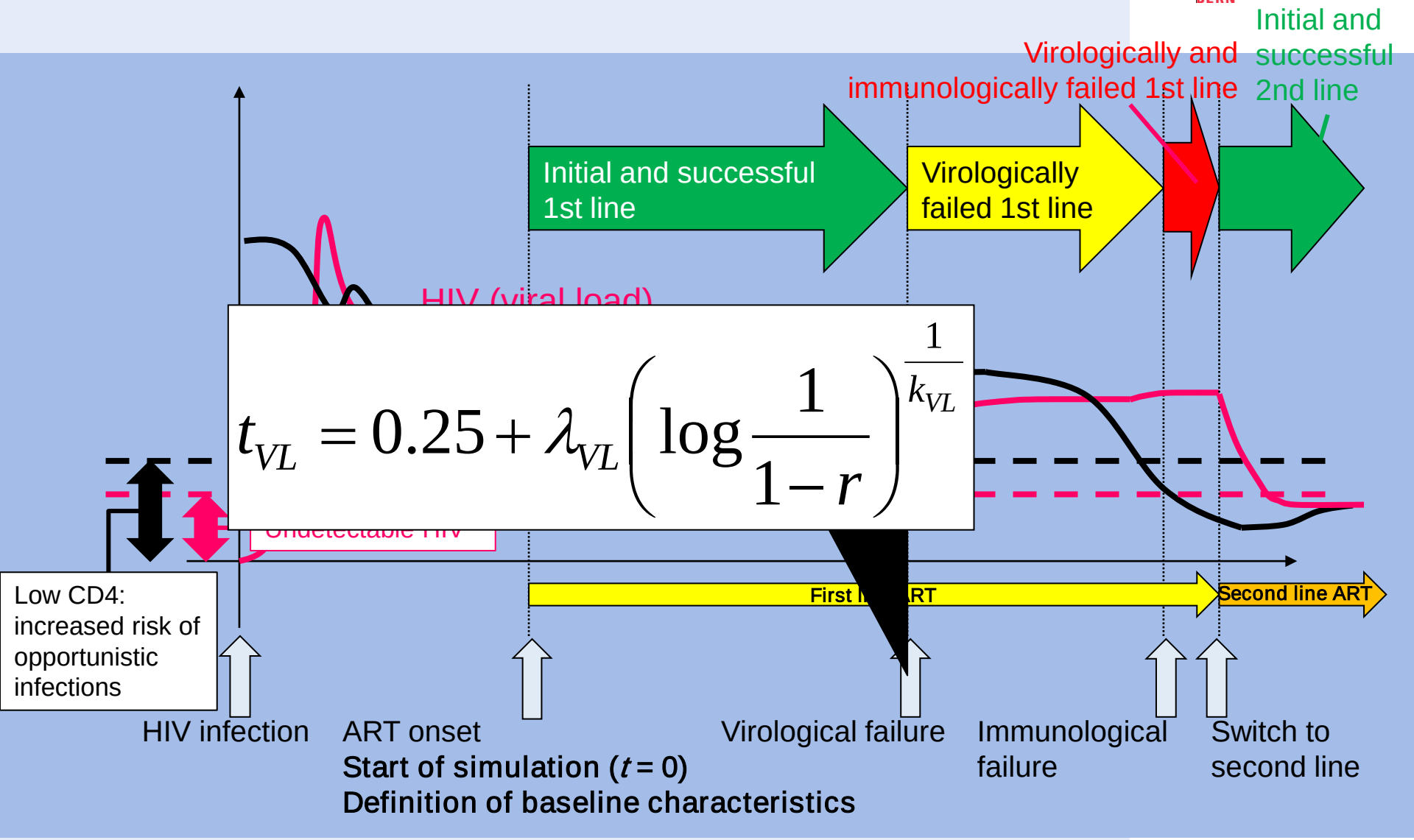
- Individual based, stochastic simulation model
- Simulates independently a number of patients receiving ART
- Programmed in MATLAB programming language

  (version 7.8.0, MathWorks Inc)

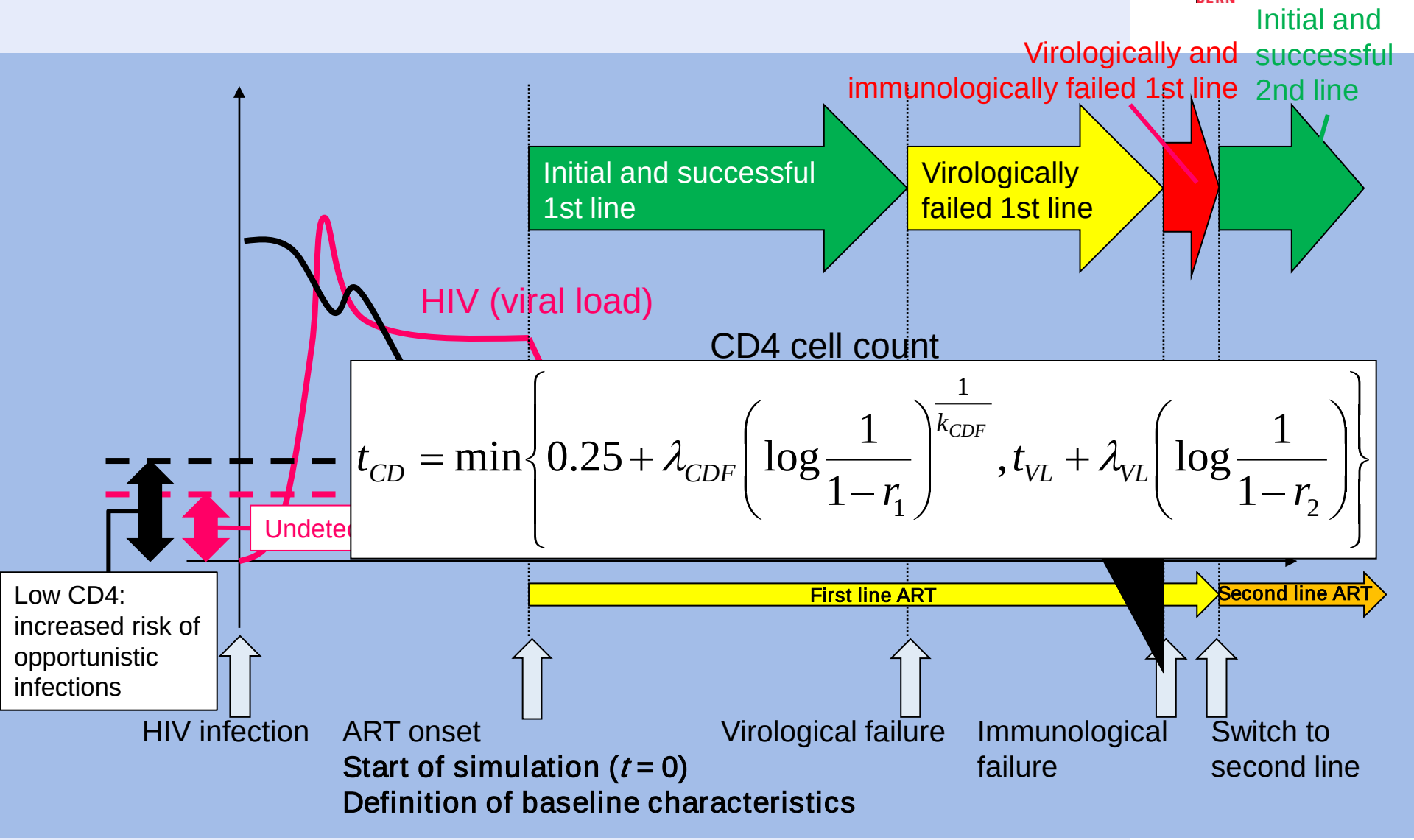
The mathematical model



The mathematical model



The mathematical model



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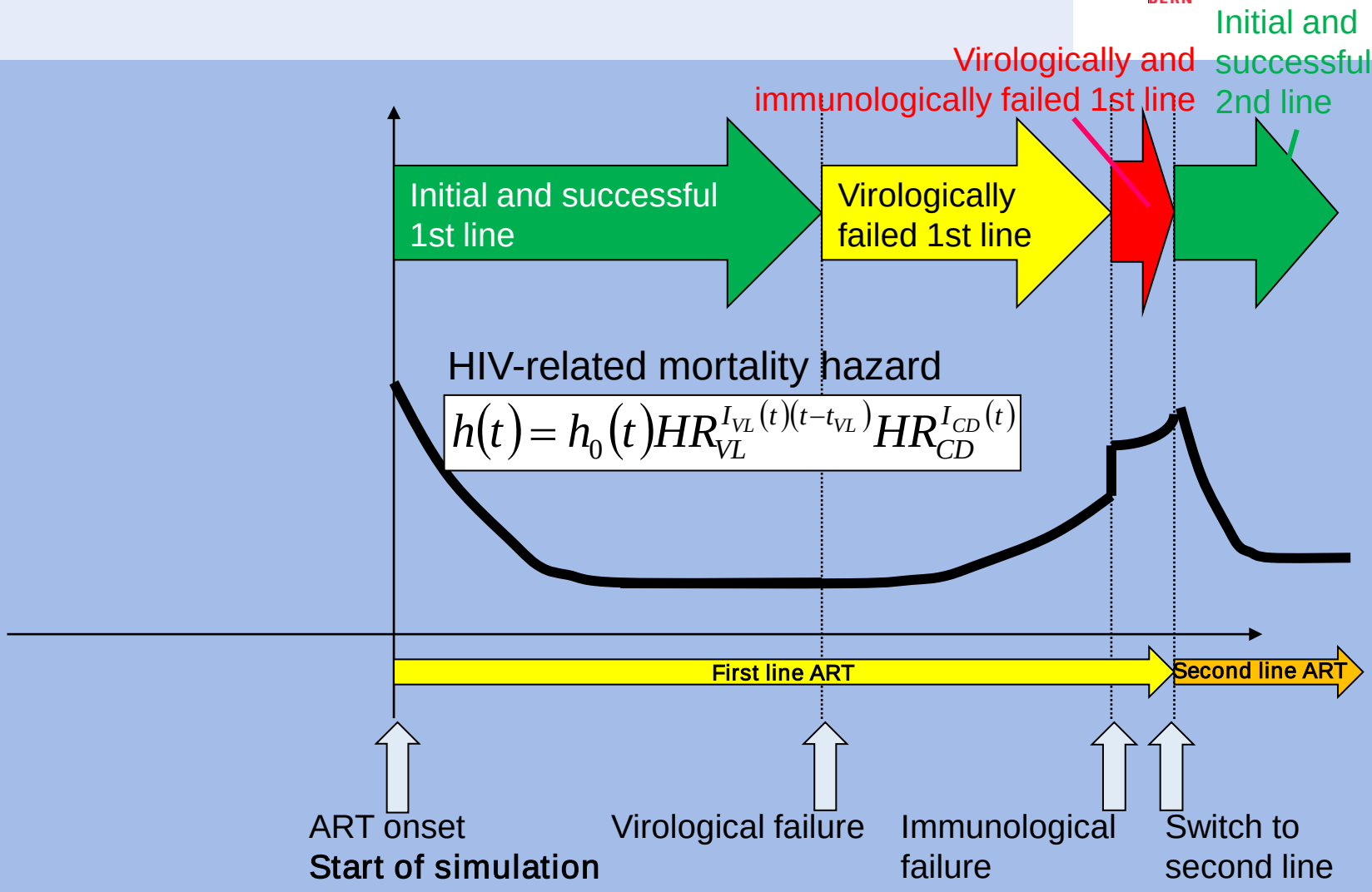

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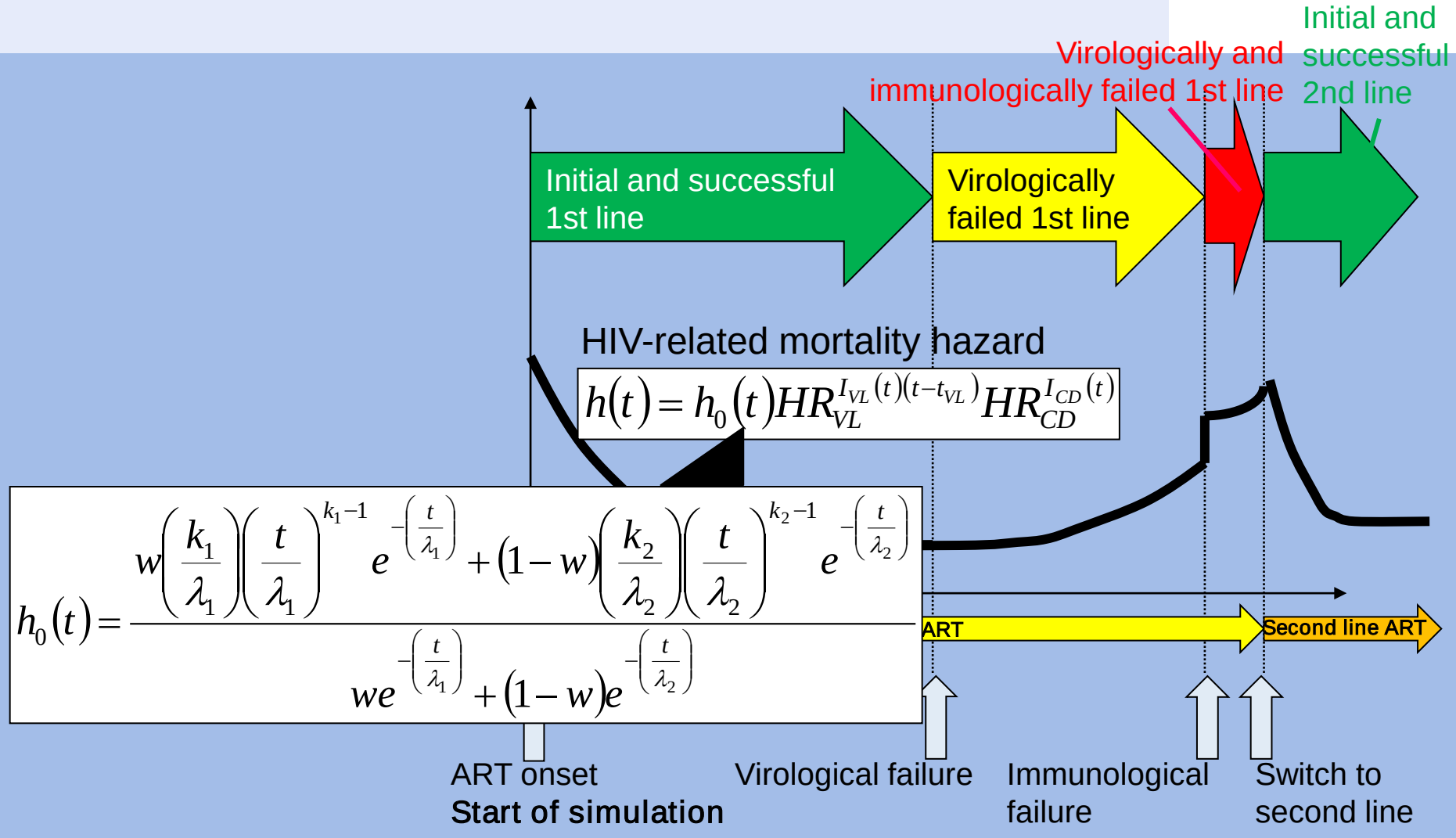
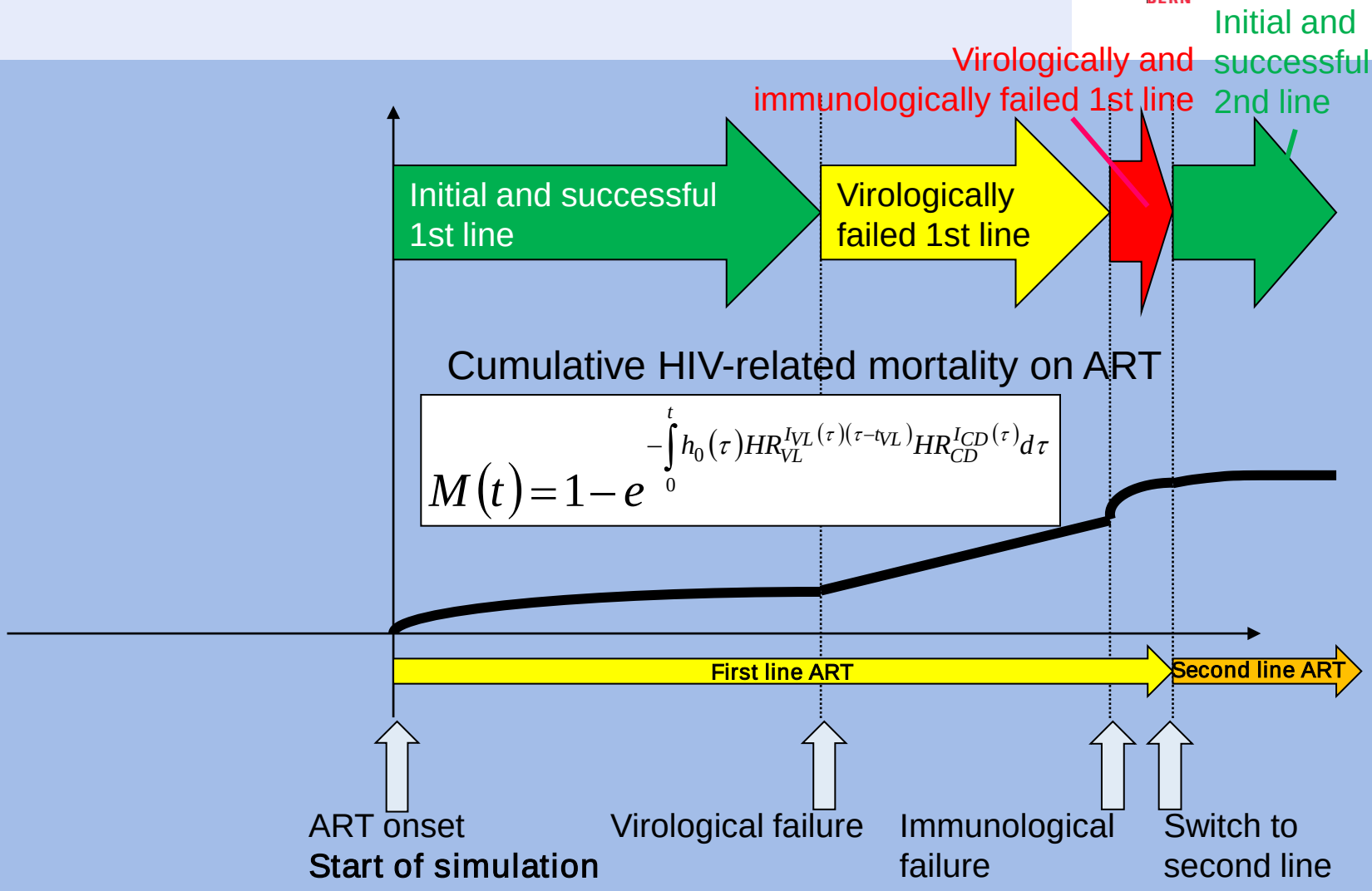


The mathematical model



The mathematical model

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MATLAB Variable Editor: ans — Page 7
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	37	38	39	40	41	42
1	37	38	39	40	41	42
2	28.8186	52.4573	25.7120	30.8659	40.1345	35.6022
3	2	1	2	1	2	2
4	0	1	0	0	0	0
5	100000	1.7101	100000	100000	100000	100000
6	100000	2.3499	100000	100000	100000	100000
7	0	0	0	0	0	0
8	100000	100000	100000	100000	100000	100000
9	0	0	0	0	0	0
10	100000	100000	100000	100000	100000	100000
11	100000	100000	100000	100000	100000	100000
12	0	0	0	0	0	0
13	100000	100000	100000	100000	100000	100000
14	0	1	0	0	0	0
15	100000	2.3499	100000	100000	100000	100000
16	0	0	0	0	0	0
17	100000	100000	100000	100000	100000	100000
18	100000	100000	100000	100000	100000	100000
19	0	0	0	0	0	0
20	100000	100000	100000	100000	100000	100000
21	100000	100000	100000	100000	100000	100000
22	405	2.4508e+03	405	405	1.9440	405
23	800	880	800	800	3.8400	800
24	1	1	1	1	3	1
25	-1	-1	-1	-1	1	-1
26	5	5	5	5	0.0240	5
27	Inf	Inf	Inf	Inf	Inf	Inf
28	0	0	0	0	0	0
29	1	1	1	1	1	1
30	-9.5282	-6.3431	-4.7648	-2.5235	-6.6663	-8.6103
31	241	241	241	241	5.7840	241
32	241	241	241	241	0	241
33	241	742.8435	241	241	0	241
34	241	1013	241	241	0	241
35	241	1093	241	241	0	241

MATLAB Variable Editor: ans — Page 8
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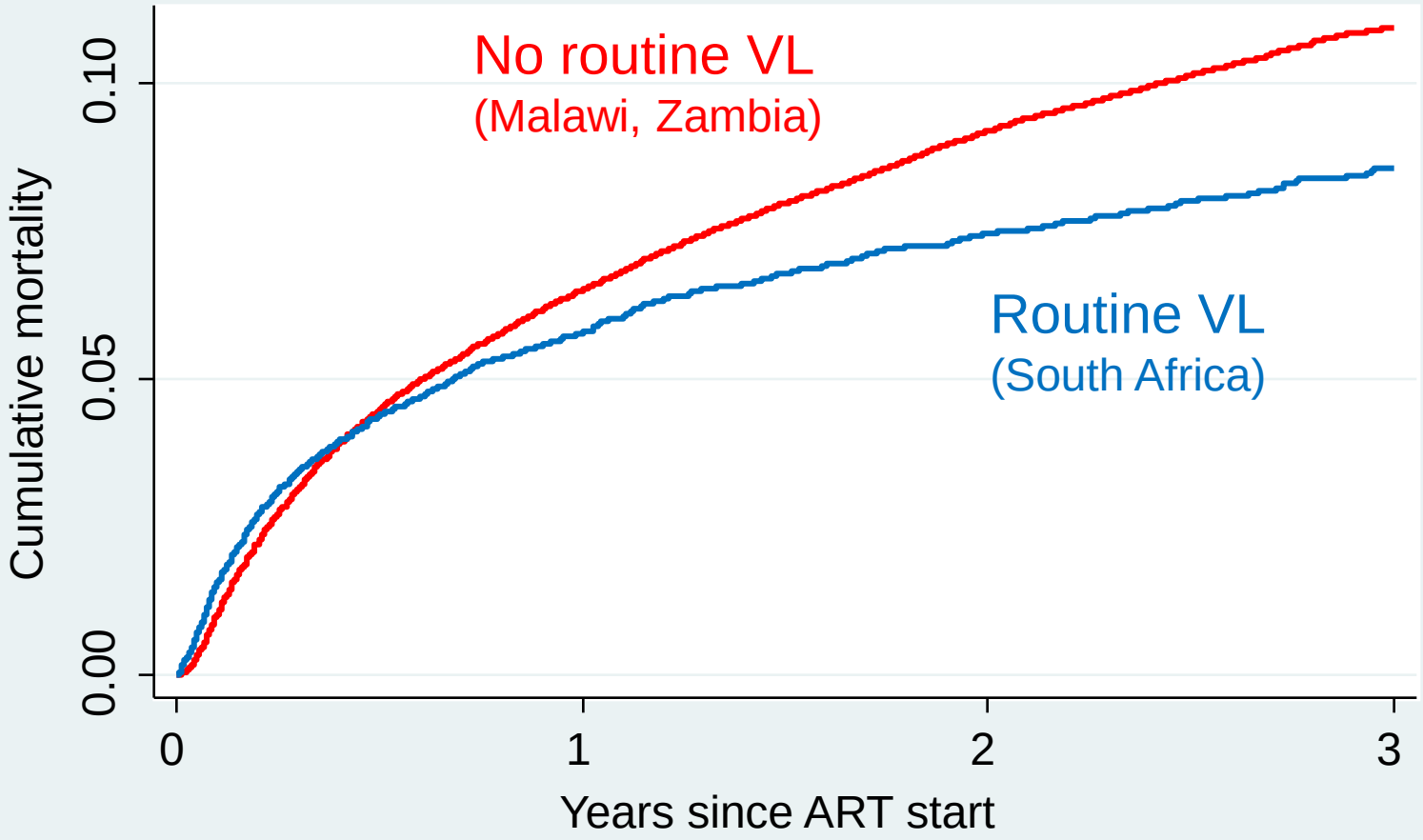
	43	44	45	46	47	48
1	43	44	45	46	47	48
2	46.4748	38.0425	27.4652	52.1228	39.1830	31.6055
3	1	2	1	1	2	1
4	0	0	0	0	0	0
5	100000	100000	100000	100000	100000	100000
6	100000	100000	100000	100000	100000	100000
7	0	0	0	0	0	0
8	100000	100000	100000	100000	100000	100000
9	0	0	0	0	0	0
10	100000	100000	100000	100000	100000	100000
11	100000	100000	100000	100000	100000	100000
12	0	0	0	0	0	0
13	100000	100000	100000	100000	100000	100000
14	0	0	0	0	0	0
15	100000	100000	100000	100000	100000	100000
16	0	0	0	0	0	0
17	100000	100000	100000	100000	100000	100000
18	100000	100000	100000	100000	100000	100000
19	0	0	0	0	0	0
20	100000	100000	100000	100000	100000	100000
21	100000	100000	100000	100000	100000	100000
22	405	405	250.5330	405	405	34.9920
23	800	800	494.8800	800	800	69.1200
24	1	1	3	1	1	3
25	-1	-1	1	-1	-1	1
26	5	5	3.0930	5	5	0.4320
27	Inf	Inf	Inf	Inf	Inf	Inf
28	0	0	0	0	0	0
29	1	1	1	1	1	1
30	-3.2492	-6.4336	-3.4694	-7.9412	-8.6466	-4.5408
31	241	241	241	241	241	104.1120
32	241	241	241	241	241	0
33	241	241	241	241	241	0
34	241	241	22.4130	241	241	0
35	241	241	0	241	241	0

Mortality

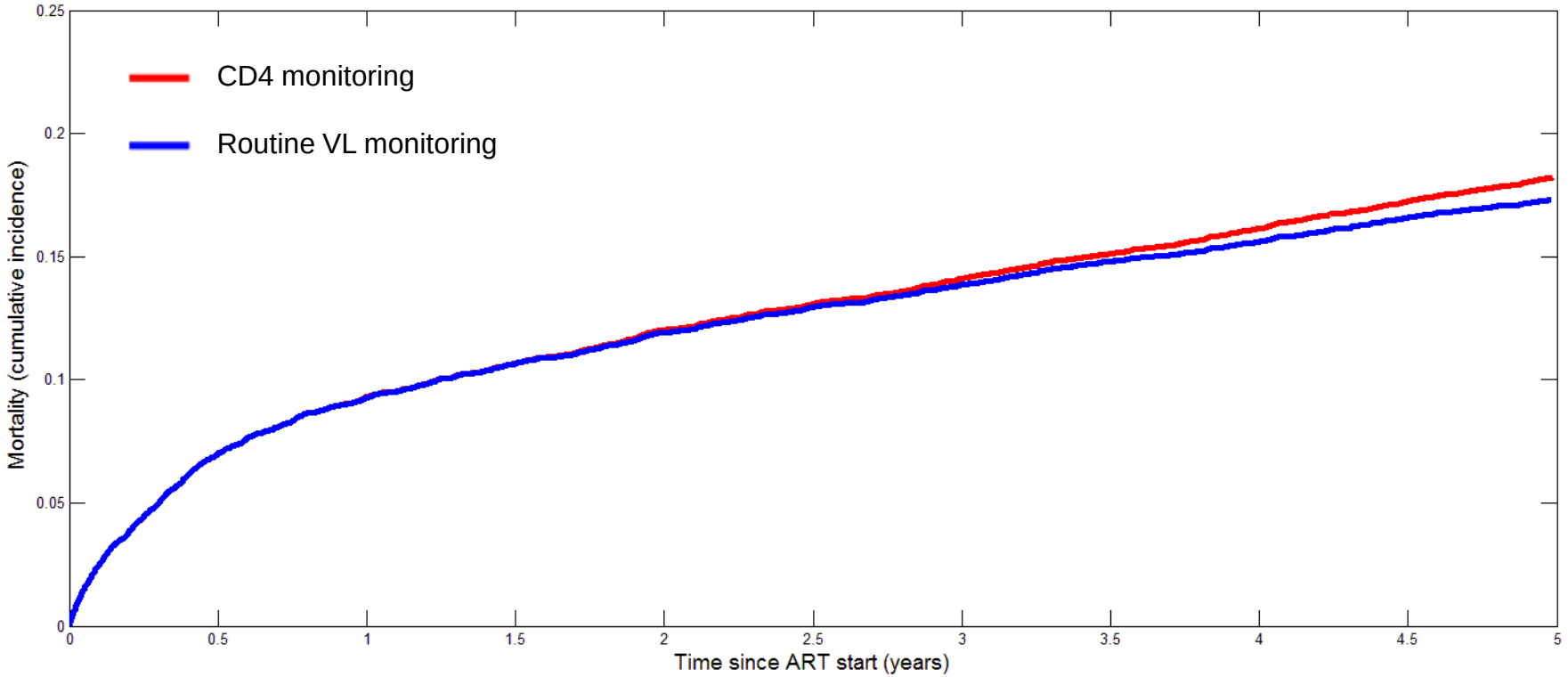


Keiser *et al.,* AIDS 2011

Mortality

- What could explain this difference?
  - Purely more accurate failure detection?
  - Increased confidence in the failure detection and lower reluctance to switch?
  - Improved adherence and lower failure rates?
  - Background mortality?
- Apart from background mortality, all other benefits are related to routine viral load monitoring!

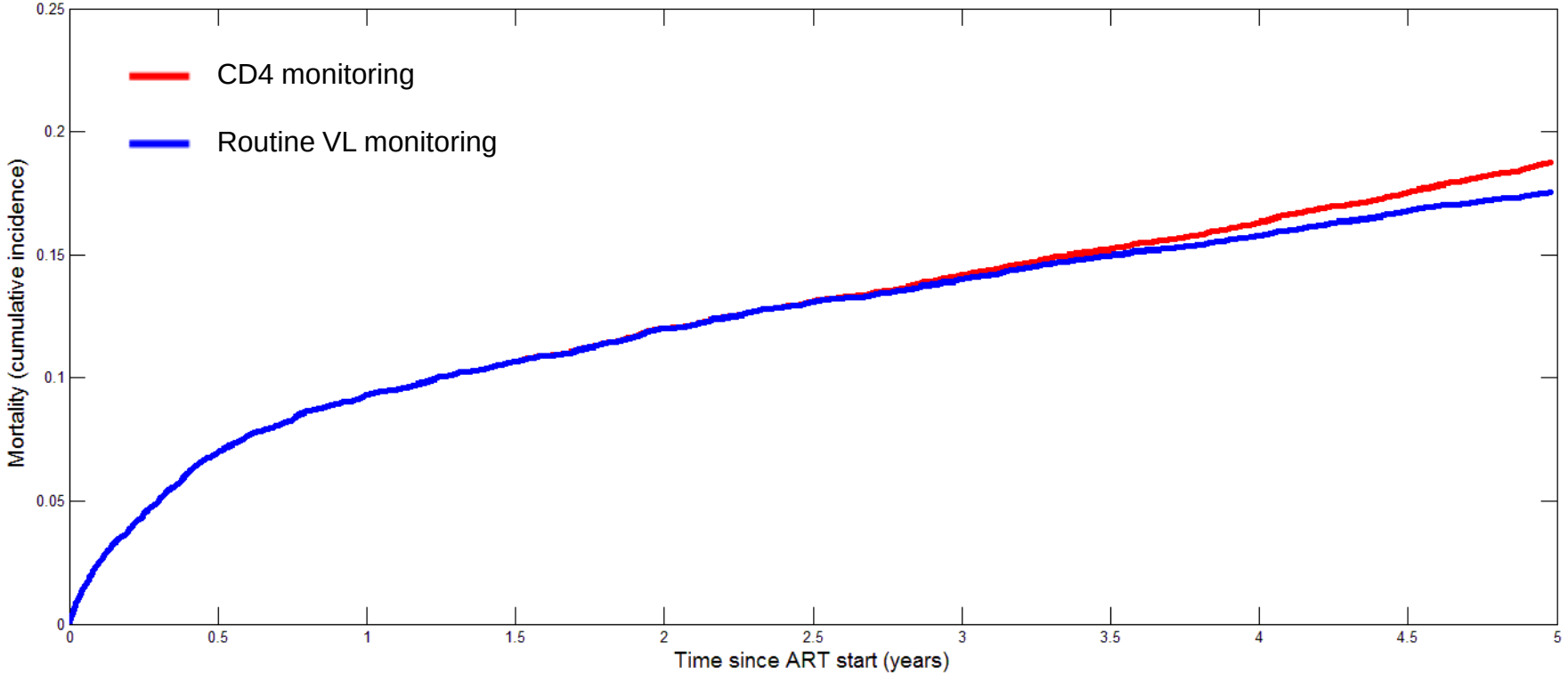
Mortality: Results



- Equal failure rates, switching exaclty according to criteria

  ⇨ No clear difference in mortality

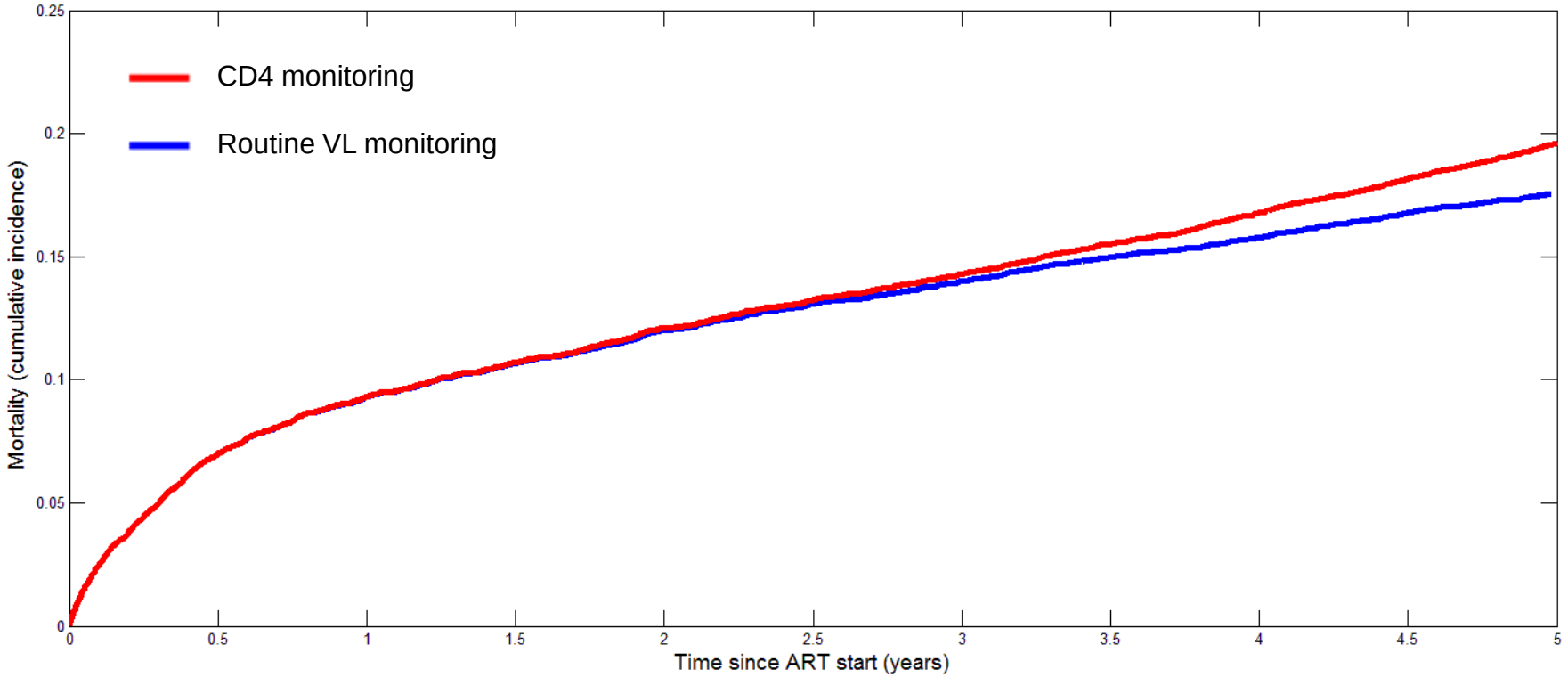
Mortality: Results



- Equal failure rates, but realistic delay to switch included

  ⇨ Difference in mortality remains moderate

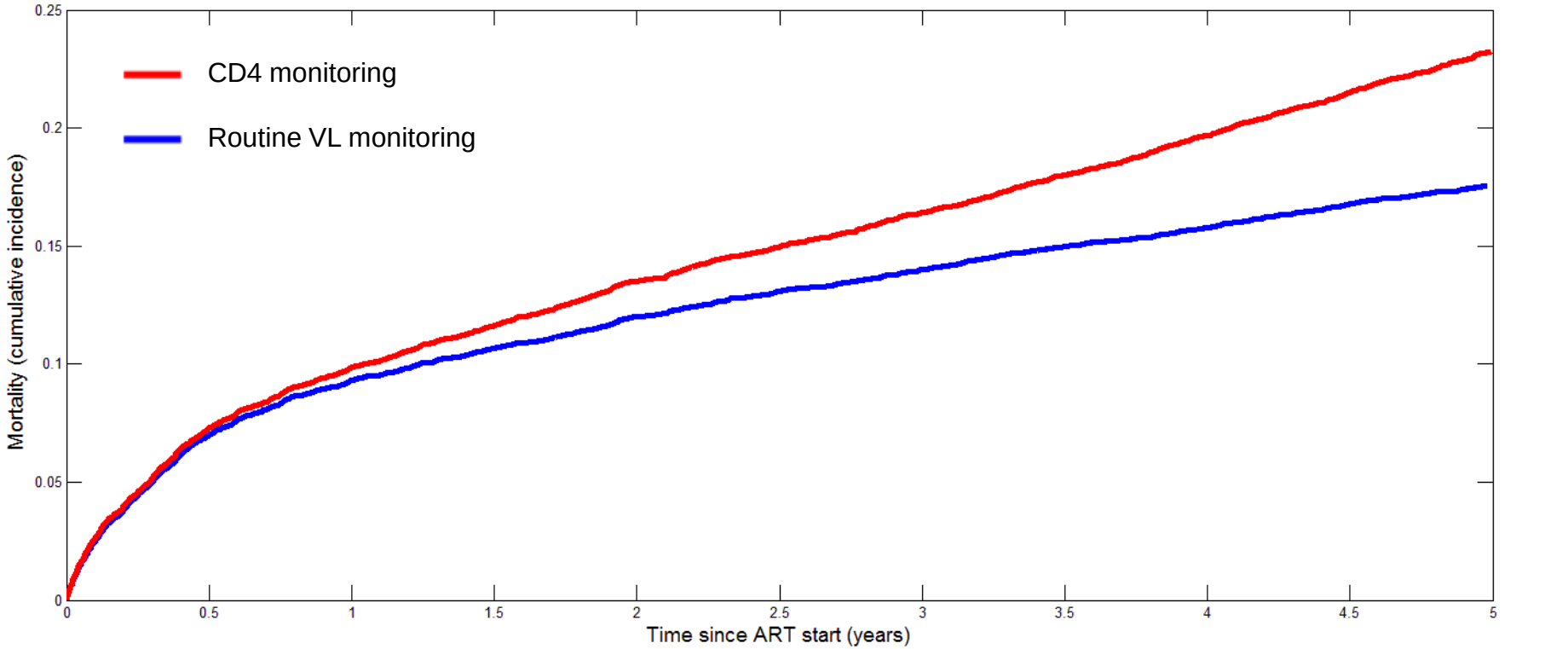
Mortality: Results



- Doubled hazard of failure if no routine viral load monitoring

  ⇨ Mortality already 12% higher after 5 years with CD4 monitoring compared to routine viral load monitoring

Mortality: Results



> Higher background mortality in CD4 monitoring cohort

⇨ Difference in mortality increased substantially

Time spent with failed ART

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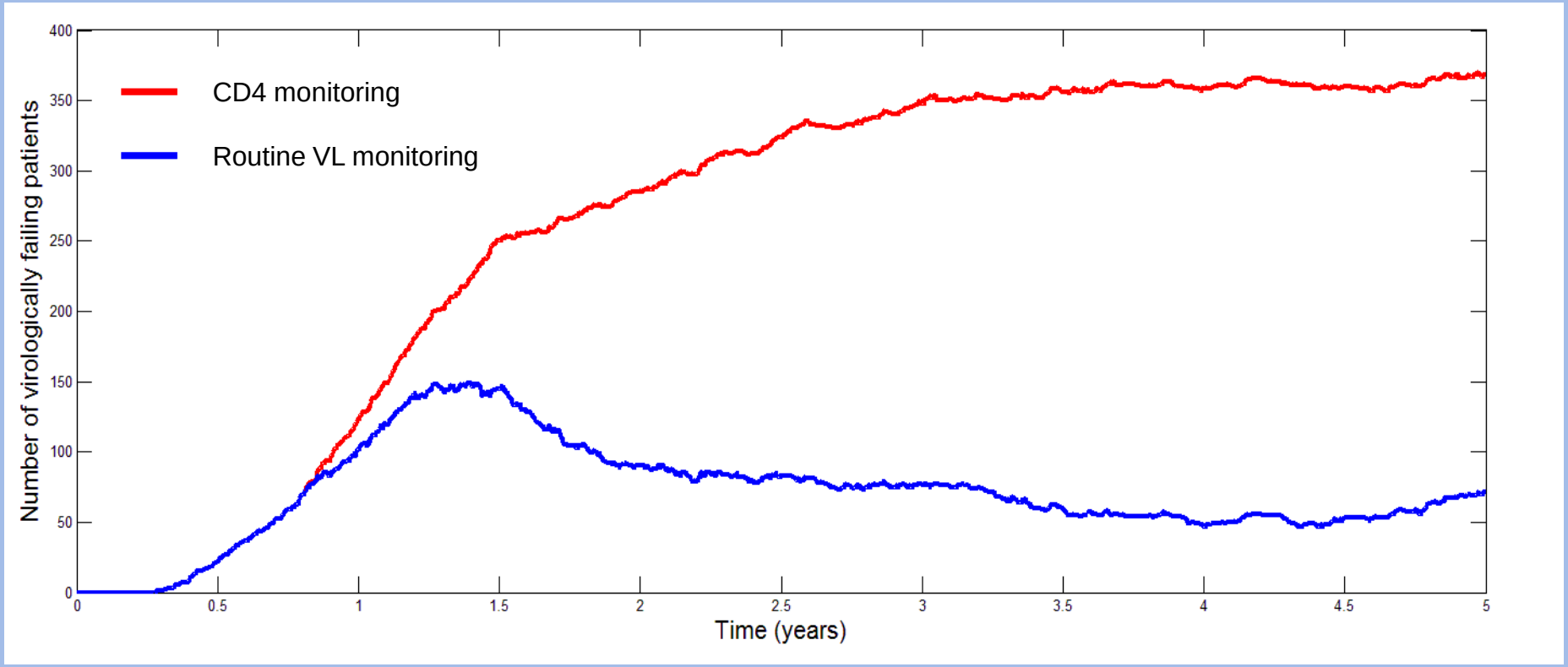
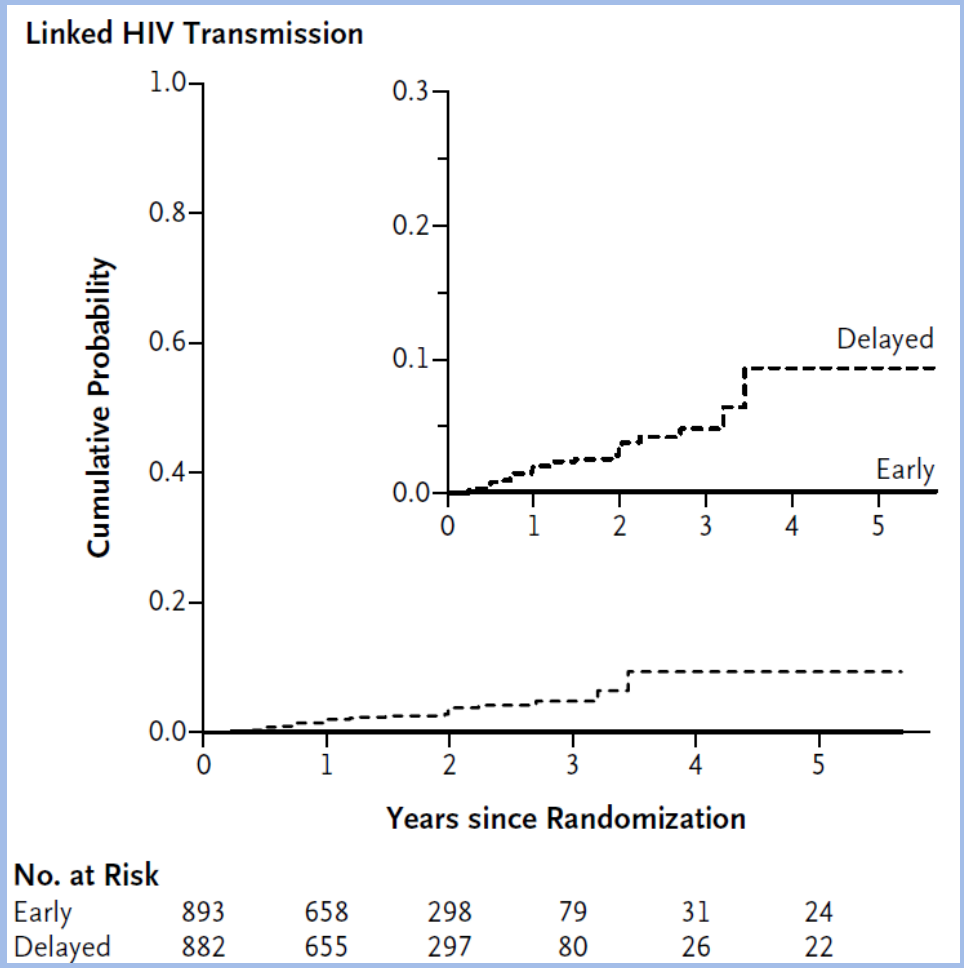


Transmission

- Individual viral load is a strong predictor of probability of transmission
- Randomised clinical trial HPTN 052: ART reduces transmission



Cohen *et al.* NEJM, *2011*

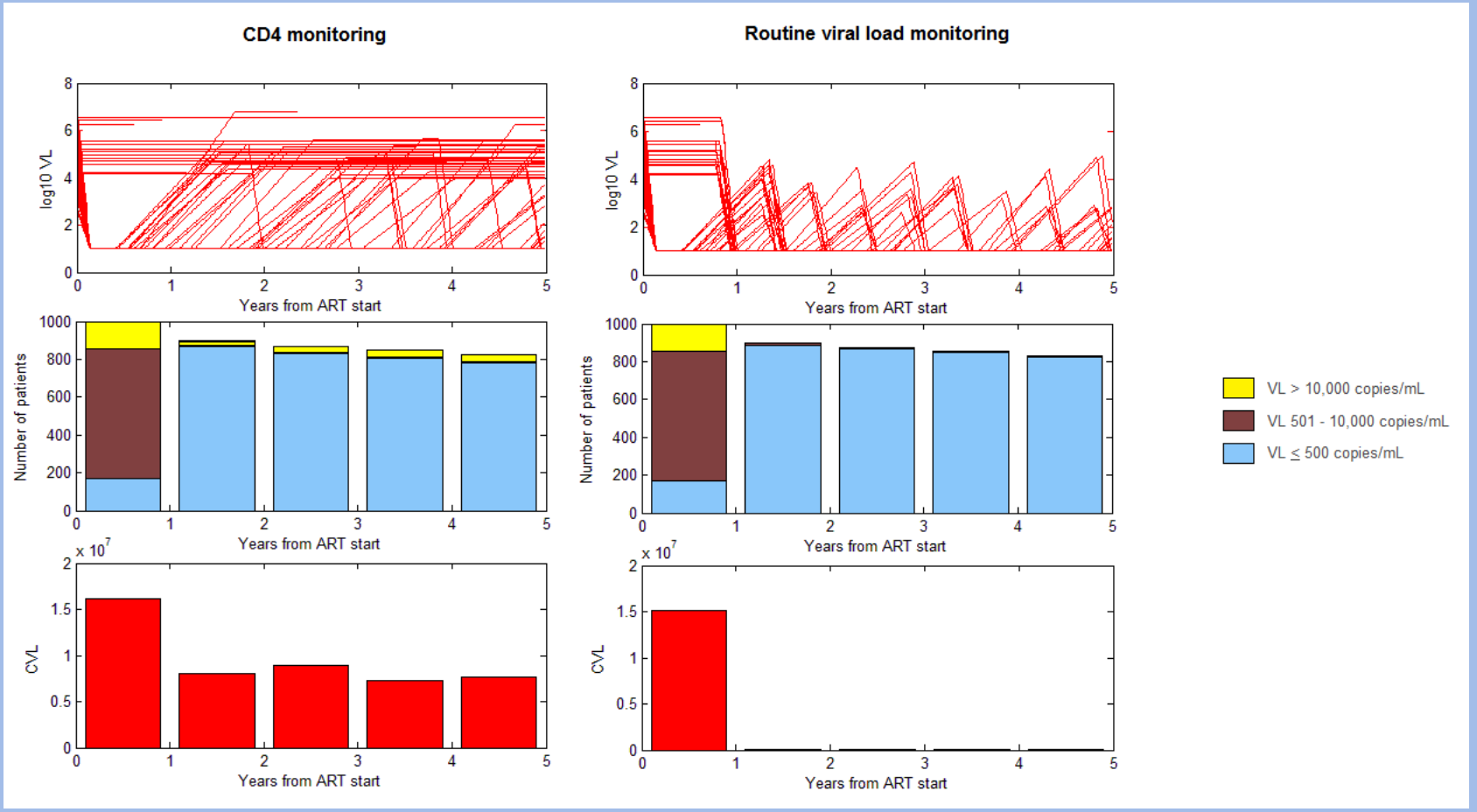
Transmission

- Transmission from treated patients currently minimal
- Introduction of “Test and Treat”
- Treatment failure may become a substantial source of transmission
- Efficient detection of ART failure needed
- To what extent can routine viral load monitoring prevent new infections?

Transmission: Methods

- Number of new infections in a time period depends also on several other factors: sexual network, risk behaviour, frequency of acts…
- Community viral load (CVL; sum of individual viral loads) has been proven to correlate with the number of new infections

Transmission: Results



Discussion

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Limitations:

- Follow up time very short
- Effect of routine viral load monitoring to adherence cannot be estimated accurately
- Real number of new infections depends not only on CVL but on a variety of assumptions

General conclusions

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- Routine viral load monitoring can reduce mortality and prevent new infections
- These benefits depend highly on the effect of routine viral load monitoring to adherence
- Our mathematical model is a useful tool to compare different strategies of ART monitoring

Outlook

- Our model can be extended to include several other factors (e.g. costs, CD4 trajectories)
- We will extend the model to a full transmission model to investiage the long-term outcomes of the epidemic
- The model can be implemented for different research questions and further to include co-infections or even model other diseases

Acknowledgements

- Olivia Keiser, Matthias Egger and the entire IeDEA Southern African team (University of Bern, Switzerland; University of Cape Town, South Africa)
- Participating sites:
  - Gugulethu and Khayelitsha ART Programmes (South Africa)
  - Center for Infectious Disease Research in Zambia
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- Swiss National Science Foundation
- Swiss School of Public Health