associazione NADIR onlus

Giovedì 24 Settembre 2015

PROGRAMMA SEMINARIO 2015

Presso Hotel Michelangelo, Piazza Luigi di Savoia 6 - Milano

INNOVAZIONE NELLA TERAPIA ANTIRETROVIRALE
GLI INIBITORI DELLE INTEGRASI: I PROTAGONISTI DI UNA NUOVA ERA
Sfide e opportunità per le persone con HIV

Oggi….si può ancora migliorare?

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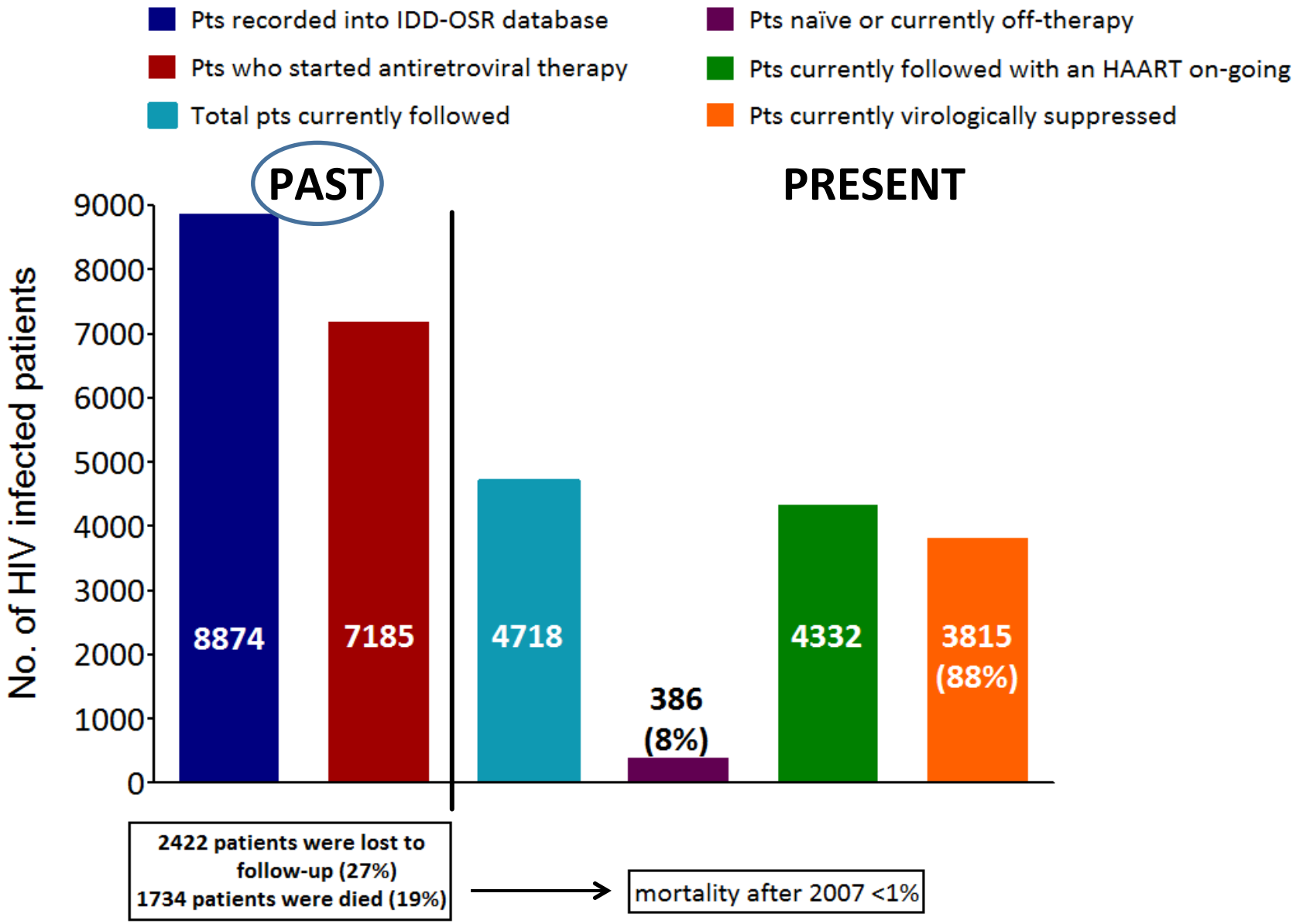
OSPEDALE SAN RAFFAELE

Università Vita-Salute San Raffaele

IDD-OSR – Cohort Data



How far we are from the top?

100%

- cART access
- Early treatment
- Retention in care
- HIV RNA plasma undetectable
- Adherence

0%

- Transmission
- Toxicity
- HIV RNA/DNA + in the blood
- Co-morbidity

HIV: NEW TREATMENT PARADIGMA

TBD: EASIER HIV DIAGNOSIS → AIM: DISCOVER HIV POSITIVE INDIVIDUALS

TBD: EARLY TREATMENT (in particular in PHI!) → AIM: MORE FAVOURABLE LONG TERM HIV CONTROL WITH cART

NEXT AIMS

TBD: LONG TERM cART:
↑ efficacy, ↑ tolerability, ↑ convenience**, ↑ safety, ↓cost
Long acting drugs → AIM: FUNCTIONAL CURE

APPROPRIATE INFECTION STAGING
TBD: studies on

Residual viremia and HIV reservoir infection evaluation under cART. *Blippers rebounding*
+
Immunological patients findings associated with protection or HIV control on cART → AIM: Selection of INDIVIDUAL for Treatment Interruption (SITI). *Host gene protective/favourable factors and molecular mechanism*

TBD: cART intensification + therapeutic vaxin + reservoir cleaning
Latency reversing agents → AIM: ERADICATION

HIV: NEW TREATMENT PARADIGMA

TBD:
EASIER HIV DIAGNOSIS

AIM: SUBMERGED EMERSION

DISCOVER HIV POSITIVE INDIVIDUALS

TBD:
EARLY TREATMENT
(in particular in PHI!)

AIM: FUNCTIONAL CARE

MORE FAVOURABLE
LONG TERM HIV CONTROL WITH cART

NEXT AIMS

TBD: LONG TERM cART:
↑ efficacy, ↑ tolerability, ↑ convenience**, ↑ safety, ↓cost
NEWS: Long acting drugs

→ GOAL:
FUNCTIONAL CURE

APPROPRIATE INFECTION STAGING

TBD: studies on

Residual viremia and HIV reservoir infection evaluation under cART.
Blippers, rebounders HIV replication feature
+
Immunological patients findings associated with protection or HIV control on cART

→ GOAL:
Selection of INDIVIDUAL for Treatment Interruption (SITI)

NEWS:
Host gene protective/favourable factors and molecular mechanism

TBD: cART intensification + therapeutic vaxin + reservoir cleaning

NEWS: Latency reverting agents

→ GOAL:
ERADICATION

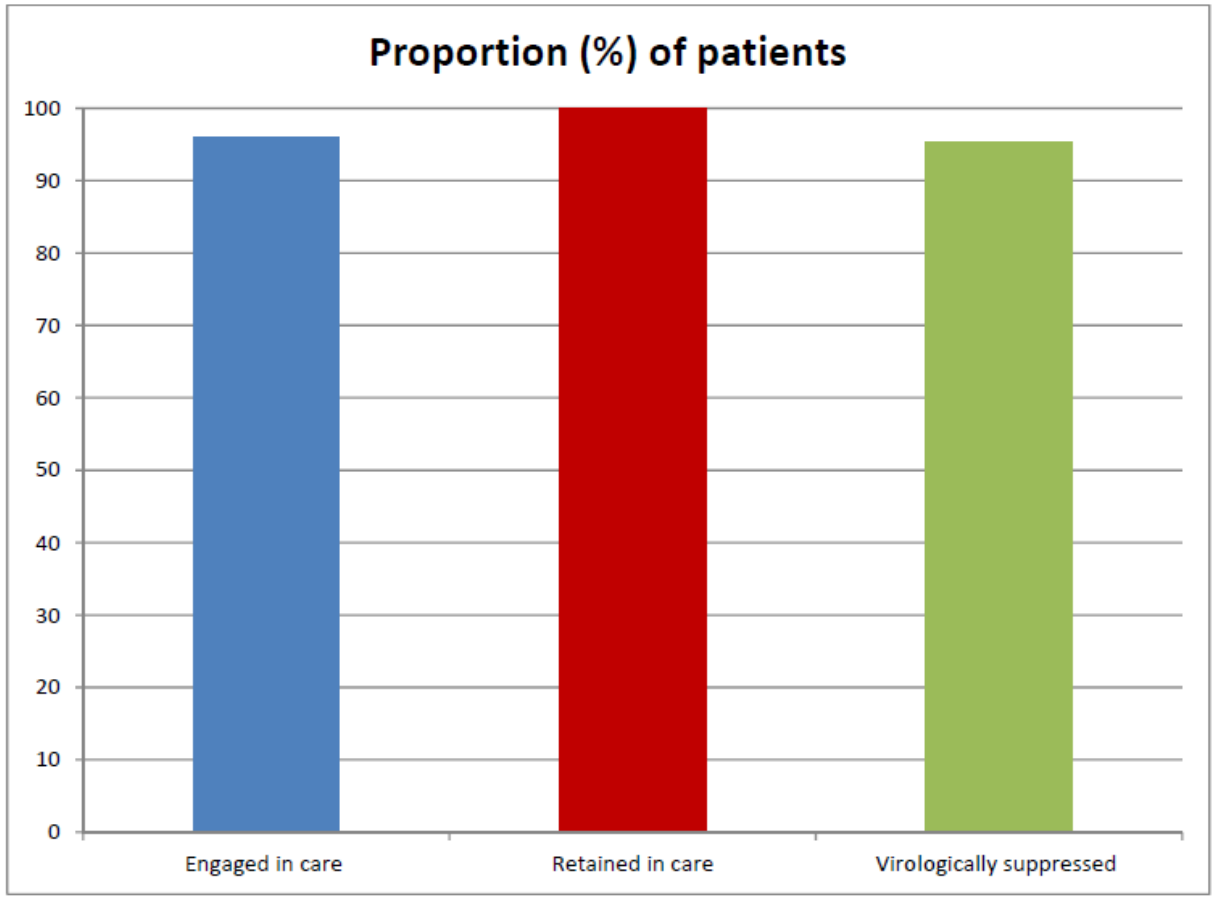
Non solo il
racconto
di ciò
che è stato!

Addressing barriers to the end of AIDS by 2030

The introduction of combination antiretroviral therapy (ART) in 1996 was the first milestone in the fight against HIV/AIDS, and its impact has been huge. Today, we have solid proof that early ART initiation provides benefit for the health of the HIV infected people[1,2] and reduces the risk of HIV transmission.[3] The concept of treatment epidemic by 2030. To make it happen, three major challenges are in front of us.

The first challenge is scientific: the discovery of an HIV vaccine. Treatment as prevention alone will not be able to stop the epidemic. Despite increasing ART access, there will be no end of AIDS without a preventive

Figure 1. Continuum of care after HIV diagnosis with a point of care salivary testing: proportion of patients retained, engaged in care and virologically suppressed.



Parisi MR et al, new microbiol 2015, in press

The NEW ENGLAND JOURNAL of MEDICINE

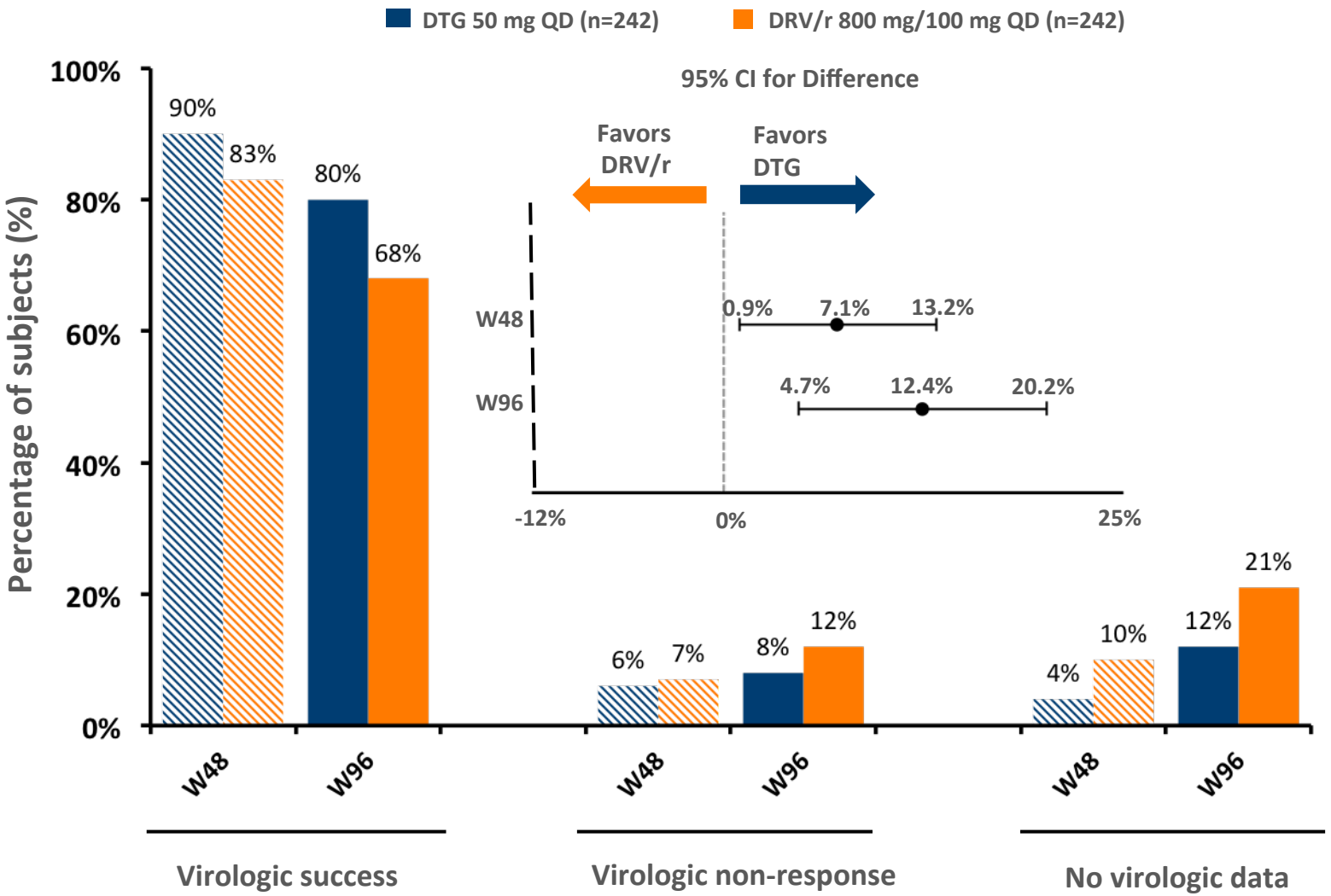
ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

Respect the rule of the superiority criterium

FLAMINGO: DTG + 2 NRTIs Superior to DRV/RTV + 2 NRTIs in Tx-Naive Pts at Wk 48 and 96



Molina JM, et al. HIV Drug Therapy Glasgow 2014; Glasgow, UK. Abstract #O153.

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 96 In Snapshot (Primary) Analysis i.e. Missing, Switch or Discontinuation = Failure						
	SPRING-2		SINGLE		FLAMINGO	
	DTG	RAL	DTG	EFV/FTC/TDF	DTG	DRV/r
OVERALL	332/411 (81%)	314/411 (76%)	332/414 (80%)	303/419 (72%)	194/242 (80%)	164/242 (68%)
INDIVIDUALS WITH HIGH BASELINE VIRAL LOAD BY BACKGROUND REGIMEN						
>100,000 c/mL						
ABC/3TC	27/37 (73%)	26/39 (67%)	95/134 (71%)	-	11/13 (85%)	7/12 (58%)
TDF/FTC	62/77 (81%)	47/77 (61%)	-	94/131 (72%)	39/48 (81%)	25/49 (51%)
INDIVIDUALS WITH LOW BASELINE CD4						
<200c/mm3	39/55 (71%)	28/50 (56%)	39/57 (68%)	45/62 (73%)	18/23 (78%)	14/24 (58%)
200 to <350c/mm^3	116/144 (81%)	103/139 (74%)	135/163 (83%)	113/159 (71%)	60/73 (82%)	36/51 (71%)
Kaplan Meier estimates of the Proportion of Subjects without Efficacy Related Discontinuation = Failure at Week 96 (PDVF or withdrawal due to lack of efficacy are counted as failure and subjects who discontinue for other reasons are censored)						
	SPRING-2		SINGLE		FLAMINGO	
	DTG	RAL	DTG	EFV/FTC/TDF	DTG	DRV/r
OVERALL	94%	92%	94%	93%	99%	98%
INDIVIDUALS WITH HIGH BASELINE VIRAL LOAD						
>100,000 c/mL	90%	84%	87%	88%	98%	96%

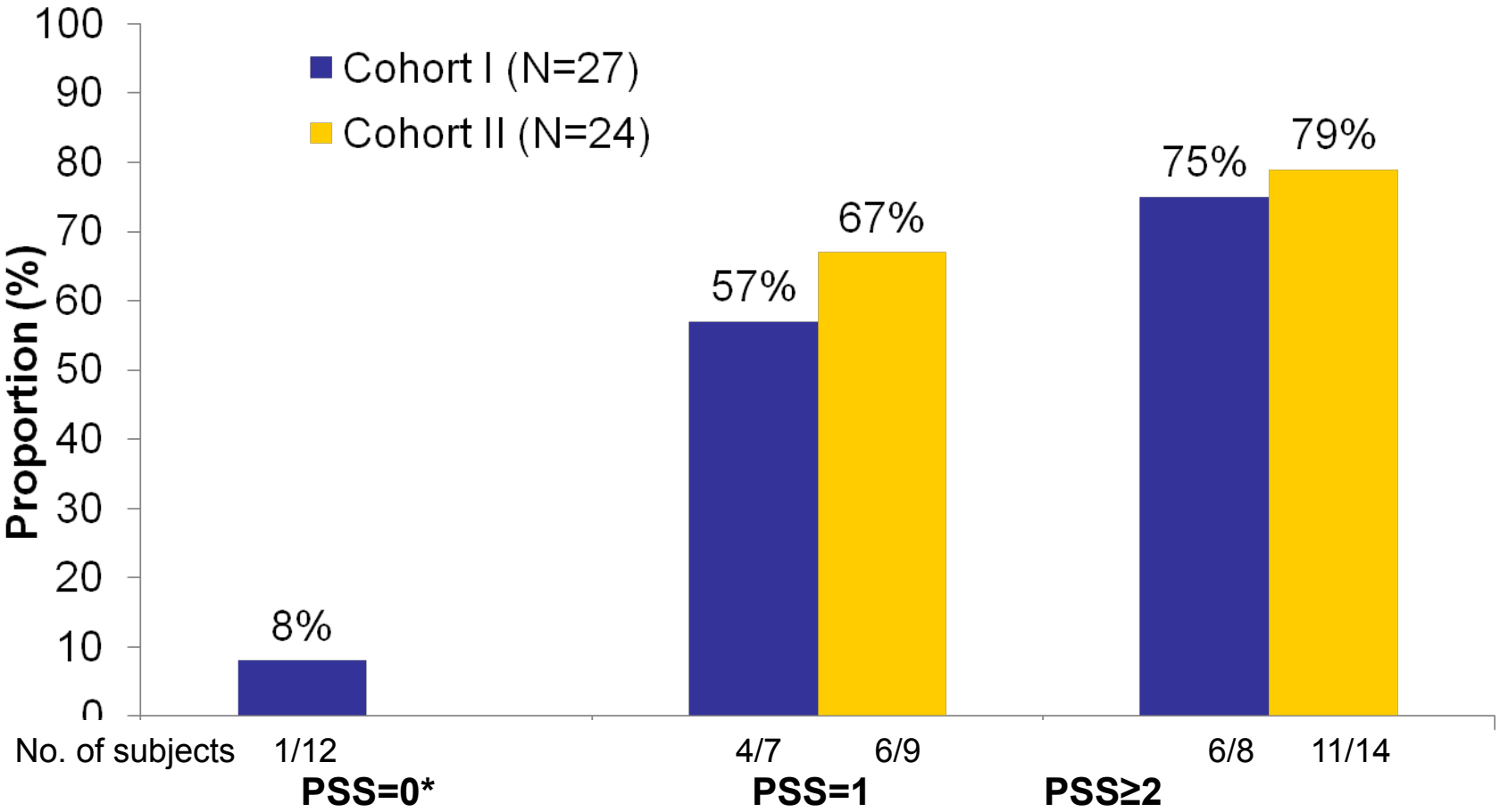
Granier C, CROI 2015

MEXP: failing patients

The top it’s not so far!

Dolutegravir (DTG, S/GSK1349572) treatment of HIV subjects with raltegravir resistance: viral suppression at Week 24 in the VIKING study

Proportion of RAL-resistant that responded at Week 24 (<50 c/mL, TLOVR) - increases with OBR activity



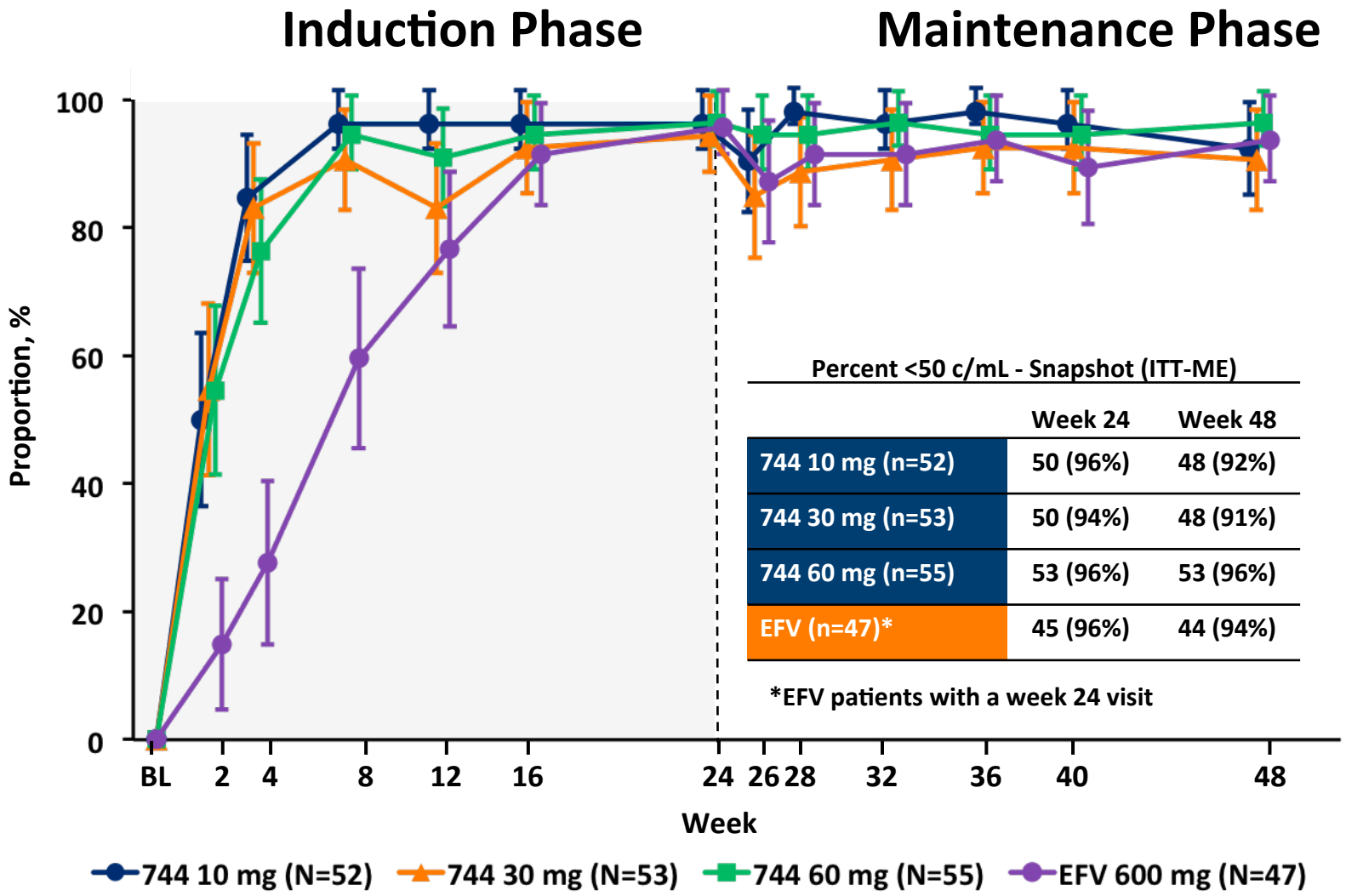
*: 1 subject in Cohort II with PSS=0.5 responded

FDC with TAF:

Efficacy ↑ = Proteinuria ↓ MOC ↑

Secondary Endpoint – Maintenance Population

Virologic Success: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



Percent <50 c/mL - Snapshot (ITT-ME)

	Week 24	Week 48
744 10 mg (n=52)	50 (96%)	48 (92%)
744 30 mg (n=53)	50 (94%)	48 (91%)
744 60 mg (n=55)	53 (96%)	53 (96%)
EFV (n=47)*	45 (96%)	44 (94%)

*EFV patients with a week 24 visit

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

?! Costs?!

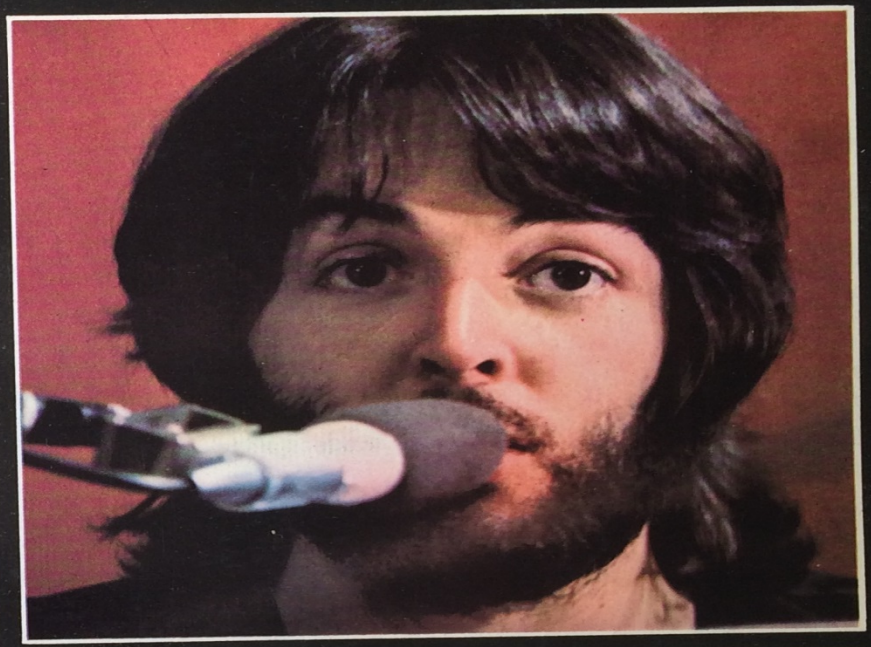
Principi d'impiego dei farmaci antiretrovirali equivalenti

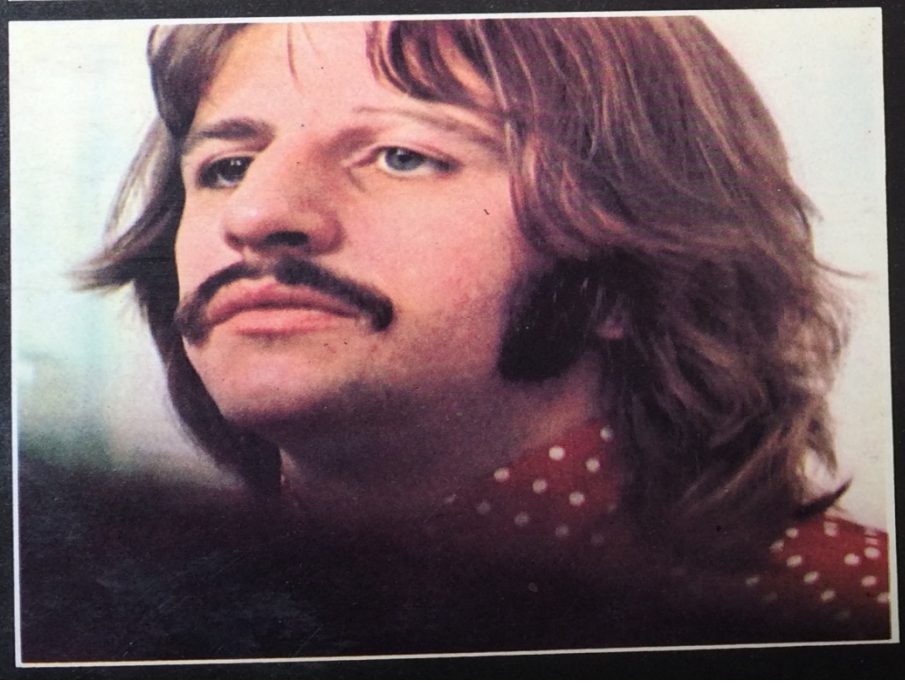
3. Pur in assenza di consistenti dati di letteratura finalizzati a questo scopo, al fine anche di garantire un responsabile impiego delle risorse, si ritiene di proporre i seguenti principi d'impiego (qualitativi) per l'introduzione delle specialità medicinali equivalenti. Si sottolinea comunque la necessità di *garantire la continuità e l'appropriatezza del regime terapeutico attraverso un'omogenea e stabile disponibilità territoriale delle specifiche specialità medicinali prescelte* (vedi parte precedente 'Possibili Criticità'):

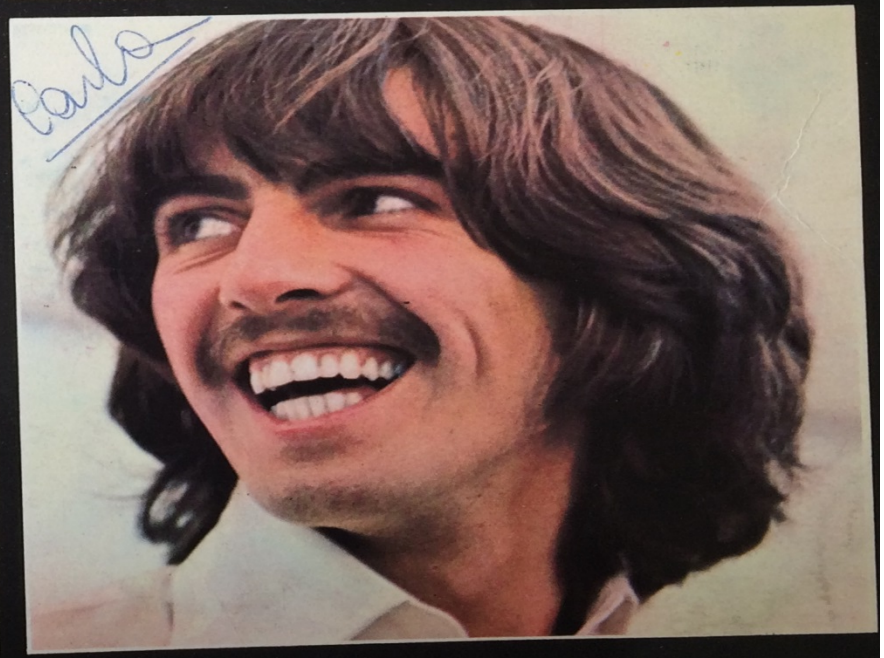
   a. Condividere con il paziente la scelta del regime terapeutico [AIII];
   b. Selezionare e monitorare il paziente, in particolare colui che presenta fattori noti di rischio di non aderenza [BIII];
   c. Valutare con attenzione l'aderenza, in occasione delle visite programmate [AIII];
   d. Identificare precocemente potenziali fattori favorenti l'insuccesso virologico [AIII].

E' comunque auspicabile il confronto di tollerabilità ed efficacia tra diversi regimi con FDC e con regimi non co-formulati, con l'introduzione di singole molecole equivalenti, in studi controllati preferibilmente istituzionali.

LET IT BE



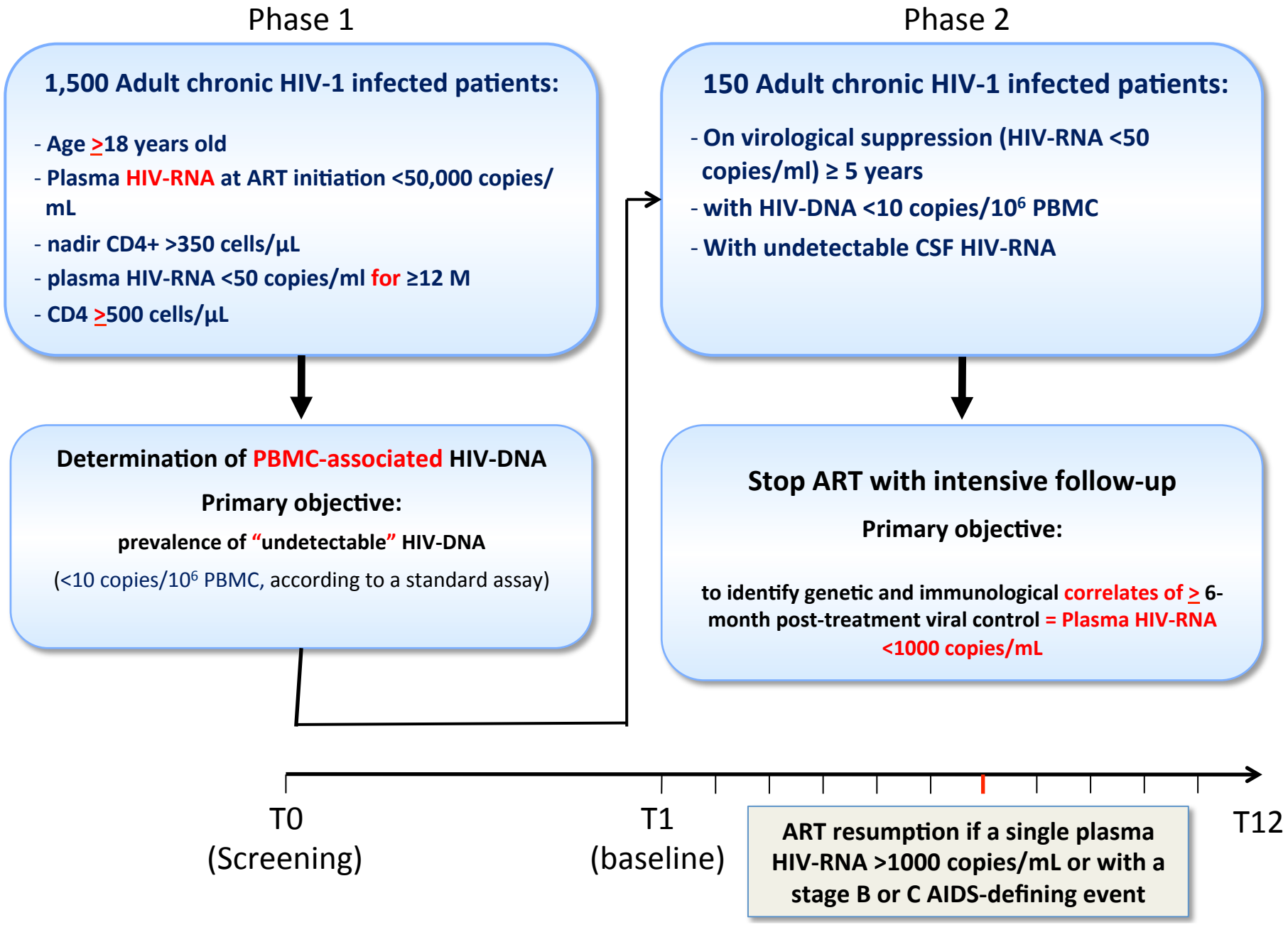




Jumping at eradication

INVICTIS:
best performers selection study

Study design



CONCISE COMMUNICATION

A low HIV-DNA level in peripheral blood mononuclear cells at antiretroviral treatment interruption predicts a higher probability of maintaining viral control

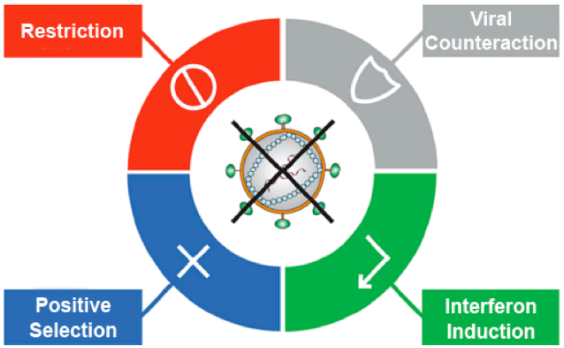
Lambert Assoumou[a,b], Laurence Weiss[c,d], Christophe Piketty[c], Marianne Burgard[e], Adeline Melard[f], Pierre-Marie Girard[g], Christine Rouzioux[d,e], Dominique Costagliola[a,b], the ANRS 116 SALTO study group

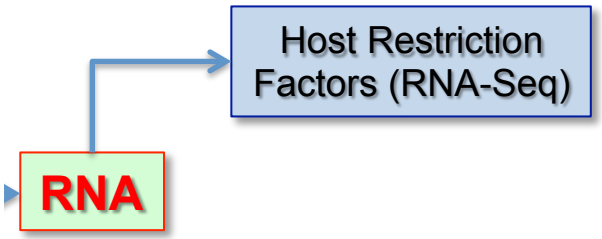
AIDS 2015, **29**:2003–2007

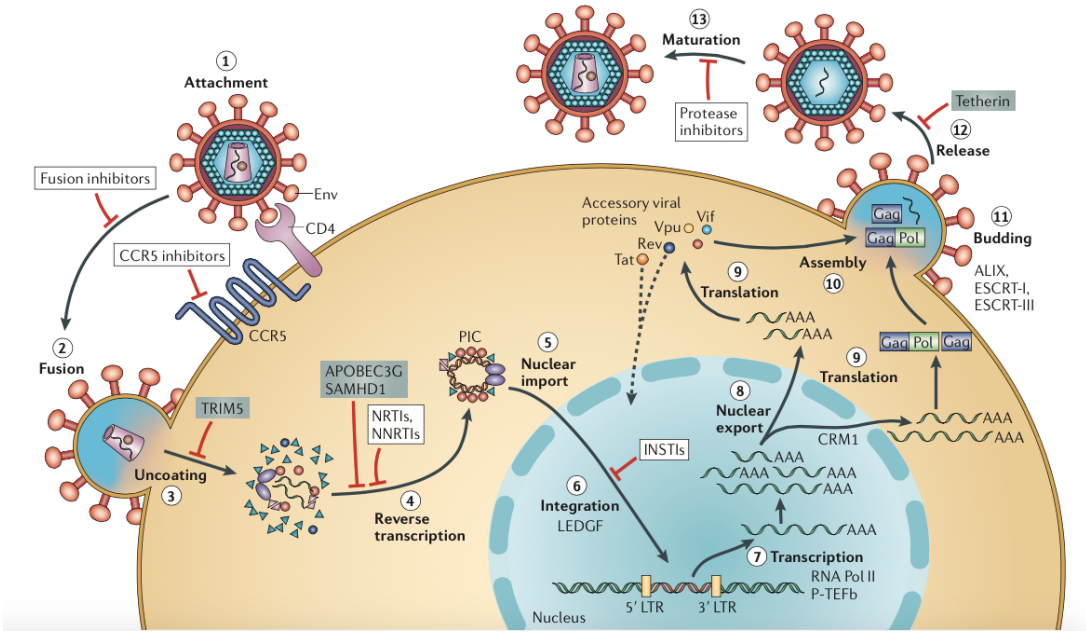
STHAI PROJECT. *Host Restriction Factors*

Restriction Factors (RF): dominant cellular factors that have evolved specifically to interfere with viral replication

- *Direct cause of a significant* ***decrease in viral infectivity***
- *Target of an equally potent* ***viral counter-restriction mechanism***
- ***Positive selection signature*** *due to a direct evolutionary competition*
- *Often strongly* ***induced by interferon***







Genetic Polymorphisms in the MHC Locus Associated with a Different Outcome of HIV-1 Disease Progression

Gene variants	Associated to	Mechanism of action
HLA class I heterozygosity	Delayed progression	Broader HLA class I antigen presentation [56–58]
HLA class I discordance	Decreased frequency of infection	Diminished risk of HIV transmission [68–70]
HLAB*57	Delayed progression	Delayed HIV-1 escape [26, 56, 59–61]
HLAB*27	Delayed progression	Delayed onset of escape mutants [26, 56]
HLAB*35	Accelerated progression	Reduced HIV peptides binding [56]
HLA supertype A2/6802	Resistance	Presentation of conserved HIV peptides [71, 72]
HLA class I Bw4-KIR3SD1	Delayed progression	Suppression of HIV infected lymphocytes (?) [65]

*allele-group gene products.

*…abbiamo dimostrato la presenza di una forte associazione (OD 6.8; p=0.003) tra lo status di ELC e la presenza di un genotipo complesso caratterizzato da **alleli C2** ad alta espressione e da uno o più **geni KIR attivatori** (2DS1, 3, 5).*

Single-Nucleotide Polymorphism–Defined Class I and Class III Major Histocompatibility Complex Genetic Subregions Contribute to Natural Long-term Nonprogression in HIV Infection

J. Guergnon,[1,2] C. Dalmasso,[3,4] P. Broet,[3] L. Meyer,[5] S. J. Westrop,[6] N. Imami,[6] E. Vicenzi,[7] G. Morsica,[8] M. Tinelli,[9] B. Zanone Poma,[10] C. Goujard,[11] V. Potard,[12] F. M. Gotch,[6] C. Casoli,[10] A. Cossarizza,[13] F. Macciardi,[14,15] P. Debré,[1,2] J. F. Delfraissy,[16] M. Galli,[10] B. Autran,[1,2] D. Costagliola,[12,17] G. Poli,[18,19] I. Theodorou,[1,2] A. Riva,[10] and the GISHEAL Consortium

FP6_GISHEAL Consortium

The Journal of Infectious Diseases 2012;205:718–24

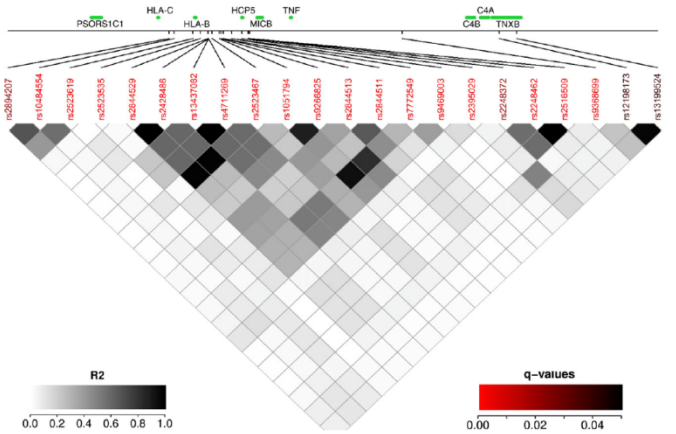


Figure 1. Linkage disequilibrium matrix (LD) for the major single-nucleotide polymorphisms (SNPs) in the major histocompatibility complex region. The LD data matrix was calculated from the PRIMO seroconverters and the Genetic and Immunological Study of HIV$^+$ European and African LTNP (GISHEAL) cohorts, respectively. Gray color intensity of each box is proportional to strength of LD property (r^2) for marker pair. Red color intensity of rs numbers is proportional to level of q value (false discovery rates) associated with the given SNP in our genome-wide association study.

Seminario Nadir 2015 - Iniziativa resa possibile grazie al supporto di ViiV Healthcare

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