Outline

Key Pathogenesis elements for ART

Strategies Beyond guidelines

Future drugs and strategies

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EACS Advanced course
AIX 2014

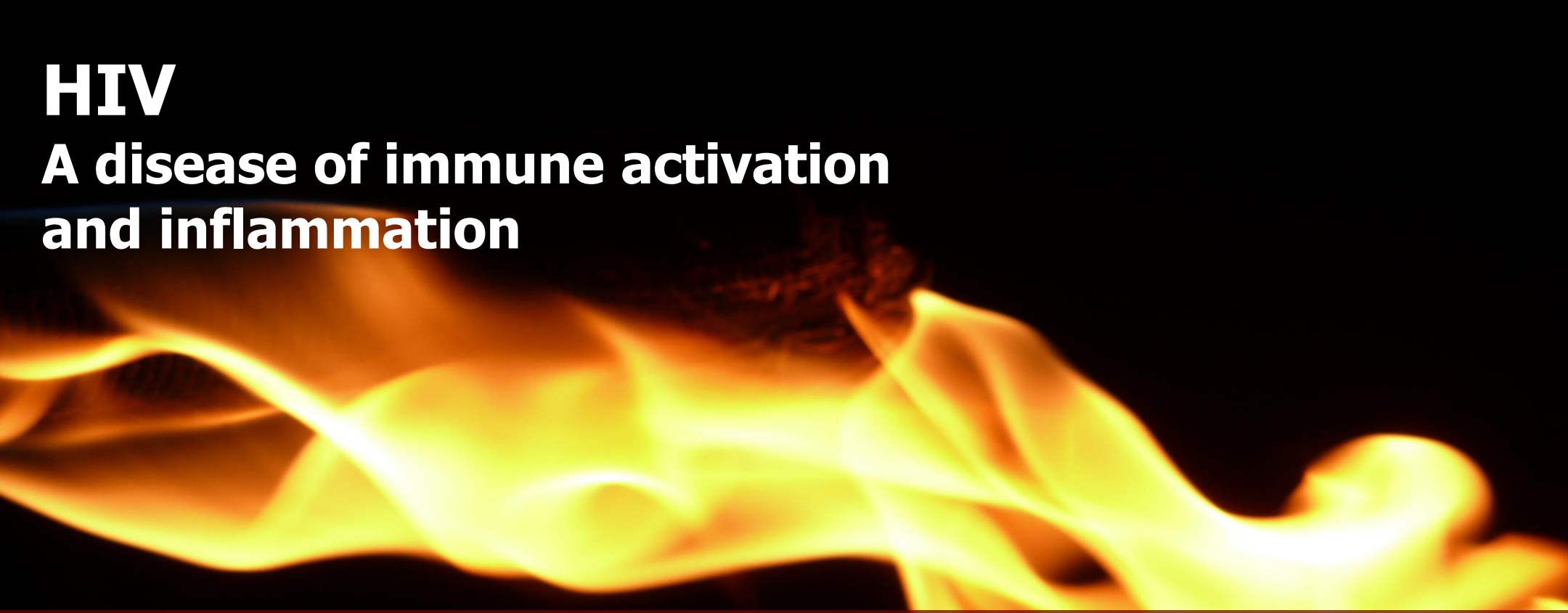
Antiretroviral Treatment Strategies
Part 2

- Viral suppression > 90%
- Better ARV drugs
- Simplified treatment
- Quasi Normalized life span
- Transmission reduced

- A unique infection with no vaccine
- No cure No remission vaccine
- Long life therapy
- Persistance of immune activation
- Comorbidities
- Cost ; ART accessibility

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

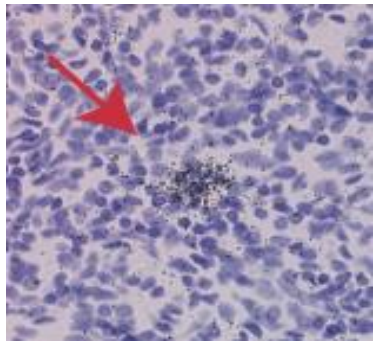
HIV
A disease of immune activation and inflammation



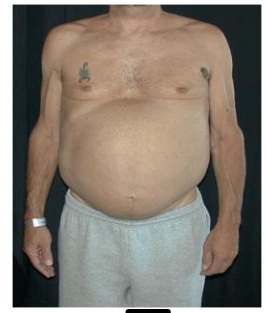
HIV replication induces immune activation
Immune activation induces inflammation
immune exhaustion
immune suppression
Inflammation induced comorbidities

Photo JDD

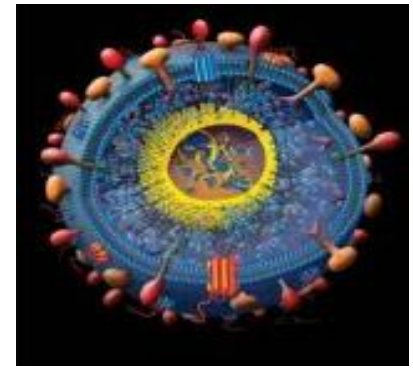
HIV production



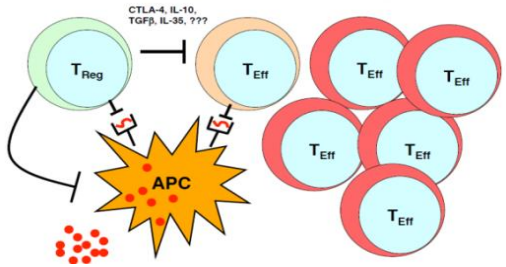
Syndrome métabolique



Coinfections CMV HBV HCV

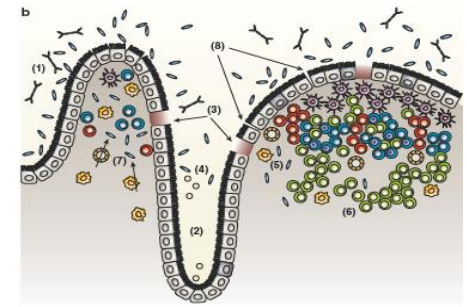


Perte de régulation CD4



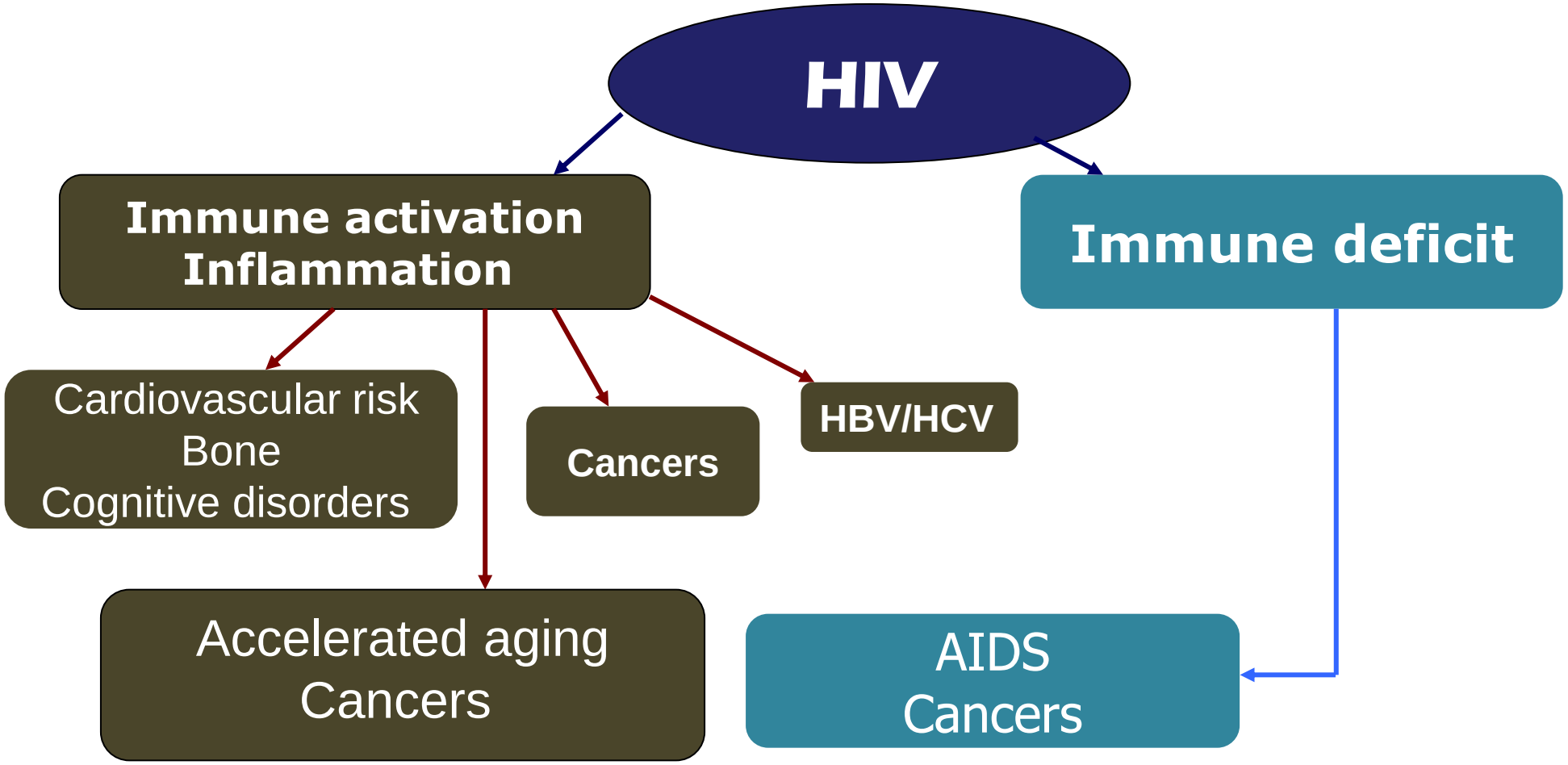
Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Translocation microbienne

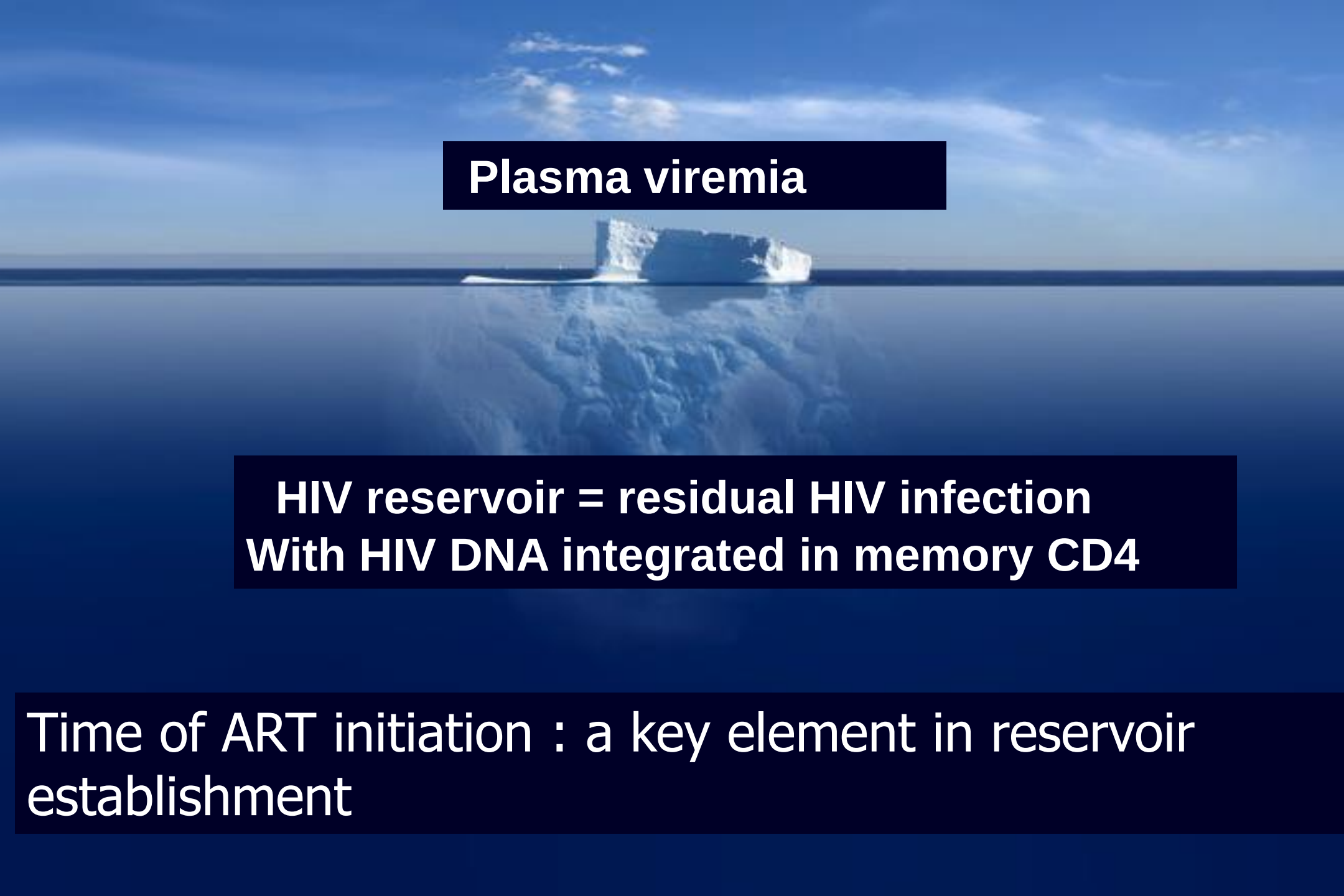


Co-morbidités Vieillissement

Pathogenesis of HIV

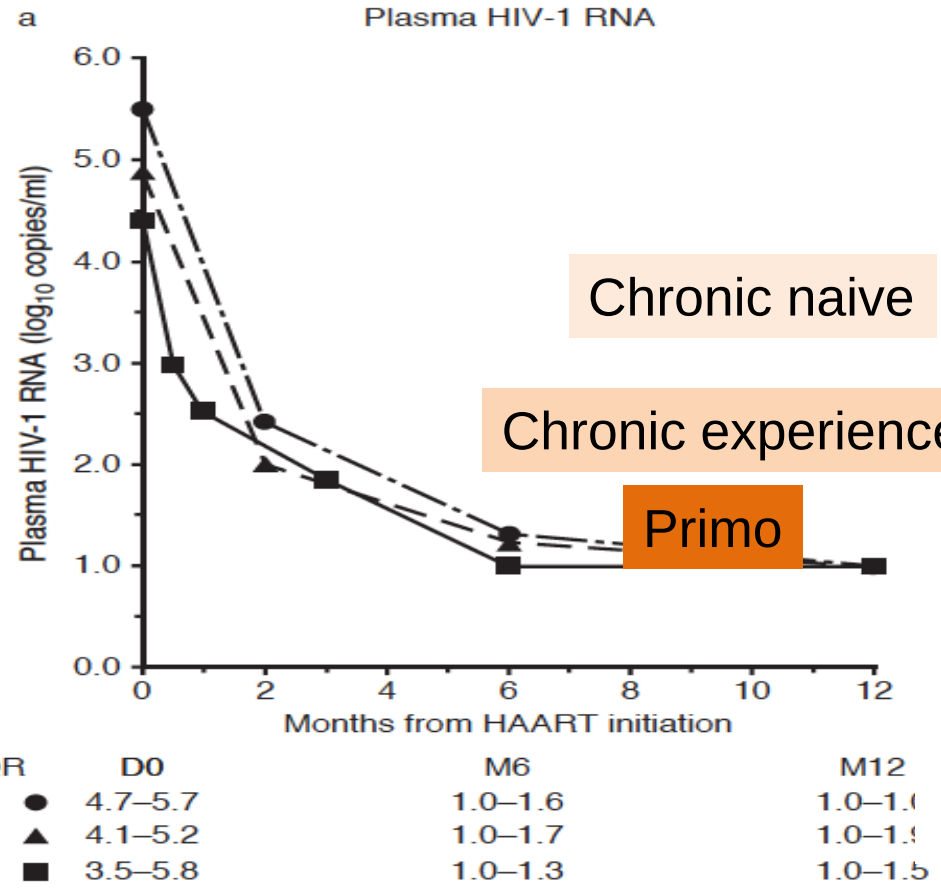


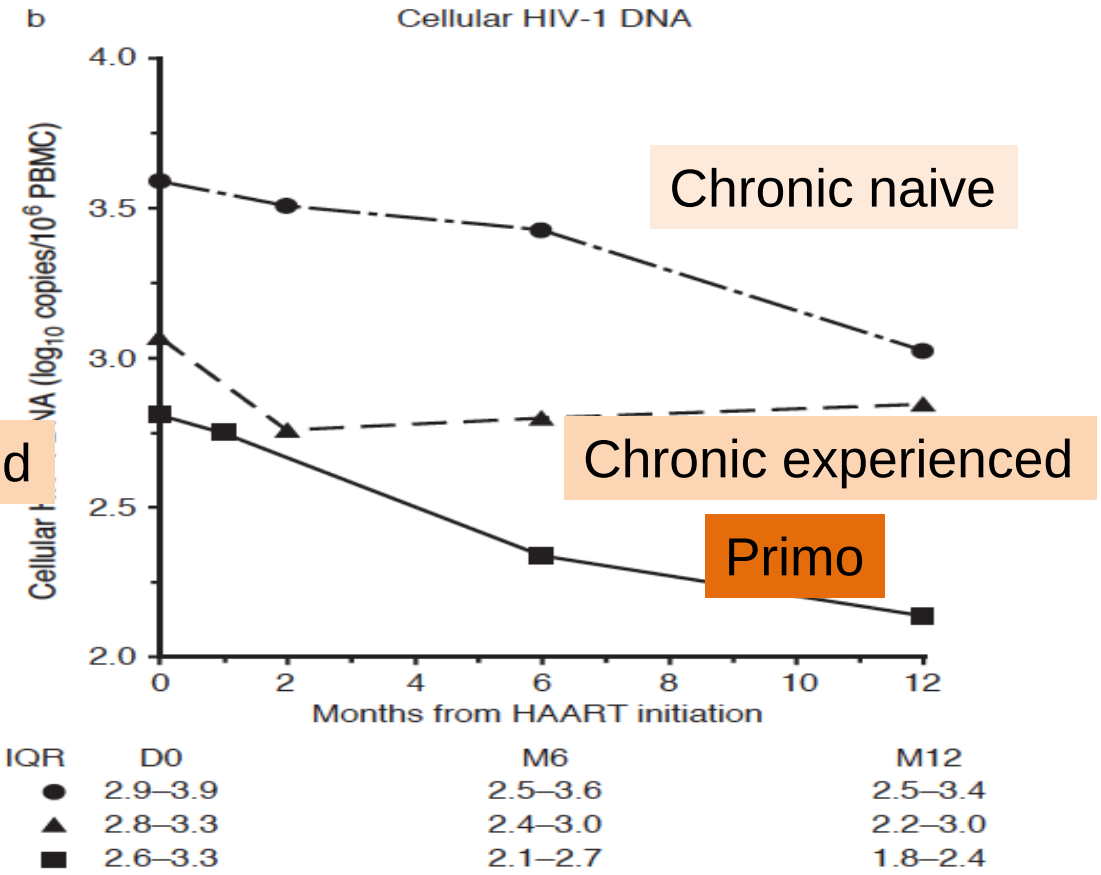
HIV is deleterious by immune suppression and activation



Time of ART initiation : a key element in reservoir establishment

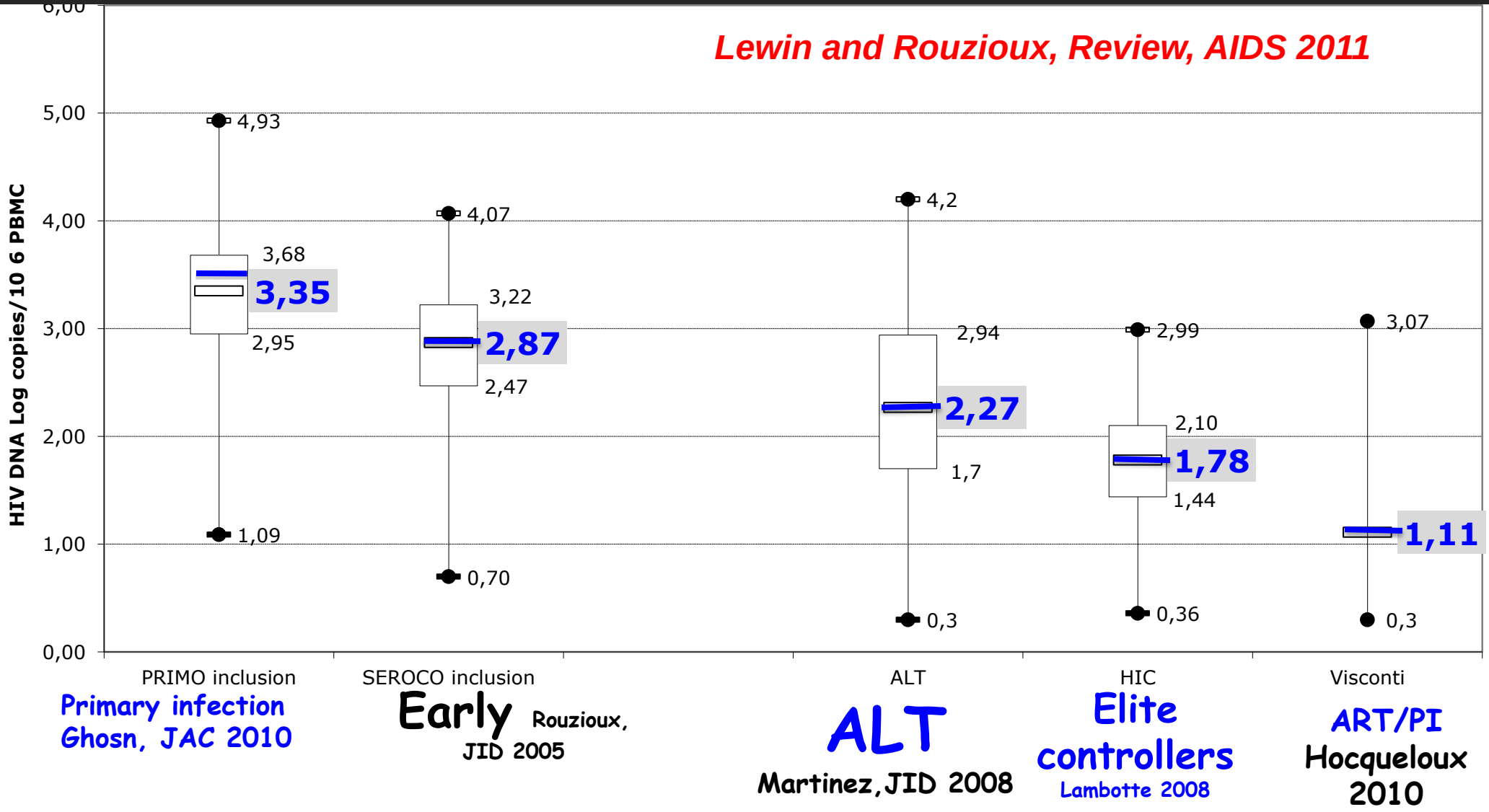
Evolution of HIV RNA and HIV DNA in patients following ART initiation





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

HIV reservoirs differs from cohorts patients



Cumulative Viral load is predictive of mortality under ART

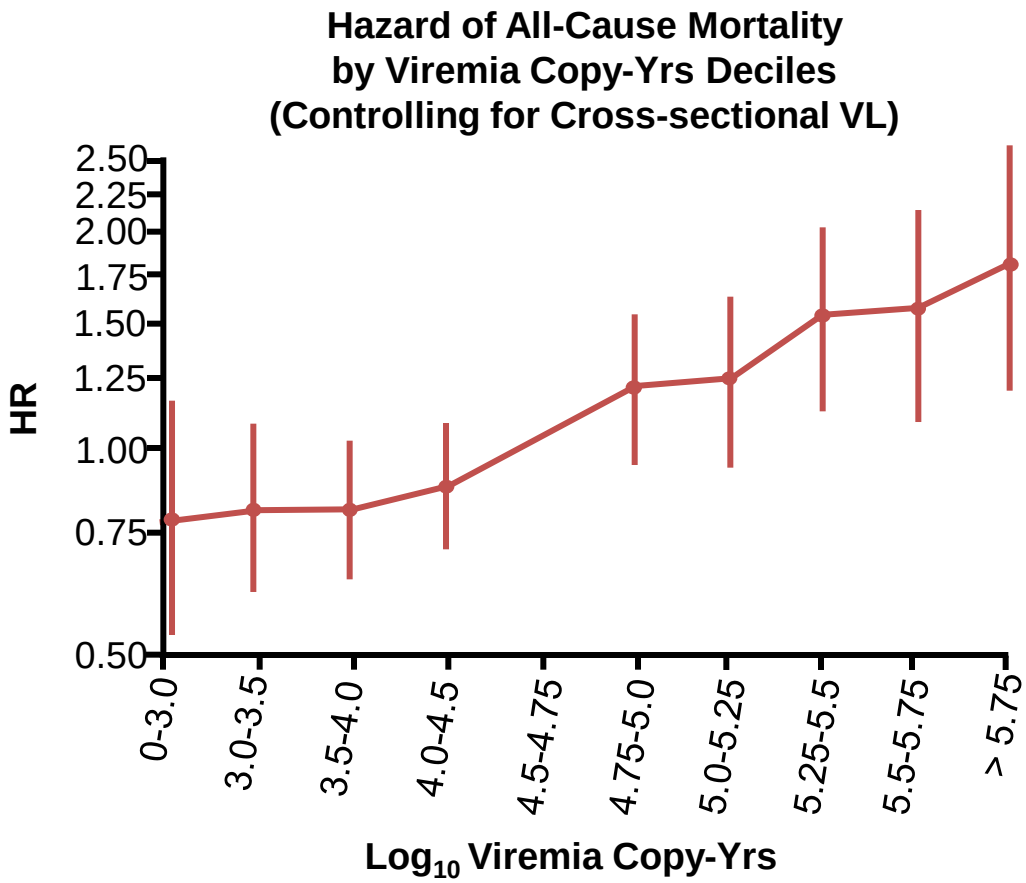
- Observationnal study
- ART Cohort Collaboration

33,563 pts

- Estimated culative viremia (copies – years
- After adjustement on age , gender , transmission , BL HIV RNA

Persistant quantitative viremia is predictive of

- **All-cause mortality**
- **AIDS-related mortality**



Mugavero M, et al. CROI 2014. Abstract 565.

Earliest control of HIV replication is the best way to preserve future

- Nadir of CD4 is a predictor for death ; morbidity (C Vasc) ;cancer ; ART failure
- Above 500 CD4 is the optimal way to preserve clinical future
- ART at PI :

  - Limitation of viral set point
  - Reservoir size limitation
  - Normalized immune activation

Antiretroviral Therapy : a key tool in prevention

HPTN 052

Essai randomisé

1763 HIV couples hétero sérodifférents avec entre 350 et 550 CD4

Preservatif recommandé
Afrique ++/ Asie
ART immédiat vs ART différé
96% suppression viro

Transmission : 1 vs 27

96% réduction transmission

Beatriz Grinsztejn et al.
Lancet Infect Dis 2014;14: 281–90

PARTNER

- Etude observationnelle europe
- **767 couples** sérodifférents (homo masculins et hétéro)
  - Rapports occasionnels non protégés
  - Pas d'utilisation de PEP ni de PrEP
- Après 894 couple-années de suivi et med 15 000 RS non protégees

Transmission : 0

Suivi nécessaire / ET du %

Rodger A, CROI 2014, Abs. 153LB

Antiretroviral therapy

- A highly effective therapy
- A highly effective prevention

…A « double hit strategy »

Goals of Antiretroviral Therapy

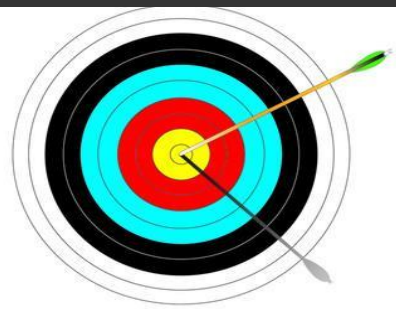
- Reduce HIV-associated morbidity and prolong duration and quality of survival
- Restore and preserve immunologic function: > 500 CD4 ; normalize CD4/CD8
- Maximally and durably suppress HIV-1 RNA
  - Persistently below level of detection (< 20-75 copies/mL, depending on the assay used)
  - Isolated “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.

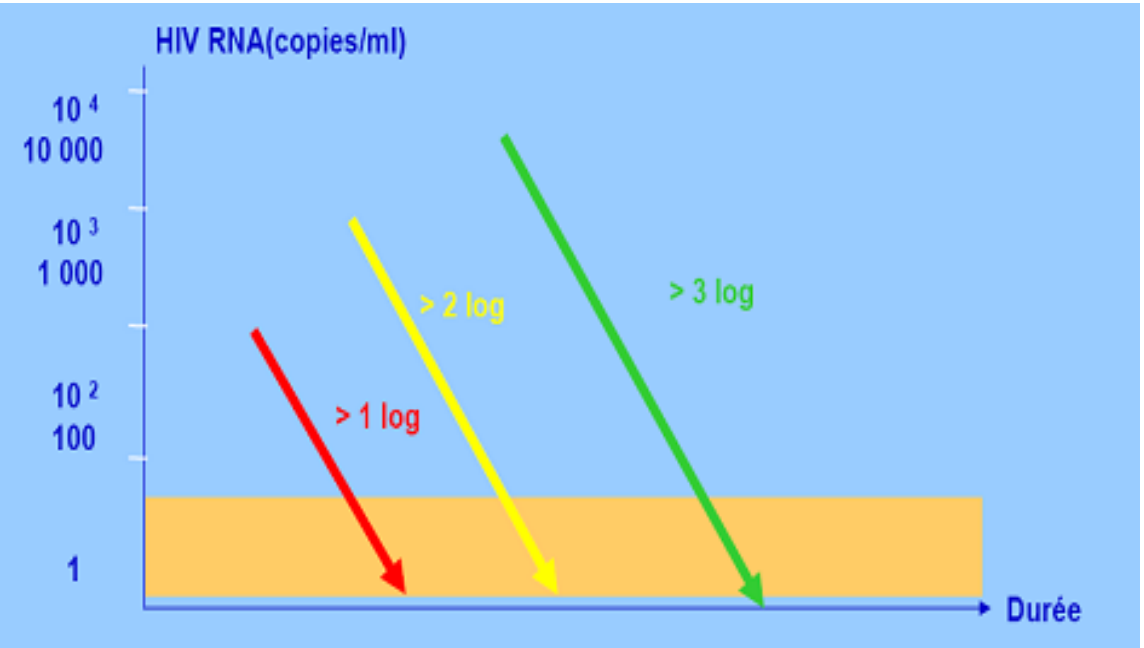
Viral replication has to maximally suppressed Ideally in the shortest time

Maximal suppression of HIV required to

- Prevent disease progression
- Decrease immune activation
- Prevent resistance



Target VL below detection



- W4 : -2 log decrease in HIV RNA
- W12 : < 400 cp/ml
- W24 : > 50 cp/ml

In BL high VL .. Full supression may require longer time

How to best manage HIV patient ?

1 Initiation

2 Virologic suppression

3 Treatment Failure

HIV therapy = a long life therapy

Antirétroviraux : 2014

NRTI	NNRTI	Protease	Inhib Integrase	CCR5
TDF	Nevirapine	Lopinavir	Raltegravir	Maraviroc
TDF/FTC				
ABC	Efavirenz[6]	Atazanavir	Elvitegravir	
ABC/3TC				
3TC/FTC	Rilpivirine	Darunavir	Dolutegravir	
	Etravirine			

Combinaisons fixes
TDF/FTC/EFV
TDF/FTC/RPV
TDF/FTC/cobi/EVG …

- **Malgré puissance et simplicité des combos fixes**
- **Standard ART est toujours une trithérapie**

➡ **Innovation nécessaire**

Reasons to individualize ART

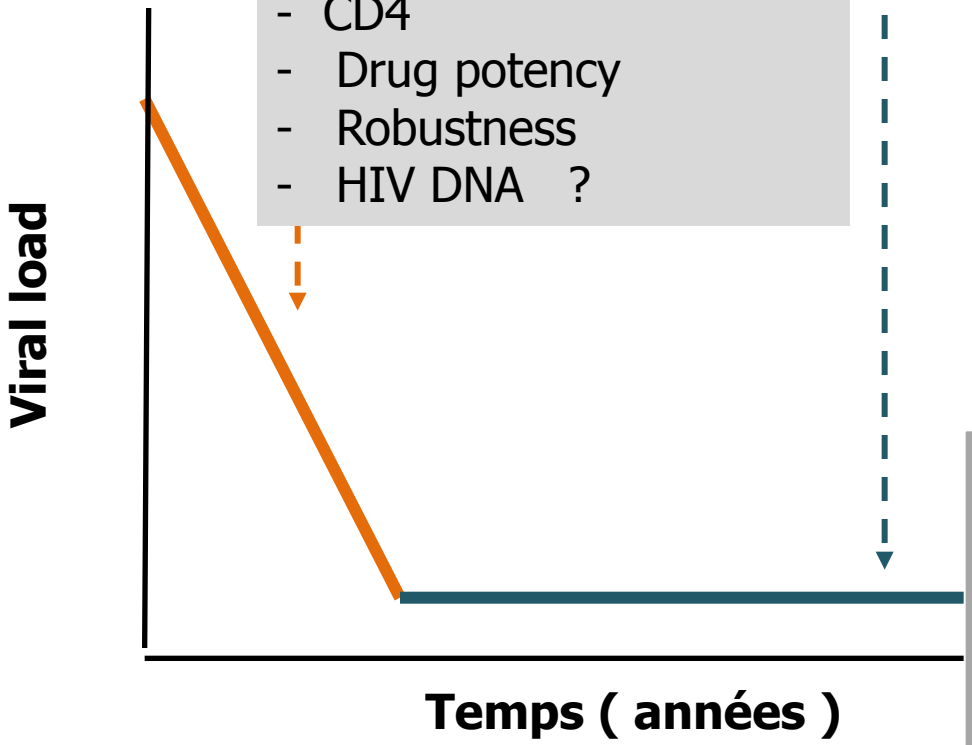
- Reduce drug burden
- Prevent / reduce long term toxicity
- Spare drug capital
  Adapt ART to CD4 and plasma VL and to reservoirs ?
- Cost reduction

Can we initiate a “non triple” ART ?

Induction

1996 Triple drug ART : a revolution

Nb drugs is function
- HIV RNA
- CD4
- Drug potency
- Robustness
- HIV DNA ?



2014

- More potent drugs
- More robust drugs
- Earlier initiation with lower VL and higher CD4

Which strategies ?

Monotherapy
Dual therapy
Reduced dosages

GARDEL: Dual ART LPV/r +3TC

Non inferior to Triple ART in ART naïve patients

GARDEL
GLOBAL ARV DESIGN ENCOMPASSING LOPINAVIR/RITONAVIR AND LAMIVUDINE VS LOPINAVIR/RITONAVIR BASED STANDARD THERAPY

Phase III, randomized, controlled, open-label study

Argentina, Chile, Mexico, Peru, Spain, US.

426 ART- naive pts
VL: 4.87 log
CD4: 320/mm3
No PI resistance

- LPV/r 400/100mg BID + 3TC 150 mg BID n=217
- LPV/r 400/100mg BID + 3TC /FTC + NRTI n=209

HIV-1 RNA < 50 W48	ITT exposed - Snapshot	ITT Snapshot VL> 5 log	Exposed
LPV/r 400/100mg BID + 3TC 150 mg BID n=217	88.3 %	87.2%	95.5%
LPV/r 400/100mg BID + 3TC /FTC + NRTI n=209	83. 7 %	77. 9 %	96.6%

- Grade 2-3 adverse events **more frequent in triple-ART** arm (88 vs 65 events)
- Hyperlipidemia more common in dual-ART arm (23 vs 16 pts)
- Limited resistance (2 with M184V in LPV/3TC)

Cahn P, et al. EACS 2013. Abstract LBPS7/6

NEAT-001/ANRS 143: DRV/RTV + RAL vs DRV/RTV + TDF/FTC in Naive Pts

- Randomized, open-label, phase III study

- 805 ART naive patients
- CD4 : 345/mm3
- CV : 4.76 log
- > 100 000 cp/ml : 35%

→ DRV/RTV 800/100 mg QD + RAL 400 mg BID (n = 401) — *Wk 96*

→ DRV/RTV 800/100 mg QD + TDF/FTC 300/200 mg QD (n = 404)

- **Primary endpoint**
  - **Virologic**: Change of treatment before Wk 32 because of insufficient response or HIV-1 RNA ≥ 50 c/mL at Wk 32 or beyond
  - **Clinical:** Death, any new AIDS-defining event, any new non-AIDS event

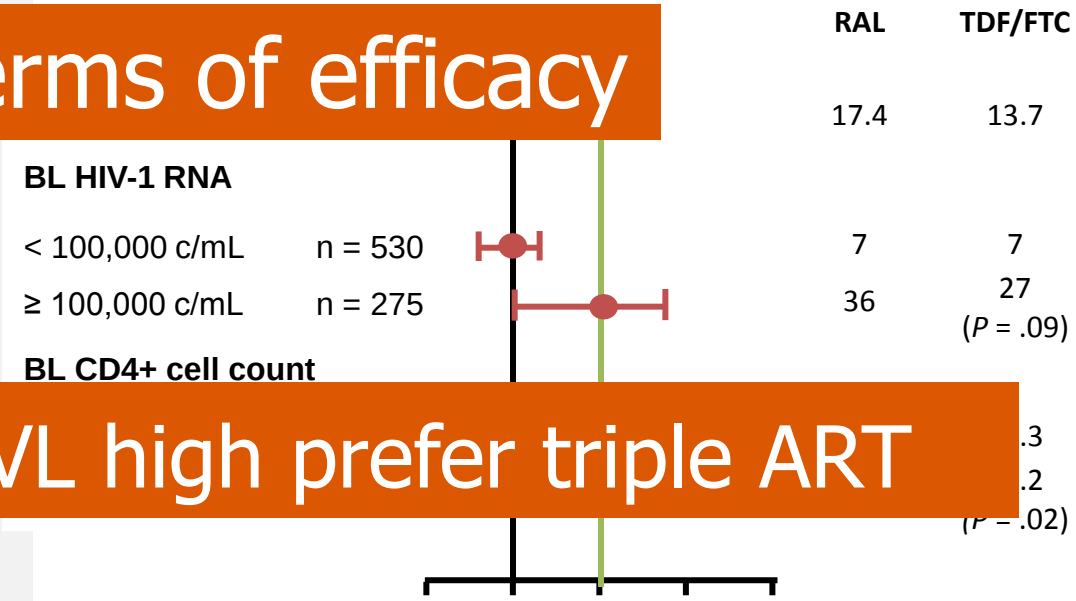
Raffi F, et al. CROI 2014. Abstract 84LB.

NEAT: RAL + DRV/RTV Noninferior to TDF/FTC + DRV/RTV at 96 Wks

- Overall, regimens noninferior by % reaching composite primary endpoint of 6 virologic and clinical endpoints at Wk
  - RAL: 17.4%; TDF/FTC: 13.7%
  - Inferior response in pts with BL CD4+ < 200 and a trend toward more primary endpoints in pts with BL VL > 100K
- S
  DVF (RAL: n = 36; TDF/FTC: n = 52)
- No pts with resistance in TDF/FTC arm vs 5 with integrase mutations and 1 with K65R

No difference in terms of efficacy

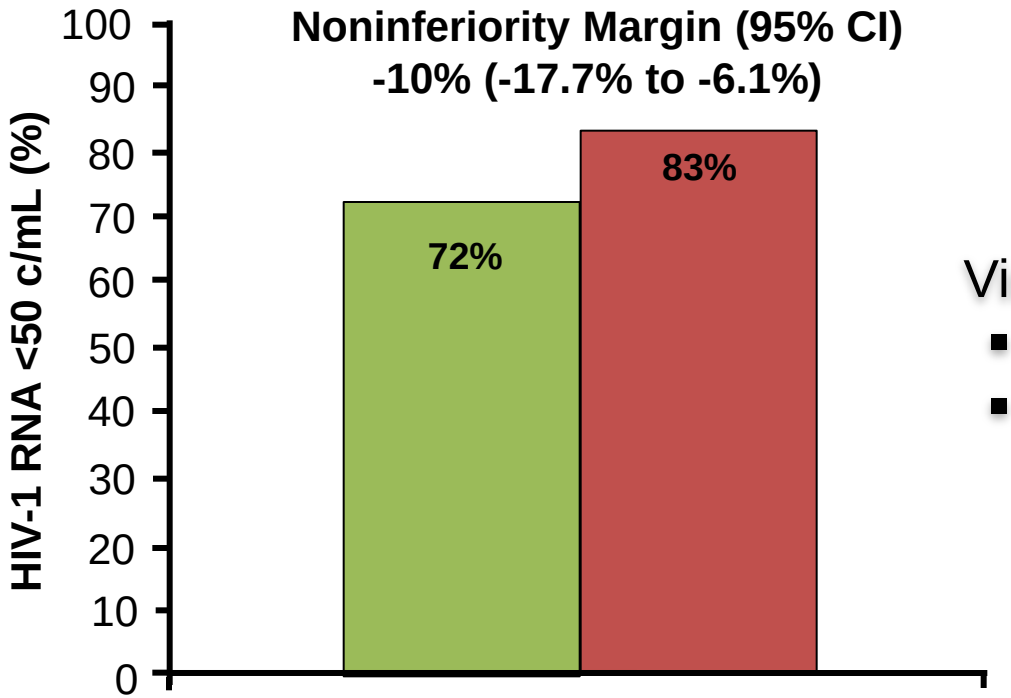
When CD4 are low or VL high prefer triple ART



- Significantly greater mean increases in fasting lipids in RAL arm

Raffi F, et al. CROI 2014. Abstract 84LB. Reproduced with permission.

MODERN Study Wk 48 Results: DRV/RTV + MVC Inferior to DRV/RTV + TDF/FTC



DRV/RTV + MVC (n = 393)
DRV/RTV + TDF/FTC (n = 398)

Virologic Failures
- DRV/RTV + MVC, n=38
- DRV/RTV + TDF/FTC n= 13

Study terminated early due to inferior efficacy
October 4, 2013, following Data Monitoring Committee recommendation

MODERN Study (A4001095 Early Termination Investigator Letter).
ClinicalTrials.gov. NCT01345630.

Alternative trithérapie
EFV 400-mg non inférieur à 600-mg EFV combiné à TDF/FTC en 1° ligne

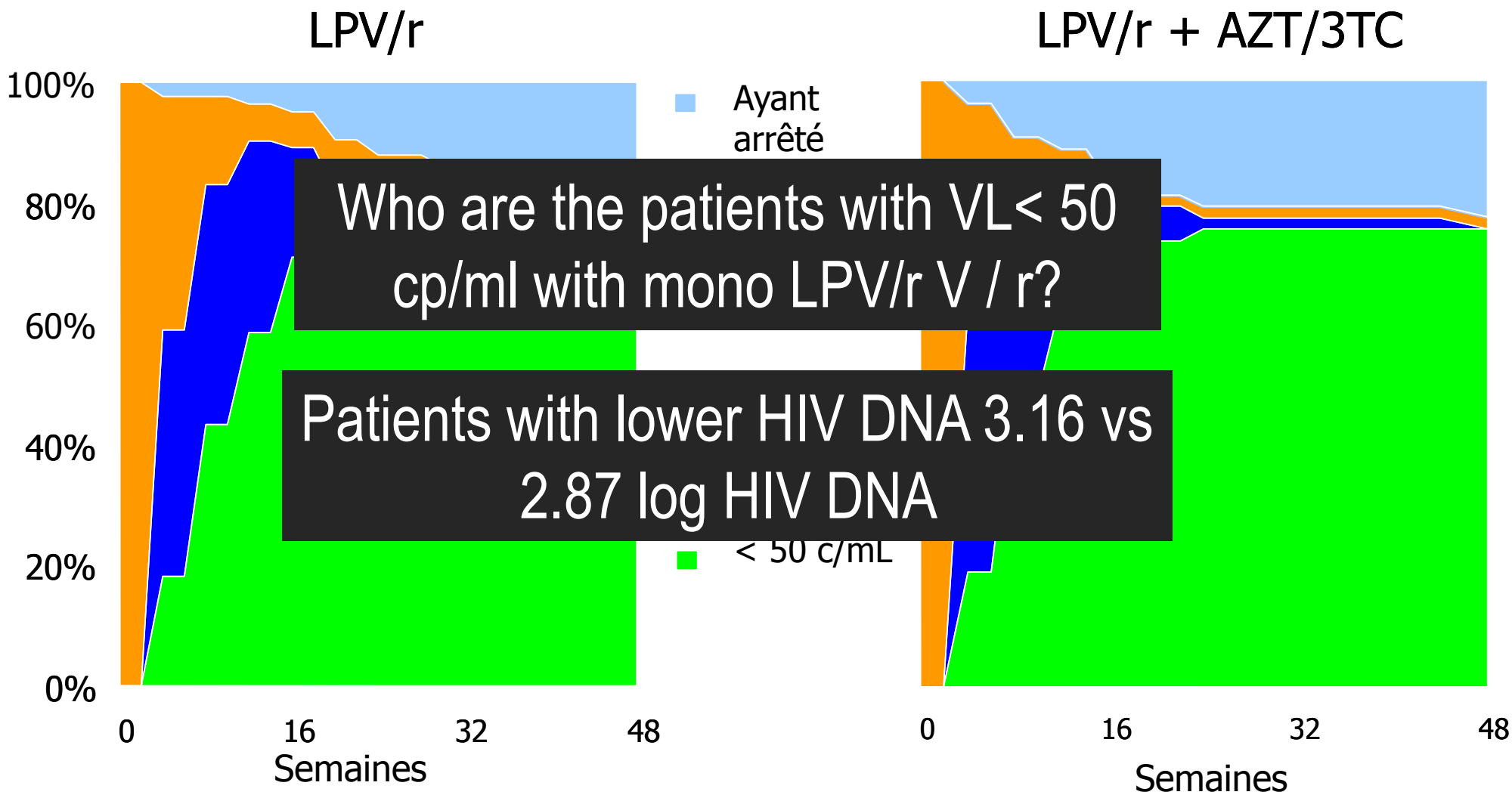
- Etude noninfériorité randomisée , double aveugle versus placebo

636 ART-naive
CD4 : 273 /mm^3
HIV-1 RNA : 4.75 log

	HIV-1 RNA < 200 cp/ml S48		
	NC=F	**ITT**	**PP**
EFV* 400 mg + Placebo + TDF/FTC n = 324	90.0 %	94.1 %	98.3 %
EFV* 600 mg + TDF/FTC n = 312	85.8 %	92.2 %	97. 4 %

- **Effets secondaires plus fréquents** avec EFV 600 **47.2%** mg vs EFV 400 mg **36.8%**; *p*=.008
- **Arrêts traitements plus fréquents** avec EFV 600 mg (intolérance) vs EFV 400 mg 1.9% vs 5.8%; *p* = .010

MONARK : Lopinavir / r mono Rx in naive patients



Who are the patients with VL< 50 cp/ml with mono LPV/r V / r?

Patients with lower HIV DNA 3.16 vs 2.87 log HIV DNA

Delfraissy, AIDS 2008

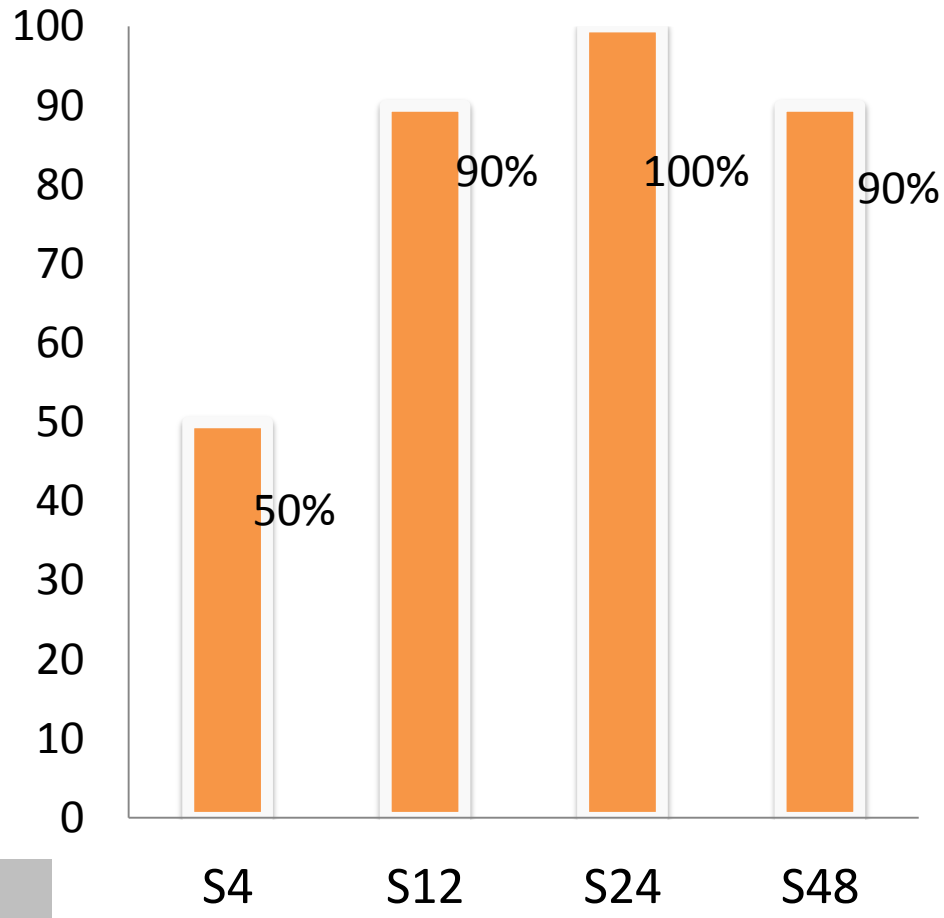
Binuke

Etude pilote de bithérapie NRTI en initiation chez des patients avec CD4 élevés et CV faible

- 20 patients
- CV < 30 000 cp/ml
  Med : 10.395 cp
- CD4 > 350/mm3
  med : 592
- Initiation avec 2 NRTI

TDF/FTC : 19

ABC/3TC : 1



Délai d'indétectabilité < 50 cp/mL
= 4 [4-12] semaines

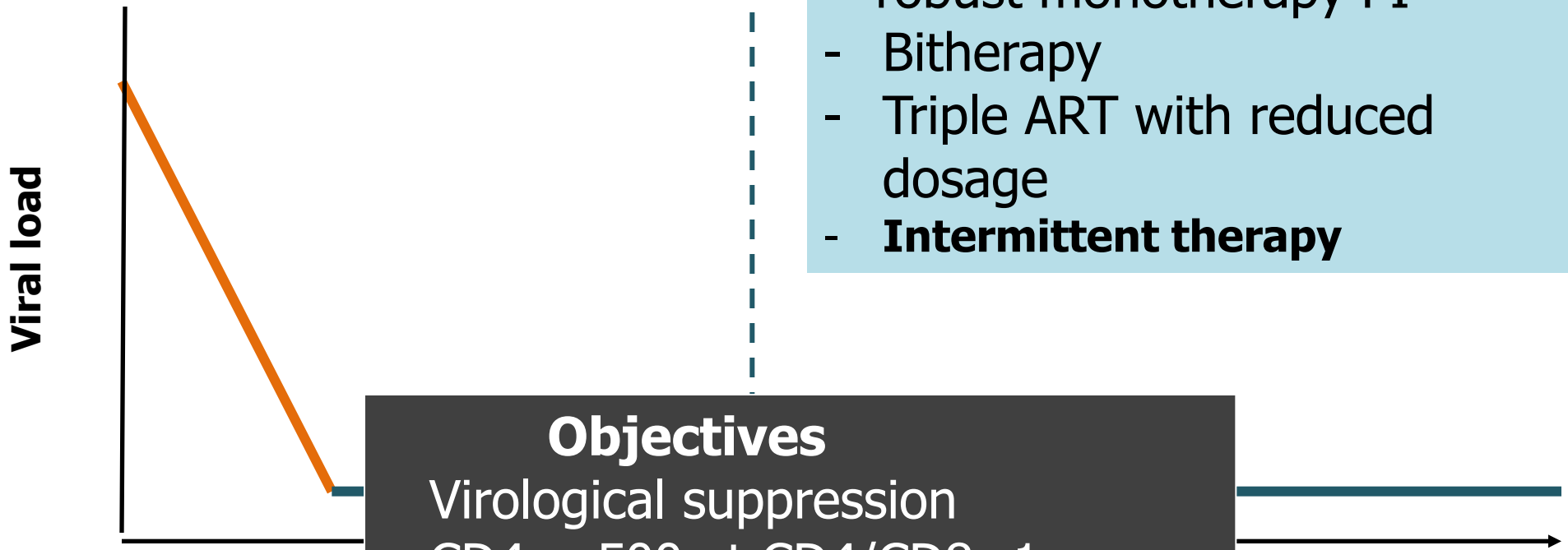
Seang Katlama 2014 JAC in press

Individualize ART for a long life therapy

Initiation =Induction

Maintenance therapy

- **Daily treatment**
  - robust monotherapy PI
  - Bitherapy
  - Triple ART with reduced dosage
  - **Intermittent therapy**



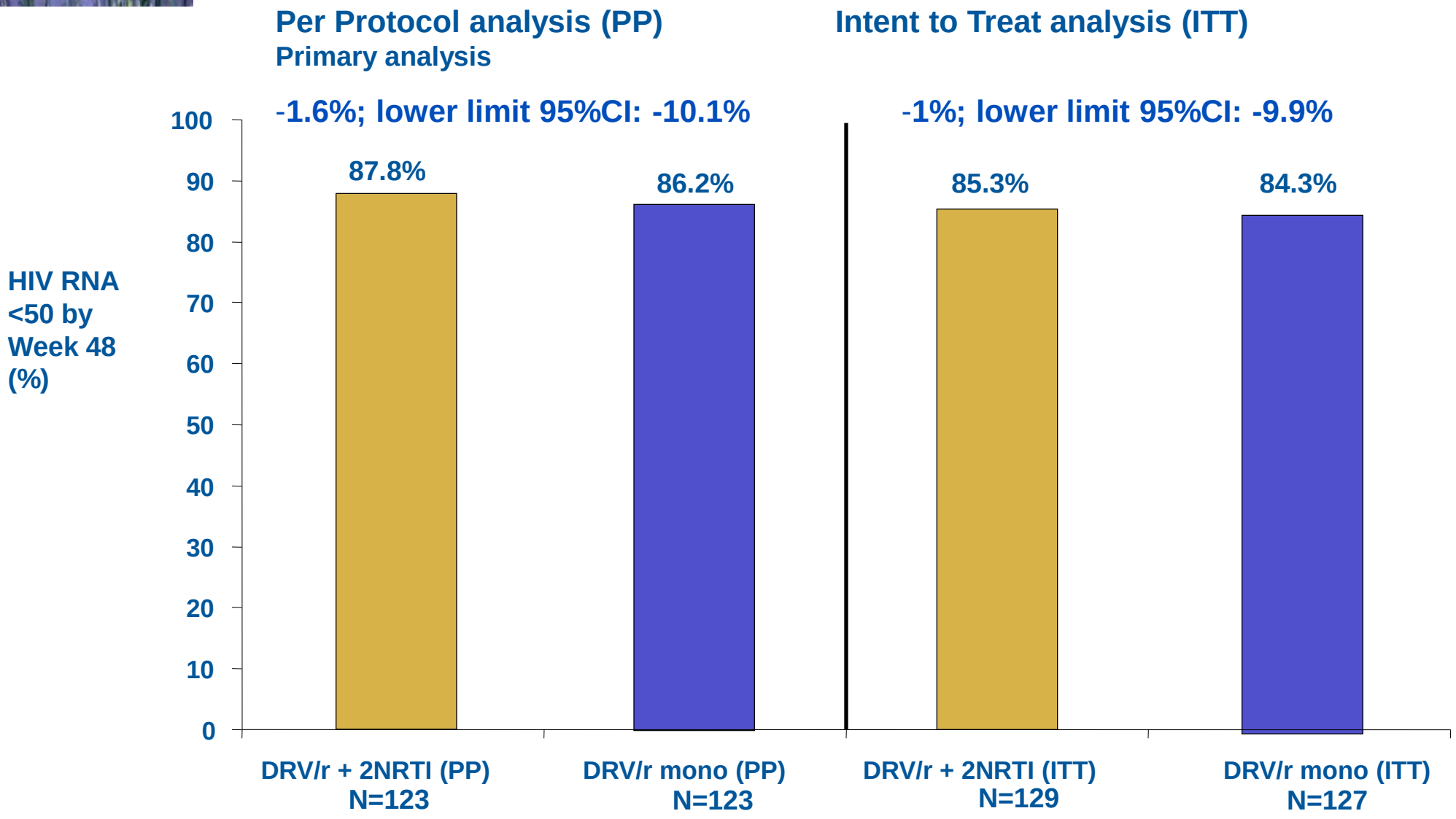
Objectives

Virological suppression

CD4 > 500 et CD4/CD8>1

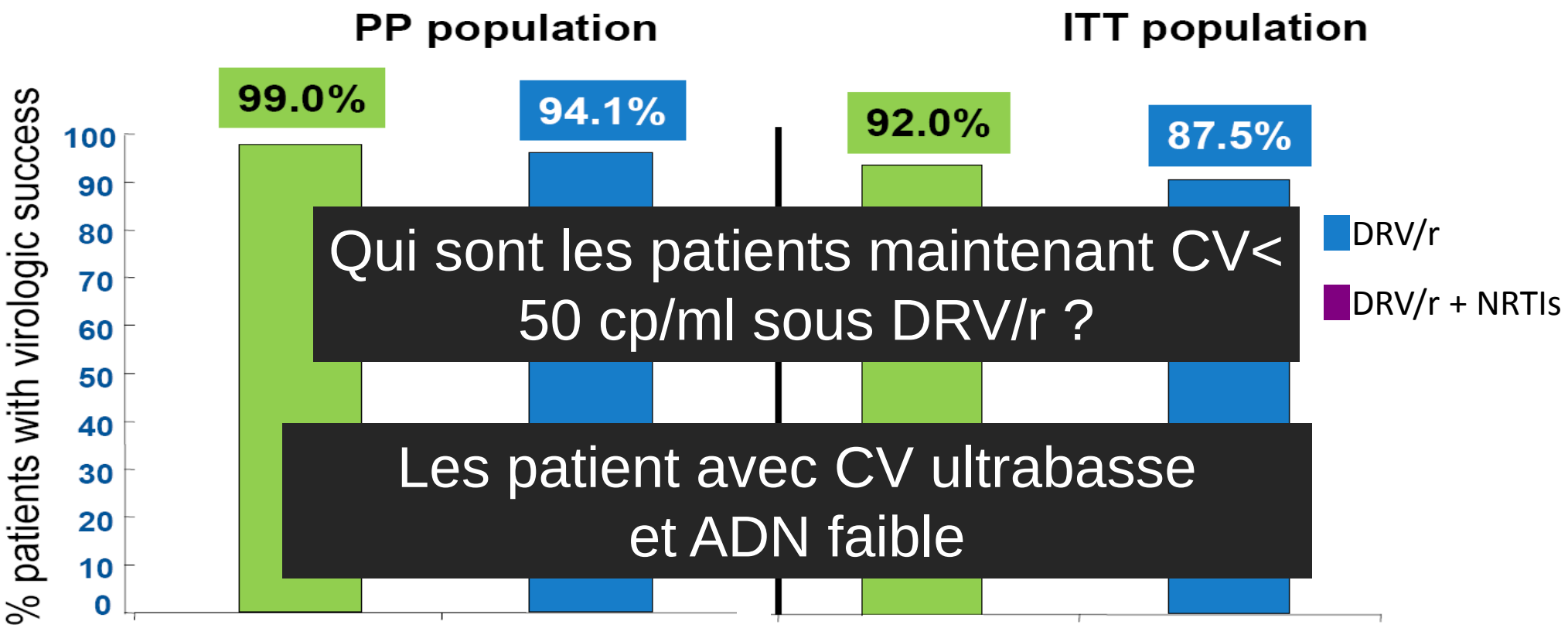
LowDNA reservoir

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



J. Arribas et al, AIDS 2010

MONOI Efficacité virologique S48



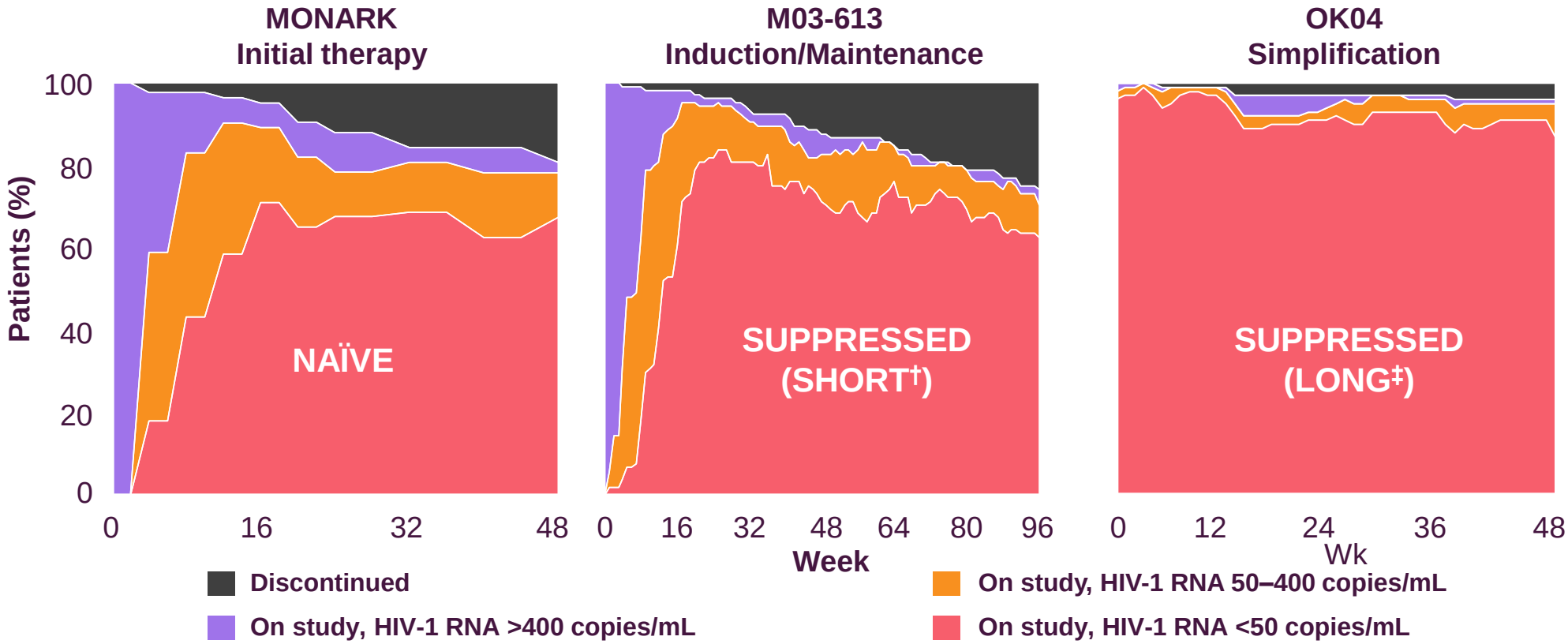
Response	Difference (Lower limit CI)
Rx success (PP, n=204))	- 4.9% (- 9%)
Rx success (ITT, n=225)	- 4.5% (-11%)

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

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

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.

Switching therapy

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

- Reconstitutes ART and resistance history
- Take into consideration BL characteristics and time of viral suppression
- The switched regimen has to include potent and robust drug(s)
- Do not keep resistant drugs that cumulates toxicity and cost

Can we reduce drug burden ?

Monothérapie
IP
molécule robuste ..DTG ?

ARV intermittent
Essai 4D ANRS

Bithérapies
Inhibiteur integrase
NRTI ETRAL ANRS

Réduction dose
IP boosté
NNRTI

New drugs

- High potency
- High tolerability
- Coformulable
- Long half life
- High genetic barrier to resistance
- Low production cost

- To reduce
  - Nb intakes
  - Need for monitoring
  - Delivery optimization

Drugs in clinical developpement

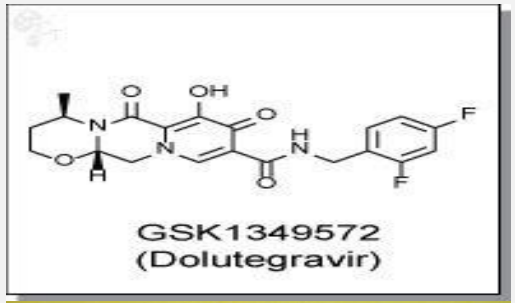
NRTI	NNRTI		Inhib Integrase	CCR5
TAF	LPA 278		GS 744 LPA GS 744	Cenicriviroc
NRTI BMS	MK-1439			

Dolutegravir
a major drug in ARV armentorium

- **High potency +**
  - 2.6 $\log_{10}$ cp/mL in 10 days
  - *Superior to* EFV et darunavir/r in naïve patients
  - *non-inferieur à* raltegravir in naïve patients
  - *Supérieur à* raltegravir inpretreated (INI naive)
  - Active in 63% patients failing INI

  High genetic barrier to resistance

  Once daily ($t_{1/2}$ =15 h) **Low dosage** (50 mg)



- **Limited PK variability /drug drug interactions**

  No CYP induction or inhibition

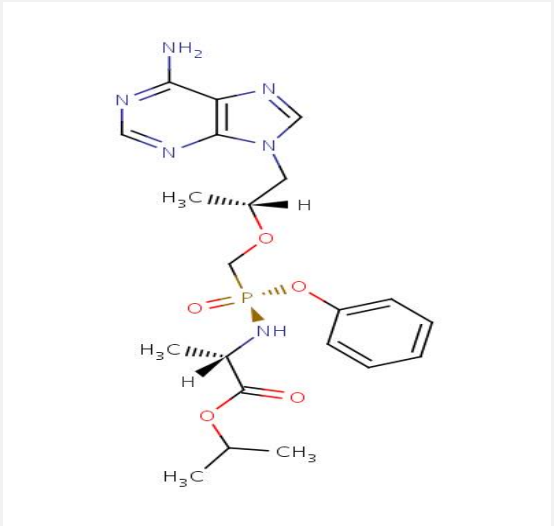
- **Excellent tolerability**

- **Low production cost**

Tenofovir Alafenamide Fumarate (TAF) a new version of an old drug

- Prodrogue NRTI, converted in active tenofovir diphosph e
- Différent du tenofovir disoproxil fumar
  - More active than TDF g VL reduction or 300% pl
  - cellular concentration ++ less i
  - Bettter tolerated kidney and bones
  - Co-formulation possible
  - Dosage : 10 mg par jour

TAF will progressively replace TDF



New long acting antiretroviral drugs
A major option for treatment and prevention

Rilpivirine LA

- Nanosuspension NNRTI
- Injections IM monthly

GSK744 LAP

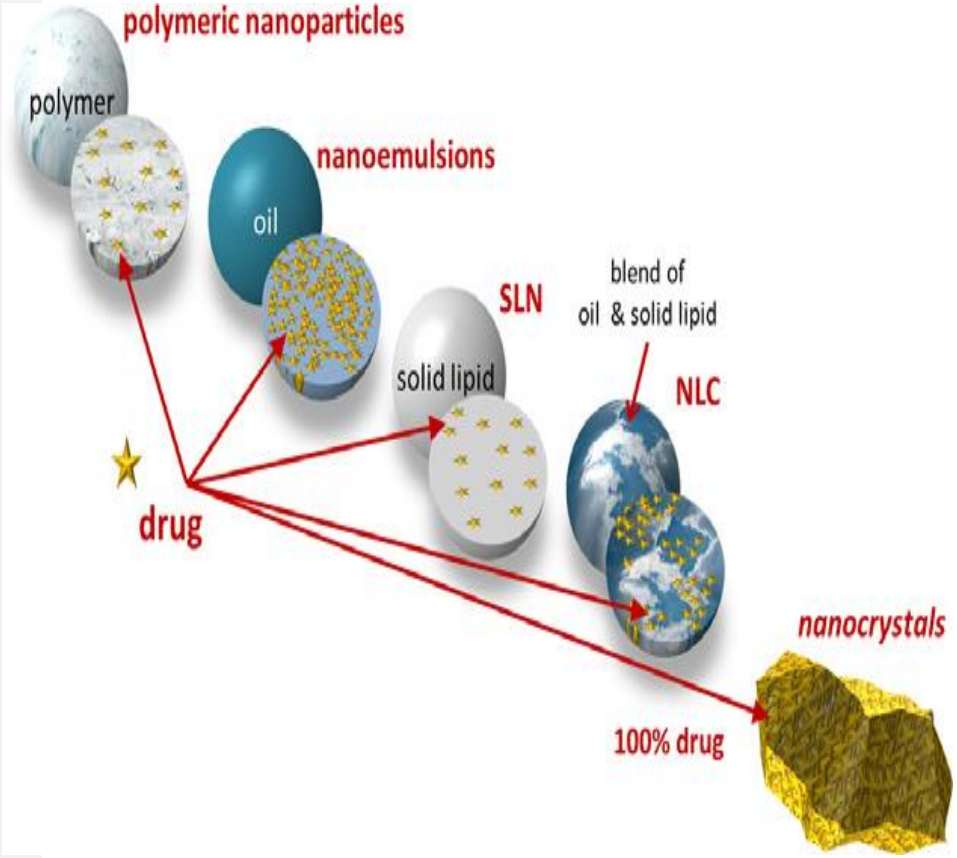
- Nanosuspension integrase inhbitor
- IM and SC /month or /3 months
  200-1200 mg tested

GSK 744 oral (Etude Latte)

10 20 30 60 mg + TDF/FTC

Efficacy : > 90%

No difference between doses



Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

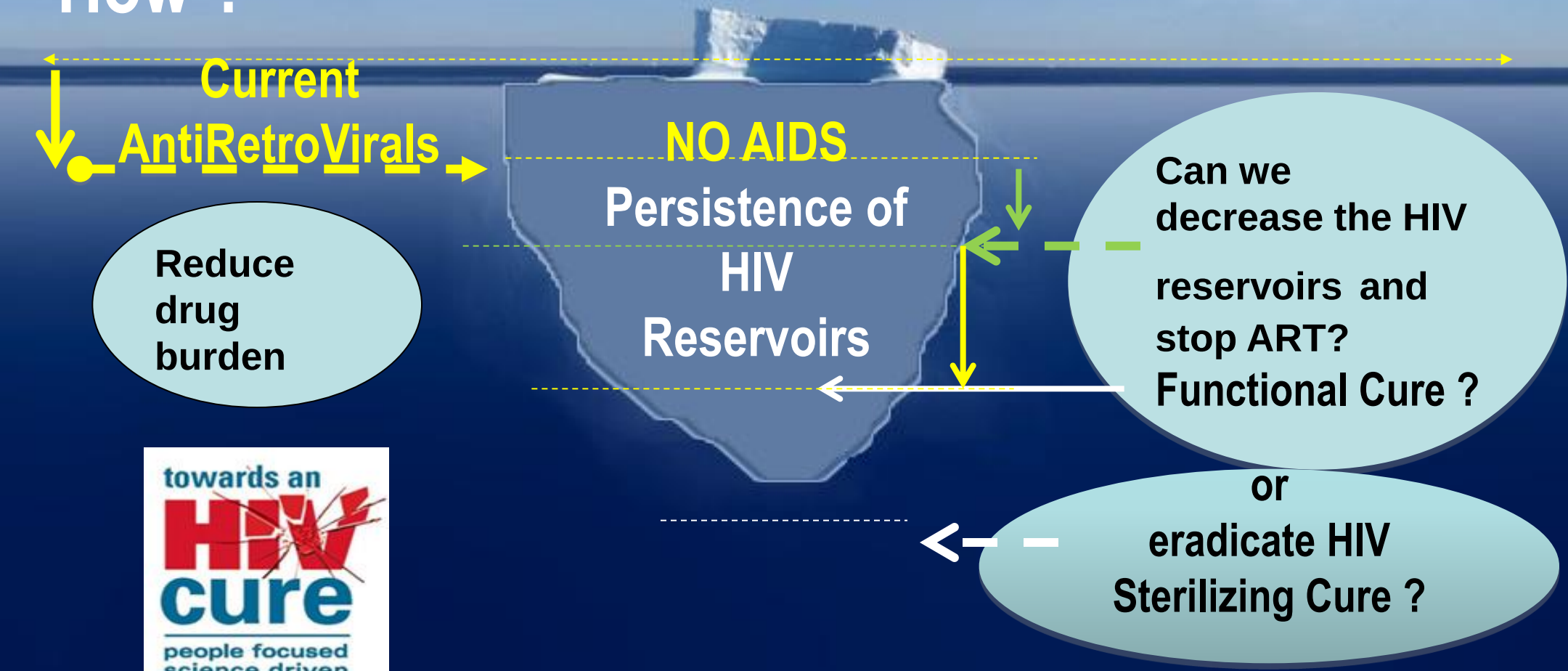
Antiretroviral Strategies

- Treat HIV as ART normalized survival and prevent partner ` transmission
- ART normalizes life of a with HIV person living
- Earlier treatment with better drugs
- Triple drug is the rule particularly for patients with high viral loads
- Individualized treatment will allow to adjust to each patient history
- Saving drugs is key to preserve ART options

Why do we need a Cure for HIV ?

➢ **To control the HIV pandemics**

How ?



towards an HIV cure
people focused
science driven

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**

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

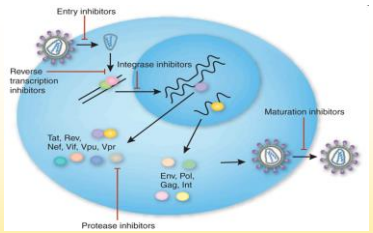
- HIV DNA was the only significant predictor of maintaining VL < 400 cp/ml
  med value : < 10 vs 233 cp / 10^6PBMCs p < 0.001

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

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

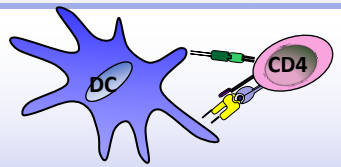
Viral Co-Infections

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