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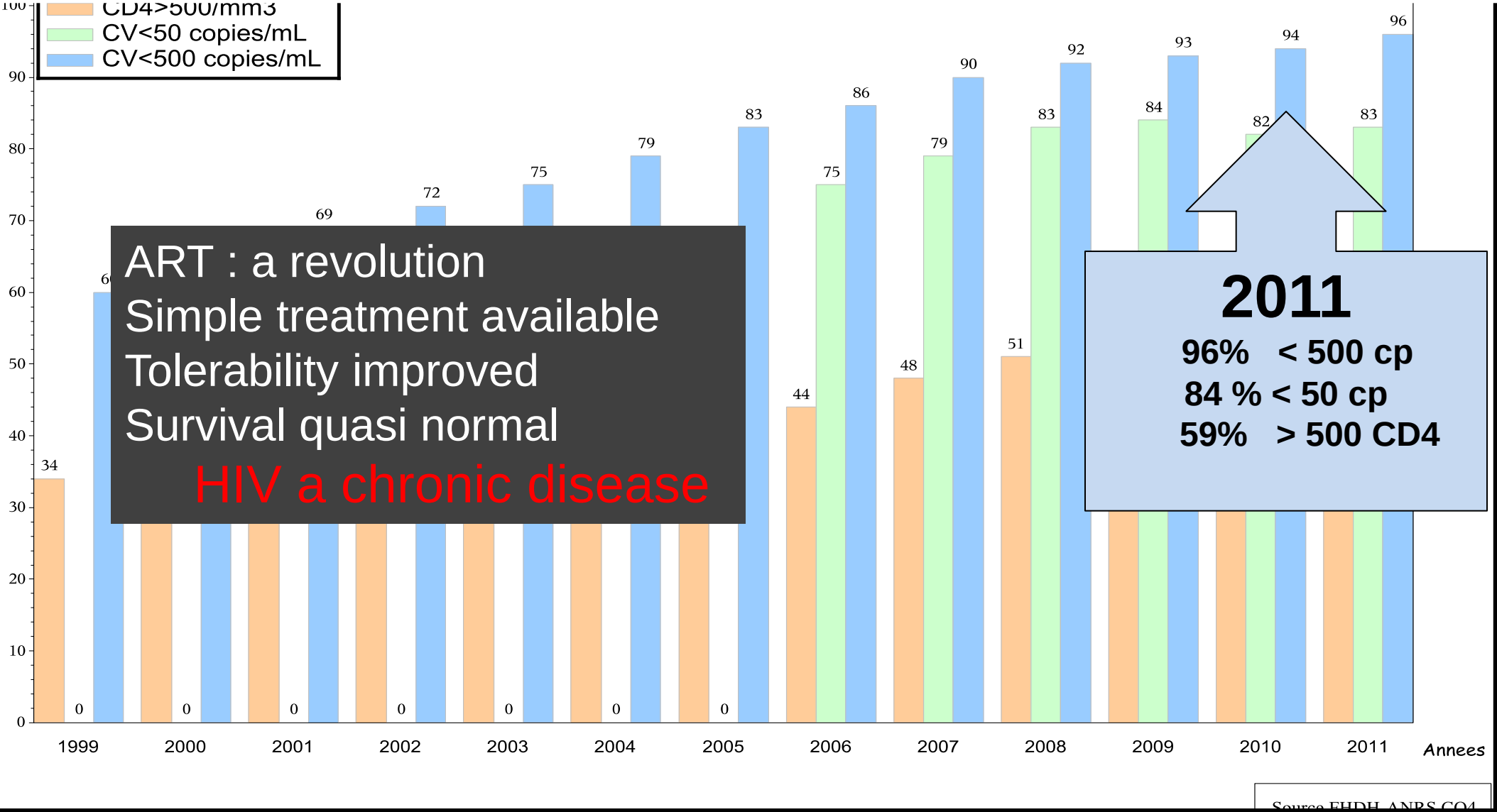
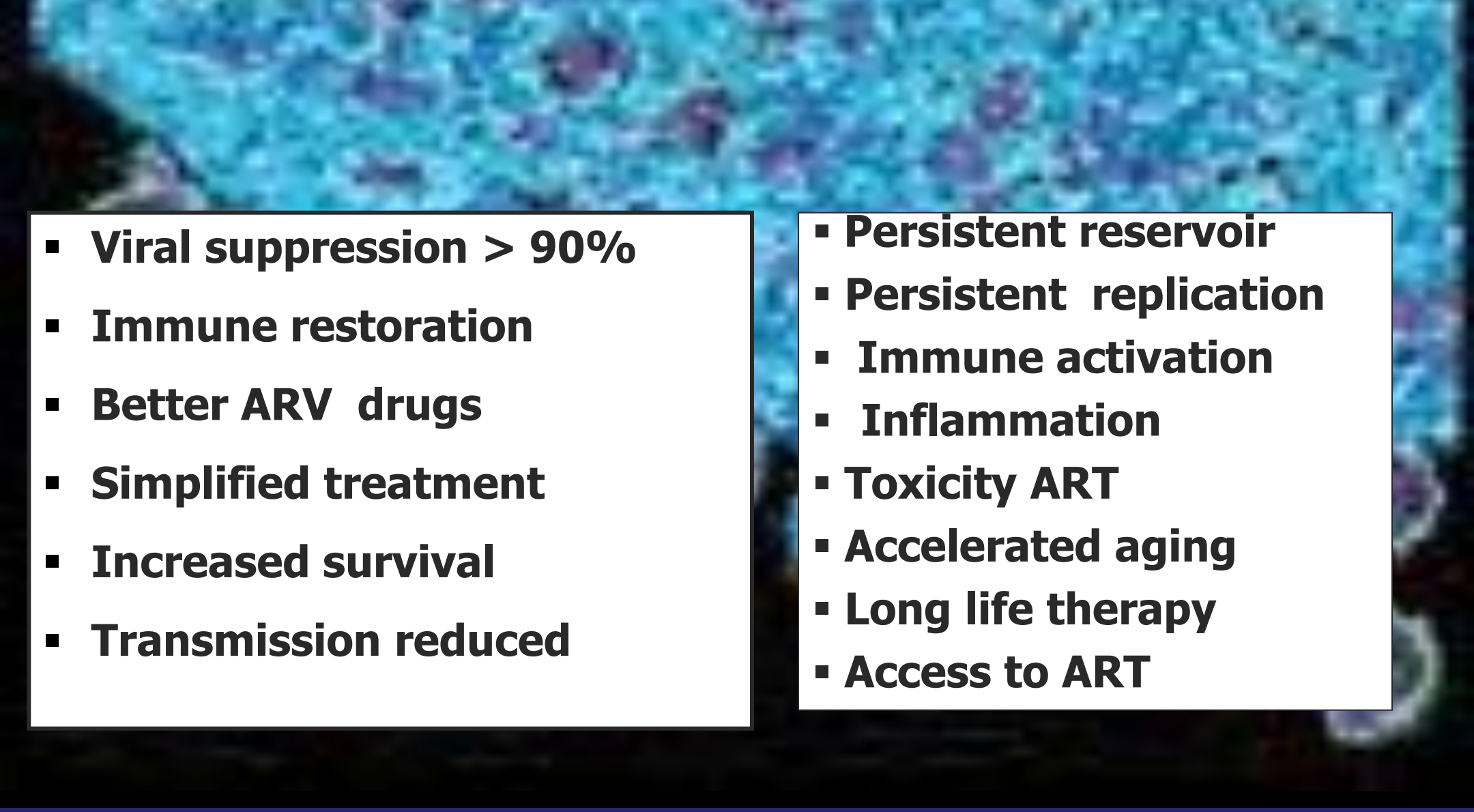
EACS Advanced course
AIX 2013

EACS
European
AIDS
Clinical
Society

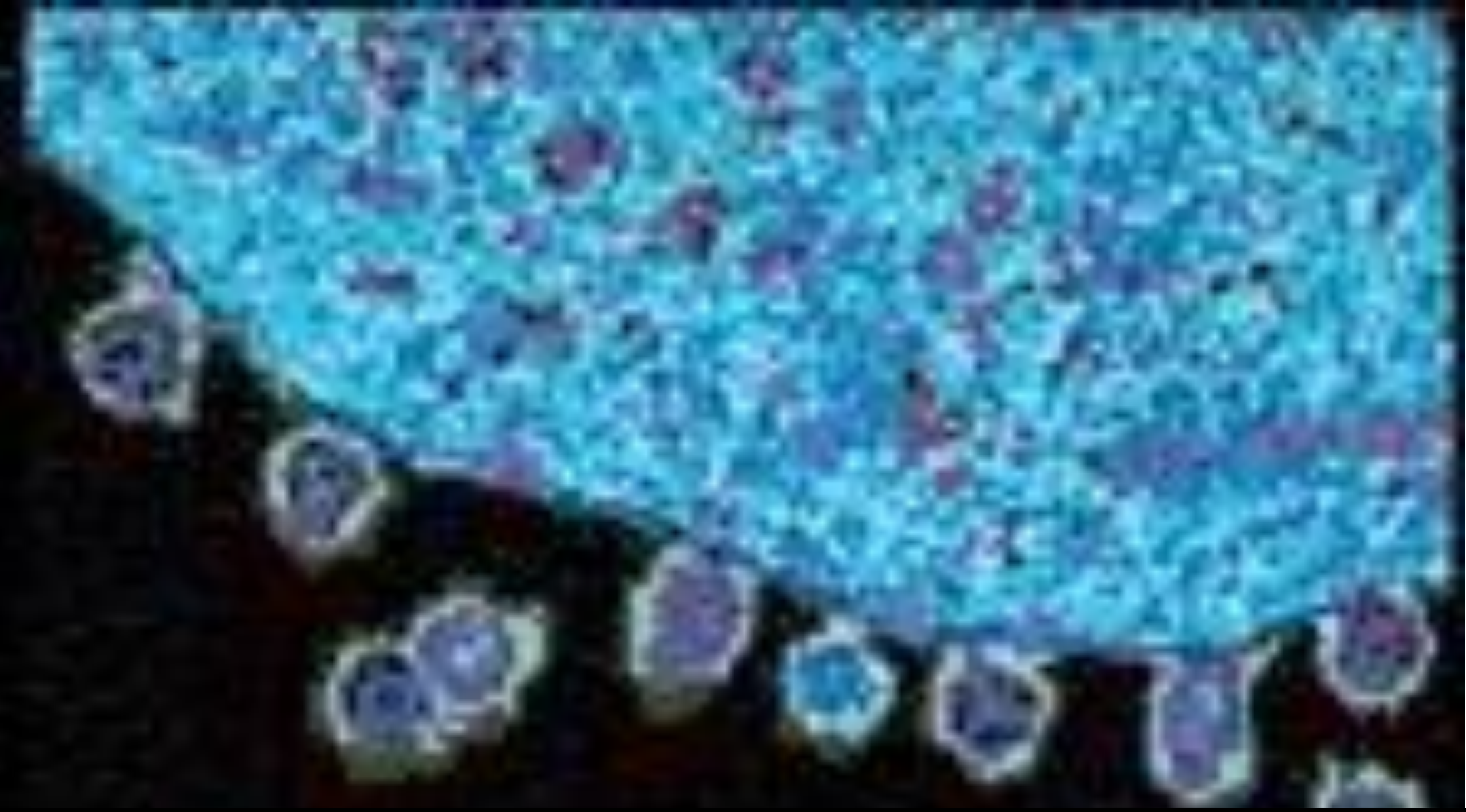
Antiretroviral Treatment Strategies

ART : A revolution
HIV : a chronic disease



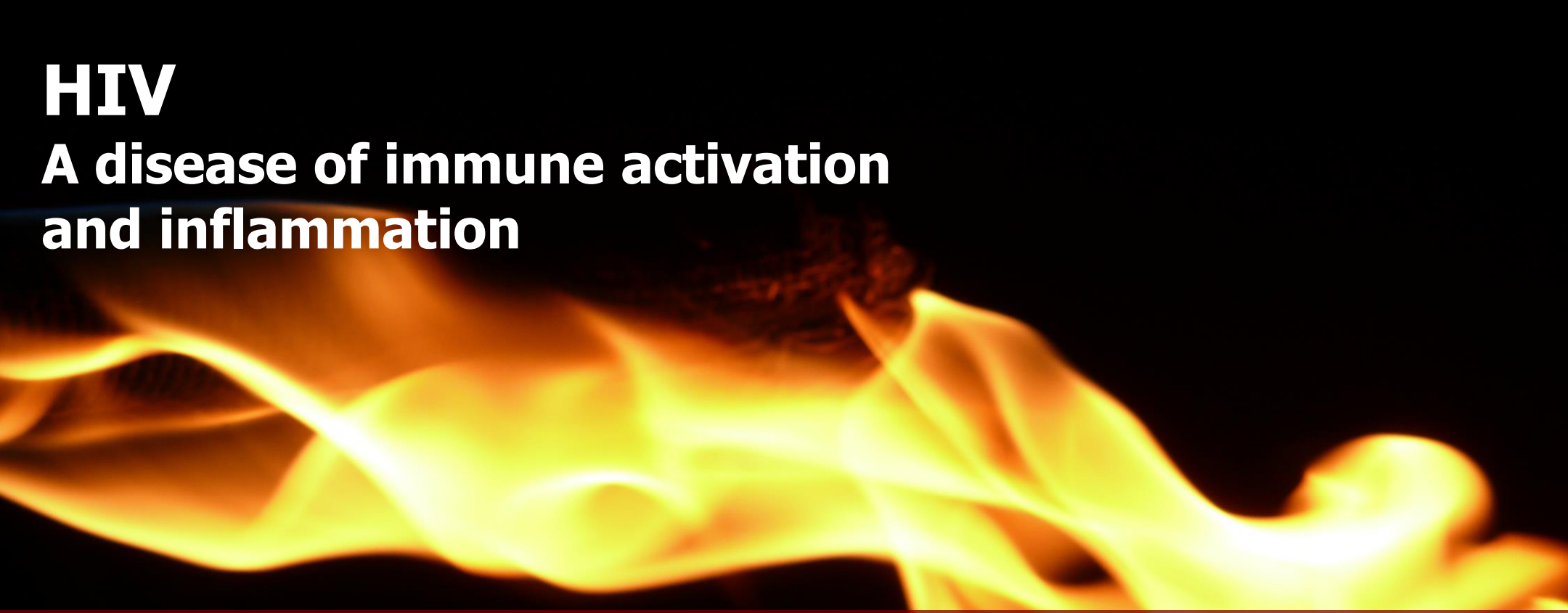


A success story of research
But a story far from being achieved



HIV Pathogenesis

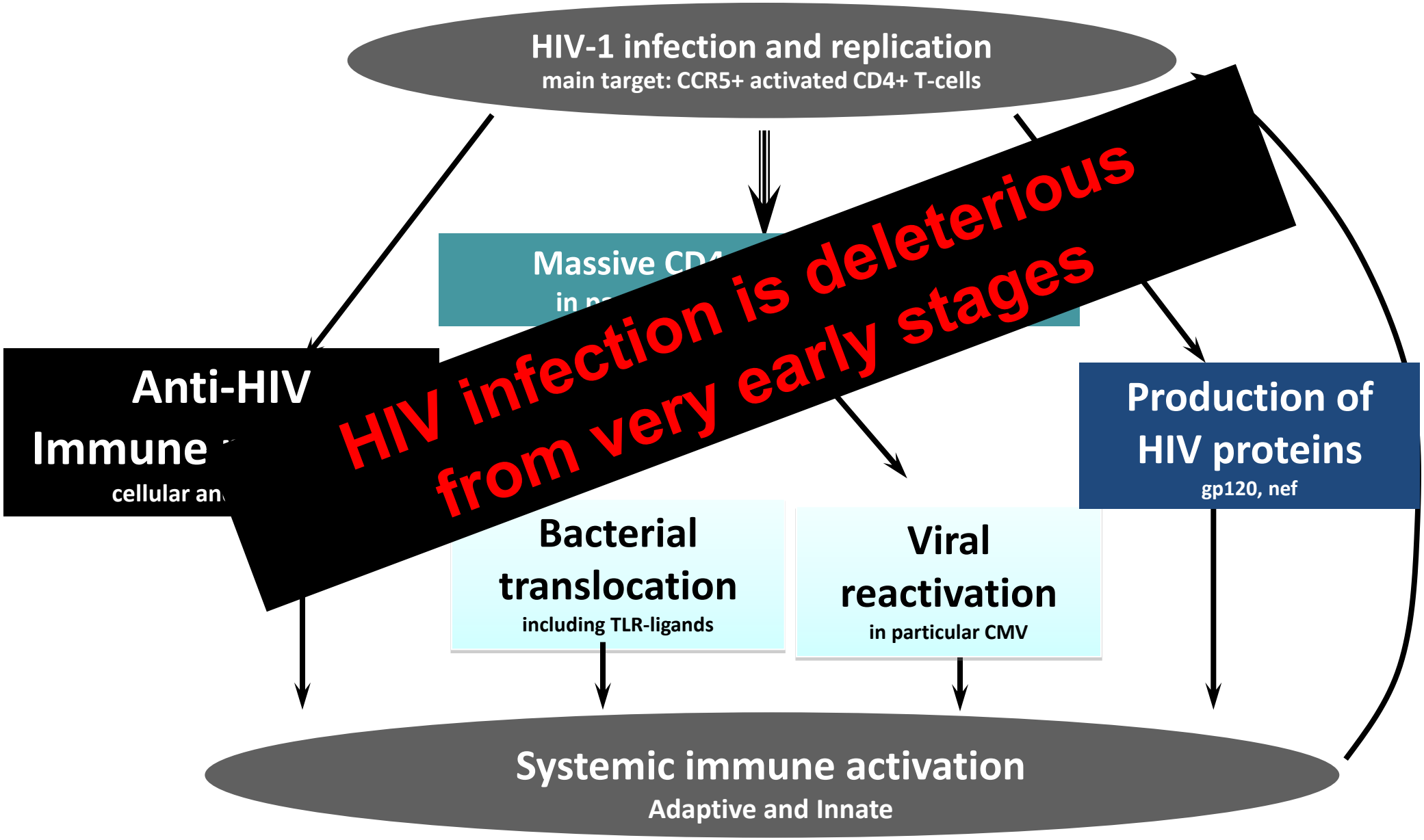
HIV
A disease of immune activation and inflammation



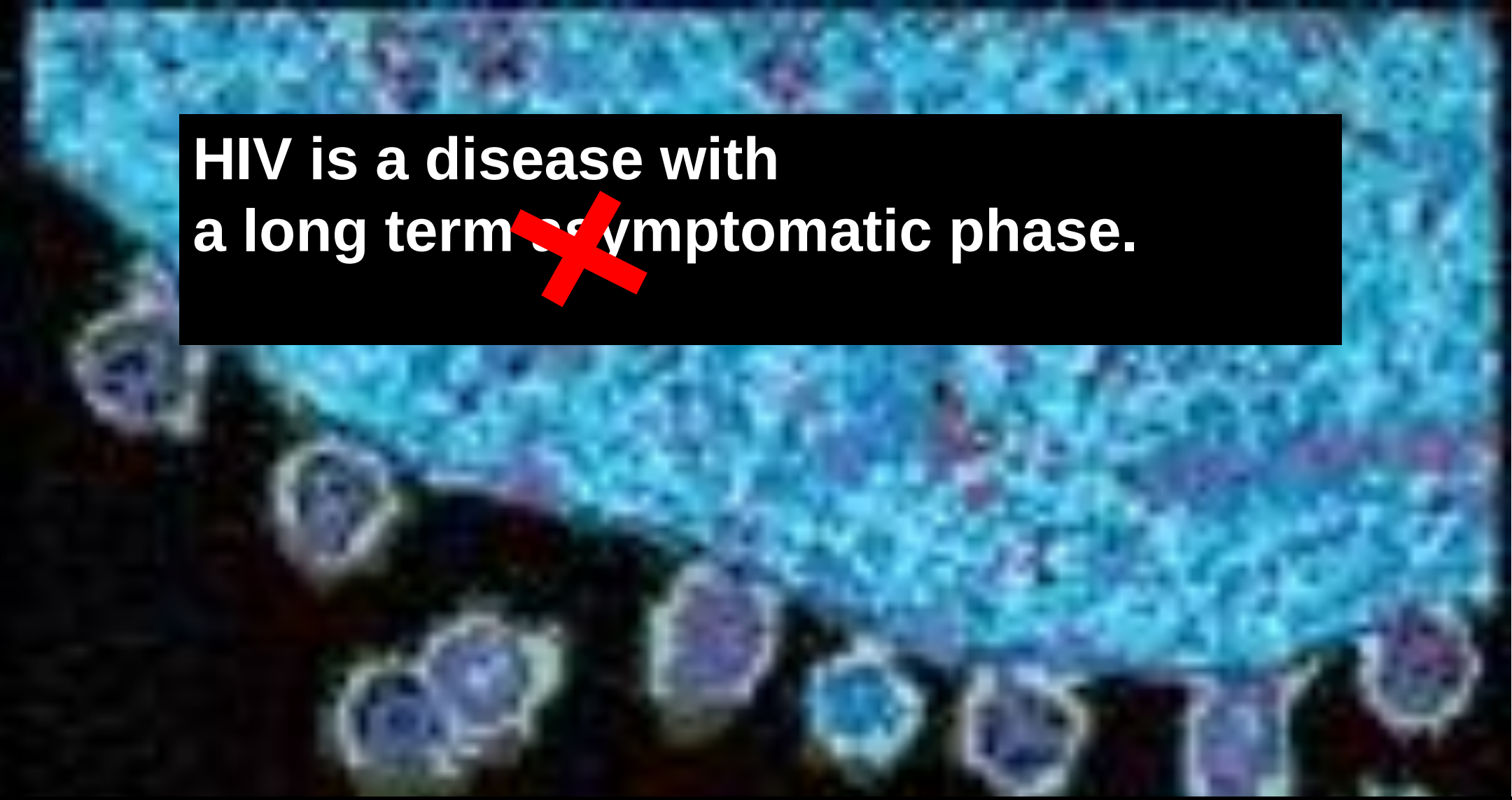
HIV replication induces immune activation
Immune activation induces inflammation
immune exhaustion
immune suppression
Inflammation induced comorbidities

Photo JDD

Immune activation and HIV replication

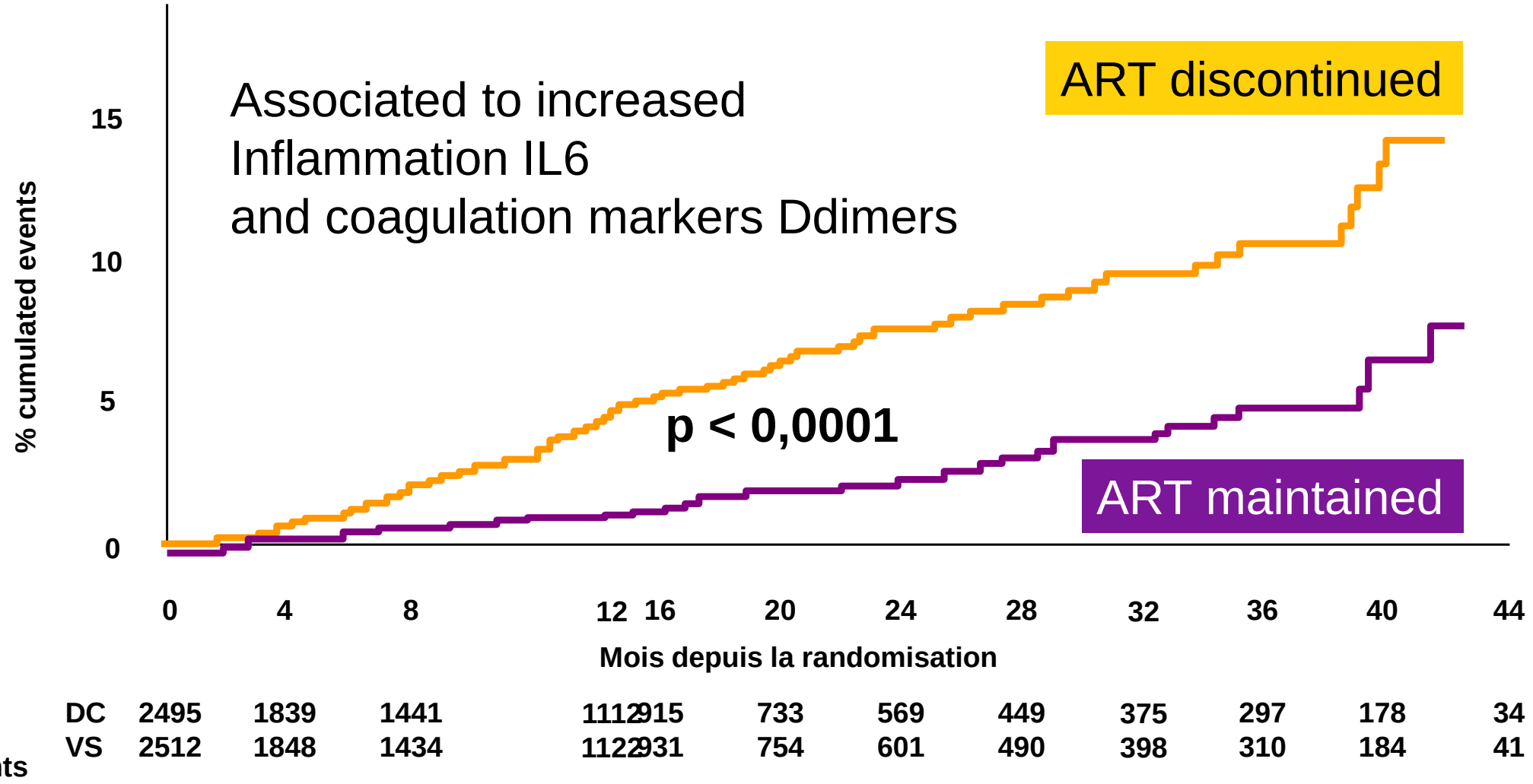


Appay et al, J Pathol 08



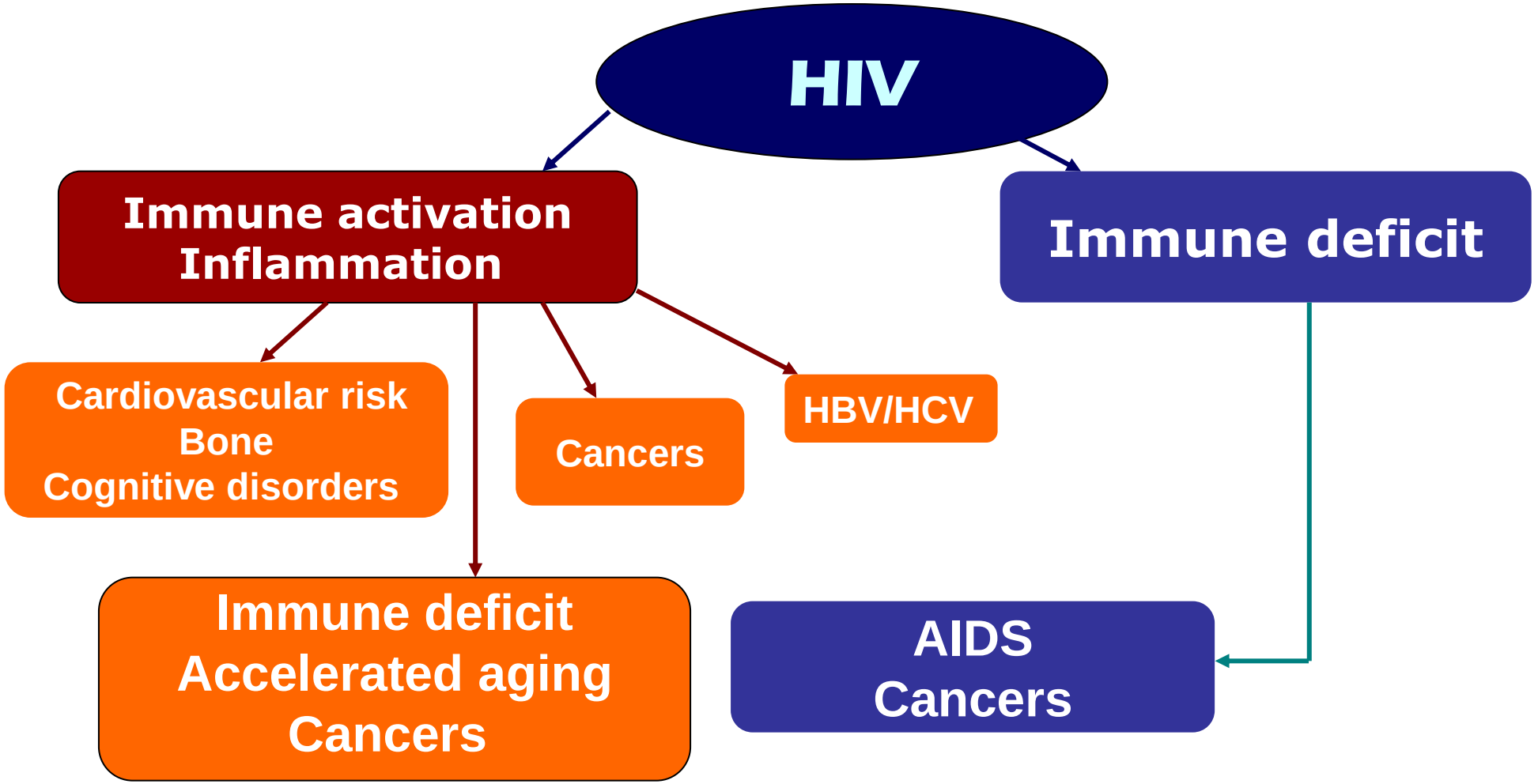
HIV infection is deleterious from very early stages

SMART HIV replication is associated to increased mortality and morbidity



El-Sadr W.,NEJM 2006,

Pathogenesis of HIV

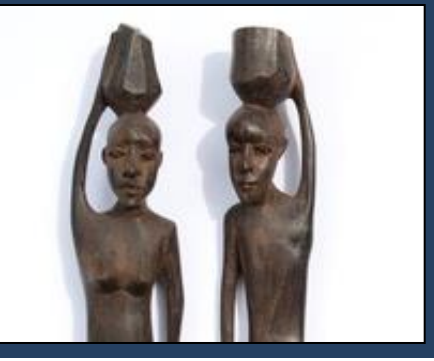


HIV is deleterious by immune suppression and activation

Why do we need to control HIV replication ?

- To prevent disease progression for every HIV infected individual
- To stop transmission between individuals

To control HIV pandemics



HPTN 052 : Transmission of HIV

Early treatment versus delayed treatment

1763 couples ; ART > 350 vs standard

HIV

- 39 cases of transmissions
- 28 related to HIV partner - 1 from immediate ART group

- 27 from differed group p= 0.0001

ART reduced by 96% the risk of transmission

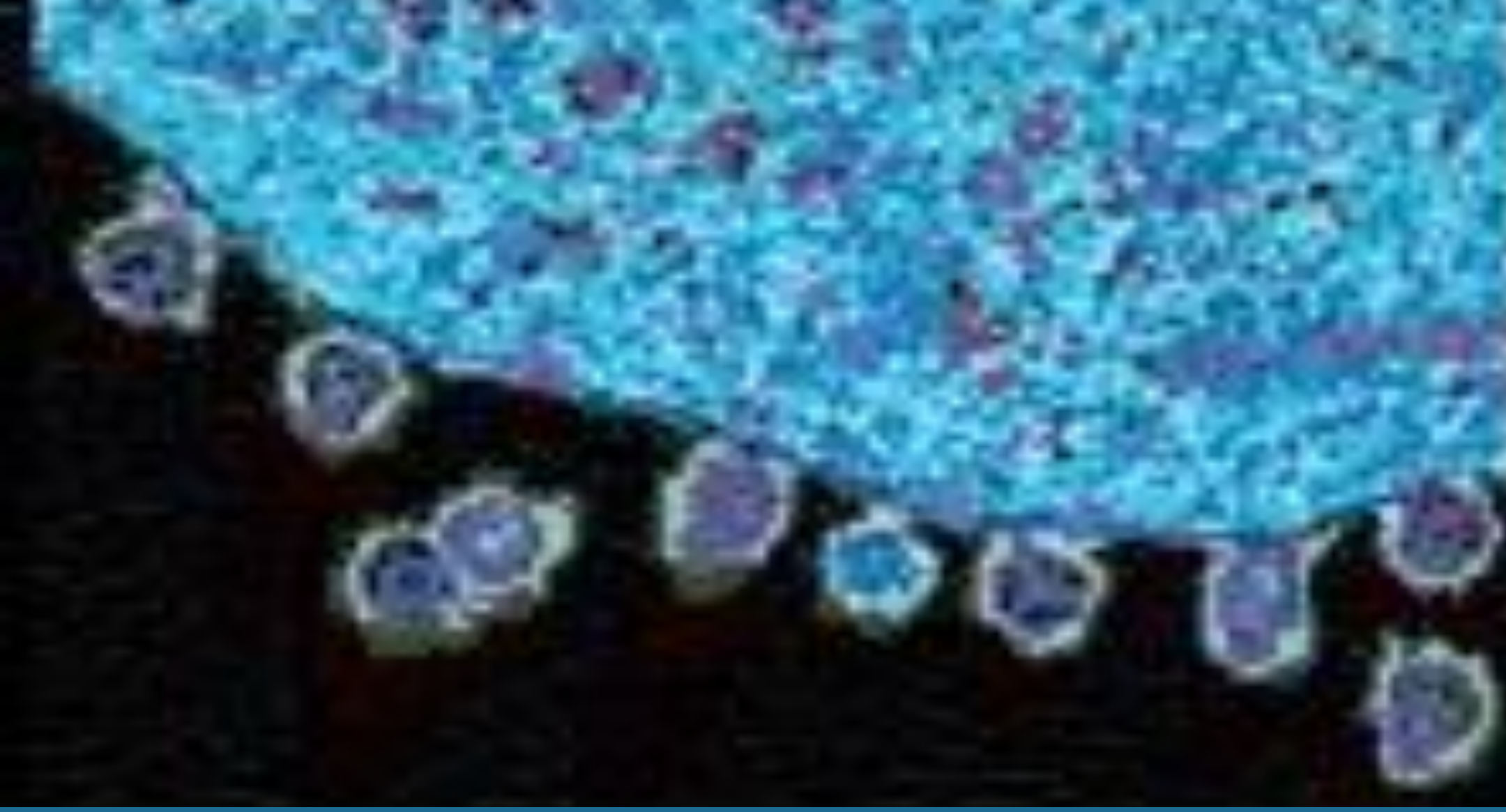
Opportunistic infections

20 extra-pulmonary TB cases

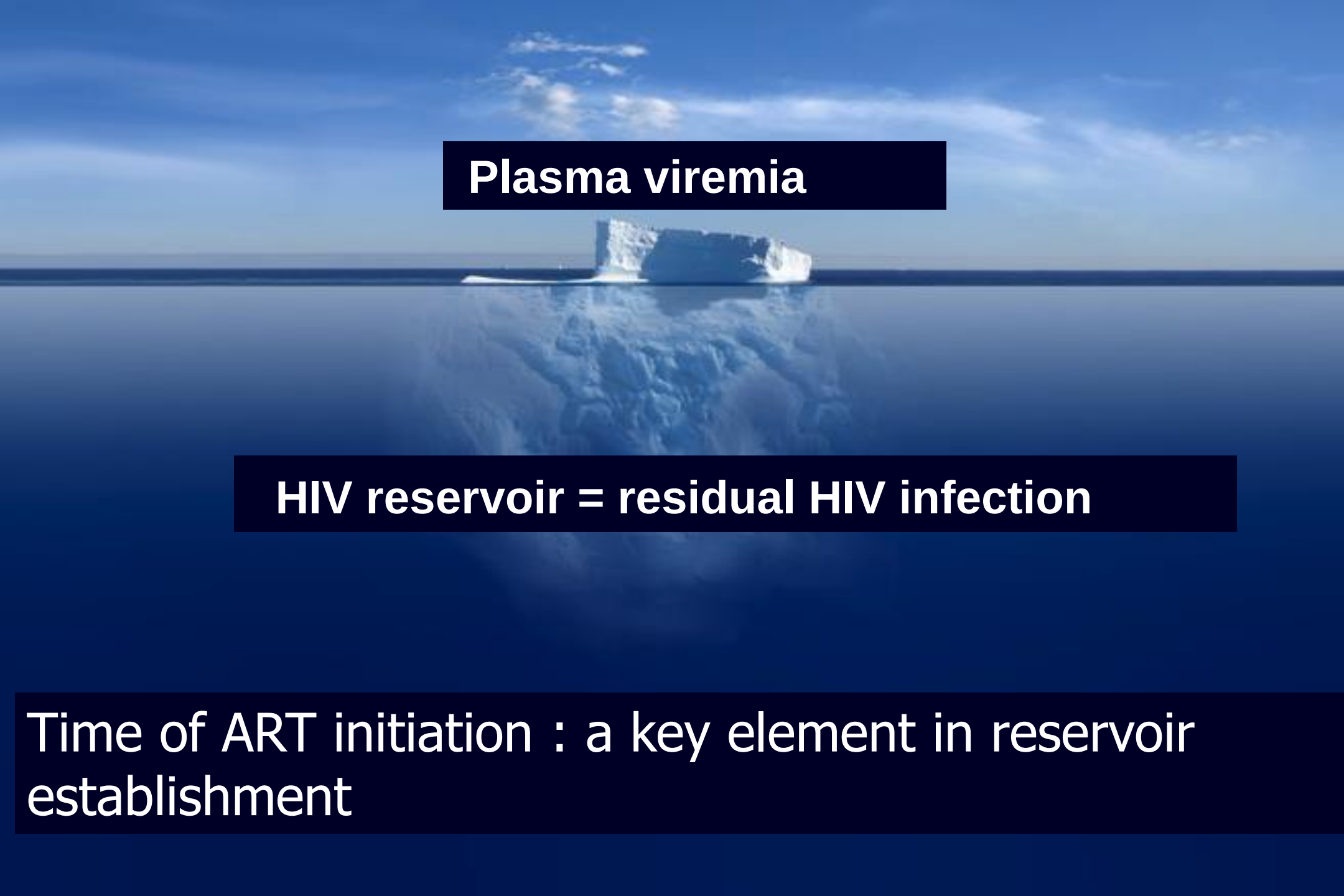
- 1 from the immédiat ART groupe

- 19 from differed group

Early ART reduces the risk of tuberculosis

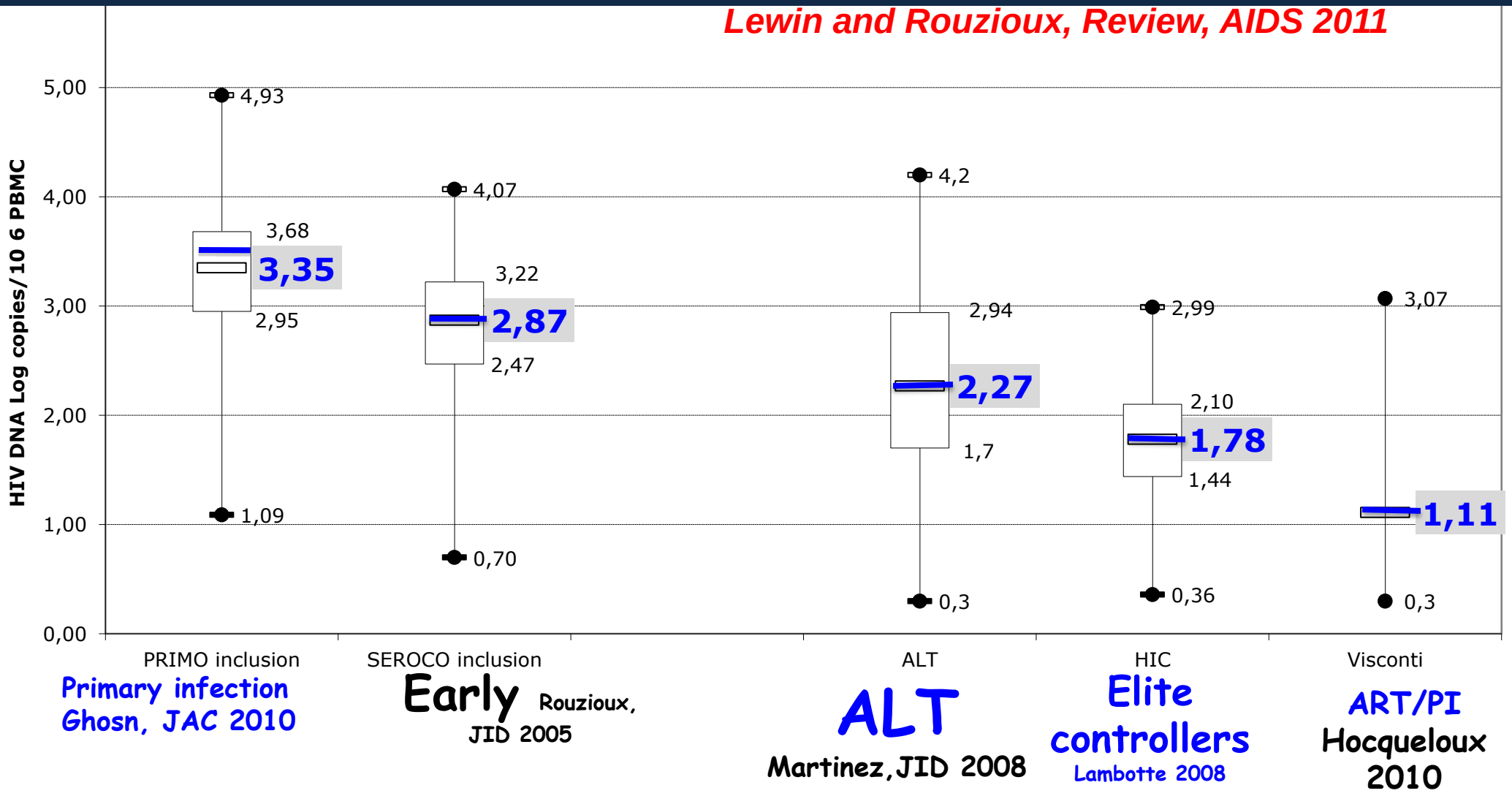


Reservoir Residual viremia and immune activation



Time of ART initiation : a key element in reservoir establishment

HIV reservoirs differs from patients groups
The ANRS Cohorts



Primary infection and reservoir dynamics

- 68 patients :initiating ART in 2 à 3 days post contamination

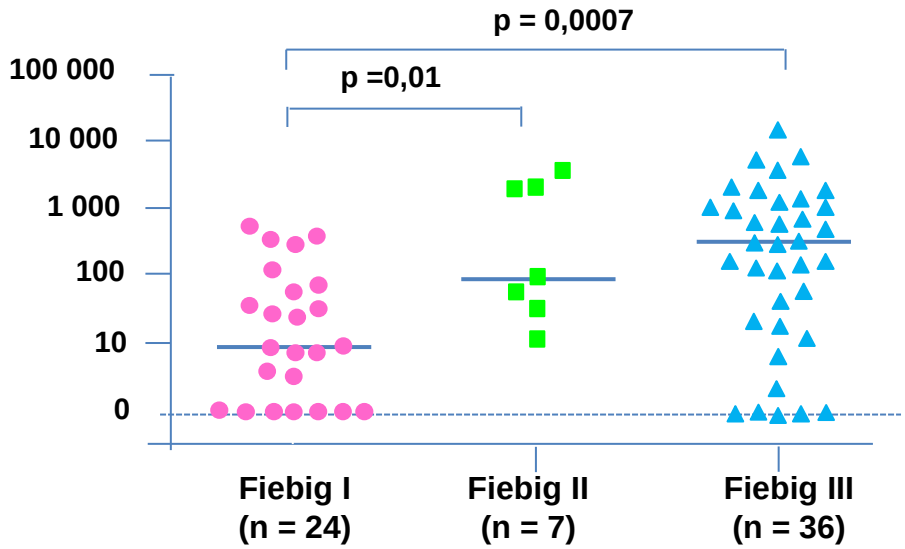
Prior ART

Total HIV DNA lower in Fiebig I stage

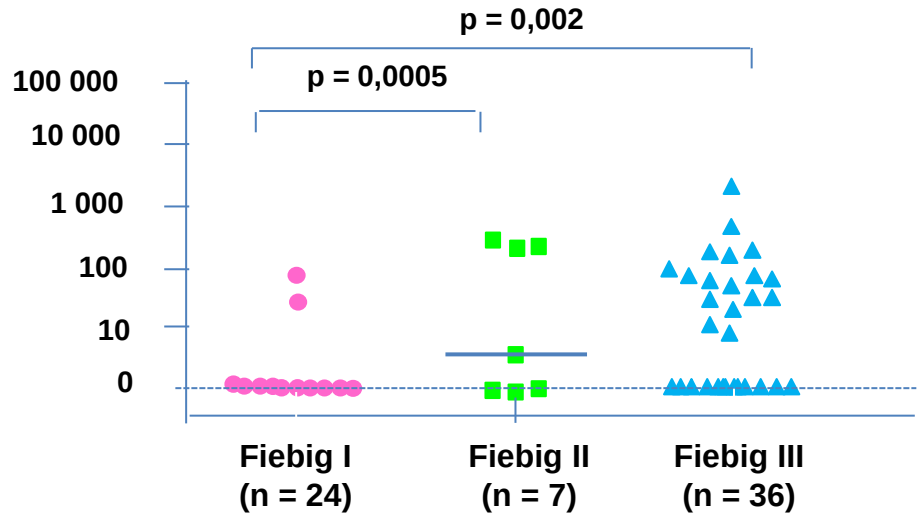
HIV DNA total undetectable in 22/24 (92 %) Fiebig I

- **Fiebig I: RNA+, p24-, 3° G ELISA neg**
- **Fiebig II: RNA+, p24+, 3G ELISA neg**
- **Fiebig III: 3rd-gen ELISA+, WB neg**

Total HIV DNA (c/10^6 PBMC)



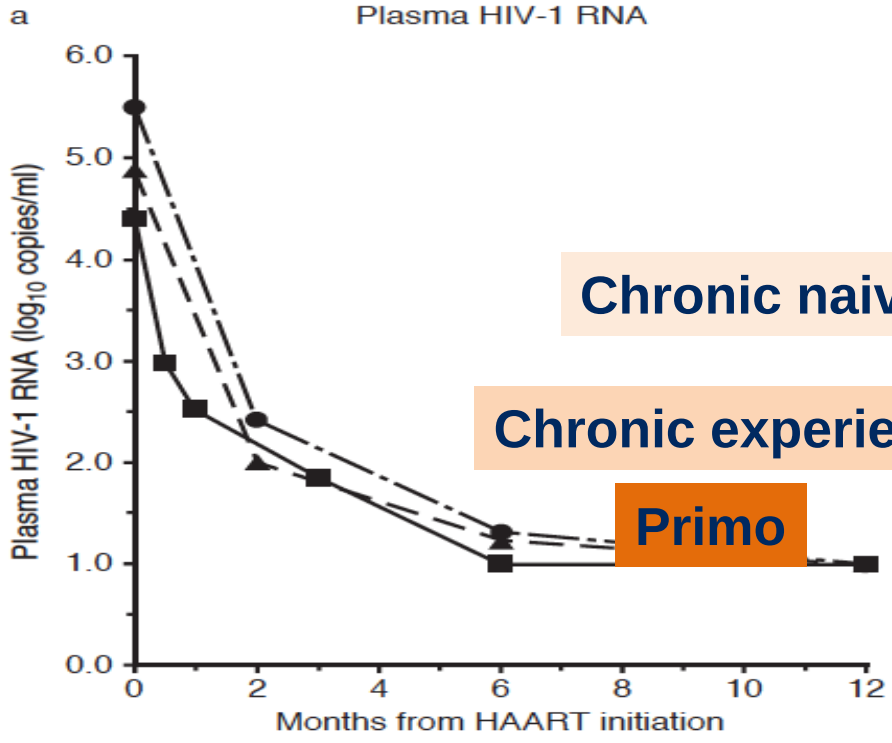
Integrated ADN VIH (c/10^6 PBMC)



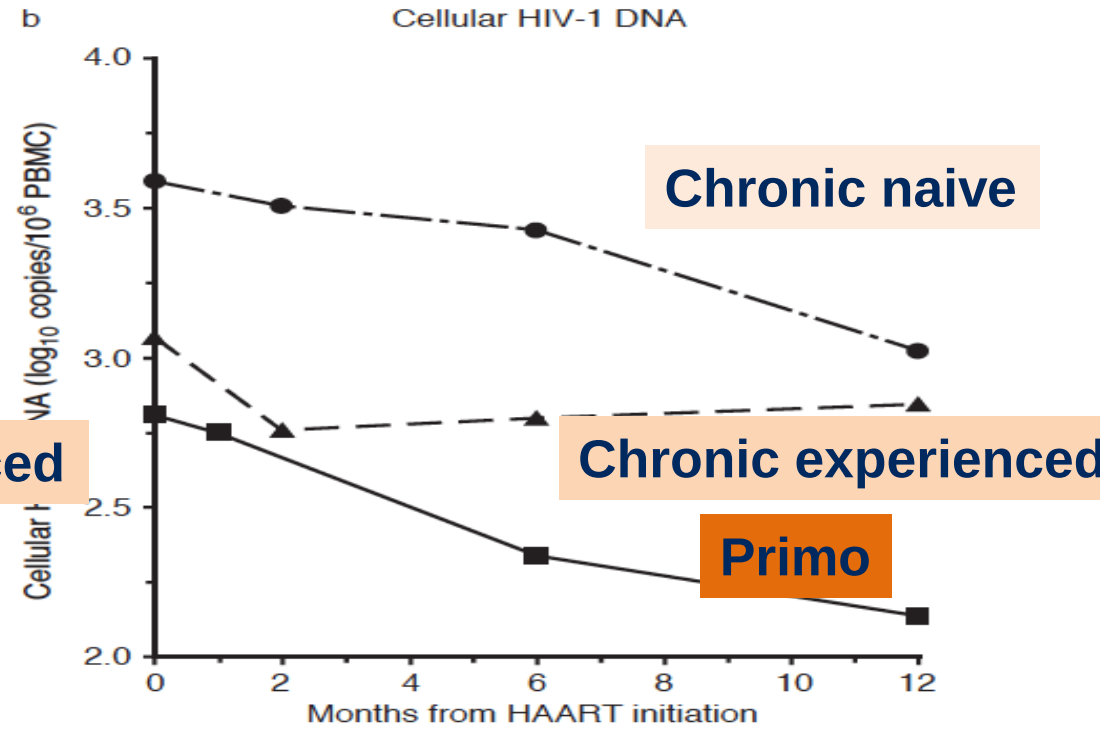
	Fiebig I (n = 24)	Fiebig II (n = 7)	Fiebig III (n = 36)
Not detectable	92 %	29 %	53 %

Ananworanich J, CROI 2013, Abs. 47

Evolution of HIV RNA and HIV DNA in patients following ART initiation



IQR	D0	M6	M12
●	4.7–5.7	1.0–1.6	1.0–1.(
▲	4.1–5.2	1.0–1.7	1.0–1.9
■	3.5–5.8	1.0–1.3	1.0–1.5



IQR	D0	M6	M12
●	2.9–3.9	2.5–3.6	2.5–3.4
▲	2.8–3.3	2.4–3.0	2.2–3.0
■	2.6–3.3	2.1–2.7	1.8–2.4

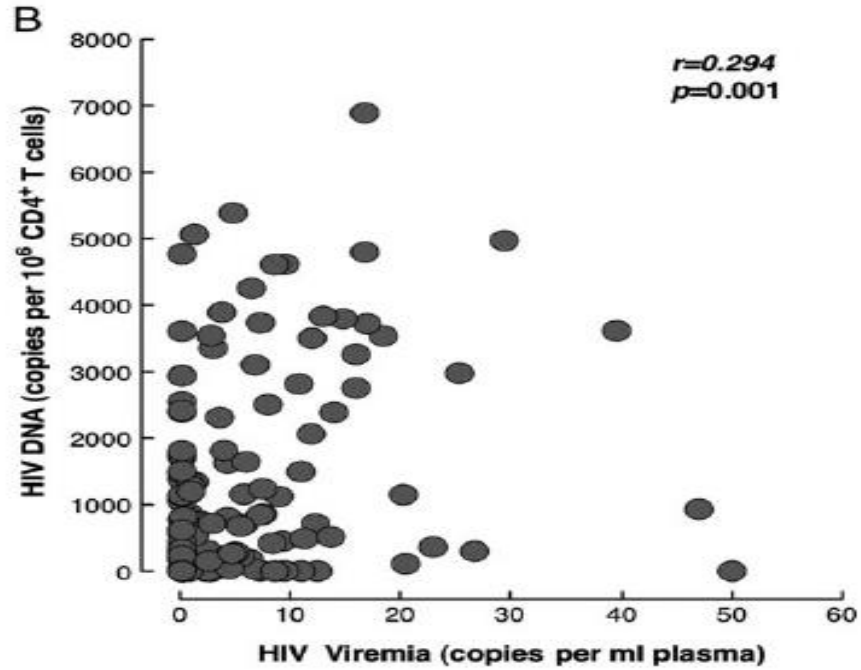
Ngo-Giang-Huong et al. AIDS. 15(6):665-673, April 13, 2001.

Relationship Between Residual Plasma Viremia and the Size of HIV Proviral DNA Reservoirs in Infected Individuals Receiving Effective Antiretroviral Therapy

Tae-Wook Chun,[1] Danielle Murray,[1] J. Shawn Justement,[1] Claire W. Hallahan,[2] Susan Moir,[1] Colin Kovacs,[3] and Anthony S. Fauci[1]

- **127 ART treated patients**
- **Med Duration : 6.5 y**
- **CD4 med : 580 /mm3**
- **HIV RNA (taqman)< 50 cp : 100%**
- **CD4/CD8 : 0.8**
- **HIV RNA us < 1 cp/ml: 37%**
- **CV médiane: 2.6 cp/ml**

- **Correlation between residual HIV RNA and CD4/CD8 and DNA**
- **No association between residual HIV RNA and activation markers (CRP, IL6, sTNFR1, CD38)**



Goals of Antiretroviral Therapy

- Reduce HIV-associated morbidity and prolong duration and quality of survival
- Restore and preserve immunologic function: > 500 CD4 ; normalize CD4/CD8
- Maximally and durably suppress HIV-1 RNA
  - Persistently below level of detection (< 20-75 copies/mL, depending on the assay used)
    - Isolated “blips” not uncommon in successfully treated patients and not thought to predict virologic failure
- Prevent HIV transmission
- Decrease maximally reservoirs

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. March 2012.

Antiretroviral therapy

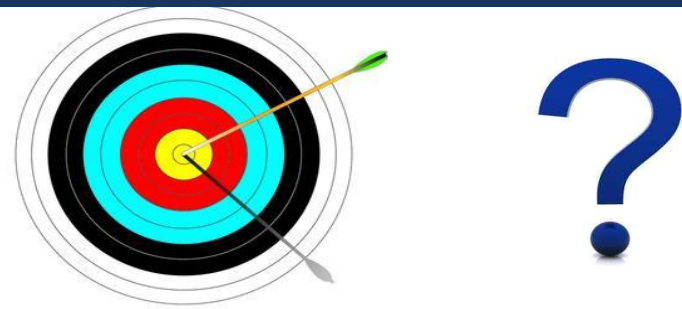
- A highly effective therapy
- A highly effective prevention

…A « double hit strategy »

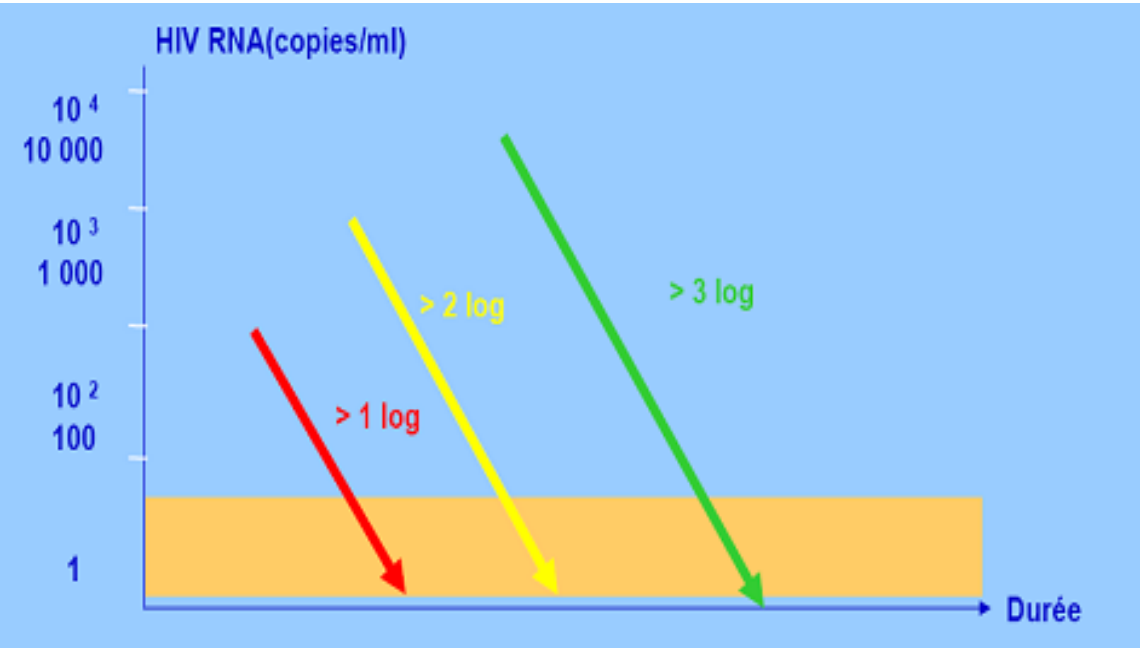
Viral replication has to maximally suppressed

Maximal suppression of HIV required to

- Prevent disease progression
- Decrease immune activation
- Prevent resistance



Target below detection



- **↙ 200 cp/ml : clinical and immunological**
- **↙ 50 cp/ml : resistance**
- **Tomorrow : 1 cp ?**

Which benefits

on reservoirs and activation ?

Control of viral replication has to be maximal

Individual level

Health

– Stop disease progression
– Optimize immune restoration
– Prevent resistance
– Optimize survival

Daily normal life

- to have children
- Maximal reduction of sexual transmission risk

Population level

- Reduced transmission
progressive control
and decrease of epidemics
- Decrease in tuberculosis
- Longer durability of efficacy of first lines ART
-Decrease of global cost of HIV


Universe : Big Bang day 0
13.82 billion years ago
When to start antiretroviral therapy ?