Nuevos paradigmas en la infección VIH

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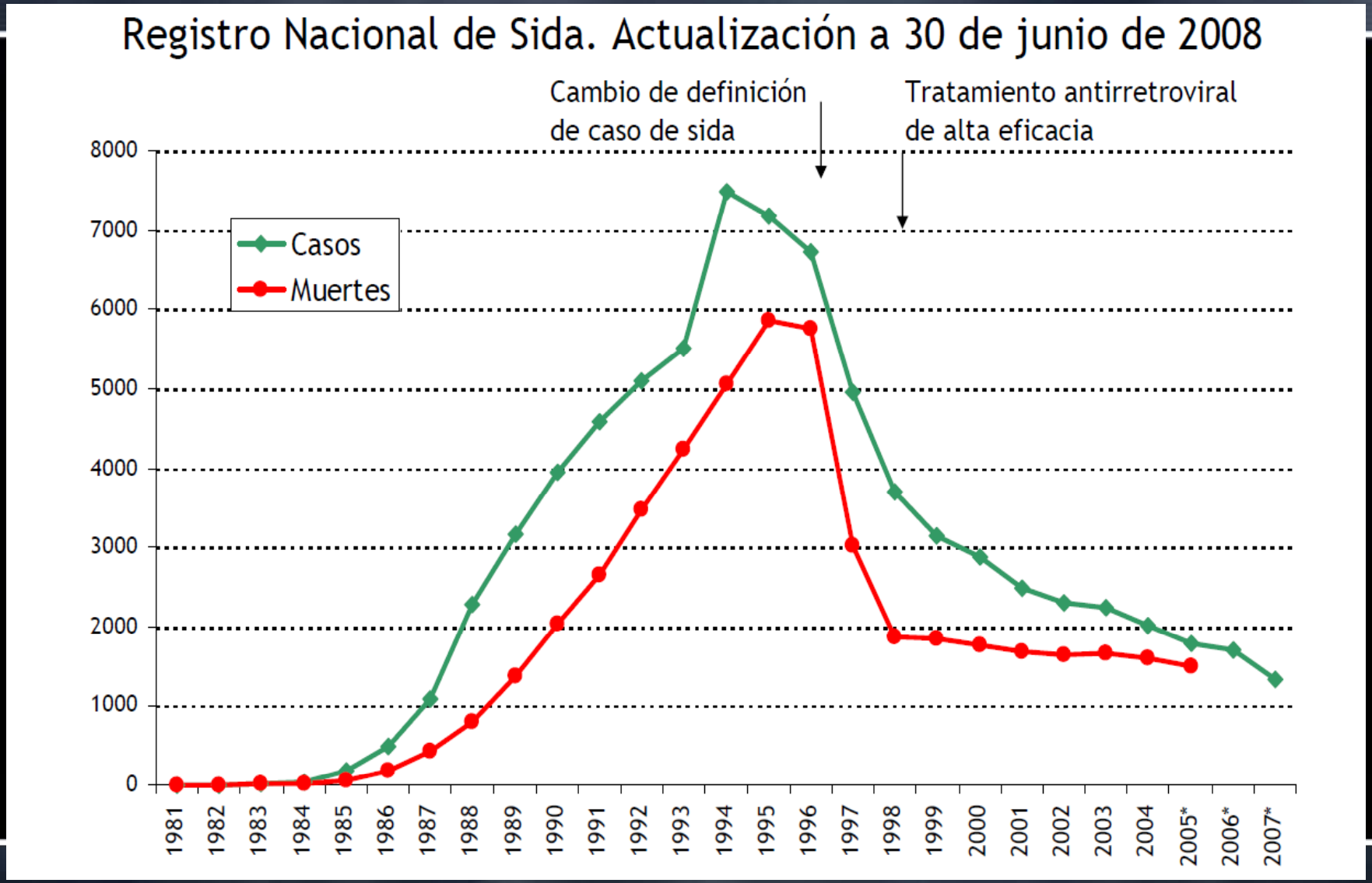
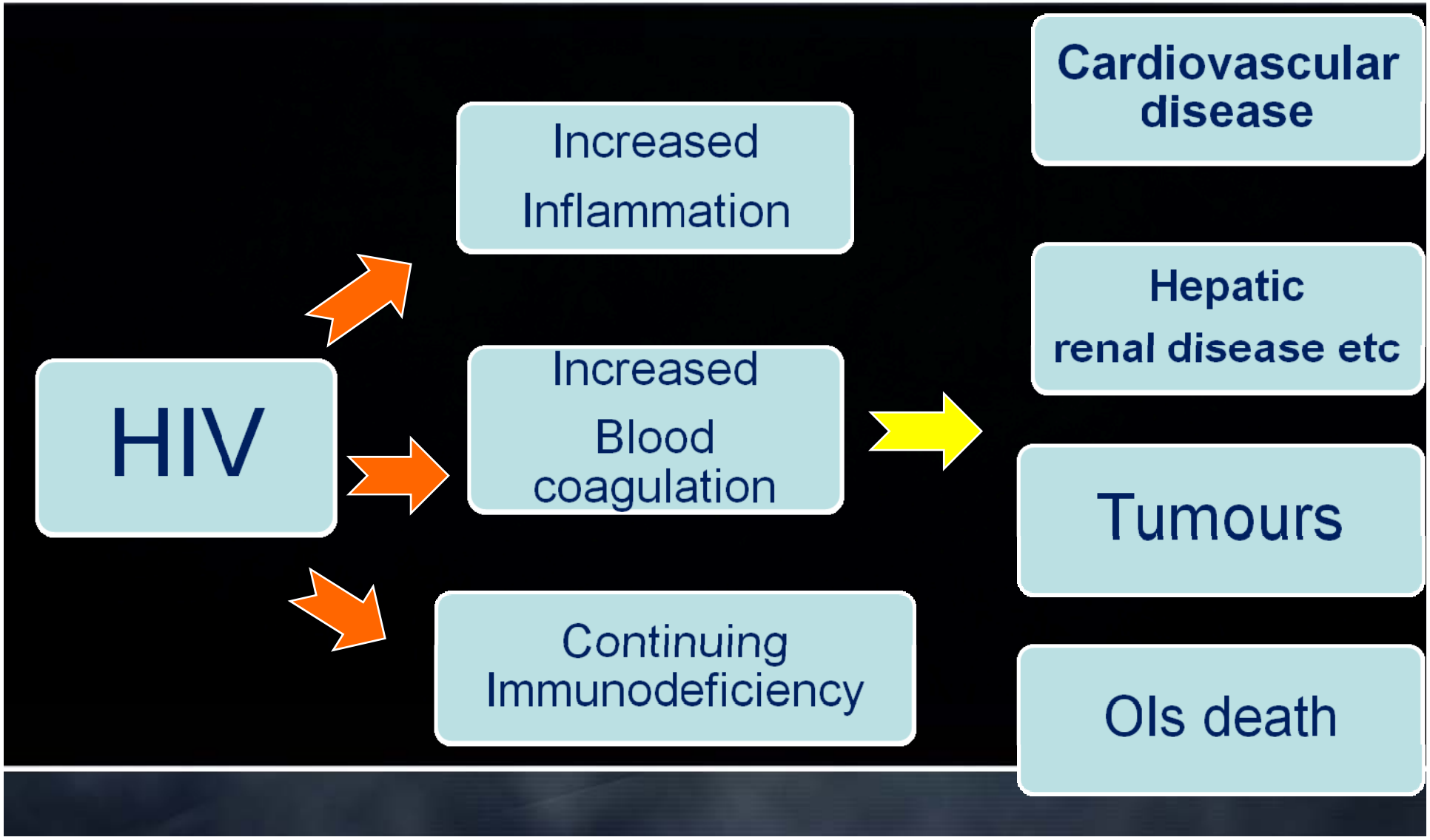
Hospital Universitari

1. Do you believe, I have to start ARV therapy ?

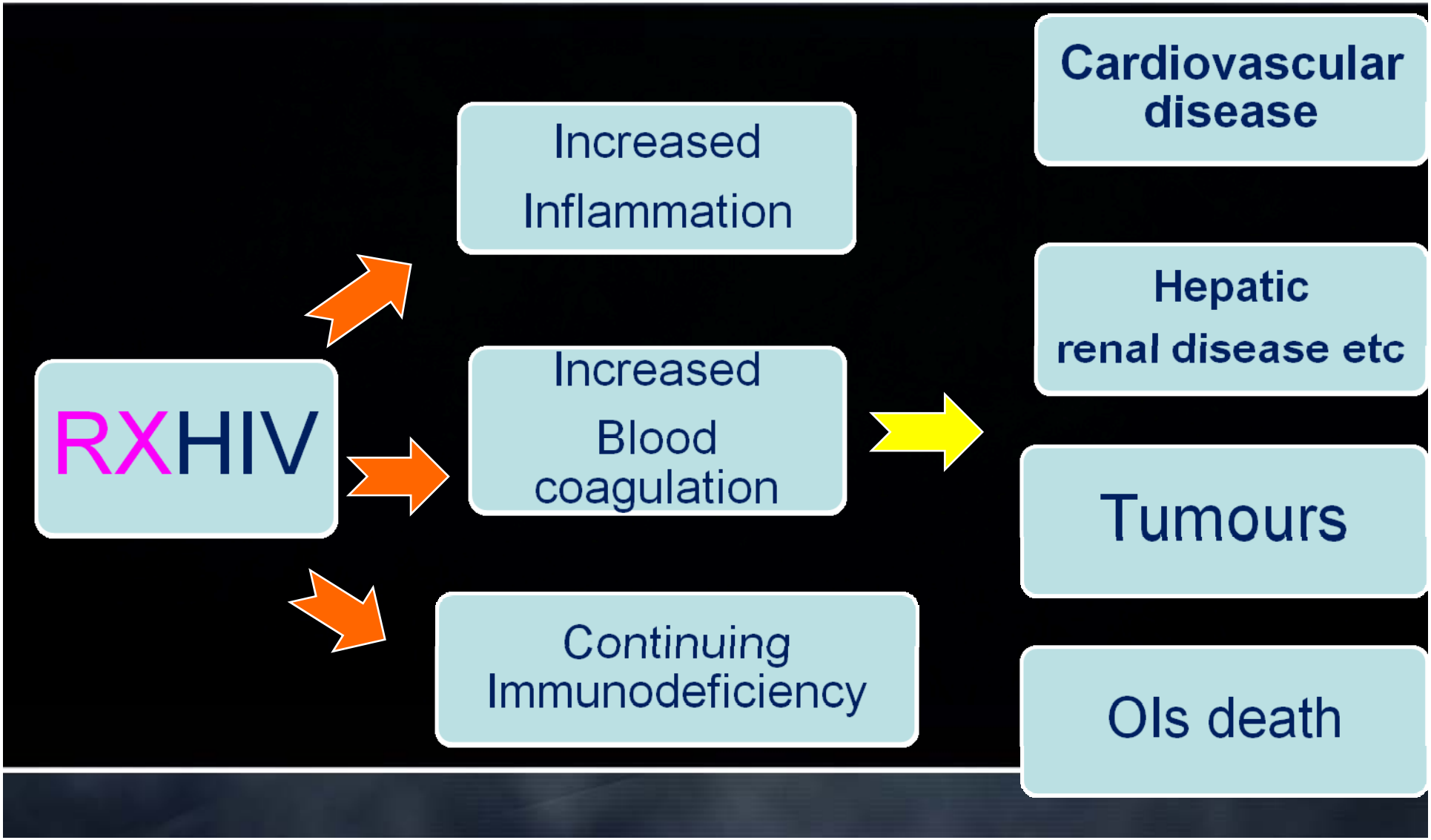
Incidence and Mortality of AIDS in Spain



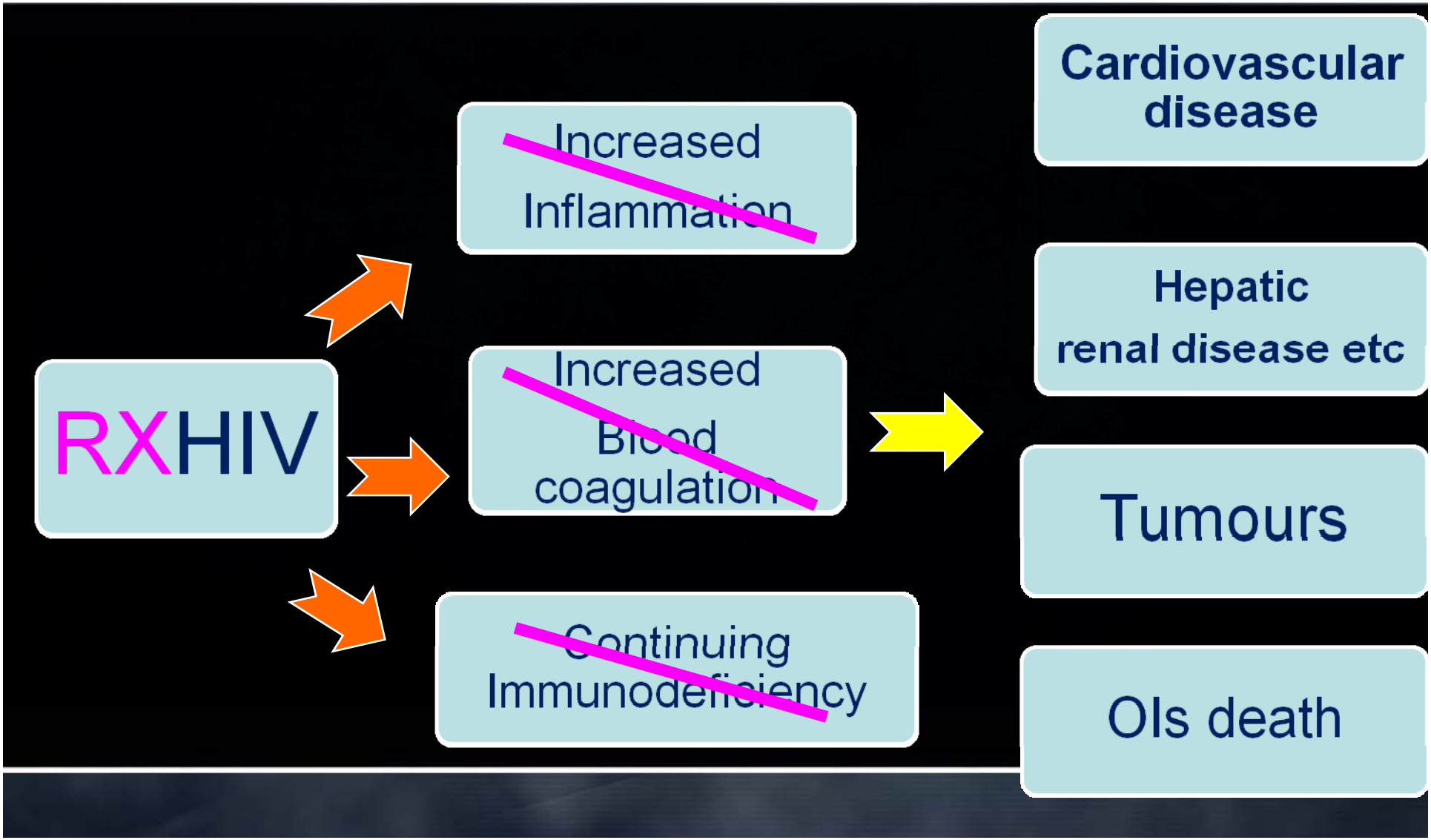
HIV and NON-AIDS complications



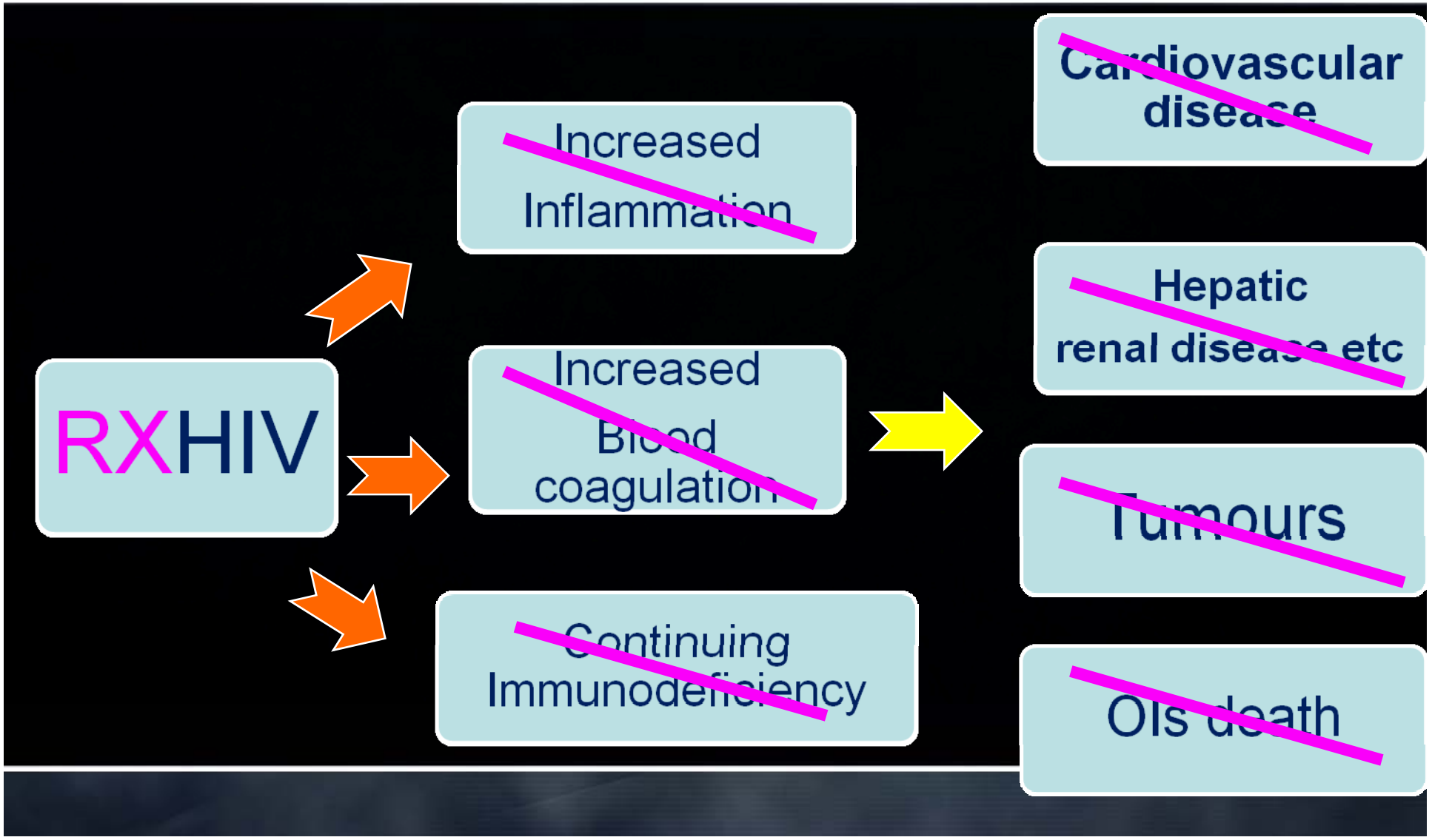
HIV and NON-AIDS complications



HIV and NON-AIDS complications



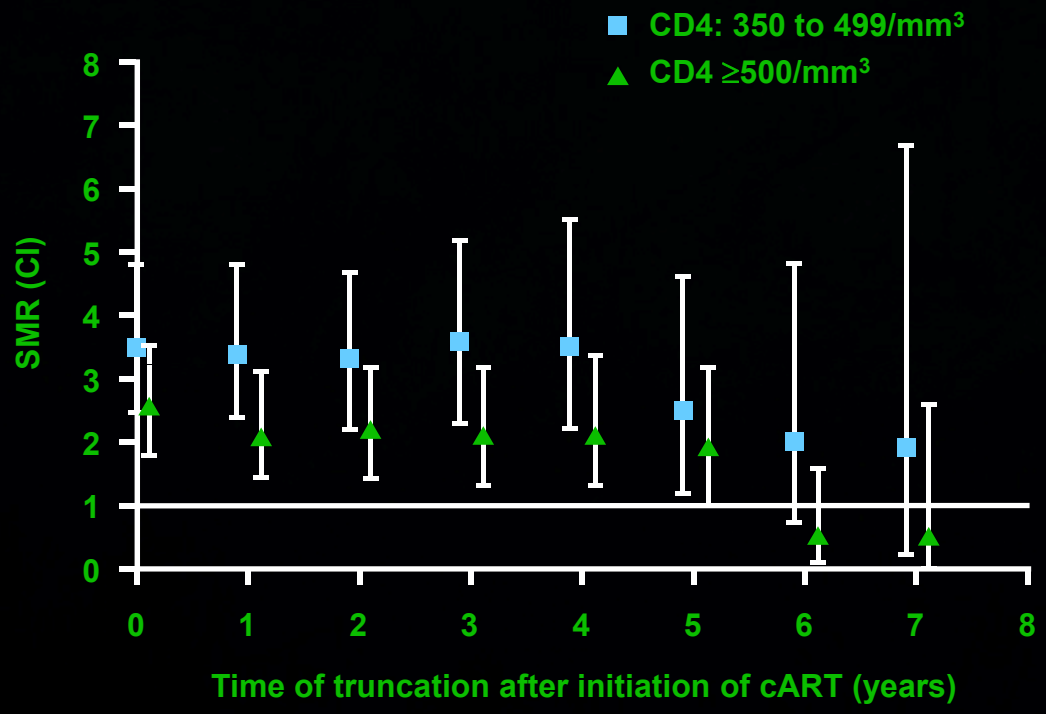
HIV and NON-AIDS complications



2.- What is my life expectancy ?

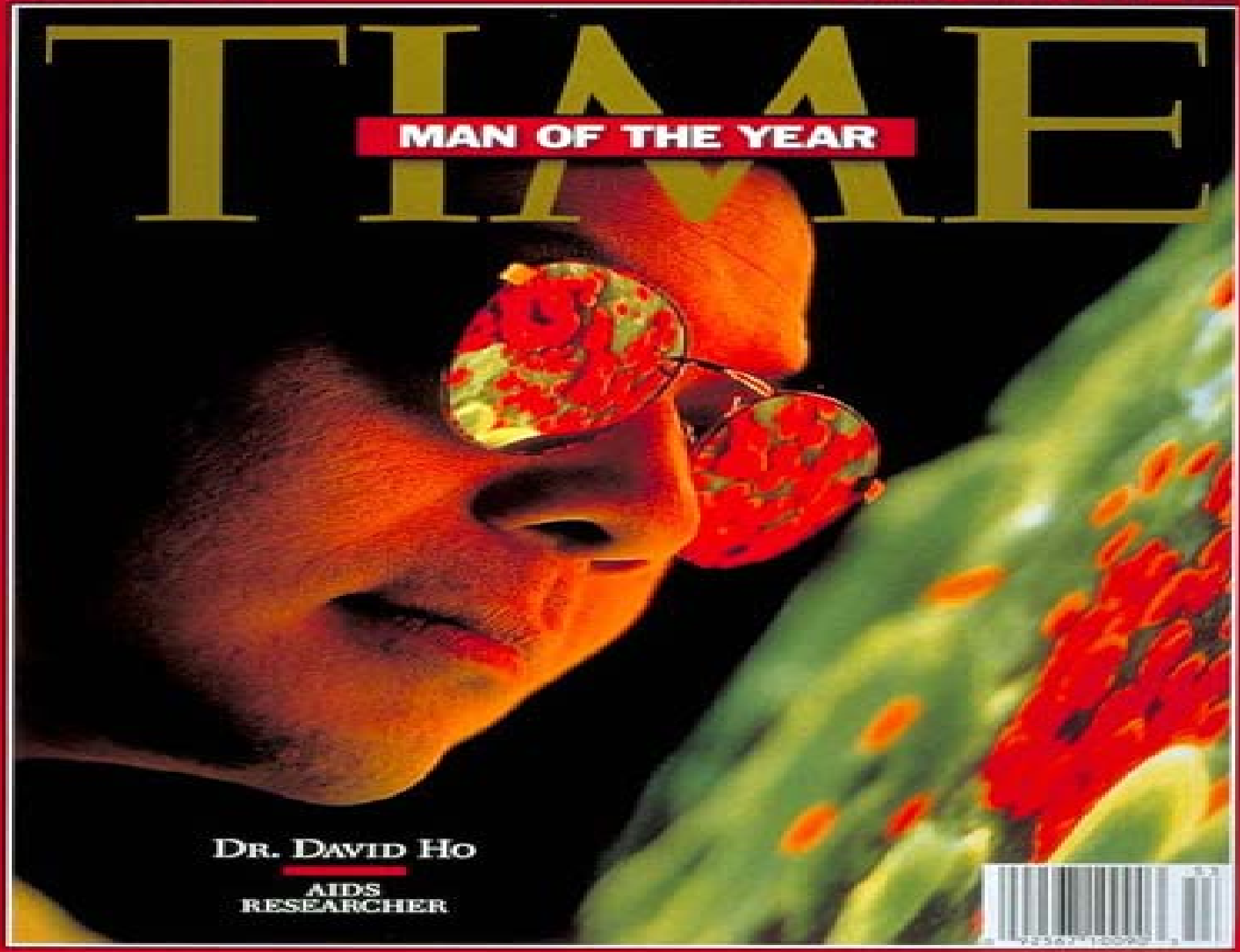
Improve Survival in HIV Patients

CD4 count ≥500mm^3 is associated with standard mortality ratio (SMR) similar to general population[1]

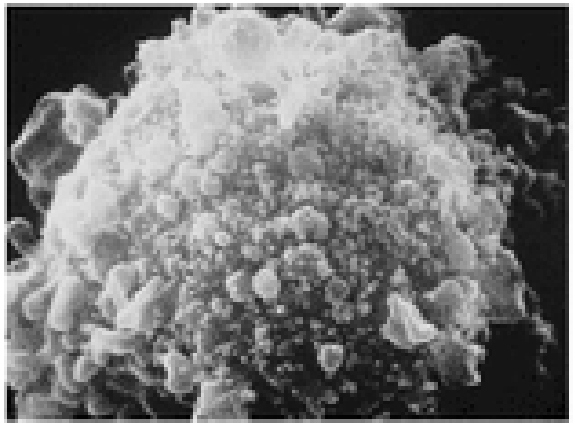


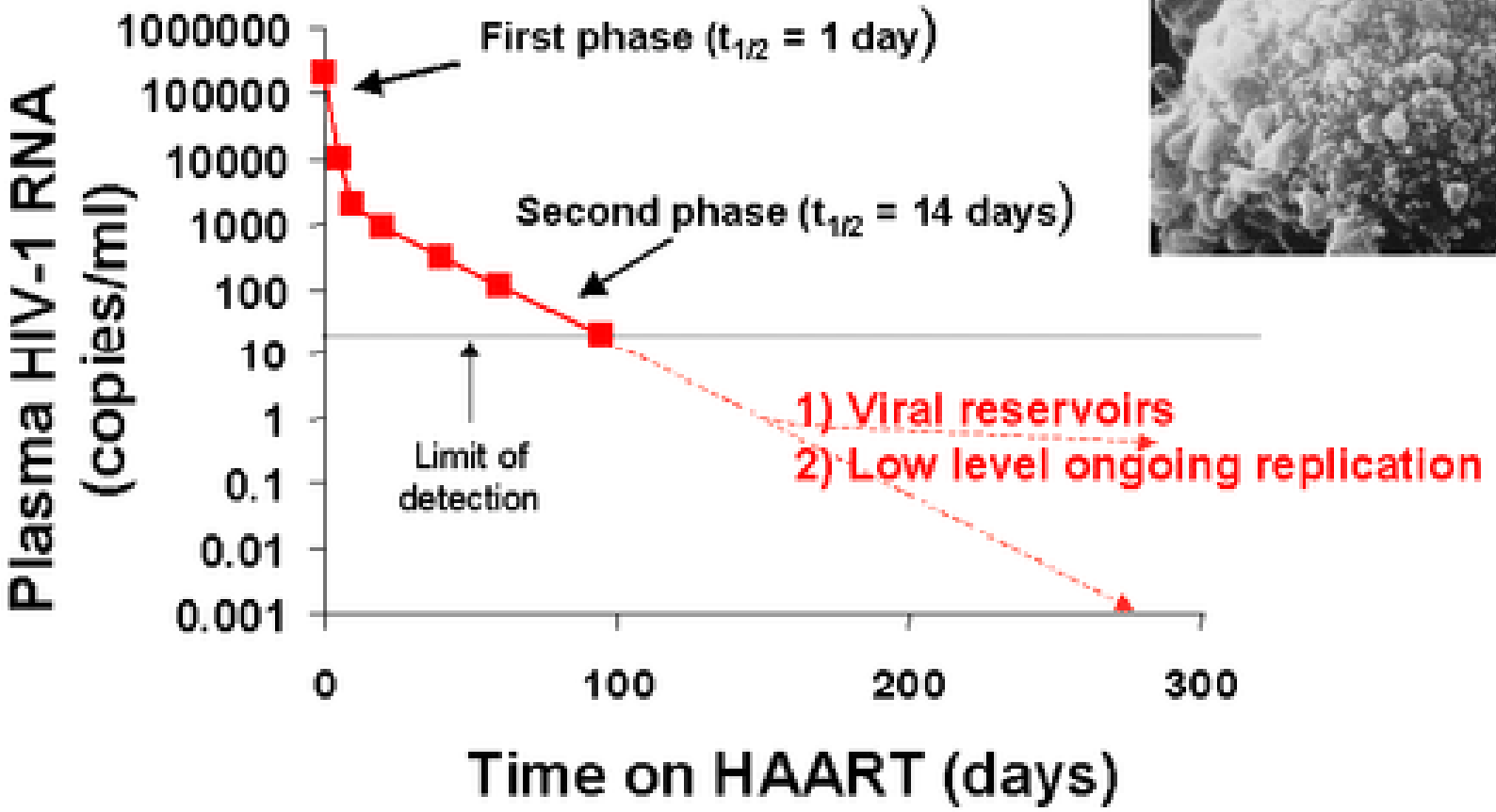
Lewden C, et al. J Acquir Immune Defic Syndr 2007;46(1):72−77

3.- Can I “cure” my HIV infection ?


TIME
MAN OF THE YEAR
DR. DAVID HO
AIDS
RESEARCHER

Dynamics of HIV-1 Replication in Patients on Antiretroviral Therapy



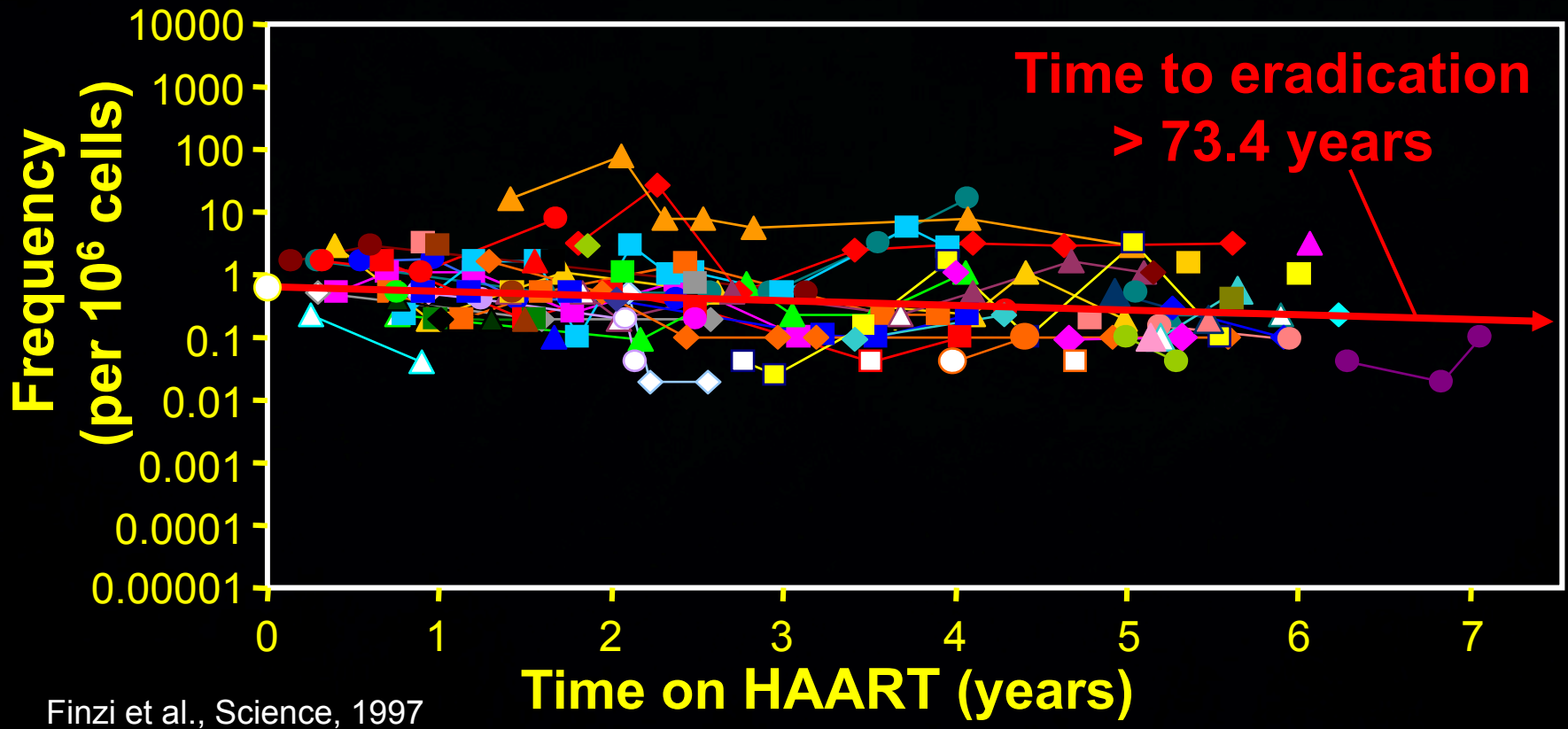


When start ARV Therapy ?

"Hit hard and hit early"

David Ho, 1996

Slow decay of latently infected CD4+ T cells $t_{1/2}$ = 44.2 months



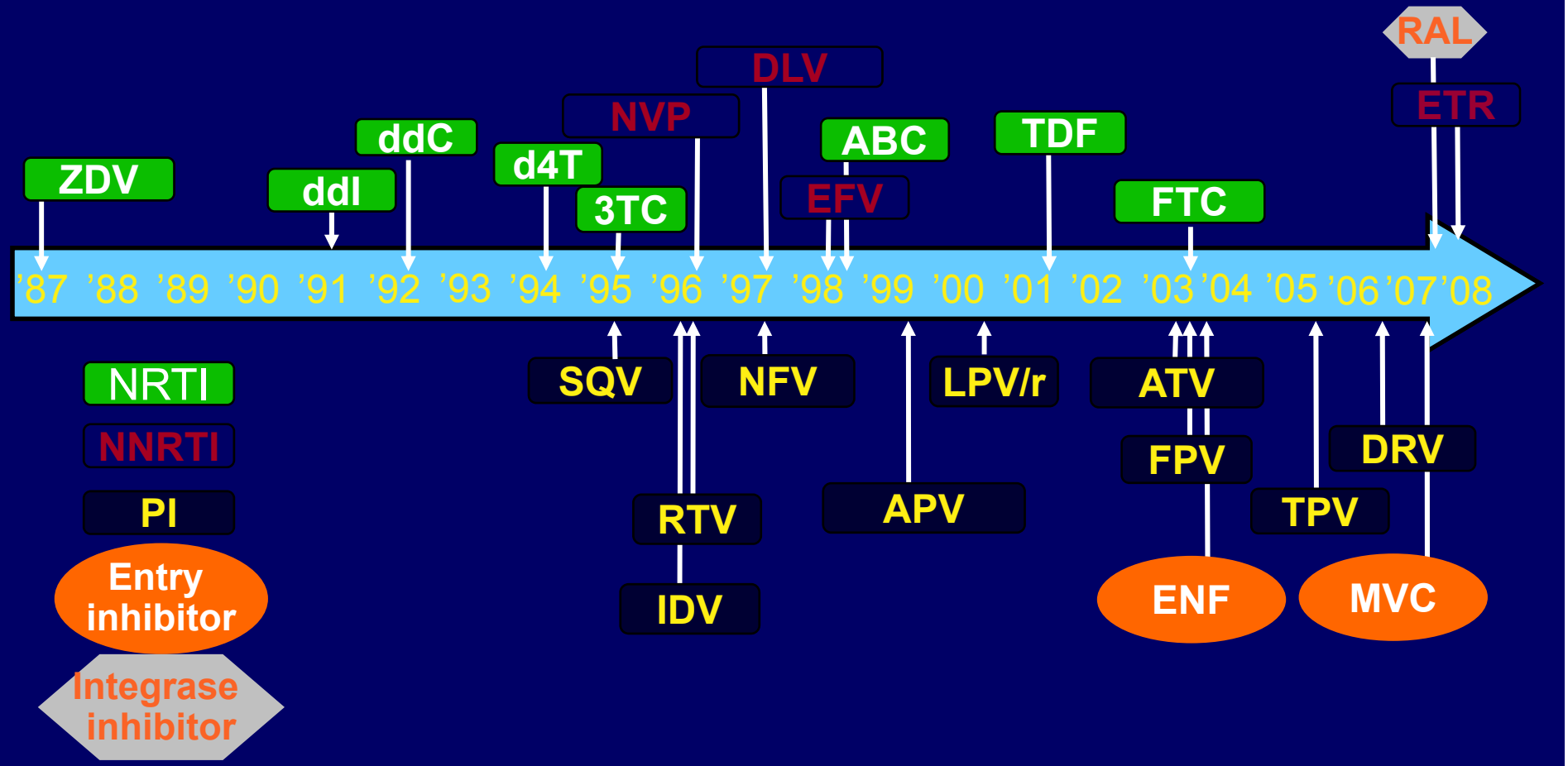
Finzi et al., Science, 1997
Wong et al. Science, 1997
Chun et al., PNAS, 1997

Finzi et al., Nature Med., 1999
Siliciano et al., Nature Med., 2003

Chun et al., Nature Med., 1995
Chun et al., Nature, 1997

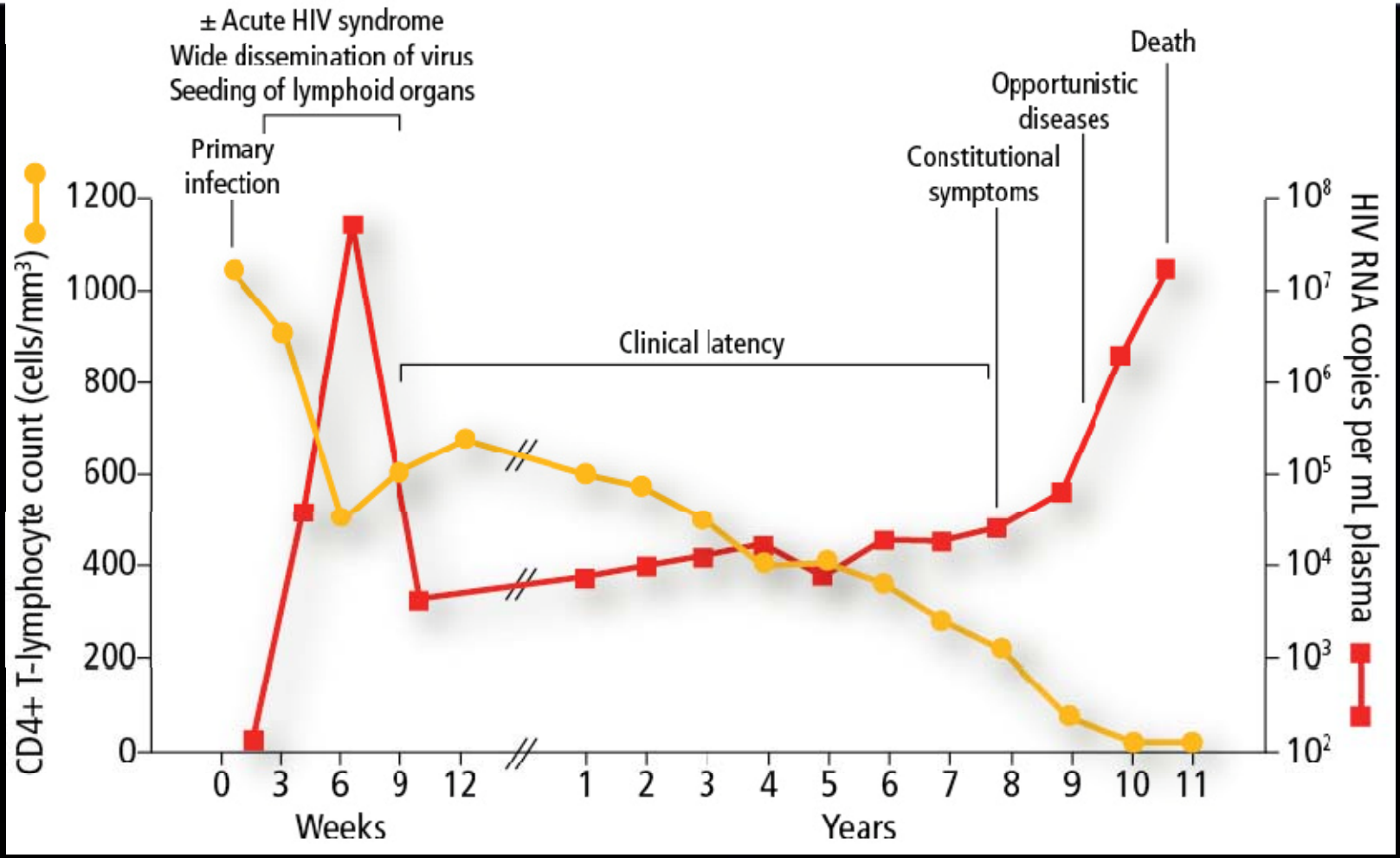

VIDEX
100
VIDEX
100

ARV Armentarium 2009



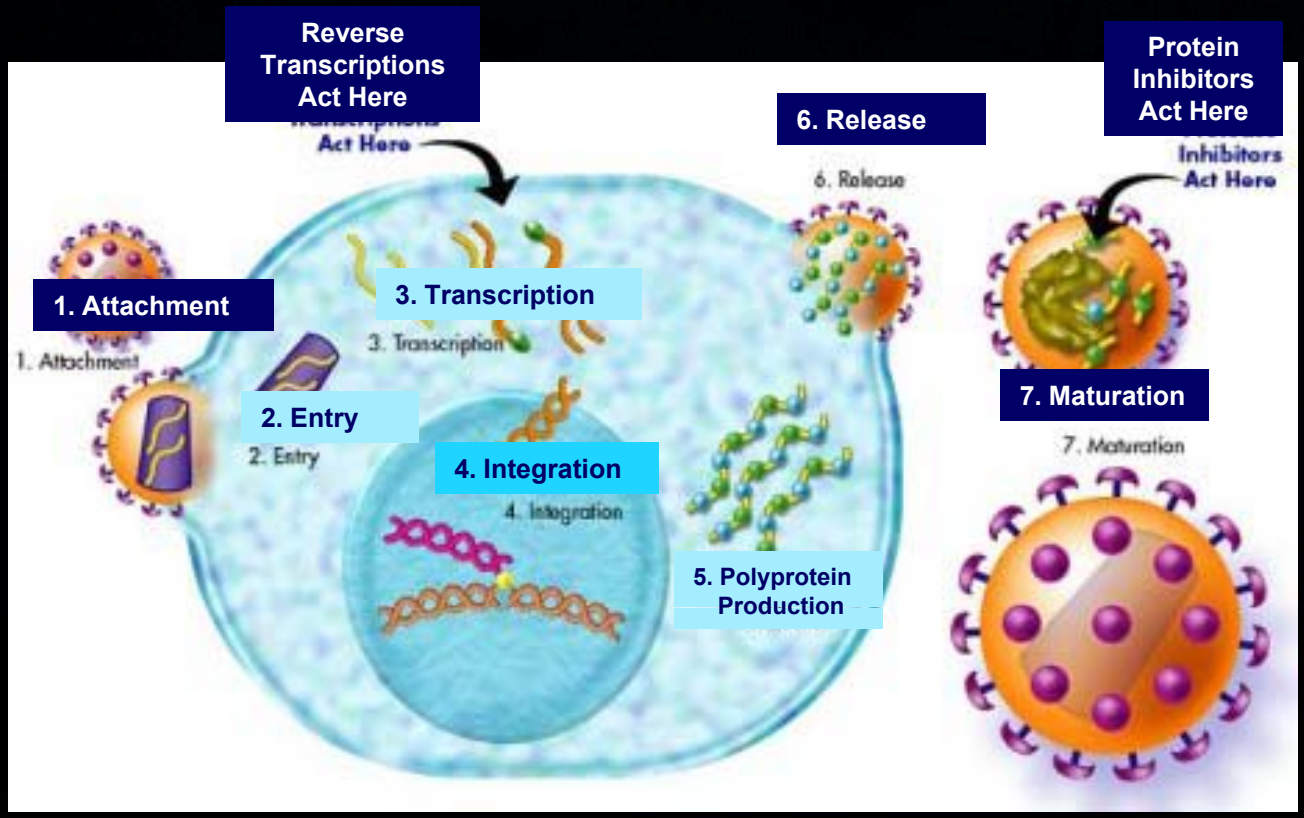
25 unique ARV agents approved, 6 different classes

Typical Disease Progression in an Untreated HIV-Infected Patient



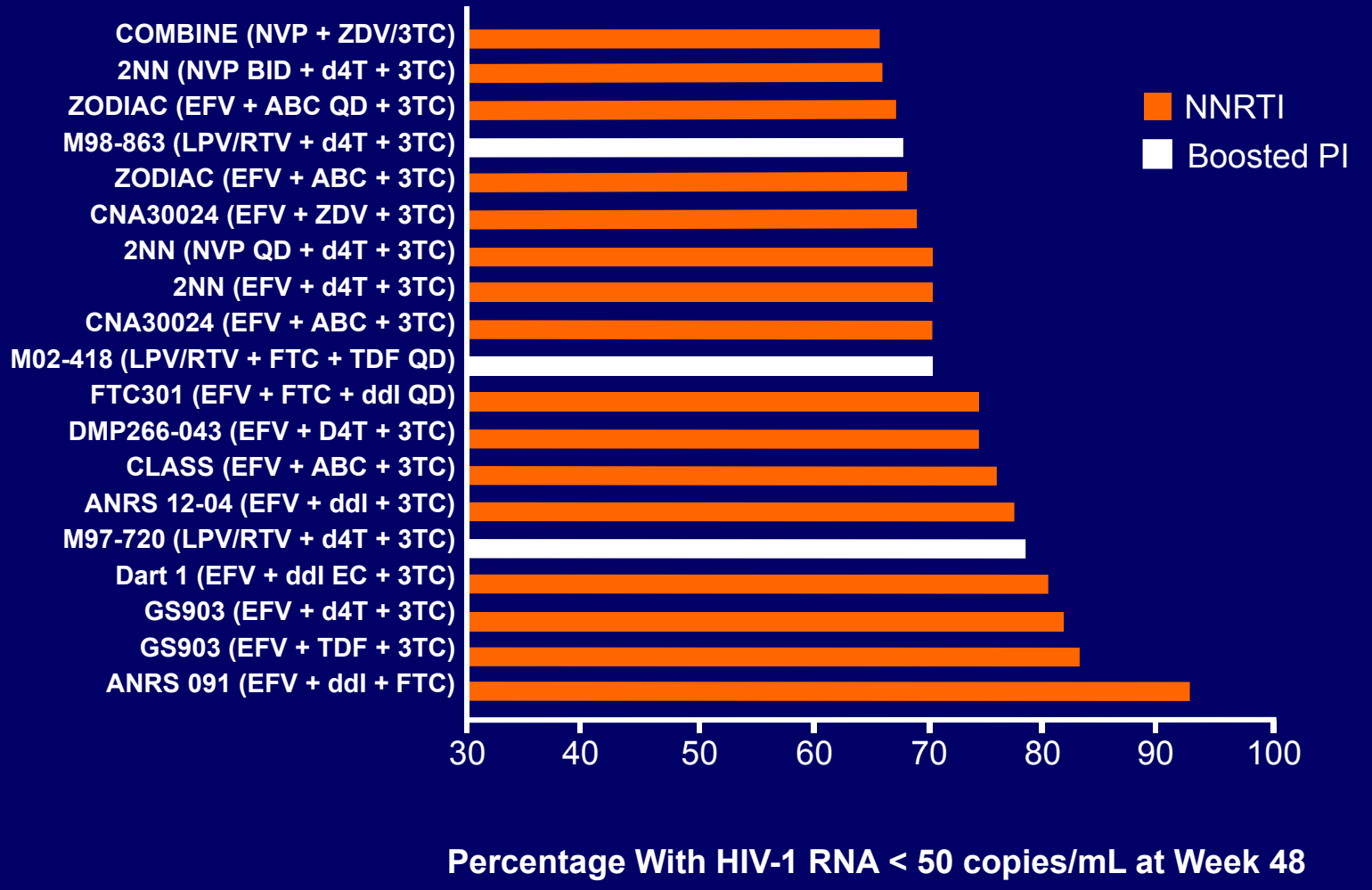
HIV Lifecycle

- Phases: binding and entry, reverse transcription, replication, budding, and maturation



4.- So, what treatment do you suggest ?

HAART: Studies in Naïve patients With > 65% Response (VL < 50 at Wk 48)



Bartlett JA, et al. AIDS. 2006;20:2051-2064.

HAART is effective!
Recent Randomized ARV Trials

Proportion with VL <50 copies/mL Week 48 (ITT)

Naïve Trials	
Gemini	64-65%
KLEAN	65-66%
ACTG 5142 (Wk 96)	77-89%
Artemis	78-84%
Merit	65-69%
MK 004	87%
Castle	76-78%
HEAT	67-68%

Experienced Trials	
Benchmrk	64%
Victor E1 (Wk 24)	64%
Motivate	42-47%
Power	46%
Duet	60-61%
TITAN	61-70%

Walmsley EACS, 2007, Eron, Lancet, 2007; Ridler, WAC, 2006; Clumeck, EACS, 2007; Saag, IAS, 2007; Markowitz, 8,JAIDS, 2007; Molina, CROI, 2008; Smith CROI, 2008, Cooper, CROI 2008, Steigbigel, CROI 2008, Zingman, CROI 2008; Lalezari ICAAC 2007, Falkenheuer, EACS, 2007; Lazzarin, Lancet, 2007; Haubrich, CROI, 2008; Johnson CROI 2008; Madruga Lancet, 2007

Safety and Tolerability of Many Current Regimens Are Excellent

Study	Drug regimen	*Discontinuations Due to AEs,* %*
AI424-089[1]	ATV + d4T + 3TC	3
	ATV/RTV + d4T + 3TC	8
GS934[2]	EFV + TDF + FTC	5
	EFV + ZDV/3TC	11
KLEAN[3]	FPV/RTV + ABC/3TC	12
	LPV/RTV + ABC/3TC	10
ARTEMIS[4]	DRV/RTV + TDF/FTC	3
	LPV/RTV + TDF/FTC	7
CASTLE[5]	ATV/RTV + TDF/FTC	2
	LPV/RTV + TDF/FTC	3
HEAT[6]	ABC/3TC + LPV/RTV	4
	TDF/FTC + LPV/RTV	6
GEMINI[7]	SQV/RTV + TDF/FTC	4
	LPV/RTV + TDF/FTC	7

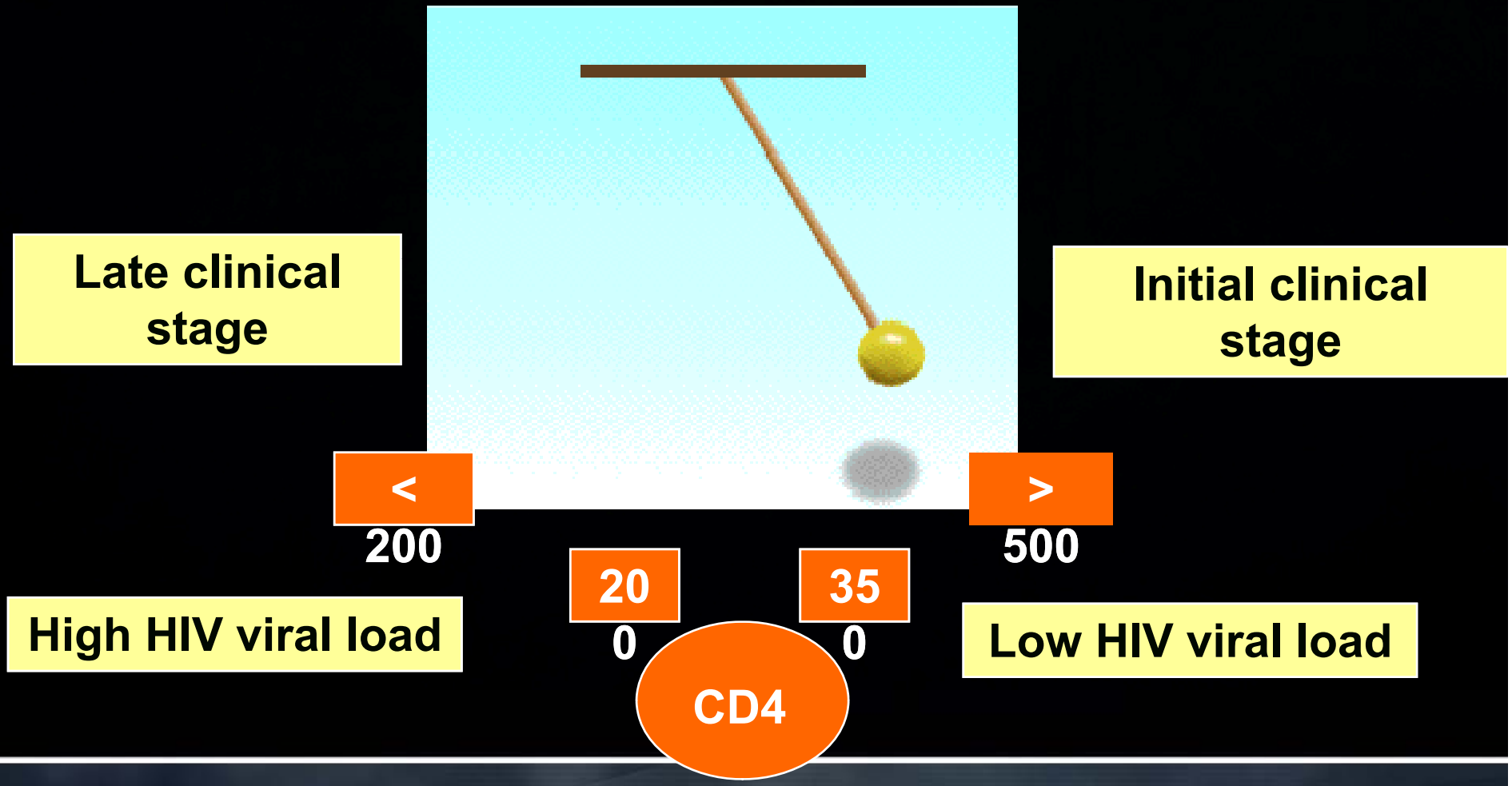
1. Malan N, et al. IAS 2007. Abstract WEPEB024. 2. Arribas JR, et al. IAS 2007. Abstract WEPEB029. 3. Eron J Jr, et al. Lancet. 2006;368:476-482. 4. DeJesus E, et al. ICAAC 2007. Abstract 718-b. 5. Molina JM, et al. CROI 2008. Abstract 37. 6. Smith K, et al. CROI 2008. Abstract 774. 7. Walmsley SL, et al. EACS 2007. Abstract PS1.4.

We have better and more tolerable therapy

It appears we have:

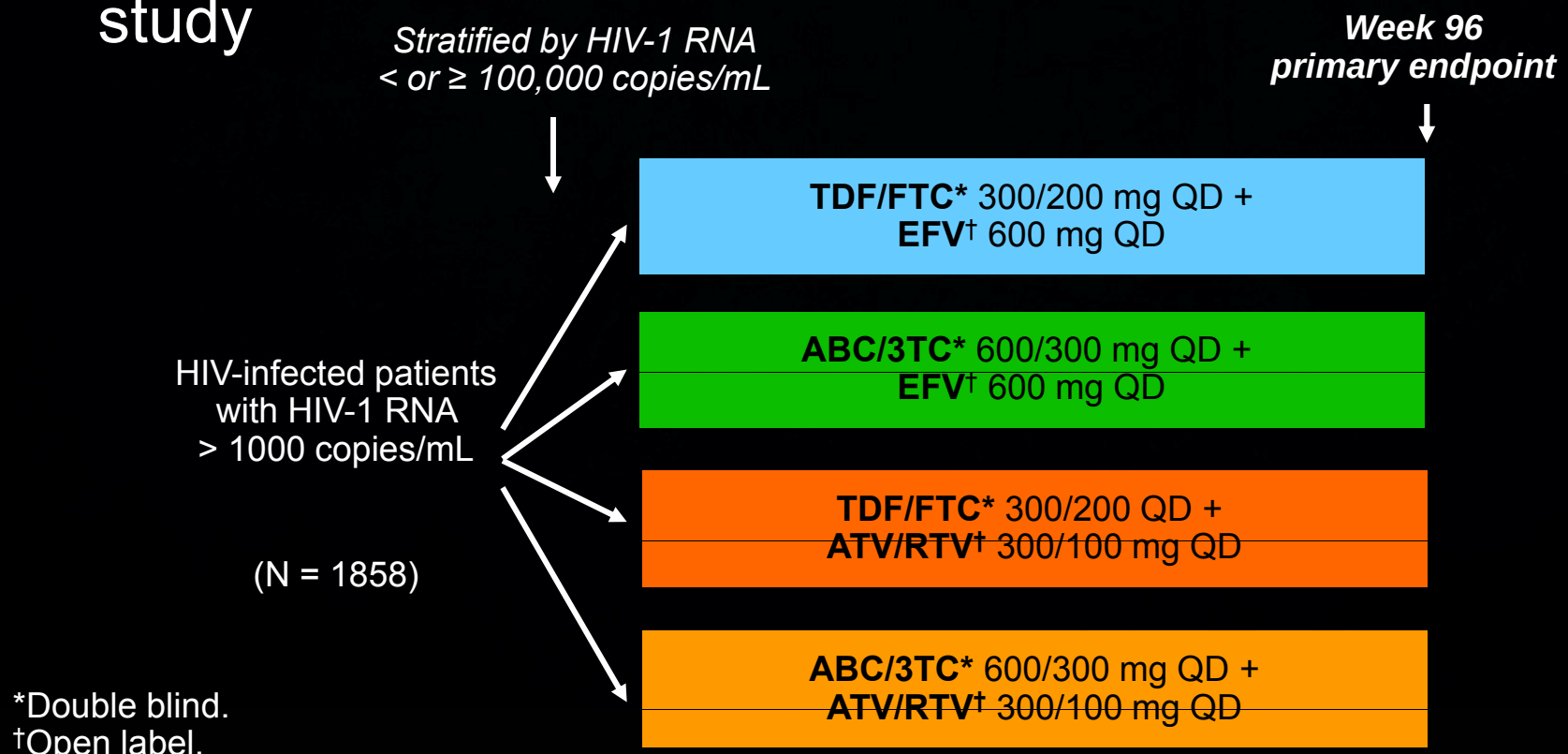
- Less short term toxicity-diarrhoea, dyslipidemia
- Less long term toxicities such as lipodystrophy
- Better formulations
  - easier to take
  - lower pill burdens-one pill once a day
  - no refrigeration

When to start ARV Therapy ?



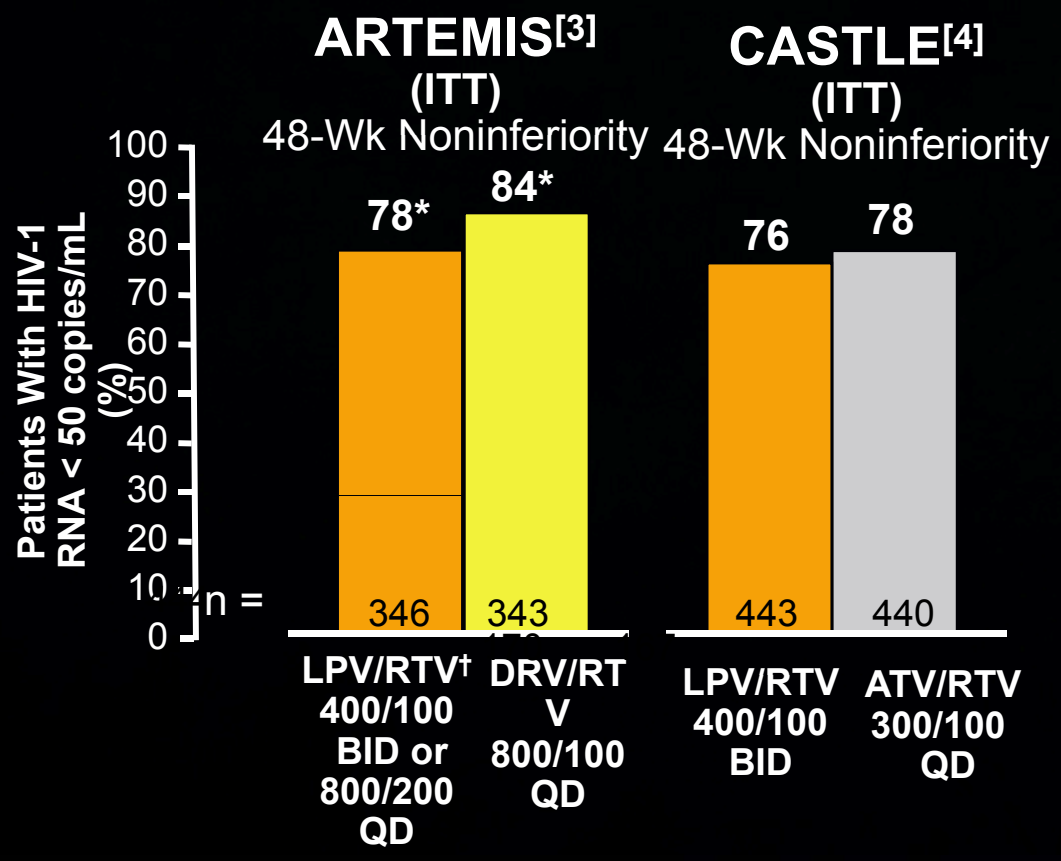
ACTG 5202: ABC/3TC vs TDF/FTC + EFV or ATV/RTV

- Randomized, double-blind, open-label phase IIIb study



Sax PE, et al. IAC 2008. Abstract THAB0303.

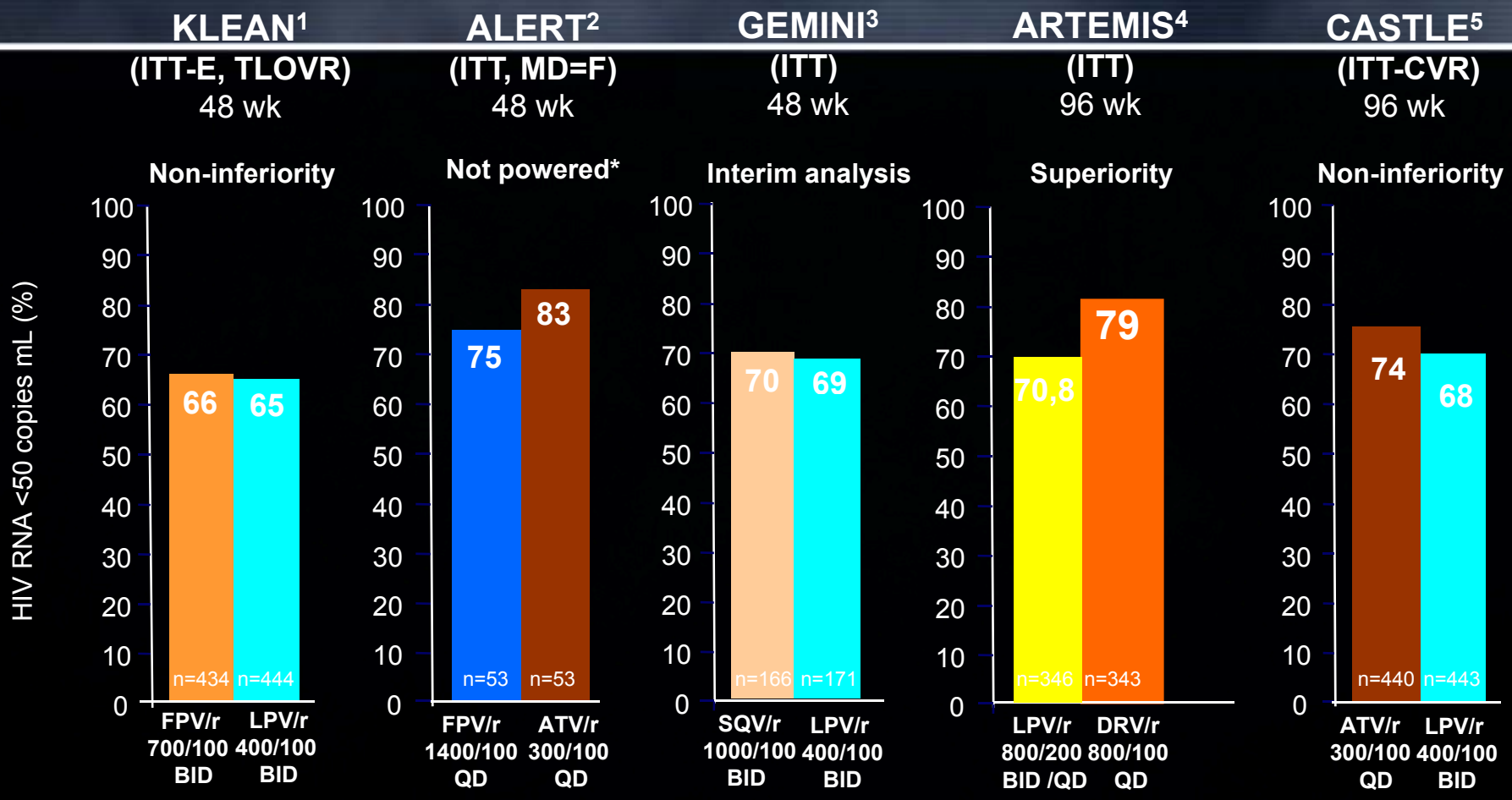
Boosted PIs in ARV-Naive Patients: Which to use ?



*$P < .05$

Ortiz R, et al. AIDS. 2008;22:1389-1397.. Molina JM, et al. Lancet. 2008;372:646-655.

Eficacia de los ARV en pacientes naïve



Neither FPV/r nor LPV/r QD are licensed in the EU. The EU licensed dose of DRV/r is 600/100 mg BID.
*ALERT study was not powered for non-inferiority.
Data in figures are from different studies and cannot be compared directly.

1. Eron J, et al. Lancet. 2006;368:476–482; 2. Smith K, et al. IAS 2007, Abstract WEPEB023;
3. Raffi F, et al. IAS 2007, Abstract WEPEB027; 4. De Jesus E, et al. ICAAC 2007, Abstract LBA H-718b;
5. Molina J-M, et al. Lancet. 2008;DOI:10.1016/S0140-6736(08)61081-8

5.- ….and what about if I have side effects or virological failure ?

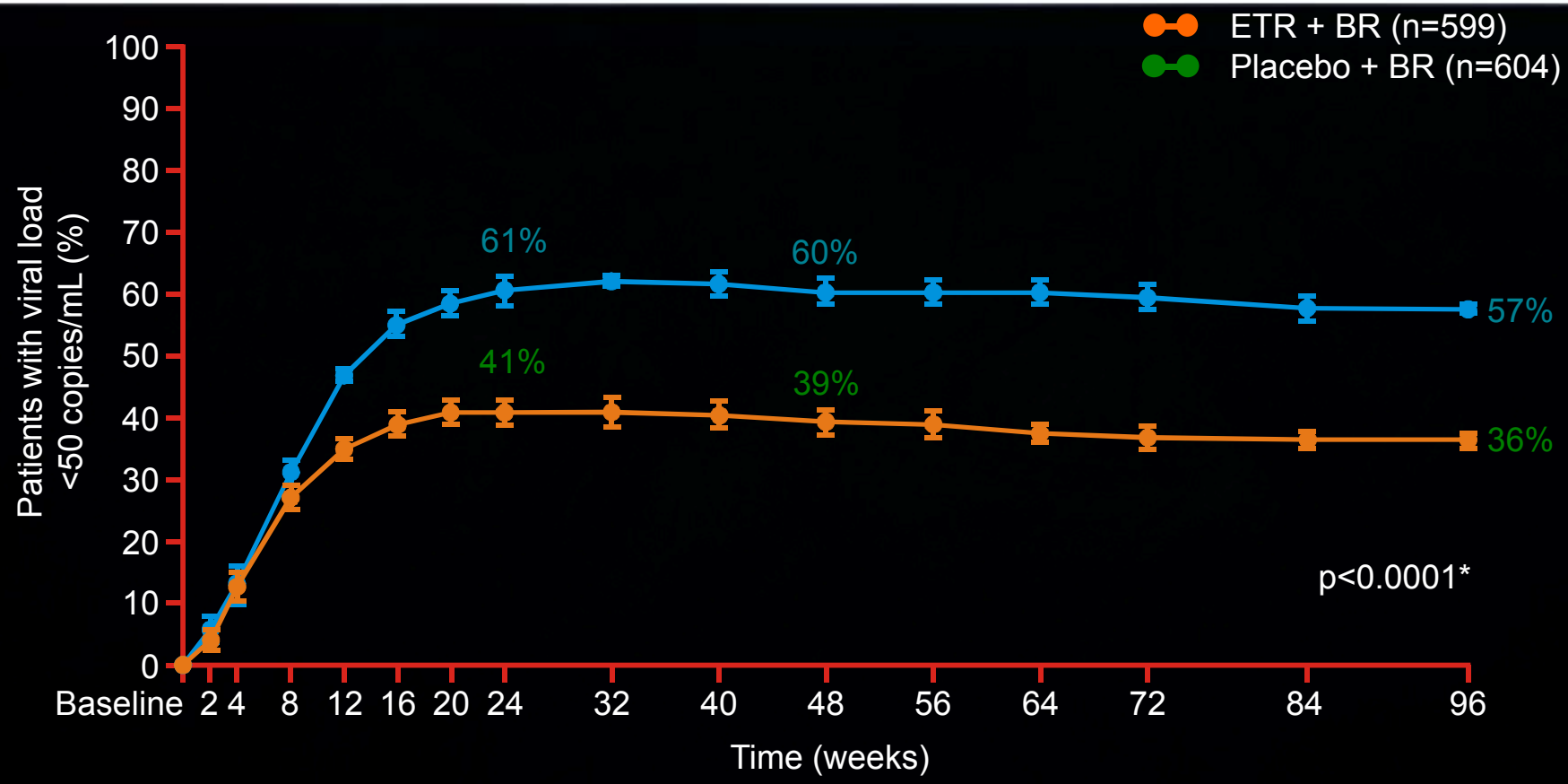
Rescue Therapy in HIV infected patients
Clinical Trials

- **Clinical Trial** **Drug**

- TORO…… Enfuvirtide
- RESIST…… Tipranavir
- POWER…… Darunavir

- DUET…… Etravirine+Darunavir
- BENCHMRK…… Raltegravir
- MOTIVATE…… Maraviroc

Patients with viral load <50 copies/mL (ITT-TLOVR): pooled 96-week analysis



- Mean change in CD4 cell count was 128 cells/mm^3 in the ETR + BR arm versus 86 cells/mm^3 in the placebo + BR arm (p<0.0001)

*Logistic regression model controlling for baseline viral load, ENF use and study number

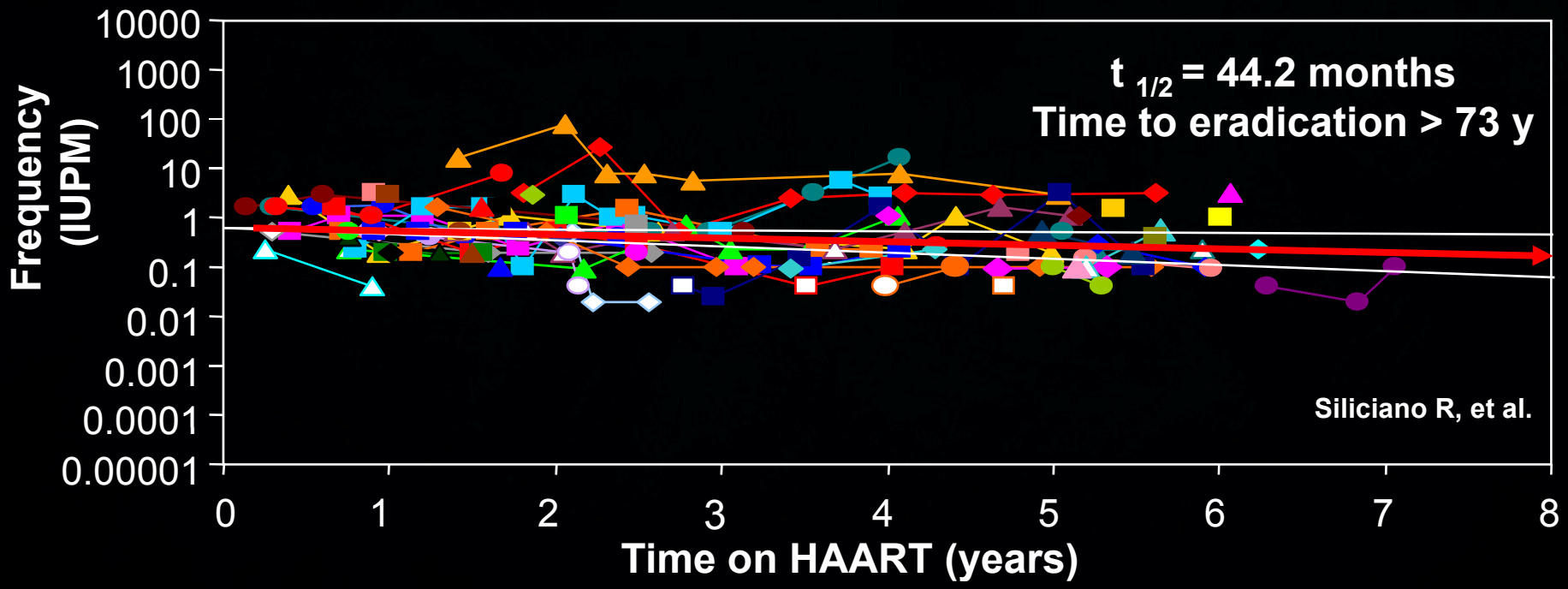
ITT = intent-to-treat; TLOVR = time-to-loss of virological response algorithm

Week 48 Virologic Efficacy of New Drugs Defined as HIV-1 RNA < 50 c/mL

Study	Drug Regimen	HIV-1 RNA < 50 copies/mL, %
TORO [1]	Enfuvirtide + OBR OBR alone	18.3 7.8
RESIST [2]	Tipranavir + OBR Comparator PI + OBR	22.8 10.2
POWER [3]	Darunavir/ritonavir + OBR Comparator PI + OBR	45.0 10.0
DUET [4,5]	Etravirine + darunavir/ritonavir-containing OBR Placebo + darunavir/ritonavir-containing OBR	60.0 40.0
MOTIVATE [6]	Maraviroc QD + OBR Maraviroc BID + OBR Placebo + OBR	41.8 46.8 16.1
BENCHMRK [7,8]	Raltegravir + OBR Placebo + OBR	63.0 33.0

1. Nelson M, et al. J Acquir Immune Defic Syndr. 2005;40:404-412. 2. Hicks CB, et al. Lancet. 2006;368:466-475. 3. Clotet B, et al. Lancet. 2007;369:1169-1178. 4. Haubrich R, et al. CROI 2008. Abstract 790. 5. Johnson M, et al. CROI 2008. Abstract 791. 6. Lalezari J, et al. ICAAC 2007. Abstract H-718a. 7. Cooper DA, et al. N Engl J Med. 2008. In press. 8. Steigbigel R, et al. N Engl J Med. 2008. In press.

Is there a possibility to speed up this process?



Time needed for eradication estimated as 73.4 years!, however it might take only up to 7,7 years of continuous therapy in individuals who initiate HAART early in HIV infection (0.3-4.4 months after the initiation of symptoms of primary HIV infection) Chun T-W et al. JID 2007;195:1762-4

6.- What about the future ?
What about the challenges ?

ARV Therapy

2010,... and THE FUTURE.

- More convenience-well tolerated regimens
- New drugs available:
  - PI: Darunavir
  - NNRTI: Etravirine
  - Integrase inhibitors: Raltegravir
  - CCR5 antagonists: Maraviroc
- New concept:
  "Detectable is unacceptable"
- Revisiting the concept of eradication

ARV Therapy: Challenges-2010

- Avoid new cases: Prevention ¡¡¡
- Cure (eradication)
- Active vaccine
- Epidemic trends in developing countries

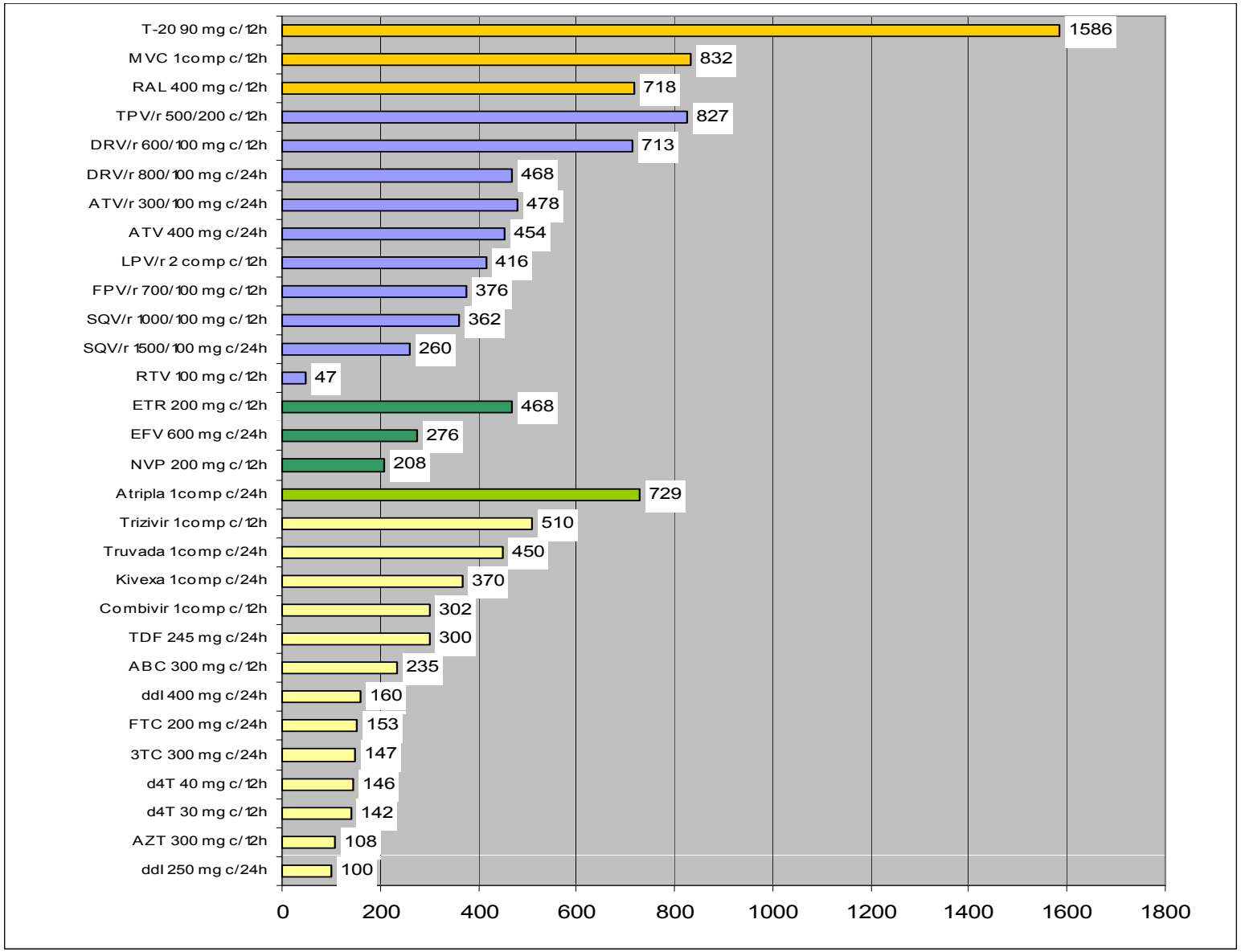
Public Health issues and HIV treatment

- If an HIV infected person has an undetectable VL can they transmit HIV to their partner?
- Can we treat our way out of the epidemic?
- Would expanding HAART to everyone diagnosed with HIV with a CD4 count below 350 cells/mm^3 together with prevention strategies , have a pronounced effect on transmission, by reducing viral load at a population level.

HIV Transmission under ART. XVII International AIDS Conference, Mexico City, SUSAT41, 2008.
Wasserfallen FM *Swiss statement for PLWHA on effective ARV treatment.* XVII International AIDS Conference, Mexico City, abstract MOPE0212, 2008. Lima VD et al. J Infect Dis 198 (online edition), 2008.

COSTE MENSUAL EN EUROS DE LOS TARV DISPONIBLES

(PVL + 4% IVA). Hospital Clínic. Año 2010



Six months after using antiretroviral therapy