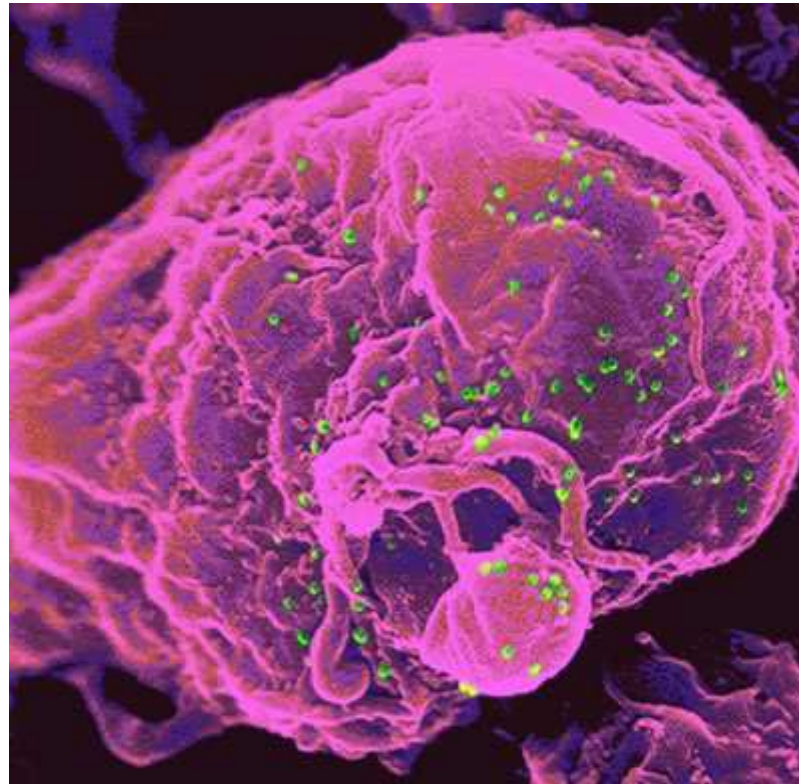
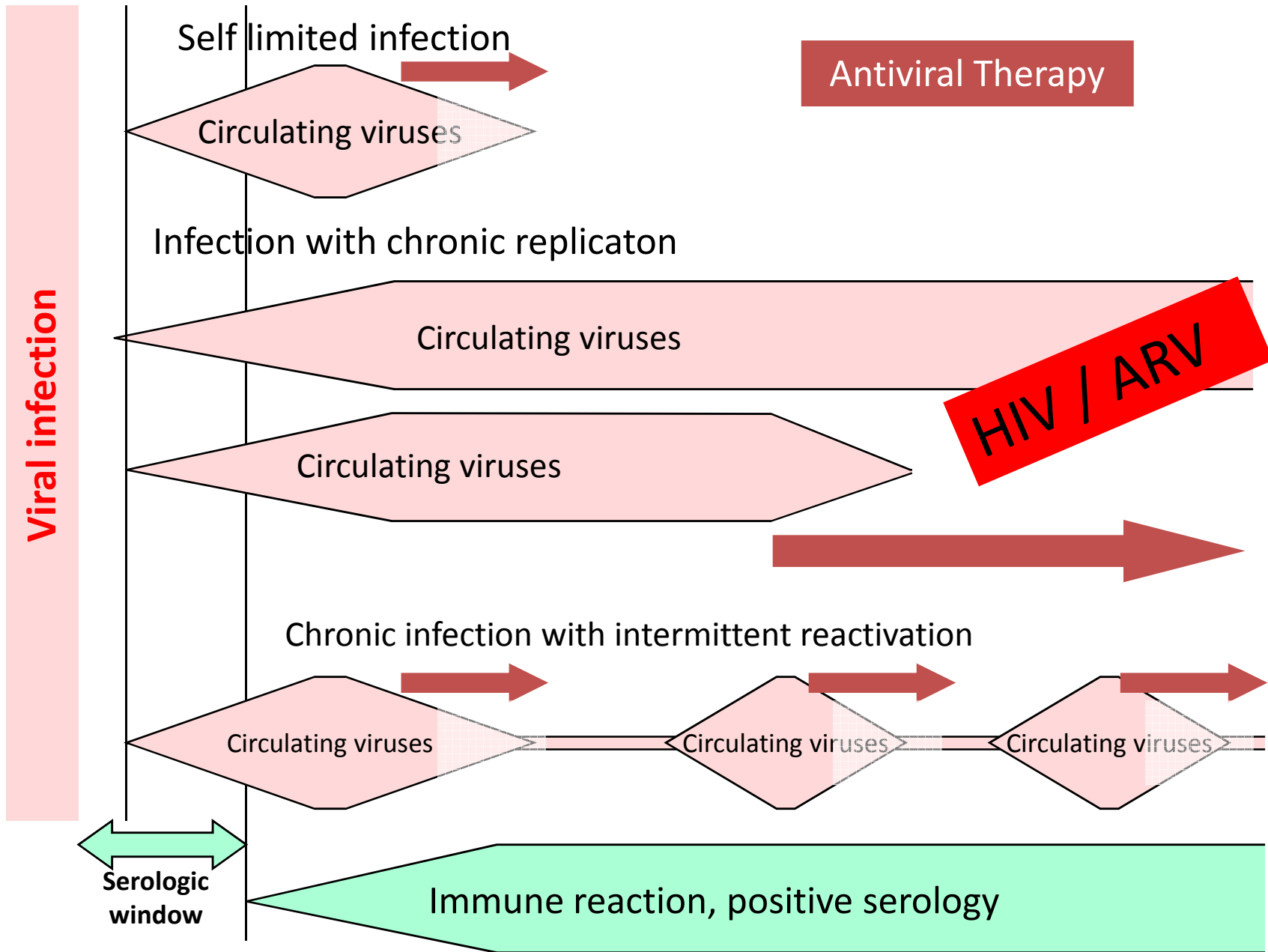


Antiretroviral treatment options

Tropical and Travel Medicine Course of the University of Athens

Ifakara, 4th September 2008





www.aidsinfo.nih.gov

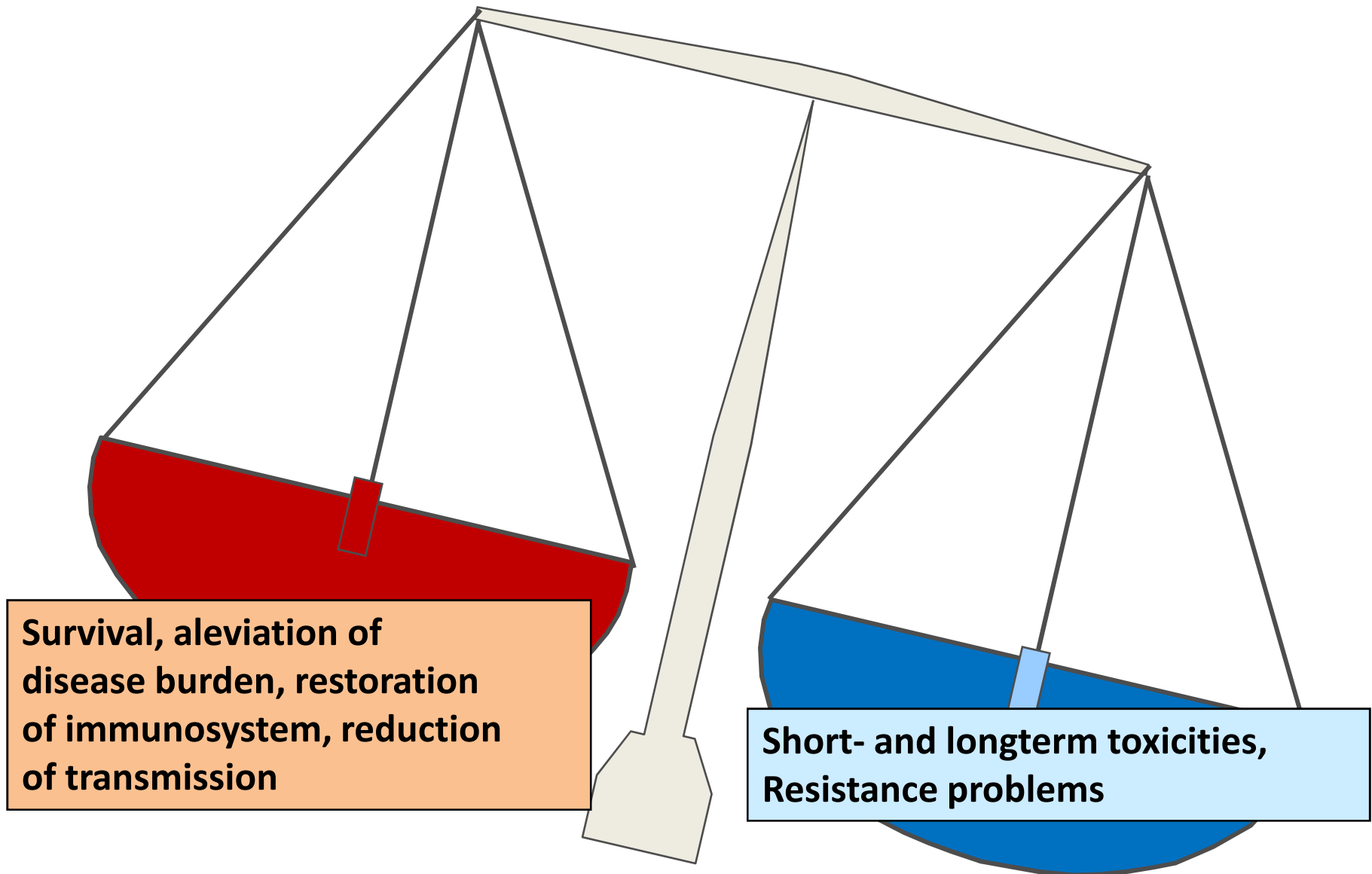
Therapeutic goals:

„...rational sequencing of drugs in a fashion that achieves clinical, virologic and immunologic goals while maintaining treatment options, limit drug toxicity and facilitate adherence...“

Goals of ART

- Maximal and durable suppression of HIV
- Restoration and/or preservation of the body's immune system
- Prevention of death and decline in disease burden
- Improve quality of life and indirectly improve the life of other family members

Start of therapy?



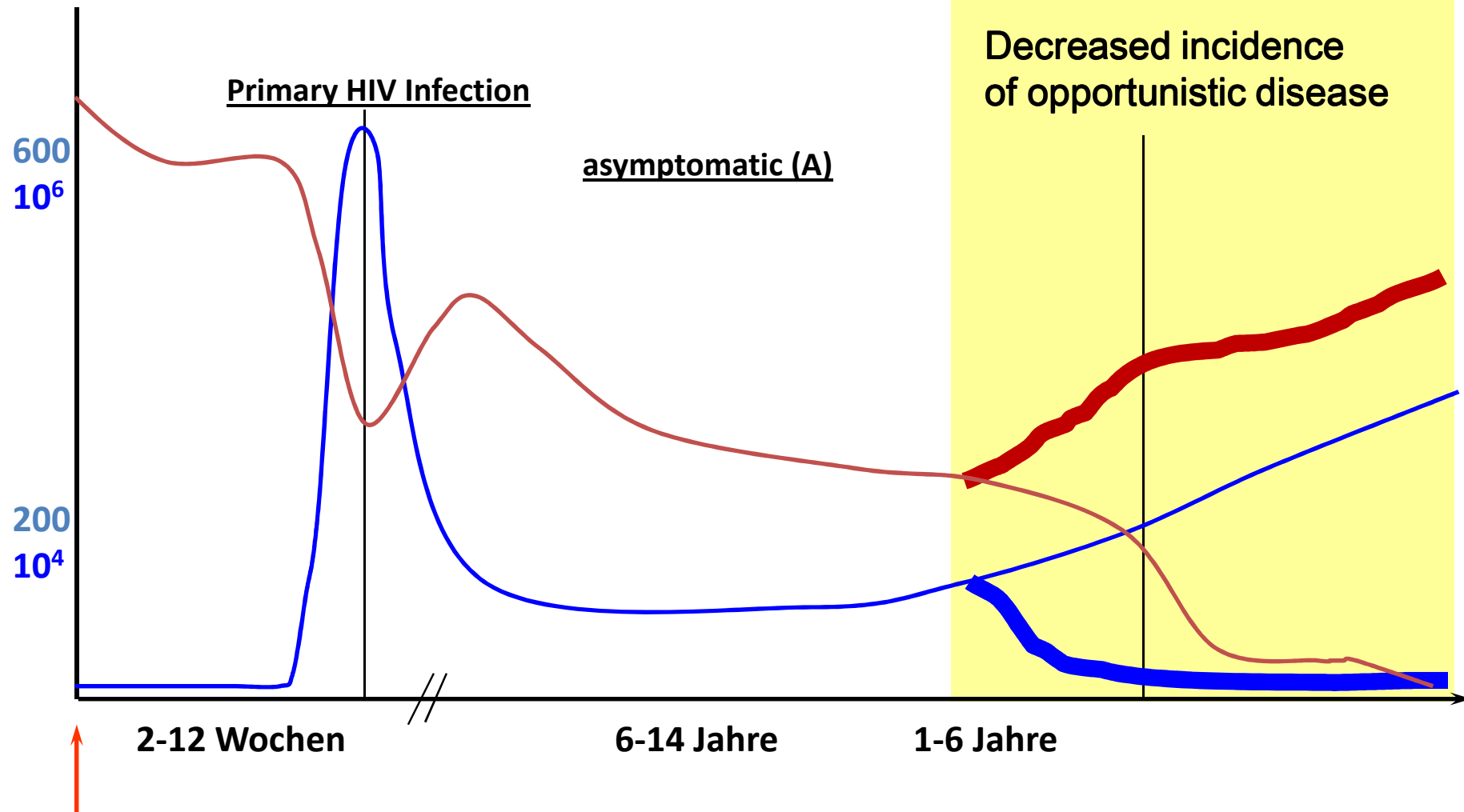
Survival, alleviation of disease burden, restoration of immunosystem, reduction of transmission

Short- and longterm toxicities, Resistance problems

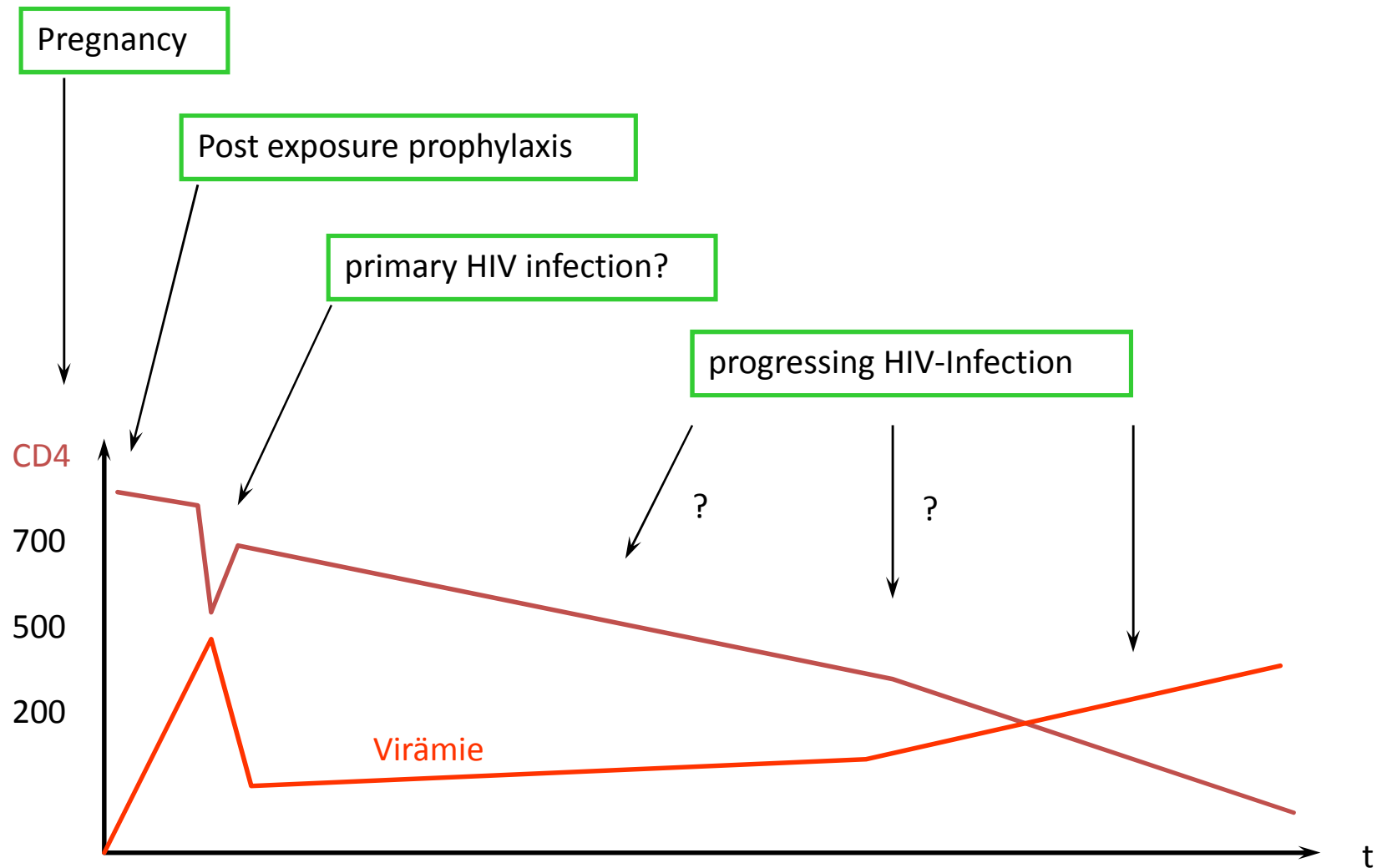
Typical course of HIV- infection

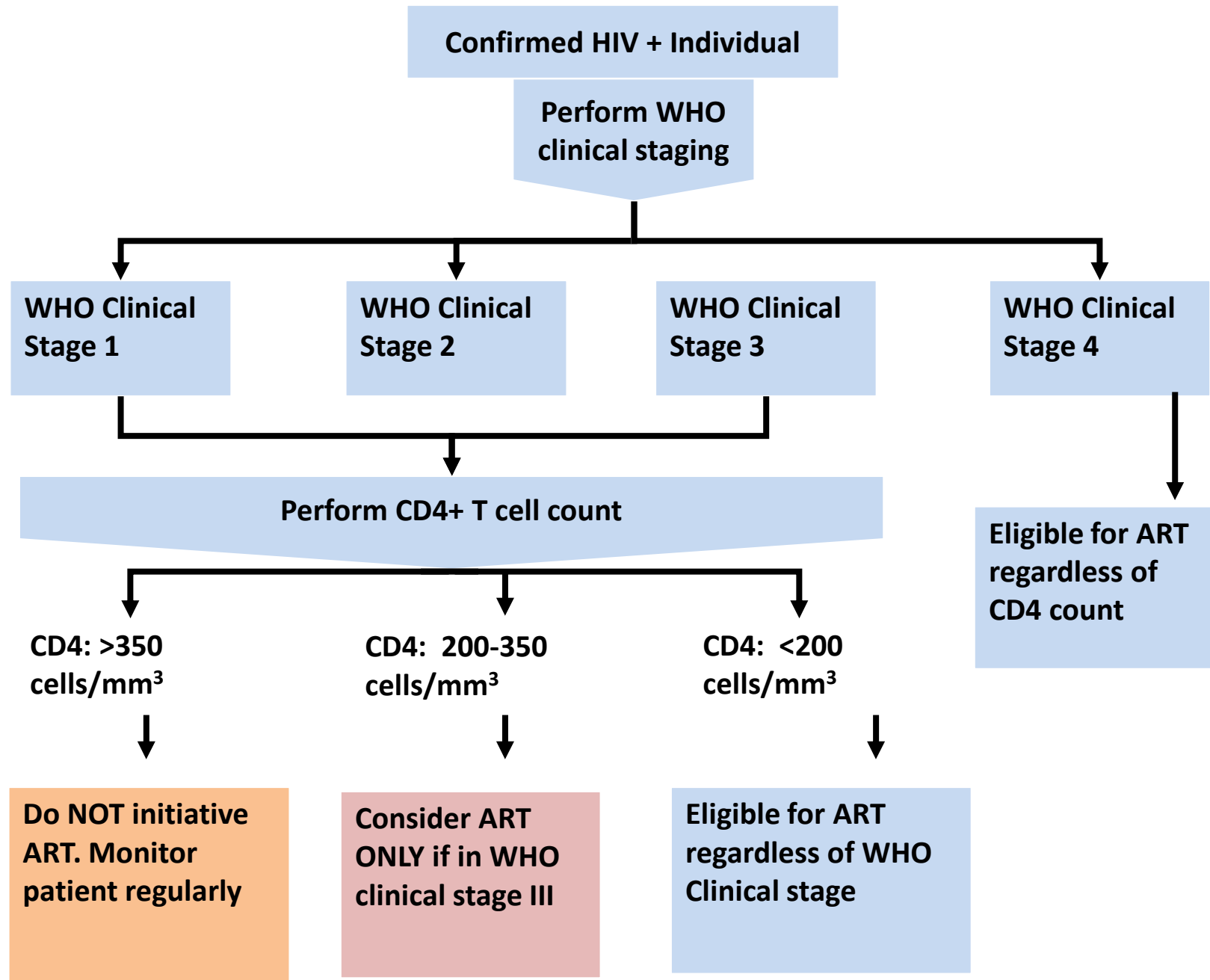
on antiretroviral therapy

Plasma HIV RNA (copies/ml)
CD4 -Count (/μl)



Indications antiretroviral therapy





When to start therapy in children

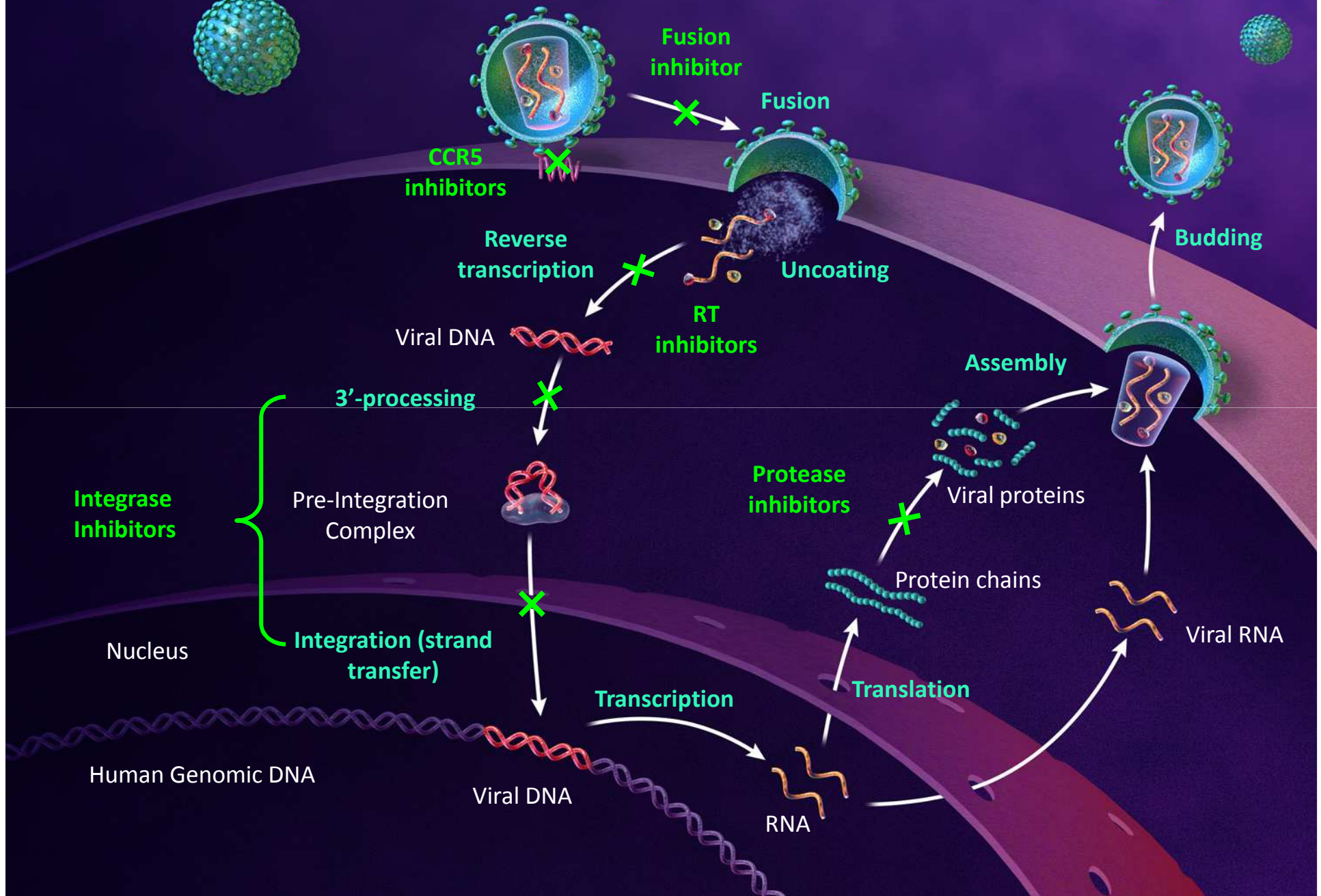
Any child WHO Stage 4

Infants < age 18 mos: CD4% < 20%

Infants > age 18 mos: CD4% < 15%

Age > 6 yrs, CD4 < 200 cells/mL as adults)

HIV Lifecycle And Existing Drug Targets



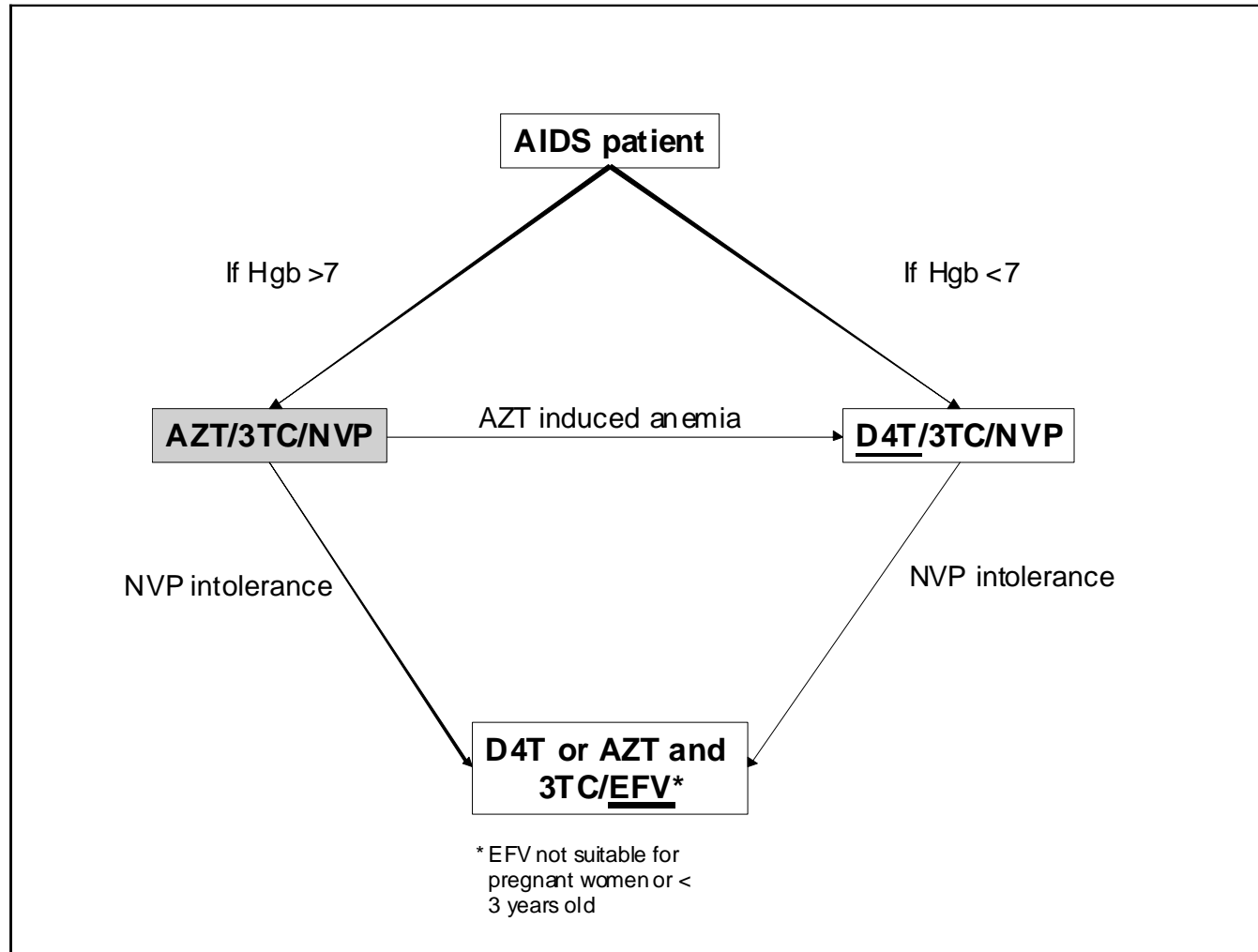
Antiretrovirals 2008

NRTI	NNRTI	PI	Fusion-Entry-inhibitors	Integrase-inhibitors
Zidovudine	Nevirapin	Saquinavir		
Didanosine	Efavirenz	Indinavir		
Zalcitabine		Ritonavir		
Lamivudine	(TMC 125)	Nelfinavir	Enfuvirtide	Raltegravir
Stavudine		F-Amprenavir/r		
Abacavir		Lopinavir/r	Maraviroc	
Emtricitabine		Atazanavir/r		
Tenofovir		Tipranavir/r		
		Darunavir/r		

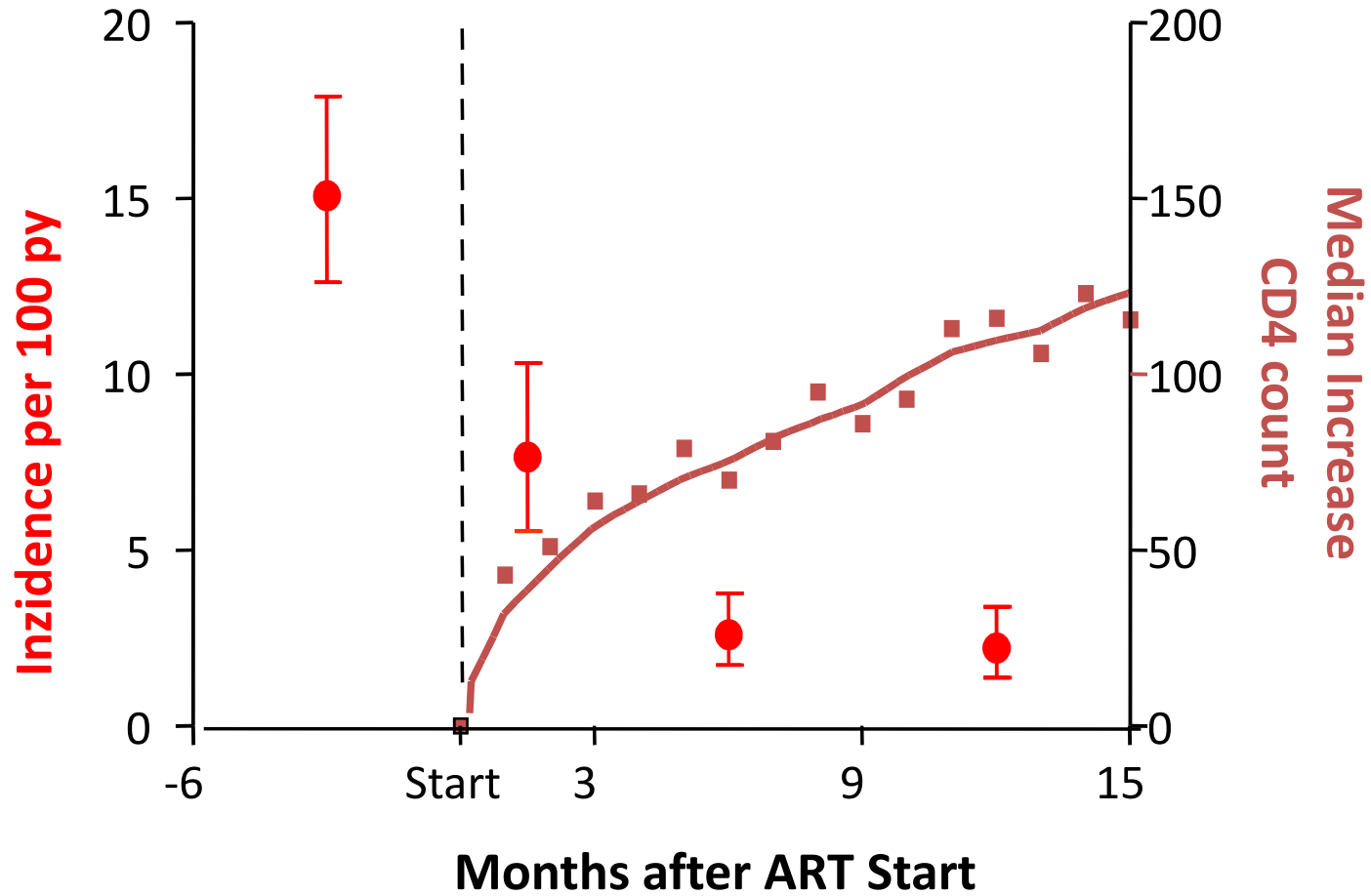
„HAART“: Highly active antiretroviral therapy

**Targeted combination of 3 drugs
e.g.: 2NRTI + (PI oder NNRTI)**

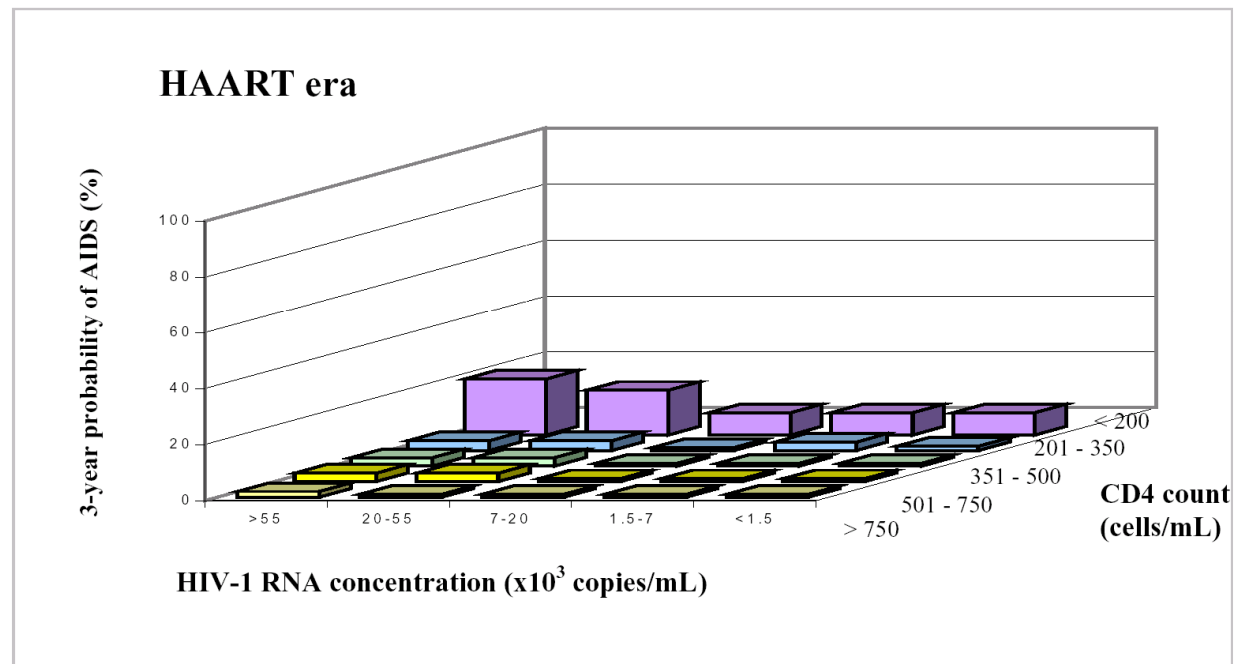
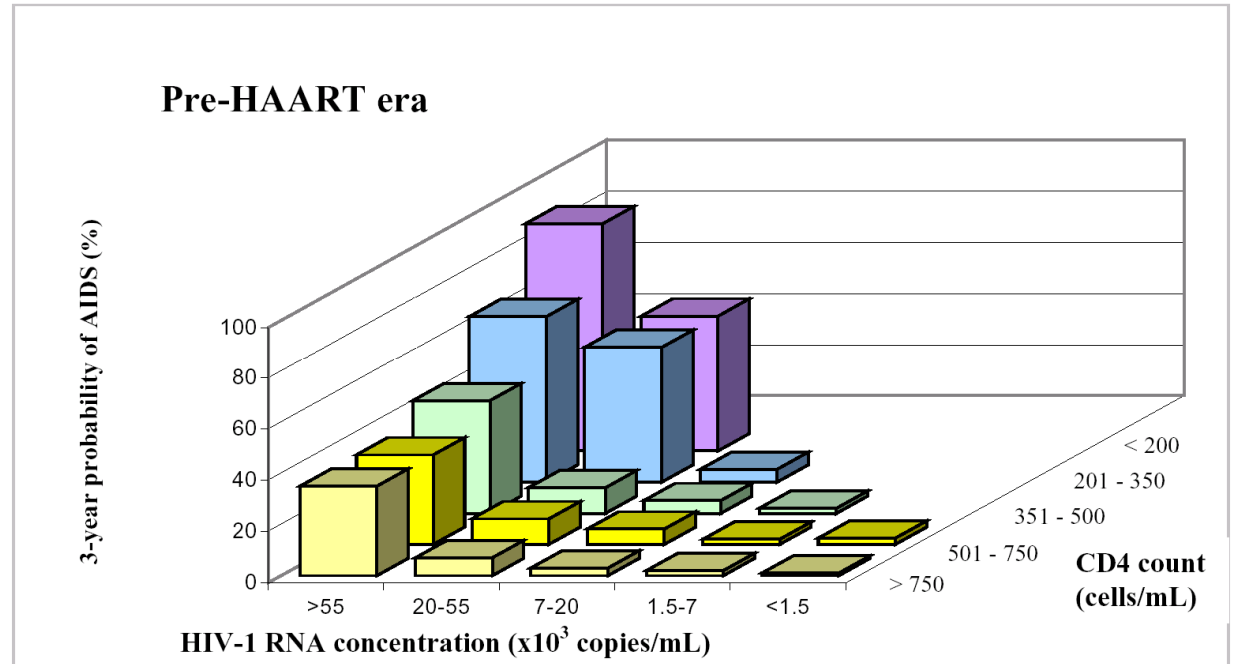
Figure 1. First-line ARV prescription decision tree



New Opportunistic Diseases



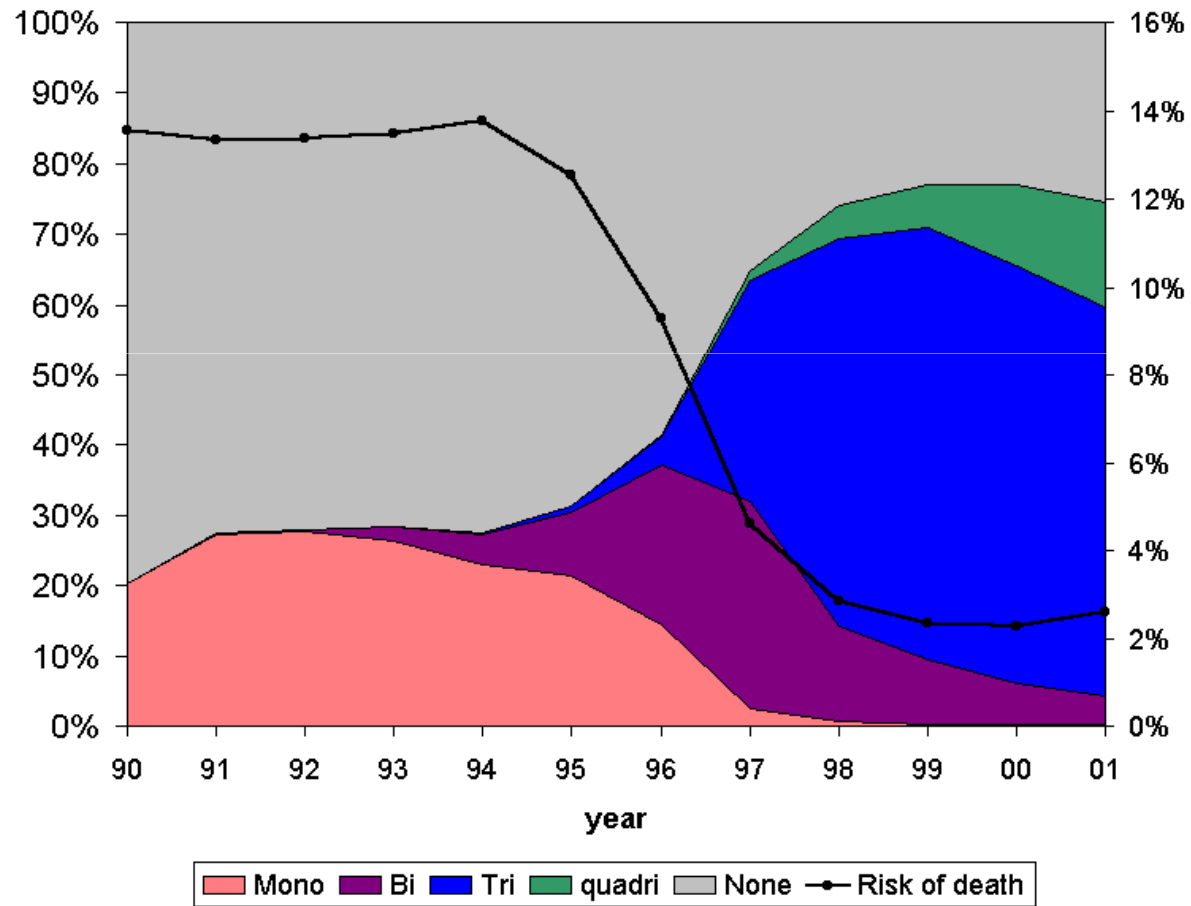
Egger
Lancet 2002



Antiretroviral Therapy and Mortality

Swiss HIV Cohort Study

AIDS 2004;18:1835



ART- LINC
ART-CC
Lancet
2006;367:817

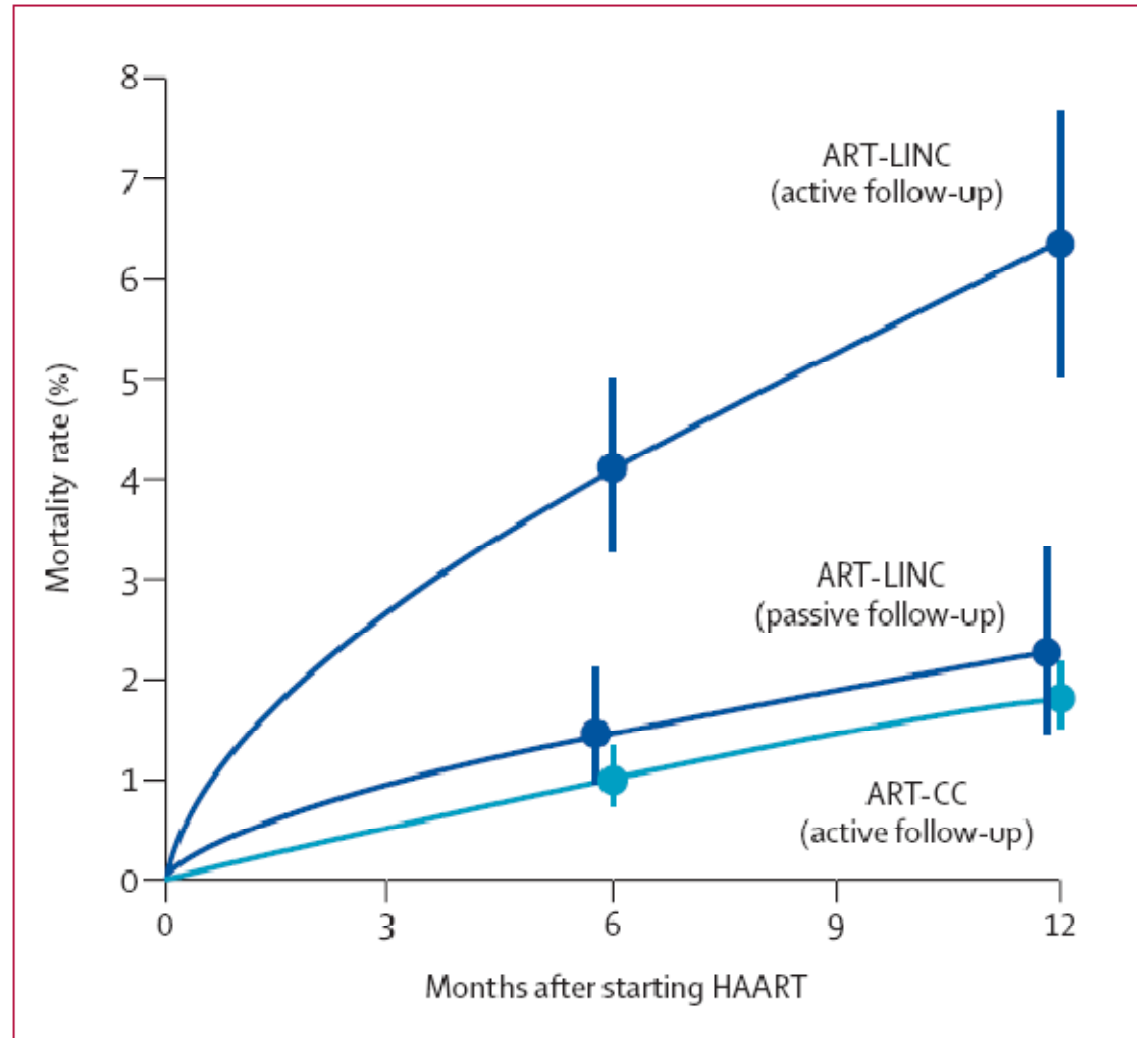
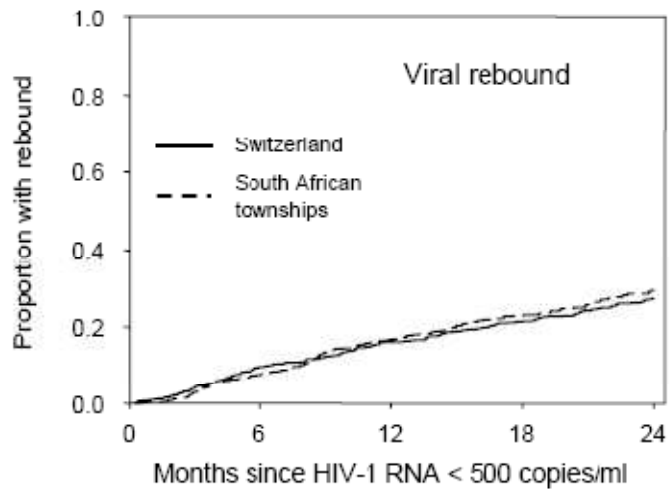
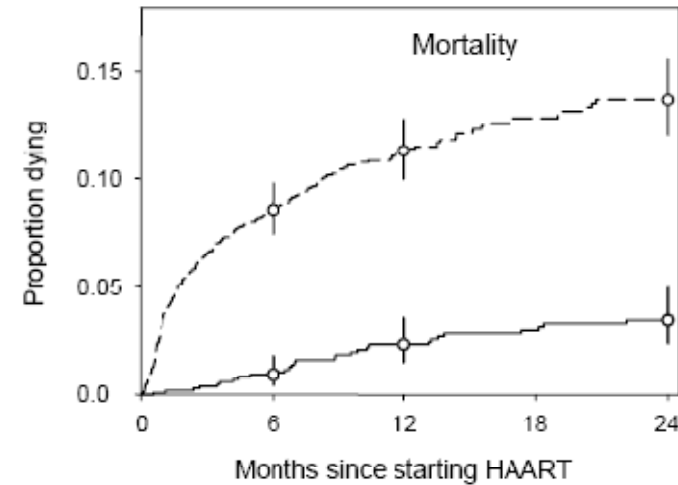
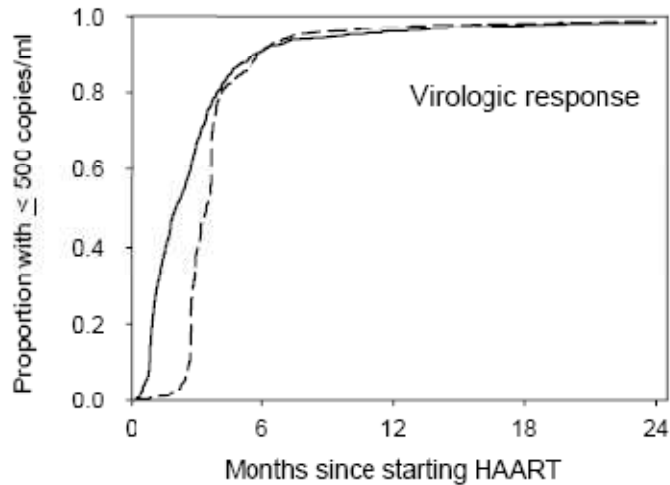


Figure 1: Estimated cumulative probability of death in HAART programmes in low-income and high-income countries
Vertical bars are 95% CIs.

Comparison Switzerland/South-Africa

Keiser et al, PLoS Medicine 2008 in revision



Study endpoints	Adjusted* hazard ratios or odds ratios (95% CI)	P value
Mortality (months 1 to 3)	5.91 (1.82-19.24)	0.003
Mortality (months 4 to 24)	1.89 (0.95-3.72)	0.07

HAART Toxicities

NRTI

Mitochondrial toxicity

- Lactate-acidosis
- Polyneuropathy
- Hematologic side effects
- Myopathy
- Lipoatrophy
- Metabolic side effects
- Hepatotoxicity
- Pancreatitis

Hypersensitivity

Nephrotoxicity

NNRTI

- Interactions
- Hepatotoxicity
- Psycho-neurologic
- Rash
- Hypersensitivity

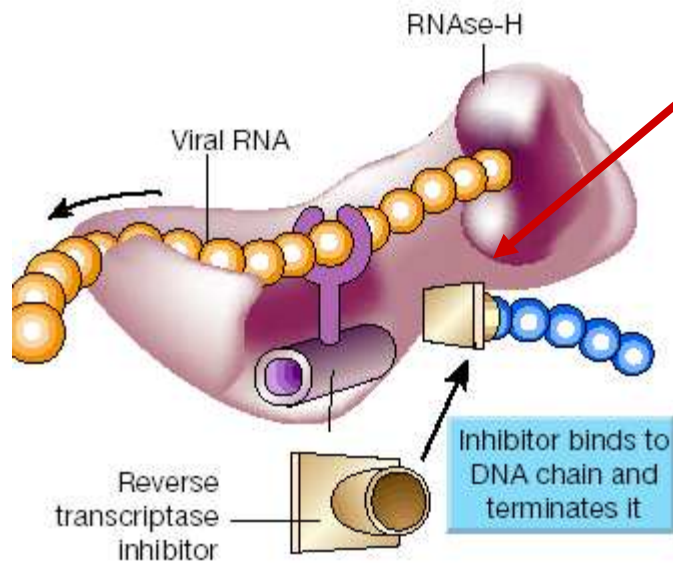
PI

- Nausea, Vomitus
- Diarrhea
- Fat accumulation
- Metabolic side effects
- Lipid disorders
- Hepatotoxicity
- Nephrotoxicity
- Interactions

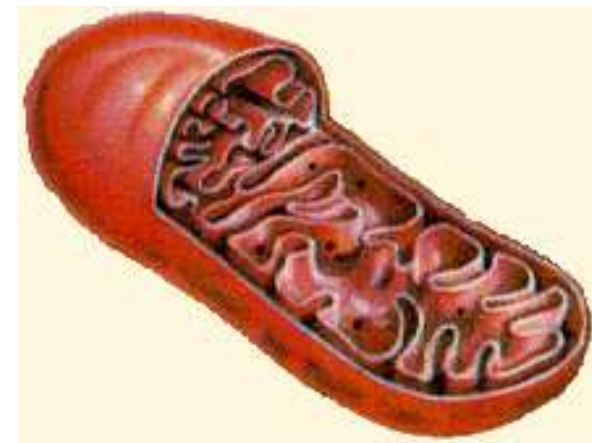
Toxicity NRTI

Nucleosid-Analogues

Inhibition of RNA dependant DNA-Polymerase (reverse transcriptase)

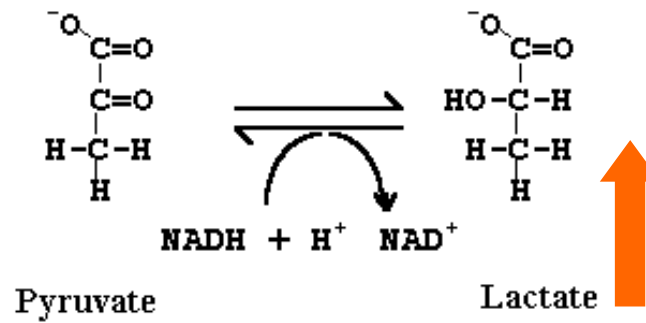


Inhibition of mitochondrial DNA-polymerase γ

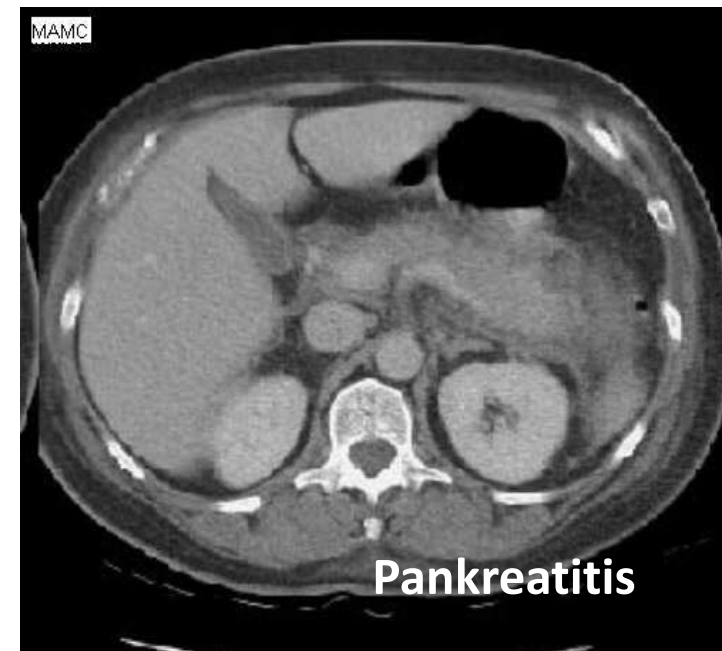
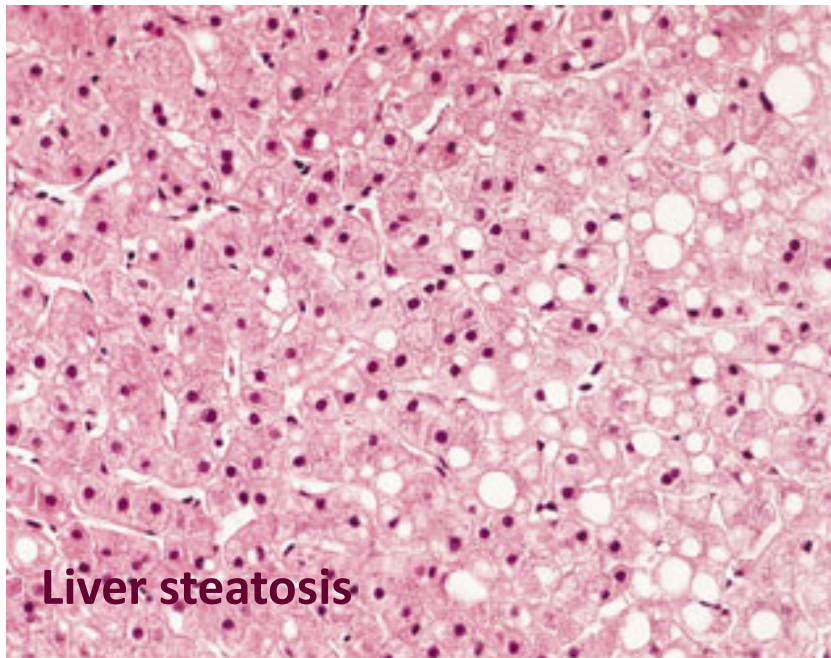
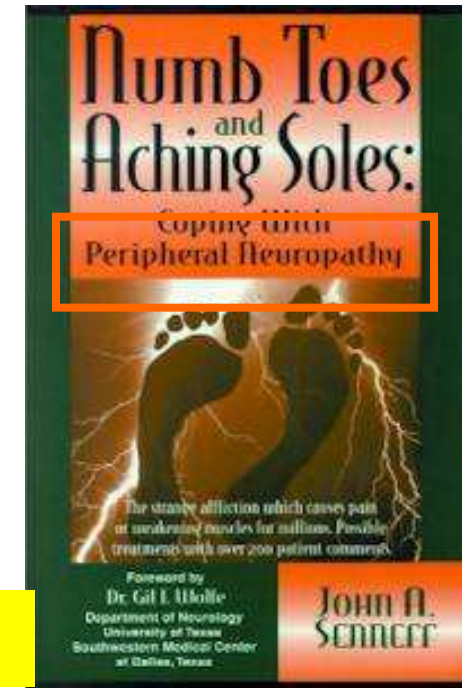


D4T>DDI>AZT>3TC,ABC,TDF

Mitochondrial Toxicity



Lactic Acidosis



HAART

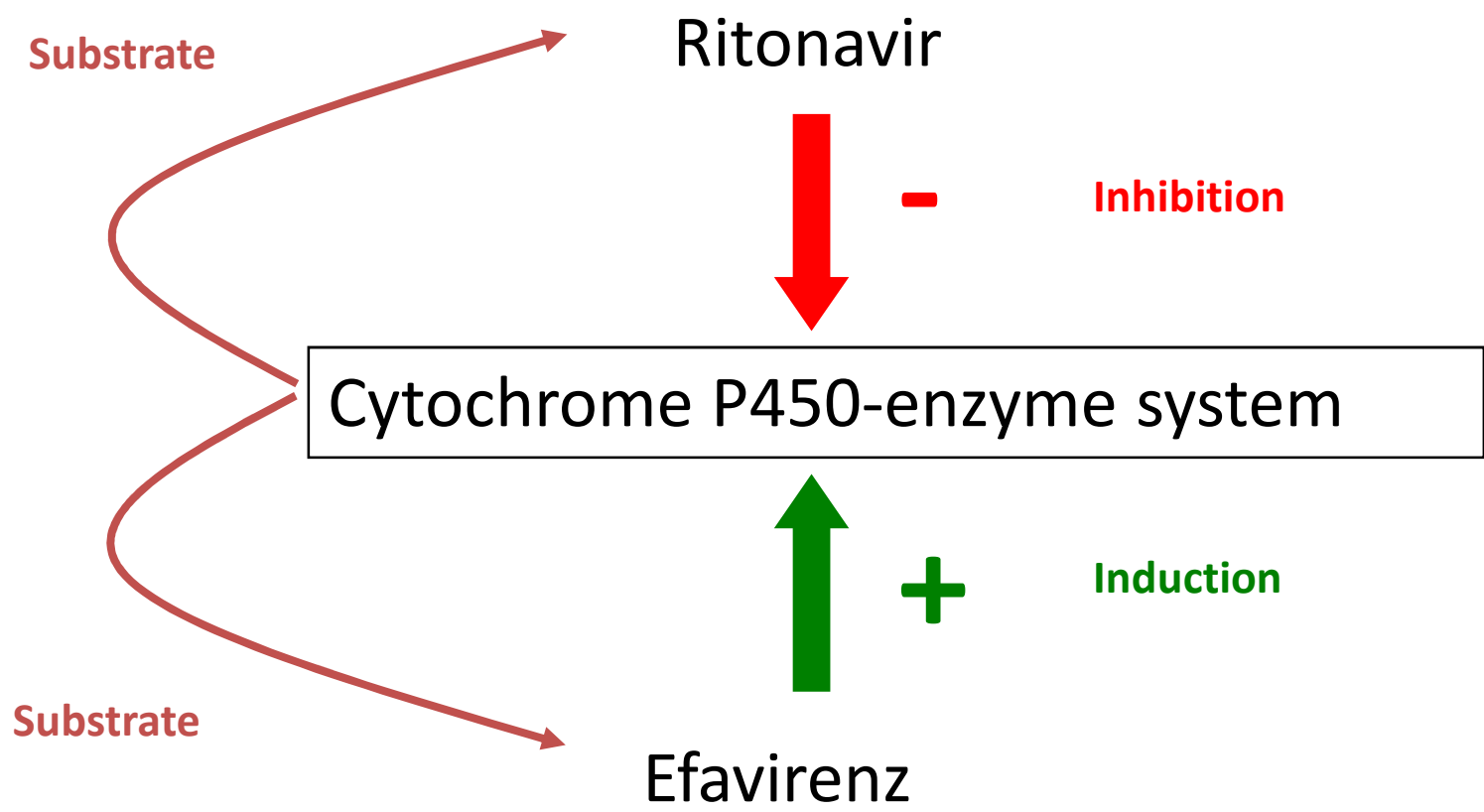
CD4 ↑
- redistribution
- regeneration
- TH-1 response ↑

CTL response ↑

Immunorestitution

Incidence of OI ↓
survival ↑
->Discontinuation of prophylaxis/
maintenance therapy

Immunopathogenic reactions
to present antigens
- Mycobacteria
- Viruses (Uveitis/Vitritis after CMV)
- Cryptococci ...
**= IRIS (Immune Reconstitution
Inflammatory Syndrome)**



Rifampicin

Inducer CYP3A4

Nevirapine

Levels ↓↓ 20-60%

Hepato-toxicity ↑↑

-> Don't use
or monitor closely

Efavirenz

Levels ↓↓ 25%

No change or
Consider 800mg/d

Monitoring under ARVs

- Full blood picture
- Liver and renal function tests
- RBG, Lipids (total Cholesterol, HDL, LDL, TG)
- Lactat
- CD4 cell count, VL
- ARV concentration levels
- Clinical assessment

Response to therapy

- Week 8 – 16: VL < 500 copies/ml

Ann Intern Med 2001; 135: 954

J Acquir Immune Defic Syndr 2000; 24: 433

↑ CD4 ≥ 50 cells/μl

JAMA 2002; 288: 222

J Infect Dis 2002; 185: 471

- Week 16 – 24: VL < 50 copies/ml

Ann Intern Med 2001; 135: 954

J Acquir Immune Defic Syndr 2000; 24: 433

Failure to therapy

Virological:

- VL > 500 copies/ml after week 24
- VL > 50 copies/ml after week 48
- Rebound VL > 500 copies/ml after viral suppression

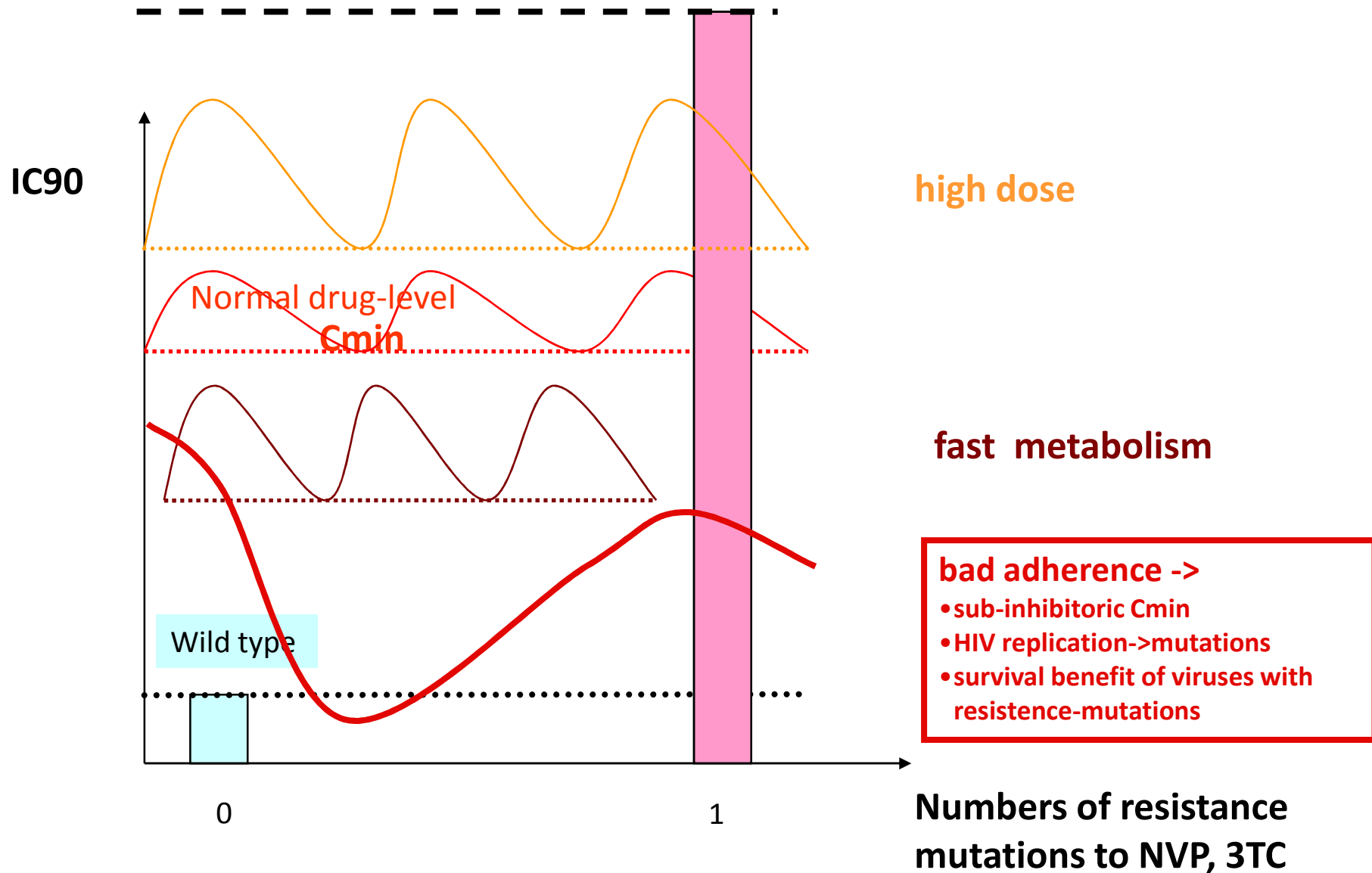
Immunological:

- lack of CD4 \uparrow > 25 – 50 cells/ μ l

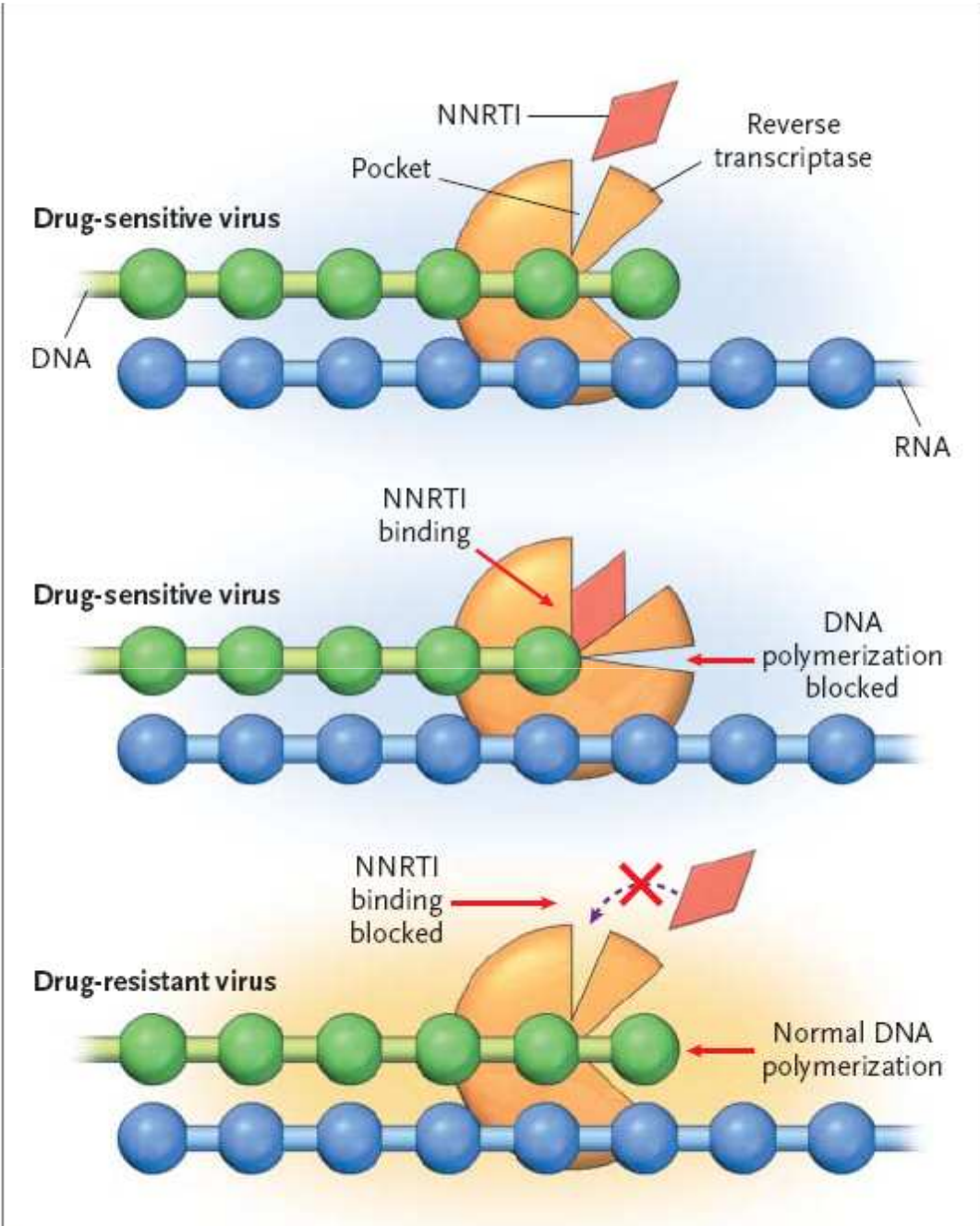
Reasons:

- Lack of antiretroviral potency
- ARV resistance
- Non-adherence
- inadequate concentration of medicaments due to interactions or malabsorption

Pharmacodynamics



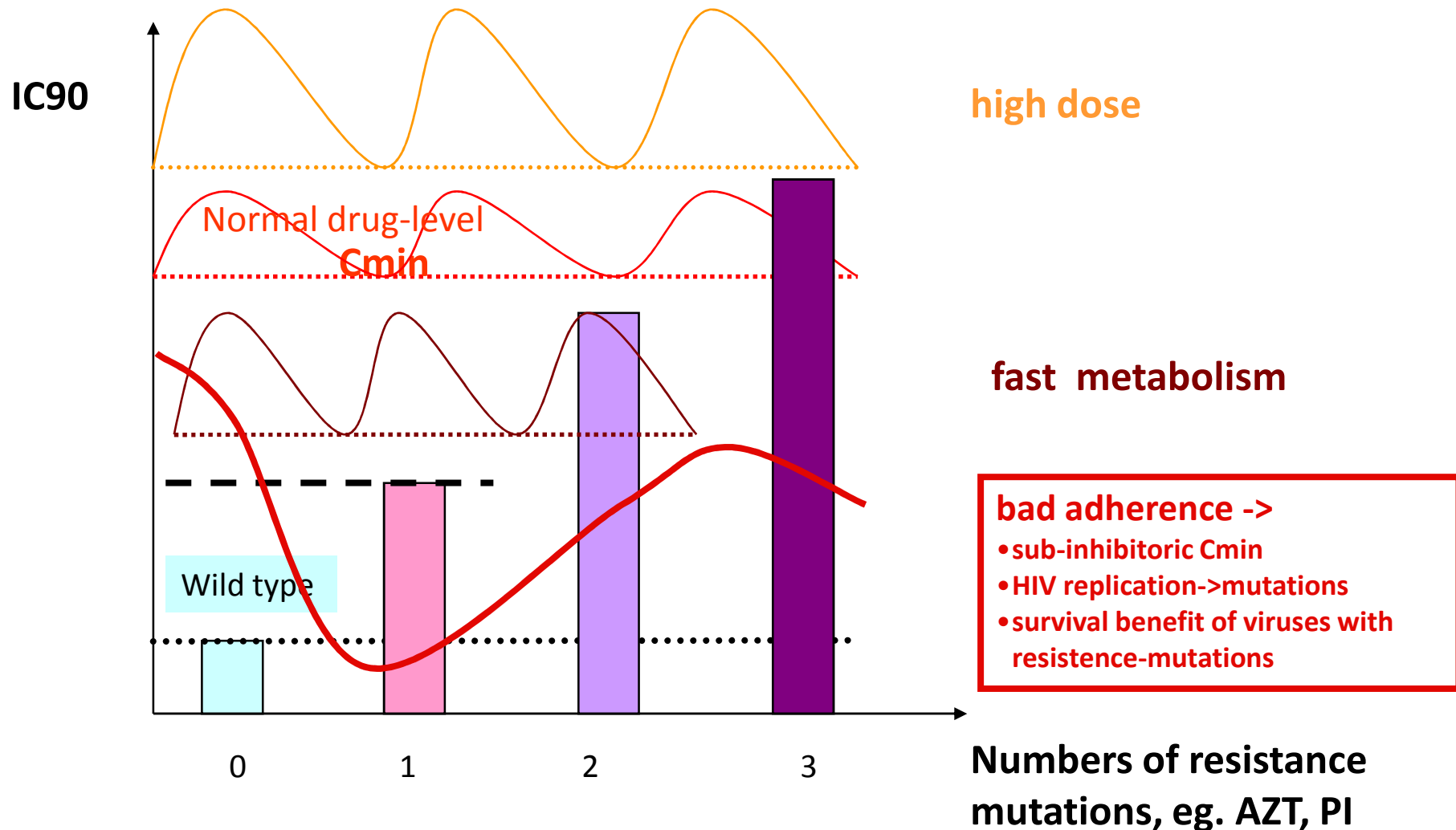
Resistance to NNRTI



Clavel NEJM 2004;350:1023h

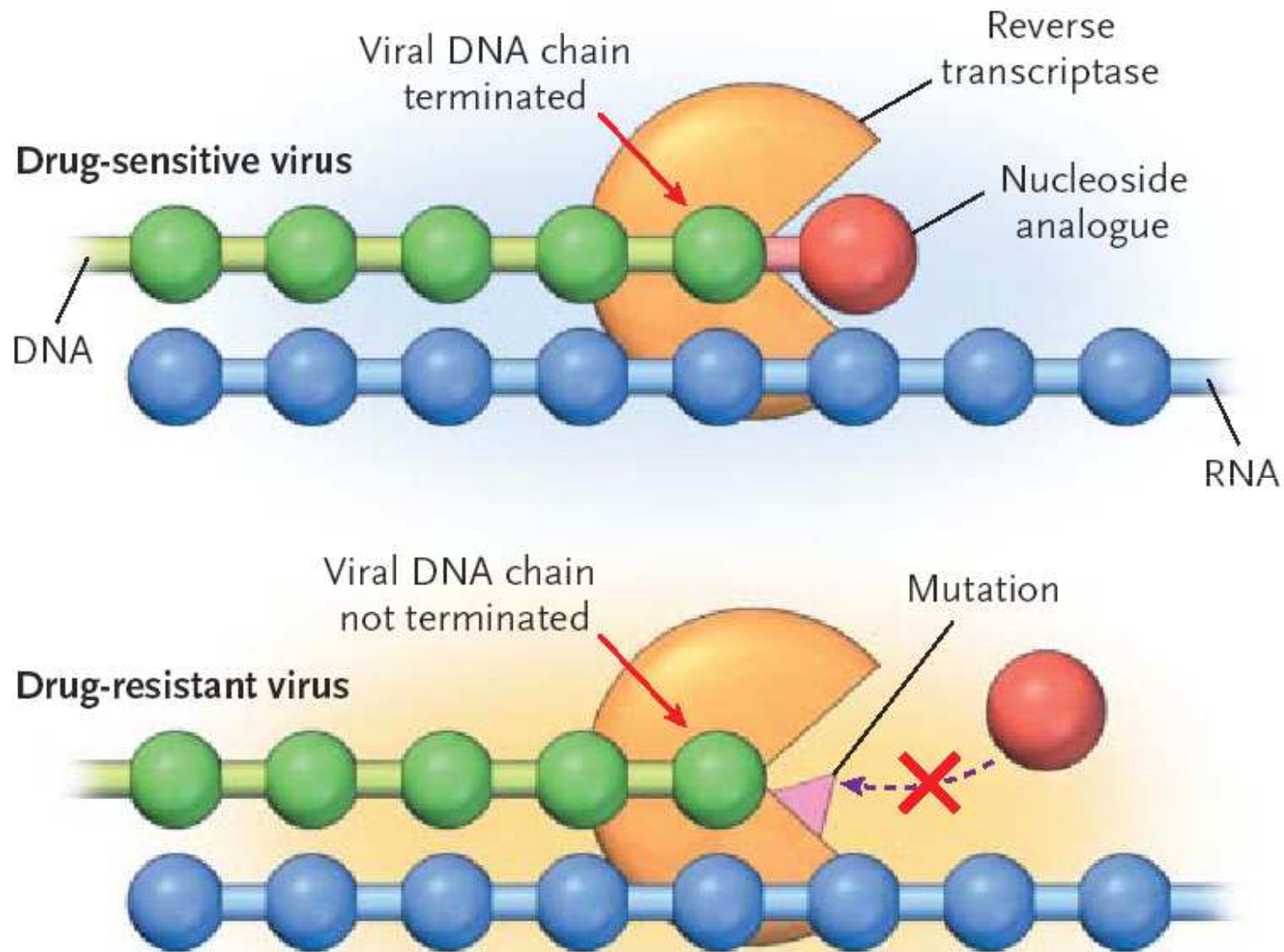
Figure 4. Mechanism of Resistance of HIV to Nonnucleoside Reverse-Transcriptase Inhibitors.

Pharmacodynamics

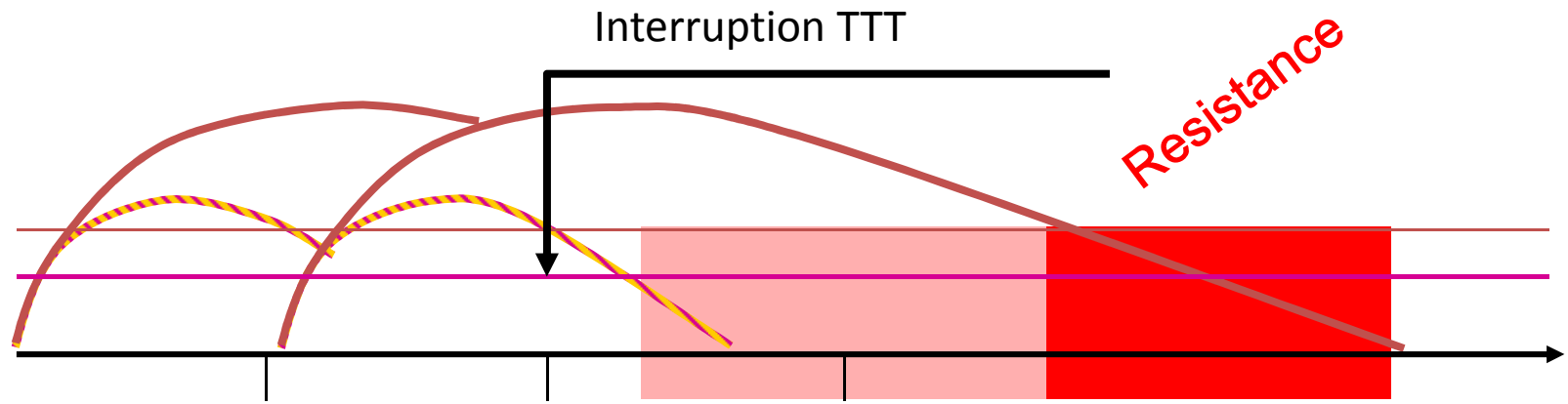
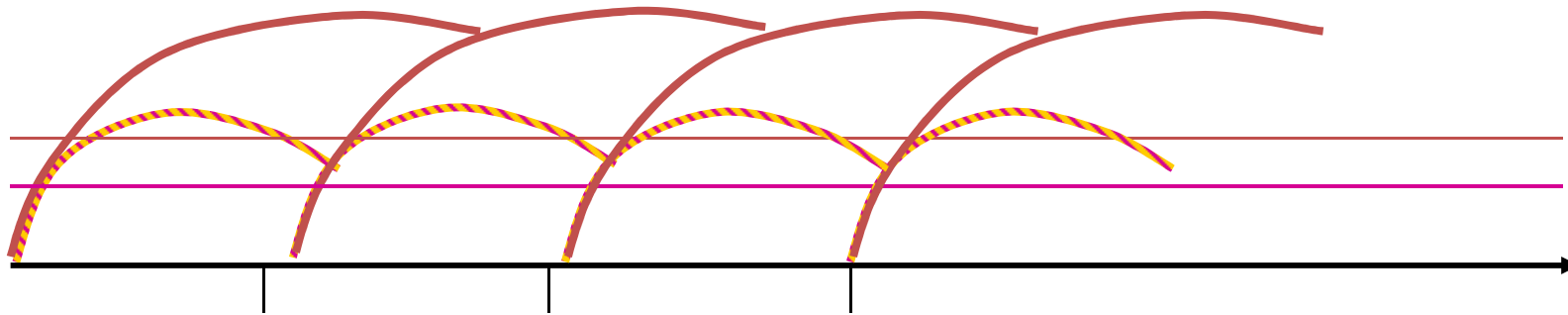
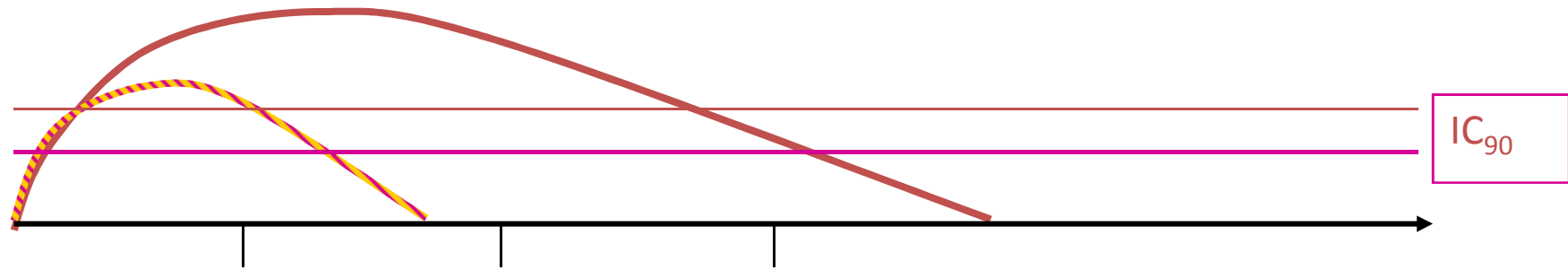


A

Resistance by Interference with the Incorporation of a Nucleoside Analogue



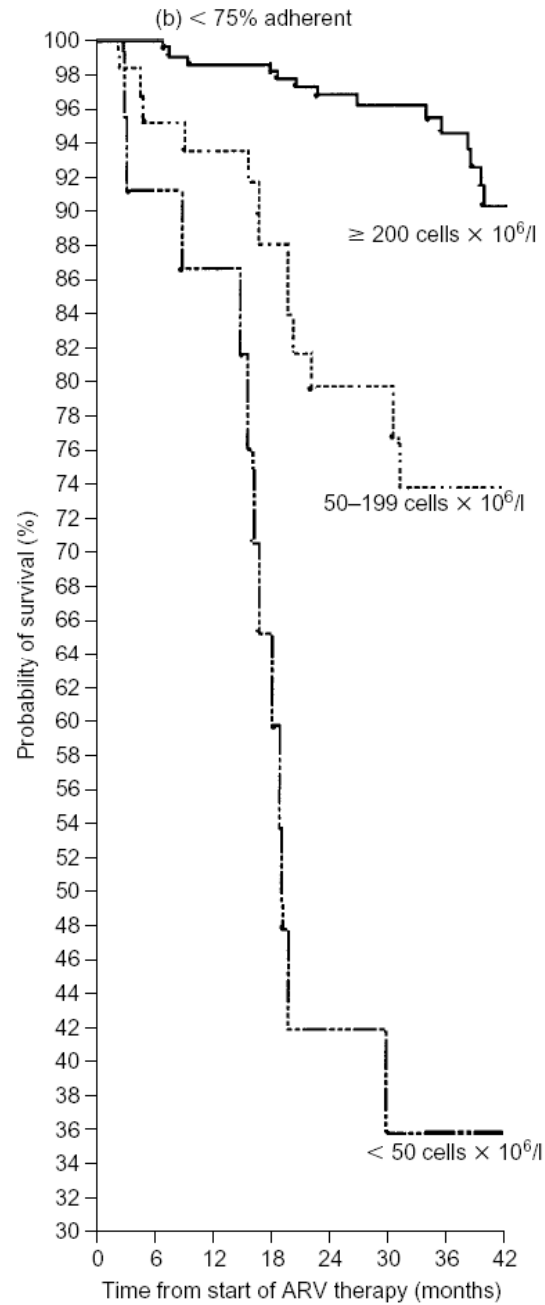
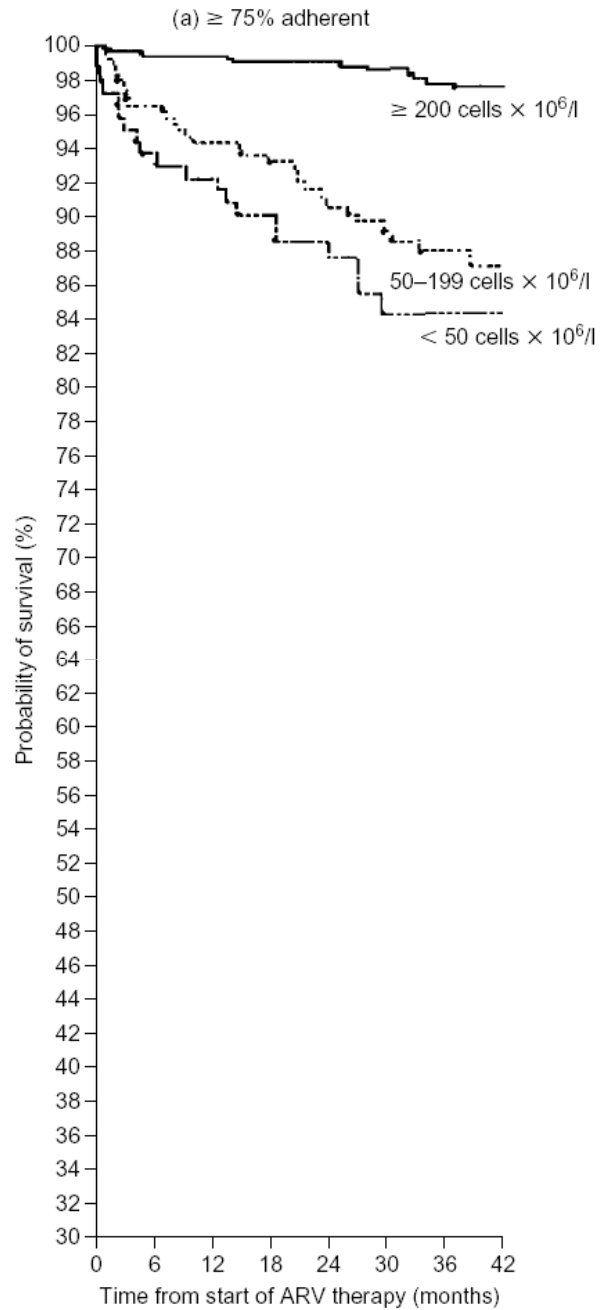
PK: long $T_{1/2}$



When to change therapy

- Intolerable and life threatening side effects
- Drug interactions (e.g. Rifampicin)
- Treatment failure
- Special conditions: TB
Pregnancy
Liver disease

Adherence



Importance of adherence

Adherence to HAART*	Viral Load <400 c/mL at 6 Months
>95% adherence	78%
90 to 95% adherence	45%
80 to 90% adherence	33%
70 to 80% adherence	29%
<70% adherence	18%

* Number of doses prescribed/number taken

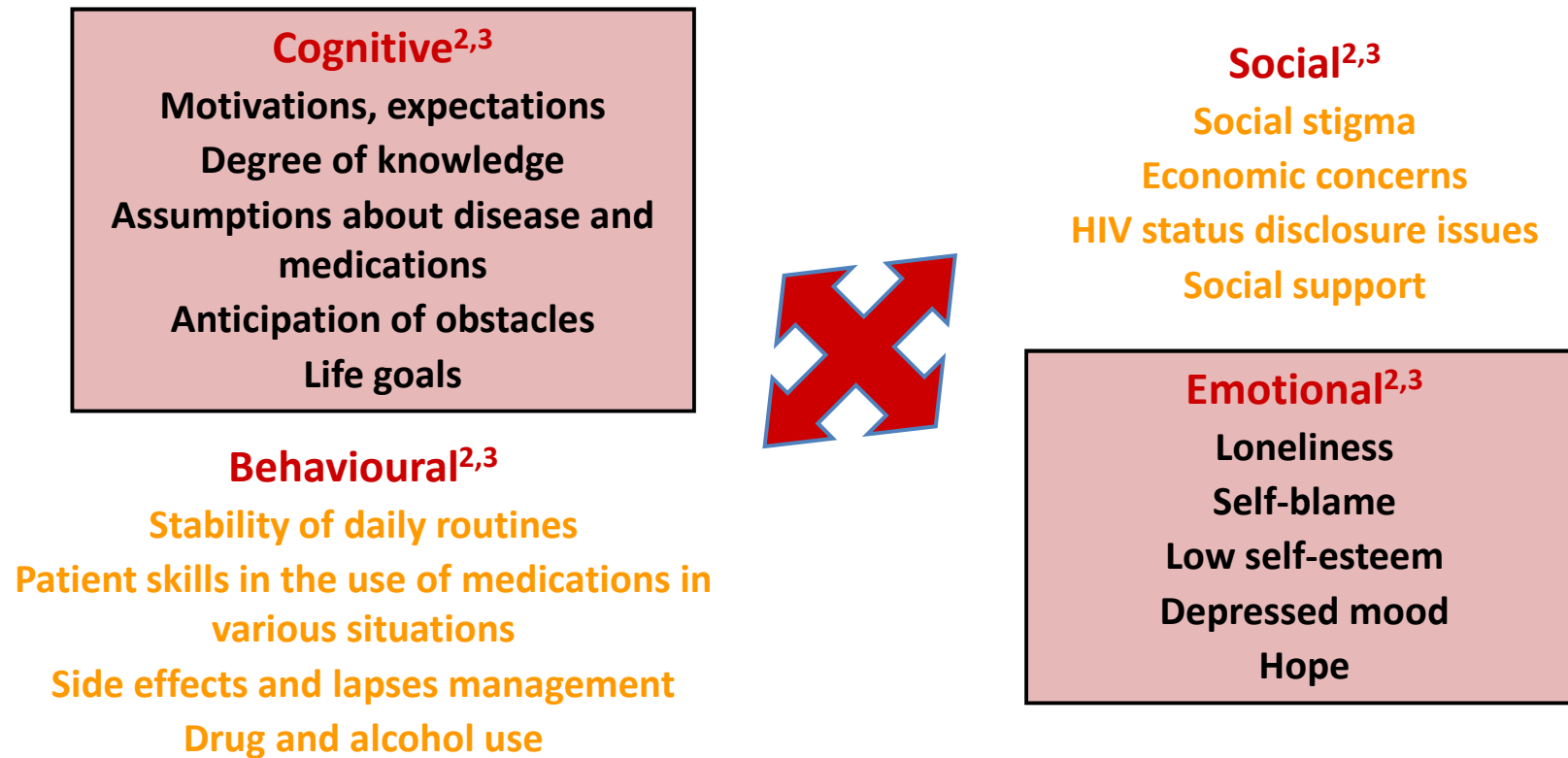
Consequences of non-adherence

- Incomplete viral suppression (1)
- Development of resistance mutations (2, 3)
- Increased risk of disease progression and mortality (4, 5)

- 1) Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV-infection. *Ann Intern Med* 2000; 133: 21 – 30.
- 2) Wainberg MA, Friedland G. Public health implications of antiretroviral therapy and HIV drug resistance. *JAMA* 1998; 279: 1977 – 83.
- 3) Mayers DL. Drug resistant HIV-1: the virus strikes back. *JAMA* 1998; 279: 2000 – 2.
- 4) Bangsberg DR, Perry S, Charlebois E, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* 2001; 15: 1181 – 3.
- 5) Wood E, Hogg RS, Yip B, et al. Effect of medication adherence on survival of HIV-infected adults who start HAART when the CD4 cell count is 0.2 to 0.35x10⁹cells/L. *Ann Intern Med* 2003; 139: 810 – 6.

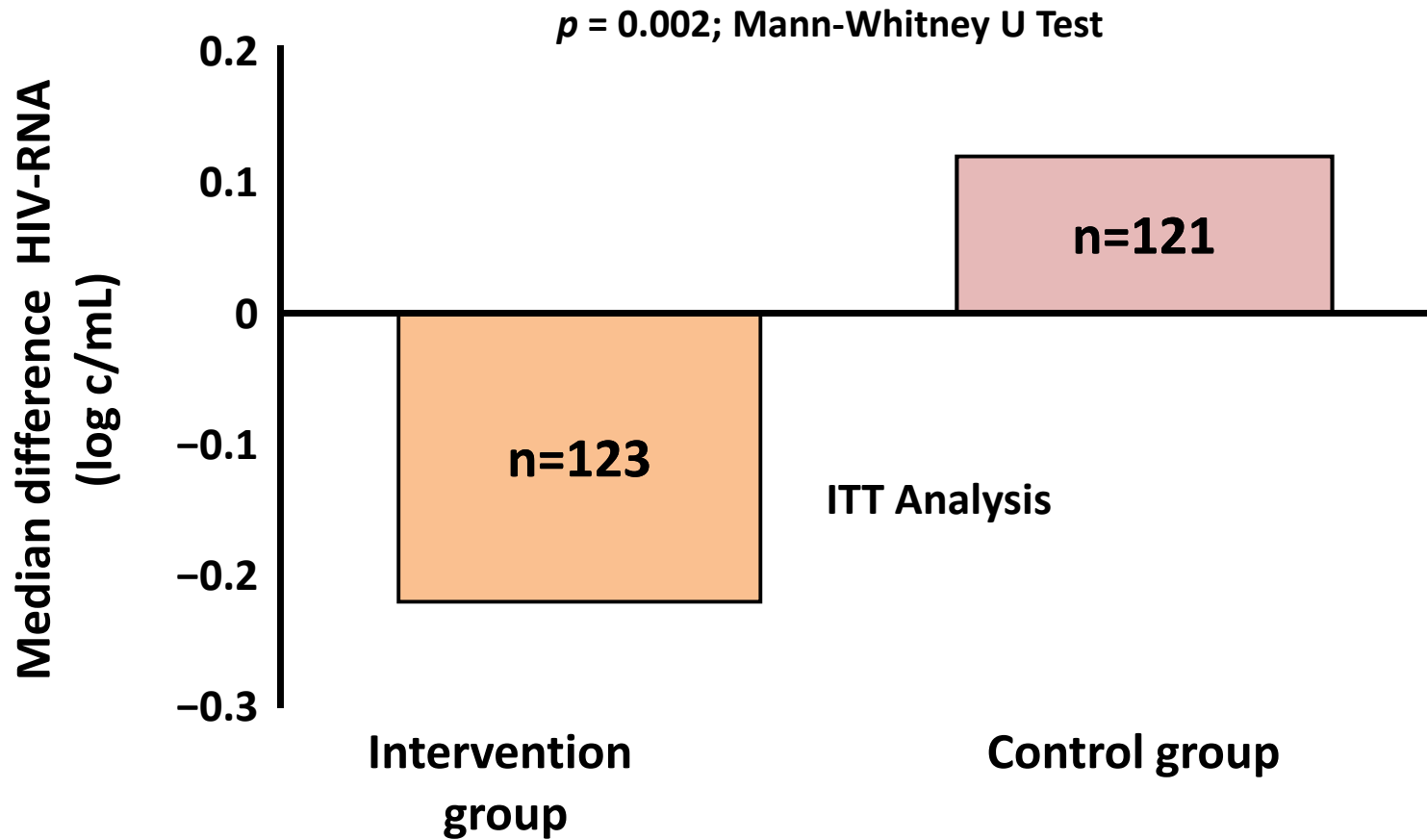
The MOTHIV model: Theory and method

Intervention with education and support^{1,2}



1. Pradier C *et al.*, *HIV Clin Trials* 2003;4:121–131; 2. Tourette-Turgis C, Rébillon M. Mettre en place une consultation d'observance aux traitements contre le VIH/SIDA - De la théorie à la pratique. Paris, Ed. *Comment Dire*, 2002; 3. Tourette-Turgis C. Personal Communication.

MOTHIV: Virological outcome after 6 months



The human perception...

- To talk doesn't mean it's heard
- To hear doesn't mean it's understood
- To understand doesn't mean it's agreed on
- To agree doesn't mean it's done
- To do doesn't mean it's kept on doing

The change of paradigm

- **„Acute Care“**

- Acute problem
- Efficient Intervention
- Physical dimension
- HCF centered
- Problem-orientated intervention

- **„Chronic Illness“**

- Chronicity
- „Chronic illness“ Management
- Physical, psychological and behavioristic dimension
- Patient-centered
- Continuum of care and „self-empowerment“

PMTCT

Pregnancy has no clear effect on HIV progression
increased rate of preterm delivery, low birth weight and stillbirth

- Transmission without BF
 - intrauterine 25 – 40%
 - perinatal 60 – 75%
- Perinatal transmission
 - Spontaneously 20.0%
 - (developing countries 19 – 36%)
 - AZT monotherapy 10.4%
 - dual NRTIs 3.8%
 - HAART 1.2%
- Breastfeeding 10 – 16%

AIDS 2001

J Acquir Immune Defic Syndr 2002

Clin Infect Dis 2005

Factors influencing transmission

- VL (41% with >100'000, lim 0% with < 1000)
- AZT (see ACTG 076)
- C-section vs vaginal delivery
1.8% vs. 6.5% (*Br Med J 2001*)
- Breastfeeding, especially first 4 to 6 months
2-fold increase with mastitis and 50-fold with breast abscess
! Cracked nipples, infant with Oral thrush, primary HIV, prolonged breastfeeding
1.7 Mio infants get HIV-positiv due to BF, 1.5 Mio would die if not breastfed (*Br. Med. J 2001*)

ATCG-076-Protokol (MMWR 2002; 51:1)

Before birth:

AZT 300 mg bid from week 14 until birth

During birth:

AZT iv 2 mg/kg in 1. hour, then 1 mg/kg/h until birth

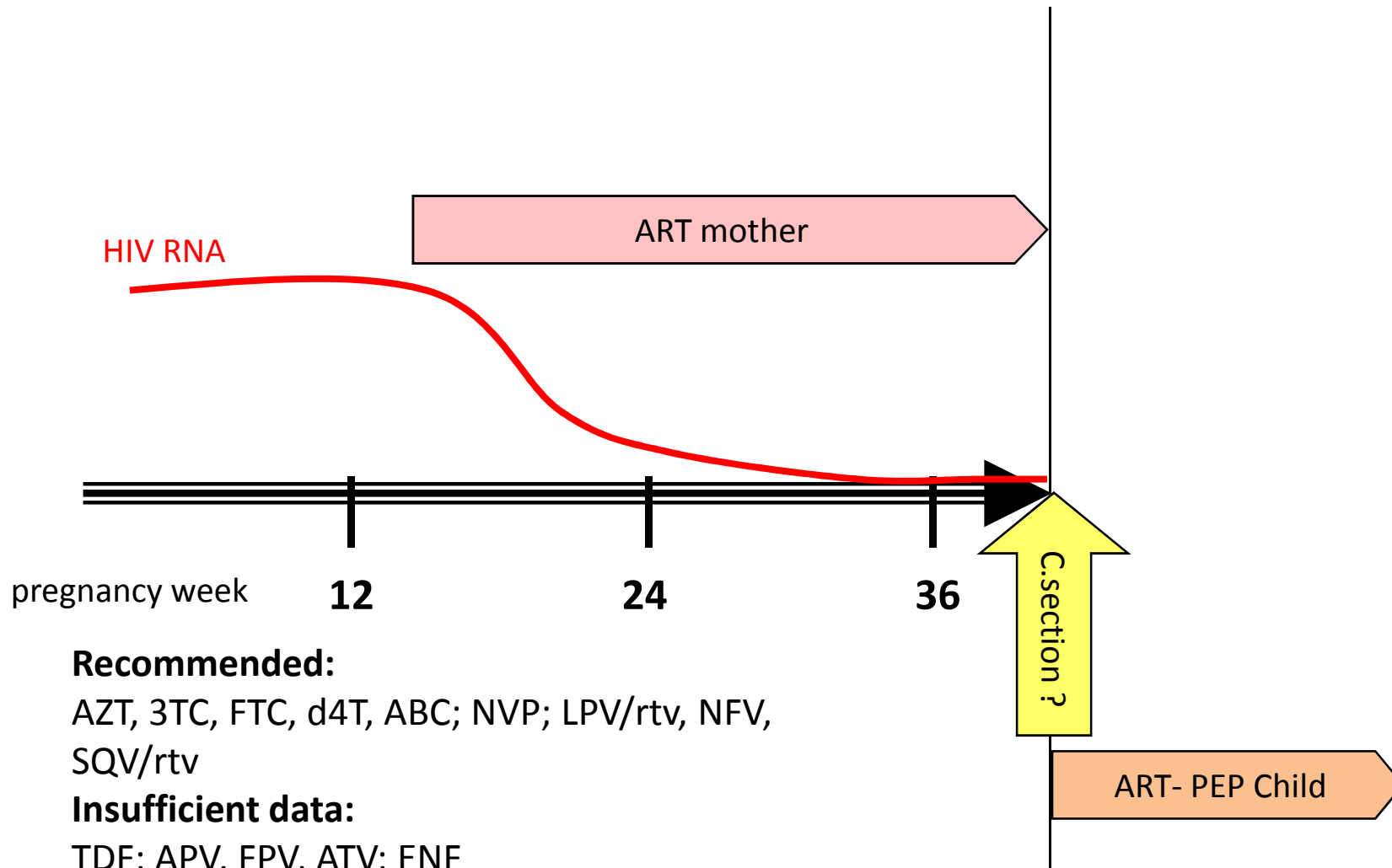
Once 200 mg NVP for mother

and 2 mg/kg for the baby

After birth:

AZT sirup 2 mg/kg q6 hours for 6 weeks for the baby

Prevention of vertical HIV transmission



Recommended:

AZT, 3TC, FTC, d4T, ABC; NVP; LPV/rtv, NFV, SQV/rtv

Insufficient data:

TDF; APV, FPV, ATV; ENF

Not recommended:

EFV