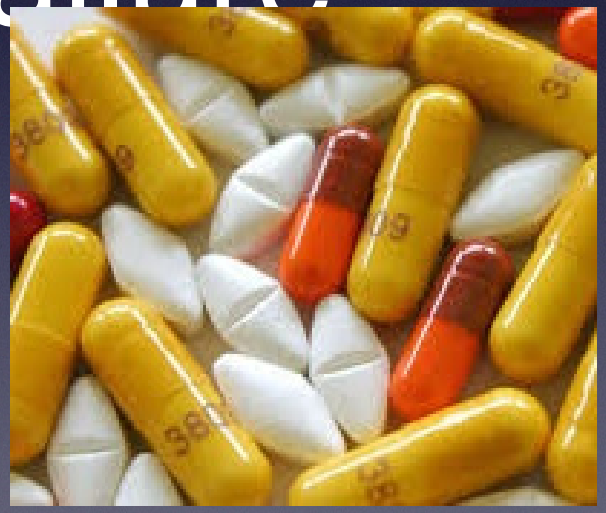
Diagnosing and managing HIV treatment failure



Dr David Stead

Eastern Cape HIV clinicians symposium
30th May 2015

Overview

- Definition of treatment failure
- Extent of the problem
- Why do patients fail?
- HIV resistance 101
- First line failures
- Second line failures
- Choosing a third line regimen

Treatment failure definitions

- Clinical:

  New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment

- Immunological:

  CD4 count falls to the baseline (or below) or
  Persistent CD4 levels below 100 cells/mm3

- Virological:

  “Treatment failure in adults and children, including infants, is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, 2 consecutive viral load measurements within a 2-month interval, with adherence support between measurements) after at least six months of using ARV drugs”

(WHO and SA DOH 2015)

1st line regimen VL monitoring:

Viral Load (VL)	Response
NOTE: Always check hepatitis B before stopping TDF. If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. If hepatitis B positive, TDF should be continued as a 4th drug in the second-line regimen	
<400 copies/mL	• VL monitoring according to duration of ART and routine adherence support • Continue routine VL monitoring as it may be 12 monthly depending on how long patient is on treatment
400-1000 copies/mL	• Assess and manage adherence carefully • Repeat VL in 6 months and manage accordingly
>1 000 copies/mL	• Adherence assessment and intense adherence support • Repeat VL in 2 months and check HBV status and Hb, if not already done • If <1000 copies/mL, repeat in 6 months and then reassess • If >1000 copies/mL and adherence issues addressed, switch to second line therapy after checking HBV status and Hb

Second-line regimen

First-line virological failure	Drugs
Failing on a TDF-based first-line regimen	AZT + 3TC + LPV/r AZT + TDF + 3TC + LPV/r (If HBV co-infected)
Failing on a d4T or AZT-based first line regimen	TDF + 3TC (or FTC) + LPV/r
Dyslipidaemia (total cholesterol >6 mmol/L) or diarrhoea associated with LPV/r	Switch LPV/r to ATV/r
Anaemia and renal failure	Switch to ABC

Impact of Viral load monitoring

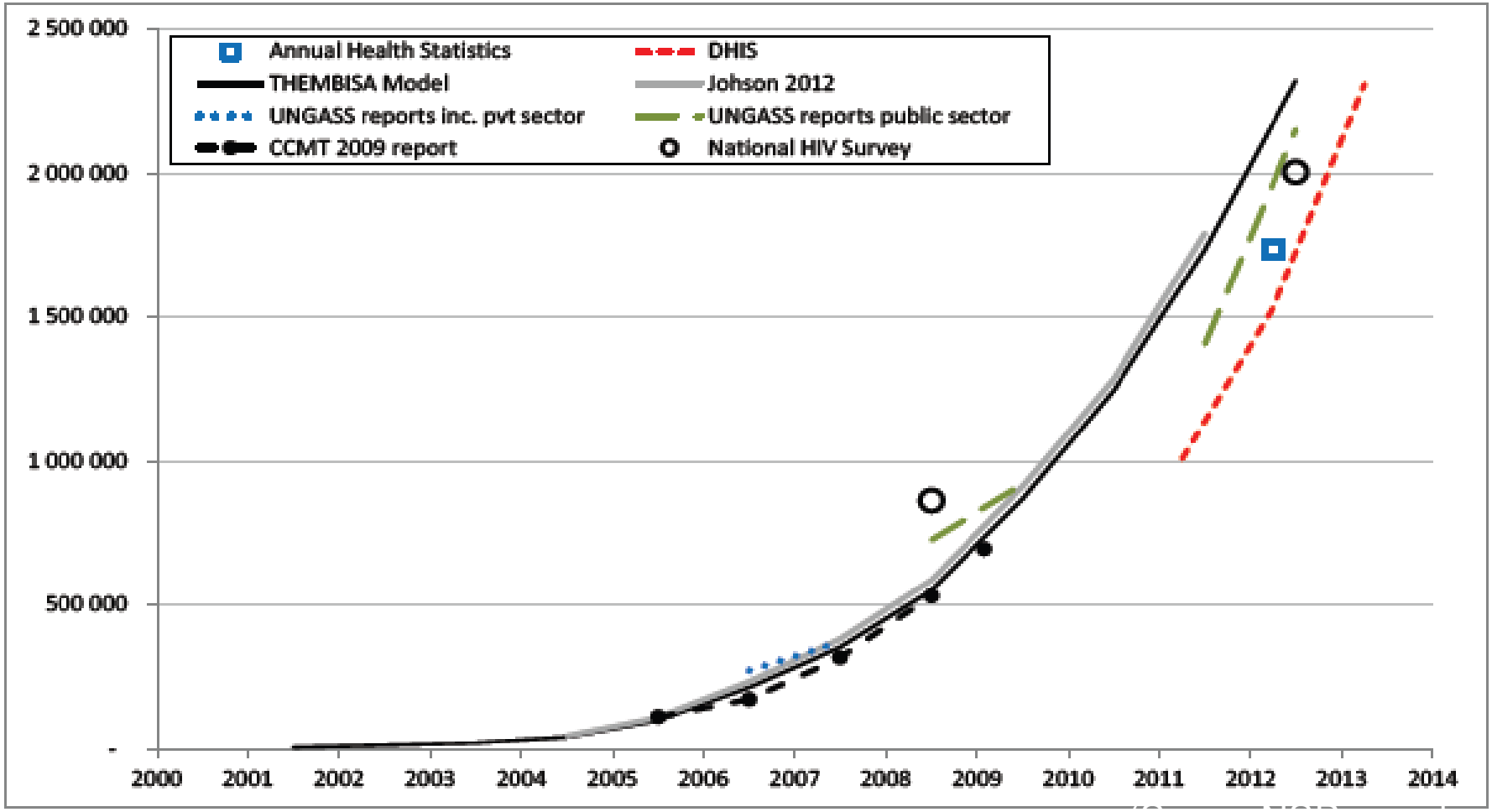
- Reduces unnecessary switching on clinical/CD4 criteria
- Reduces delay in switching from a failing regimen, and resistant mutation accumulation

	AZT resistance	TDF resistance
No VL	60%	50%
VL monitoring	10%	30%

(De Luca et al. JID 2013)

Extent of the problem in South Africa

Figure 5: Total patients on antiretroviral therapy by reporting source and calendar period



(Sanac-NSP report 2014)

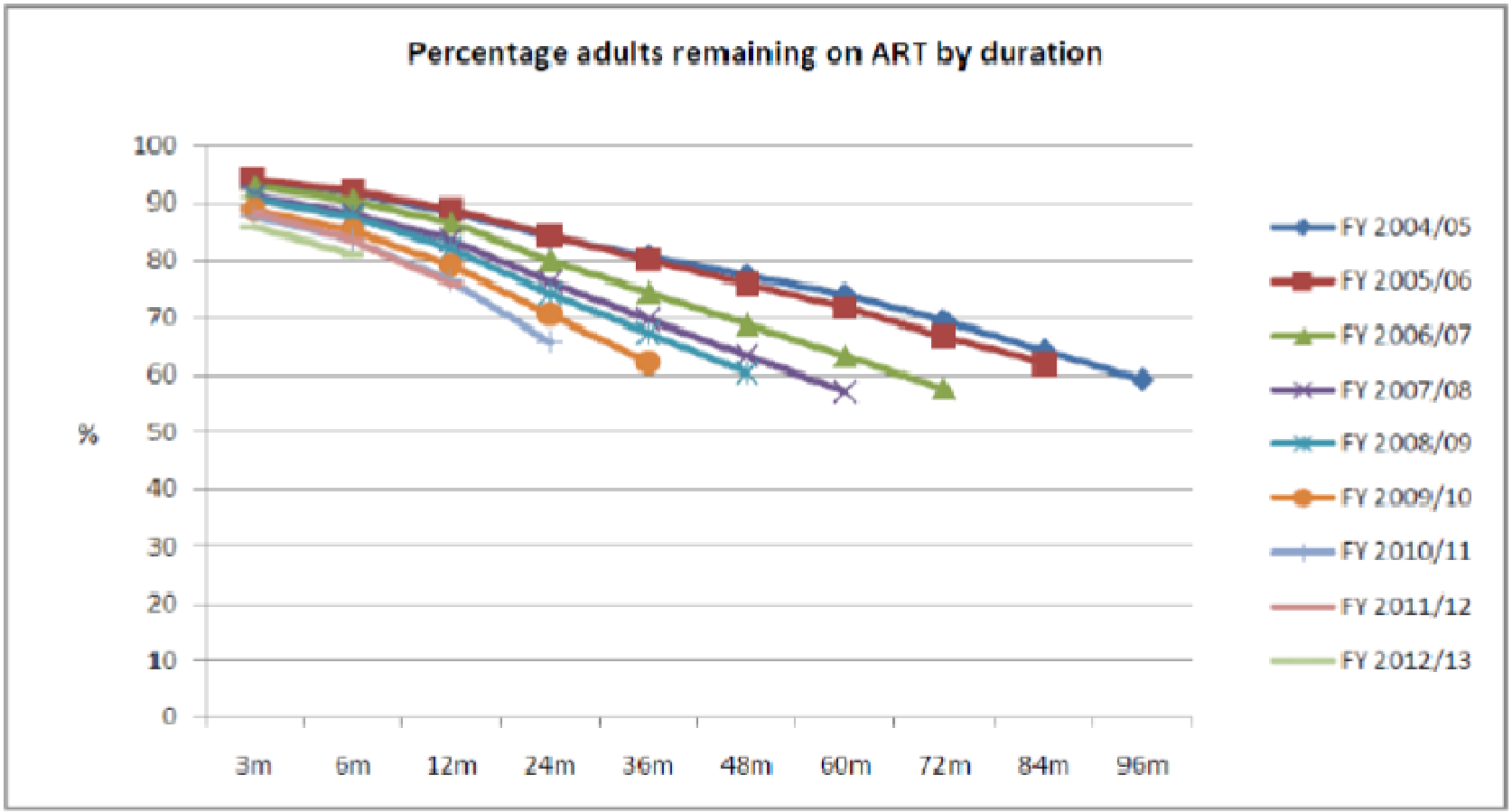
Table 8: Viral load testing and suppression in adults and children on ART in South Africa by duration of follow-up and financial year of outcome reporting[2]

	Adults		Children	
	FY 2008/09	FY 2012/13	FY 2008/09	FY 2012/13
Patients remaining on ART				
1 year	42 370	115 839	3 535	5 537
5 years	3 273	11 622	329	1 469
Viral load done				
1 year	42.0%	37.6%	40.1%	36.6%
5 years	56.3%	37.2%	55.6%	35.8%
Viral load <400 copies/ml				
1 years	83.7%	77.4%	77.2%	62.3%
5 years	87.9%	74.0%	79.4%	69.9%

(Sanac-NSP report 2014)

SA retention in ART care

Figure 18: Adult remaining in care by year started ART (cohort)

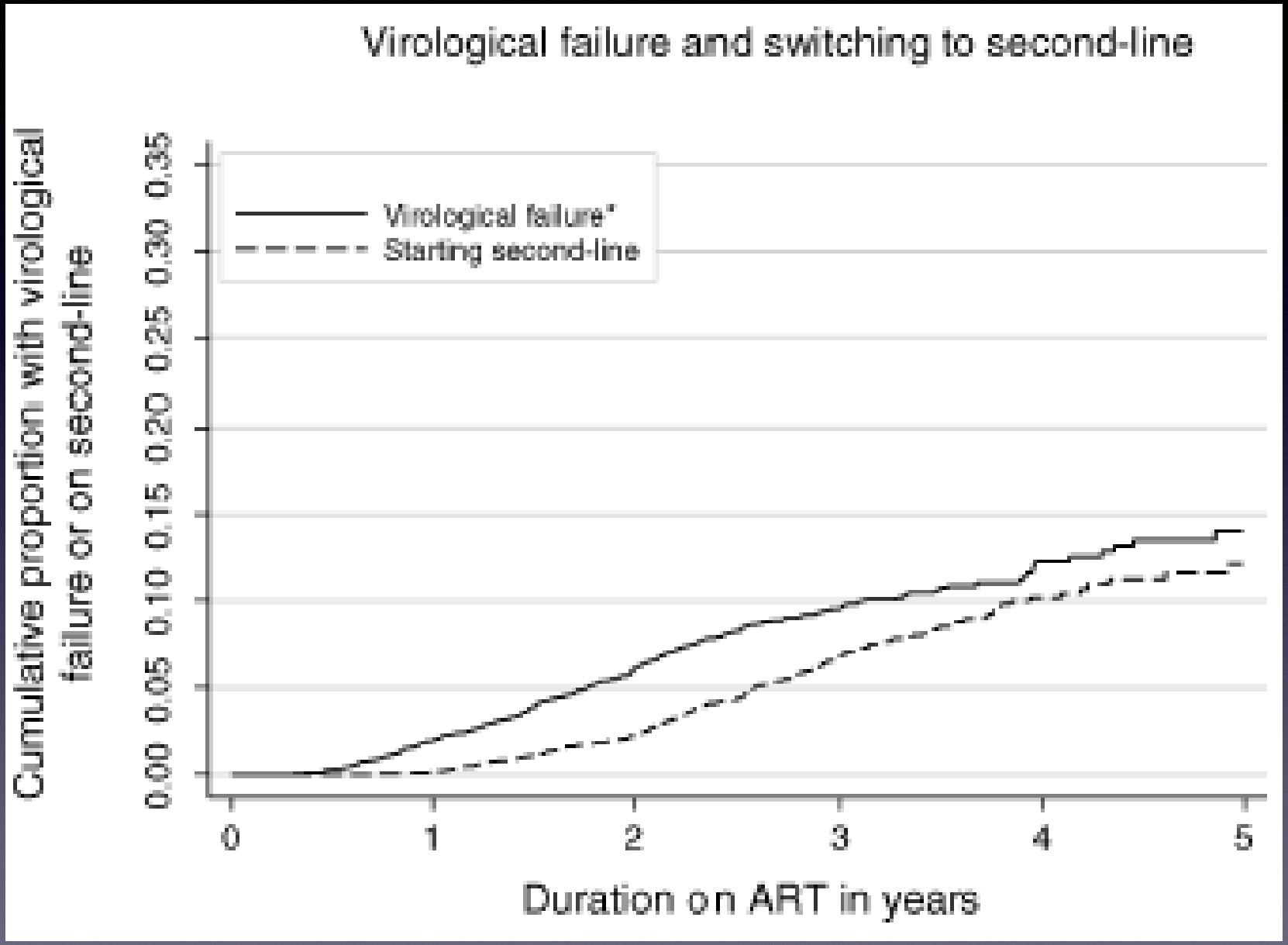


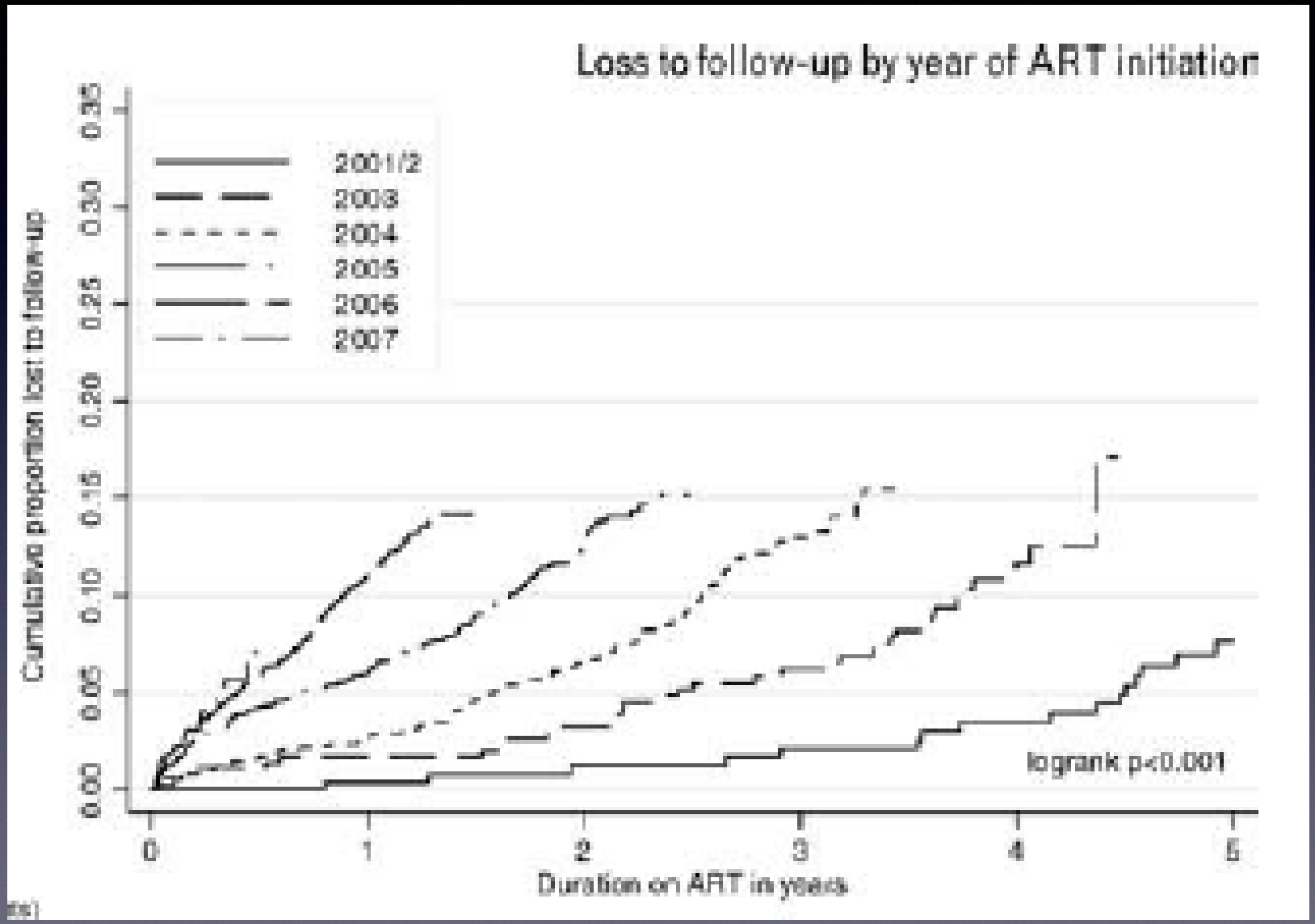
http://www.health.gov.za/docs/reports/2013/ARTProgramme.pdf#sthash.zqUZIUpO.dpuf

Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa

Andrew Boulle[a], Gilles Van Cutsem[a,b], Katherine Hilderbrand[a,b], Carol Cragg[c], Musaed Abrahams[b], Shaheed Mathee[c], Nathan Ford[a,b], Louise Knight[b], Meg Osler[a], Jonny Myers[a], Eric Goemaere[b], David Coetzee[a] and Gary Maartens[d]

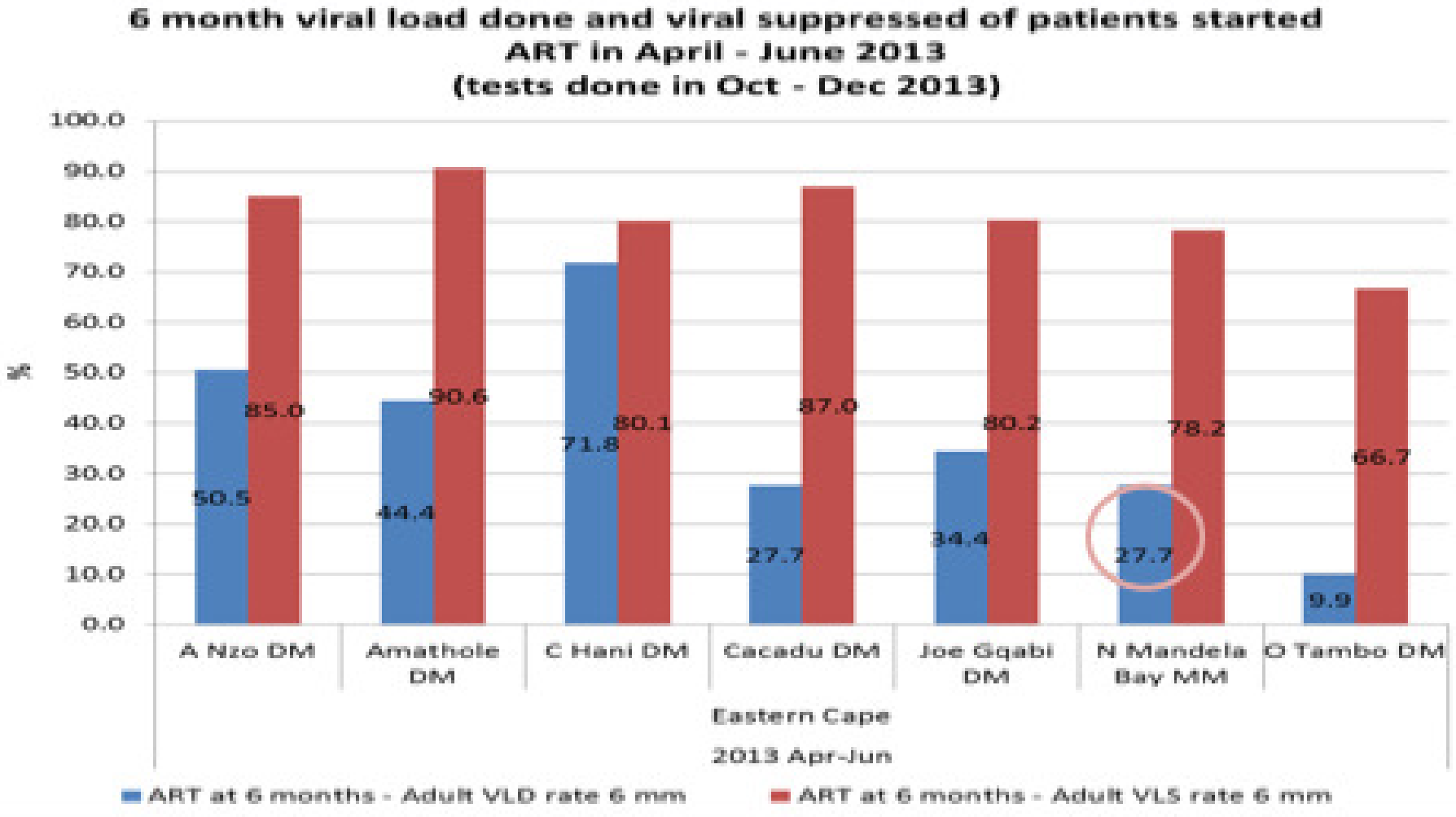
AIDS 2010, **24**:563–572


Virological failure and switching to second-line
Cumulative proportion with virological failure or on second-line
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Virological failure*
Starting second-line
0
1
2
3
4
5
Duration on ART in years

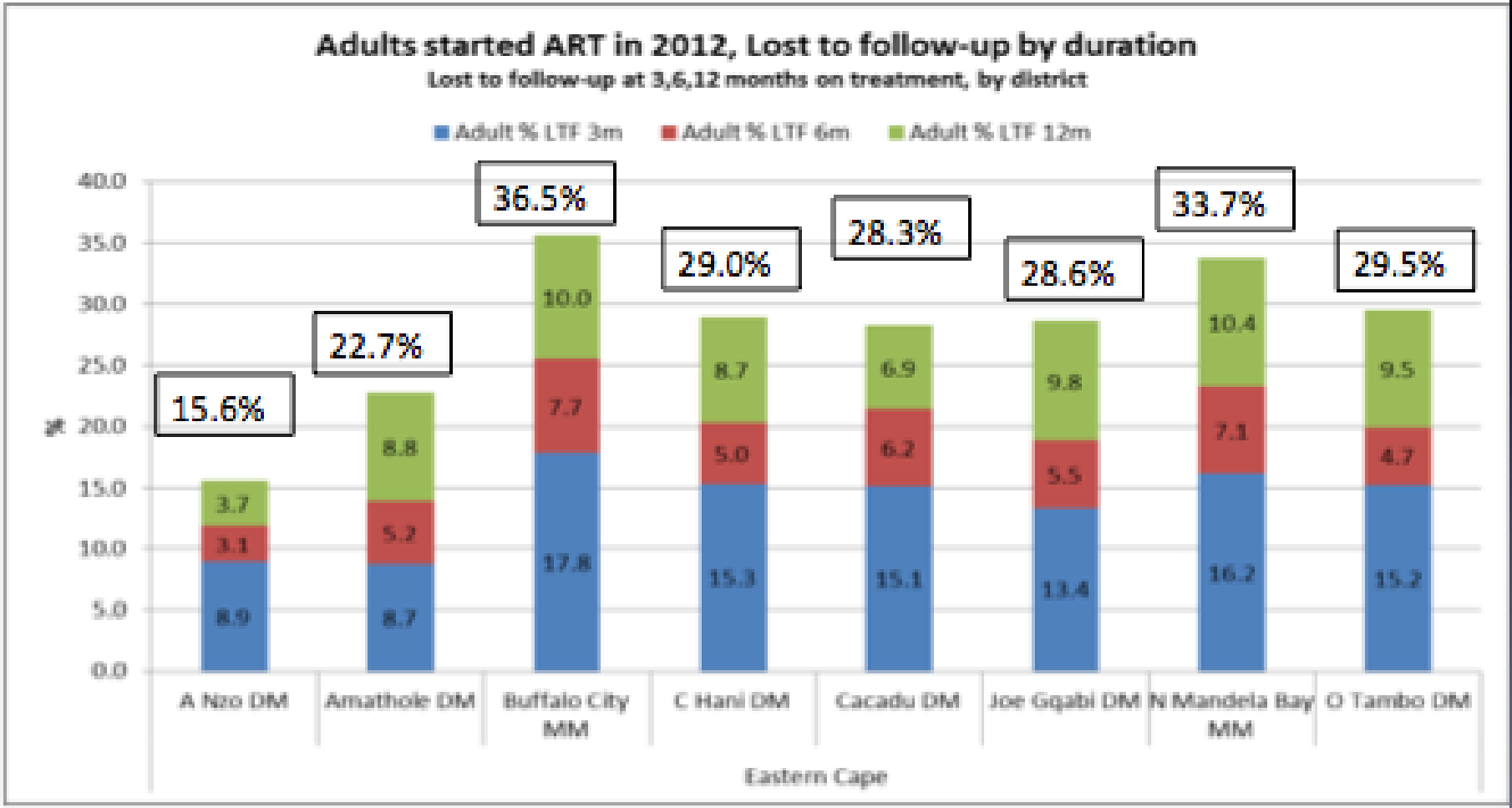

Loss to follow-up by year of ART initiation
2001/2
2003
2004
2005
2006
2007
Cumulative proportion lost to follow-up
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0
1
2
3
4
5
Duration on ART in years
logrank p<0.001

And the Eastern Cape?

Inter district comparison for VLD/VLS at 6 months



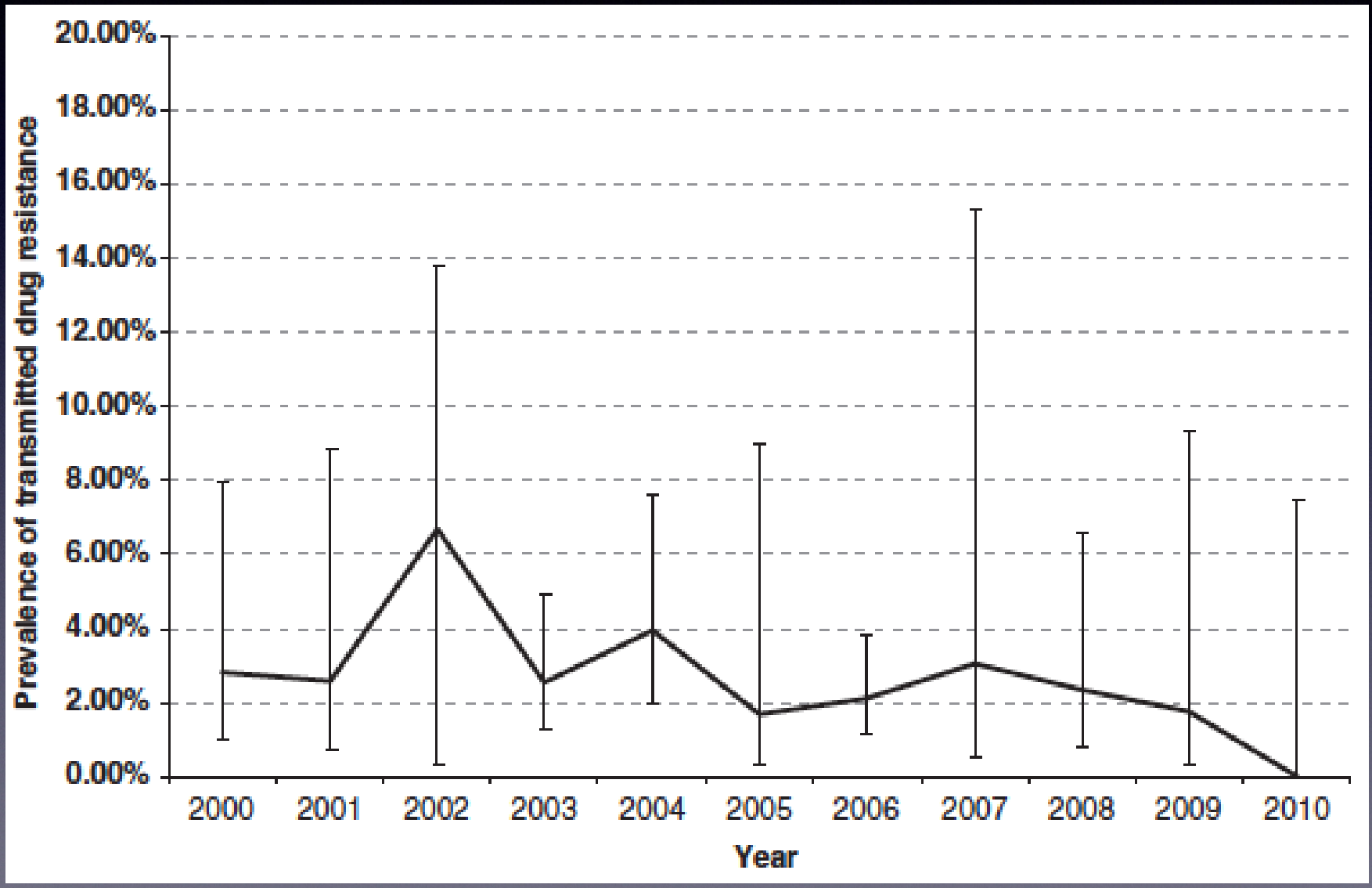
Inter-district comparison of Adult LTF, by duration



Why do patients fail?

- Primary resistance
- Poor adherence
- Drug interactions
- Malabsorbtion
- Systems failures (stock outs etc)

Transmitted drug resistance in South Africa: 2000-2010



(Manasa J eta al. AIDS Res Hum Retroviruses. 2012)

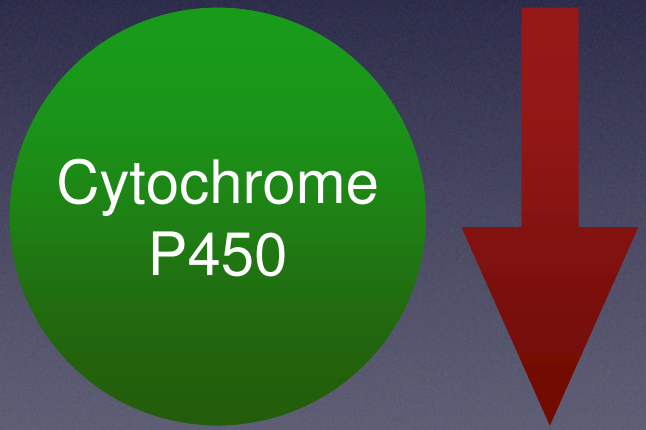
Adherence check list

- Inadequate treatment literacy
- Side effects
- Depression/ other psych disease
- Poverty & food insecurity
- Substance use
- Social problems
- Work related issues

Drug interactions

Substrates:

- NNRTI's
- PI's
- Integrase inhibitors



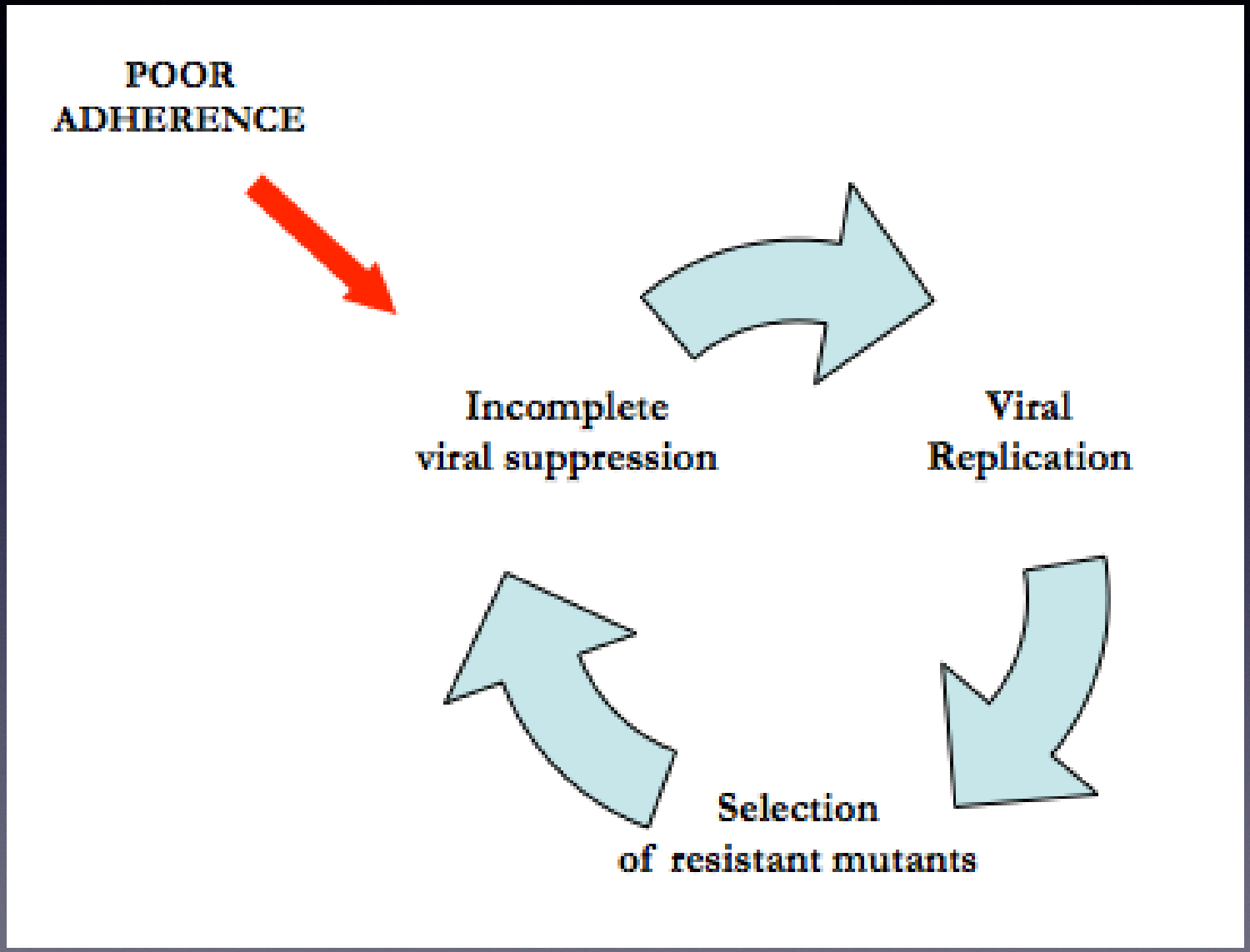
Inducers:

- Rifampicin
- Anti-convulsants

Why do patients fail?

- Primary resistance
- Poor adherence
- Drug interactions
- Malabsorbtion
- Systems failures (stock outs etc)

HIV resistance 101


POOR
ADHERENCE
Incomplete
viral suppression
Viral
Replication
Selection
of resistant mutants

Key factors predisposing to resistance developing

- High rate of HIV production and turnover
- 1 to 10 billion / day
- Reverse Transcriptase is error prone
- +/- 3 mutations for each viral genome transcribed
- Mutations exist at all alleles in the HIV genome
- Highly heterogenous pool of viruses differing by one or more mutations
- Drug resistant mutants precede the introduction of drugs and are selected out if replication continues in presence of drug

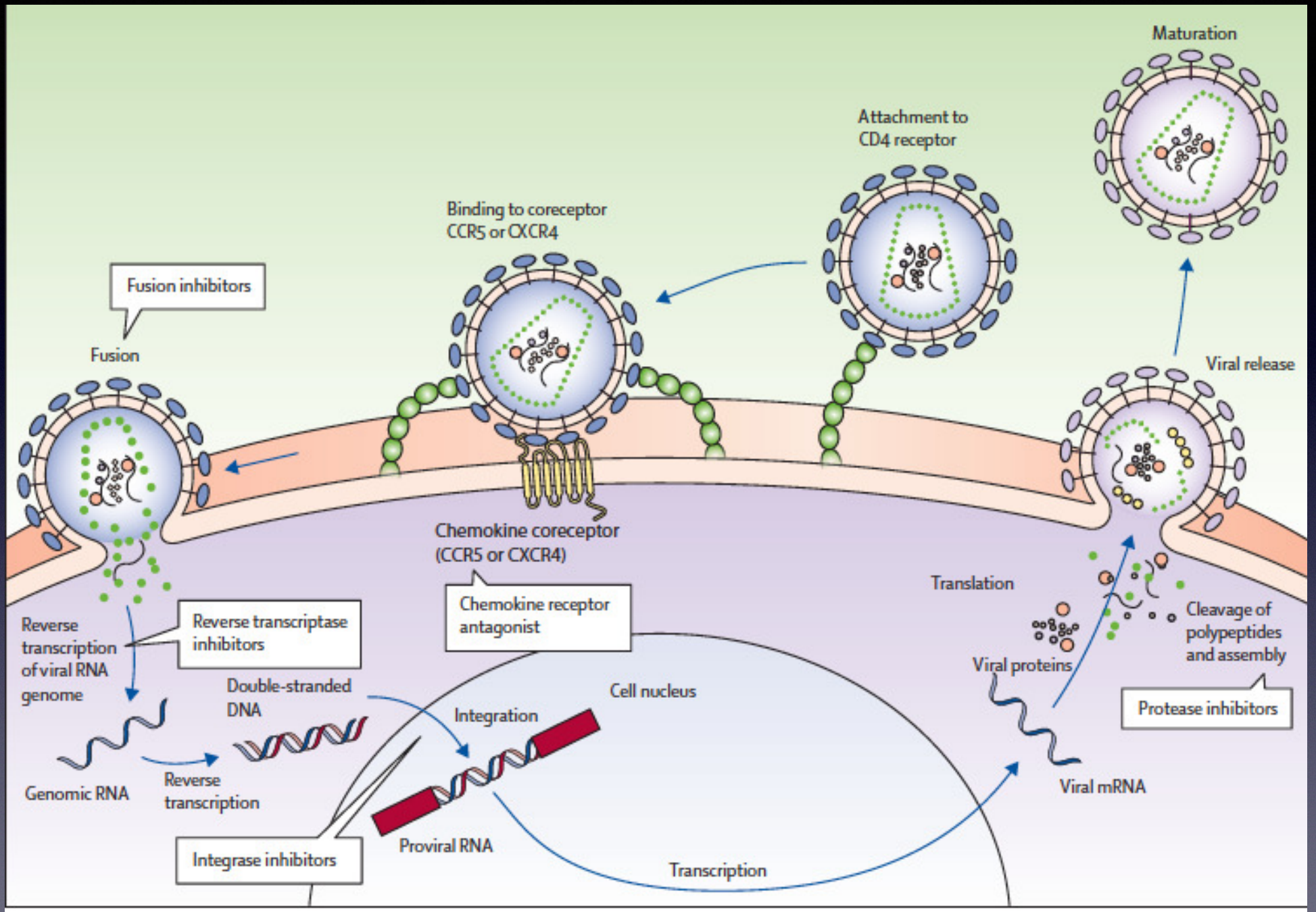
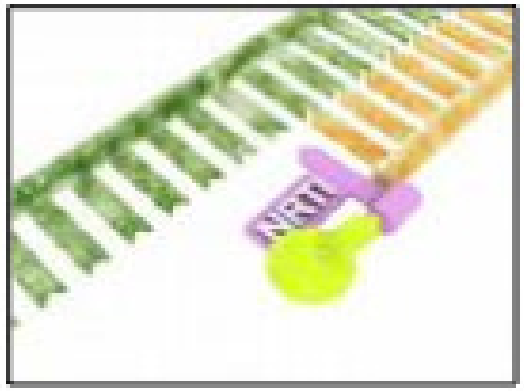


Figure 2: **HIV life cycle showing the sites of action of different classes of antiretroviral drugs**
Adapted from Walker and colleagues,[36] by permission of Elsevier.

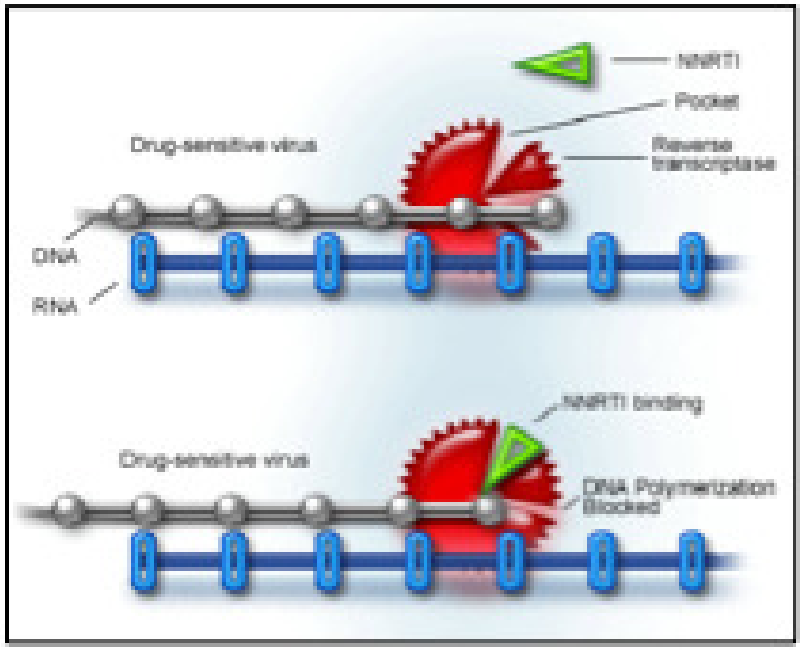
Reverse trancriptase enzyme inhibition:

NRTI's:



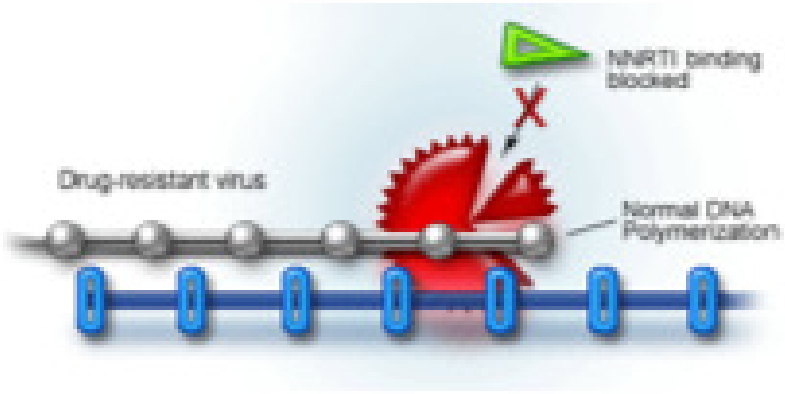
- 'false' drug nucleosides inserted into DNA, blocking further polymerization

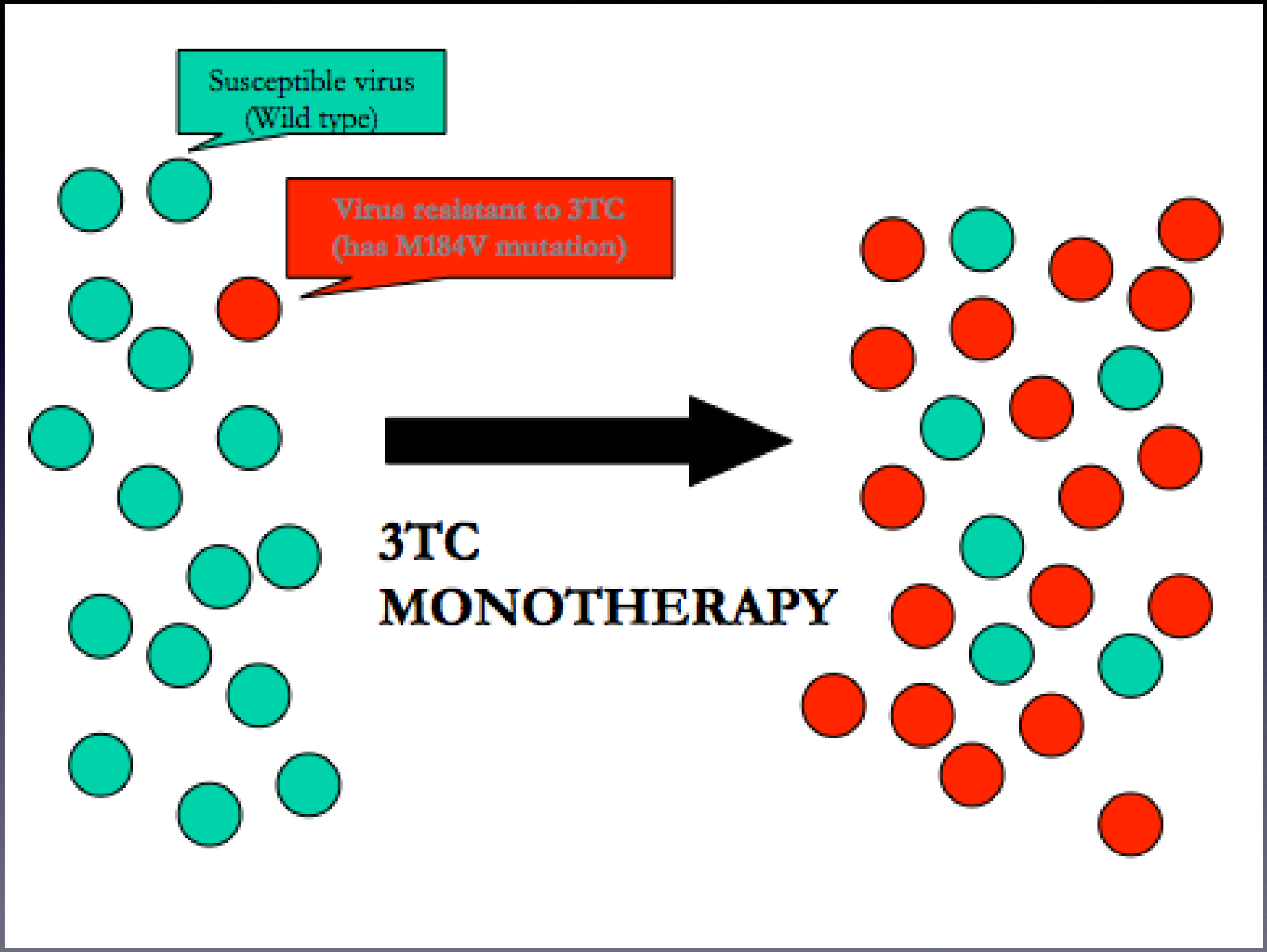
NNRTI's:

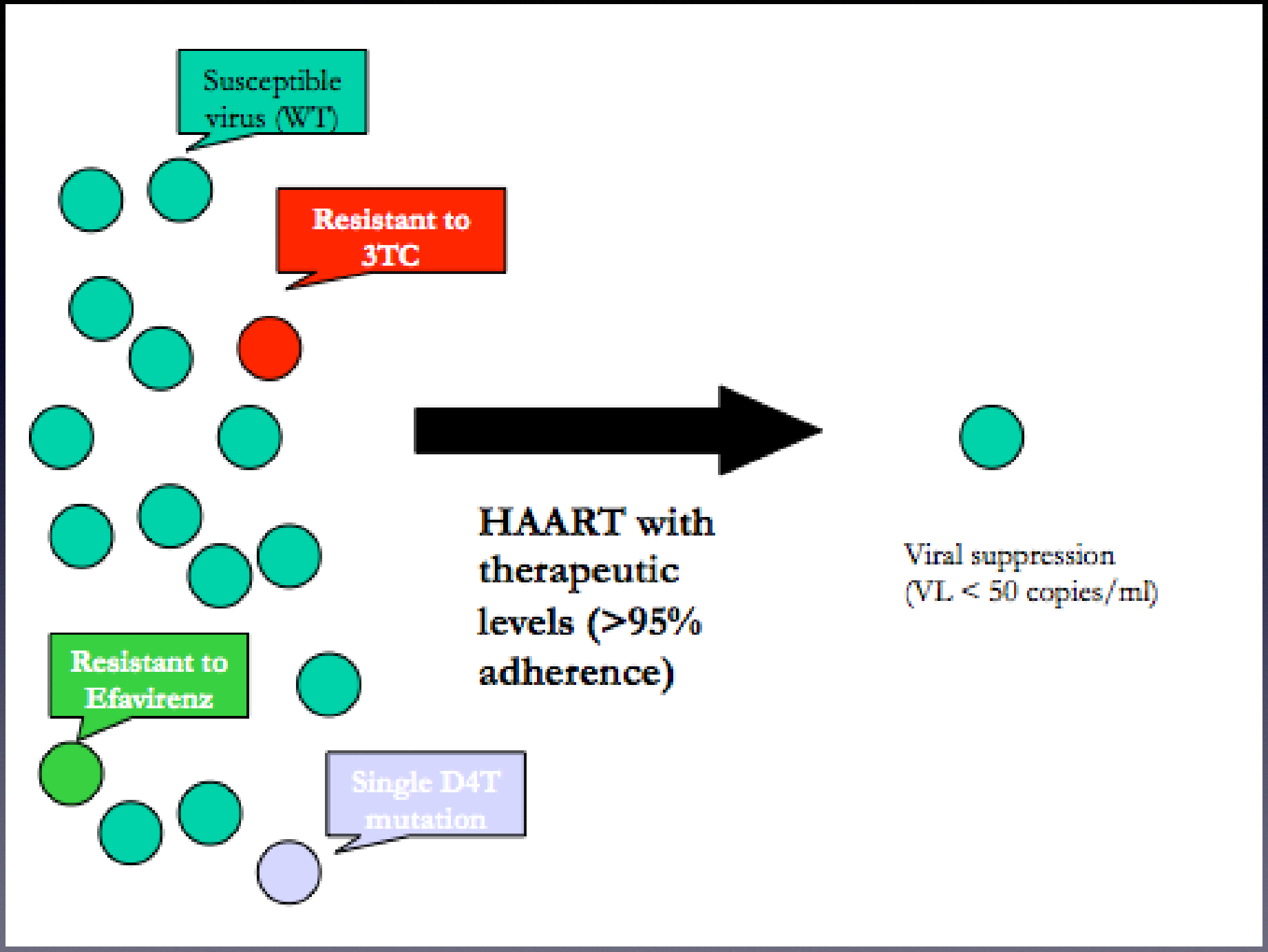


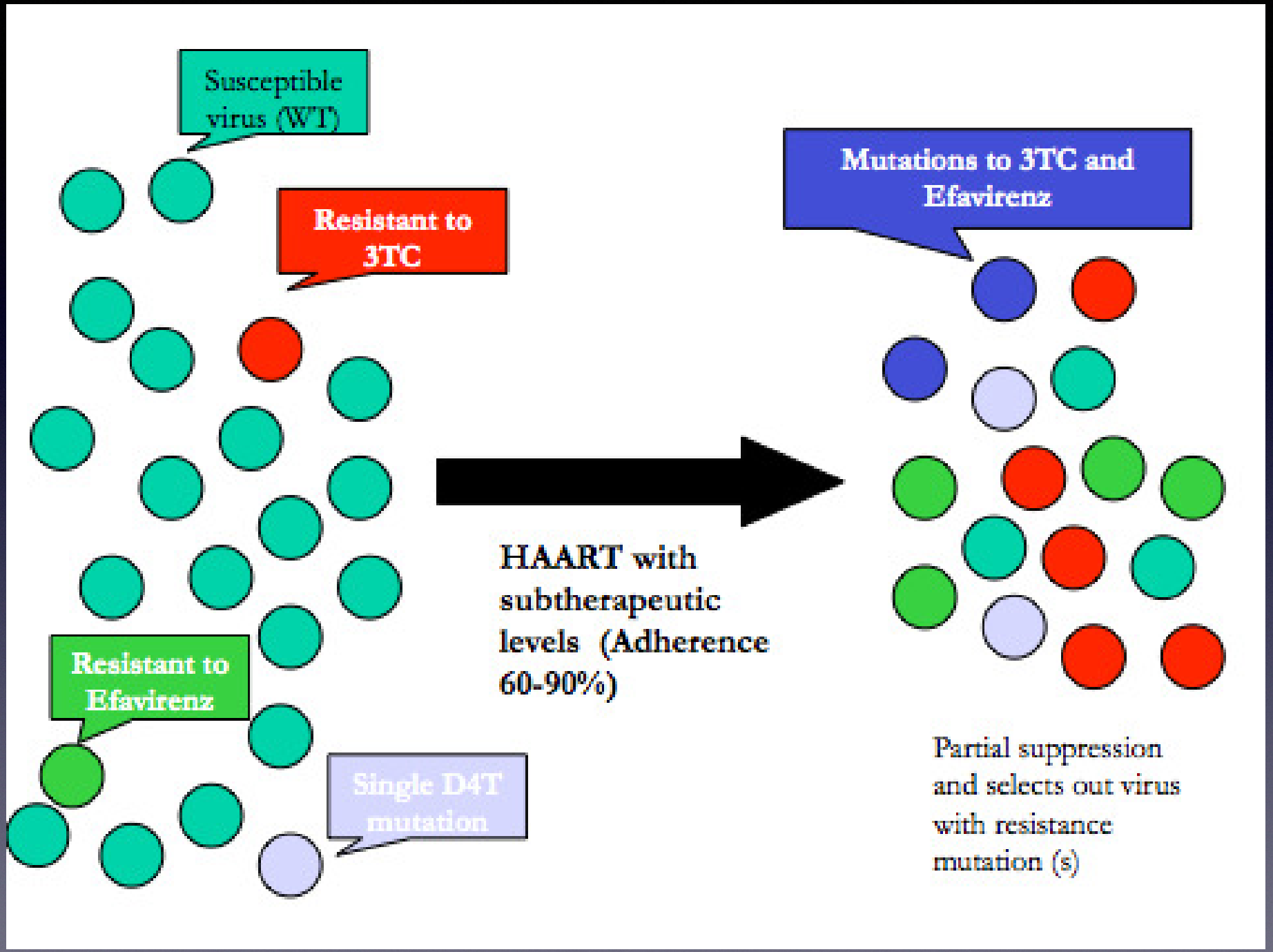
Mutations:

- Base substitutions
  - eg. M184V
- Insertions




Susceptible virus
(Wild type)
Virus resistant to 3TC
(has M184V mutation)
3TC
MONOTHERAPY

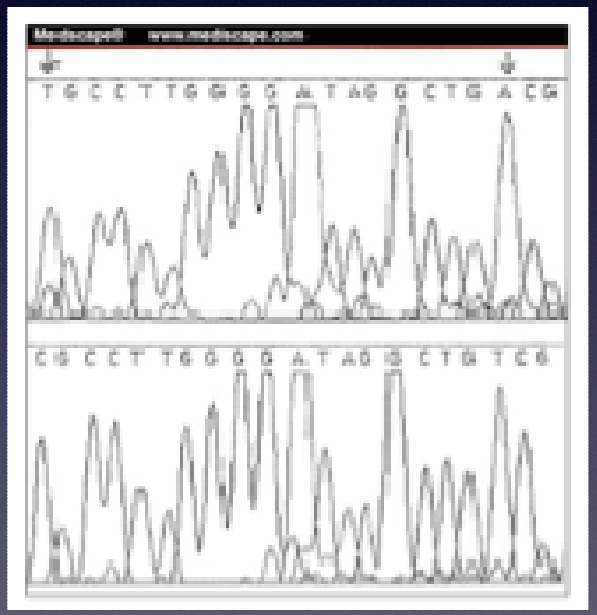

Susceptible virus (WT)
Resistant to 3TC
Resistant to Efavirenz
Single D4T mutation
HAART with therapeutic levels (>95% adherence)
Viral suppression
(VL < 50 copies/ml)


Susceptible virus (WT)
Resistant to 3TC
Resistant to Efavirenz
Single D4T mutation
HAART with subtherapeutic levels (Adherence 60-90%)
Mutations to 3TC and Efavirenz
Partial suppression and selects out virus with resistance mutation (s)

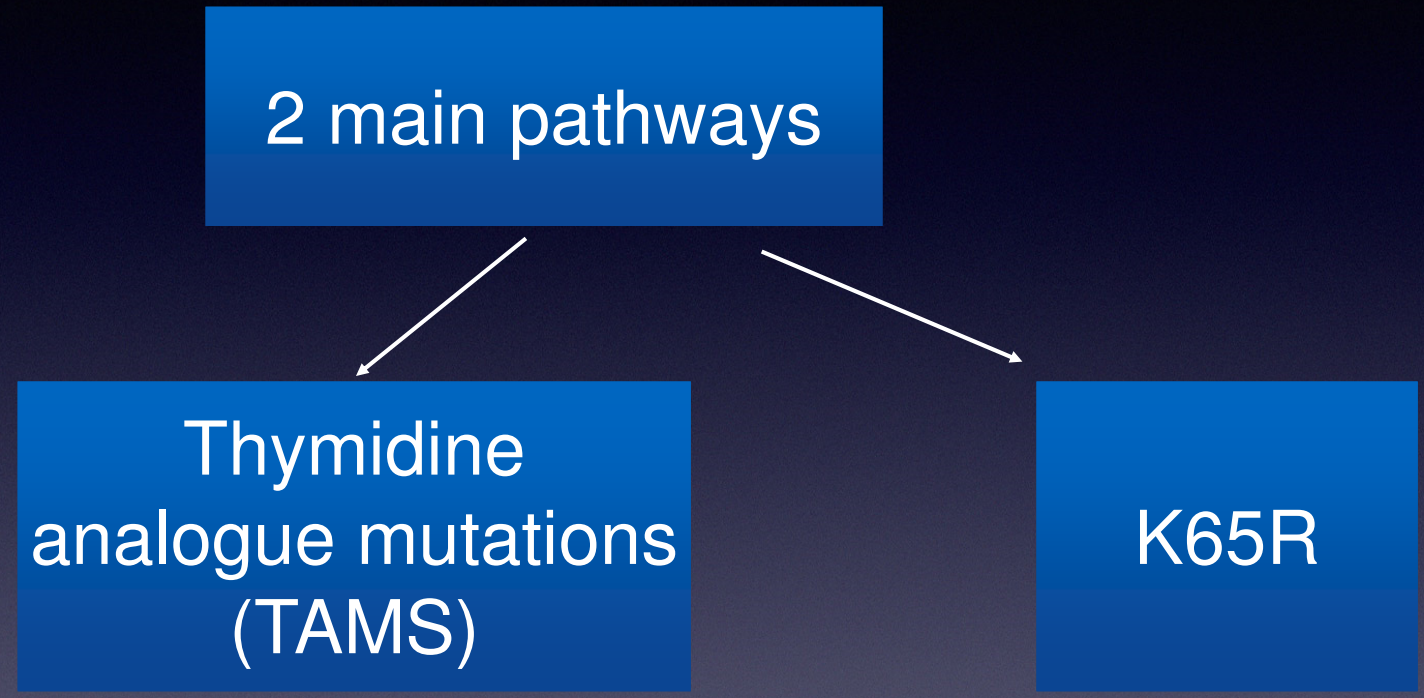
Genotyping

- Sequence RT and protease (and integrase) genes to detect resistance mutations

- Mutation detected if
- VL > 1000 copies/ml (failing ART)
- >20% of virus population carries mutation



NRTI resistance



	Thymidine analogue mutations (TAMS)	K65R
Selected by:	d4T, AZT	TDF, ABC, d4T
Resistance to:	d4T, AZT, ABC, TDF	TDF, ABC, ddI
Sensitizes to:		AZ T

Rate of Accumulation of Thymidine Analogue Mutations in Patients Continuing to Receive Virologically Failing Regimens Containing Zidovudine or Stavudine: Implications for Antiretroviral Therapy Programs in Resource-Limited Settings

Alessandro Cozzi-Lepri,[1] Andrew N. Phillips,[1] Javier Martinez-Picado,[2,3] Antonella d'Arminio Monforte,[4] Christine Katlama,[5] Ann-Brit Eg Hansen,[6] Andrzej Horban,[9] Johann Bruun,[10] Bonaventura Clotet,[2] and Jens D. Lundgren,[7,8] for the EuroSIDA Study Group[a]

- At first genotype (1 year after VF): median 3 TAMs
- Thereafter TAMs accumulated at a rate of 1/4.3 years

(JID, 2009)

M184V/I

- Single mutation high level resistance to 3TC and FTC
- Reduces viral fitness by 1/3
- Slows selection of TAMs
- When it occurs with TAMs:
- Increases susceptibility to AZT, d4T and TDF
- Increased resistance to ddI and ABC
- Also resensitizes to TDF in presence of K65R

Abacavir

- Selects for:
  - L74V: compromises ABC & ddI
  - Y115F: compromises ABC
  - K65R: compromises TDF, ABC, ddI