

Benefits of antiretroviral therapy: do we need Immunotherapy and Vaccines ?

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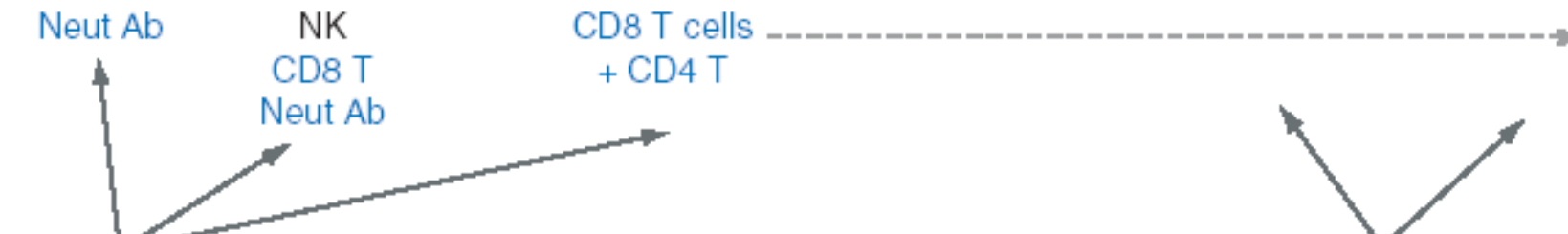
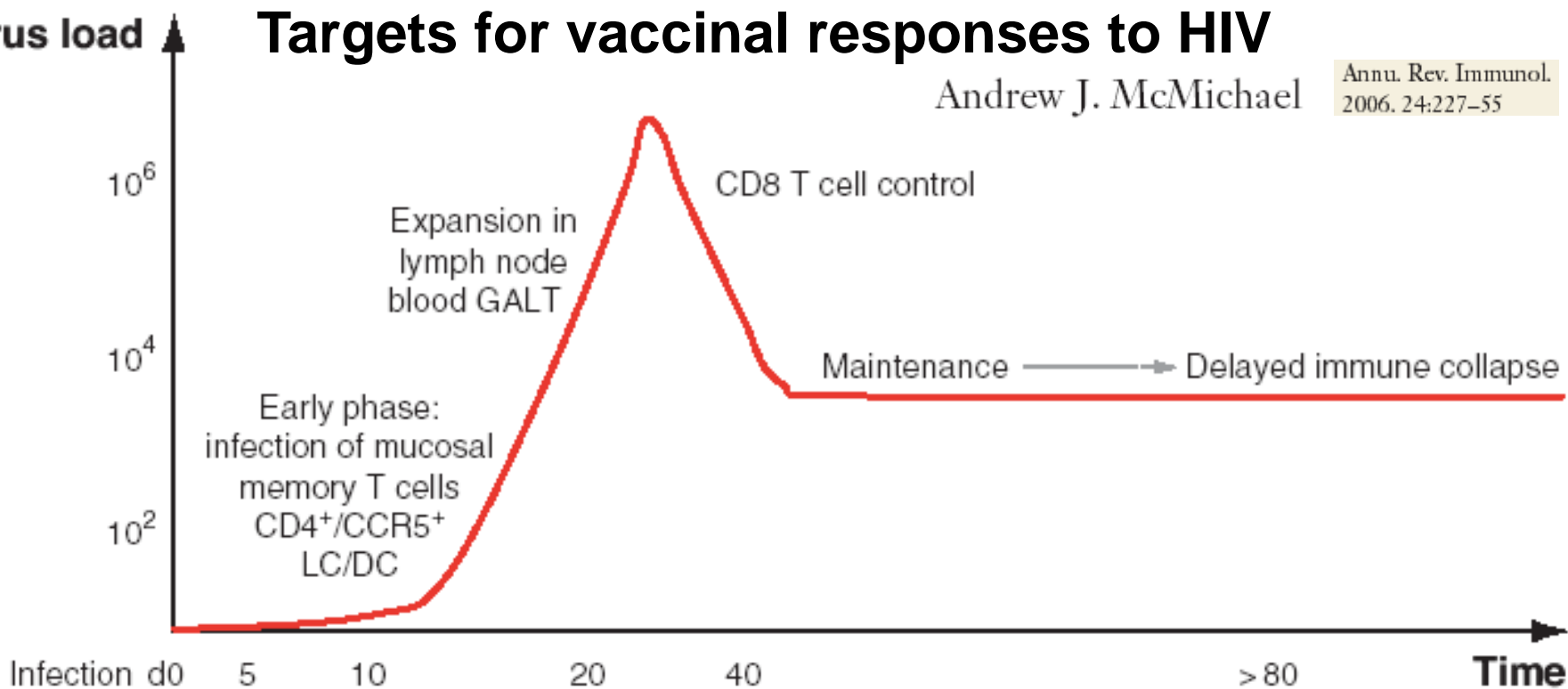
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Targets for vaccinal responses to HIV

Andrew J. McMichael

Annu. Rev. Immunol.
2006. 24:227-55



**Prophylactic
Immunization**

**Therapeutic
Immunization**

Prevention Abortive infection ←-----→ Damage limitation -----→

Obstacles against HIV vaccines : HIV escape

- **Immediate and definitive HIV Integration in host genome = Trojan Horse**
- **Weak neutralizing antibodies**
- **Major HIV Variability in Antibody and CD8 cell epitopes**
(Envelope, Tat, Nef, Gag)

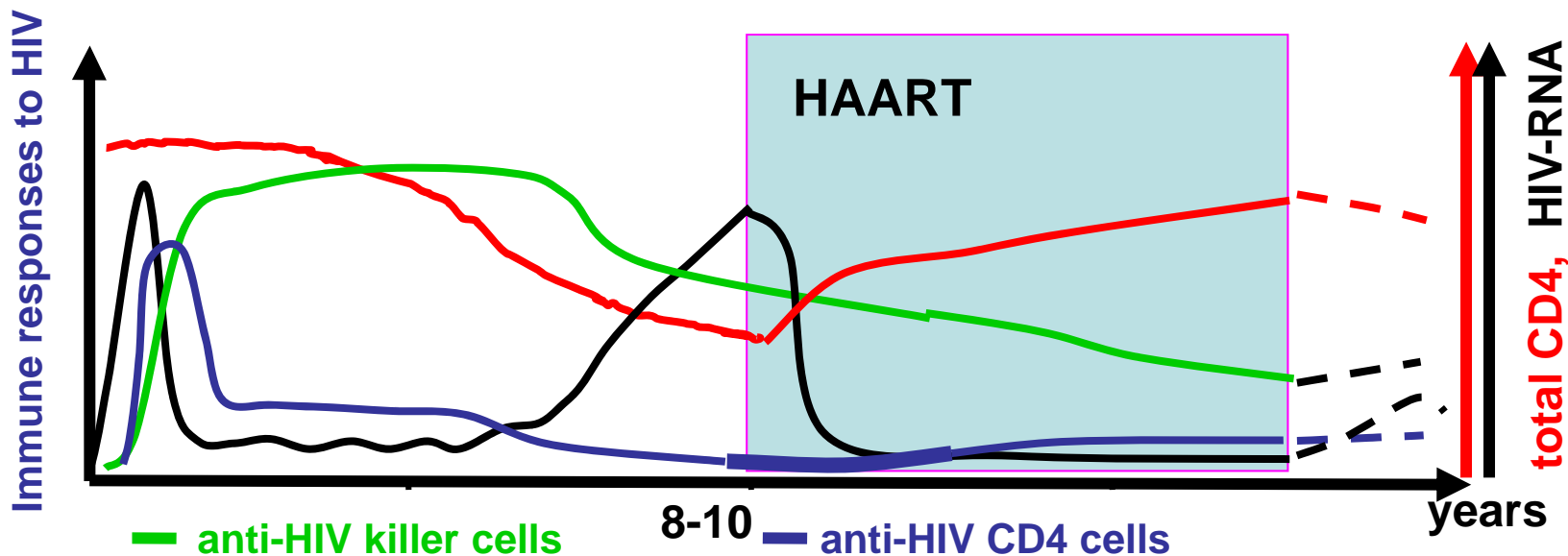
These Difficulties are illustrated by the lack of spontaneous recovery from the infection

Described Immune Correlates of protection against HIV

- **CD8 T Lymphocytes specific for HIV:**
 - ✓ **Inverse relationship between viral load and HIV-specific CTL** frequencies during primary infection (*Koup, 93...*), or chronic (*Ogg, 98, Kiepela 07...*) and in LTNP (*Klein, 95, Kalams 99, ...Martinez 05, ...*)
 - ✓ **Stronger correlation between multifunctional CD8 T cells and VL** (*Betts, 06....*)
 - ✓ **Loss of SIV control after CD8 cell déplétion** (*Schmitz, Zhang, 99*)
- **CD4 Thelper-1 Lymphocytes specific for HIV :**
 - ✓ **Inverse relationship between VL and HIV-specific CD4 Th1 cells** during primary infection and in LTNP (*Rosenberg, 97, 2000...Martinez 2005...*)
- **Antibodies against HIV?**
 - ✓ **No significant relationship between neutralizing Ab and viral control**
 - ✓ **Control of SIV/SHIV** after transfers of anti-enveloppe antibodies

HIV and its immune partners :

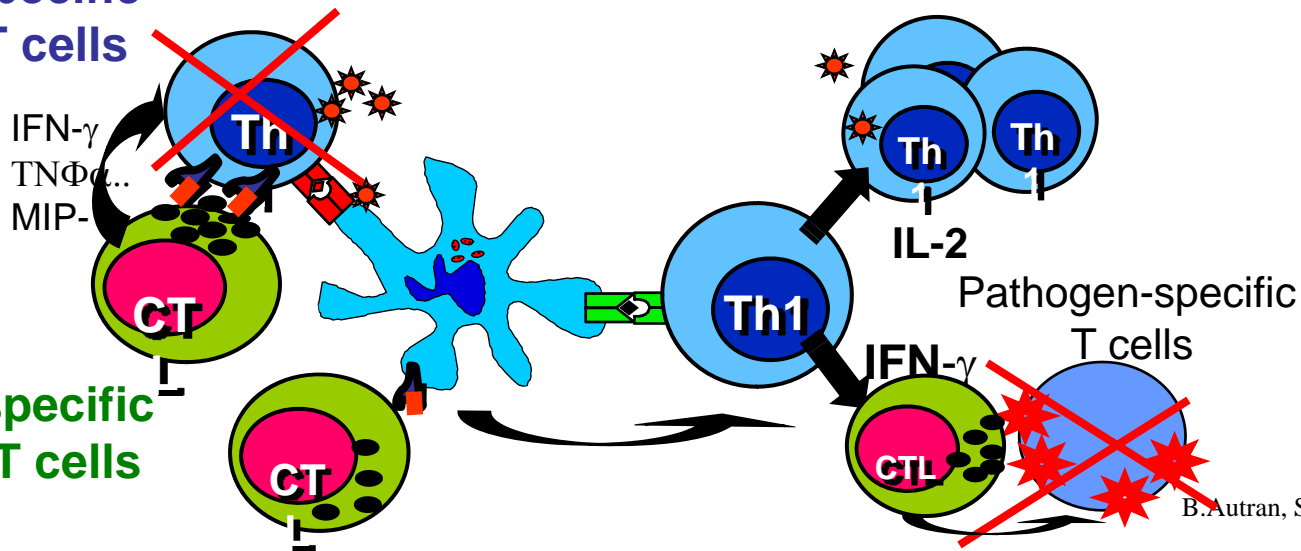
Is Immune control feasible in the absence of therapy?



Can
HIV-specific
T cells
be
Protective

HIV-specific
CD4 T cells

HIV-specific
CD8 T cells





HIV VACCINE
TRIALS NETWORK

News Release

FOR IMMEDIATE RELEASE

Vaccination and Enrollment Are Discontinued in Phase II Trials of Merck's Investigational HIV Vaccine Candidate

Interim Analysis of STEP Study Shows Vaccine was not Effective

WHITEHOUSE STATION, N.J., and Seattle, Sept. 21, 2007 -- Vaccination in a phase II clinical trial of Merck & Co., Inc.'s investigational HIV vaccine (V520) is being discontinued because the vaccine was not effective. The announcement was made today by the co-sponsors of this clinical trial, Merck & Co., Inc., and the HIV Vaccine Trials Network (HVTN), which is funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health.

Echec du Vaccin recombinant Adénovirus anti-HIV Merck

- **Vaccin: Adénovirus-5 recombiné pour gènes HIV (clade B) Gag, Pol, Nef**

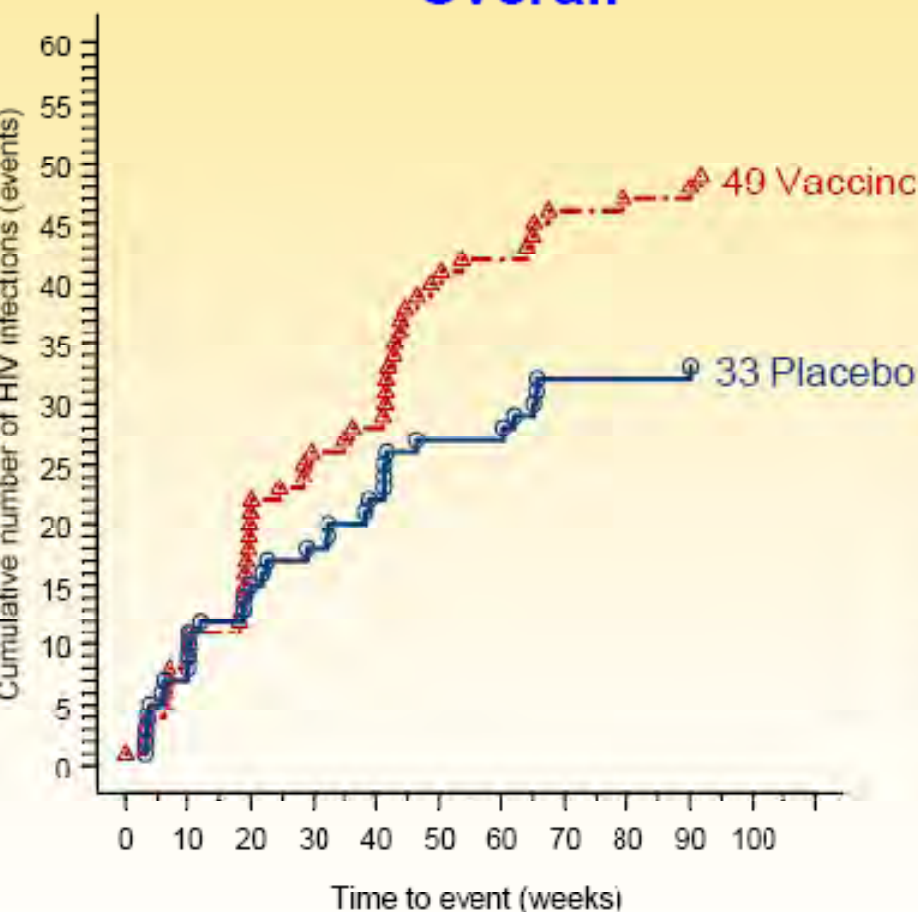
Testé en phase I: bonne tolérance

immunogénicité dépendant de l'immunité pré-existante / Ad5
60-85% répondeurs (env. 500 SFC/million PBMC)

- **Etude STEP (HVTN 502-MerckV520): essai de Phase II «Test of concept»**
 - multicentrique, en double aveugle randomisé, 3 injections vaccinales :
 - 3000 volontaires 18-45 ans, à haut risque d'infection VIH
 - 2 critères primaires:
 - Prévention de l'infection
 - Réduction du « set point » viral après contamination
 - Analyse intérimaire :
 - 1500 volontaires ayant peu d'immunité pré-existante anti-Ad5

Cumulative Number of HIV Infections: MITT population (males)

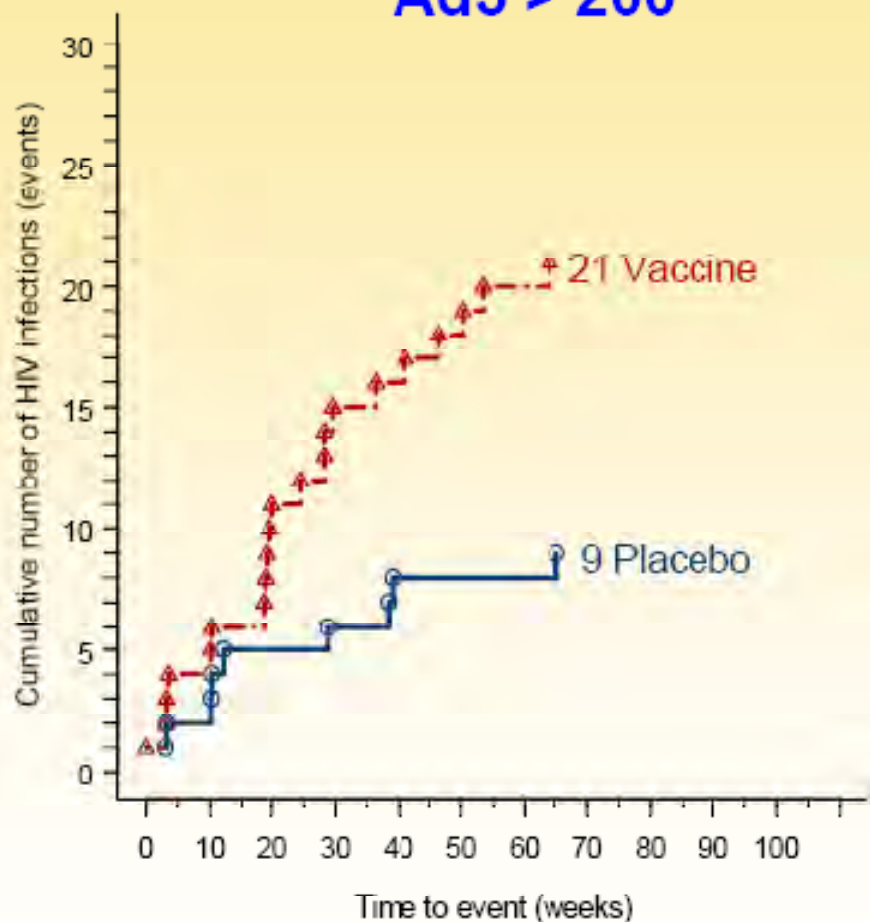
Overall



1-tailed p-value = 0.044 (for $VE_{INF} < 0$)

2-tailed p-value = 0.077 (for $VE_{INF} \neq 0$)

Ad5 > 200



1-tailed p-value = 0.020 (for $VE_{INF} < 0$)

2-tailed p-value = 0.029 (for $VE_{INF} \neq 0$)

- Test of concept provided definitive results 33 months after first participant enrolled
 - Vaccine neither prevented infection nor lowered viral setpoint
- Greater number of infections in vaccine than placebo recipients
 - This trend appeared to be concentrated in Ad5 seropositive strata (randomization w/i strata)

Increased risk of HIV infection is **most evident in uncircumcised men with pre-existing Ad5 immunity** [estimated vaccine HRs 4.2 to 4.8].

• Other Negative Results ?

- **Therapeutic vaccine** against HIV with an HIV-rec vCP:
Significant higher HIV replication in vaccinees vs Placebo
after ART interruption (*Autran AIDS 2008*)

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand.

[Rerks-Ngarm S](#), [Pitisuttithum P](#), [Nitayaphan S](#), [Kaewkungwal J](#), [Chiu J](#), [Paris R](#), [Preamsri N](#), [Namwat C](#), [de Souza M](#), [Adams E](#), [Benenson M](#), [Gurunathan S](#), [Tartaglia J](#), [McNeil JG](#), [Francis DP](#), [Stablein D](#), [Birx DL](#), [Chunsuttiwat S](#), [Khamboonruang C](#), [Thongcharoen P](#), [Robb ML](#), [Michael NL](#), [Kunasol P](#), [Kim JH](#); the MOPH-TAVEG Investigators.

• METHODS:

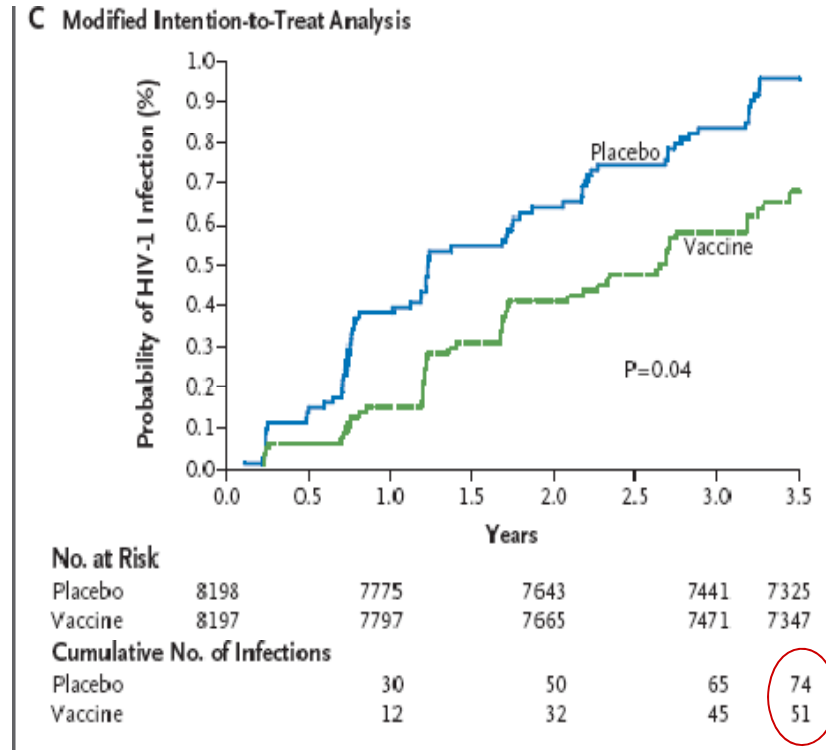
- A randomized, multicenter, double-blind, placebo-controlled efficacy trial,
 - in 16,402 healthy men and women 18 and 30 years
 - primarily at heterosexual risk for HIV infection,
- 4 priming injections of a **recombinant canarypox vector vaccine** (ALVAC-HIV [vCP1521])
- + 2 booster injections of a **recombinant glycoprotein 120** subunit vaccine (AIDSVAX B/E).
- coprimary end points: at end of the 6-month vaccination series and every 6 months thereafter for 3 years.
 - HIV-1 infection and
 - early HIV-1 viremia,

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand.

A modest benefit :

RESULTS:

- Intention-to-treat analysis:
 - vaccine efficacy: 26.4% ($p=0.08$).
- **Modified intention-to-treat analysis:**
 - (excluding 7 subjects HIV-1 infected at baseline),
 - **vaccine efficacy : 31.2% ($P=0.04$).**



CONCLUSIONS:

- « This ALVAC-HIV and AIDSVAX B/E vaccine regimen :
 - may reduce the risk of HIV infection
 - in a community-based population with largely heterosexual risk. »
 - Vaccination did not affect the viral load or CD4+ count after HIV infection
 - No immune correlates of protection (Neut Abs, IFN-g producing T cells)

The search for an anti-HIV Vaccine: The Post-STEP Era

- **T cell based Vaccines approach ?**
 - **The VRC DNA-Ad5 Phase III Vaccine trial:**
 - **A multiclade Env DNA + Ad5-HIV Env-Gag-Pol-Nef:**
 - => a smaller study in the US in circumcised Adeno-5 seroneg. Only
 - **New Vectors Developments:**
 - **Chimeric AdenoVirus** constructs: Ad-28 or Ad-35 (*D Barouch et al.*)
 - To replace the Ad5 spikes targeted by neutral. Abs by Ad28 or 35 spikes
 - = **Immunogenic** in Macaques pre-immunized with Ad5 Vacc.
 - **New PoxViruses** or other T cell based vaccines ?
 - **New conserved HIV antigens for broader Immunity ?**
 - Multiclade Immunogens ? (VRC approach)
 - Chimeric Immunogens
- **The Neutralizing Antibody Come back**

Therapy in HIV infection

What do we need ? Why ? When ?

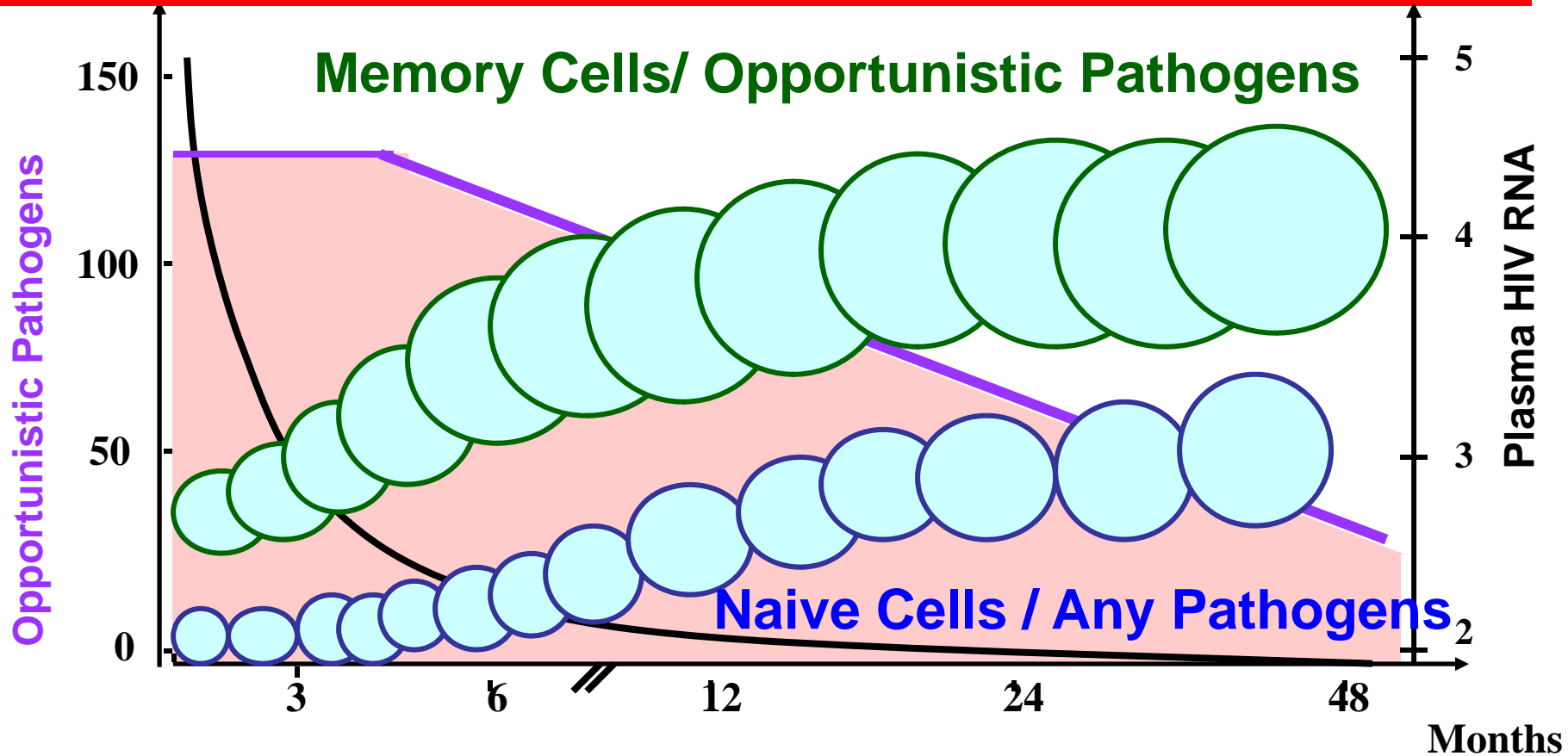
IMMUNE DEFECTS

- **CD4 depletion**
- Memory CD4 Th cells / recall Ag
 - exposes to Opp Inf
- Naïve CD4 T cells and Thymus
 - reservoir for new T cells specific for new pathogens
- **Poor immune control of HIV**
- HIV-specific CD4+ Th1 cells
- HIV-specific CTL

GOALS

- **To correct CD4 cell numbers**
- **To Restore Immune defenses against pathogens and OI**
- **To Restore Immunity to HIV**

Restoration of Immune Defenses against pathogens with ART

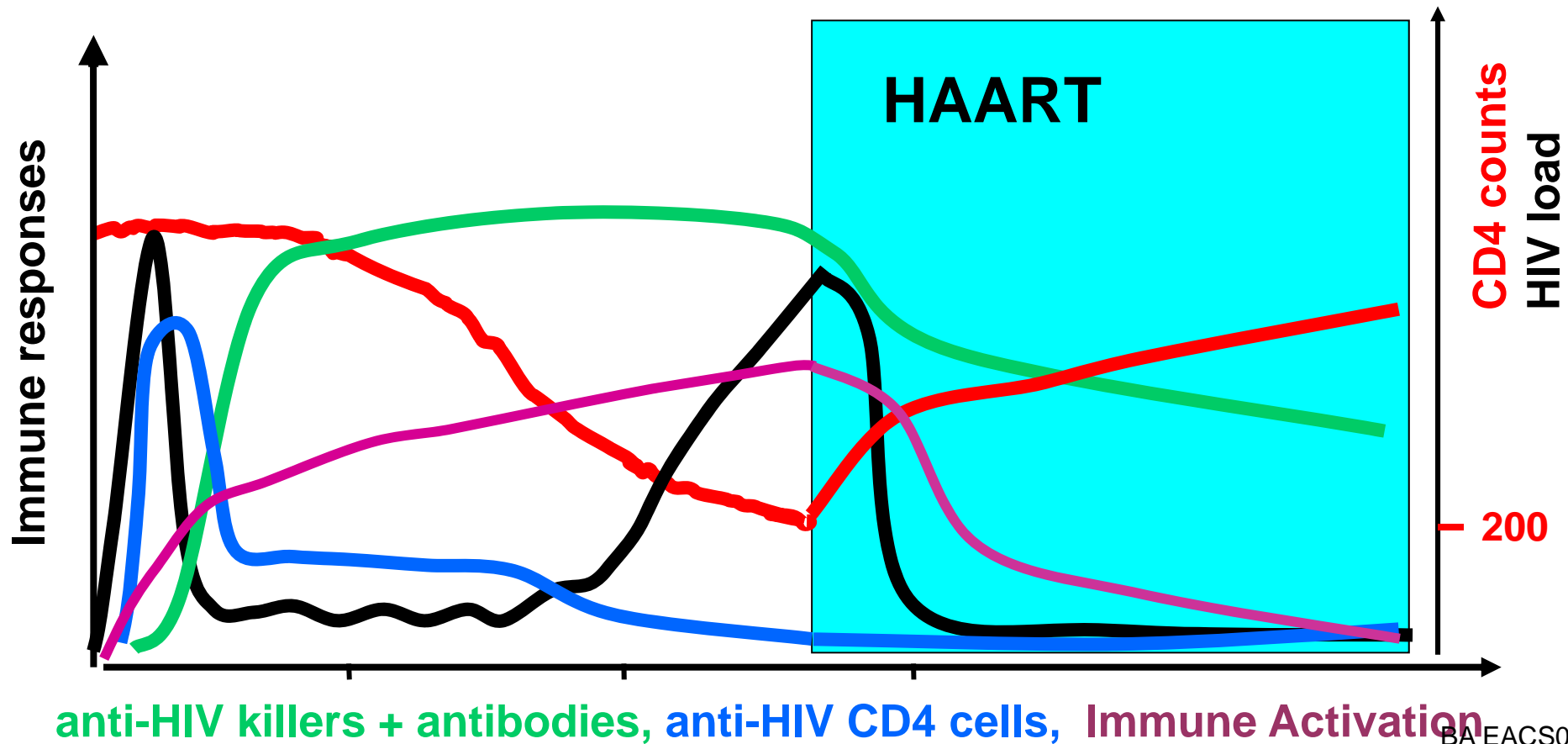


- **Restore defenses to all pathogens** (*Autran97; Li98, Lederman 98, Rinaldo 99, Garcia 99, Pontesili99.....*)
- **Allow arrest of prophylaxis against Opport. Inf** (*Furrer,99 Reiss 99,Ledereberger 01, Jouan 01..*)

ImmunoTherapy and vaccines in HIV infection :

Why ? When ?

- to restore CD4 counts or anti-HIV immune responses ?
- in untreated disease vs treated disease ?



Rationale for HIV-specific Immune Interventions

➤ **Successes** of Immune Reconstitution:

- CD4 homeostasis
- Defenses against pathogens and interruptions of prophylaxis
against Opp.Inf.

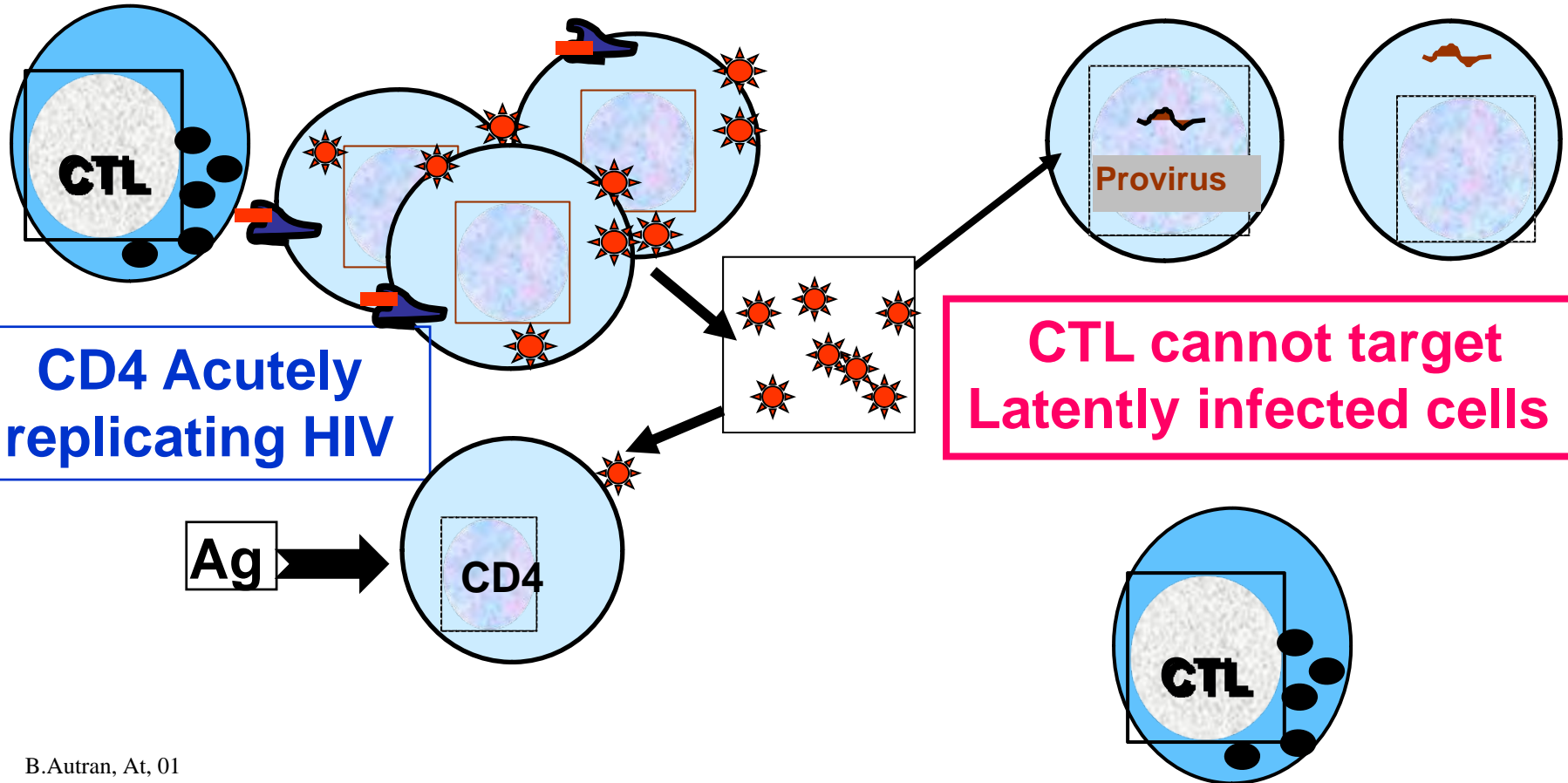
➤ **Limits** of anti-retroviral therapy:

- **Poor restoration of immune defenses against HIV**
- **Lack of HIV eradication and life long therapies**
- **Costs and toxicity of long term therapy**
- **Short duration of treatment interruptions**

CTL and HIV Dynamics

CTL are activated by CD4 T cells replicating HIV

HAART or Latently infected CD4



Poor restoration of HIV-specific immunity during antiretroviral therapy

« Suppressive » HAART :

- Delays HIV-specific CTL in primary infection
Reduces pre-existing CTLs in chronic infection

(Dalod 98, Ogg 98, Gray 98, Kalams 99, Pontesilli 99, Rinaldo 99, Mollet 2000...)

- Preserves HIV-specific CD4 T cells in primary infection
Prevents their restoration in chronic stages

(Autran 97, Rosenberg 97,2000; Pitcher 99, Plana 99, Pontesilli 99.....)

✓ Reflects reduced exposure to HIV ?

- despite persistent minimal virus replication

(Furtado 99, Zhang 99, Stevenson 2000)

Rationale for HIV-specific Immune Interventions

➤ **Successes** of Immune Reconstitution:

- CD4 homeostasis
- Defenses against pathogens and interruptions of prophylaxis
against Opp.Inf.

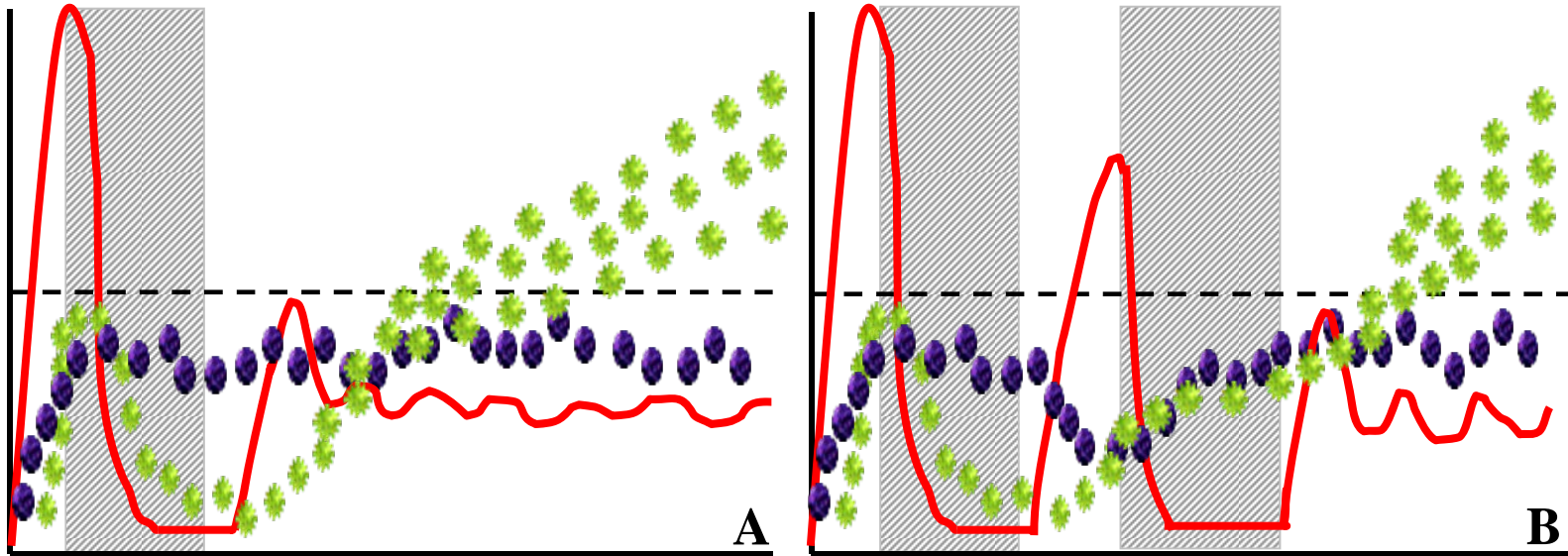
➤ **Limits** of anti-retroviral therapy:

- **Lack / poor restoration of CD4 / CD8 T cells to HIV**
- **Toxicity of drugs : requiring HAART interruptions**

Boosting Immunity to HIV with HAART interruptions: Can the virus help?

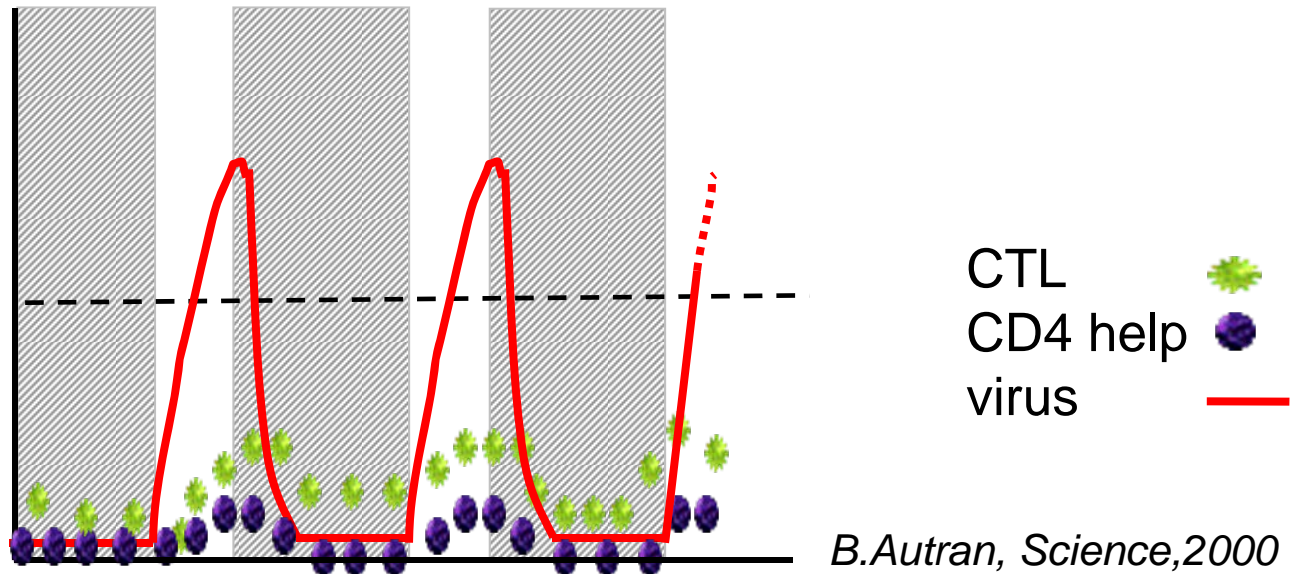
Primary infection

E. Rosenberg et al., Nature 2000



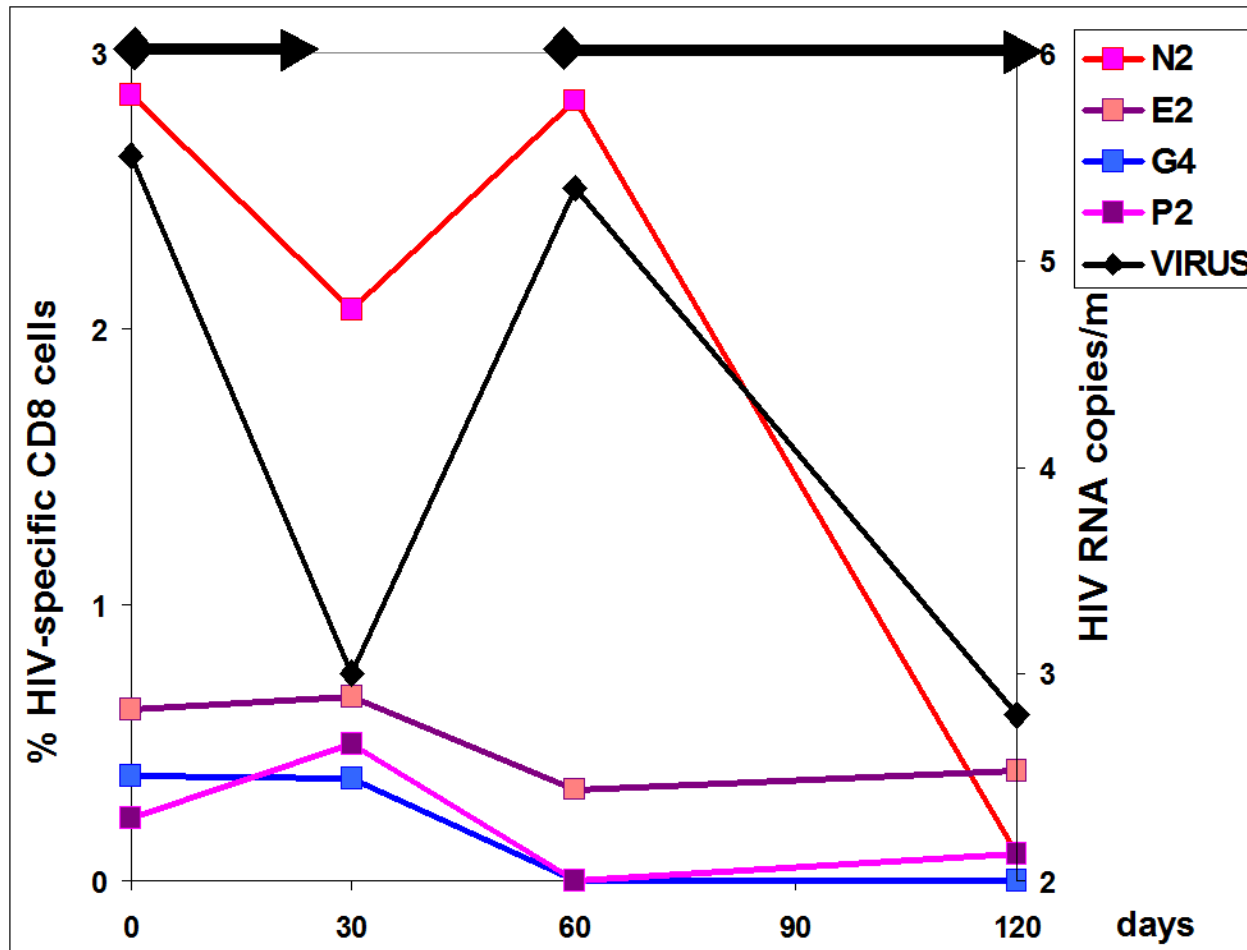
Chronic Infection:

G. Carcelain et al. J. Virol., 2000



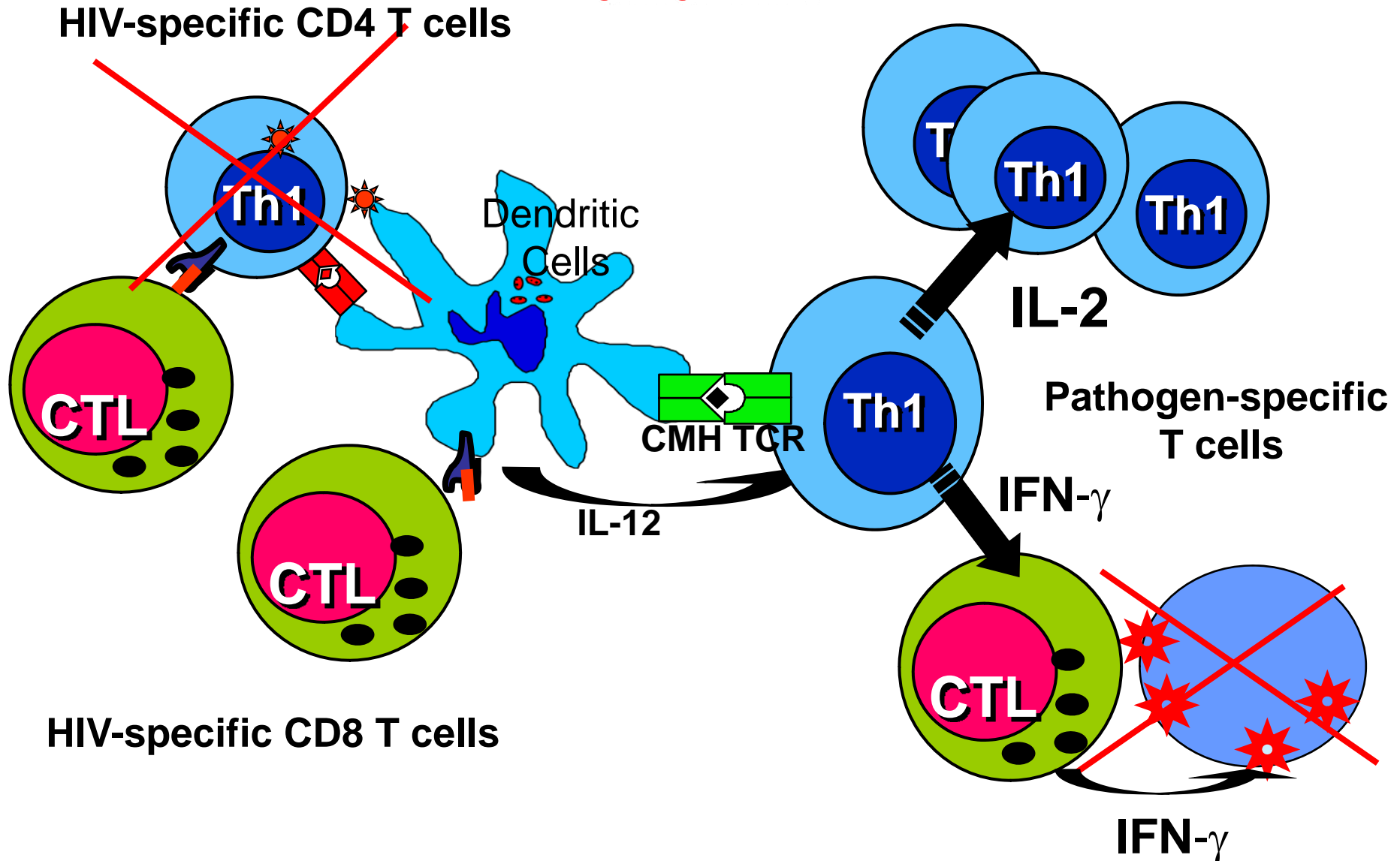
B. Autran, Science, 2000

Rebonds des cellules CD8 anti-HIV pre-existantes et immuno-dominantes avec les IT (péché Ag?)

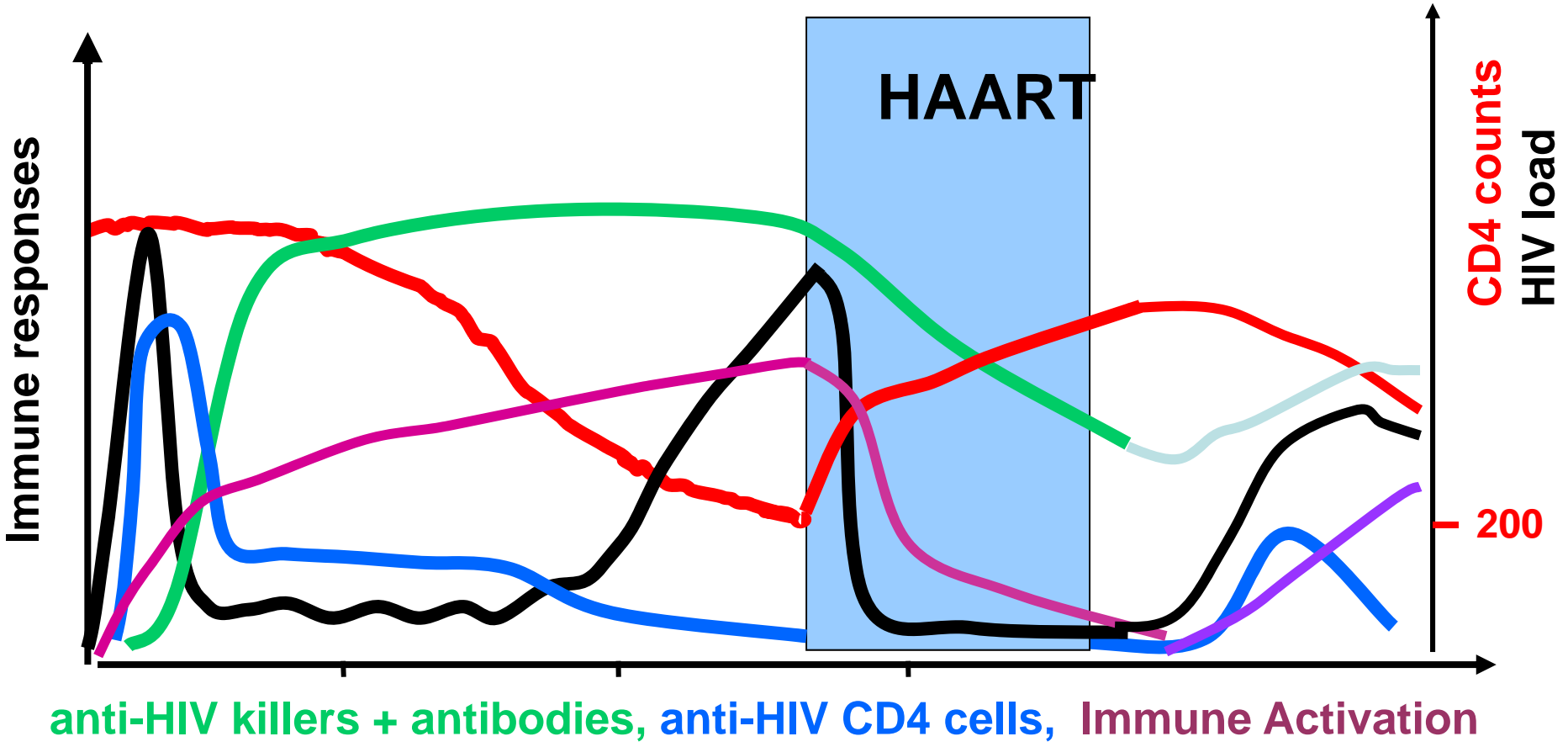


- . HIV-RT (P2), gag (P4), env (E2) and nef (N2)-specific IFN- γ production (FACS)
- . Baseline CD4: $14/\text{mm}^3$; undetectable HIV-specific CD4 T cells

CD4 Th1 cells, CTLs, Dendritic cells and HIV



Rechute de réplication virale et de la déplétion CD4 au cours des interruptions thérapeutiques



STI restore weak and transient T cell responses to HIV in chronic HIV infection

→ Restoration of HIV-specific CD4 Th1 cells

despite prolonged HAART and CD4 cell depletion at HAART initiation

- But transient and highly sensitive to virus replication: disappearing at day 7-10 (*Carcelain 2001, Rosenberg 00*)

→ Some amplification of HIV-specific memory CD8 T cells

despite weak HIV-specific CD4 Th1 cells

- But involving pre-existing HIV-specific CD8 cells mostly
(*Rosenberg 00Mollet, 2000, Oxenius 2000, Carcelain 2001, Ruiz 2001*)

→ Unable to control relapses of virus replication

→ Recent demonstration of enhanced risk for

cardiovascular diseases

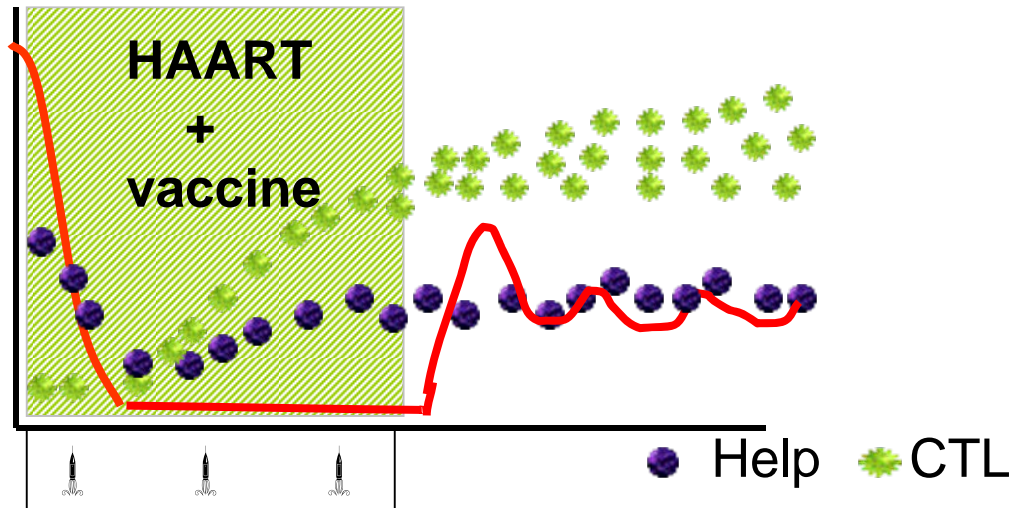
Rationale for Therapeutic Immunisation against HIV in the HAART era

➤ **Limits** of anti-retroviral therapy:

- **Lack of HIV eradication > Life long treatment + HAART Toxicity**
- **Lack of restoration of CD4 response to HIV and Decay of effector CD8 responses to HIV** (*Autran 97, Li 98, Lederman 98, Dalod 98, Ogg 98, Gray 98, Rinaldo 99, Pontesilli 99, Oxenius 99, Mollet 00....*)
= linked to HIV antigen shortage with HAART
- **Lack of protection against HIV:**
 - **Rapid rebounds (7-12 d) after HAART interruptions** (*Neumann 99,...*)
despite Re-expansion of HIV-specific effector after virus relapse
 - transiently protective in Primary Infection (*Rosenberg, 2000....*)
 - but not in Chronic Infection (*Carcelain, 2001, Oxenius 2001, Ruiz 2002.....*)

➤ **Strategies to restimulate protective immunity to HIV**

Therapeutic Immunisation Strategies against HIV



To re-immunize against HIV by boosting immunity :

- with non pathogenic, strong HIV immunogens
- before virus relapse,
- to limit :
 - time on therapy
 - disease progression during time « off ART »

Questions:

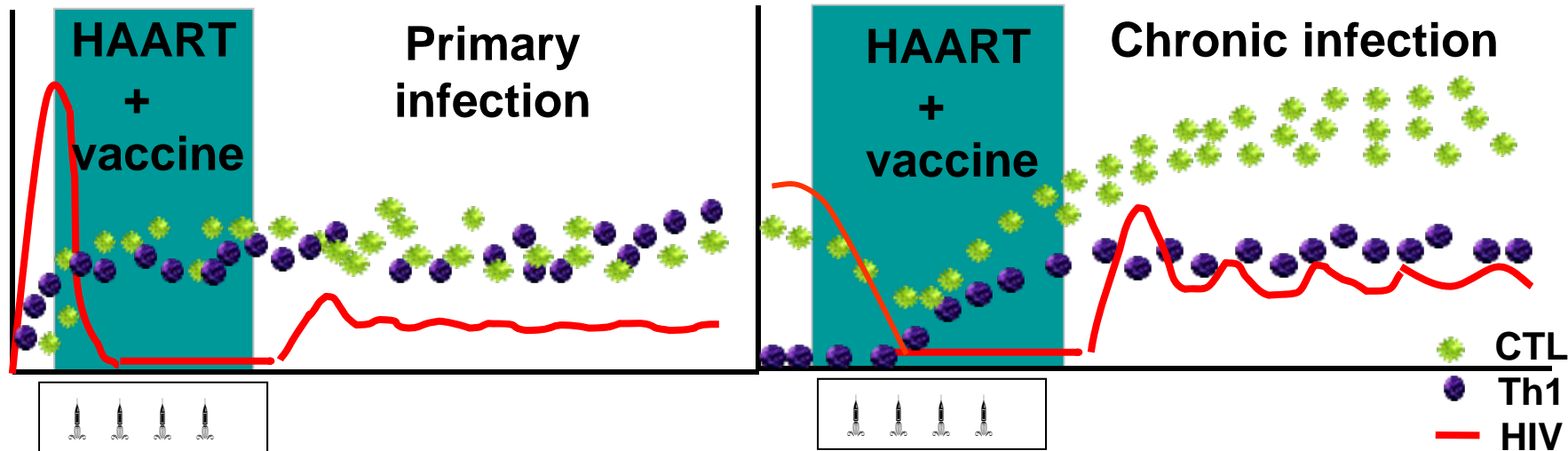
Which correlates of protection ? Which vaccines? Which setting?

Therapeutic Vaccines against HIV ?

Is Post-exposure vaccination against viral diseases a Model ?

- Developed by Pasteur in 1886 for rabies
- Aims : - to accelerate or potentiate installation of a protective immunity
mostly based upon generation of **Neutralizing Antibodies**
- **to prevent severe diseases due to viral infections**
- Applied to **acute phases** of numerous viral infections:
 - Rabies (days): Still the only cure, smallpox (days): during the pandemic,
 - Hepatitis B in infants (days post-birth): the current major application,
- **Questions: Is this strategy applicable to :**
 - **chronic infections such as HIV ?**
 - **T cell correlates of immune protection ?**

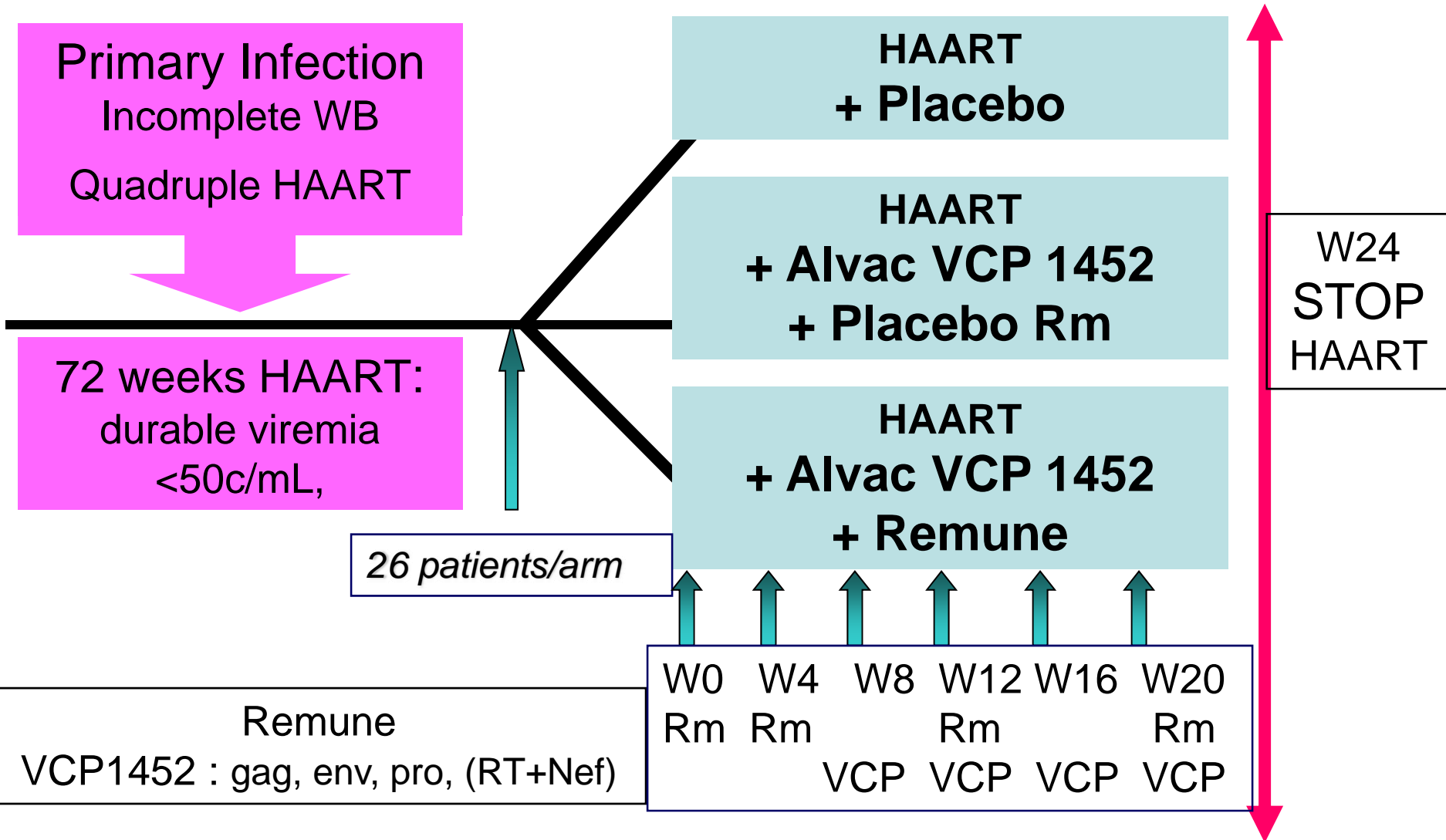
Rationale for Therapeutic Immunisation against HIV & Background results with the HIV-rec. Canarypox vector



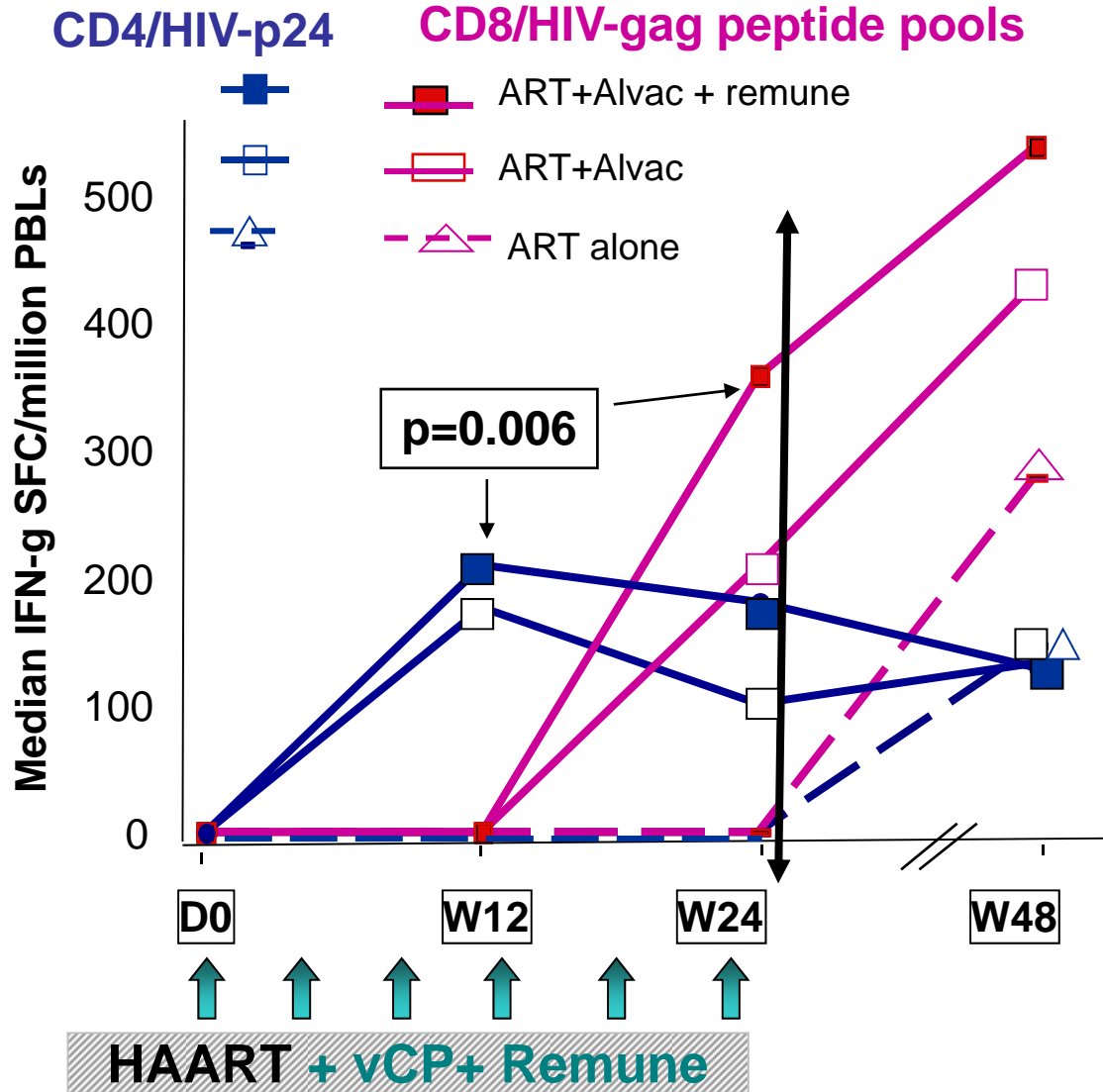
- M Markowitz et al. (*J Inf Dis*, 2002) : vCP + gp160
- S Kinloch et al. (*J Inf Dis*, 2002) : vCP + Remune
- C Goujard et al. (*J Inf Dis* 2007) vCP+Lipopept.+IL2
 - **Safety:** Immunization and ART interruption
 - **Immunogenicity** for T cells / HIV CD4? CD8?
 - **No impact** on ART interruption

- Tubiana et al. (*Vaccine* 2005) vCP
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- M Kilby et al. (*J Inf Dis*, 2006) vCP +/- IL2
 - **Safety:** Immunization and ART interruption
 - **Immunogenicity** for T cells / HIV : CD4? CD8?
 - **Significant, modest, impact** on duration of ART interruption and HIV levels

Therapeutic Immunization in primary HIV infection : QUEST, a GSK Multicentric study:

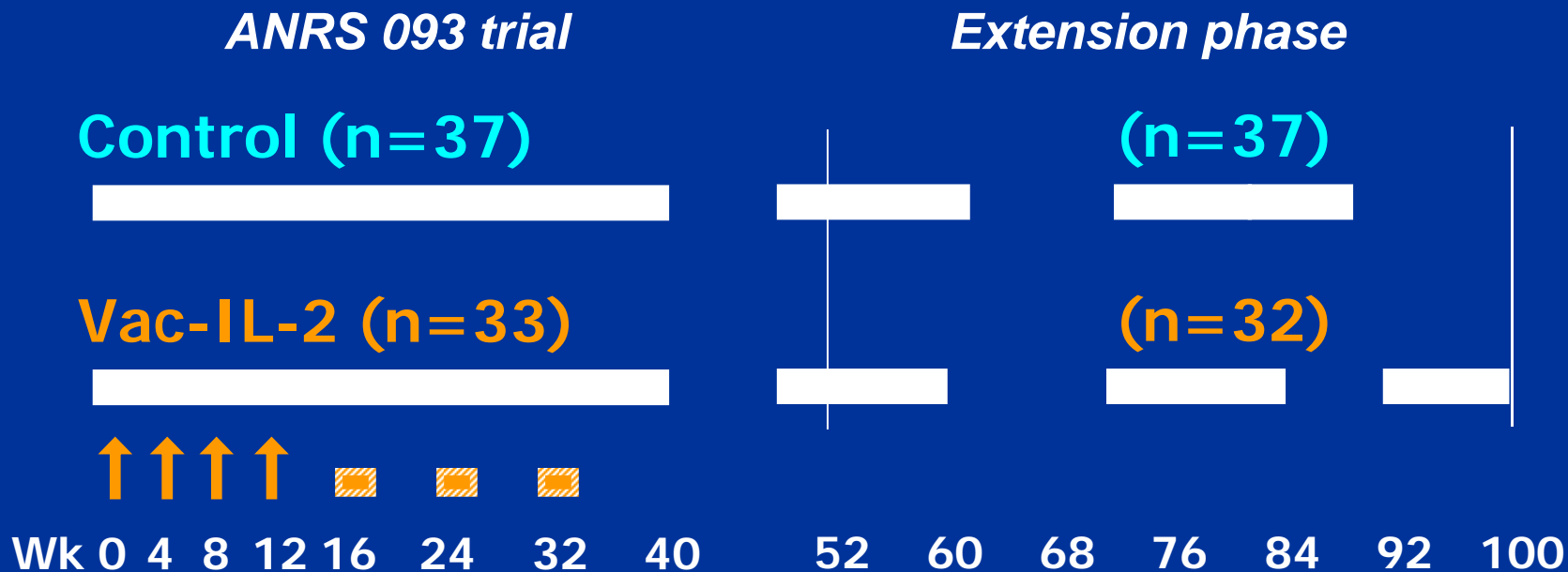


QUEST: Significant Anti-HIV CD4 and CD8 T cell responses (IFN-g) to vaccines and HIV



- **Significant induction of CD4 and CD8 responses to HIV by vaccines,**
- **NOT Correlated with HIV control**
- **Similar to responses to TI in the control arm**

Study design



- HAART
- ↑ Alvac HIV vCP1433+Lipo-6T
- ▨ IL-2 SC (4.5 MIU, bid, 5 days)

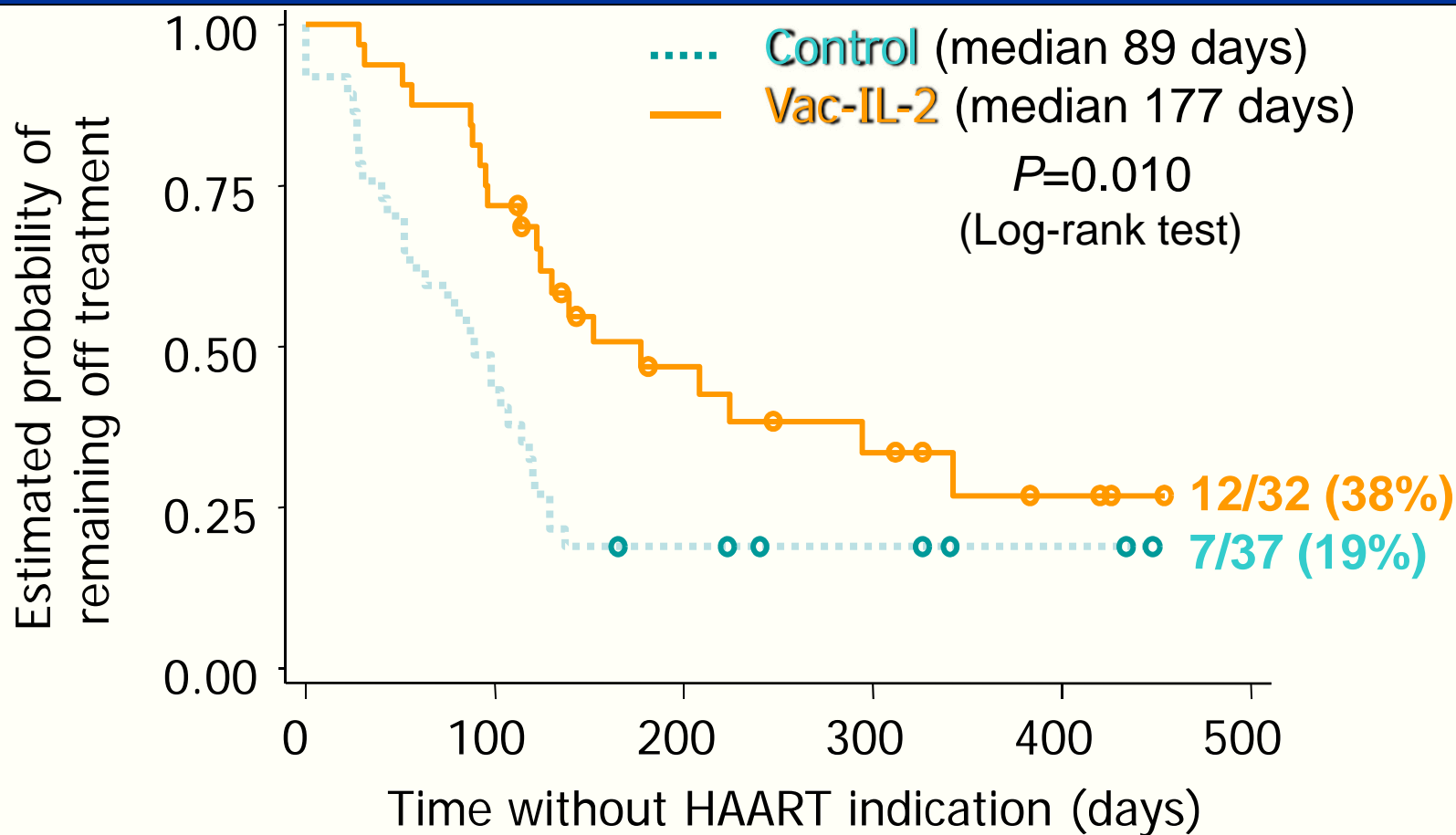
HAART stopped (TI) at Wk 40 or >Wk52 if HIV RNA < 50 cp/mL

Reinitiated if

- HIV RNA > 50 000 cp/mL 4 wks after TI
- HIV RNA > 10 000 cp/mL 8 wks after TI or thereafter



Cumulative time without HAART indication (intent-to-treat analysis)

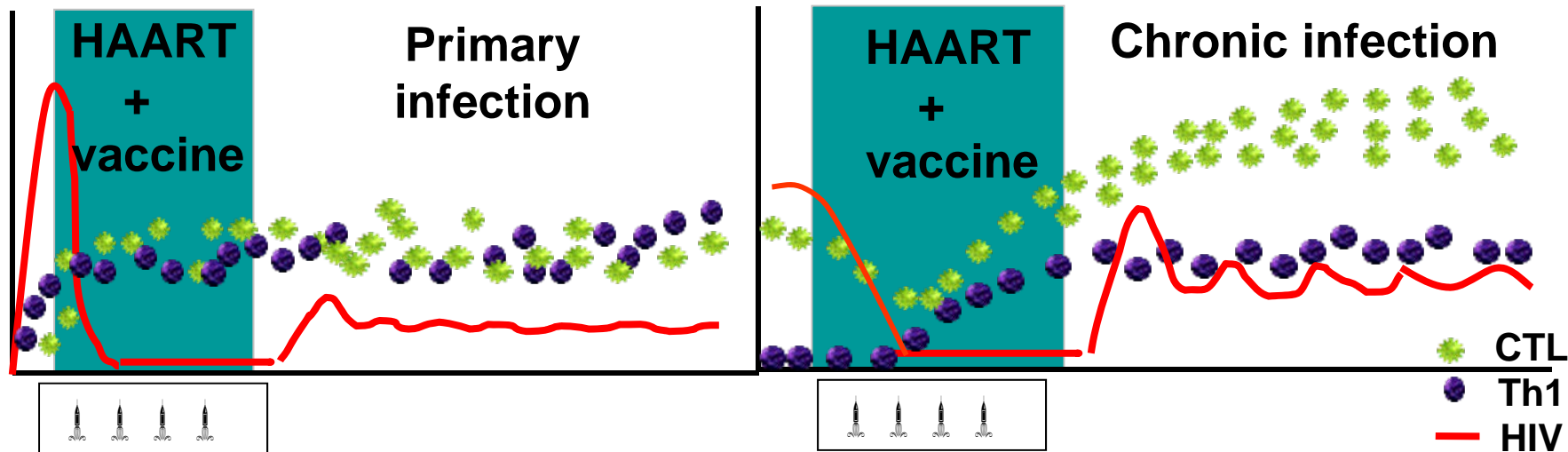


★ Defined as the total number of days with plasma HIV RNA below 10 000 cp/mL during subsequent treatment interruptions from wks 40 to 100

Regression analyses of factors associated with the time without HAART indication

<i>ON STUDY</i>	n Patients	Time without HAART (% , mean)	<i>P</i>
Treatment			
Control	37	26.5	<i>0.016</i>
Vac-IL-2	32	42.8	
LPR to 11 HIV peptides (wk16)			
0	41	26.1	<i>0.0027</i>
≥ 1 peptide	27	46.7	
ELISPOT IFN-γ response (wk36)			
0	34	33.7	<i>0.037</i>
1-2	25	25.8	
3-6 HIV pools	9	53.4	

Rationale for Therapeutic Immunisation against HIV & Background results with the HIV-rec. Canarypox vector



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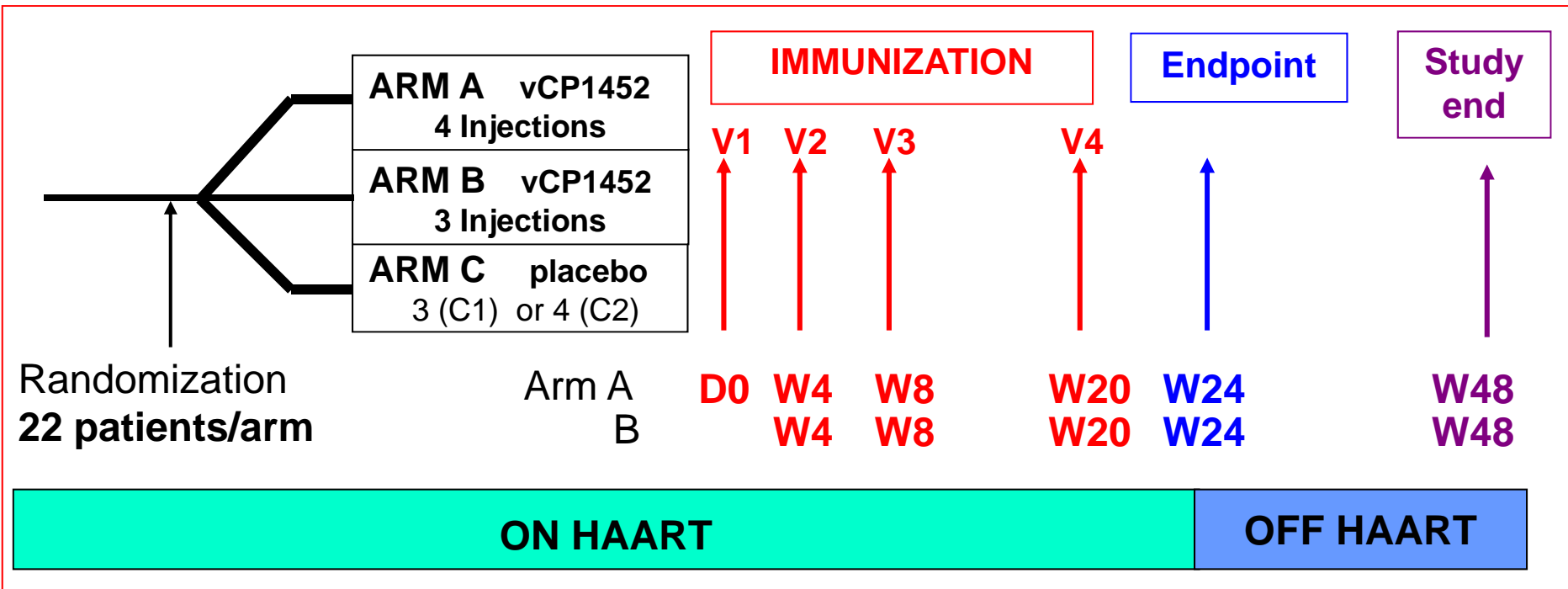
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 - **Significant, modest, impact on duration of ART interruption and HIV levels**

Therapeutic Immunisation in Primary HIV infection

- **Primary Infection : Failure of**
 - Canarypox + inactivated HIV (QUEST) (*Kinloch et al, J.Inf.Dis, 2005*)
 - vCP+lipopetides + IL2 (*PrimoVac: ANRS095*) (*Gougeard et al. CROI, 2004*)
 - **Factors for failure in acute BUT not in Chronic infection?**
 - **Primary infection :**
 - Low CD8 T cell responses to HIV pre- and post-immunisation :
 - Good CD4 T cell responses to HIV pre-immunisation
 - Good immune response to HIV challenge in the non-immunized arm
 - **Chronic Infection:**
 - Lack of CD4 T cell response to HIV pre-immunisation
restored by immunisation
 - Memory CD8 T cells boosted by immunisation
 - Weak or moderate response to HIV challenge in the Non –immunized arm
- => A weak vaccine makes a difference only in chronic infection ??**

MANON 02: Study design

Vaccine: vCP1452 canarypox recombinant for HIV-MN gp120, BRU-gag, protease & antigenic regions of Nef and RT, plus vaccinia virus-derived E3L/K3L genes.



Criteria to resume ART during treatment interruption:

- **from W24 to W40** : If CD4 cells decline < 250/mm³ or a loss of CD4 >50% of baseline value twice consecutively within 2 weeks
- **from W40 to W48** : If VL is twice consecutively > 50 000 copies/ml within 4 weeks

Manon-02: Patients baseline characteristics

	ALVAC 3 injections			ALVAC 4 injections			Placebo			P
	N	Median	[Q1Q3]	N	Median	[Q1Q3]	N	Median	[Q1Q3]	
Age (years)	22	40.5	36.5 - 50.9	21	47.3	37.7-49.8	22	42.1	39.6-46.3	Ns
Sex ratio Male / Female	16 / 6			20 / 1			17/ 5			Ns
CD4 Nadir cells/mm ³	22	268	219 - 289	21	217	168 - 300	22	215	88 - 284	Ns
VL at HAART Initiation log ₁₀ cp/mL	17	4.7	3.2 - 5.0	16	5.0	4.5 - 5.4	17	4.4	2.6 - 4.8	0.04
Duration of HAART (years)	22	5.9	4.5 - 7.5	21	6.7	4.2 - 9.3	22	6.5	4.5 - 9.4	Ns
Baseline CD4 cells/mm ³	22	618	508 - 723	21	653	594 - 745	22	588	513 - 715	Ns
Baseline VL log ₁₀ cp/mL	22	2.6	2.6 - 2.6	21	2.6	2.6 - 2.6	19	2.6	2.6 - 2.6	Ns

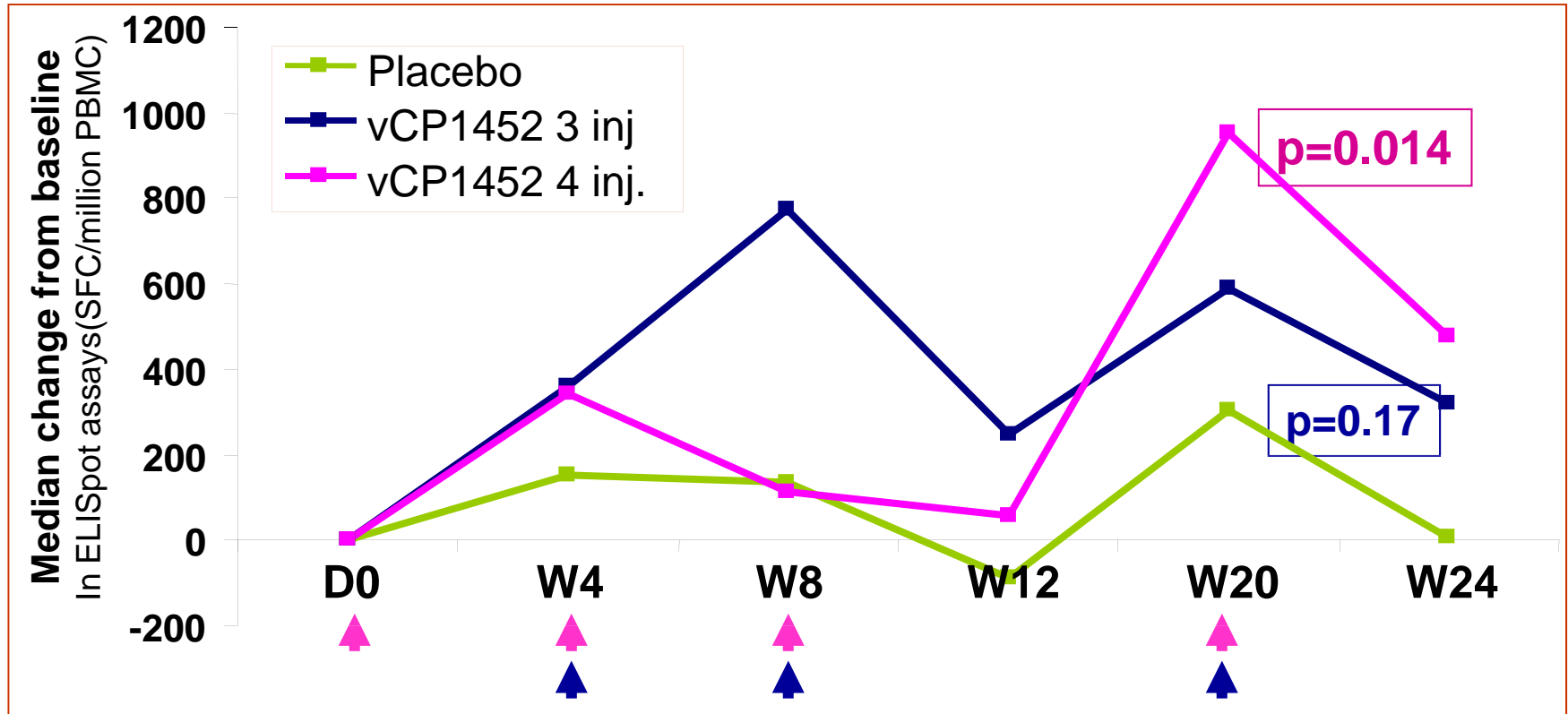
Study Status:

66 enrolled, (65 received all immunisations)

64 evaluable at W24 (56 available for ELISpot analysis)

54 interrupted HAART

Manon-02 Primary End Point : Significant increase from baseline in HIV-specific PBMC after 4 vaccine injections but not after 3 vaccine injections, compared to placebo

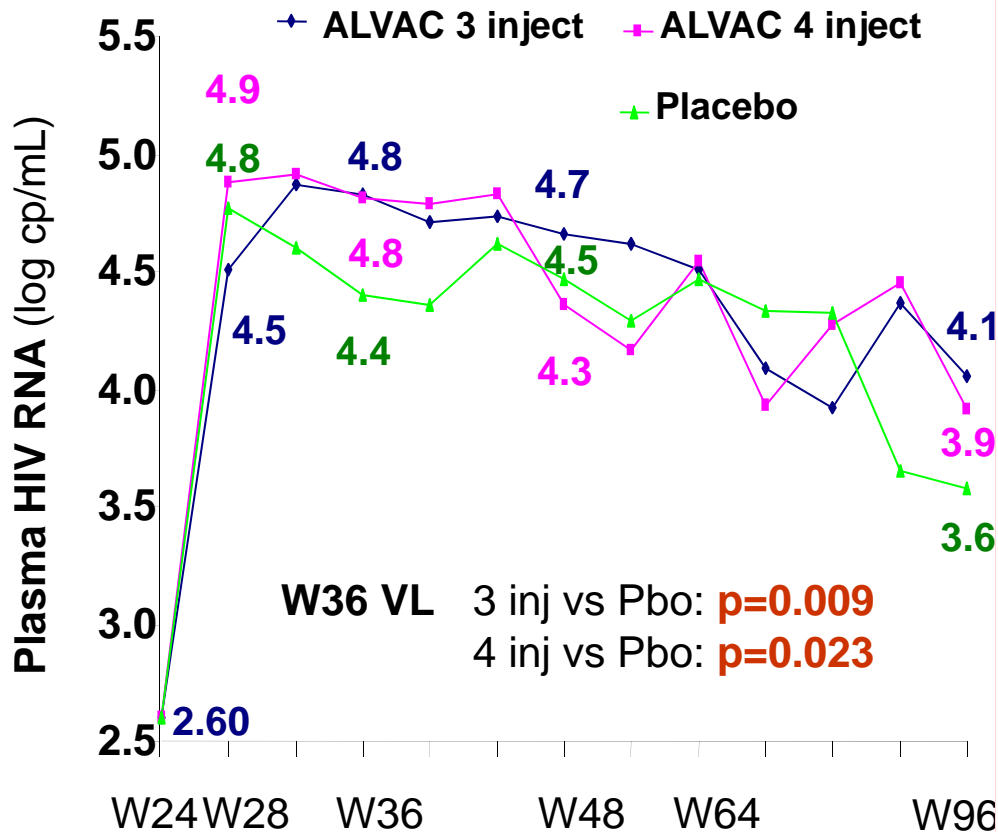


- **Baseline** HIV-specific T cell numbers: **1,009** and **1,203** SFC/million PBMC in the 3 & 4 inject Arms vs **1,095** in the placebo:: NS
- **Breadth**: Increase in N peptide pools recognized / patient: **+2.5** and **+2** in the 3 & 4 inject. Arms, vs +1 in the placebo arm : NS

ELISpot assays performed using a standardized single SOP in Paris and Boston Core Labs with pools of 15-mer peptides (10/pool) covering the vaccine HIV-1Gag, Nef, RT sequences. Threshold for positivity > 50 SFC/million PBMC,

Manon-02 ART Interruption : Higher Plasma HIV Load after 4 vaccine injections compared to Placebo

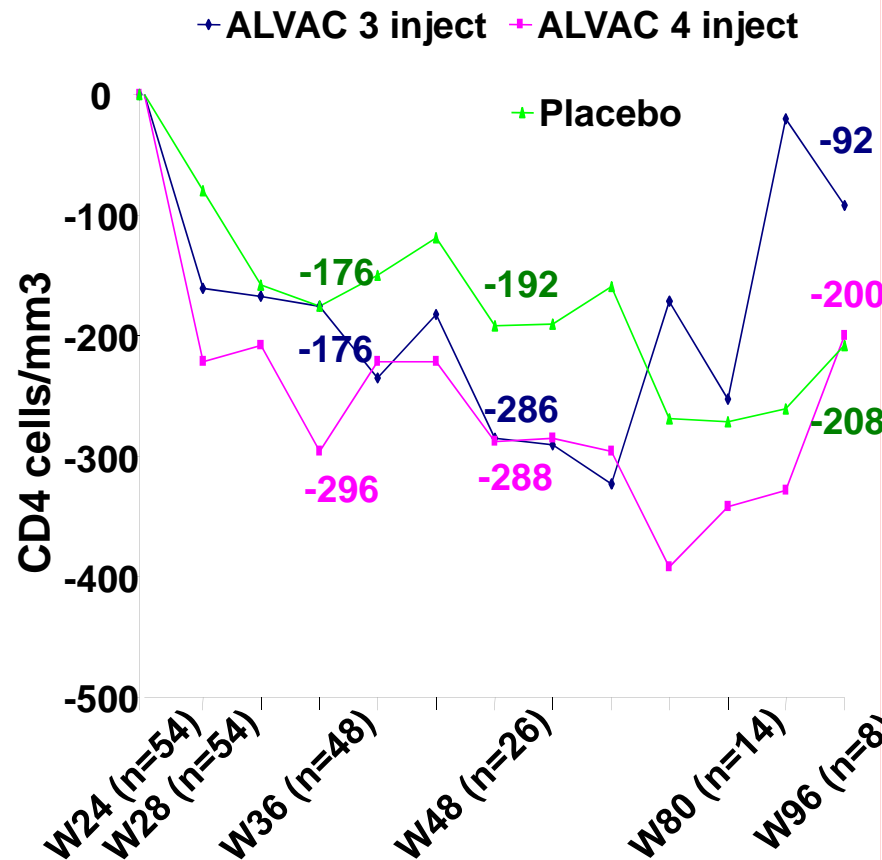
Plasma Viral Load



Mean AUC for pVL

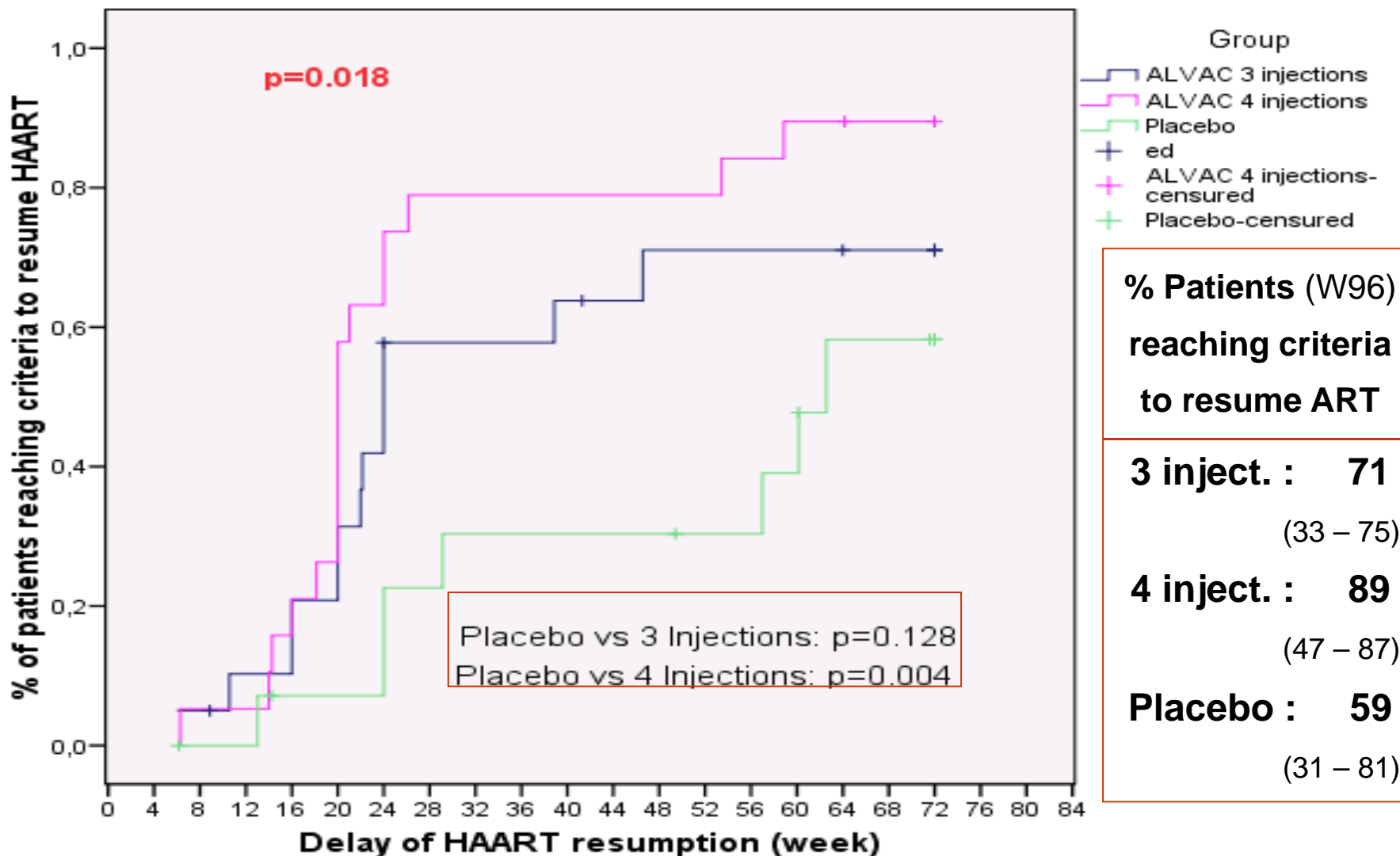
3 inject. vs placebo: **p= 0.096**
4 inject. vs placebo: **p= 0.017**

CD4 counts



No significant differences in CD4 count changes

Manon-02 Interruption : Higher % of patients reaching criteria to resume ART per protocol in the immunized arms



Manon-02: Concluding Remarks (1)

Therapeutic immunization with the HIV-recombinant canarypox vaccine (vCP1452) in treated chronically-infected patients shows:

- **A significant immunogenicity for T cells of 4 but not of 3 injections** ,
compared to placebo, with
 - modest but significant increase in the magnitude (+500 SFC/million PBMC)
 - no significant broadening and no booster effect of the last injection
- **A lack of efficacy with even significant:**
 - **increase in HIV replication** during TI in the two vaccine arms
despite no differences in changes from pre-ART values when available,
 - **shortened delay to reach criteria of ART resumption**
- **The safety** of the procedure even during the post-immunization TI

Manon-02: Concluding Remarks

- **2 factors independently influence the relative risk of resuming ART :**
 - 1. Immunization : 4 fold increase after 4 vCP1452 injections**
3 fold increase after 3 vCP1452 injections
and a borderline significance for the magnitude of ELISpot numbers at W24
 - 2. HIV infection characteristics:**
 - **The CD4 nadir : 2 fold increase** (lack of dysbalance for the nadir between groups)
 - **Baseline HIV-DNA content and Pre-ART viral load > 50,000 cp/ml were close to significance**

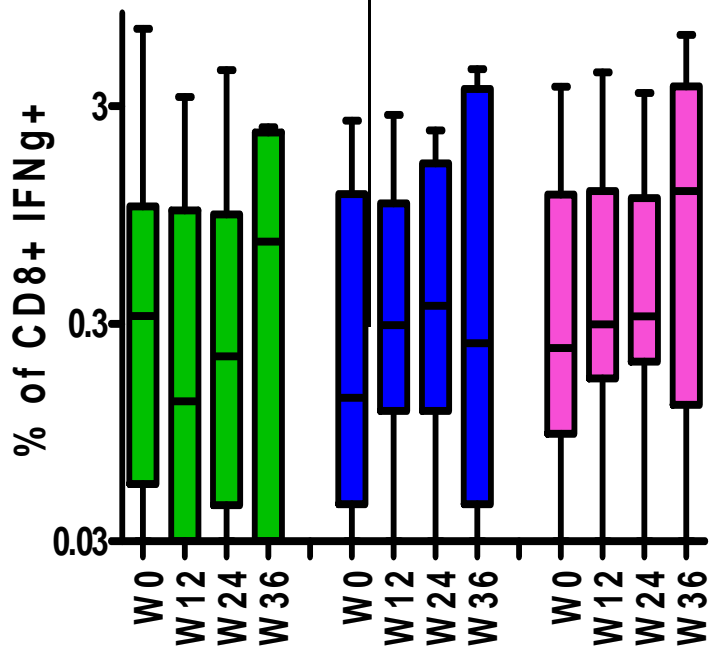
Manon-02: The Significant increase in HIV-specific T cells

after 4 vaccine injections (Autran et al. AIDS, 2008)

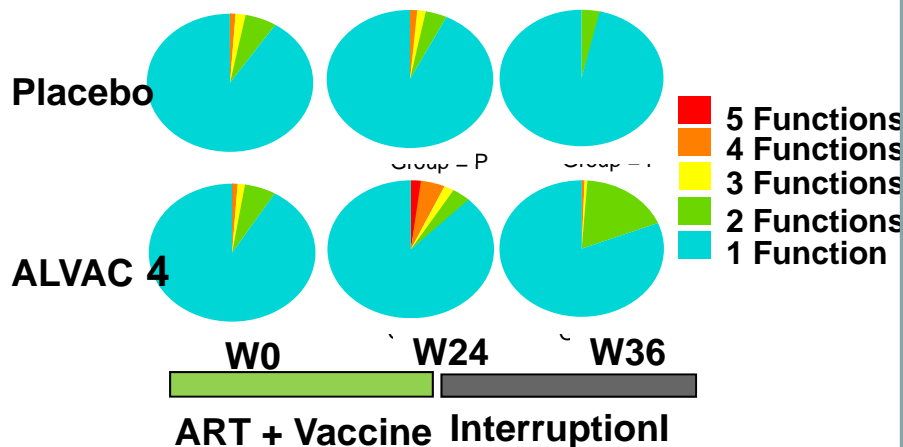
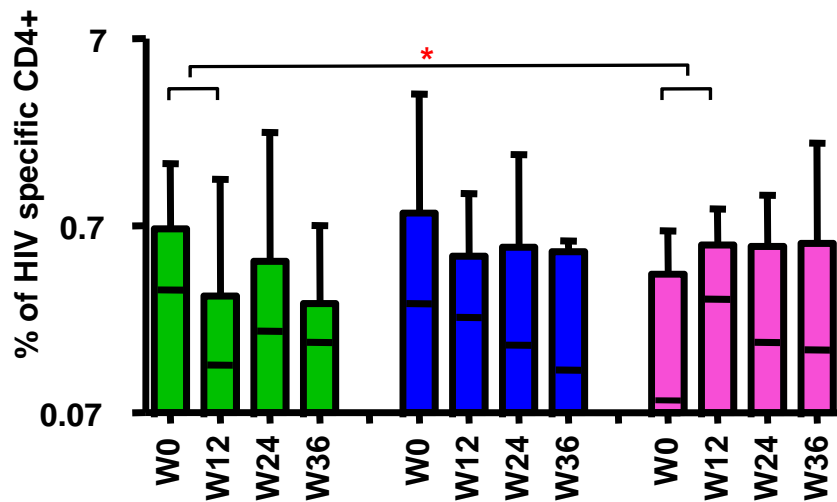
involved only HIV-specific CD4 T cells



ICS: NO significant in CD8 T cell responses



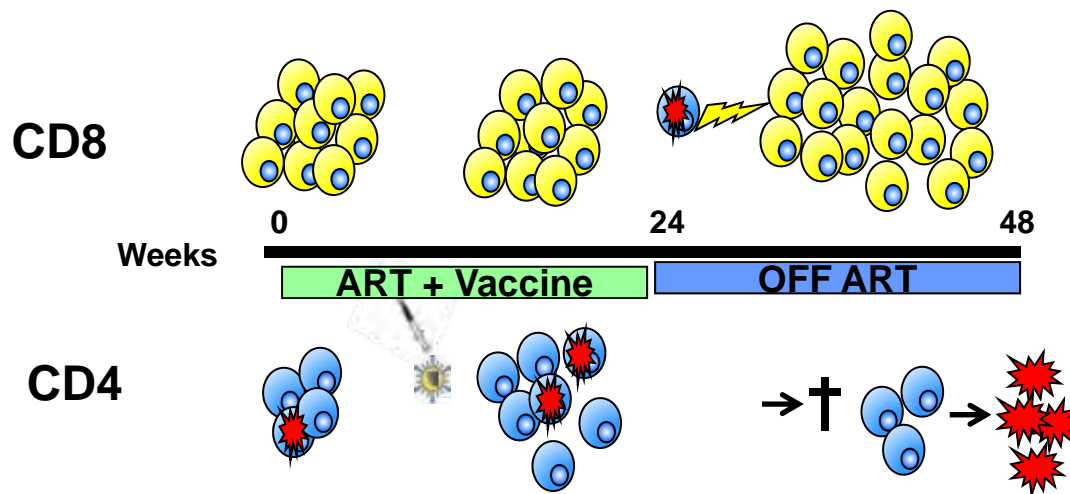
ICS: Significant CD4 T cell responses



The « Yang »: HIV preferentially infects HIV-specific CD4 T cells

D Douek et al. Nat Med. 2000

- Therapeutic immunization with the HIV-rec. canarypox vaccine (Manon-02 trial)
 - Enhanced HIV replication after ART interruption in immunized patients
 - **The immunization procedure facilitated HIV production from an increased reservoir** by:
 - Boosting **HIV-specific CD4+ target cells** for the virus
 - without amplifying HIV-specific CD8 T-cells



- **The Manon-02 results reflect :**
 - **the limited vaccine immunogenicity: predominant activation of HIV-specific CD4 T cells potentiating the niche for the virus,**
without appropriate activation of HIV-specific CD8 T cells
 - **the study population : CD4 nadir**
- **The Manon-02 safety results do not raise concerns about the therapeutic vaccine strategy** including TI provided a limited TI is accompanied by strict criteria to resume ART
- **Future studies should :**
 - **test vaccines capable of eliciting “good” HIV-specific CD8 T cells**
 - **check for baseline balance** in : pre-ART VL and HLA

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H Mohand Ait

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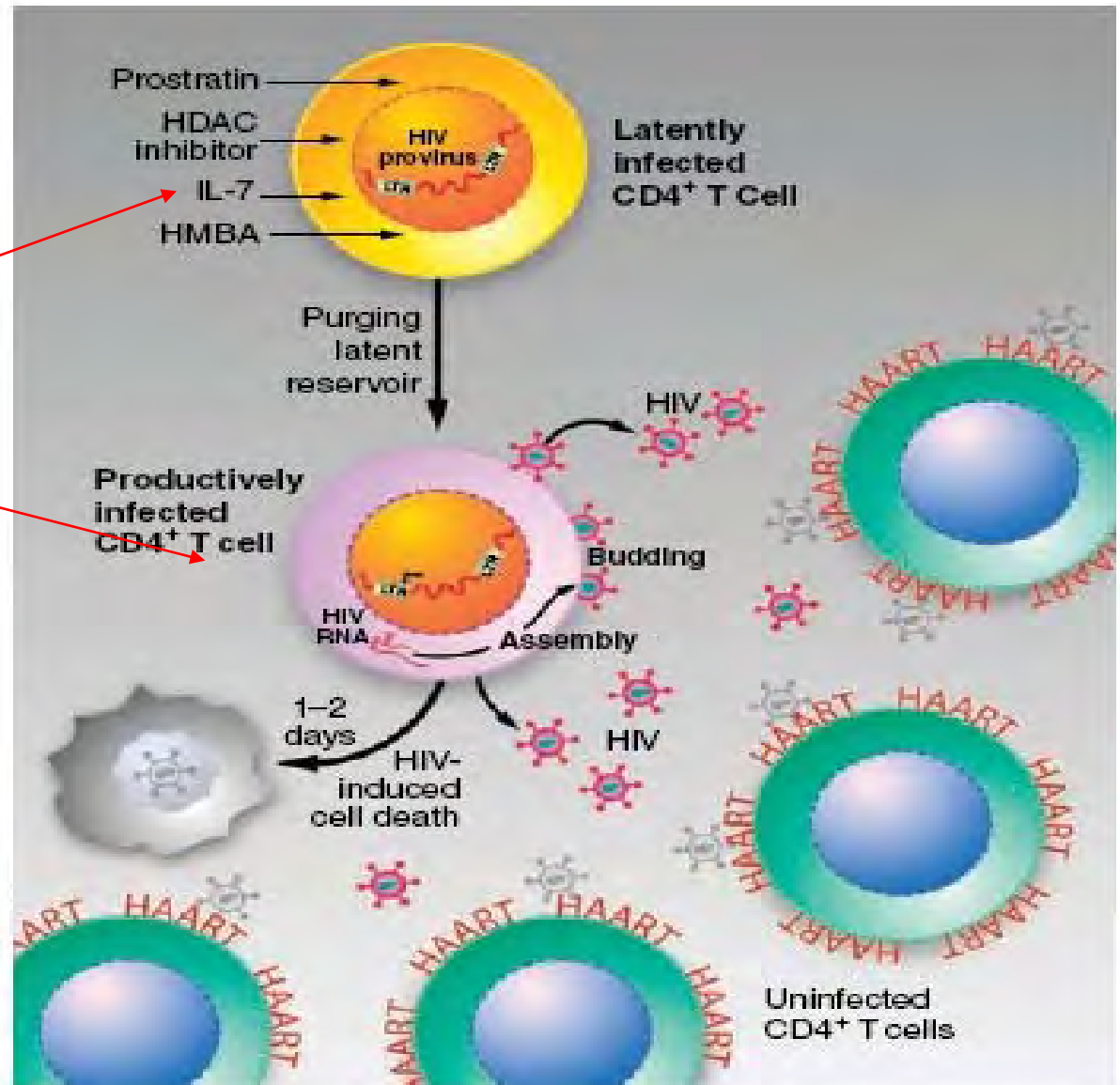
Germany, W Goethe-Univ, Frankfurt :

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The Challenge of Finding a Cure for HIV Infection

Douglas D. Richman,^{1*} David M. Margolis,² Daria Hazuda,⁵ Roger J. Pomerantz⁶



IL-7

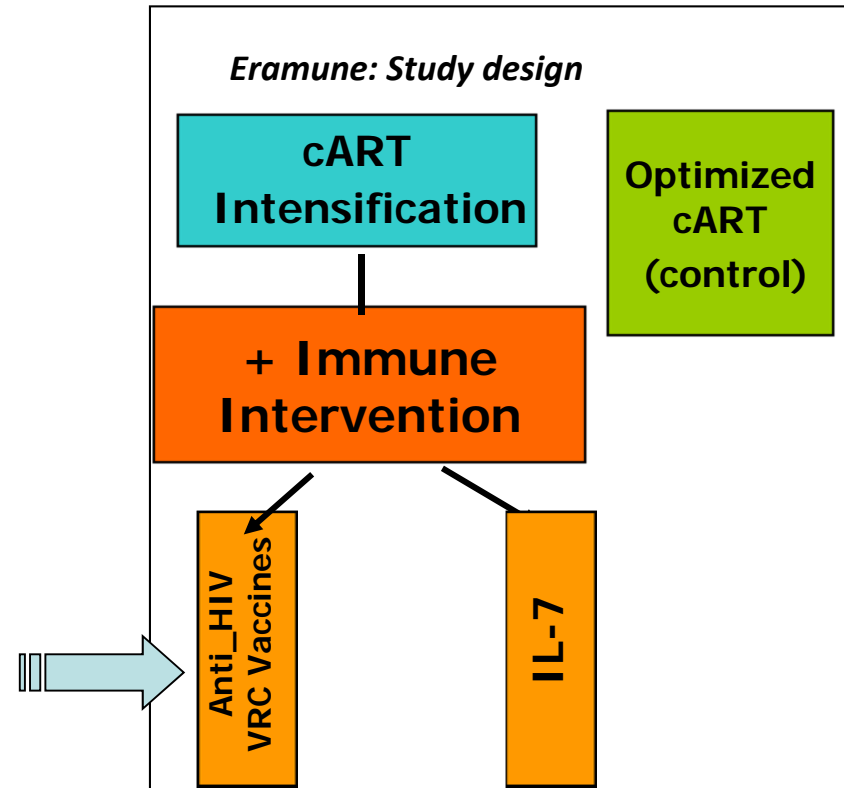
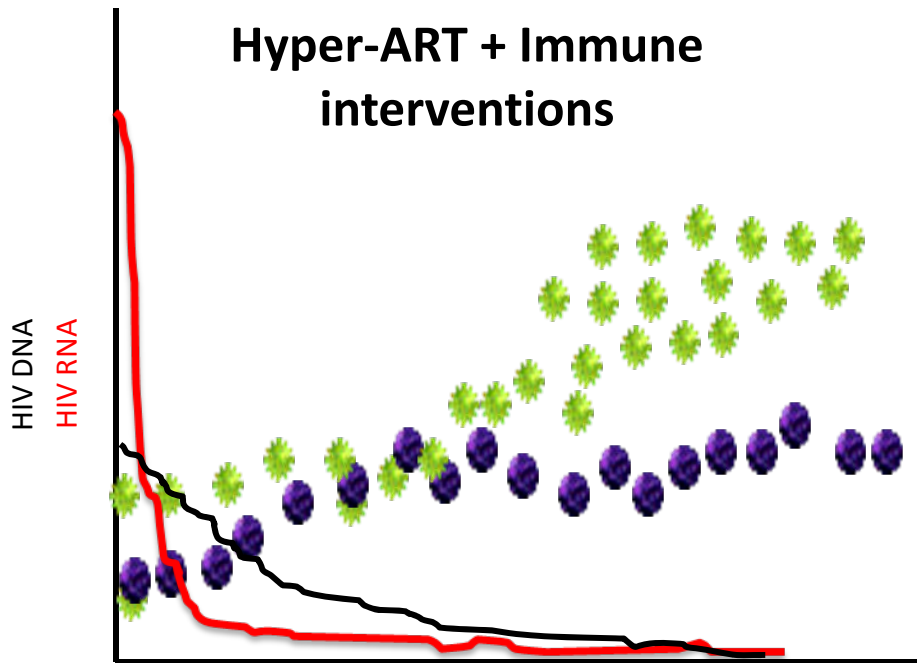
Purging the HIV reservoirs?

CTLs

Is exhaustion of HIV Immune Reservoirs feasible ?

The Eramune Projects

- Can the most potent combinations of ARV + immune interventions
 - That activate « latently » infected cells
 - That target cells actively replicating HIV
- Exhaust the HIV reservoirs ?



**Univ Pierre et Marie Curie Paris-6, CHU Pitié-Salpêtrière,
IFR Immunité-Cancer-Infection**

Immunology, INSERM U945

Immunity to viruses

A Samri **B Descours**
A Guihot **V Martinez**
G Carcelain

immunogenetics HIV immunosenescence

I Theodorou **V Appay,**
J Gueurgnon **J Almeida**

INSERM U943

Statistics : D. Costagliola et al.

Clinics: C Katlama, R Tubiana, MA Valantin....

Virology: V Calvez AG Marcellin

ALT ANRS CO15 Cohort and study group:

Virology and serology : **C Rouzioux, V Avettand** , Univ. Paris-5

Clinics: JP Clauvel, Saint-Louis Hosp. Univ Paris-7
 D Sicard, Cochin Hosp. Univ. Paris-5