Imperial College London

Antiretroviral therapy and immunomodulation

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December 2011

Treatment of HIV infection

Natural history HIV disease and when to treat

Principles of antiretroviral therapy

Monitoring of patients on antiretroviral therapy

Future Challenges

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Natural history HIV disease and when to treat

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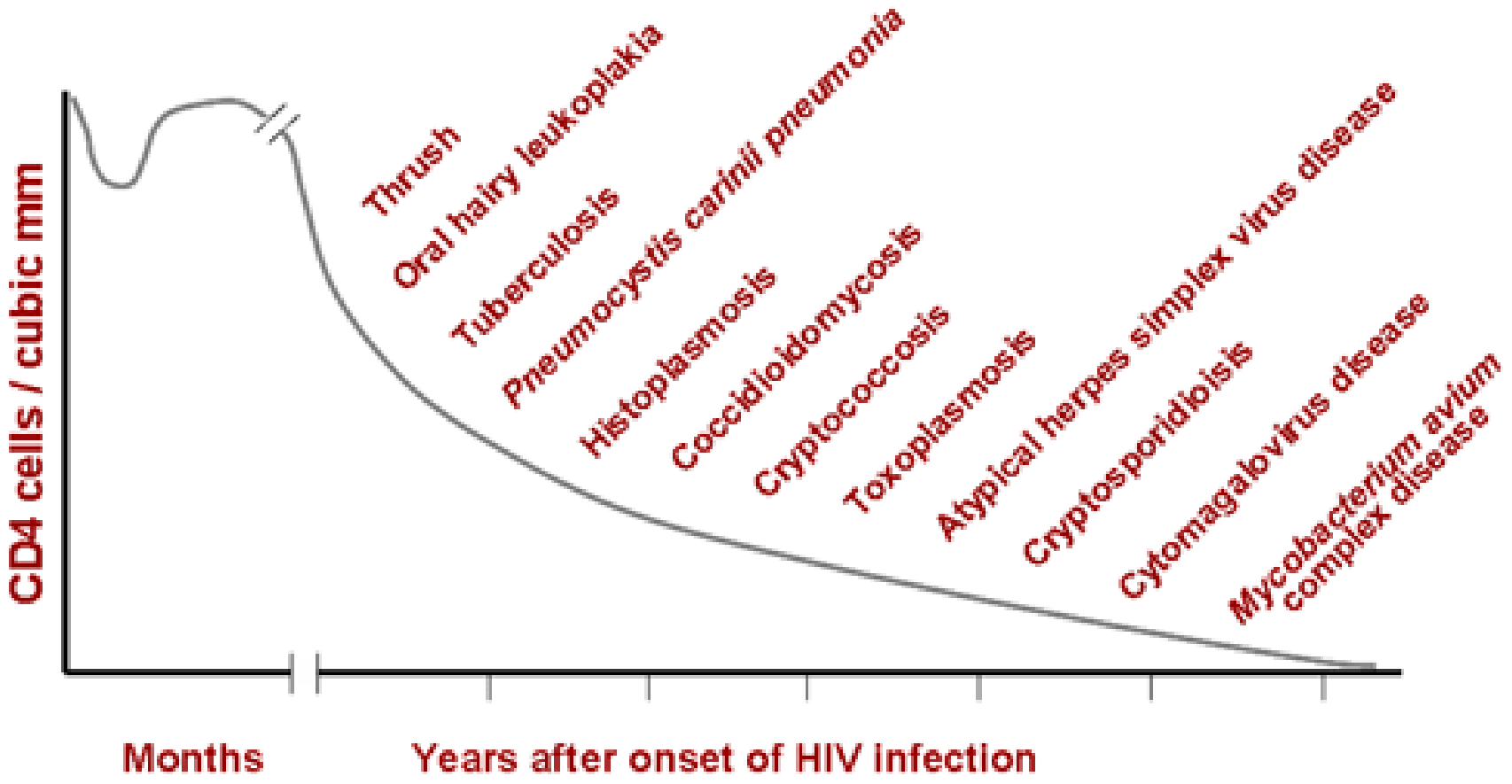
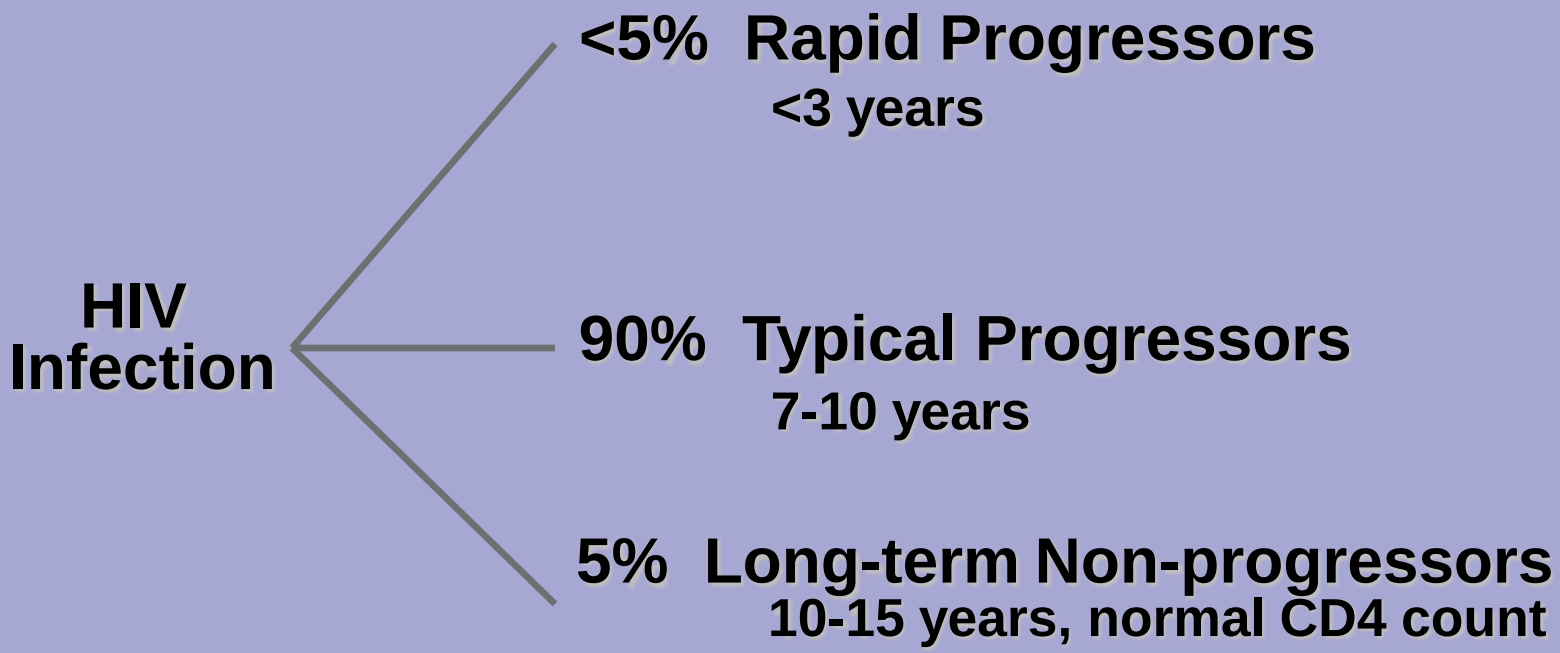
Monitoring of patients on antiretroviral therapy

Future Challenges

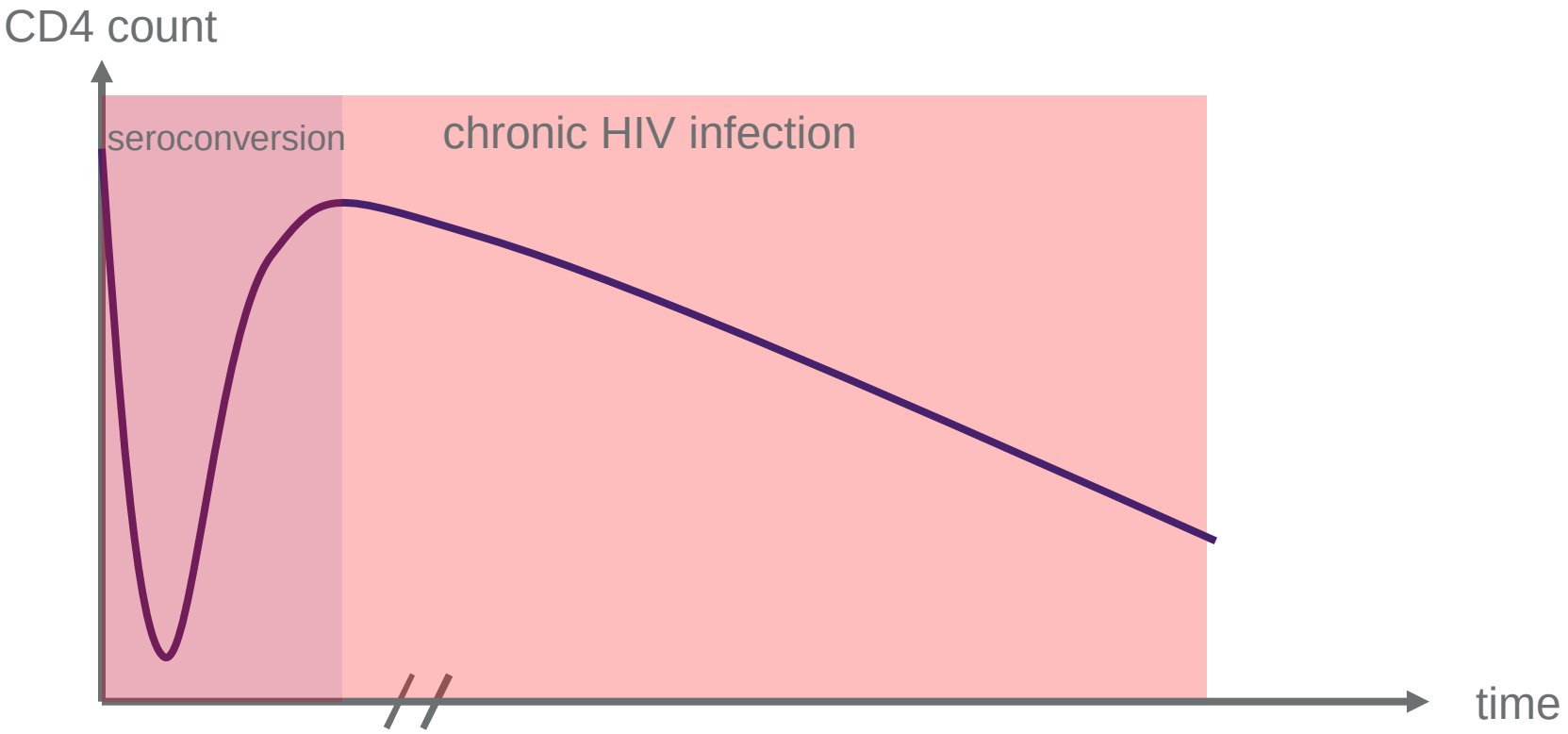
Natural History of HIV-1 Infection



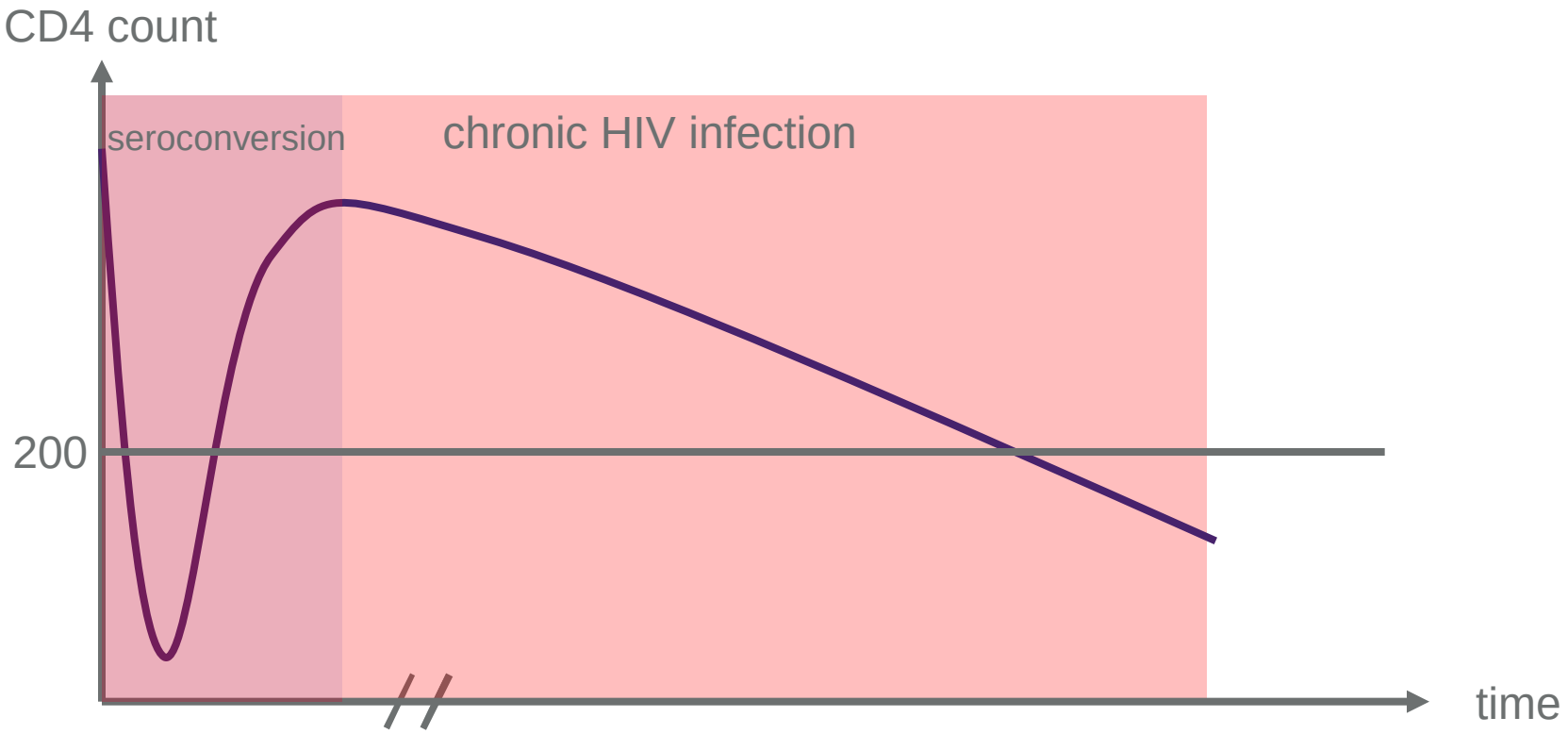
Patterns of HIV Disease Progression



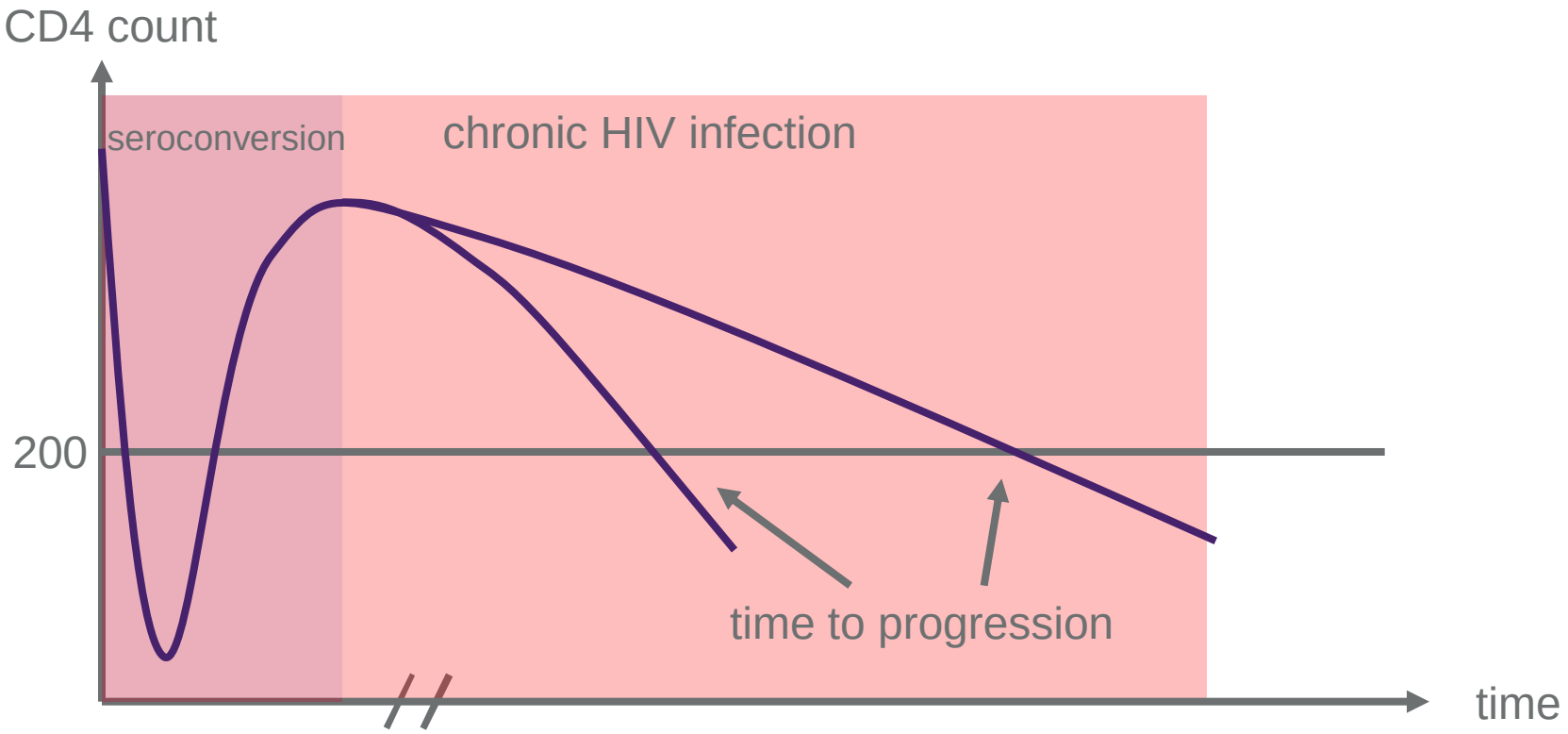
Disease progression



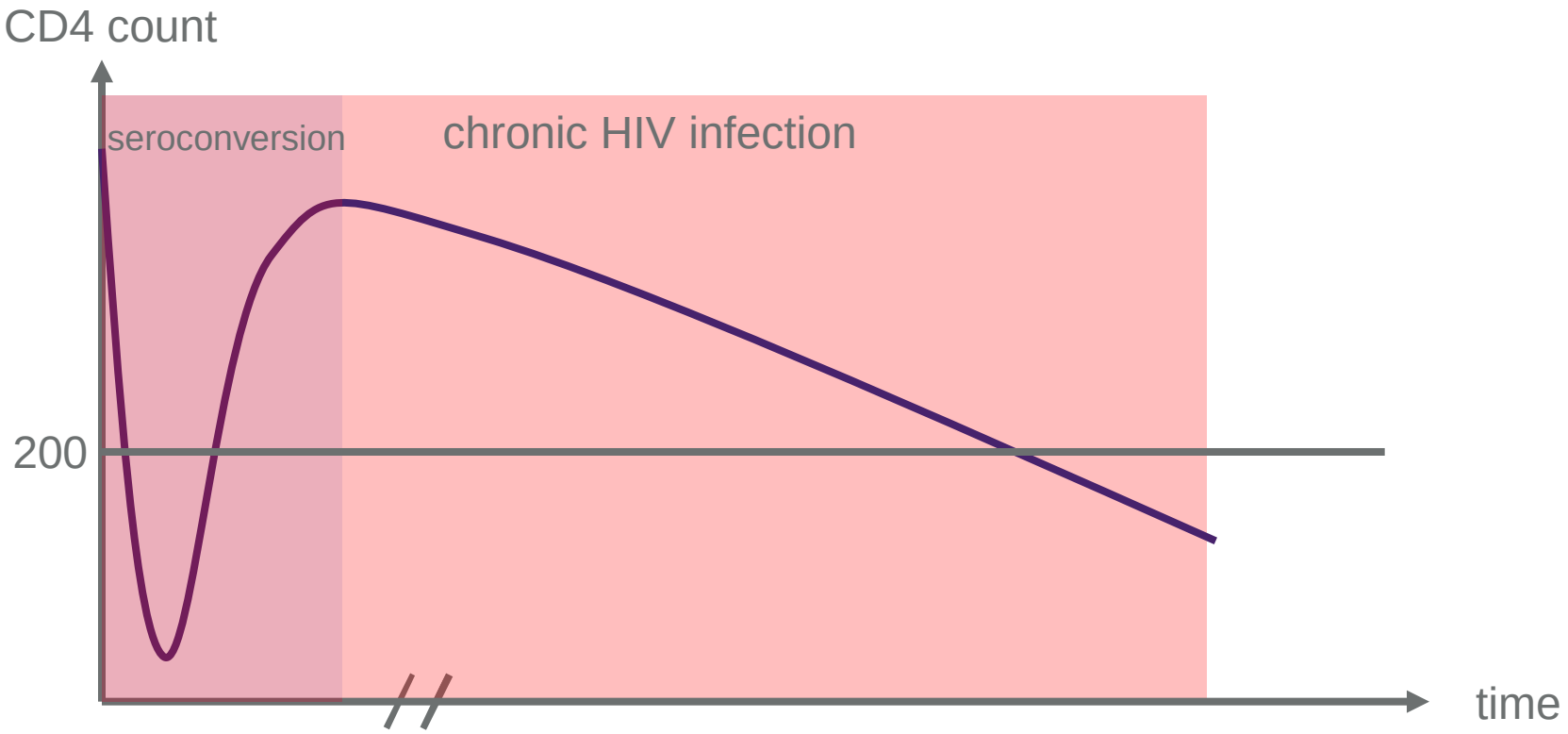
Disease progression



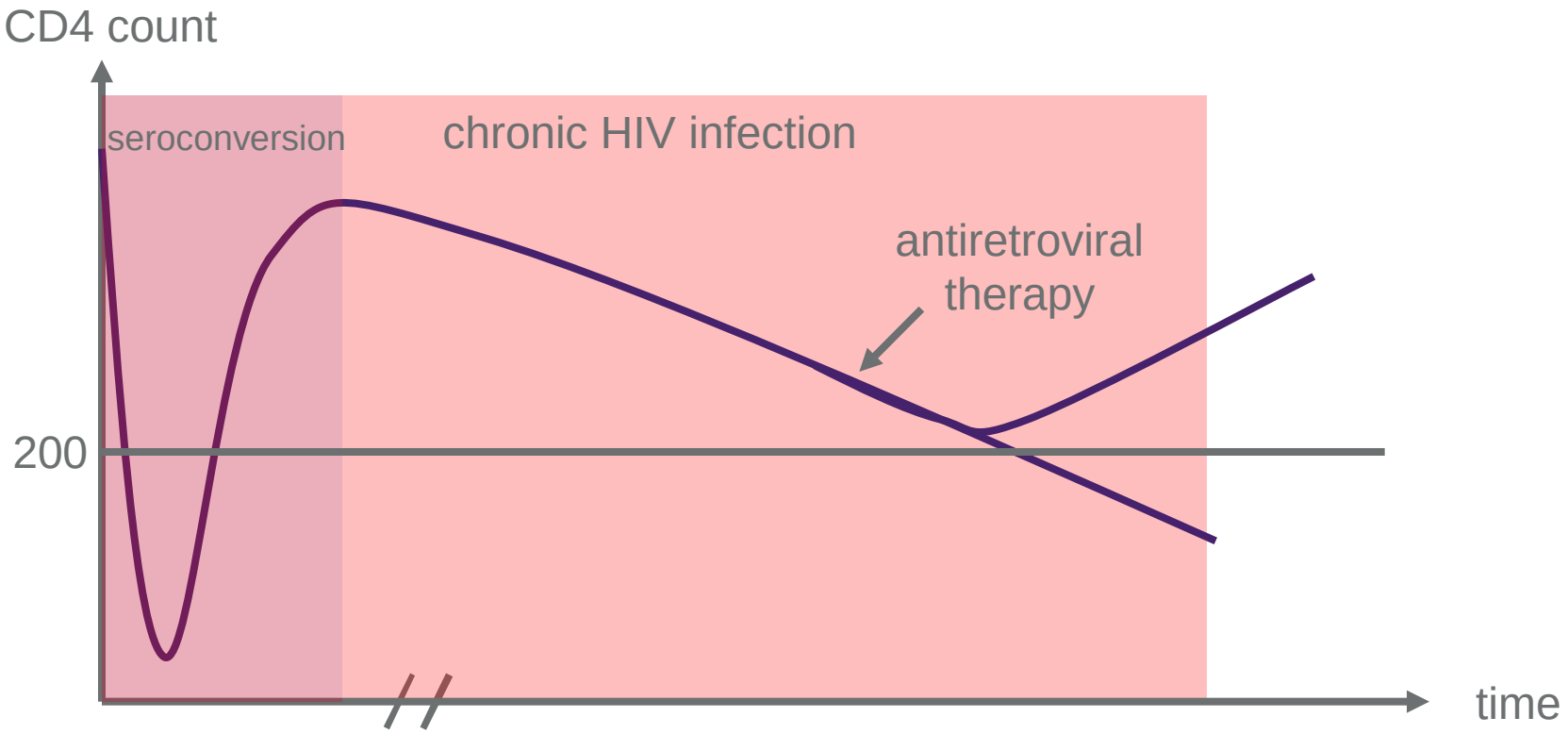
Disease progression



Disease progression



Disease progression



SMART Study

CD4+ cell count >350 cells/mm^3

N= **5,472**

n = 2,752

Virologic Suppression (VS) Strategy
[Continuous use of ART to maintain viral load as low as possible]

n = 2,720

Drug Conservation (DC) Strategy
[Defer use of ART until CD4+ < 250; then *episodic* ART based on CD4+ cell count to increase counts to > 350]

Findings (11 Jan 06): 167 primary endpoints, 16 months average follow-up, 1.5% lost to follow-up

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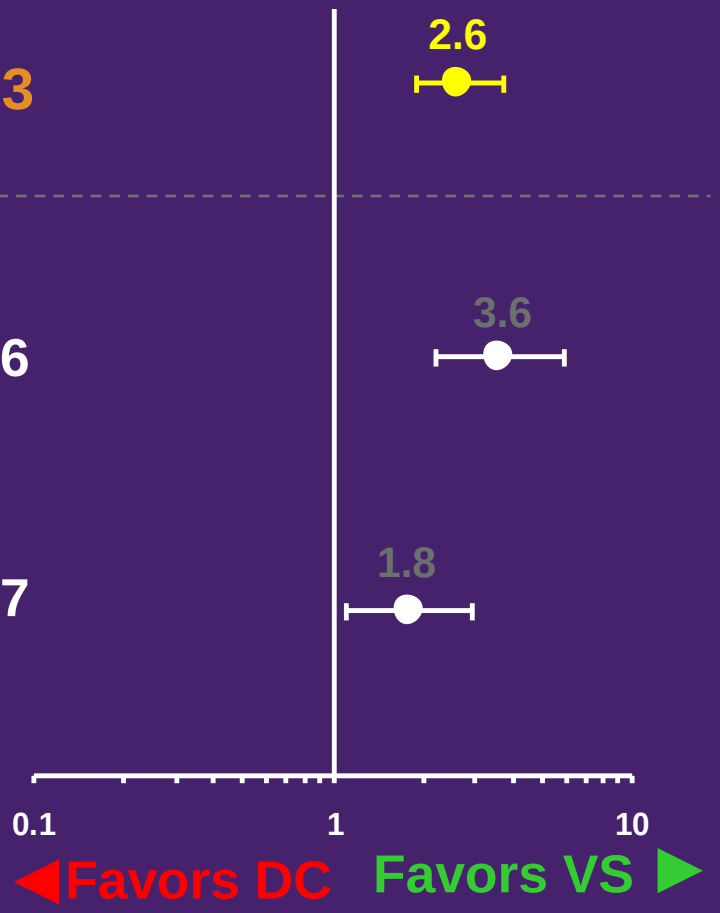
Main SMART Findings : Primary Endpoint (OD/Death)

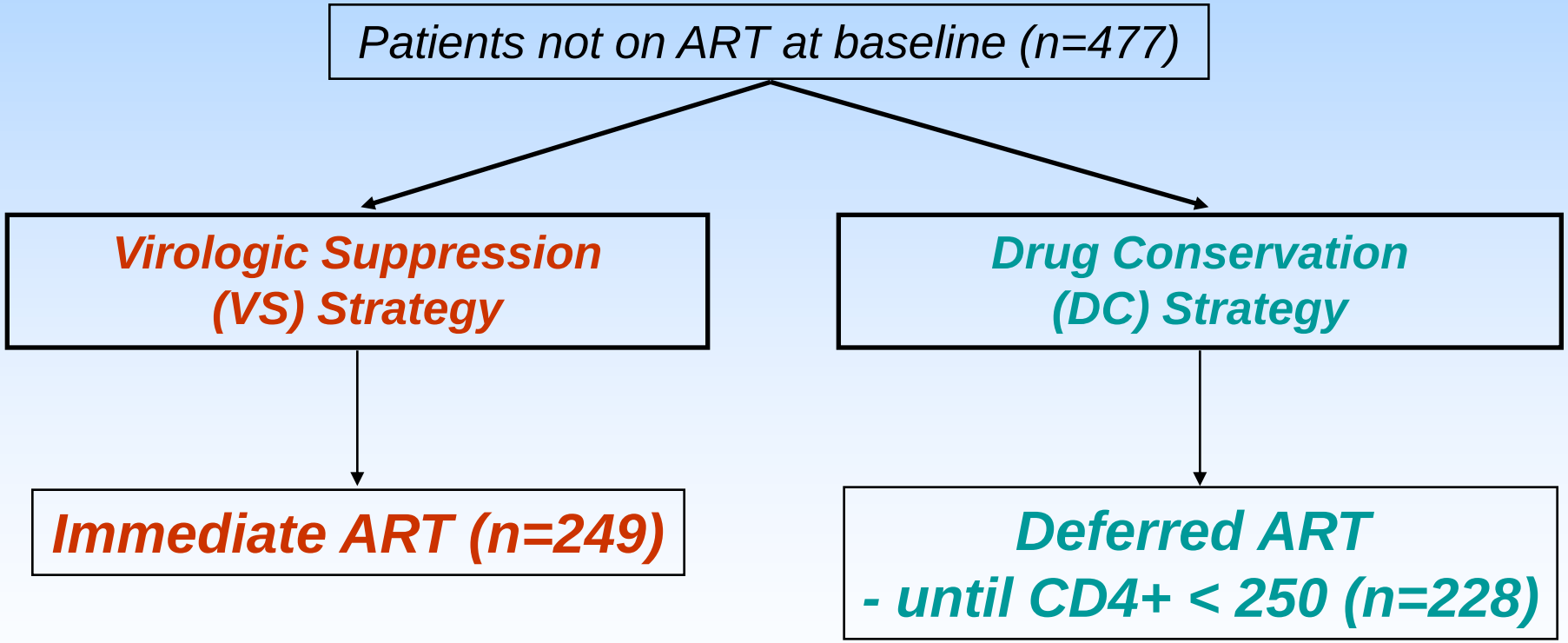
Endpoints	No. of Patients with Events	Rate* DC	Rate* VS	Hazard Ratio (DC/VS) (95% CI)
Opportunistic disease or death (OD/death)	**167**	**3.3**	**1.3**	**2.6**
• OD (fatal or non-fatal)	95	2.1	0.6	3.6
• Non-OD deaths	72	1.3	0.7	1.8



* Per 100 person-years

SMART subset analyses

A subset of SMART participants not on ART at baseline were examined; this analysis further informed the design of START

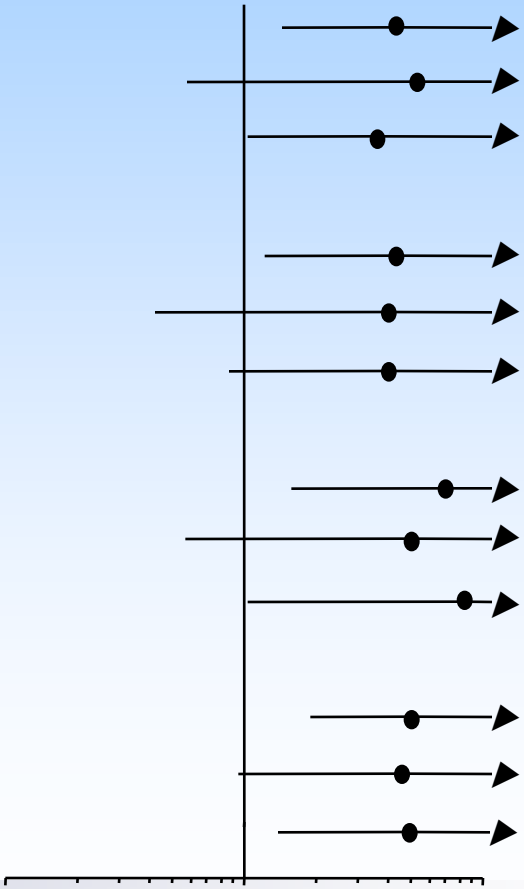


SMART subset

No. Events (rate per 100 person years)

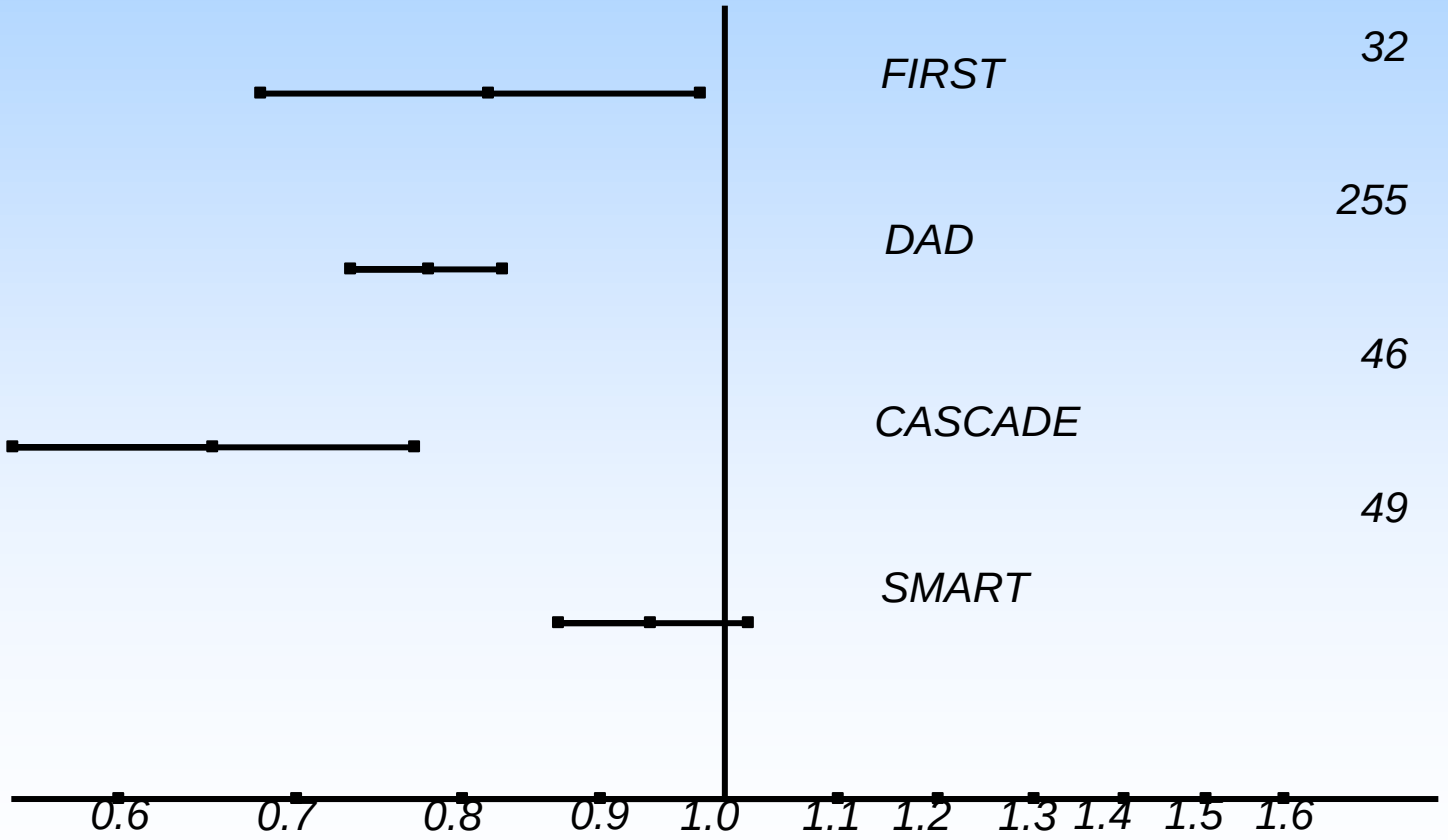
	Deferred ART	Immediate ART	HR (Def/Imm)	p-value
OD/Death				
Overall	15 (4·8)	4 (1·1)	4·4	0·009
ART naïve	4 (2·7)	1 (0·5)	5·3	0·13
Off ART	11 (6·8)	3 (1·6)	3·7	0·05
OD				
Overall	11 (3·5)	3 (0·8)	4·4	0·02
ART naïve	3 (2·0)	1 (0·5)	4·1	0·22
Off ART	8 (4·9)	2 (1·1)	4·1	0·07
Serious Non-AIDS				
Overall	12 (3·9)	2 (0·5)	7·1	0·01
ART naïve	4 (2·8)	1 (0·5)	5·1	0·15
Off ART	8 (4·9)	1 (0·5)	8·4	0·04
Composite				
Overall	21 (7·0)	5 (1·3)	5·1	0·001
ART naïve	7 (4·9)	2 (1·0)	4·6	0·06
Off ART	14 (9·0)	3 (1·6)	5·0	0·01

HR and 95% CI



Association between current CD4 count and risk of non-AIDS malignancy

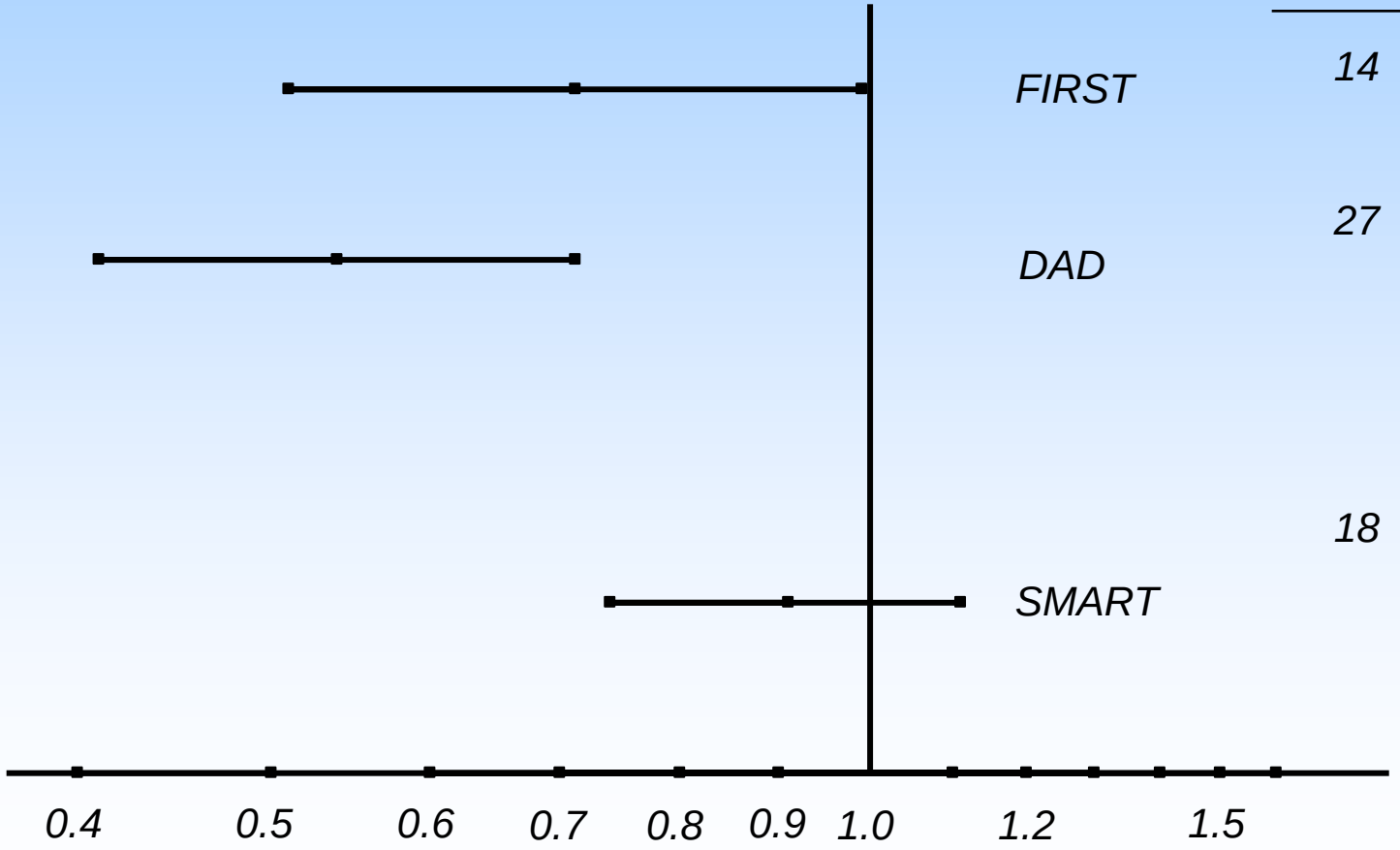
(Adjusted hazard ratio per 100 cell higher current CD4 count)



	Number of events	Includes non-fatal
FIRST	32	Yes
DAD	255	No
CASCADE	46	No
SMART	49	Yes

Association between current CD4 count and risk of renal disease / death

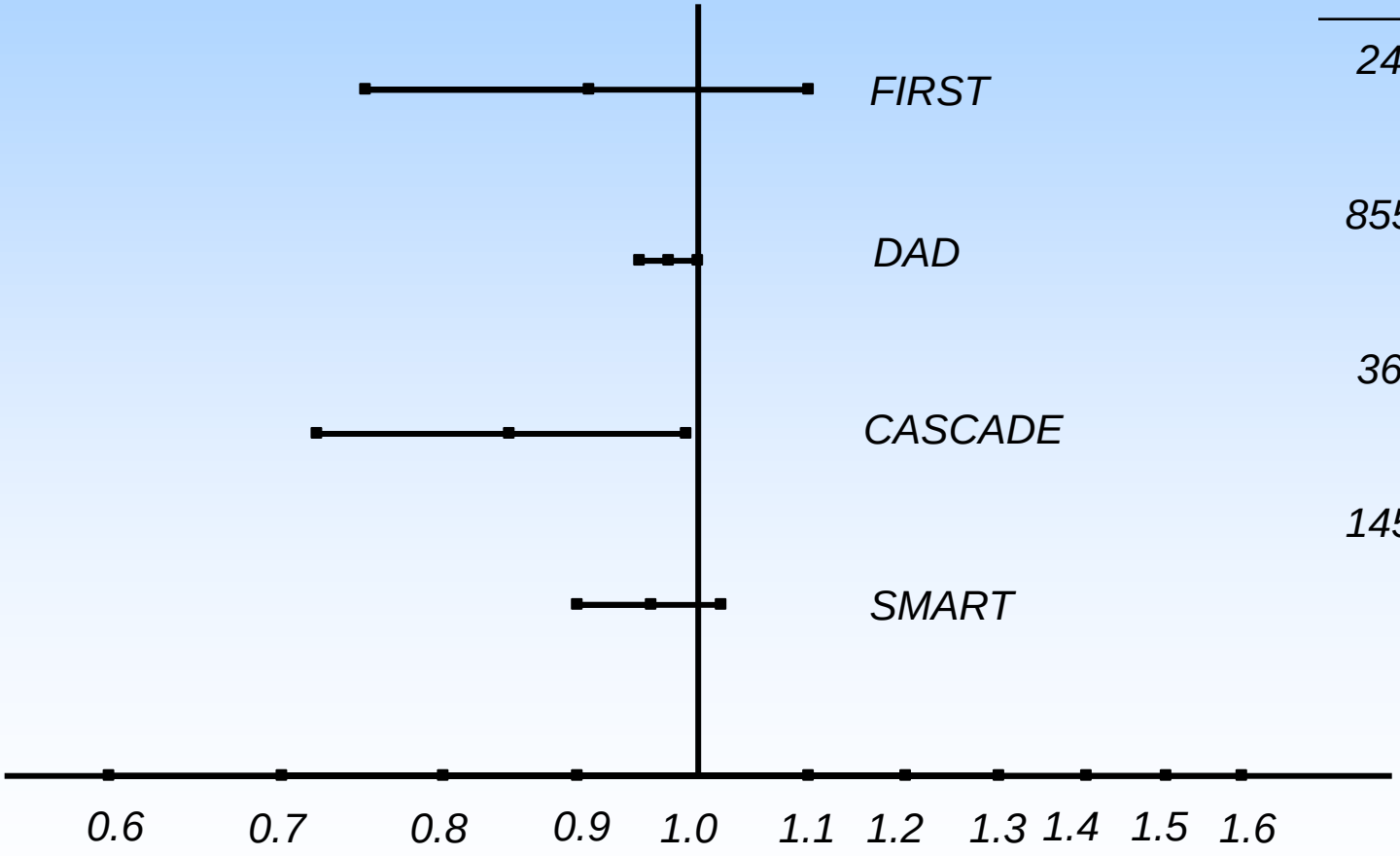
(Adjusted hazard ratio per 100 cell higher current CD4 count)



	Number of events	Includes non-fatal
FIRST	14	Yes
DAD	27	No
SMART	18	Yes

Association between current CD4 count and risk of CVD events / death

(Adjusted hazard ratio per 100 cell higher current CD4 count)



Number of events	Includes non-fatal
24	Yes
855	Yes
36	No
145	Yes

When should antiretroviral therapy be initiated?

	Early ART	Deferred ART
PROS	Reduce risk of death/AIDS/serious non-AIDS	Preserve drugs for use when needed
	Reduce HIV transmission	*Reduce costs*
CONS	Increased side effects	Higher risk of AIDS/non-AIDS events/death
	Limit future options	*Increased HIV transmission*
	Increased costs	

START design

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3

Early ART Group

Initiate ART immediately following randomization

N=450 in pilot phase and estimated as N=2,000 for definitive trial

Deferred ART Group

Defer ART until the CD4+ count declines to < 350 cells/mm^3 or AIDS develops

N=450 in pilot phase and estimated as N=2,000 for definitive trial

BHIVA guidelines

Table 2 Recommendations for when to initiate therapy

Presentation	
Established HIV infection	
CD4 <200 cells/μL	Treat
CD4 201–350 cells/μL	Treat as soon as possible when patient ready
CD4 351–500 cells/μL	Treat in specific situations with higher risk of clinical events – see section 3.3
CD4 >500 cells/μL	Consider enrolment into 'when to start' trial
AIDS diagnosis	Treat (except for tuberculosis when CD4 >350 cells/μL)

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Natural history HIV disease and when to treat

Principles of antiretroviral therapy

Monitoring of patients on antiretroviral therapy

Challenges for next 5 years

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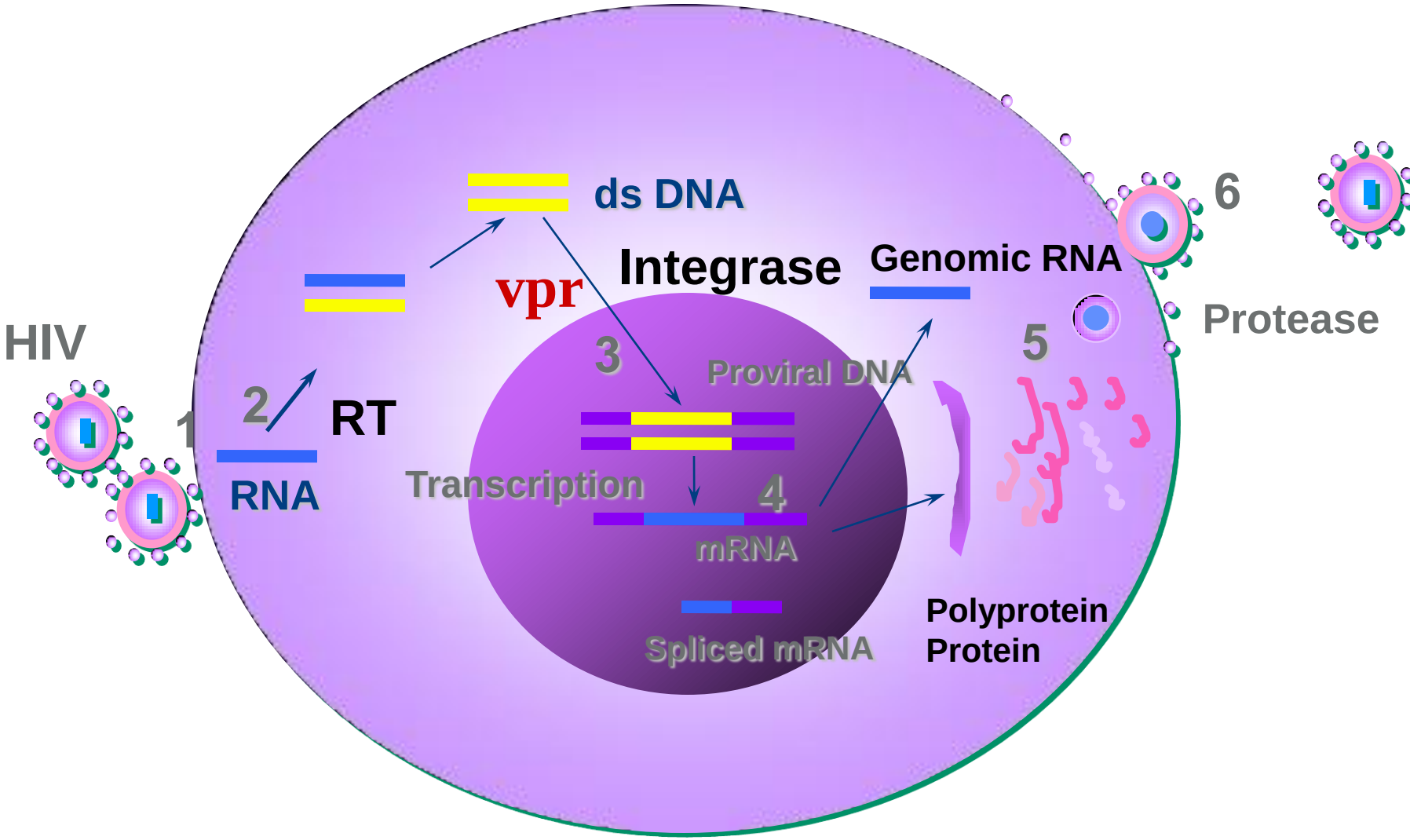
HIV lifecycle in CD4+ cell



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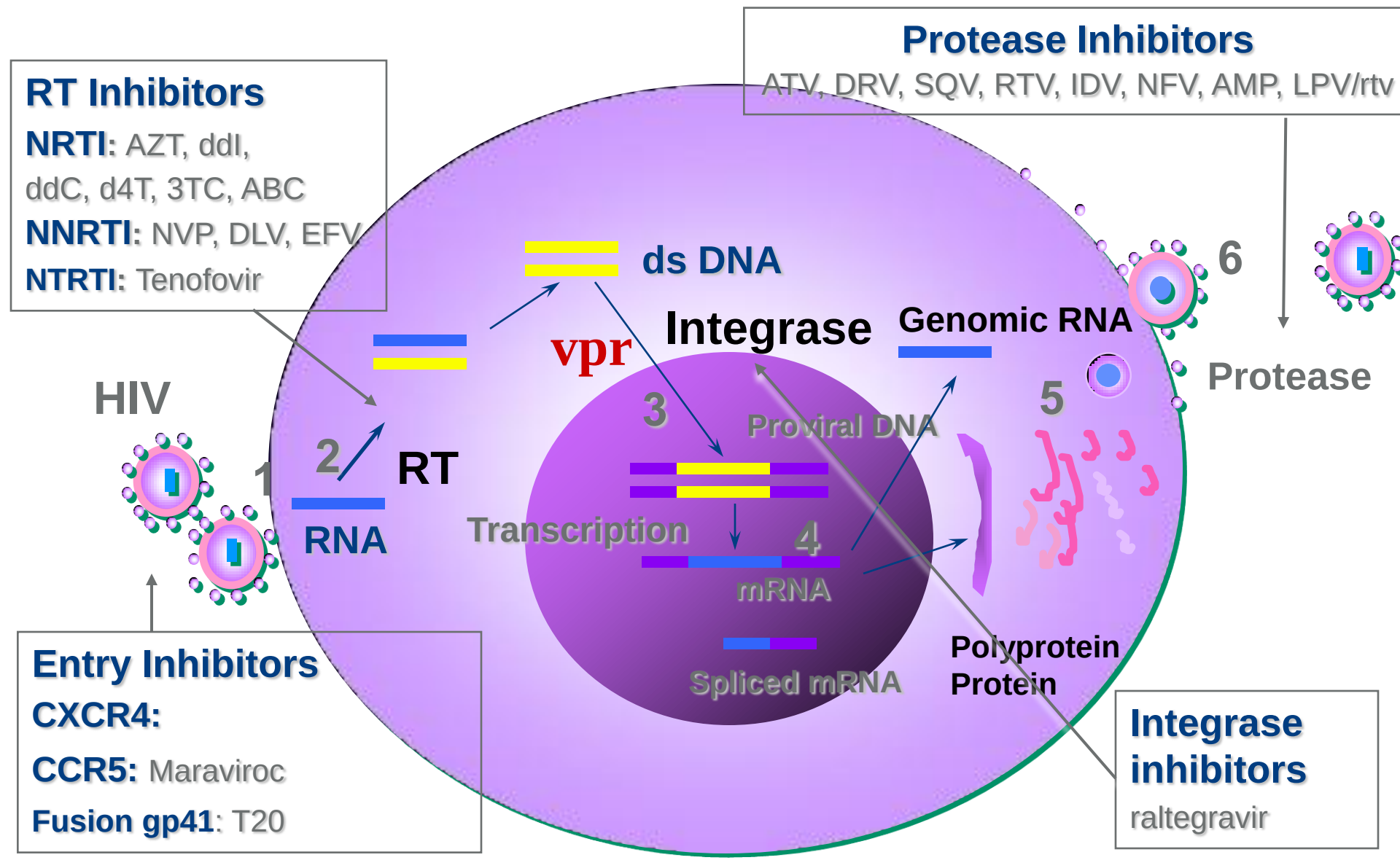
HIV lifecycle in CD4+ cell



History

AZT – anti cancer drug developed in 1960's

In HIV acts as analogue for thymidine in growing pro-viral DNA chain

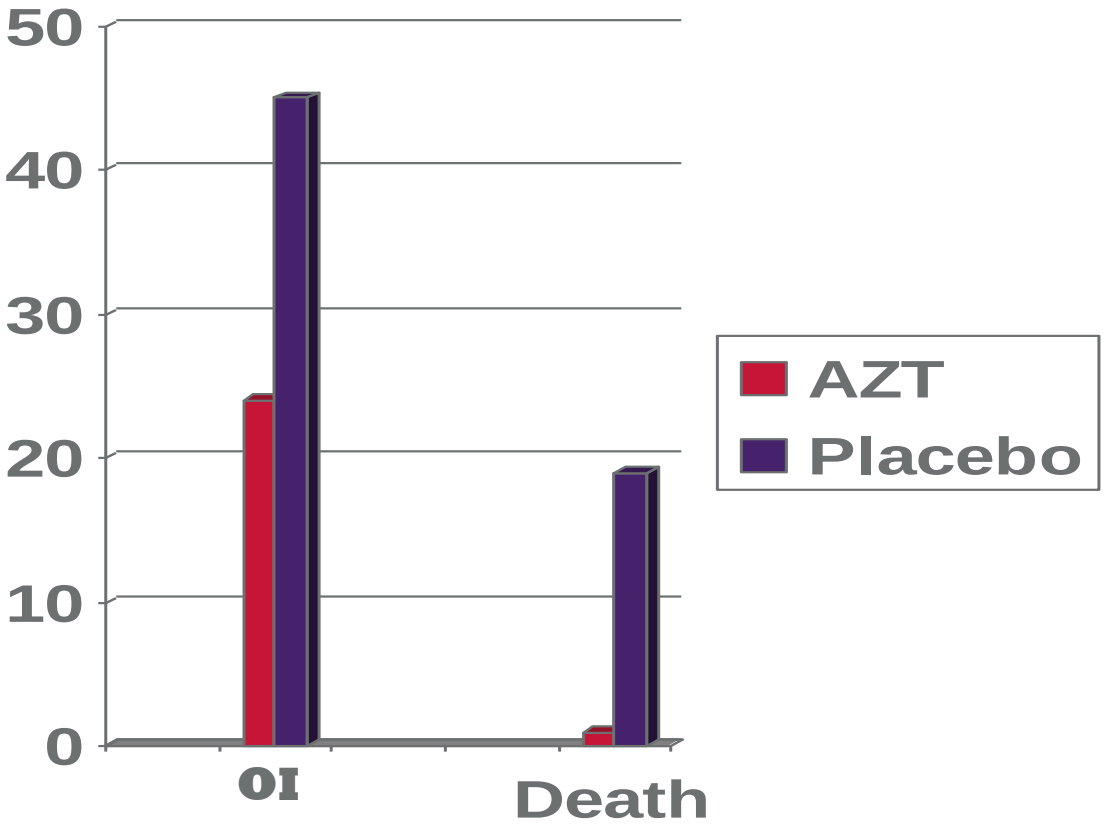
Early placebo controlled trial showed markedly reduced mortality in treatment arm

AZT monotherapy

About 145 patients in each group (placebo vs. AZT)

24 weeks

P=<0.0001



Resistance

HIV replicates rapidly – 10^{11} viral particles produced each day

Error prone reproduction - Drug resistant mutants have no advantage – less "fit"

Drug pressure selects out and creates mutants

Good viral suppression with little replication – less chance to produce mutants

Triple therapy

1996 – introduction of two new potent classes of drugs

- PIs and NNRTIs, suppression of viral load to low levels

Trials of PI based therapy shows reduction in mortality at 24 weeks

- No more placebo controlled trials
- Surrogate marker (i.e. CD4/Viral load), cohort studies

Rational drug design

Protease enzyme structure established

Protease inhibitors designed to block enzyme

Currently licensed antiretrovirals

NRTI	NNRTI	Protease I	Integrase I	Entry I
abacavir	**efavirenz**	**amprenavir**	**raltegravir**	**enfuvirtide (T20)**
didanosine	**nevirapine**	**atazanavir**	*elvitegravir*	**maraviroc**
emtricitabine	**etravirine**	**fosamprenavir**		
lamivudine	**rilprivirine**	**indinavir**		
stavudine		**lopinavir**		
zidovudine		**ritonavir**		
tenofovir		**saquinavir**		
		tipranavir		
		darunavir		

NRTI FDC		PI FDC	
Combivir ®	**zidovudine / lamivudine**	**Kaletra ®**	lopinavir/ritonavir
Kivexa ®	**abacavir / lamivudine**	Cross class FDC	
Trizivir ®	**zidovudine / lamivudine / abacavir**	**Atripla**	**tenofovir / emtricitabine/ efavirenz**
Truvada ®	**tenofovir / emtricitabine**		

ESPRIT

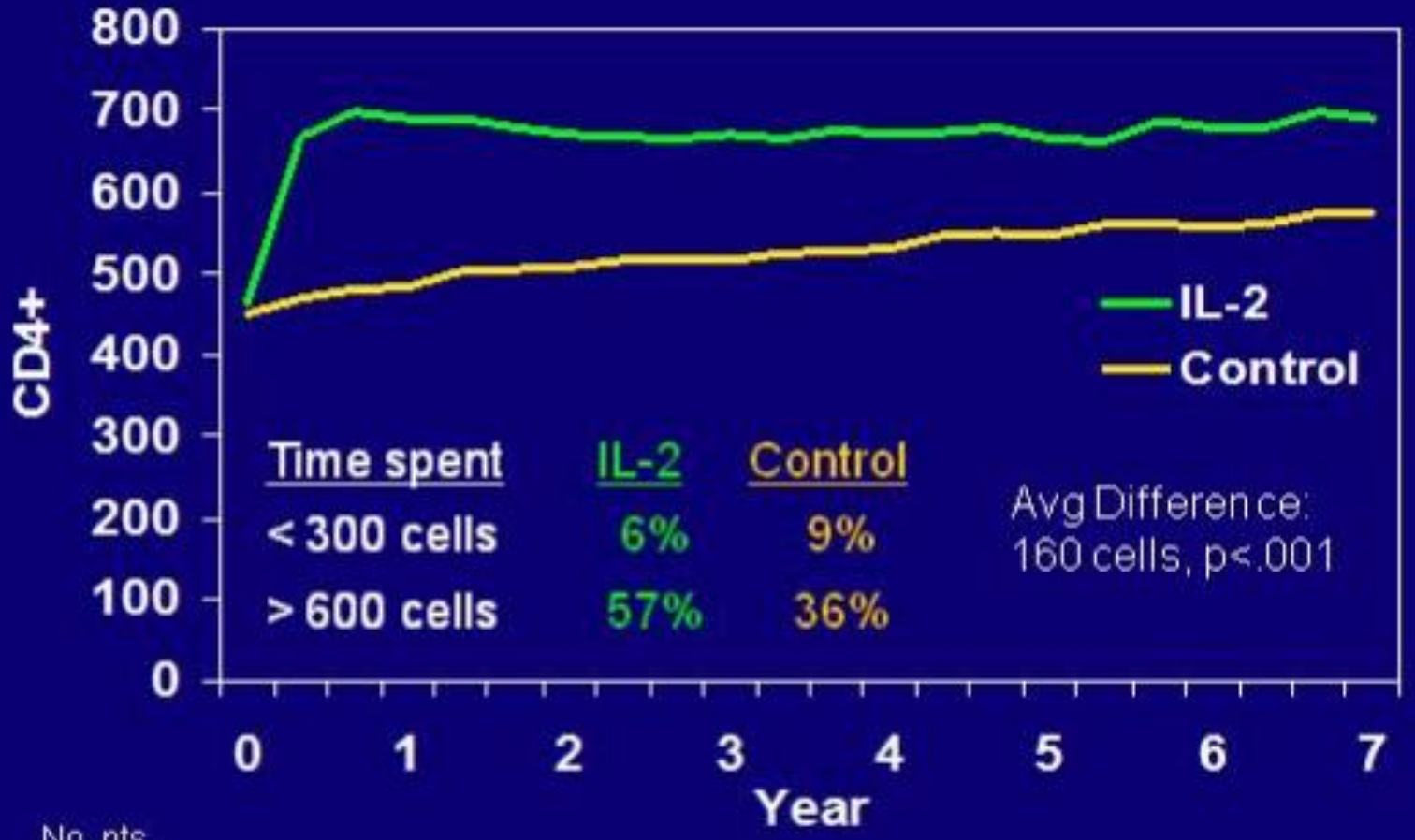
Study Design

Patients taking ART with CD4+ counts ≥ 300/μL

N = 2071	N = 2040
IL-2	**Control**
ART plus: • 3 cycles of IL-2 (7.5 MIU twice daily for 5 days, 8 wks apart) • additional cycles to maintain goal (2x baseline or ≥ 1000 CD4+ cells)	ART without IL-2

Plan: 320 primary events
Closure date 15 Nov 2008
323 primary events observed
Median follow-up = 7 years

Median CD4+ During Follow-up



No. pts								
IL-2:	2071	1846	1829	1797	1757	1721	1410	878
Control:	2040	1928	1861	1803	1739	1648	1350	824

insight

Percent with HIV-RNA ≤ 500 Copies/ml

No. pts								
IL-2:	2065	1943	1864	1827	1770	1735	1418	889
Control:	2036	1921	1856	1791	1724	1643	1350	821

Primary Endpoint

Opportunistic Disease or Death

IL-2		Control			
No.	Rate*	No.	Rate*	HR (95% CI)	p-value
158	1.13	165	1.21	0.93 (0.75, 1.16)	.52

Predicted HR based on CD4+ difference = 0.74

** rate per 100 person years*

Other Major Endpoints

Endpoints	Patients with Events IL-2	Patients with Events Control	HR (95% CI)
Death	107	116	0.90
Serious Non-AIDS	188	185	0.99
Grade 4 Event	466	383	1.23 *p=.003*

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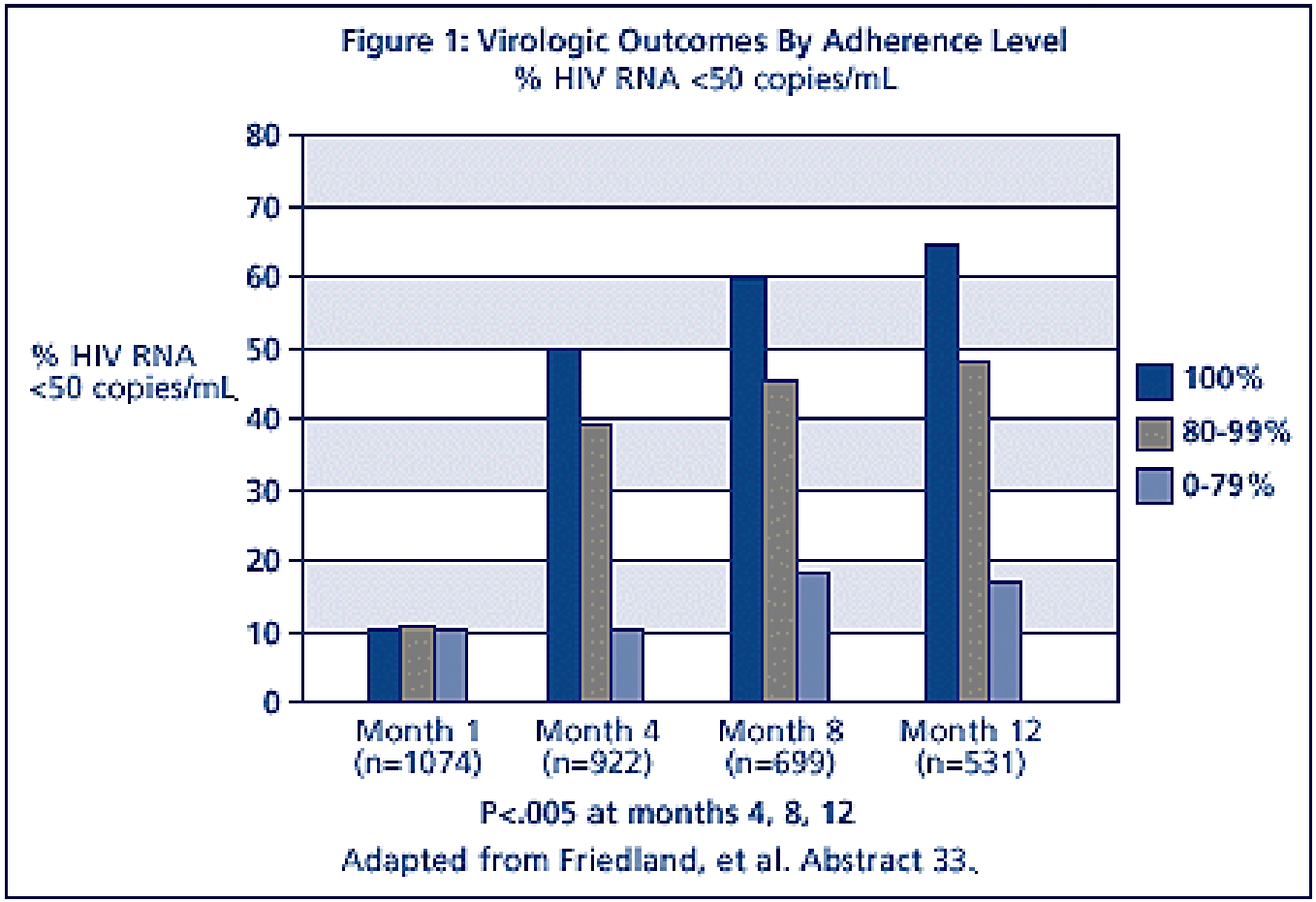
Challenges for next 5 years

Adherence



Adherence support – specialist nurses and pharmacist advice

BD or OD regimens likely to be preferable

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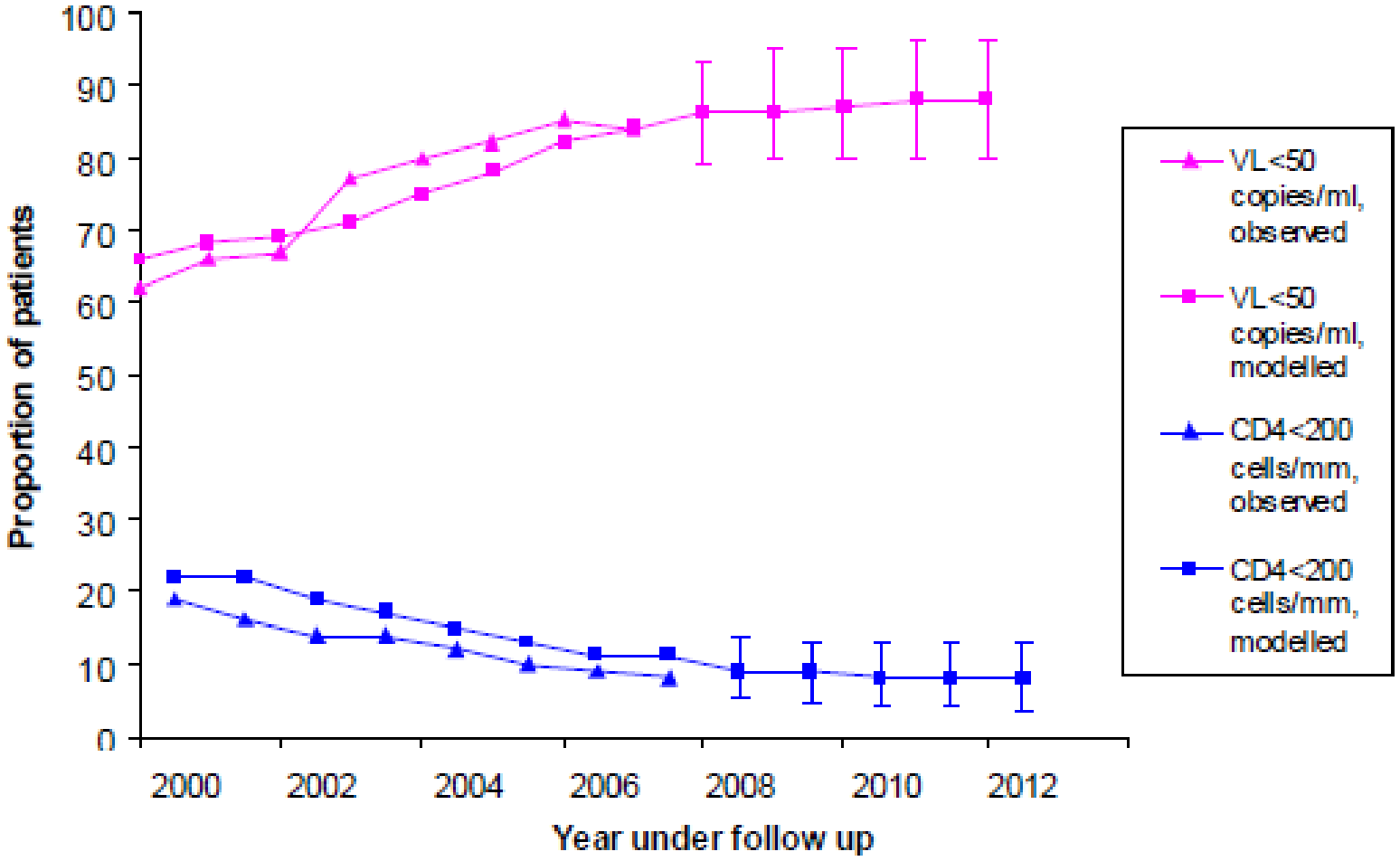
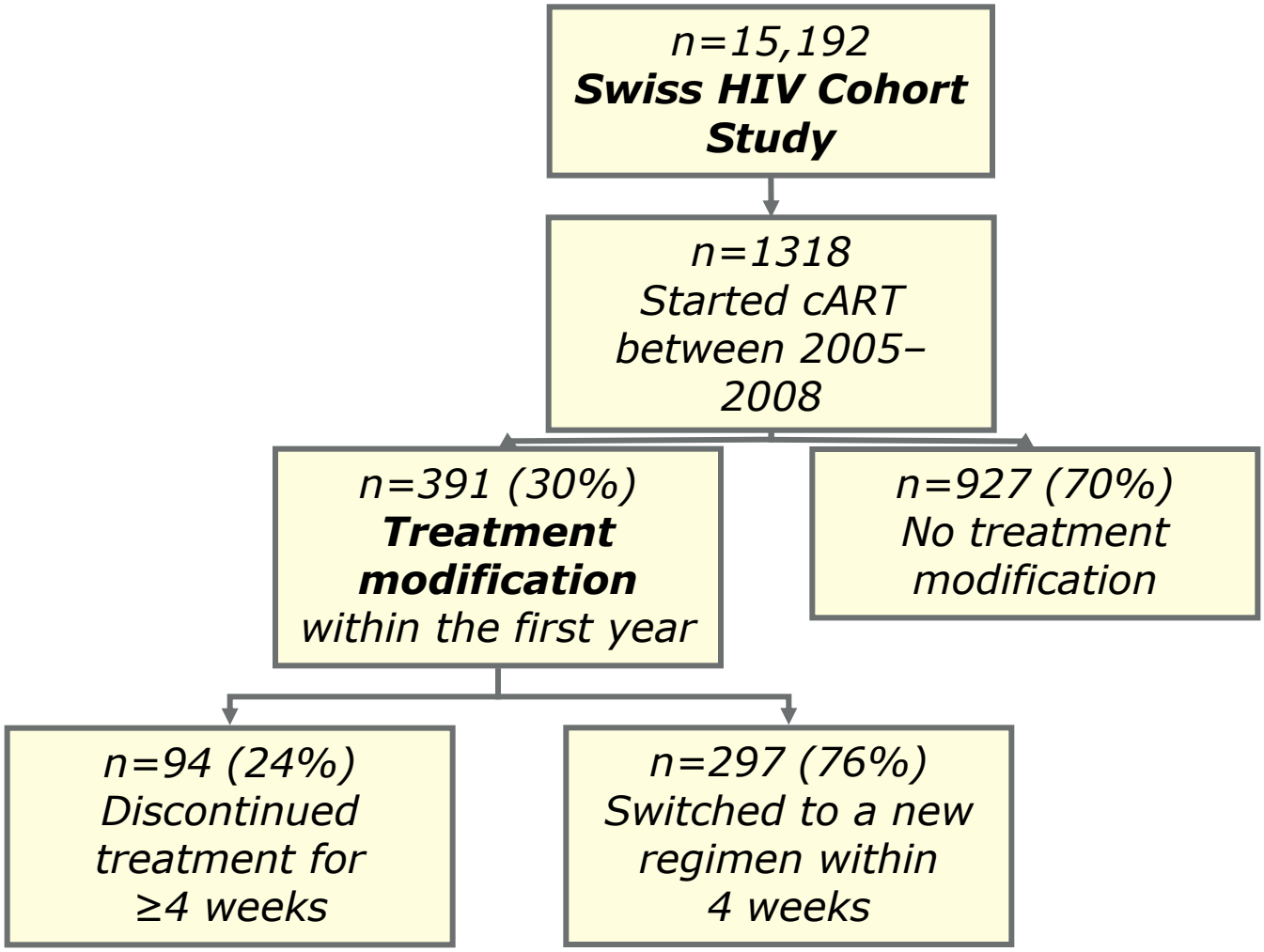
Trends in HIV Viral load UK CHIC 2000-2006



Bansi L et al. HIV Medicine 2010; 11: 432-438.

30% modify antiretroviral therapy in the first year, the SHCS 2005–2008



Elzi L et al and the Swiss HIV Cohort Study, EACS 2009

Side effects

NRTI	NtRTI
abacavir	tenofovir
didanosine	
emtricitabine	
lamivudine	
stavudine	
zidovudine	

Mitochondrial Toxicity
Lipoatrophy
Individual Drug toxicities

Side effects

NRTI	NtRTI
abacavir	**tenofovir**
didanosine	
emtricitabine	
lamivudine	
stavudine	
zidovudine	
Mitochondrial Toxicity	
Lipoatrophy	
Individual Drug toxicities	

Mitochondrial Toxicity

zidovudine – anaemia
stavudine – peripheral neuropathy
didanosine – pancreatitis, peripheral neuropathy
lamivudine – well tolerated
tenofovir – ? renal toxicity

Lactic acidosis

- stavudine and didanosine

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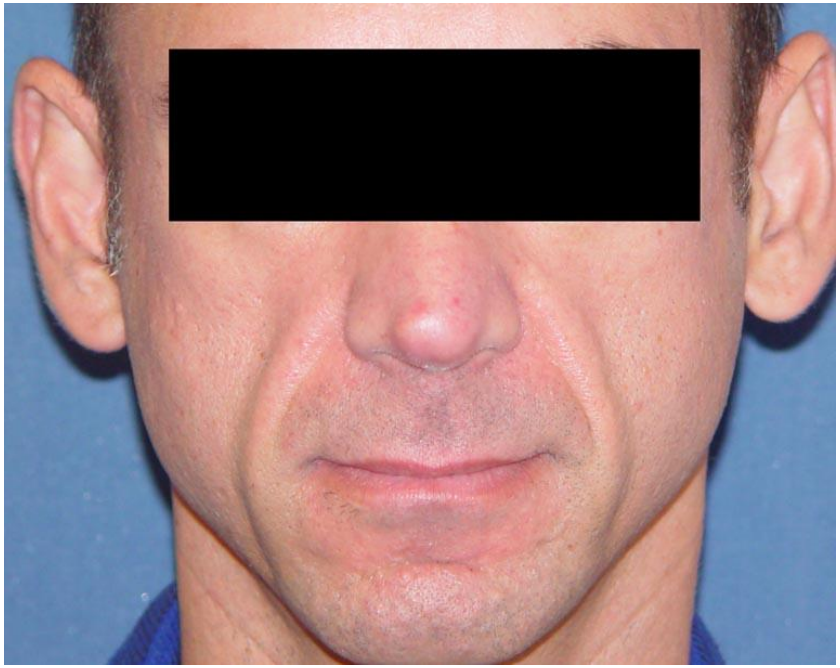
Side effects

NRTI	NtRTI
abacavir	tenofovir
didanosine	
emtricitabine	
lamivudine	
stavudine	
zidovudine	

Mitochondrial Toxicity
Lipoatrophy
Individual Drug toxicities

Lipoatrophy



Side effects

NRTI	NtRTI
abacavir	tenofovir
didanosine	
emtricitabine	
lamivudine	
stavudine	
zidovudine	
Mitochondrial Toxicity Lipoatrophy Individual Drug toxicities	

Lipoatrophy

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Side effects

NRTI	NtRTI
abacavir	tenofovir
didanosine	
emtricitabine	
lamivudine	
stavudine	
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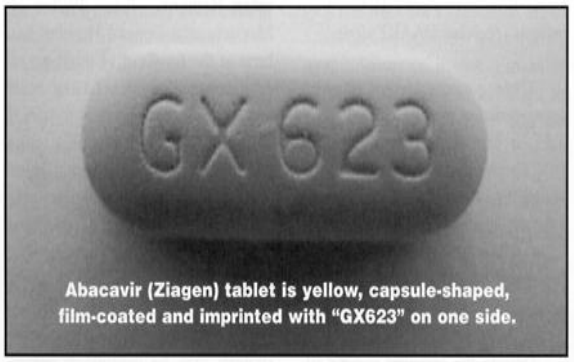
Mitochondrial Toxicity
Lipoatrophy
Individual Drug toxicities

Individual drug toxicity

Abacavir hypersensitivity
4% caucasians have genetic hypersensitivty

Rechallenge with drug may be fatal

HLA-B57 01



Abacavir (Ziagen) tablet is yellow, capsule-shaped, film-coated and imprinted with "GX623" on one side.

Side effects

NNRTI
efavirenz nevirapine **Rash, hepatotoxicity** **CNS effects**

Nevirapine – allergic rash and hepatitis/Stevens-Johnson syndrome

- Worse in immune competant(HCWs)

Efavirenz – Insomnia, vivid dreams, psychosis, rash.

Protease problems

PI
amprenavir
atazanavir
fosamprenavir
indinavir
lopinavir
nelfinavir
ritonavir
saquinavir
tipranavir
Metabolic
Drug Specific
Pill burden

Metabolic

- Hyperlipidaemia
- Hyperglycaemia
- Body fat accumulation

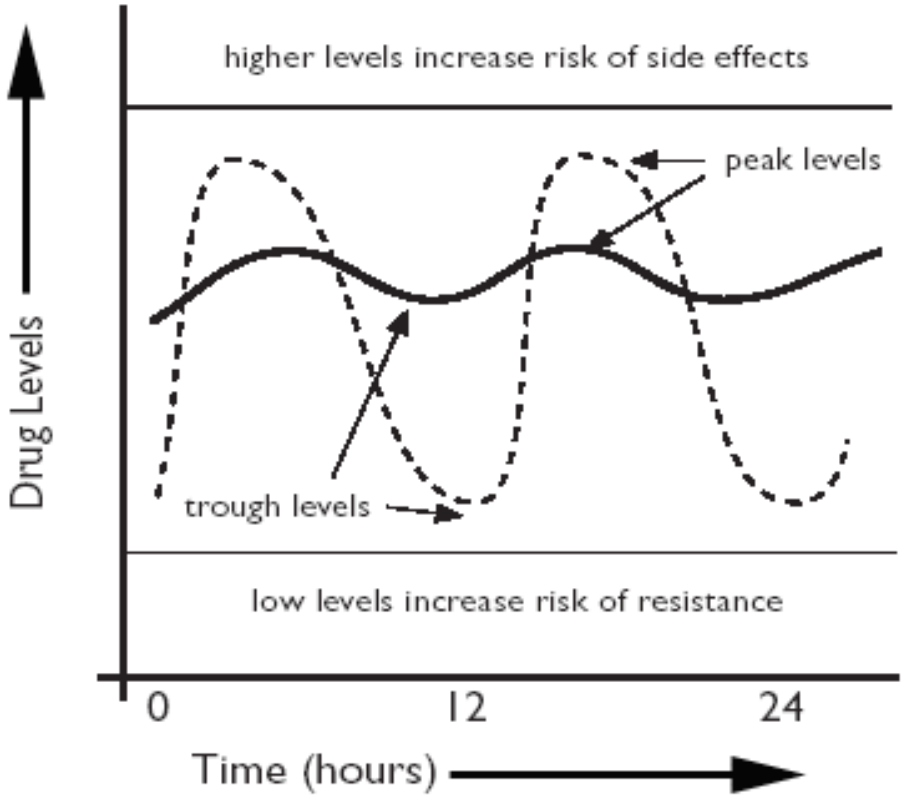
Specific

- indinavir – renal stones
- atazanavir – scleral icterus

Protease inhibitors

PI
amprenavir
atazanavir
fosamprenavir
indinavir
lopinavir
nelfinavir
ritonavir
saquinavir
tipranavir
Metabolic
Drug Specific
Pill burden

Metabolised via CYP 3A4



T20 – fusion inhibitor

Structure of GP41 defined

GP41 blocking agent designed

Used in patients with resistance to all current classes

- Twice daily, subcutaneous injection

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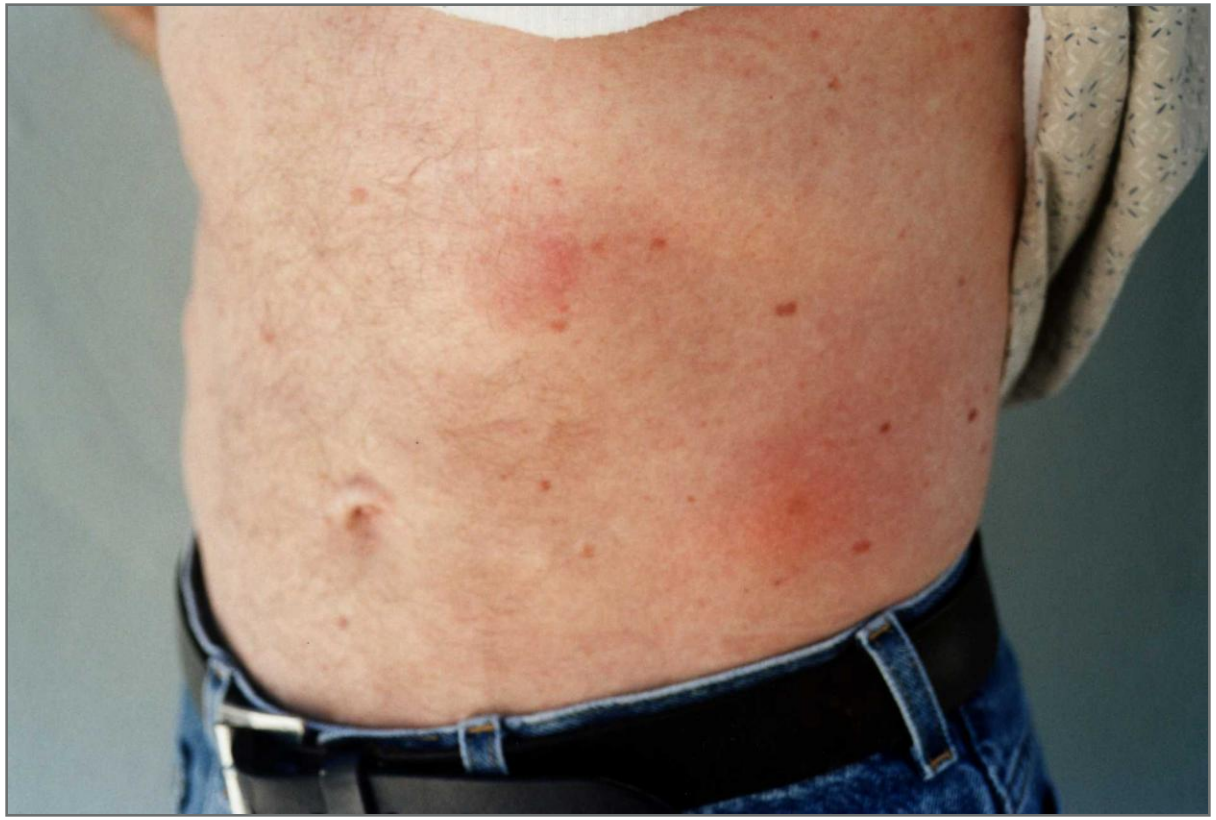
Side effects

FI
enfuvirtide (T20)
ISR

Injection site reactions



Side effects

NRTI	NtRTI	NNRTI	PI	FI
Mitochondrial toxicity **Lipoatrophy**		**rash and hepatitis** **CNS toxicity**	**metabolic** **pill burden**	**Injection site reactions**

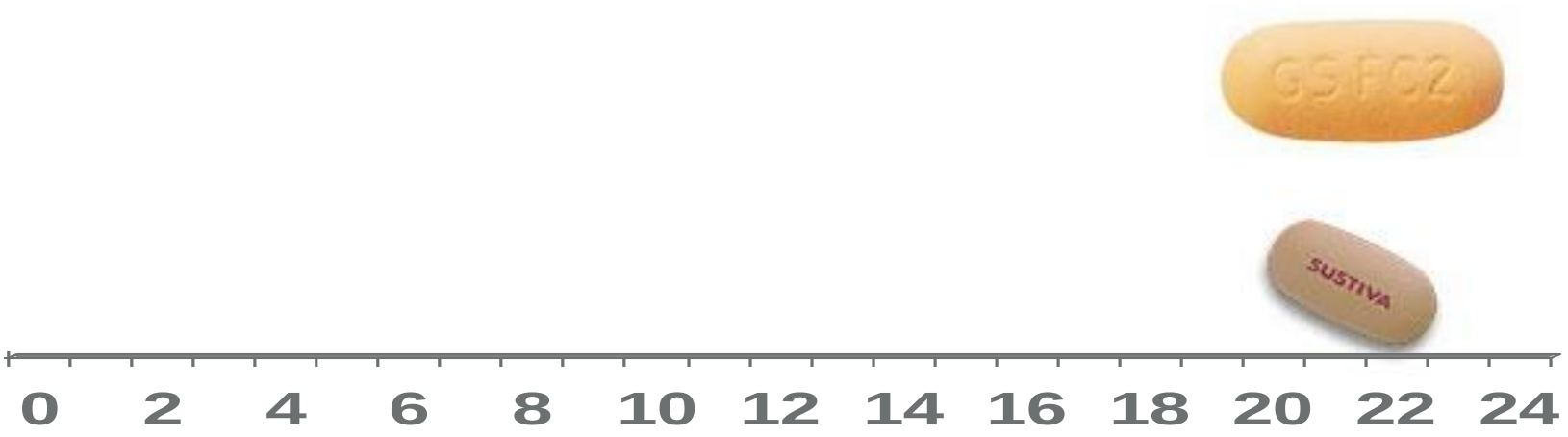
General problems:

- **Drug-drug interactions**
  advantageous / disadvantageous / disastrous

Combination therapy

1st line therapy

- abacavir 600 mg daily
- lamivudine 300 mg daily
- efavirenz 600 mg daily



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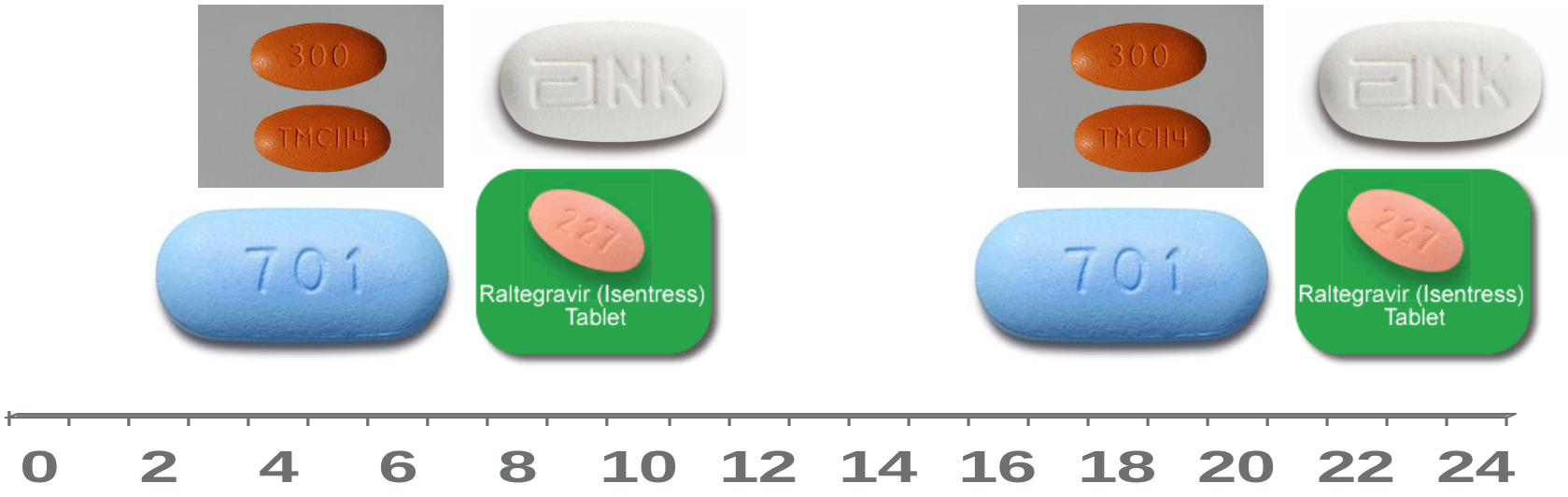
Combination therapy

Later therapy

- Truvada one table daily
- darunavir 800 mg twice daily
- ritonavir 100 mg twice daily
- raltegravir 400 mg twice daily



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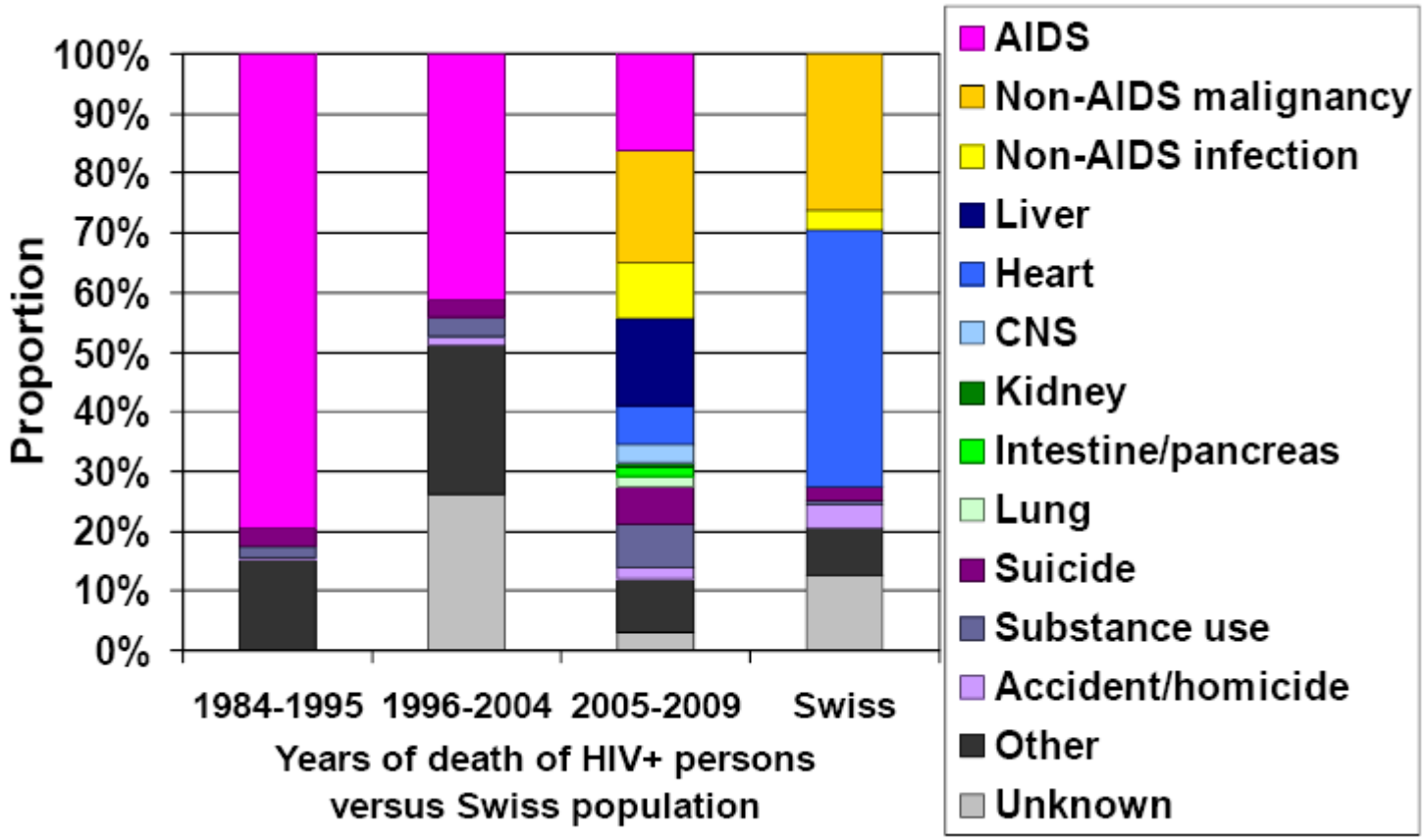
Future challenges

Cause of Death



M Rubbik et al CROI 2011 Abstract 789

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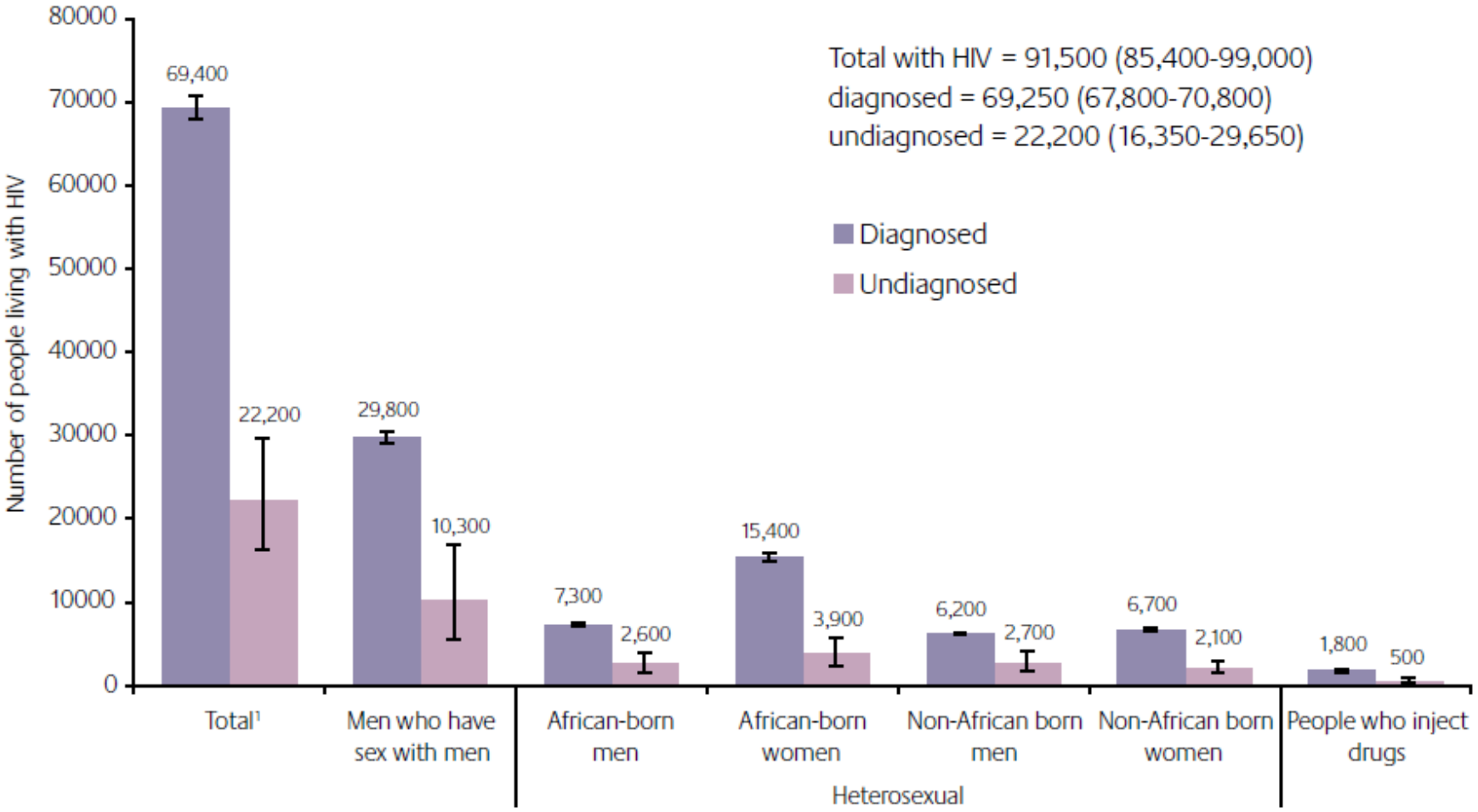
Figure 2: Estimated number of people living with HIV (both diagnosed and undiagnosed) in the United Kingdom: 2010



1 Total includes children under the age of 15

Figure 6: Late diagnosis of HIV infection by exposure group: United Kingdom, 2010

1 within three months of diagnosis

Late diagnosis

High morbidity and mortality

Immune reconstitution disease

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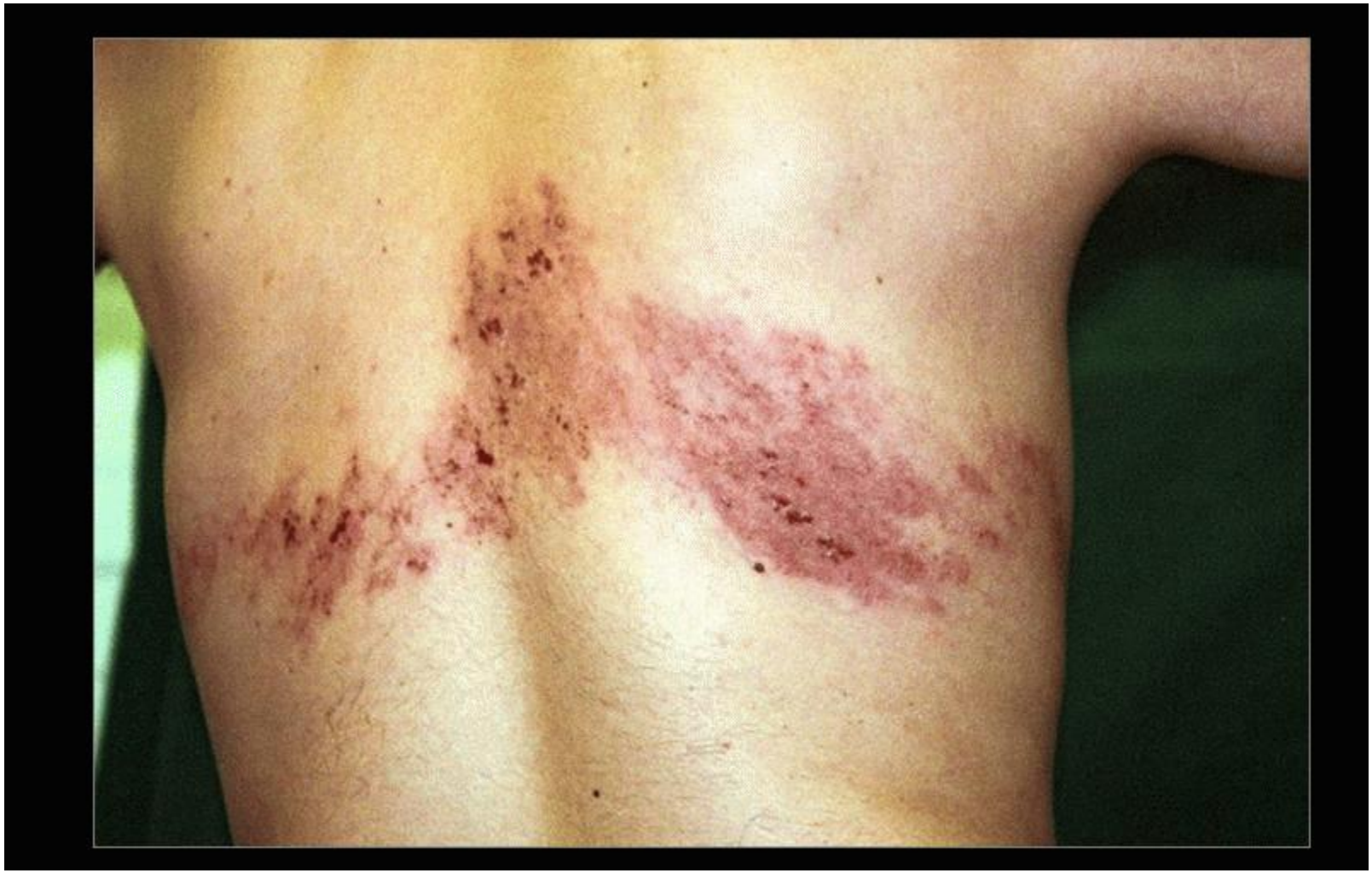
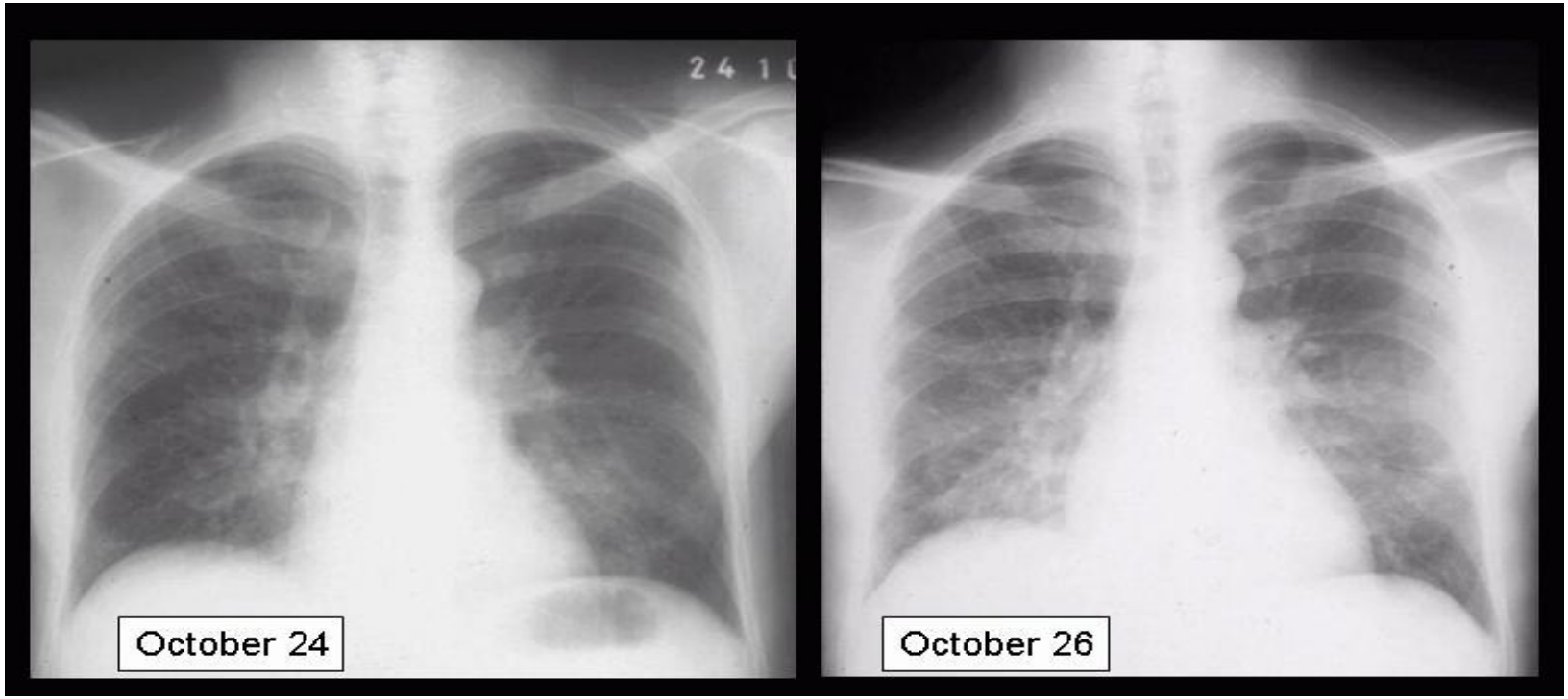
Immune reconstitution disease



Immune reconstitution disease



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