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Paestum (SA) 14-15 maggio 2004

La terapia dell'infezione da HIV: passato, presente e futuro.

Prof. Adriano Lazzarin
Università Vita-Salute San Raffaele, Milano

Università Vita-Salute San Raffaele
Scuola di Specializzazione in Malattie Infettive

The past

Stop AIDS ARC

➡ *Fight against wild type virus*

The present

Avoid HIV disease progression

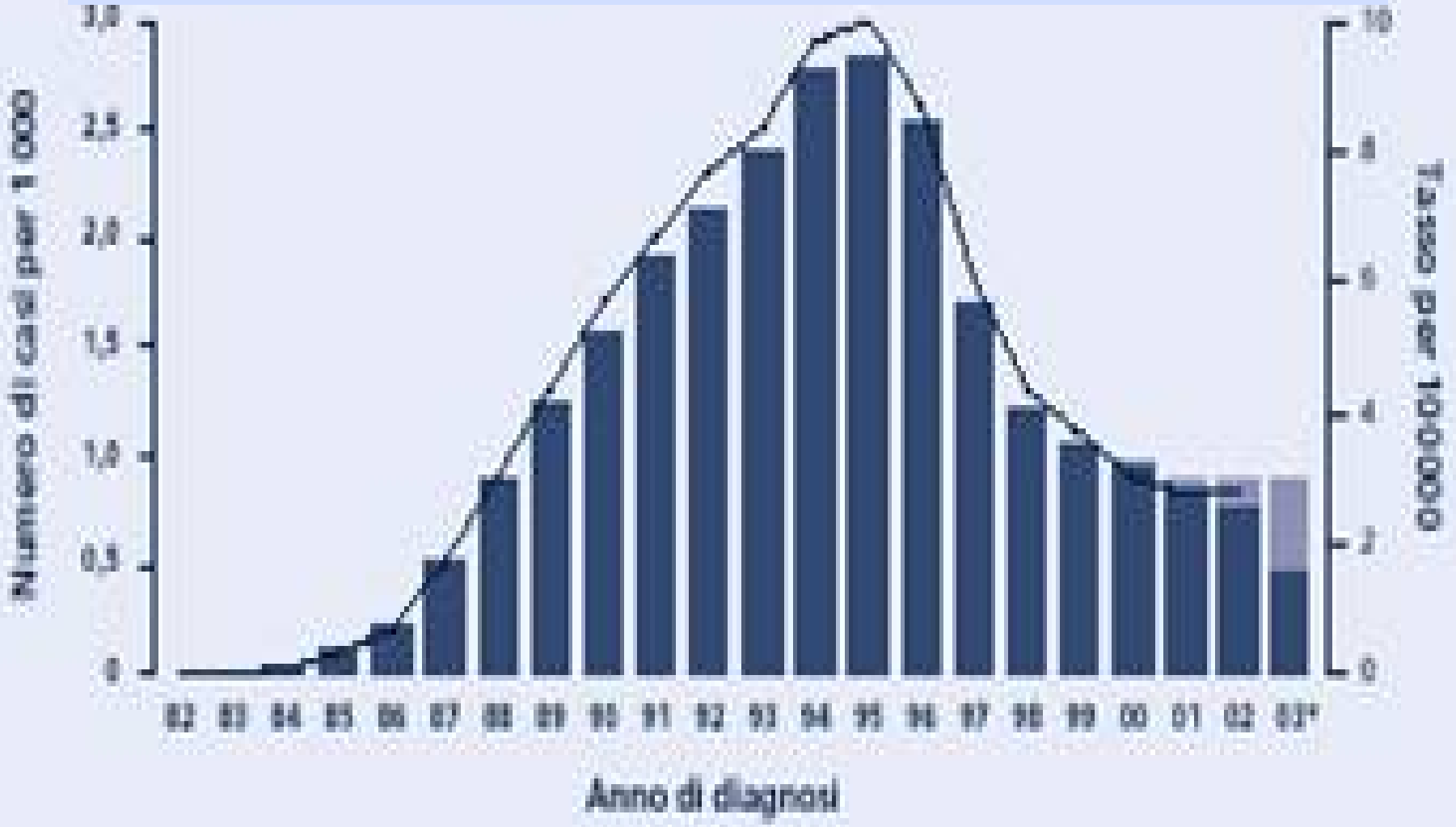
➡ *Control of the replication of resistant virus*

The future

Achieve immunerecovery

➡ *Consider ethiopatogenetic treatments*

Passato: Tempi difficili



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

March 23, 2004

Presente: Estado novo

"Il regime delle linee guida"

Antiretroviral regimens or components that should not be offered at any time

These are summarized as follows:

- Monotherapy.
- Dual nucleoside therapy.
- 3-NRTI regimen with abacavir + tenofovir + lamivudine.
- 3-NRTI regimen with didanosine + tenofovir + lamivudine.
- Didanosine + stavudine.
- Efavirenz in pregnancy
- Zidovudine plus stavudine
- Saquinavir hard gel capsule (Invirase ®) as a single PI.
- Zalcitabine plus stavudine or zalcitabine plus Didanosine
- Atazanavir plus indinavir
- Emtricitabine plus lamivudine as 2 NRTI backbone
- Hydroxyurea

Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral Naïve Patients.

NNRTI-Based Regimens

Preferred Regimens

efavirenz + lamivudine + zidovudine (or tenofovir DF or stavudine *) – except for pregnant women or women with pregnancy potential**

PI-Based Regimens

Preferred Regimens

lopinavir/ritonavir (co-formulated as Kaletra®) + lamivudine + zidovudine (or stavudine*)

Triple NRTI Regimen – Only when a preferred or alternative NNRTI- or a PI-based regimen cannot or should not be used as first line therapy

abacavir + lamivudine + zidovudine (or stavudine)

Futuro:
La luce in fondo al tunnel

Terapia ARV personalizzata

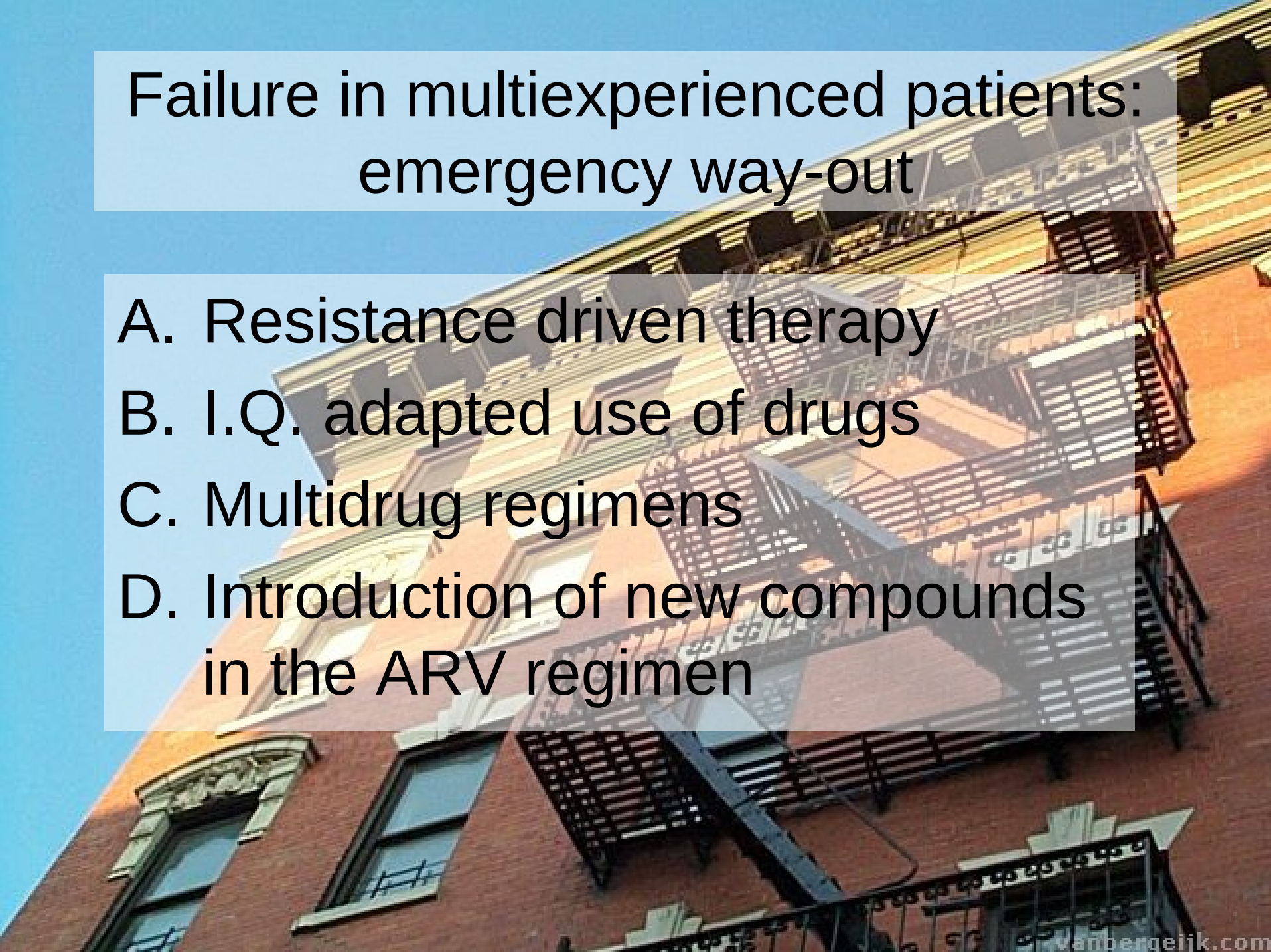
Da trilogia: “I sotterranei della libertà”. Jorge Amado

Resistance up-date on Centro S. Luigi cohort

120 multiexperienced patients without any available antiretroviral treatment

Failure in multiexperienced patients: emergency way-out

A. Resistance driven therapy
B. I.Q. adapted use of drugs
C. Multidrug regimens
D. Introduction of new compounds in the ARV regimen



A) Resistance driven therapy

☞ *Choose (new) available drugs with different resistance profile!*

Tenofovir

Fosamprenavir

Atazanavir

Tipranavir

B) I.Q. adapted therapy.

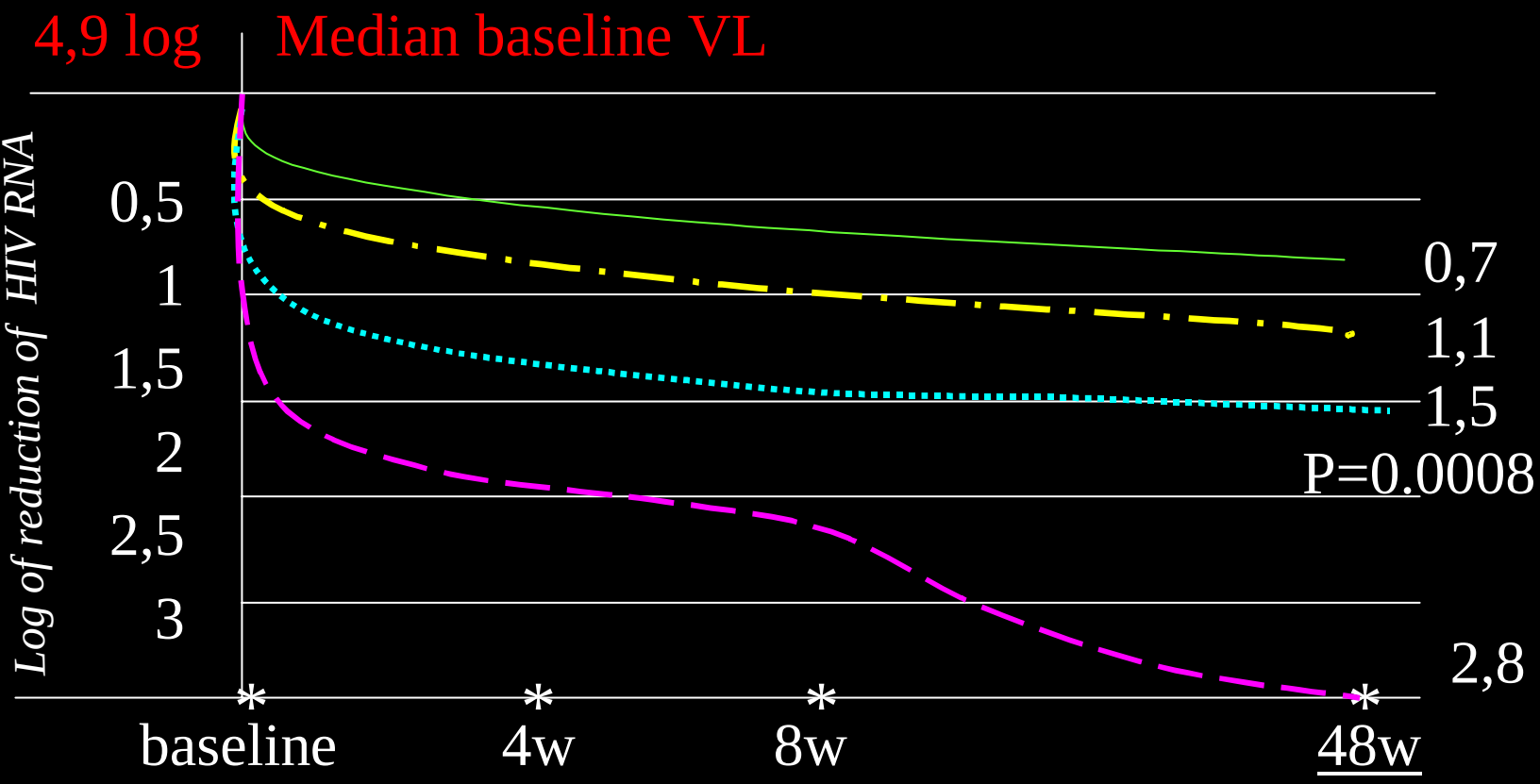
☞ *PI boosting regimens*

With

TDM/IQ, VIQ, NIQ, GIQ

or Without pharmacokinetics help

- P.Is/boosting doses of ritonavir
- DUAL PI (PI/r/PI)
- Atazanavir/Amprenavir
- Atazanavir/Saquinavir



NIQ < 0,6

NIQ 0,6 – 2,6

NIQ 2,6-14.5

NIQ >14,5

* TDM determination

***** 41% pts <50 copies HIV RNA***

C) Multidrug regimens

☞

MegaHAART

GIGHAART

D) Introduction of new compounds in ARV regimens

- Integrase inhibitors
- Entry inhibitors
- Immunomodulators
- Vaxins

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Enfuvirtide in Patients Infected with Drug-Resistant HIV-1 in Europe and Australia

Adriano Lazzarin, M.D., Bonaventura Clotet, M.D., Ph.D., David Cooper, M.D., D.Sc., Jacques Reynes, M.D., Ph.D., Keikawus Arasteh, M.D., Mark Nelson, M.B., B.S., Christine Katlama, M.D., Hans-Jürgen Stellbrink, M.D., Jean-François Delfraissy, M.D., Joep Lange, M.D., Ph.D., Les Huson, Ph.D., Ralph DeMasi, Ph.D., Cynthia Wat, M.B., B.S., John Delehanty, Ph.D., Claude Drobnes, Ph.D., and Miklos Salgo, M.D., Ph.D., for the TORO 2 Study Group*

N Engl J Med 2003;348:2186-95.

TORO 1 and TORO 2 trials: 96 week virological and immunological response of enfuvirtide with an optimized background regimen

ENF + OB	Weeks	24w	48w	72w	96w
	N°pts	247	225	193	175
% HIV RNA <400 copies/mL	OT	37,4	34	29,2	26,5
	ITT	42,4	44,6	44,6	48

TORO 1 and TORO 2 trials: 96 week virological and immunological response of enfuvirtide with an optimized background regimen

ENF + OB	24w	48w	72w	96w
	247	225	193	175
% CD4 + 50 c/μL	48,6	50,5	44,9	37,8
% CD4 + 100 c/μL	29,8	35	38	31,5
% CD4 ≥ 200 c/μL	7,4	14,5	18,1	18,5

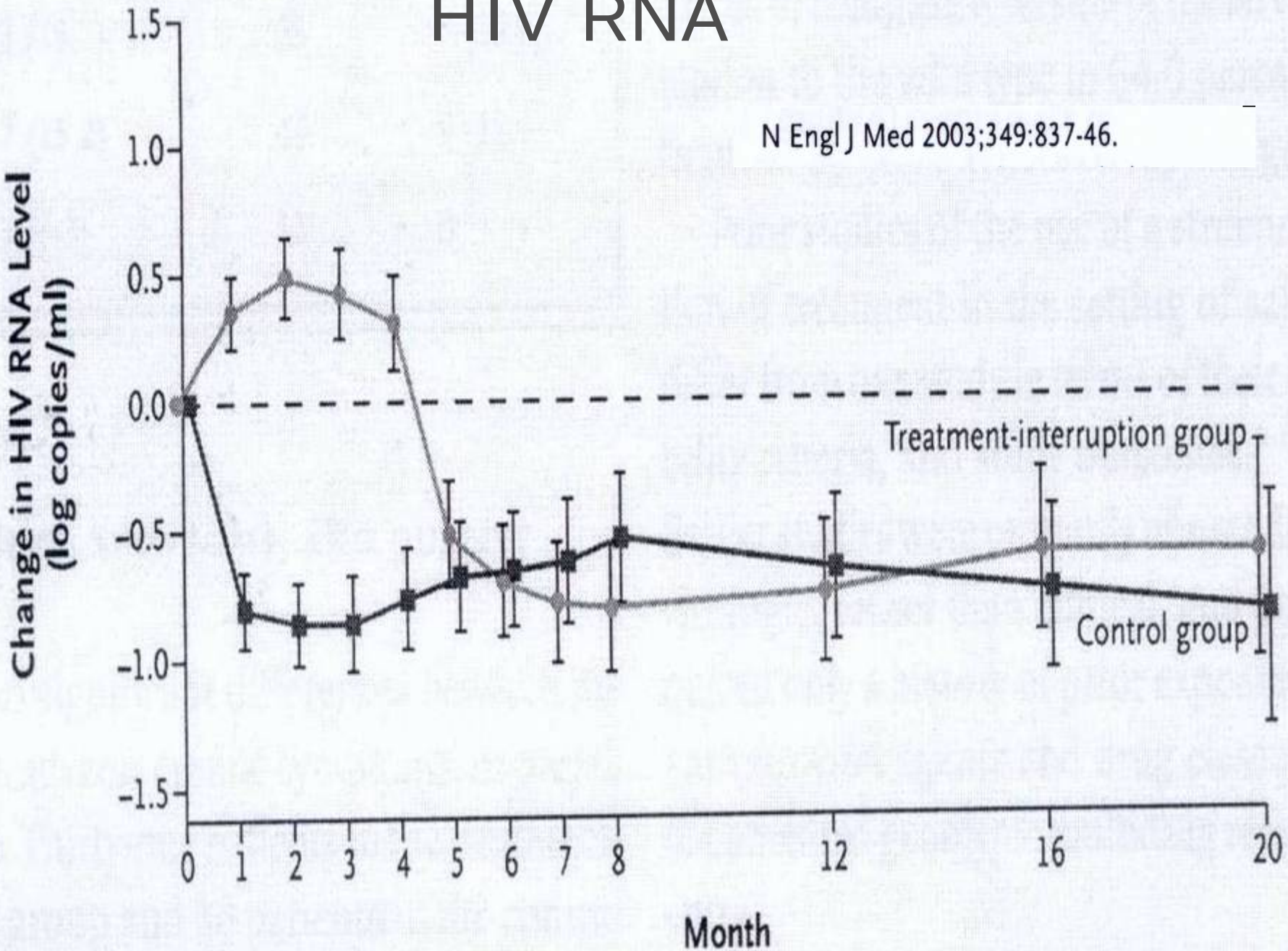
Of those OT at week 96, the % with +50, +100 or ≥200 c/μL improvements from BL were 75.8%, 63.3% and 36.7%

Strategic Treatment Interruptions as part of salvage therapy

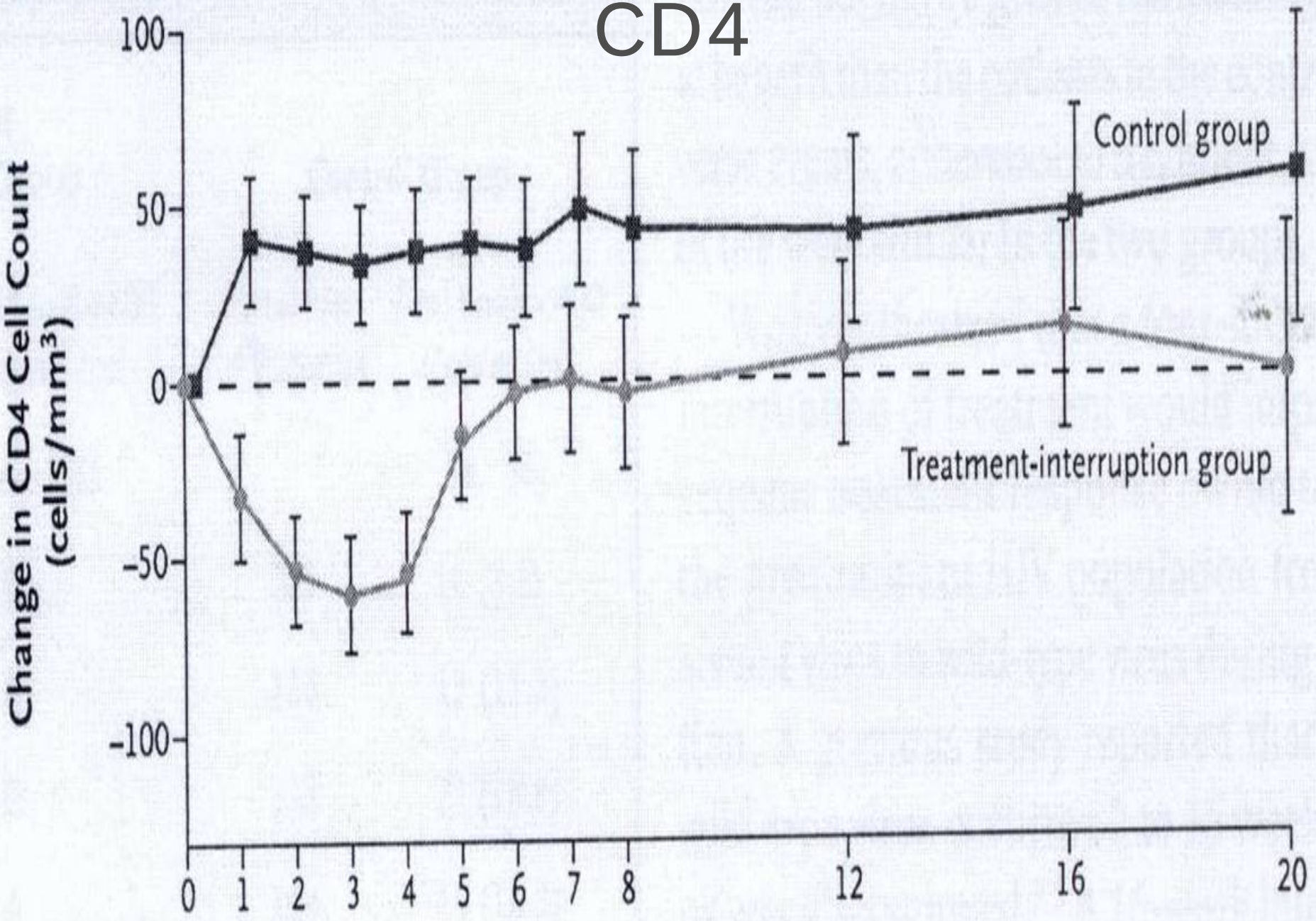
HAART.

DIFFICILE SEPARARSENE!

HIV RNA

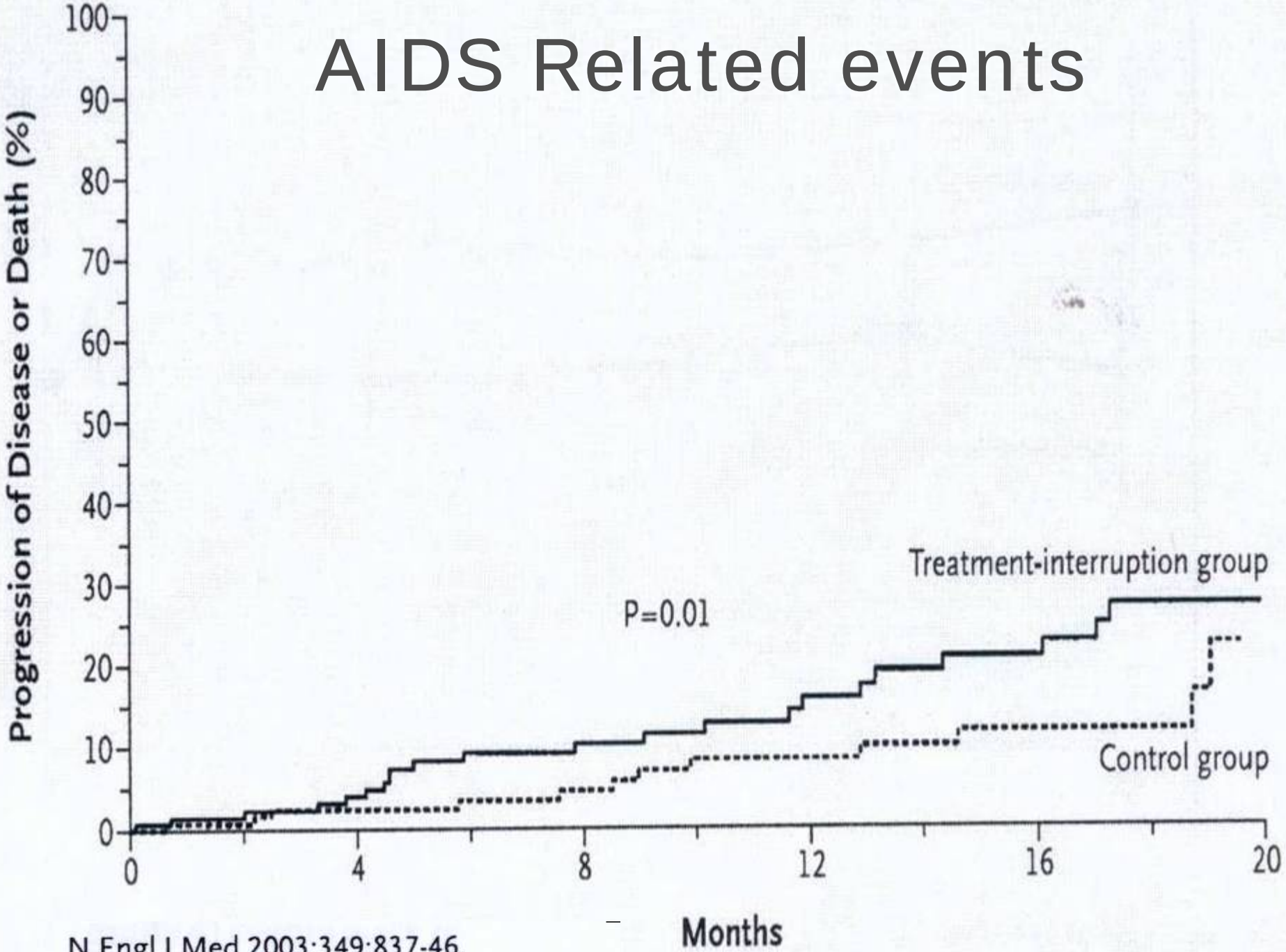

N Engl J Med 2003;349:837-46.
Change in HIV RNA Level (log copies/ml)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Treatment-interruption group
Control group
0
1
2
3
4
5
6
7
8
12
16
20
Month

CD4



N Engl J Med 2003;349:837-46.

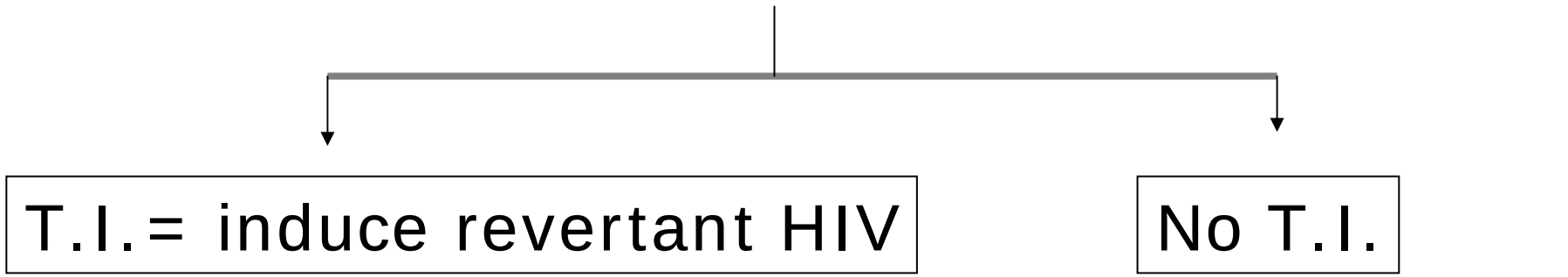
AIDS Related events



N Engl J Med 2003;349:837-46.

After J.Lawrence STI-NEJM-paper

Rescue therapy in MDR failing pts



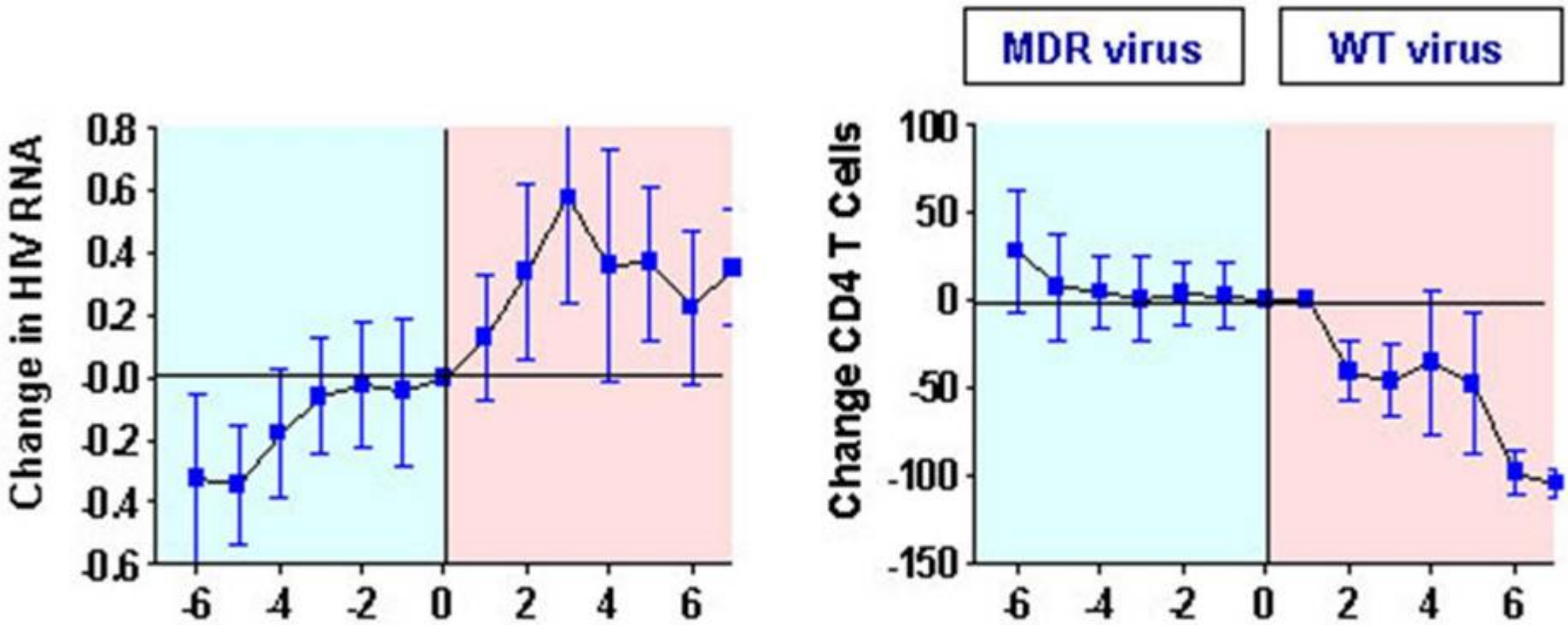
T.I.= induce revertant HIV

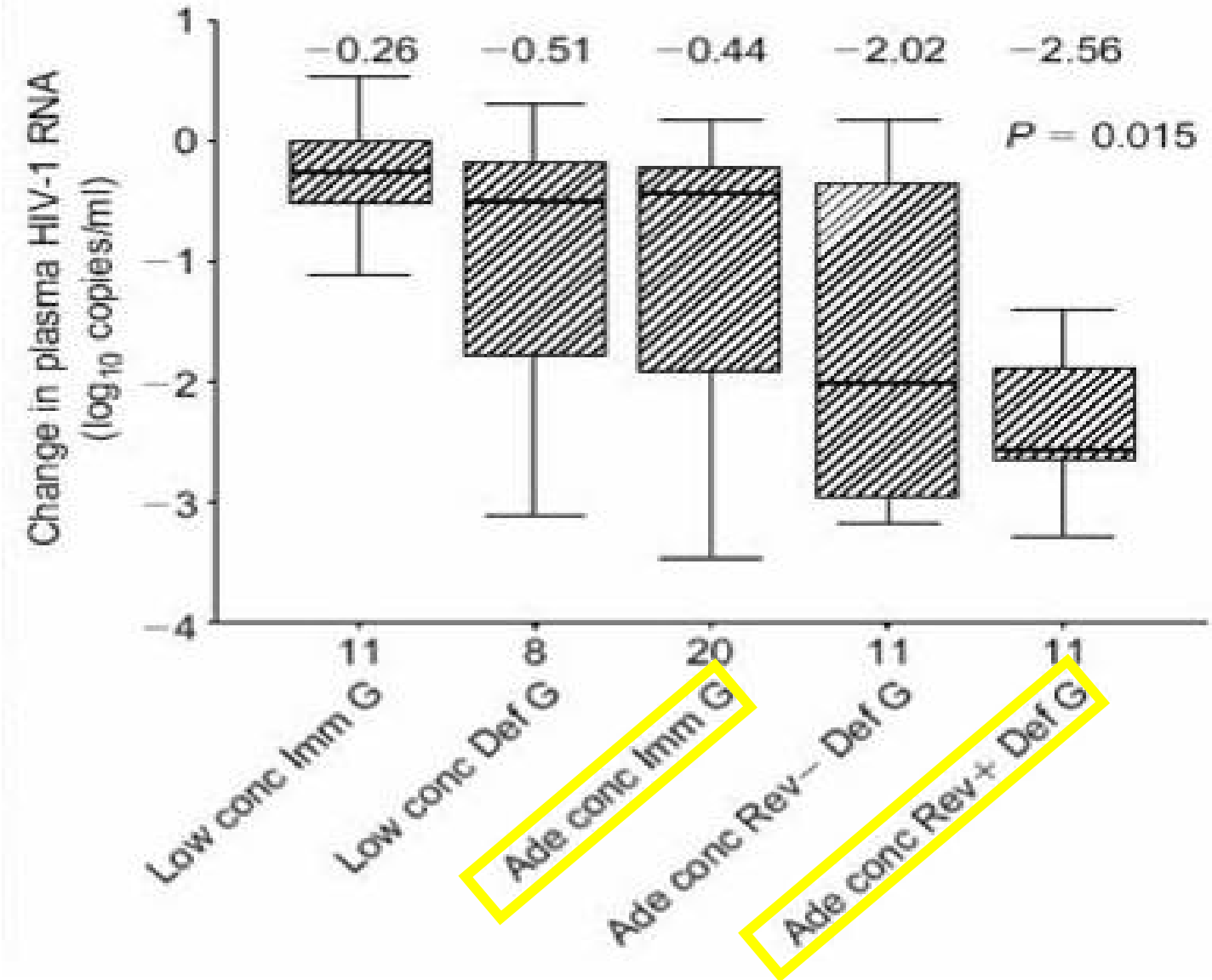
- P.I. sparing Rx.
- NRTI sparing Rx.

No T.I.

- Control the prevalent emerging HIV strain.
- Reduce the replication capacity of HIV.

Effect of emergence of wild-type HIV results in rapid CD4+ T cell depletion





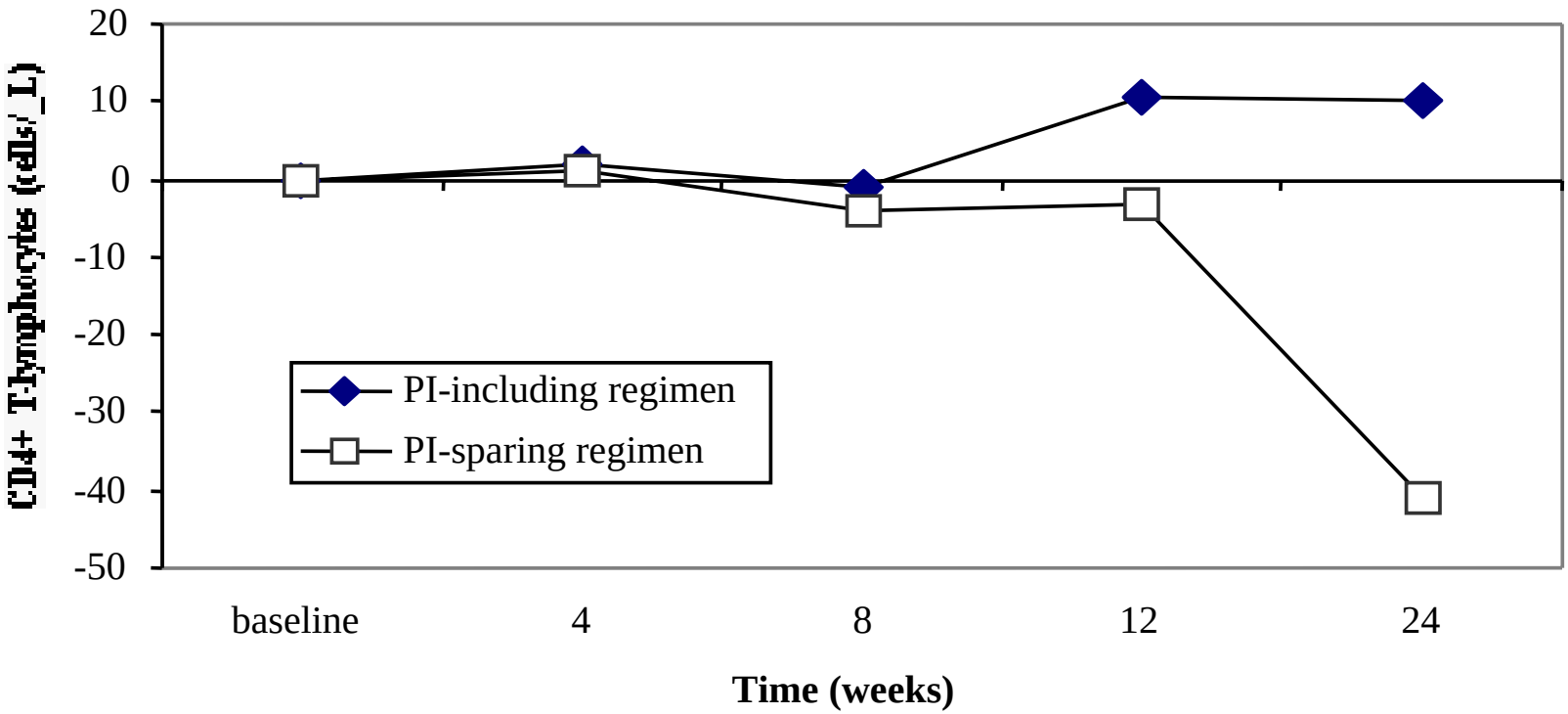
C.Katlama- AIDS 2004,18:217–226

Statement: Multiple failure

- The goal of therapy in the face of virologic failure without fully suppressive options is prevention of HIV-related complications and prevention or increase in CD4 count.

J.G. Bartlett 2003

Median change of CD4+ cell counts as compared to baseline among patients treated with a boosted-PI-including or a PI-sparing regimen.



Carry-over of HIV-1 protease sequence conferring resistance to protease inhibitors (PI) after shift to PI-sparing regimen

Pts reintroducing PI	5/5
Pts shifted to a PI Rx	4/4

Re-occurrence of HIV-1 protease gene mutations conferring resistance to PI

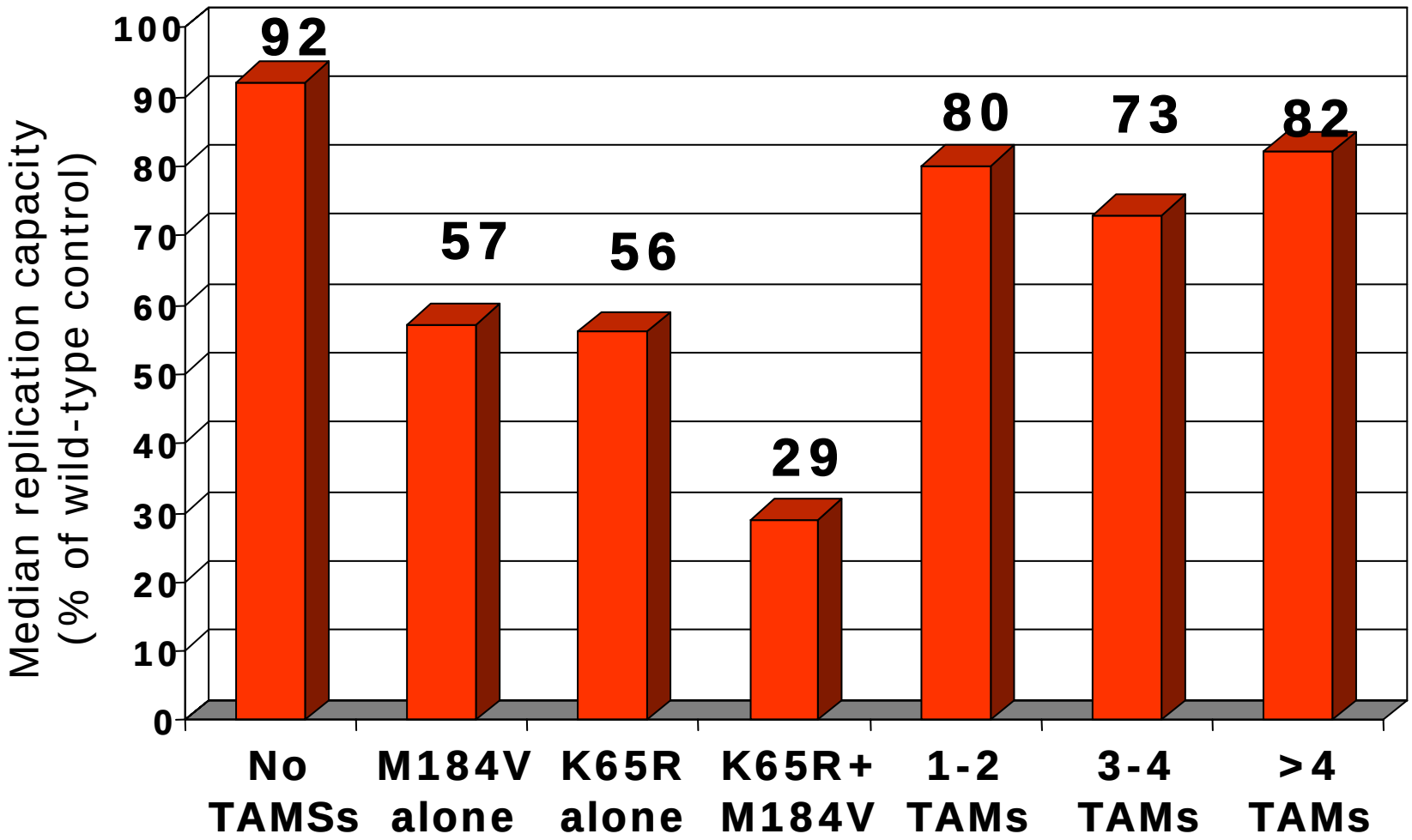
Boeri E, et al. AIDS Res.Hum.Retrov. (2003)

Control of prevalent emerging strains with HAART-maintenance strategy

- 34 MDR failing patients
  (CD4 240, HIV RNA 24500)
- Resistance driven
  (3-4 drugs modified every 4.7 months)
- 14 months later
  CD4 ~ 60 cell/mmc higher vs baseline

Maggiolo F, AIDS 2002

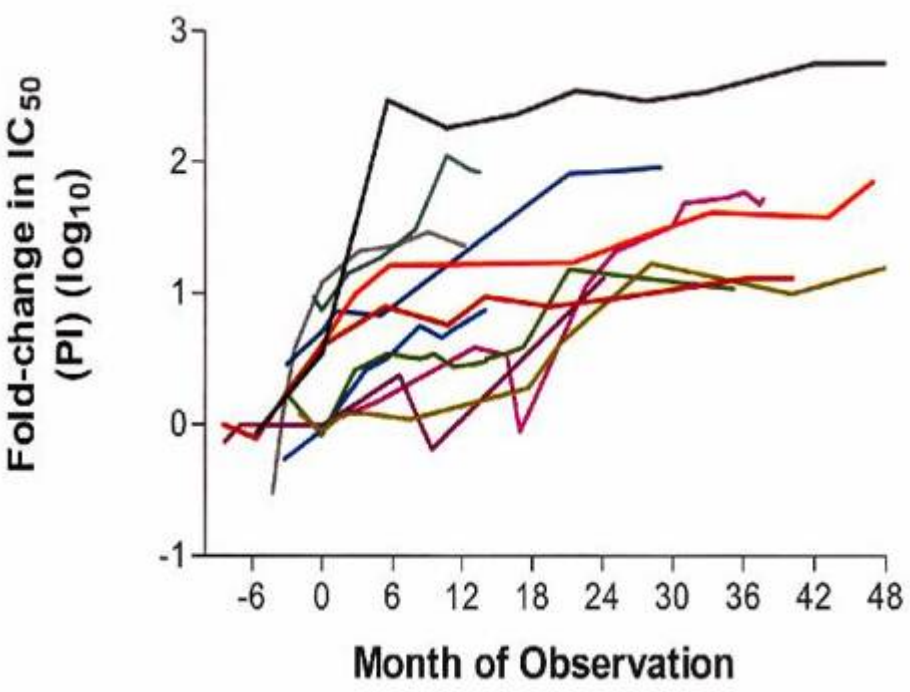
Replication capacity of HIV

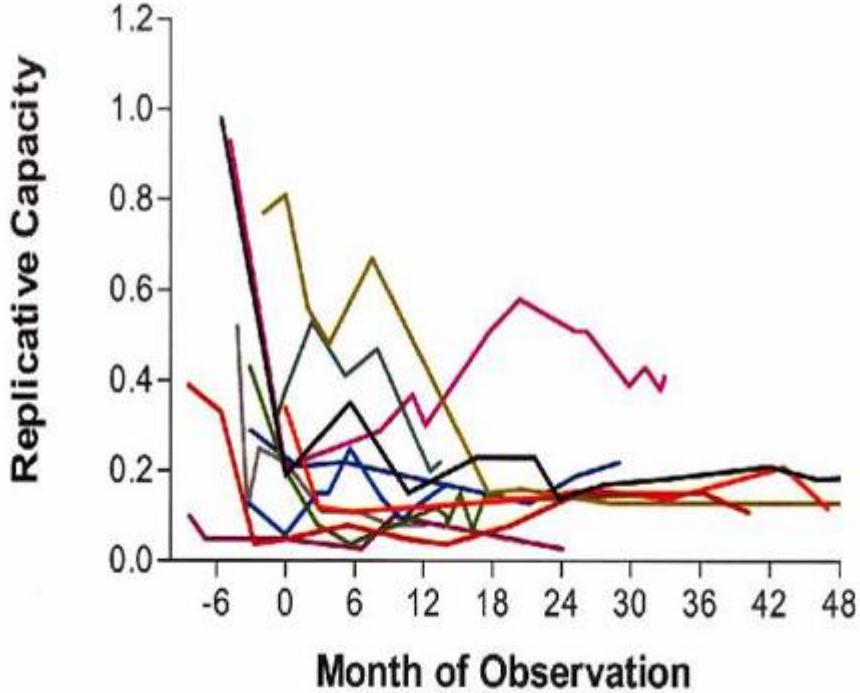


*p<0.05 (vs no TAMs

Miller et al. 10th CROI; February 10-14, 2003; Boston Abstract 616

Viral evolution during Long-term failure of HAART



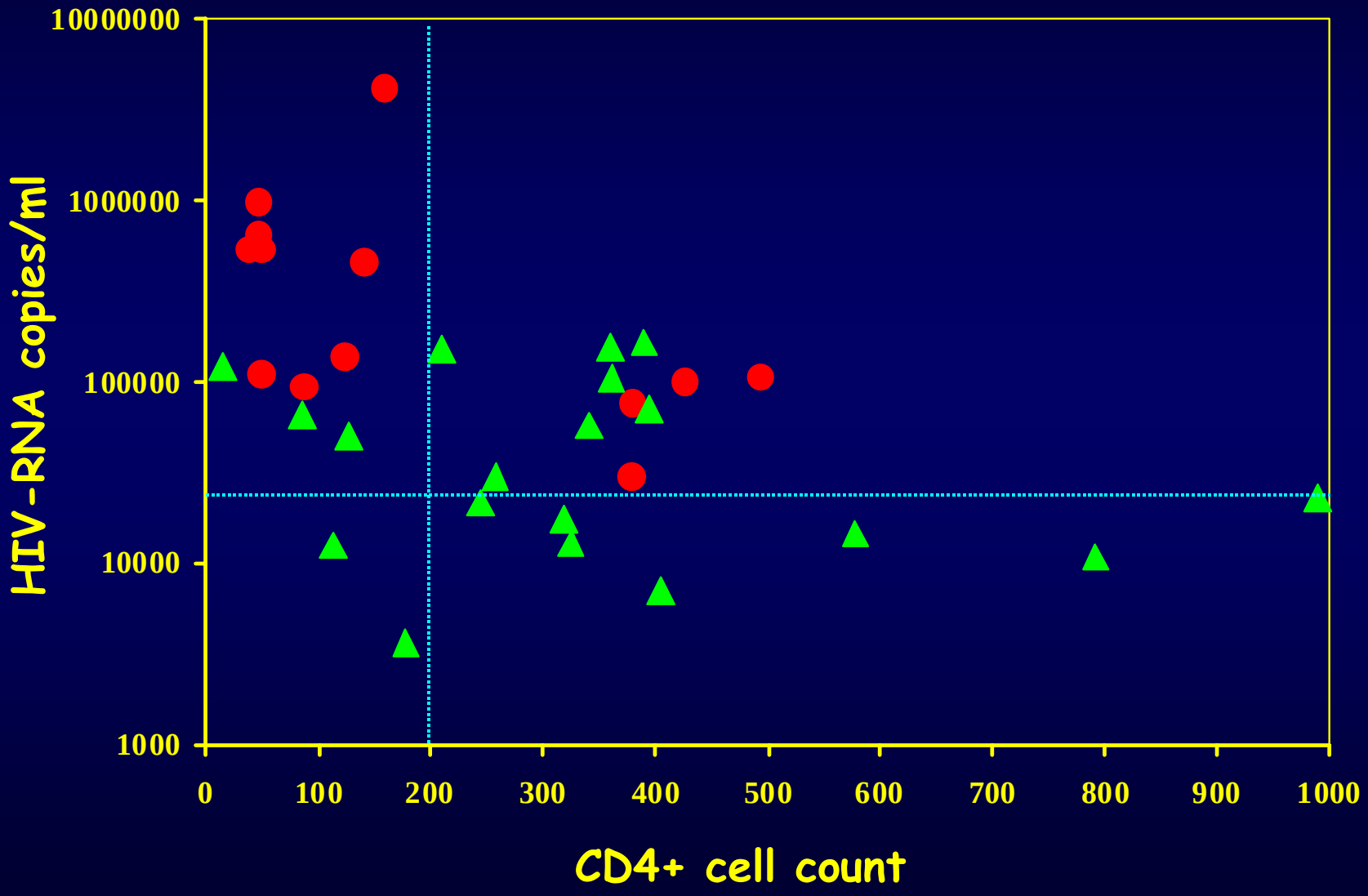


Hypothesis: HIV may be constrained in its ability to become both highly resistant and highly fit, thus resulting in durable partial suppression

Barbour JD et al. J Virology 2002;76:11104-12.

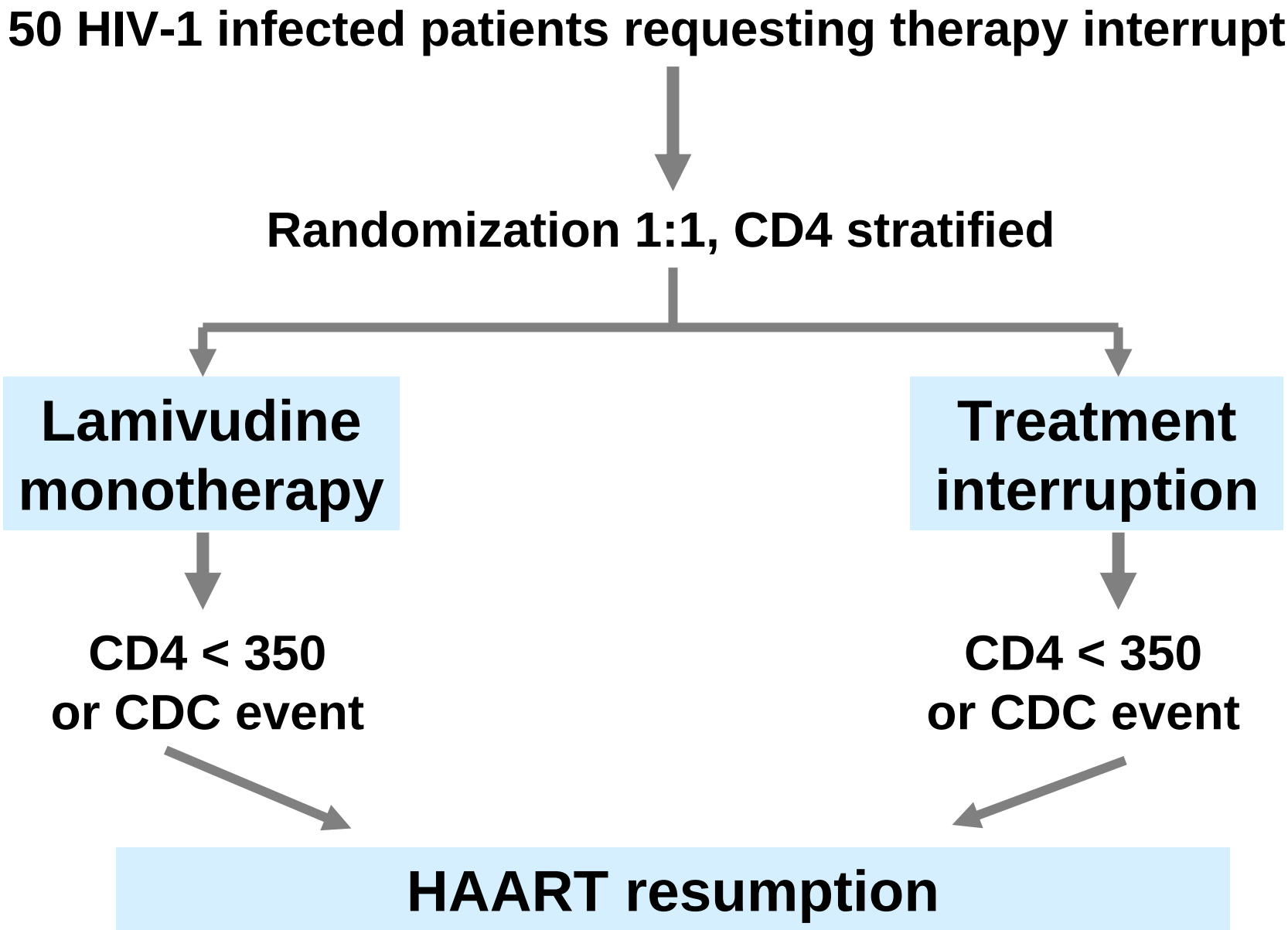
● Patients with HIV-1 isolates with replicative fitness >50%

▲ Patients with HIV-1 isolates with replicative fitness <50%



Andreoni, J Med Virol,69:1-6,2003

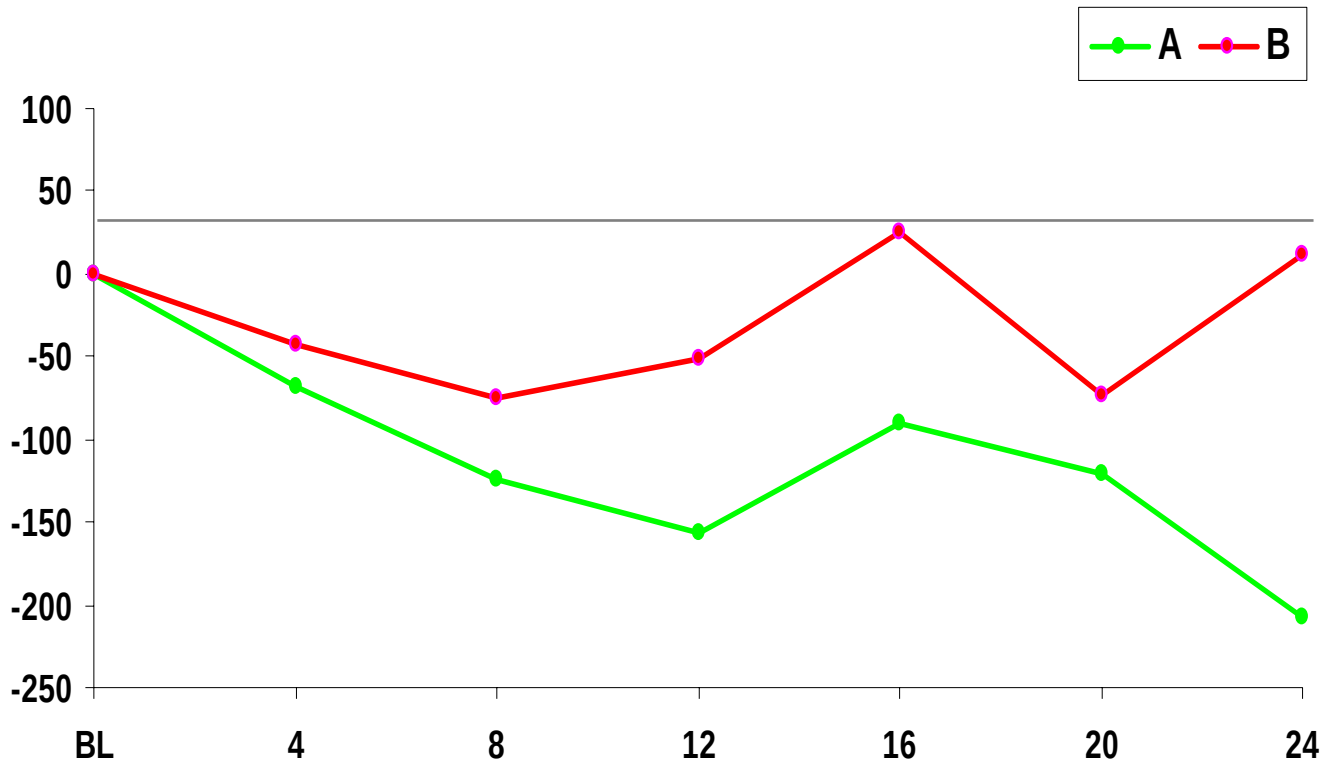
Study design



Study discontinuations

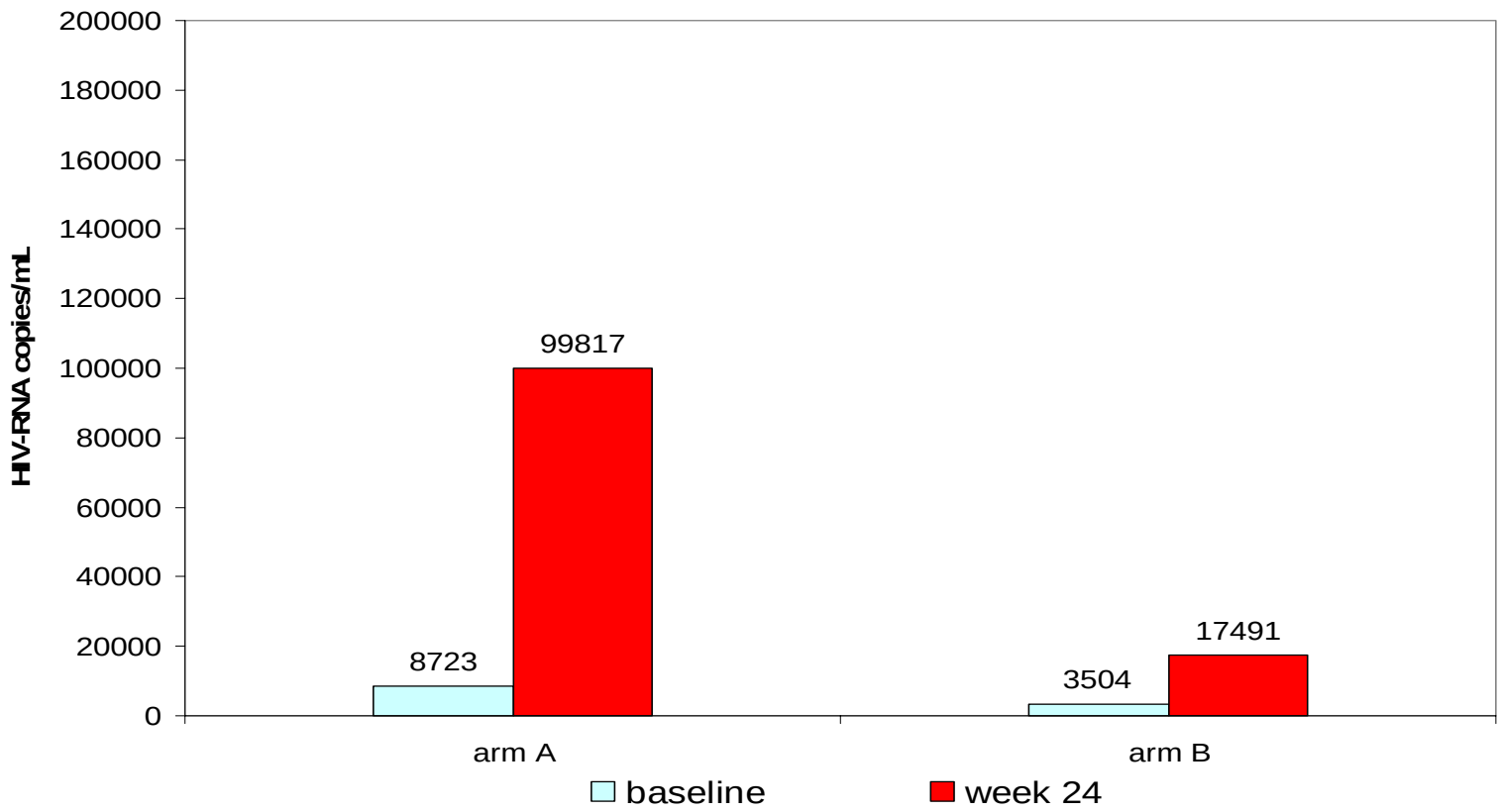
	Arm A	Arm B
N (%)of patients	**15/25 (60%)**	**9/25 (36%)**
Protocol failure [No. (%)]	14 (56%)	8 (32%)
HAART resumption		
Consent withdrawal	1	0
Fortuitous death	0	1

E-184V study. Median CD4 change from baseline



N° (A)	25	23	22	19	15	13	8
N° (B)	25	21	17	16	14	14	9

Median HIV-RNA (copies/mL)in patients on-study at week 24



E-184V study
pol genotypic evolution

	Arm A (treatment interruption)	**Arm B** (3TC monotherapy)
184V mutation	**6/20 (30%)**	**15/15 (100%)**
Revertion to wild-type RT	**7/20 (35%)**	**0/15**
Revertion to wild-type Pro	**2/20 (10%)**	**0/15**
Increase in N° of mutations	**0/20**	**0/15**

E-184V study
Preliminary conclusions

In HIV-1 failing patients lamivudine monotherapy, as compared to therapy interruption may:

- **reduce the frequency of immunologic failure**
- **induce lower CD4 decrease and less viral rebound**
- **without increasing the number of mutations detected at baseline**

Then, follow carefully → HAART success "*road map*"

- Early treatment
- Easy to take drugs
- Drugs without short or long term AE
- Optimal therapy
  (high efficacy/tolerability ratio)
- Induction/maintenance regimens
- Smart treatment plan
- "Stupid virus"

“Trench warfare” strategy

- Late treatment
- Drugs tolerability
- Change ARVT as little as possible
- Rescue plans of action

NO DISEASE PROGRESSION

“Offensive war” strategy

- Early treatment
- Drugs potency
- ARVT switch plans
- Treatment interruption plans of action

CONTROL HIV INFECTION

When to start antiretroviral therapy

Potential Benefits and Risks of Early Therapy

Potential benefits of early therapy

- Earlier suppression of viral replication
- Preservation of immune function
- Prolongation of disease-free survival
- Lower risk of resistance with complete viral suppression
- Possible decrease in the risk of HIV transmission.

Potential risks of early therapy

- Drug-related adverse effects on quality of life
- Drug-related serious toxicities
- Early development of drug resistance due to suboptimal viral suppression
- Risk of transmission of virus resistant to antiretroviral drugs (if suboptimal suppression)
- Limitation of future treatment options
- Unknown durability of current available therapy

Potential Benefits and Risks of Delayed Therapy

Potential benefits of delayed therapy

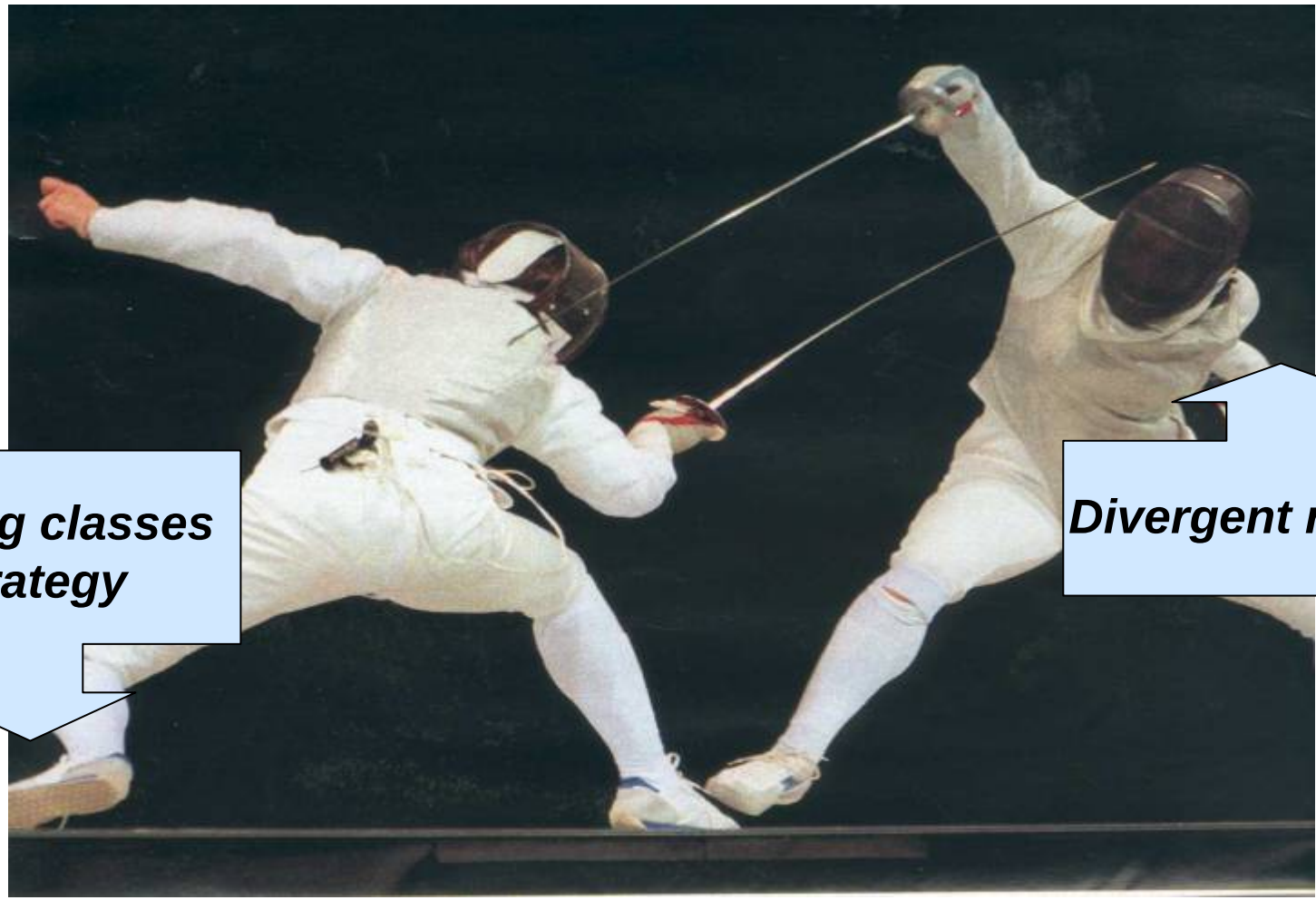
- Avoid negative effects on quality of life
- Avoid drug-related adverse events
- Preserve future treatment options
- Delay in development of drug resistance

Potential risks of delayed therapy

- Possible risk of irreversible immune system compromise
- Possible greater difficulty in viral suppression
- Possible increased risk of HIV transmission

ARV: What come next ?

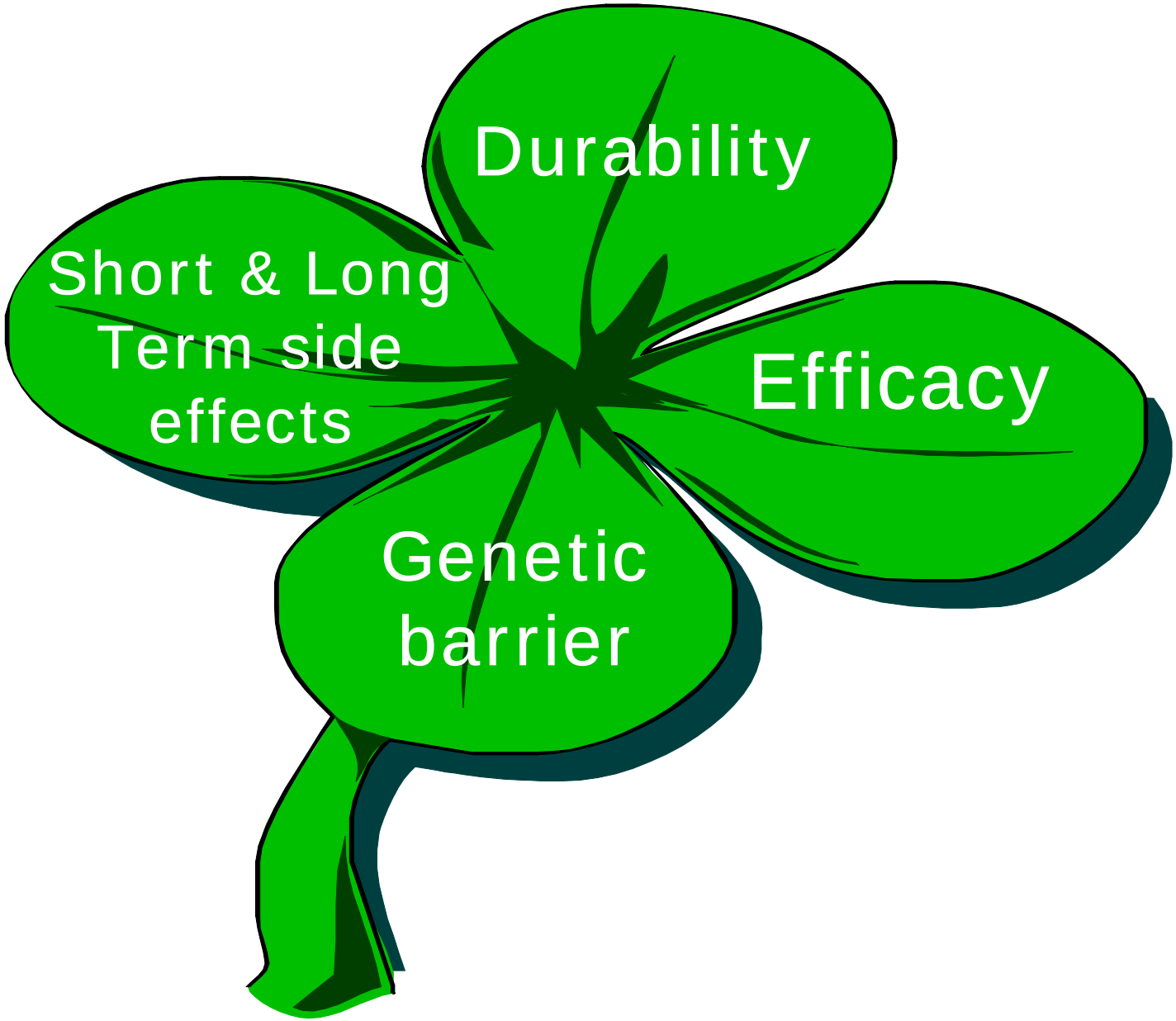
One of the various pending questions



Sparing classes
Strategy

Divergent regimen

Class-sparing regimens: main concerns



Advantages and Disadvantages of Class-Sparing Regimens Used in HIV-1 Therapy (1)

Regimen	Possible Advantages	Possible Disadvantages	Impact on future options
PI-based HAART Regimen **(NNRTI- and FI-sparing)**	▪ Clinical, virologic, and immunologic efficacy well-documented. ▪ Resistance requires multiple mutations. ▪ Avoid NNRTI- and FI-associated side effects. ▪ Targets HIV at two steps of viral replication (RT and PI)	▪ Some regimens difficult to use and adhere to. ▪ Long-term side effects often include lipodystrophy*, hyperlipidemia, and insulin resistance.	▪ Preserves NNRTIs and FI for use in treatment failure. ▪ Resistance primes for cross-resistance with other PIs

Advantages and Disadvantages of Class-Sparing Regimens Used in HIV-1 Therapy (2)

Regimen	Possible Advantages	Possible Disadvantages	Impact on future options
NNRTI-based HAART Regimen **(PI- and FI-sparing)**	▪ Virologic, and immunologic efficacy well-documented ▪ Spares PI & FI-related side effects ▪ Easier to use and adhere compared with most regimens	▪ Resistance conferred by single or limited number of mutations	▪ Preserves PIs and FI for use in treatment failure. ▪ Resistance usually leads to cross-resistance across entire NNRTI class

Advantages and Disadvantages of Class-Sparing Regimens Used in HIV-1 Therapy (3)

Regimen	Possible Advantages	Possible Disadvantages	Impact on future options
Triple NRTI regimen **(NNRTI- and PI-sparing)**	▪ Generally easier to use and adhere to compared with Pis ▪ Sparing PI, NNRTI, and FI side effects	▪ Inferior virologic efficacy	▪ Preserves PI, NNRTI, and FI classes for use in treatment failure

NRTI-Sparing Regimens

BiKS Study

- LPV/r (533/133 mg BID) + EFV (600 mg QD)
  - 24-week results of open-label 48-week pilot trial; *n*=86
  - Naïve or NNRTI-naïve with ≤ 1 PI failure

HIV RNA	OT	ITT
<400 c/mL	93%	78%
<50 c/mL	76%	64%

Ferré V, *et al. 2nd IAS*, Paris 2003, #36;

NRTI/NNRTI Sparing

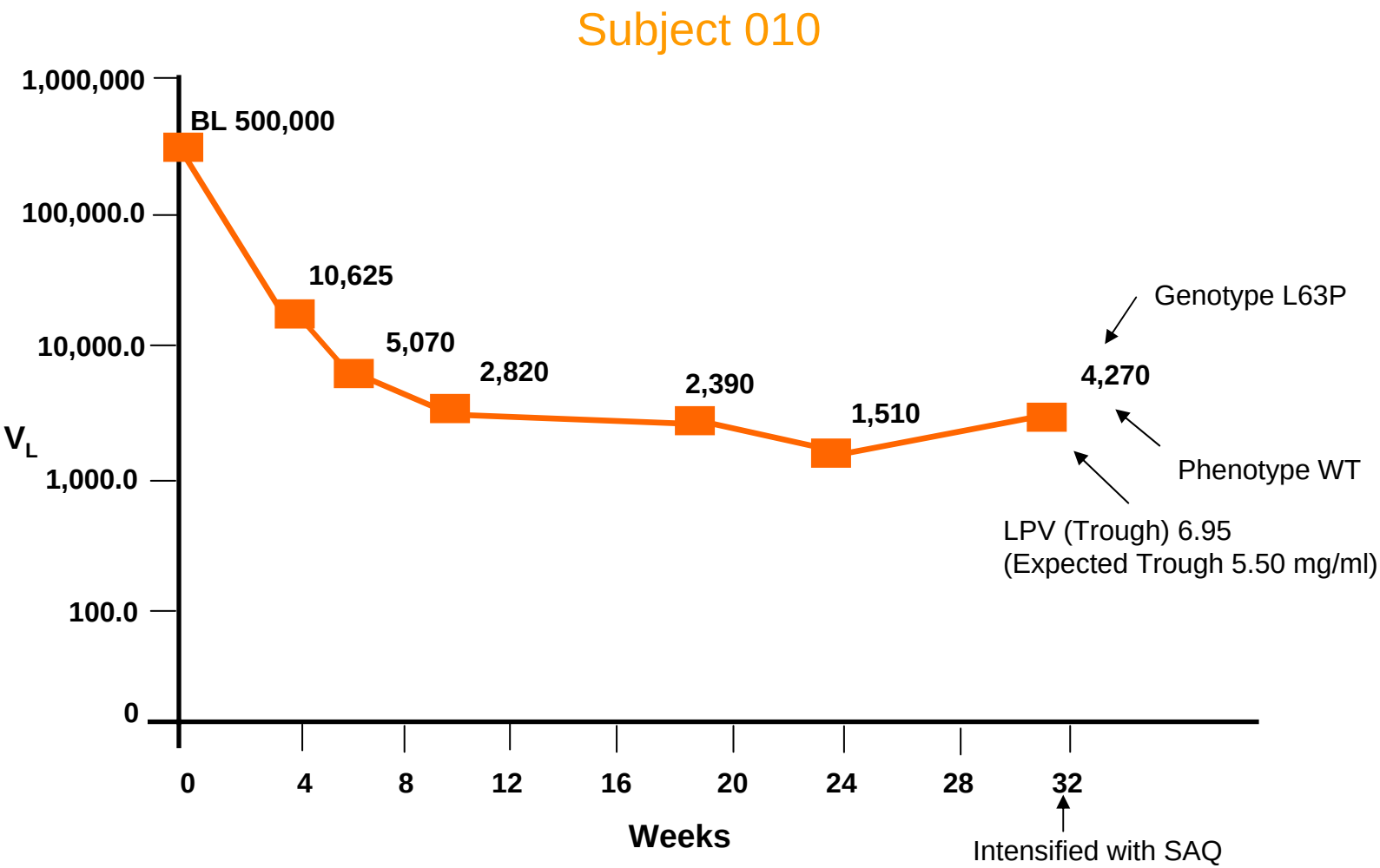
PIN Study

- LPV/r (400/100 mg BID) + SQVsgc (1000 mg BID)
  - 48-week results, open-label trial; *n*=20
  - PI-naïve, HIV RNA >1000 c/mL
  - 2 intensified with TDF for VL >50 c/mL after week 12

HIV RNA	OT	ITT
<400 c/mL	85%	75%
<50 c/mL	80%	70%

Hellinger J, *et al. 2nd IAS*, Paris 2003, #571A

V_L Decay Curve of the Subject (1/30) with Virologic Non-Response

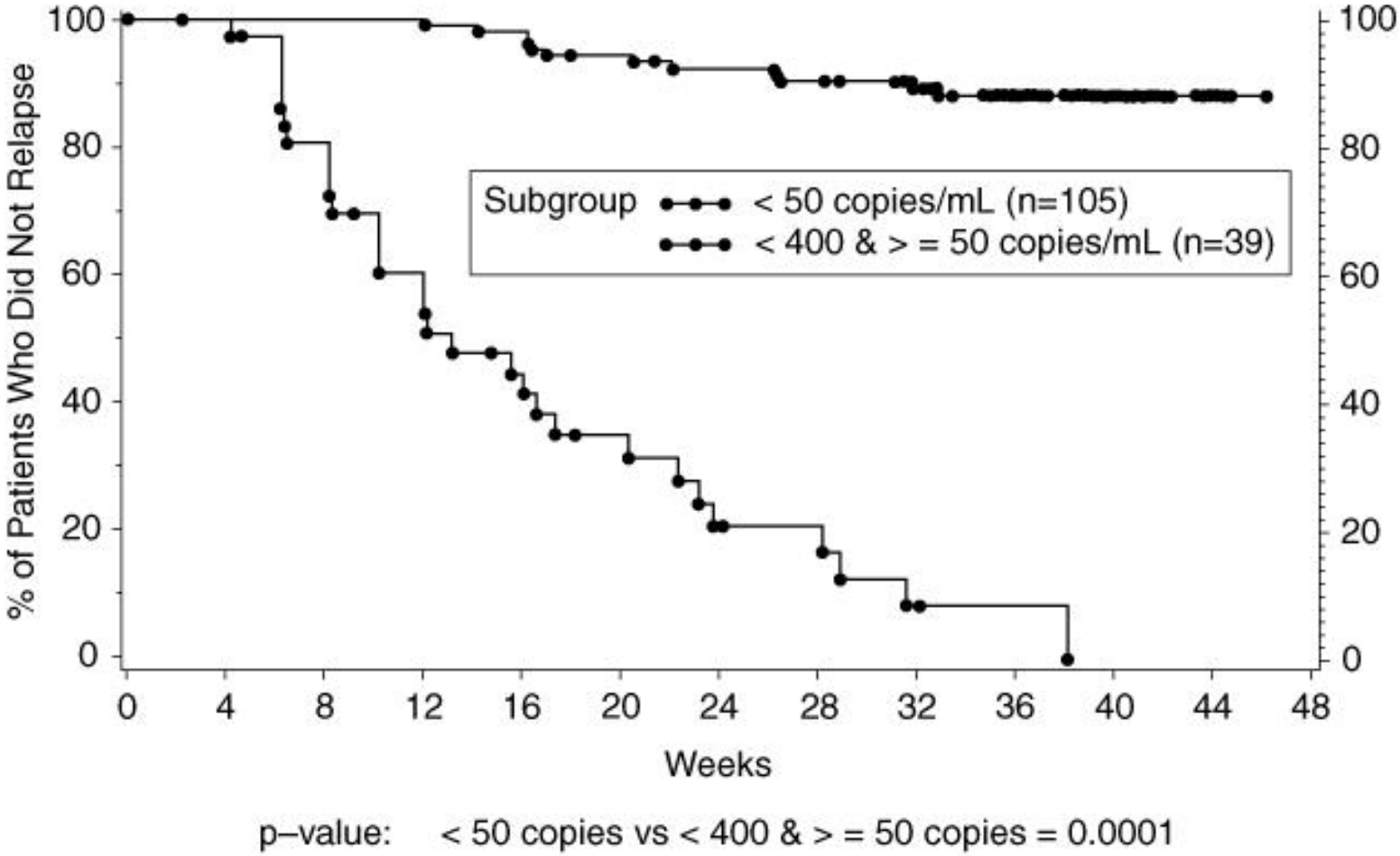


Gathe, J. et al. 43rd ICAAC, Sept. 2003; ABS 2608


BACK TO
the future
Is single drug ARV possible?

Single drug ARV: remember the low genetic barrier and/or difficult situations.

A smart start is the keystone for a long term control of HIV replication



Polis, Lancet 2001,358:1760-5.

Make
it
happen!