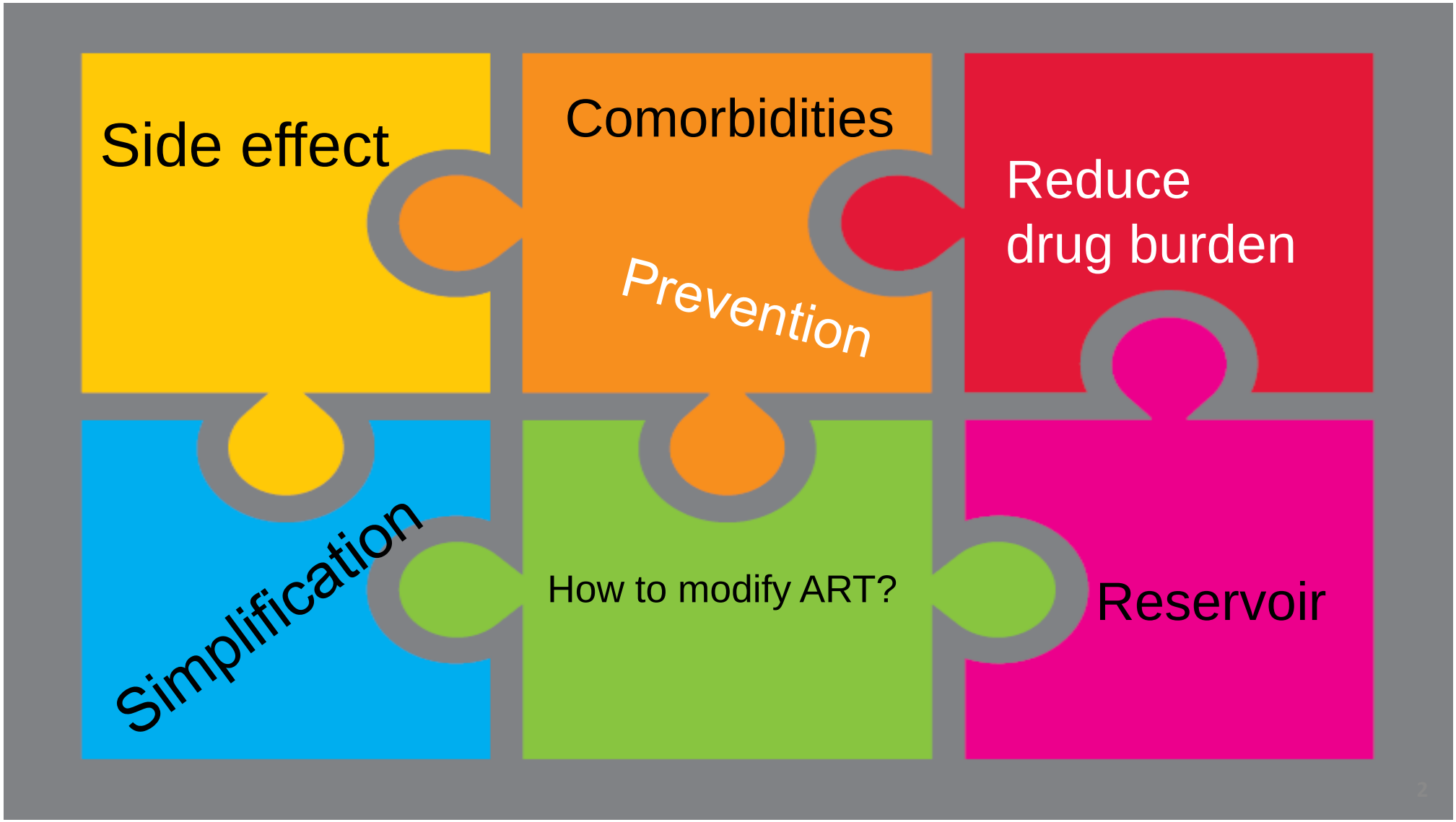
How to best manage HIV patient ?

1 Treatment Failure

2 Treatment success

HIV therapy = a long life therapy

Why do we want to change a suppressive ART ?



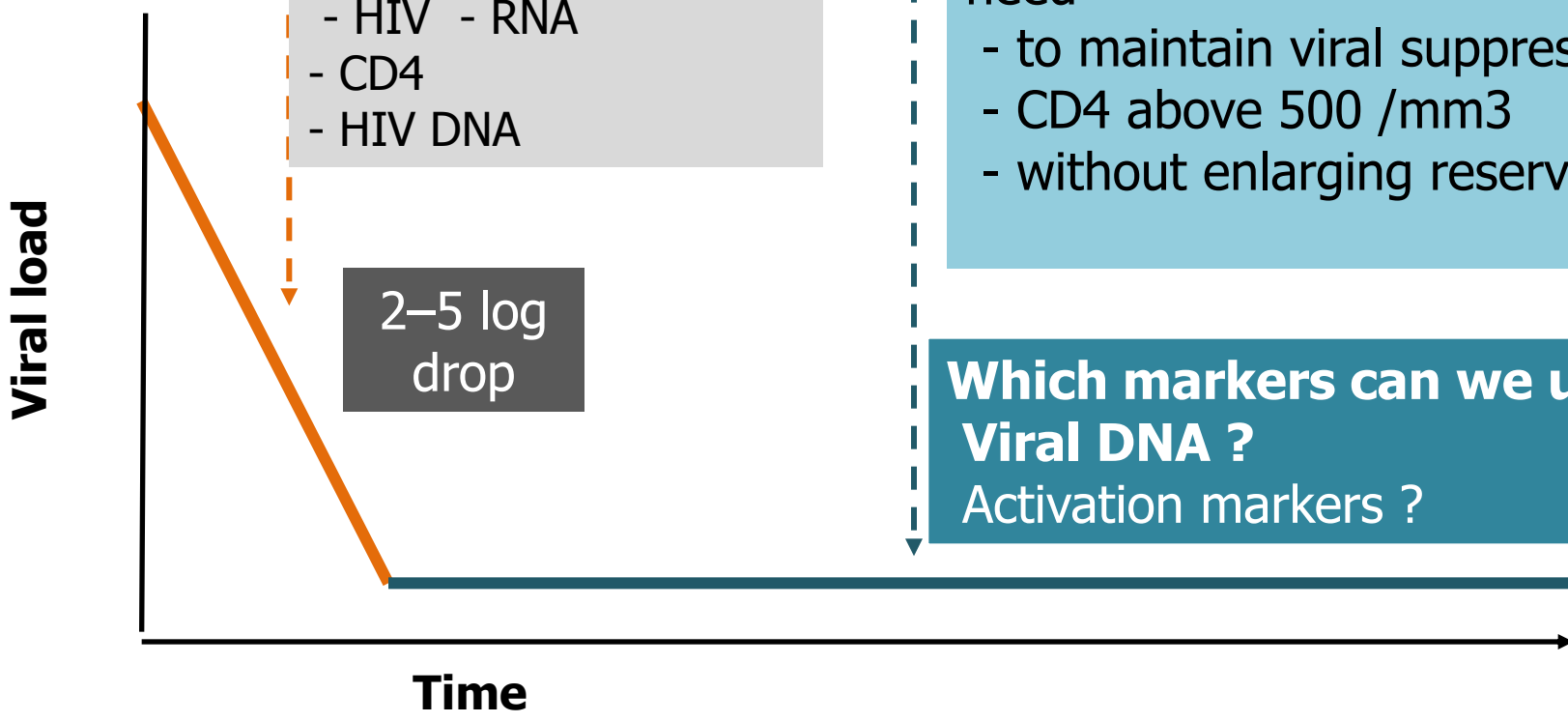
Concepts in Induction Maintenance ART

Induction

Maintenance strategy

Nb drugs required
Depending on
- HIV - RNA
- CD4
- HIV DNA

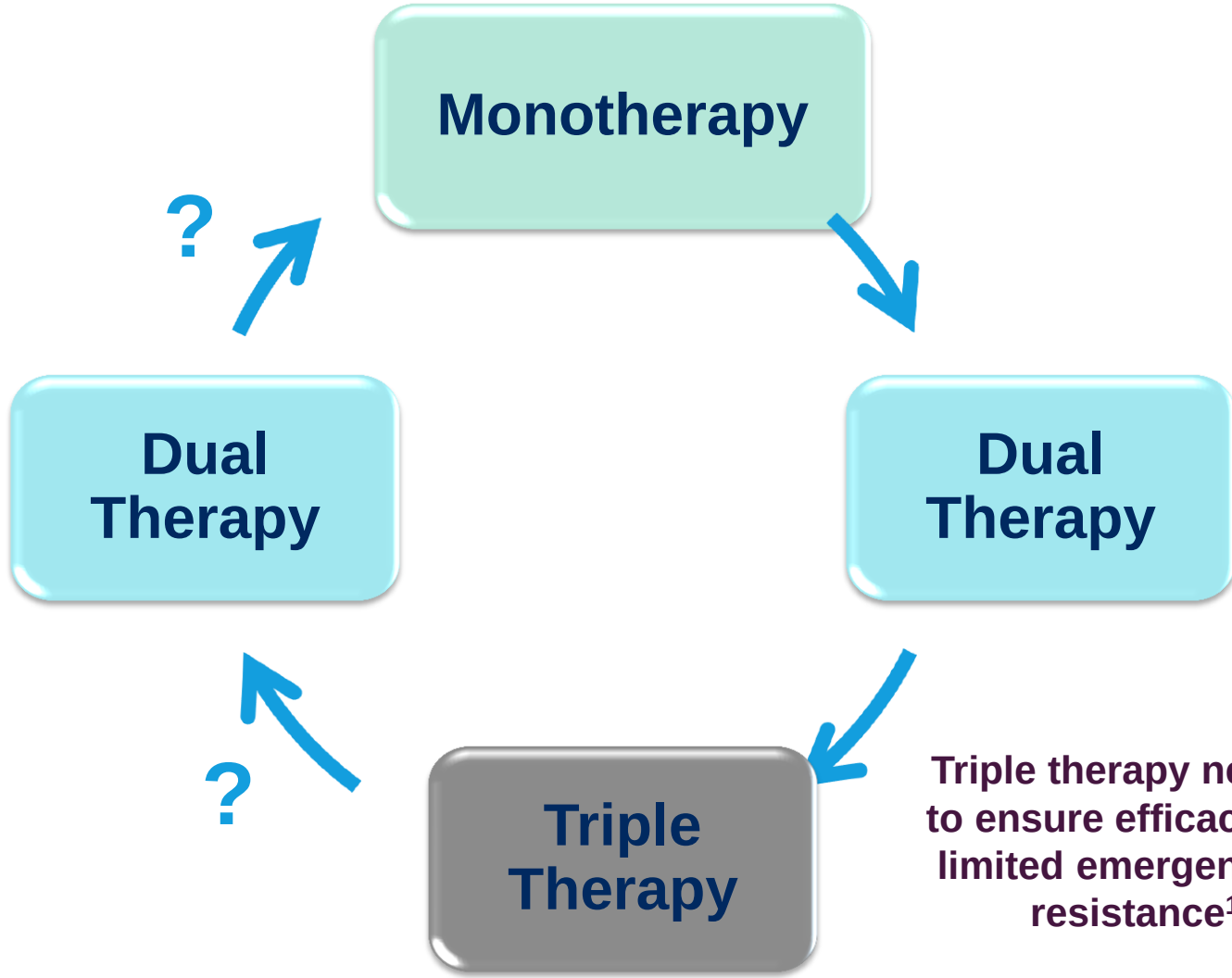
Which antiviral potency do we need
- to maintain viral suppression
- CD4 above 500 /mm3
- without enlarging reservoir ?



Which markers can we use ?
Viral DNA ?
Activation markers ?

Simplication with drug burden reduction

Newer efficacious and well tolerated ARVs with higher potency and genetic barrier to resistance



Triple therapy needed to ensure efficacy and limited emergence of resistance[1]

Drugs with relatively low potency and genetic barrier to resistance

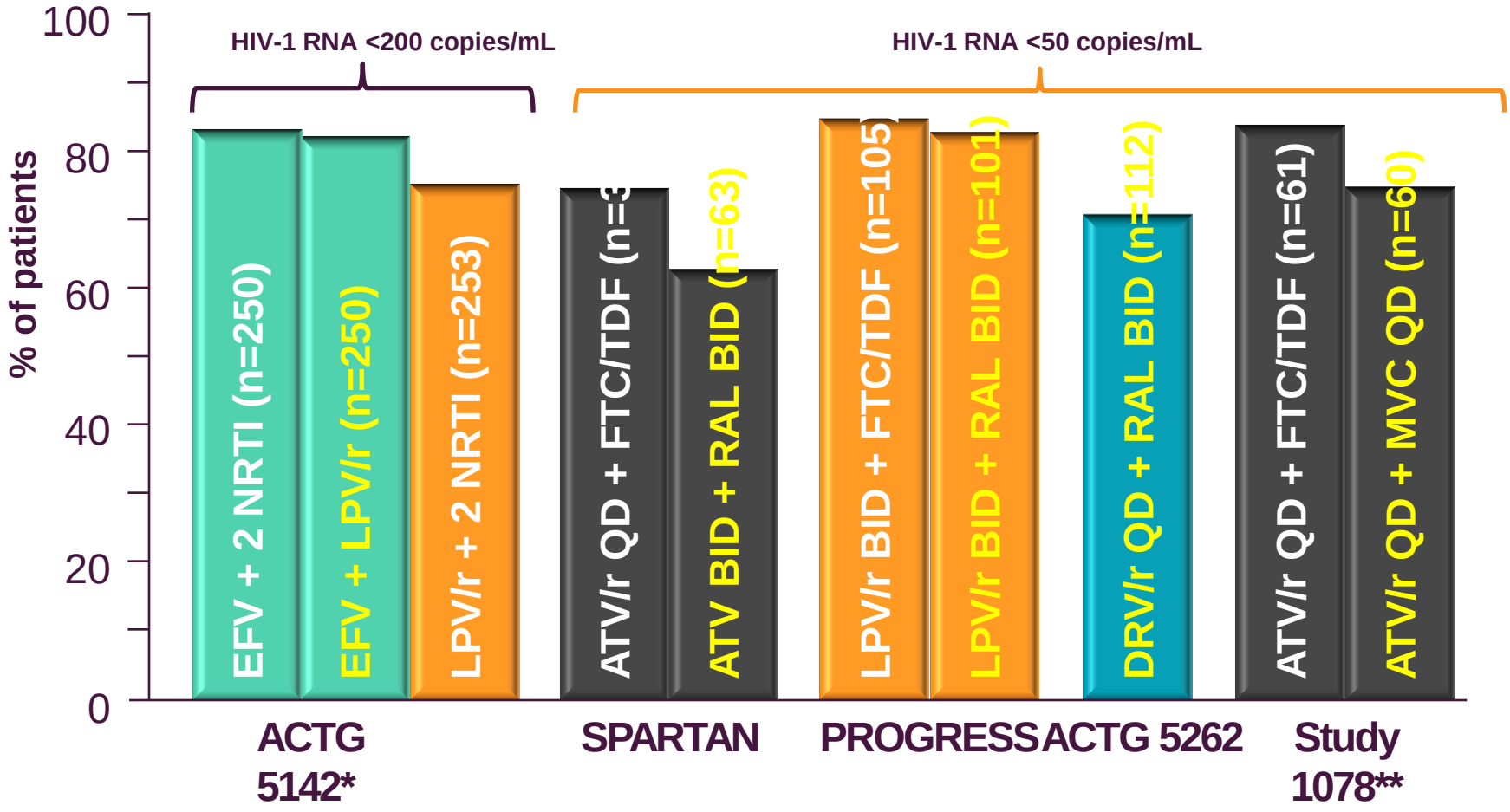
1. Perez-Valero I, et al. J Antimicrob Chemother. 2011;66:1954–62.

Switching therapy

- **Objective : maintain viral suppression**
- Decrease drug burden
- Decrease/ prevent toxicity
- Simple regimen
- Robust regimen

- Reconstitutes ART and resistance history
- The switched regimen has to include potent and robust drugs
- Do not let a drug in a position of functionnal monotherapy
- Do not keep resistant drugs that cumulates toxicity and cost

Modern dual-therapy studies : 48-week results



Created from 1. Portsmouth S, et al. AIDS 2011, Rome, Italy. Oral presentation TUAB0103; 2. Riddler SA, et al. NEJM 2008;358:2095–106; 3. Kozal MJ, et al. HIV Clin Trials 2012;13:119–30; 4. Reynes J, et al AIDS Res Hum Retro. 2012 Aug 3. [Epub ahead of print]. DOI: 10.1089/aid.2011.0275; 5. Taiwo B, et al. AIDS 2011;25:2113–22; 6. Mills A, et al. AIDS 2012, Washington, USA. Oral Presentation TUAB0102.

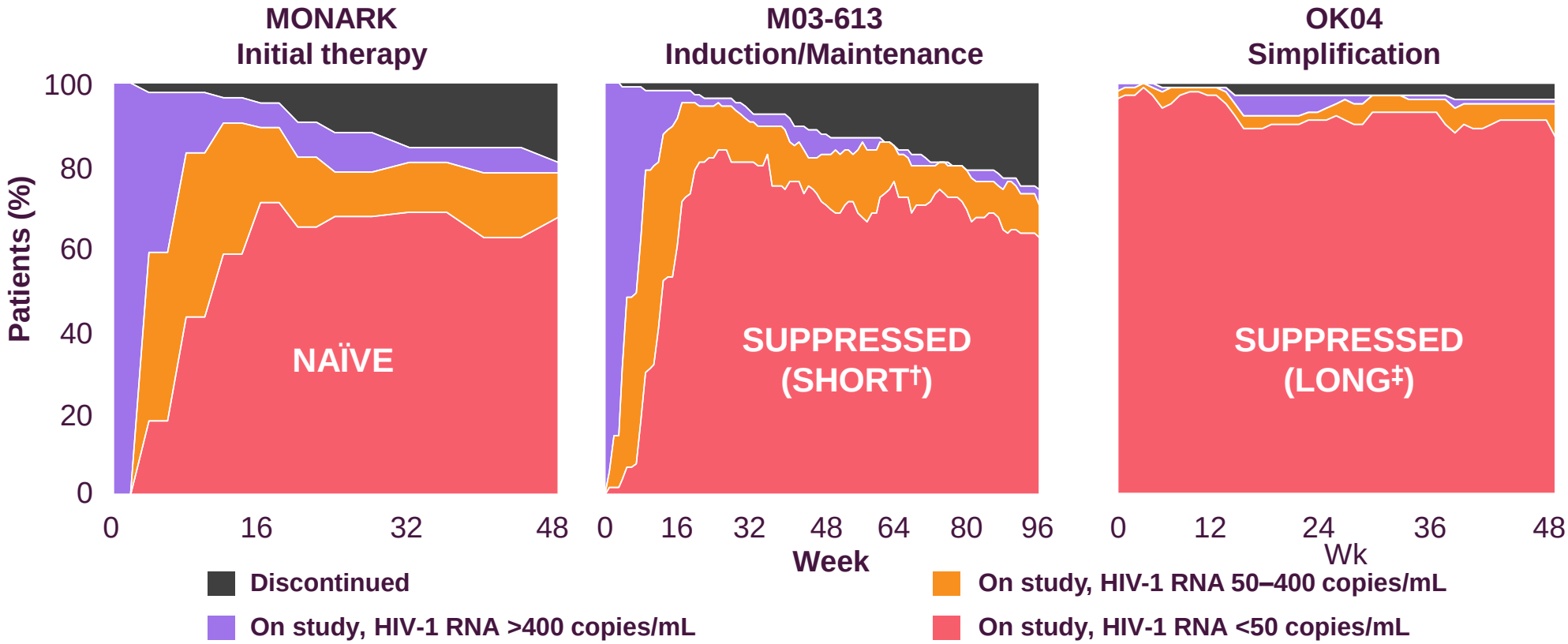
Dual therapy

Summary of safety outcomes in studies of dual-therapies in ARV-naïve patients*

Study	Regimen	Follow up	Lipids	Renal	Bone	Other
ACTG 5142[1]	LPV/r + EFV	96 weeks	Elevated	Not reported	Not reported	-
PROGRESS[2]	LPV/r + RAL	96 weeks	Elevated	Improved	Improved	CPK ↑
SPARTAN[3]	ATV† + RAL	96 weeks	Neutral	Not reported	Not reported	Bilirubin ↑
ACTG 5262[4]	DRV/r + RAL	48 weeks	Elevated	Not reported	Not reported	-
Study 1078[5,6]	ATV/r + MVC	96 weeks	Not reported	Not reported	Improved	Bilirubin ↑

PI/r monotherapy

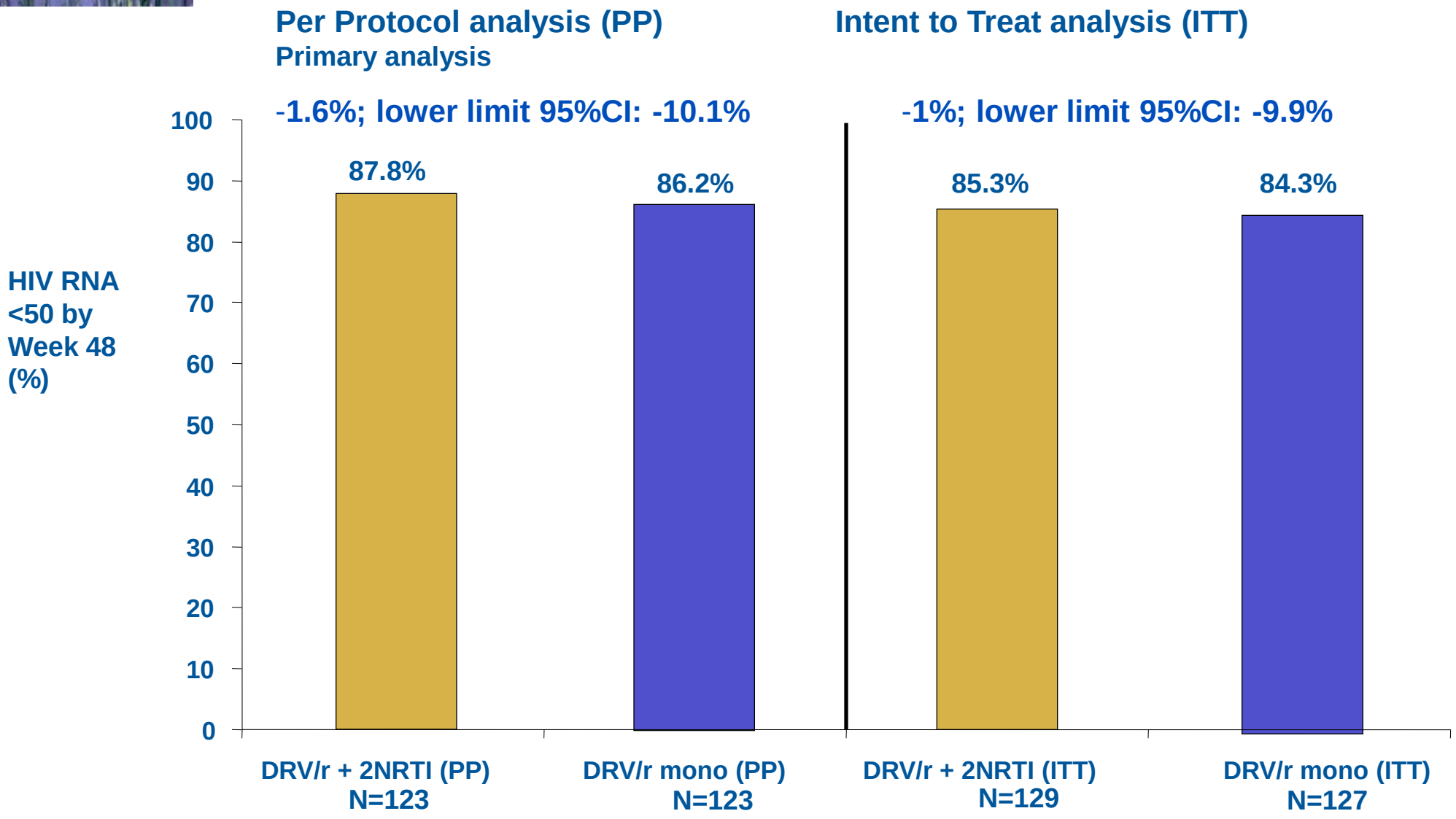
Monotherapy with LPV/r*[1]



*Boosted PI monotherapy is an off-label approach.
†Short-term suppression: ≤24 weeks;[2] ‡Long-term suppression: >6 months.[3]

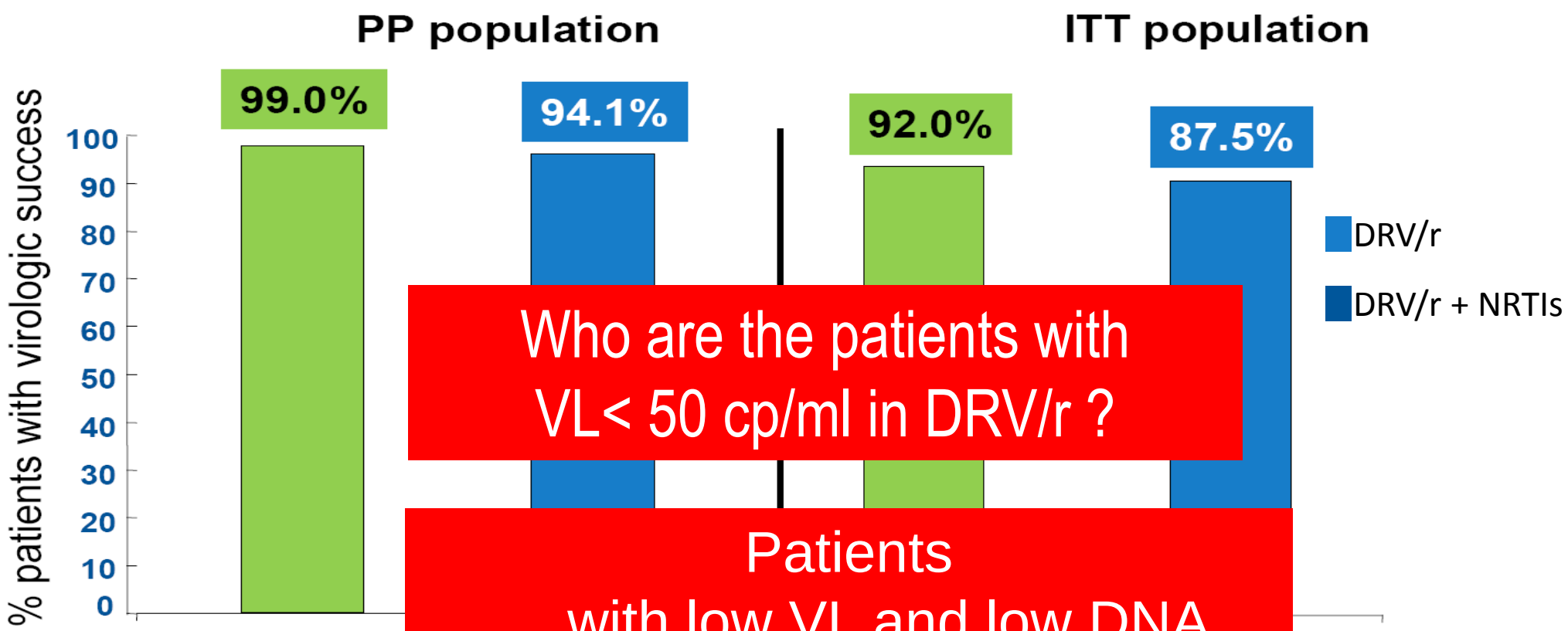
Adapted from 1. Arribas JR, EACS 2009, Cologne, Germany. Oral Presentation; 2. Cameron WD, et al. J Infect Dis. 2008;198:2234–40; 3. Arribas JR, et al. JAIDS 2005;40:280–7.

MONET: Primary Efficacy Analysis: HIV RNA <50 copies/mL at Week 48



J. Arribas et al, AIDS 2010

MONOI Primary Endpoint W48



Who are the patients with VL< 50 cp/ml in DRV/r ?

Patients with low VL and low DNA

Response	Difference (Lower limit CI)
Rx success (PP, n=204))	- 4.9% (- 9%)
Rx success (ITT, n=225)	- 4.5% (-11%)

-9% > -10% → mono DRV/r non inferior to DRV/r + 2 NRTIs

-11% < -10% → failure to demonstrate non-inferiority

ENCORE1: 400-mg EFV Noninferior to 600-mg EFV With TDF/FTC for Initial ART

- **Randomized, double-blind, placebo-controlled, noninferiority phase III trial**
  - **Part of ongoing effort to identify ARVs effective at lower doses (and cost)**

Stratified by clinical site and HIV-1 RNA at screening (< 100,000 or ≥ 100,000 copies/mL)

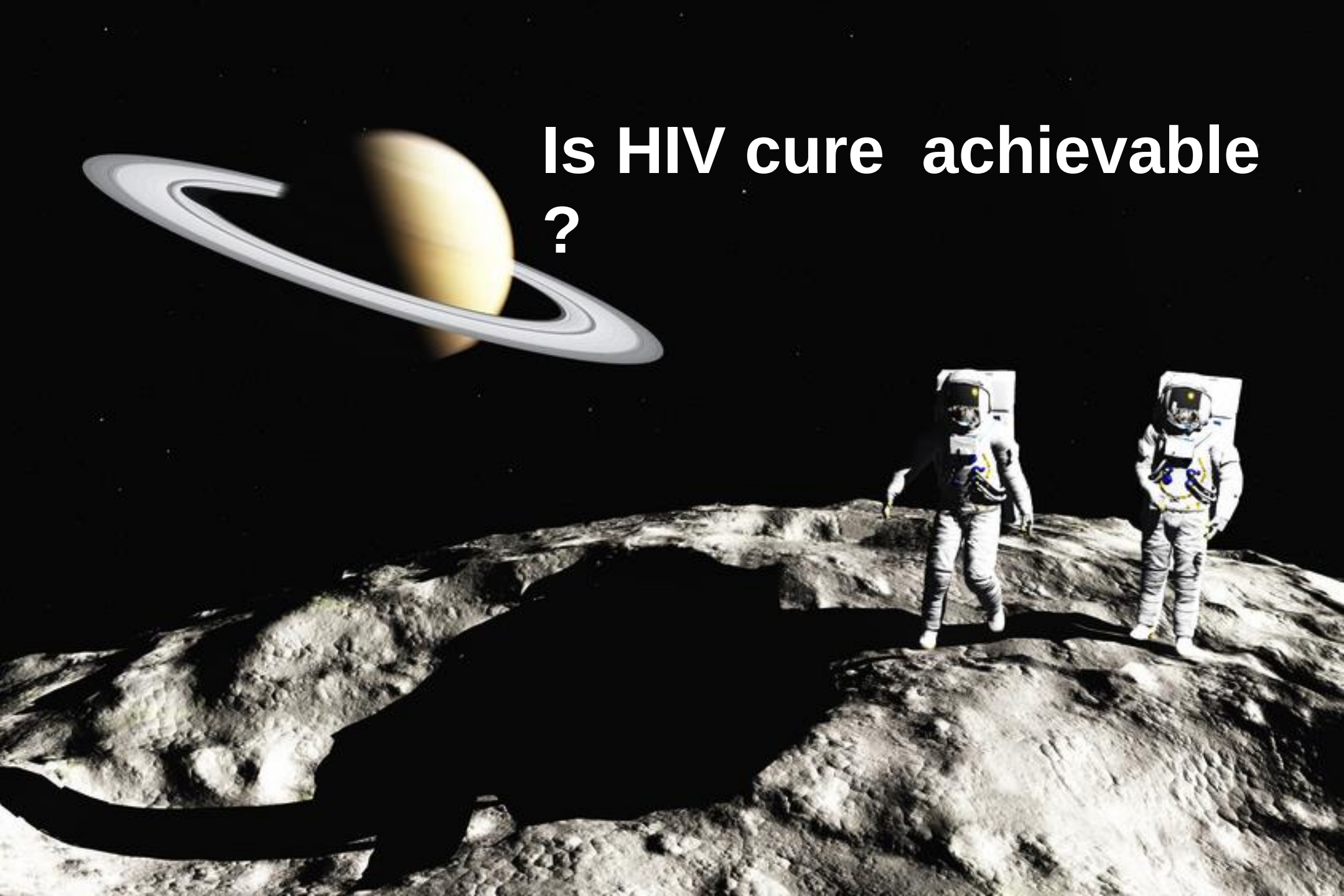
ART-naive pts, CD4+ 50-500 cells/mm^3, HIV-1 RNA > 1000 copies/mL (N = 636)

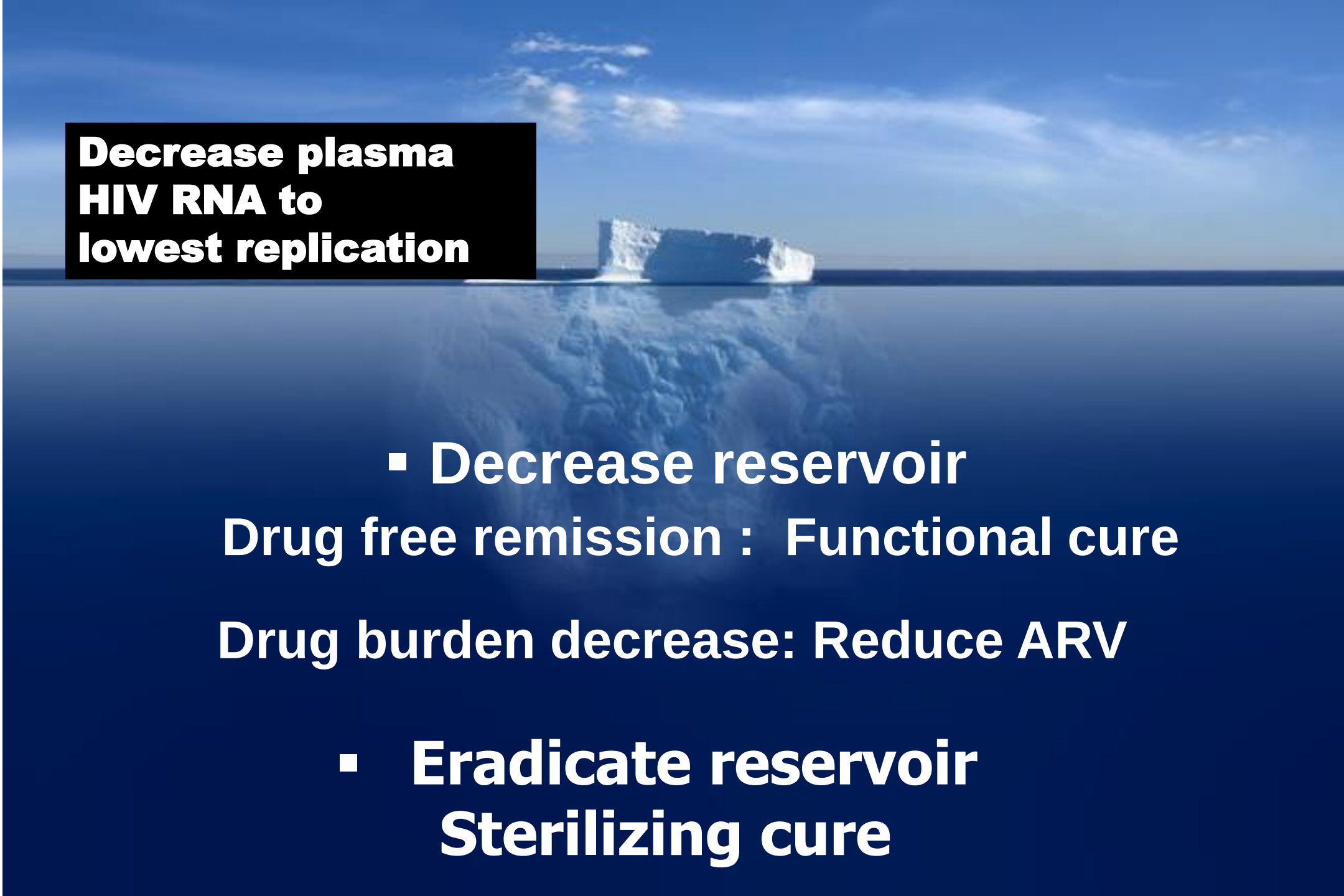
	HIV-1 RNA < 200 c/mL at Wk 48, %
	NC = F
EFV* 400 mg + placebo + TDF/FTC 300/200 mg **(n = 324)**	**90.0**
EFV* 600 mg + TDF/FTC 300/200 mg **(n = 312)**	**85.8**

- **No significant difference in SAEs between treatment arms**
- **More pts with AEs for EFV 600 mg vs EFV 400 mg (47.2% vs 36.8%; *P* = .008)**
- **More pts discontinued EFV 600 mg due to AE vs EFV 400 mg (1.9% vs 5.8%; *P* = .010)**

Puls R, et al. IAS 2013. Abstract WELBB01.

Is HIV cure achievable ?




Decrease plasma HIV RNA to lowest replication
▪ Decrease reservoir
Drug free remission : Functional cure
Drug burden decrease: Reduce ARV
▪ Eradicate reservoir
Sterilizing cure

Is Cure achievable ?

Elite controllers

Never treated

Special phenotype:

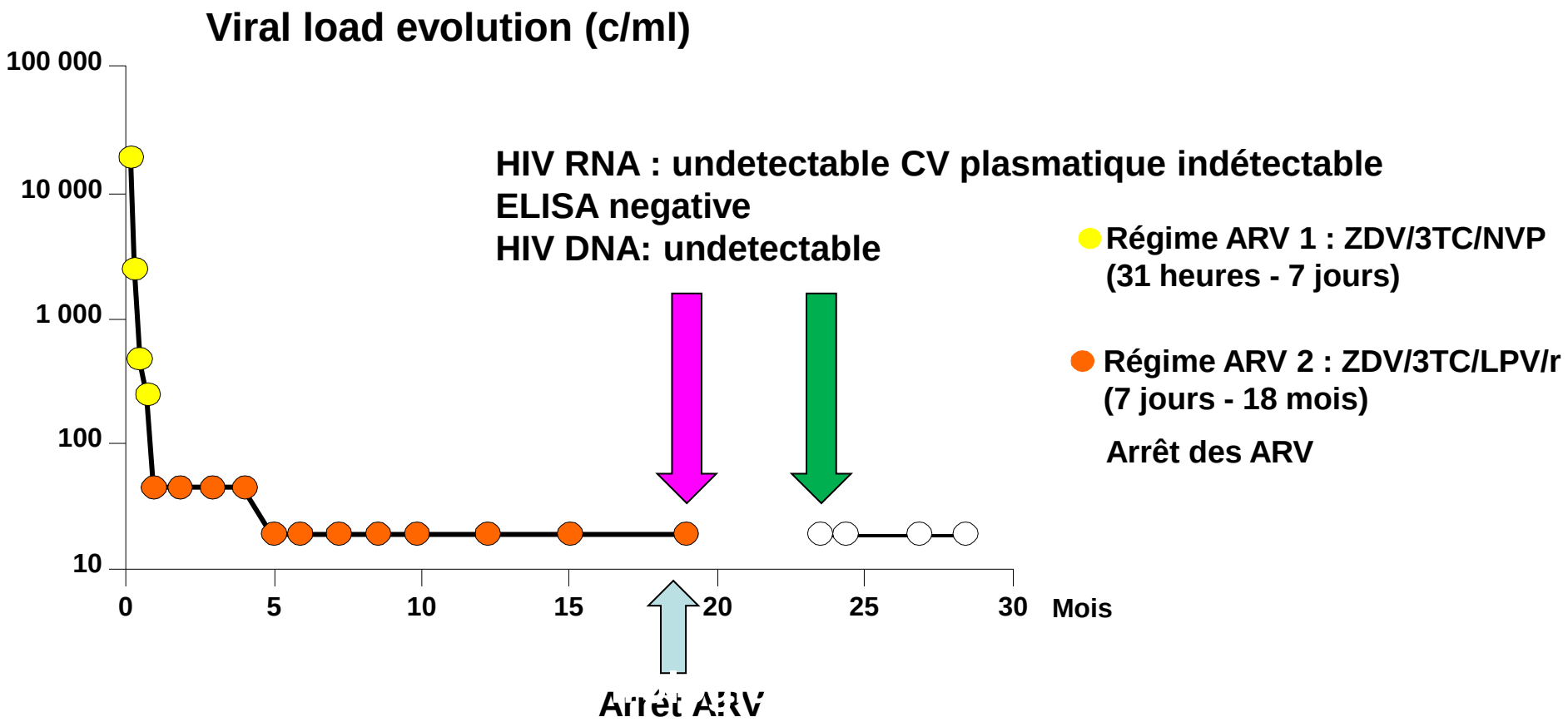
HLA /Strong CD4 and CD8 response/High level cytokine towards HIV/Preserved central memory cells/Low immune activation

Berlin patient : CCR5 defective stem cell graft

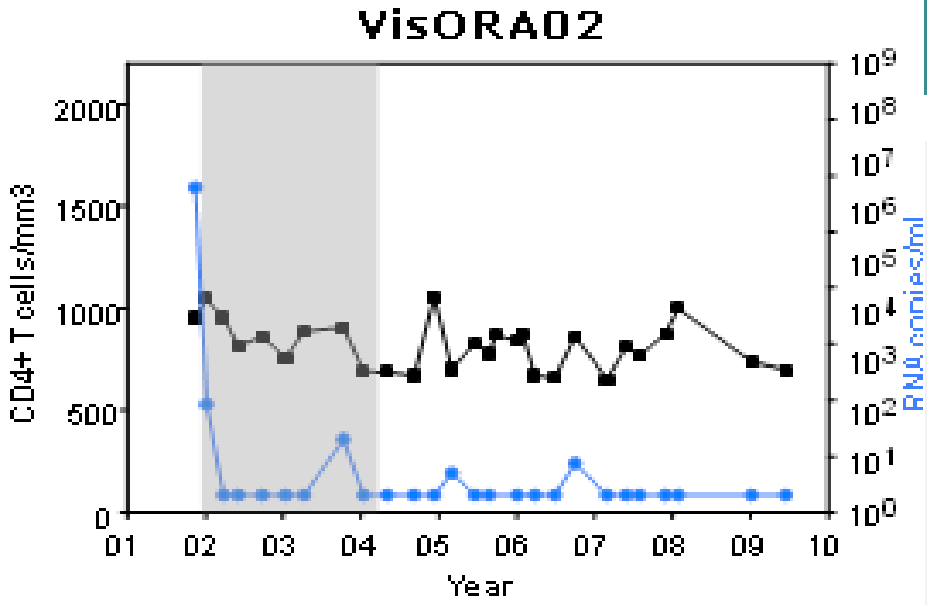
- **Mississipi baby**
- **Visconti patients**
  - Treated at early stage of infection
- **Chronic long term patients ? Salto**

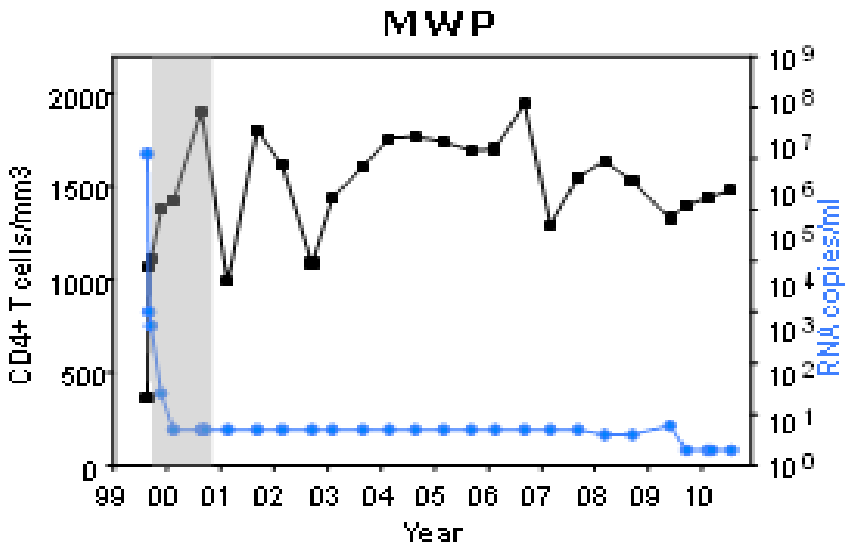
Mississipi baby

- Born 35 weeks gestation ;mother tested at delivery low VL 2423 cp/ml
- ART started at H31 . 13 000 cp/ml up M18 then lost to FU
- M24 : functionnal cure



Visconti Patients
Post ART controllers





- **12 patients treated at PHI**
  ART Duration (med): 35mths
  Duration Off ART : 5 years
- **CD4 count**
  - pre ART 489 (371-955)
  - at ART stop: 931 (354-1639
  -last value : 837(388-1598
- **HIV RNA**
  - preART : 5.0 log (3 - 7.3)
  - last value : 1.7 log (1.7 -2.4)
- **After > 6 years OFF ART**
  Median RNA= <20 copies/mL
  Median DNA = 83 copies/M PBMC
  Very limited CD8 activation

A. Saez-Cirion et al., # F-126 – CROI 2011 (Boston)

SALTO ANRS 116

Treatment interruption in early treated patients with CD4 > 350 and VL < 50 000 cp/ml

95 patients

- Age 40 years (IQR: 36–45).
- **Pre-cART values**
  CD4 : **454** /mL (392–576)
  VL : **4.3** $\log_{10}$ cp/ml (3.9 – 4.5)
  CD4 nadir : **382** /mL (340–492).
- **Duration of cART : 5.3 years** (4.0–6.0)-
- **Baseline values**
  CD4 count : **813** cells/mL (695–988),
  DNA : **206** copies/10^6 PBMCs
  (IQR: 53–556)

12 months post TI

- 7/95 patients still had a VL<400 cp/ml
  KP: 7.5%, CI: 3.7-14.6)

- 4 kept a VL<400 copies/mL up to 36 months;
- All had CD4 cell >500/mm^3

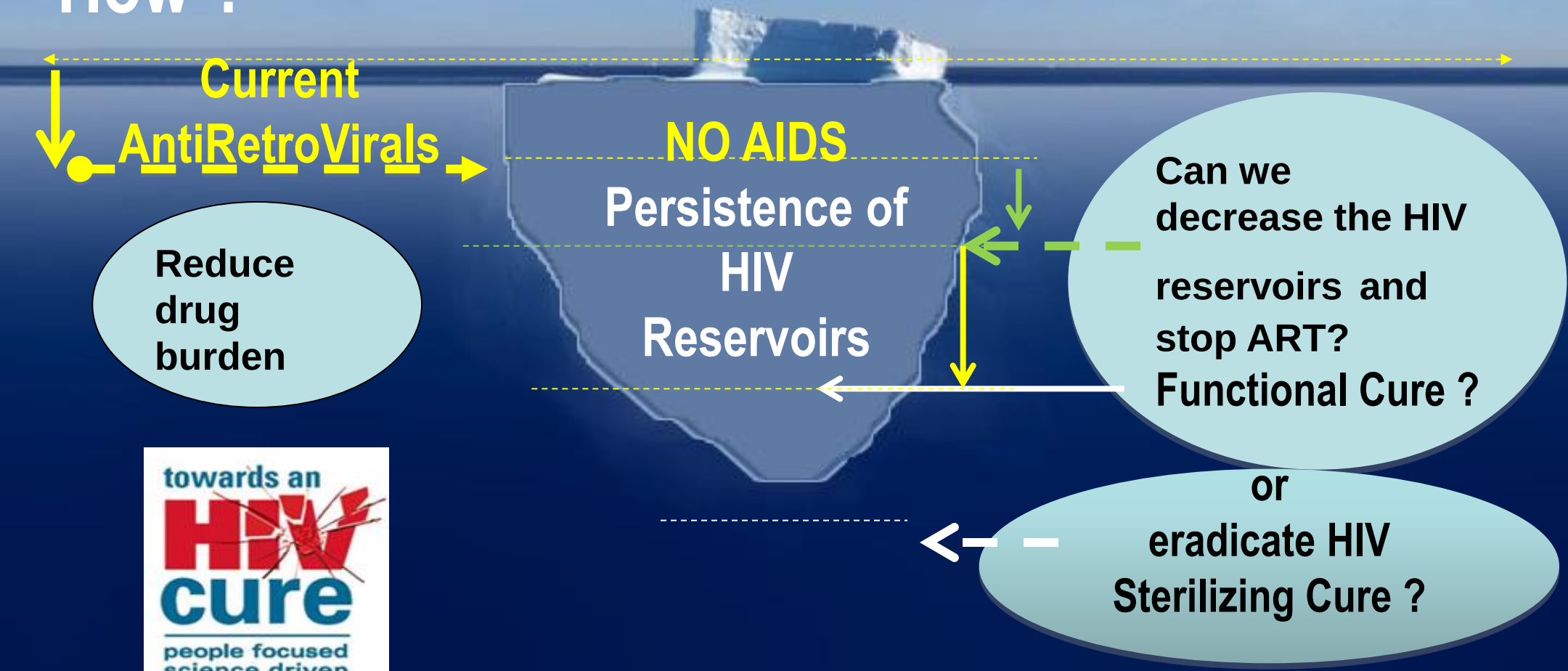
- HIV DNA was the only significant predictor of maintaining VL < 400 cp/ml
  med value : < 10 vs 233 cp / 10^6PBMCs p < 0.001

Piketty et al, J Med Virol, 2010;82:1020-3 Assoumou et al, CROI 2013

Why do we need a Cure for HIV ?

➢ **To control the HIV pandemics**

How ?

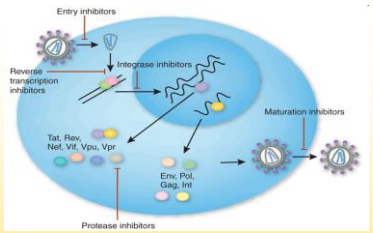


towards an HIV cure
people focused
science driven

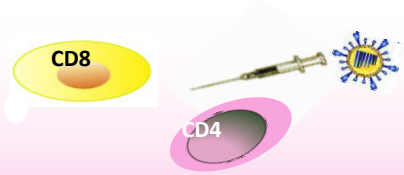
Potential strategies to reduce HIV reservoirs

Maraviroc
Anti-inflammatory drugs
- Statins
- OH-Chlorochin

Massive CD4 T-cell depletion
Bacterial translocation



ARV Intervention
- Intensification
- Nevirapine



Cellular Immunity
Immune Intervention
- Anti-HIV vaccine
- IL7

Systemic Inflammation

Pre-Probiotics

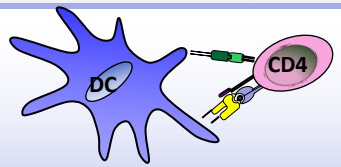
Viral Co-Infections

Antiviral drugs

Immune Activation

Residual Replication

Gene therapy



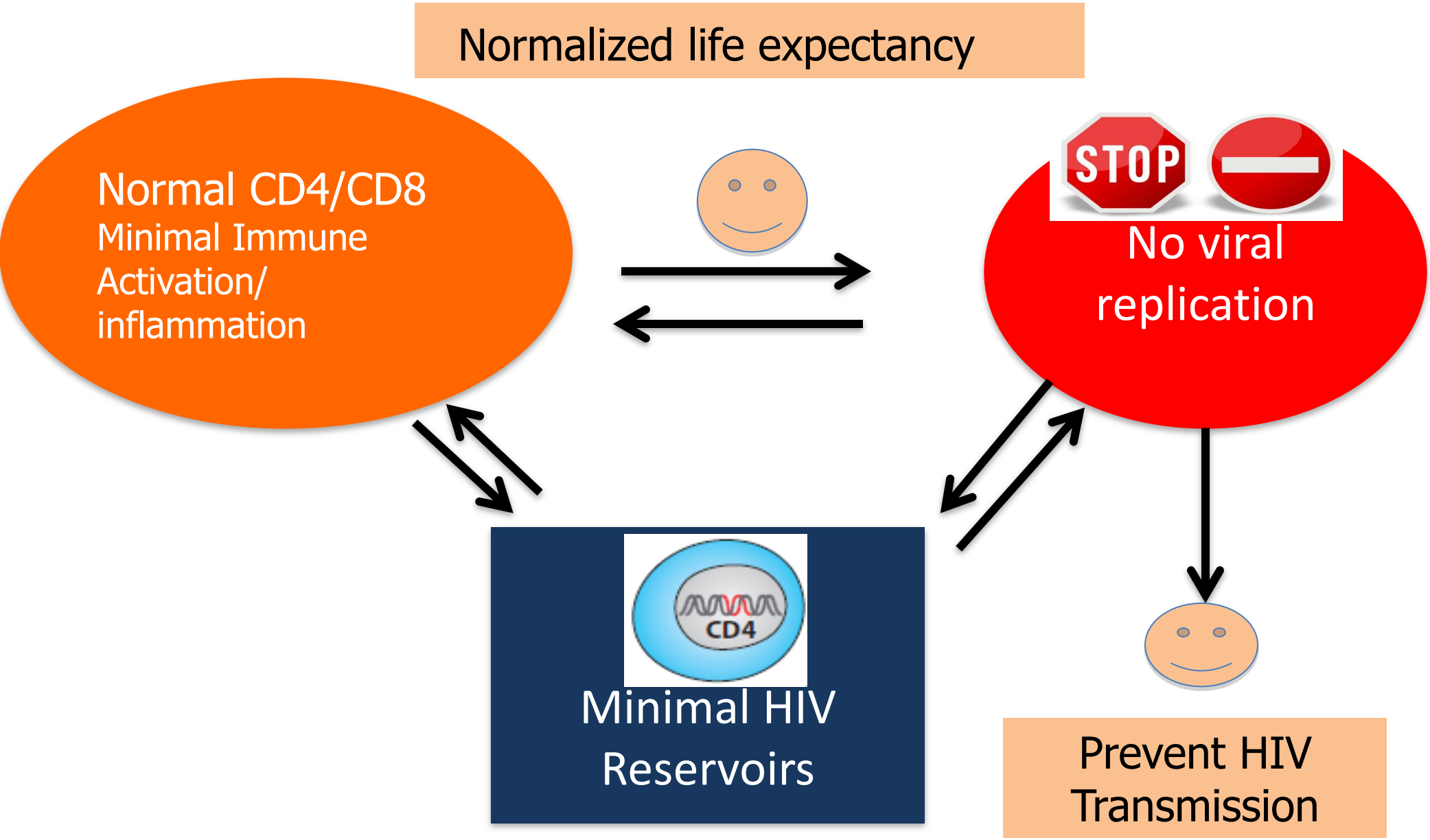
Anti-co-stimulatory molecules
- anti PD1 / anti PDL1
- anti-CTLA4
- anti-CD137

HIV Reservoirs Latency

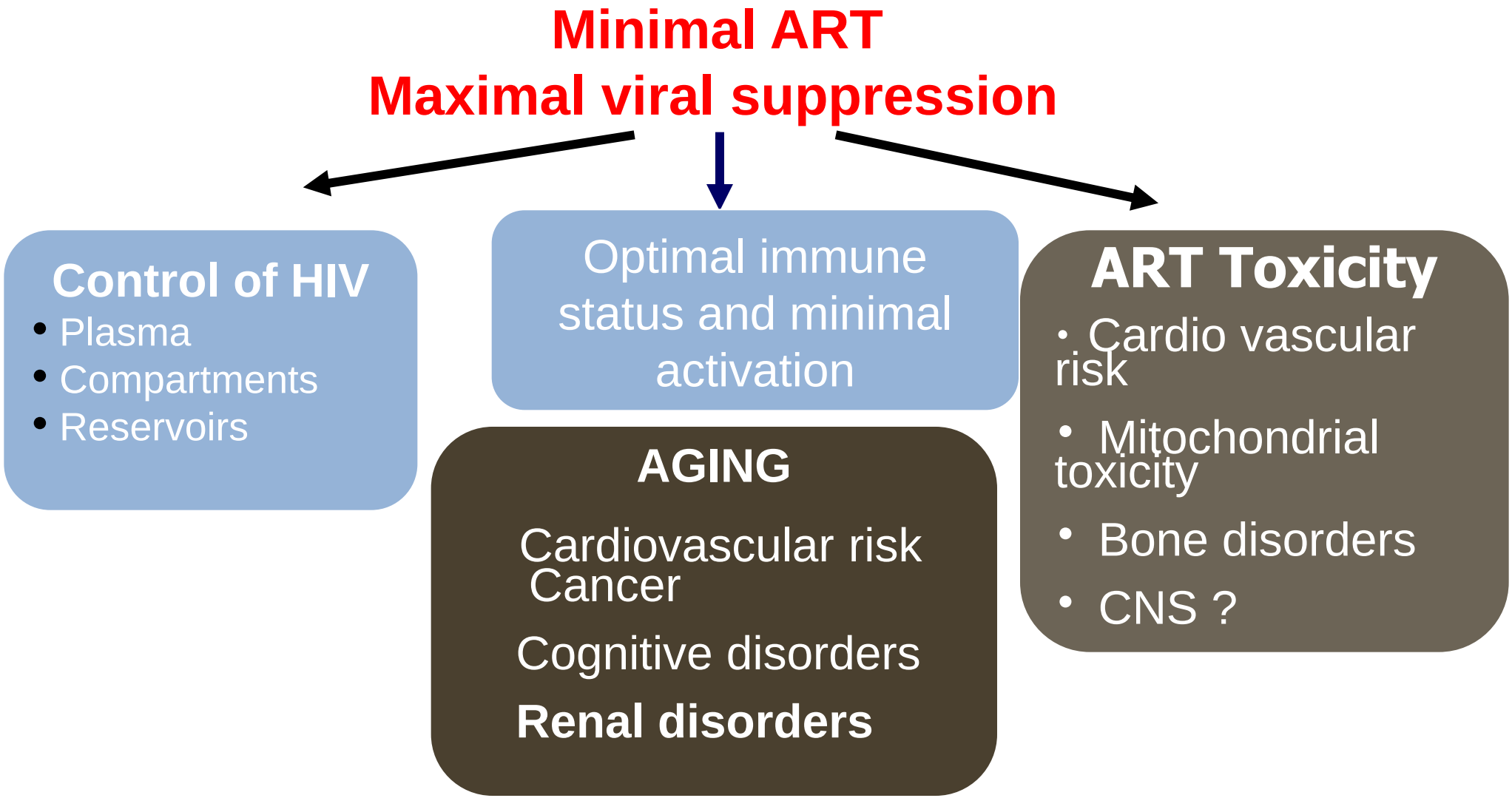
Quiescent T cells activation
- IL7

Pre/post-transcriptional factors disruption
- HDACi
- HMBA

Goals of Anti RetroViral Therapy



Need for individualized therapy in Long-term virological suppression




HIV is a global challenge
Scientific
Medical
Social
Human rights and dignity
EACS
European
AIDS
Clinical
Society

- Test any individual with sexual life
- Early treatment
- Maximal viral suppression
- Restore immunity > 500 CD4
- Treatment as confort for life
- Treatment as a control for epidemics