Immune Reconstitution :

Quantitative and Qualitative aspects

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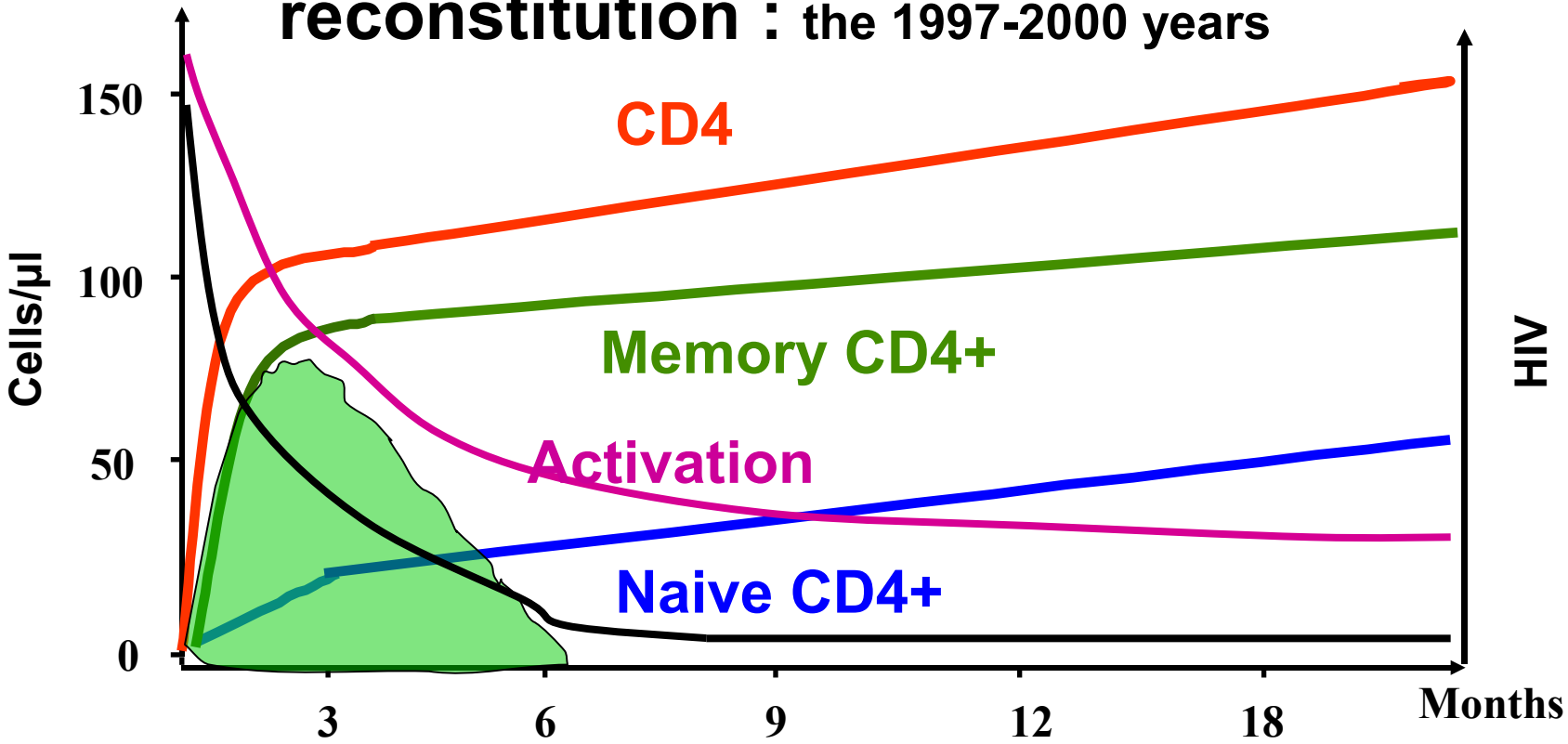
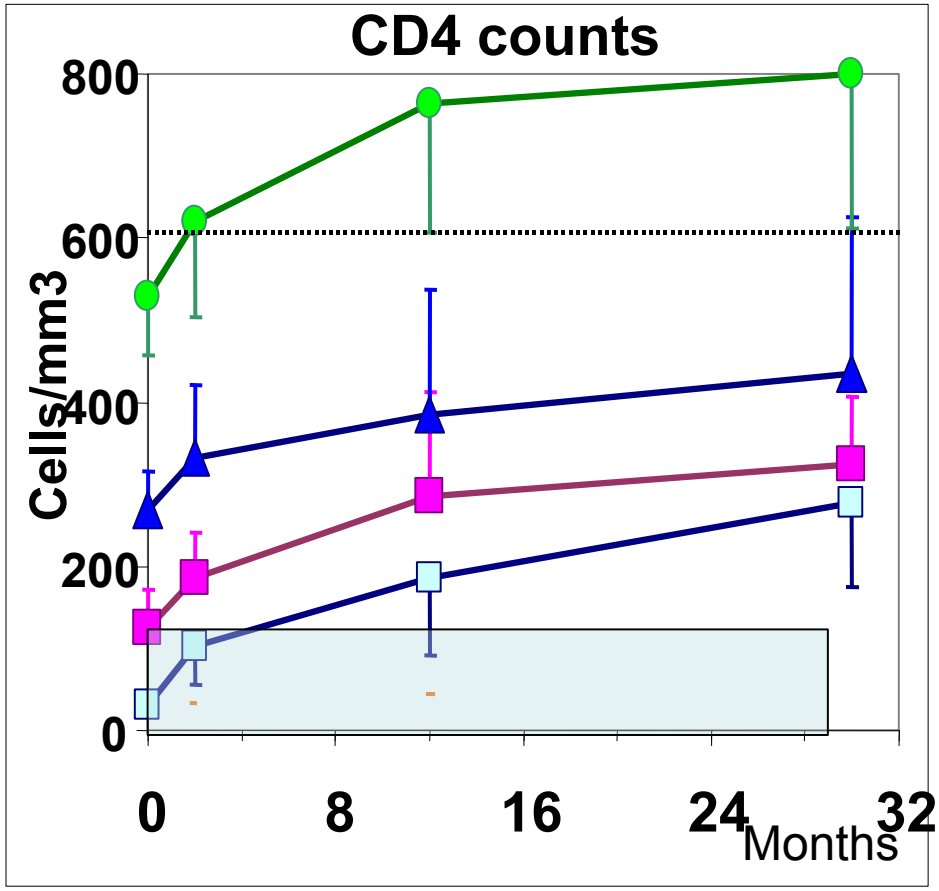
The 3 phases of the ART-induced immune reconstitution : the 1997-2000 years

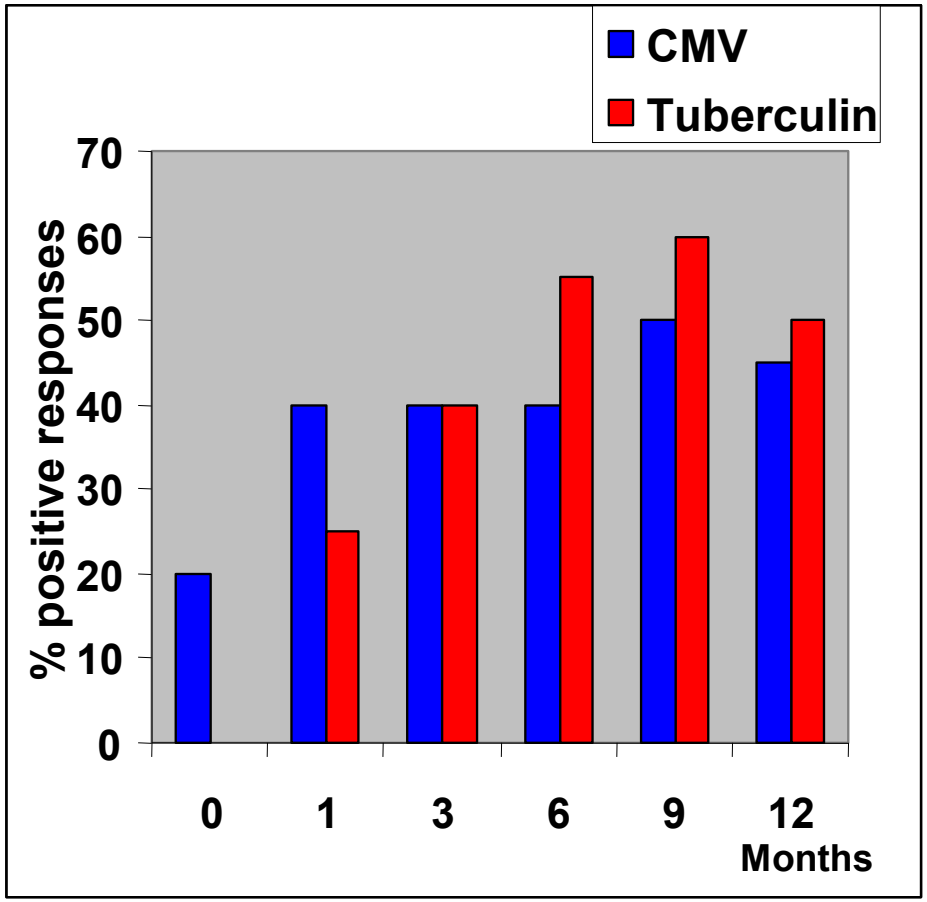


1. Early Memory CD4 T cell Redistribution : « Fake » quantitative restoration of CD4 counts but no functionnal restoration
2. Decreased activation with virus control : allows functional restoration
3. Late Naive T cell regeneration > long term CD4 T cell quantitative expansion and Restoration of defenses against OI

(Autran 97, Pakker 98, Li 98, Lederman 98, Bucy 98, Gorochov 98….)

Quantitative and functional CD4 cell reconstitution with HAART





300 patients treated with HAART, viral loads <200 copies/ml

Rapid CD4 counts restoration in end stage disease with high risk of CMV retinitis

Restoration of proliferative CD4 responses to CMV in end stage disease

(Autran 97, Li 98, Lederman 98, Rinaldo 99,

Similar prognostic significance of CD4 counts during disease and immune reconstitution

Immunological recovery and antiretroviral therapy in HIV-1 infection

Manuel Battegay, Reto Nüesch, Bernard Hirschel, Gilbert R Kaufmann /infection.thelancet.com Vol 6 May 2006

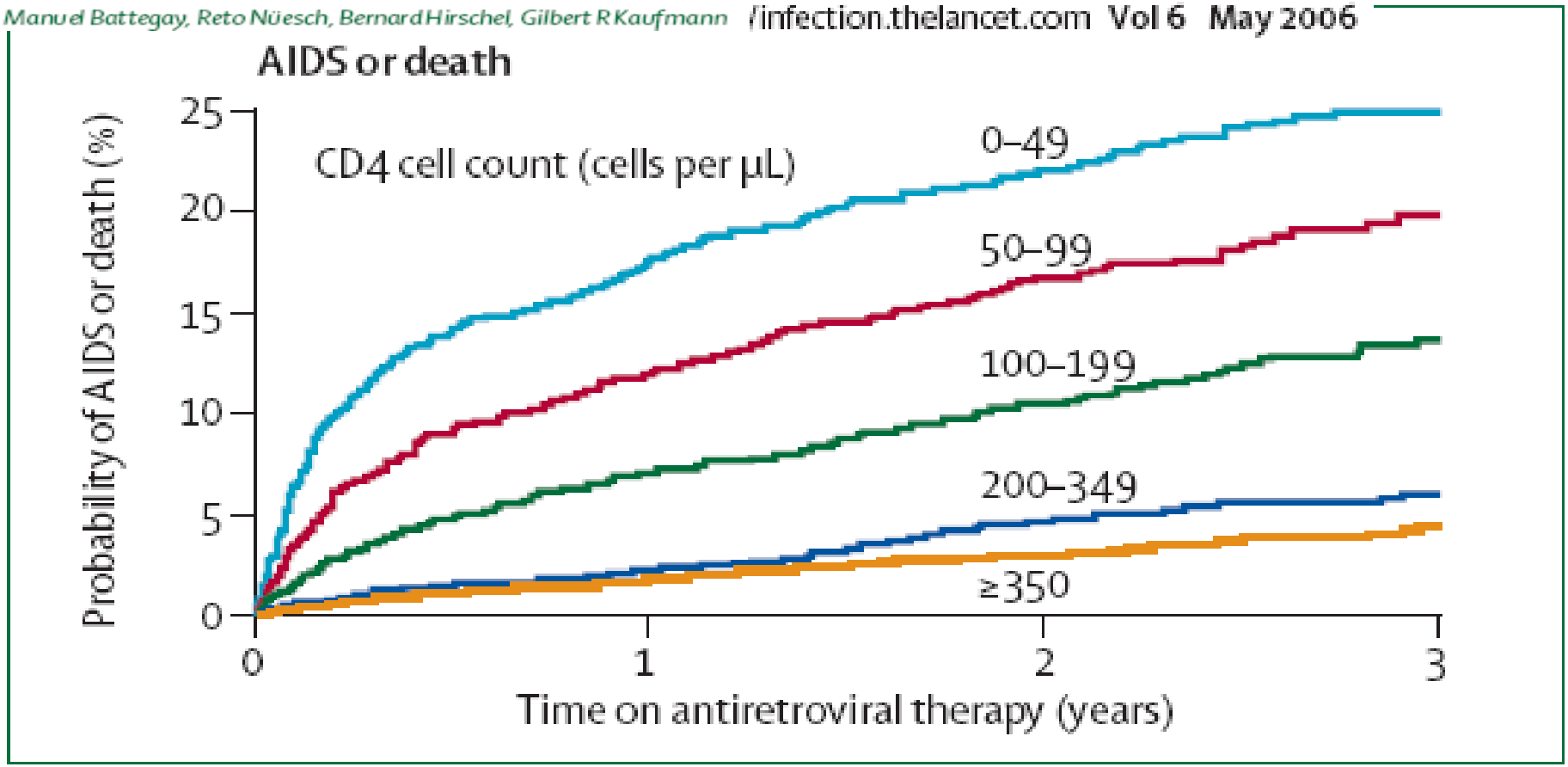
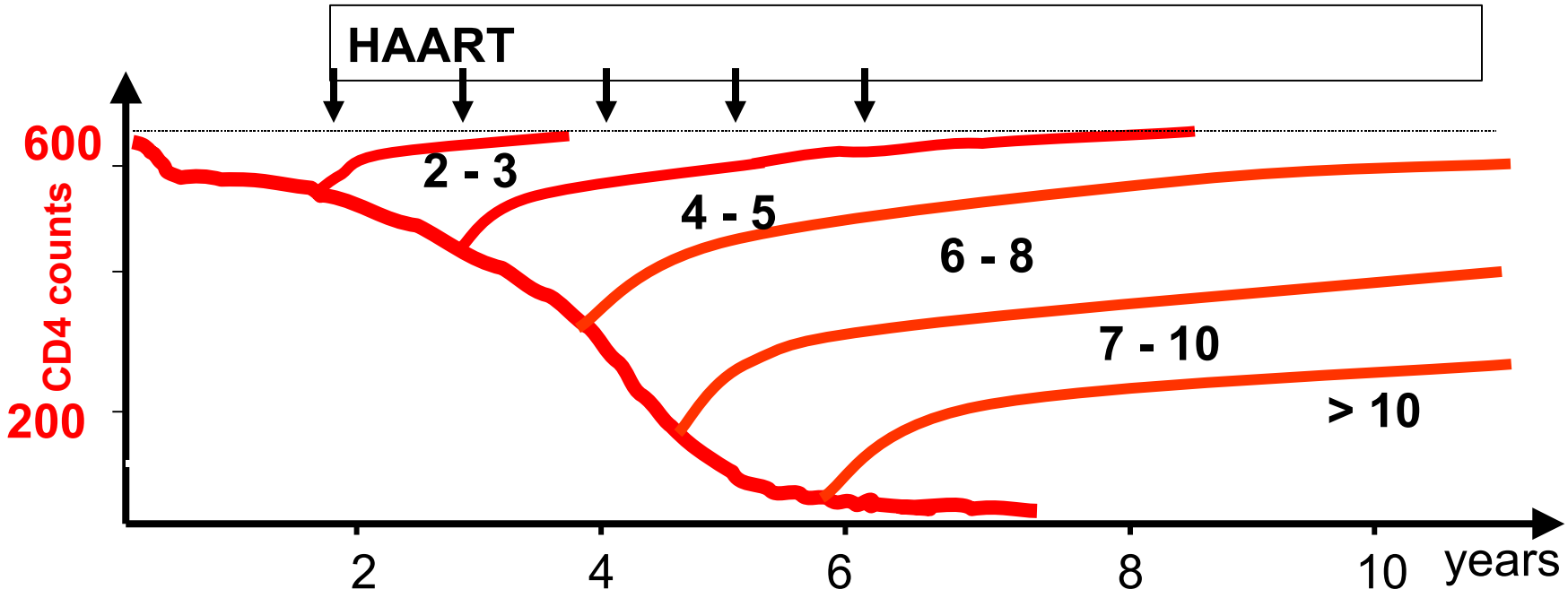


Figure 1: Kaplan-Meier plots of the probability of progression to AIDS or death[8]

Schematic prediction of Time to restore normal CD4 counts acording to CD4 cell depletion at time of ART initiation

(B Autran et al. 1998)



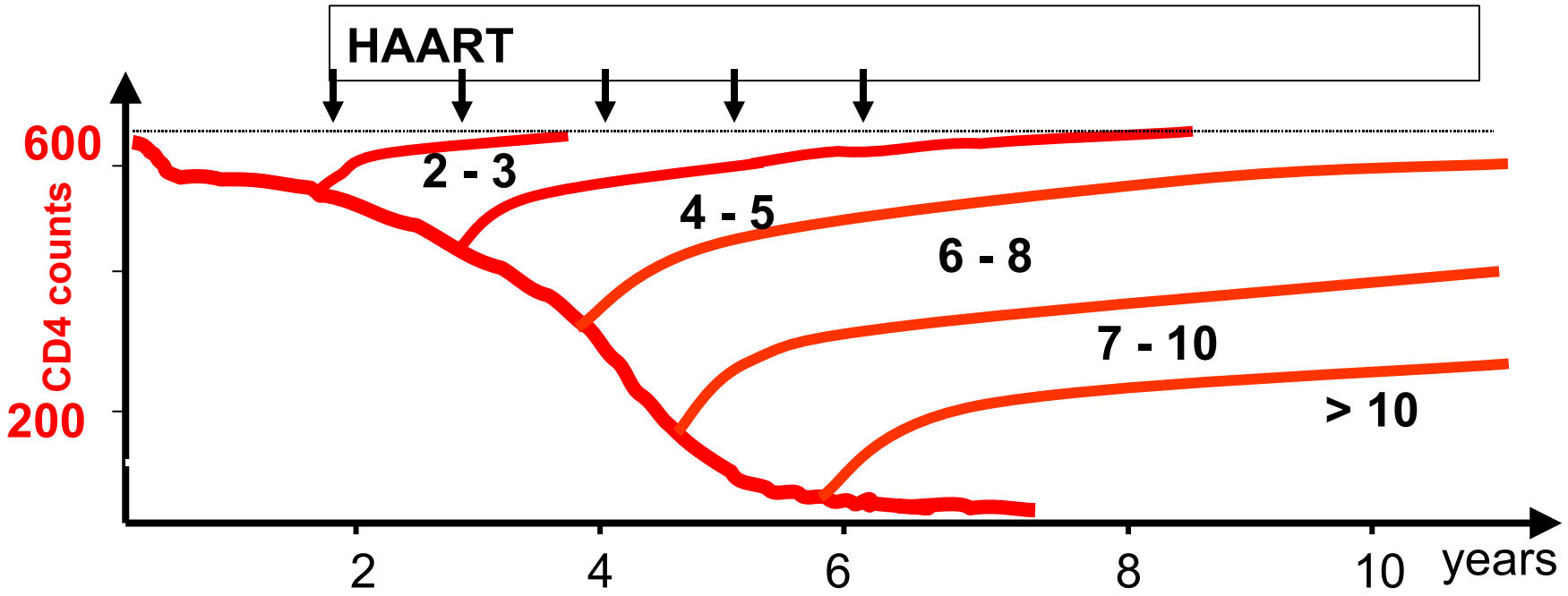
Factors influencing quantitative CD4 T cell reconstitution:

- **Positively:** **- amplitude of HIV control at initiation of ART**
  - rapid CD4 decrease before ART initiation *(Renaud et al, 1999)*
- **Negatively:** **- outbreaks of virus replication (blips, STI)** *(Bategay, 2006)*
  - HCV co-infections *(Koziel 2007)*
  - X4 virus tropism for naive CD4 T cells *(Delobel, 2006)*

BA JNI2007

Schematic prediction of Time to restore normal CD4 counts acording to CD4 cell depletion at time of ART initiation :

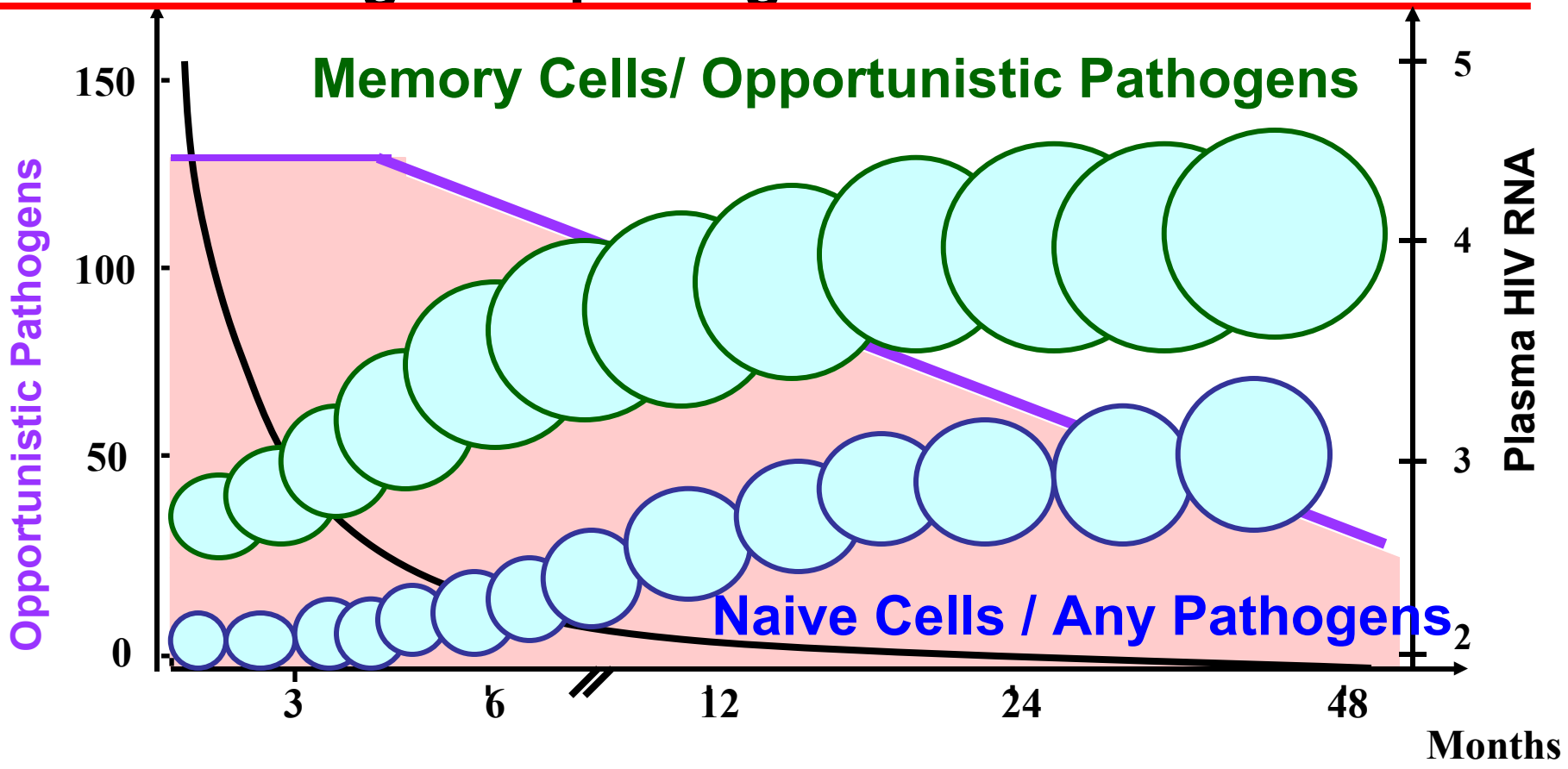
Where are we today ?



Do drugs influence the quantitative CD4 T cell reconstitution:

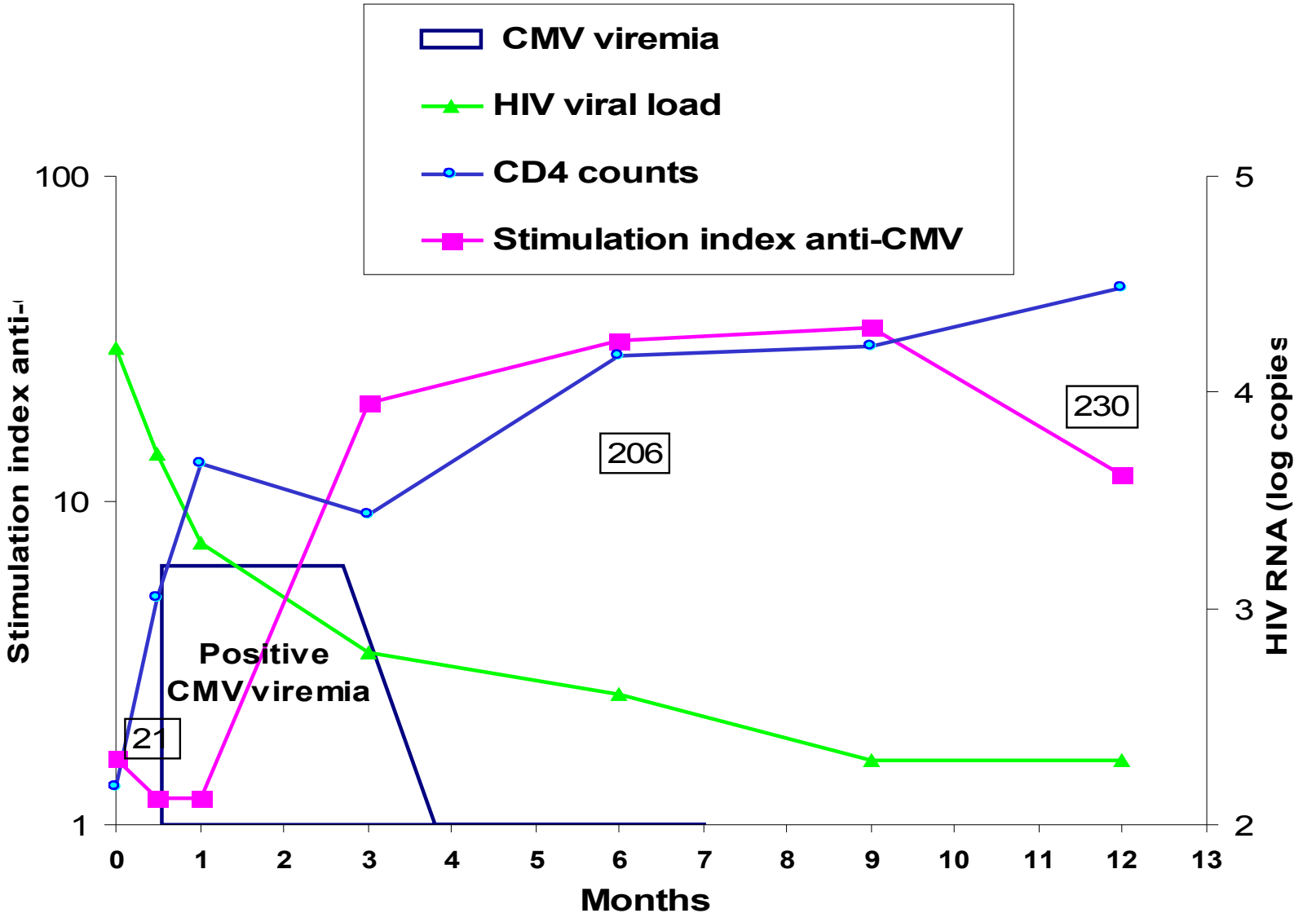
- **Similar Immune restoration with PI sparing and PI containing regimens (INITIO)** *(Samri et al. Antiviral Ther. 2007)*
- **Do new drugs generate a distinct profile of immune restoration ???**
  - **entry inhibitors ?**
  - **integrase inhibitors ?**

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..)*

Recovery of Memory CD4+ T cell reactivity to CMV allows control of CMV viremia with HAART

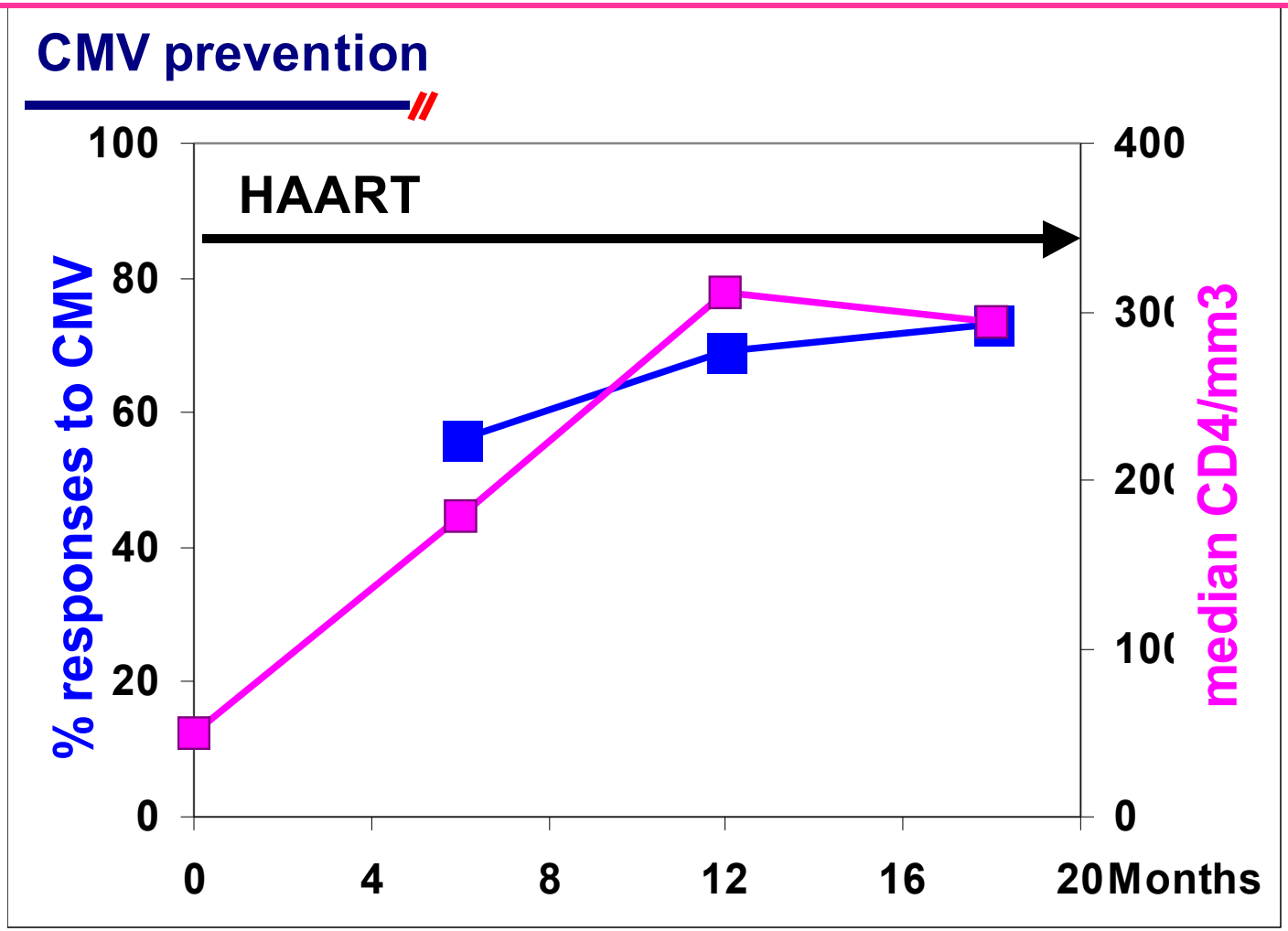


Li et al. AIDS Res. Retrov., 99

Restoration of a CMV-specific T cell reactivity with HAART allows to withdraw prophylaxis against CMV retinitis in advanced disease

47 patients:

With prior CMV retinitis,



2 relapses after arrest of anti-CMV therapy,

Jouan et al, AIDS, 2001

Restoration of T cell-mediated immune protection against CMV disease

- **Benefits from HAART:**

=> Restoration of CD8 T cell-mediated Immune protection against CMV retinitis:

=> Comparison of the CMV-specific CD8 T cell magnitude, repertoire breadth and differentiation in:

HN: **Healthy HIV-** (n=11)

LTNP : **HIV+HCMV+** Long Term Non Progressors (n=10), med CD4: 733/mm3

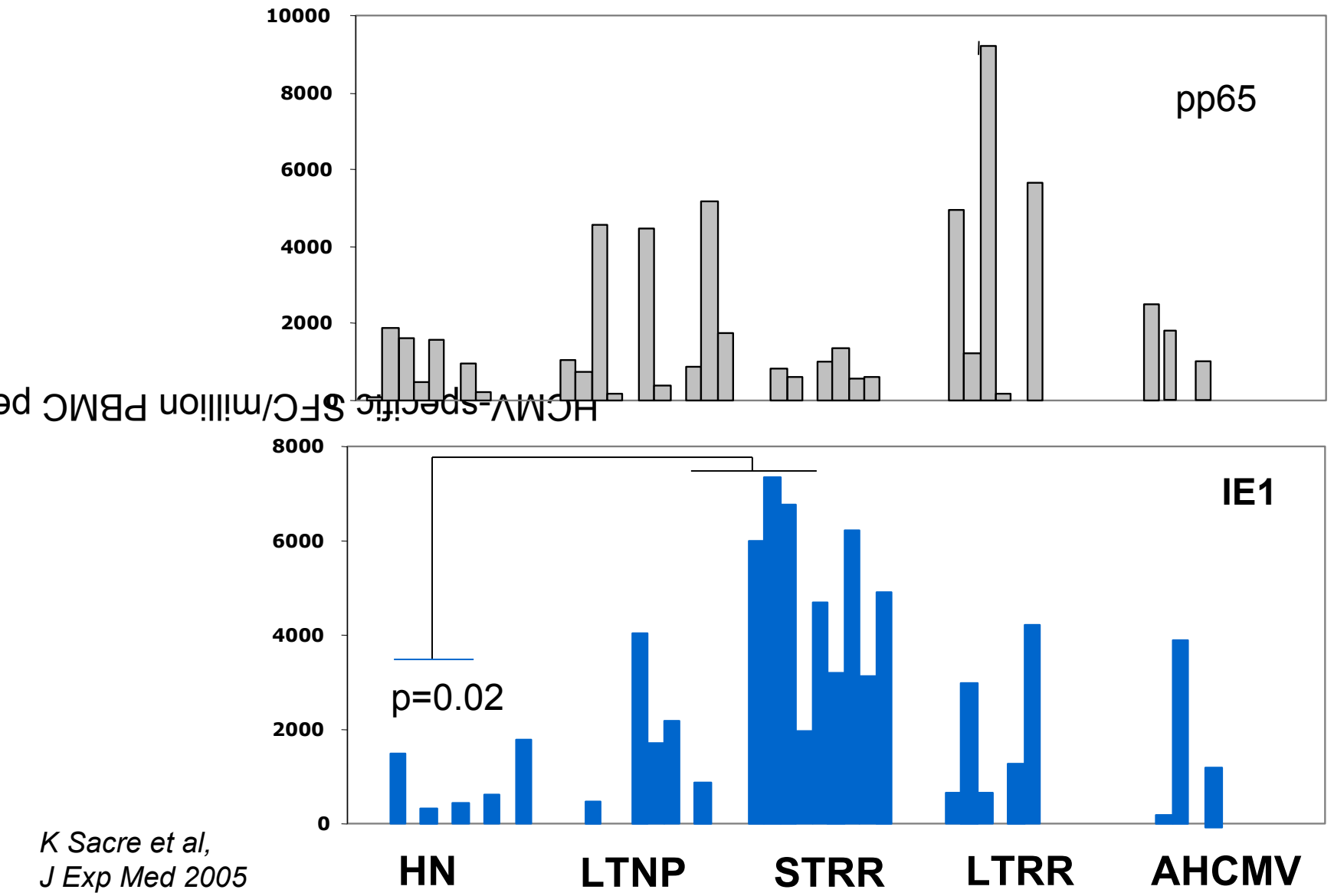
HIV+ **Recovering from CMV retinitis** on ART, after stopping GCV :

- **Short Term** Recovery (18 months, n=8) **:** CD4:357/mm3
- **Long Term** Recovery (>50 months, n=6) :, med CD4: 345/mm3

Acute CMV retinitis : (n=8) : med CD4:50/mm3

K Sacre et al. J Exp Med 2005

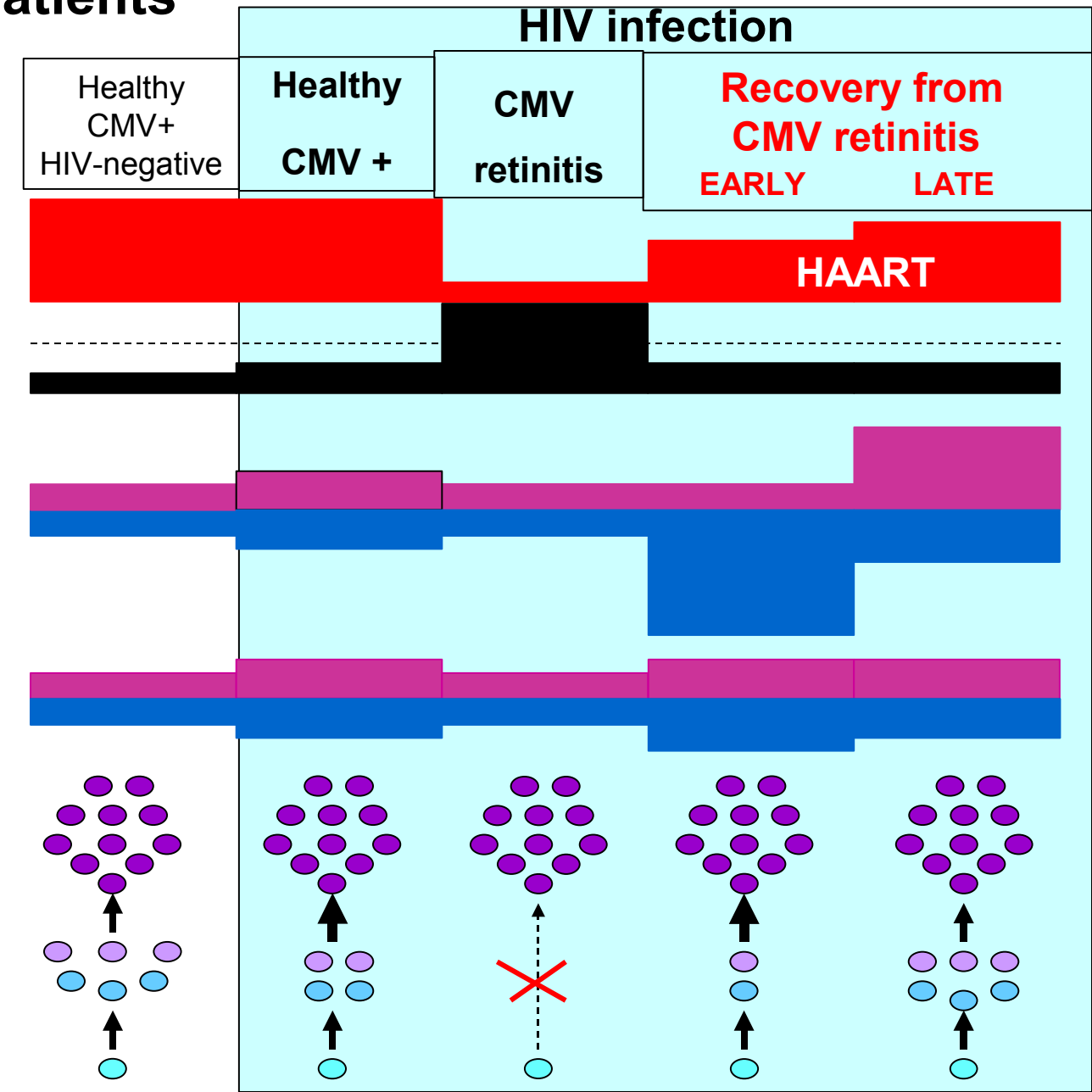
Short Term Recovery of strong **responses** against the CMV early IE1 antigens after CMV retinitis



K Sacre et al,
J Exp Med 2005

Restoration of Immune Protection against CMV retinitis in HAART treated patients

Sacre et al. , JEM 2005



Sequential Restoration of Immune protection against opportunistic pathogens

- **CMV retinitis:**
  - Loss of CD4 responses to HIV => Limited repertoire & diversity of short-lived anti-CMV CD8 T cells => Loss of CMV control
  - Gancyclovir: control of CMV replication

    BUT no restoration of immunity to CMV
- **HAART:**
  - **Controls HIV =>Restores CD4 counts**
    - **Restores protective Immunity against CMV:**
      - **CD4 responses to CMV**
      - **CD8 cells to CMV –IE1 antigens**
        - » Large breadth and diversity
        - » long-lived memory CD8 T cells

=> Restores Long Term control of CMV without gancyclovir

Rapid restoration of protective memory responses against opportunistic pathogens with HAART

- Reduction in morbidity / mortality *(Hogg, 97, Pallella,98…*
  - ⇨ Discontinuation of prophylaxis against Opportunistic Infections: PCC. Pneumoniae, CMV retinitis *(Furrer,99, Jouan 2001…)*
  - ⇨ at all stages of the disease : illustrating the lack of definitive immune alterations

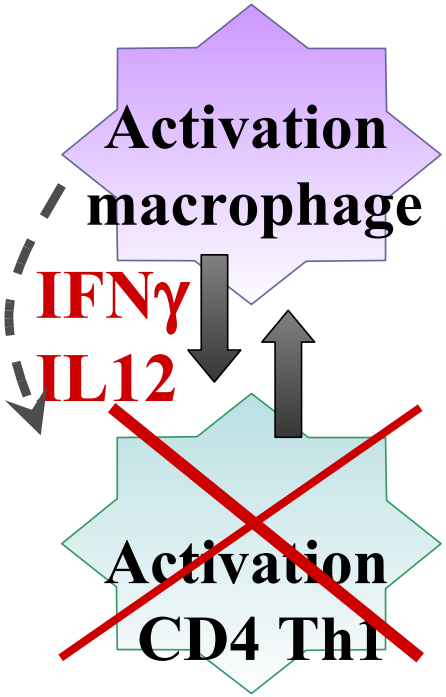
⇨ **BUT Induces the Immune Restoration Syndrome (IRS,.)**

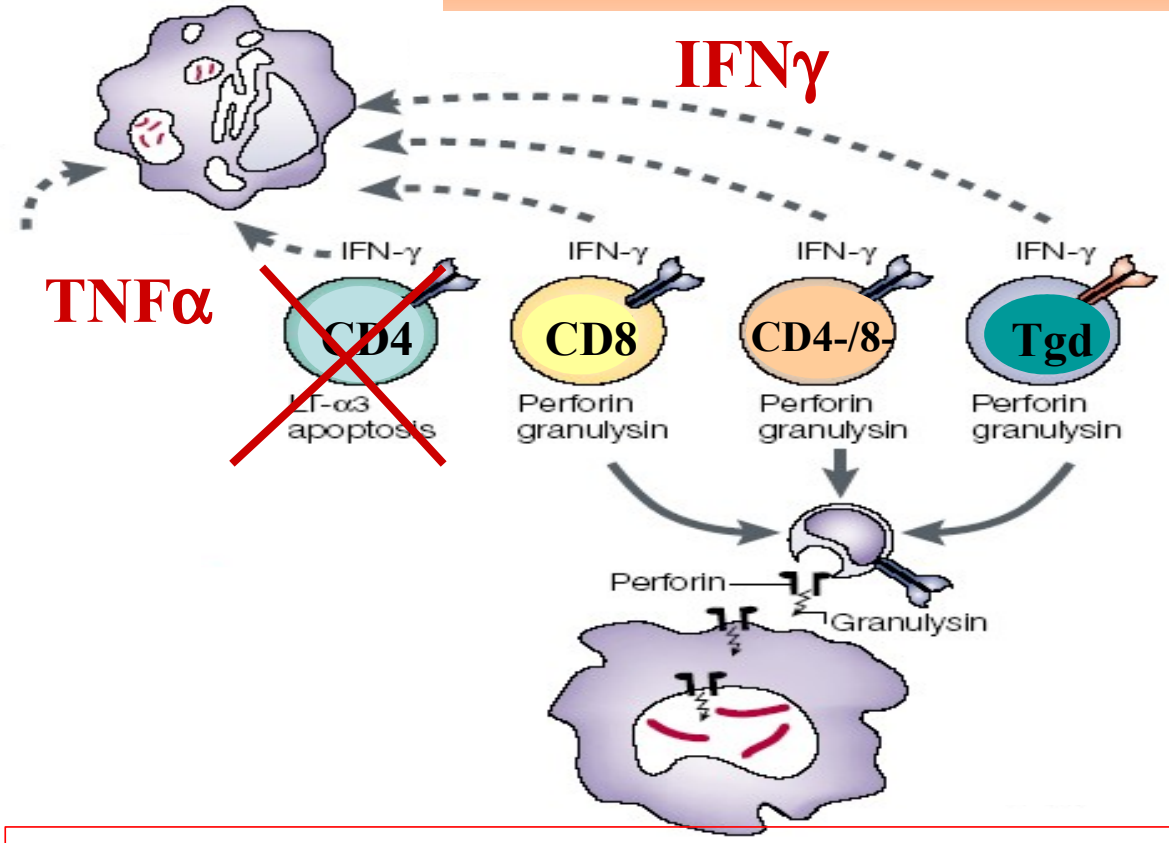
M French , 98, 2006, Monsuez 99, Breton 2005……..

- during opportunistic infections concommitantly treated with HAART
- reactivation of pathogen-associated symptoms +/- systemic inflamatory syndrome without microbiological relapse, or of auto-immune diseases
- particularly frequent during mycobacterial infections (MAI, TB : 40%)

TB and VIH

- Diminution Nb activated macrophages
- Diminution of intra-cellular BK lysis





Disparition of Ag-specific responses, = Anergy to TB antigens

Consequences of CD4 defects in HIV infection:

Poor Granuloma, without caseum, poorly functionals

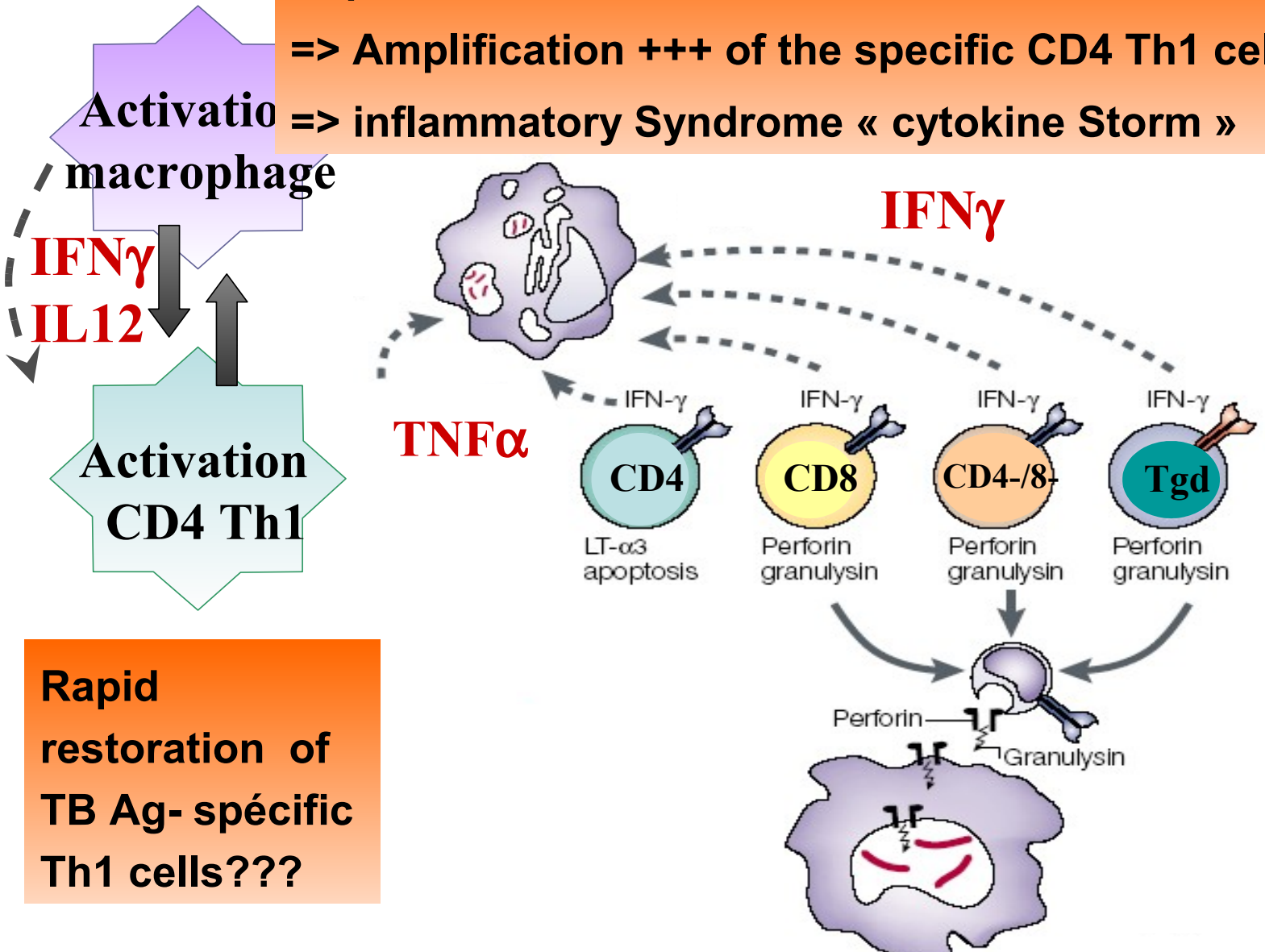
Disseminated pauci-symptomatic Tuberculosis

IRS: Hypothesis

Rapid Restoration of CD4 counts and function with HAART

=> Amplification +++ of the specific CD4 Th1 cells to Mtb

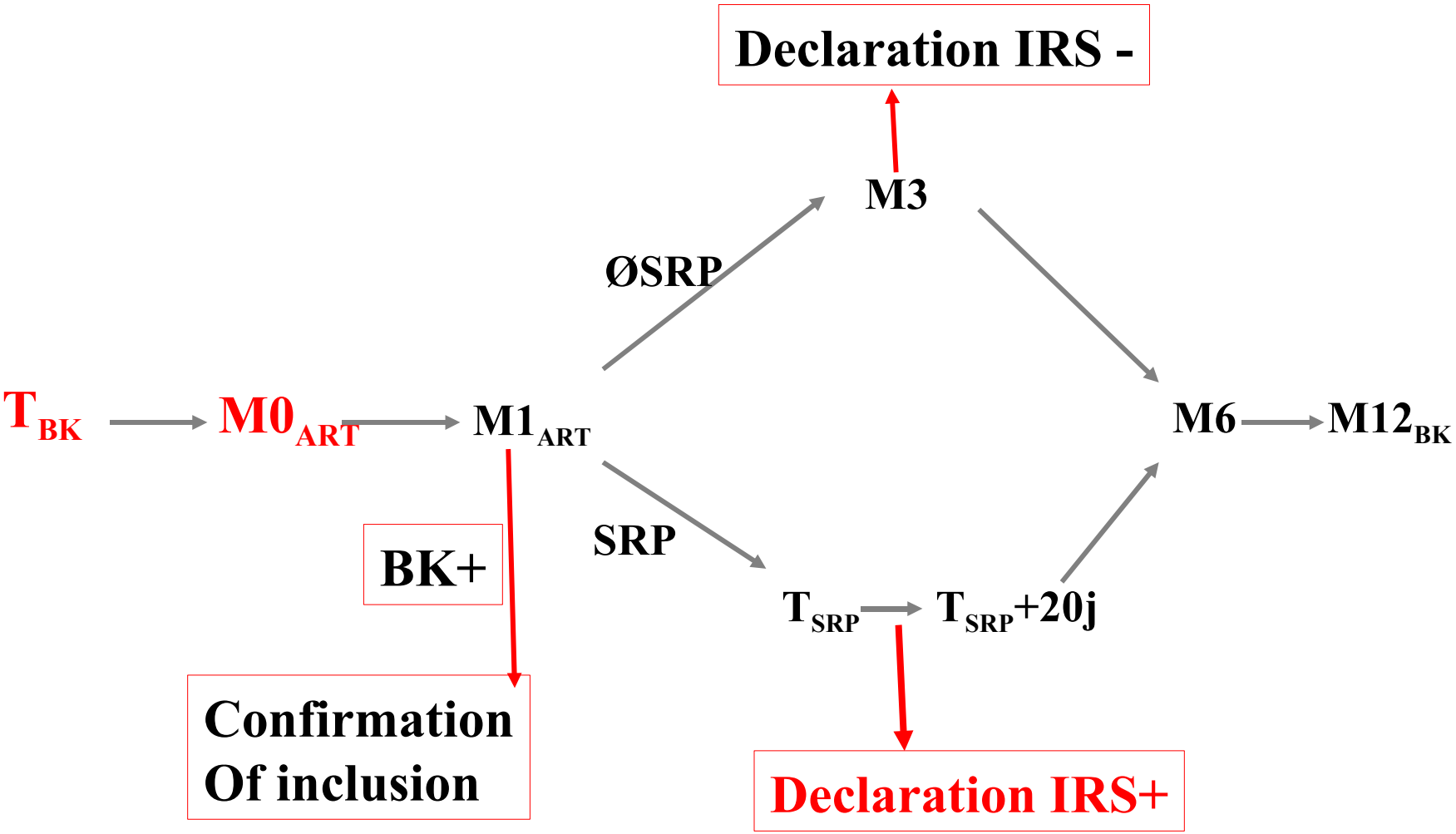
=> inflammatory Syndrome « cytokine Storm »



Rapid restoration of TB Ag- spécific Th1 cells???

A. Bourgarit 05

ANRS EP-21: PARADOX-TB: A prospective analysis of the Immunological characteristics of the TB-associated IRS



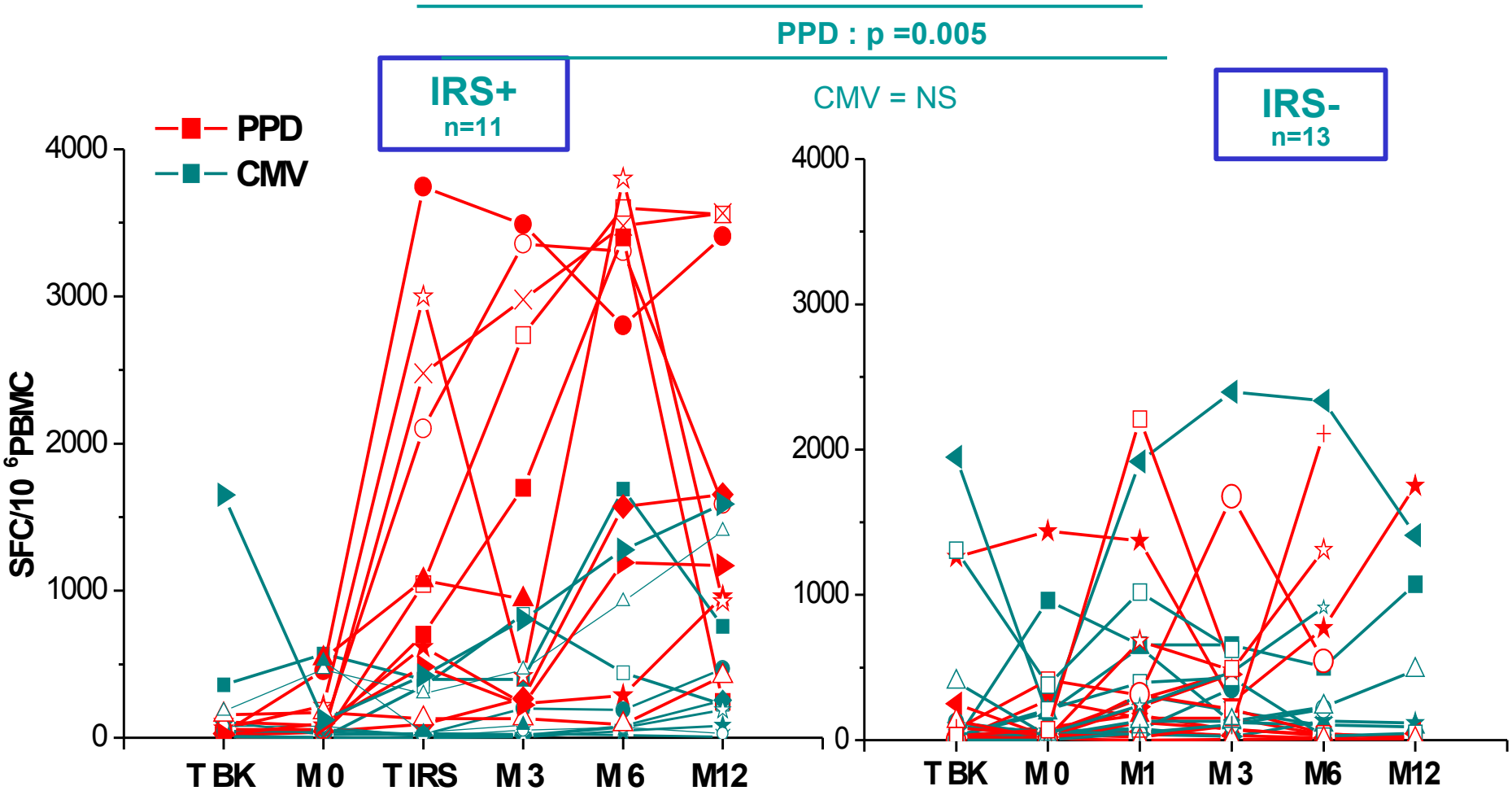
Bourgarit et al. AIDS, 2006

ANRS EP-21: PARADOX-TB : Patients Characteristics

		IRS+	IRS-	p
n		11	13	
M/F		6/5	9/2	NS
Age		38 (30-56)	36 (26-63)	NS
Pulmonary TB		2/11	4/13	NS
Disseminated TB	9/11	9/13	NS	
BAAR+		3/8	4/13	*NS*
HIV Infection	CD4 (/mm3)	26 (6-145)	54 (15-267)	*NS*
	CV (Log)	6 (4.8-6.5)	5.2 (4.3-8)	*NS*
M0HAART	Délai /TBK (j)	36 (7-77)	50 (14-111)	*NS*
IRS	Délai / M0 (j)	23 (7-85)		
	CD4	108 (59-430)	163 (9-580)(M1)	*NS*
	ΔCD4 /M0 (/mm3)	+54 (-1;+393)	+77 (-50;+250)	*NS*
M3	CD4	117 (58-399)	132 (49-410)	*NS*
	ΔCD4 /M0 (/mm3)	+86 (-74;+367)	+73 (-88;+354)	*NS*
	CV <200 7/10	8/11	*NS*	

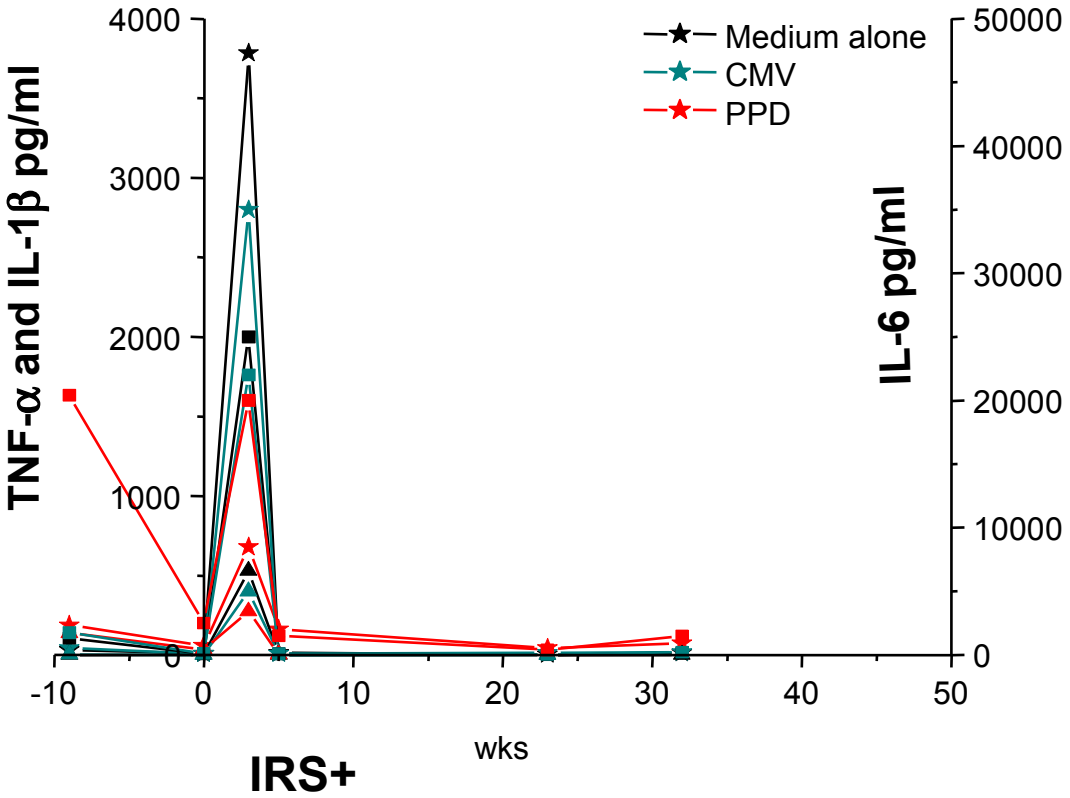
Bourgarit et al. AIDS, 2006

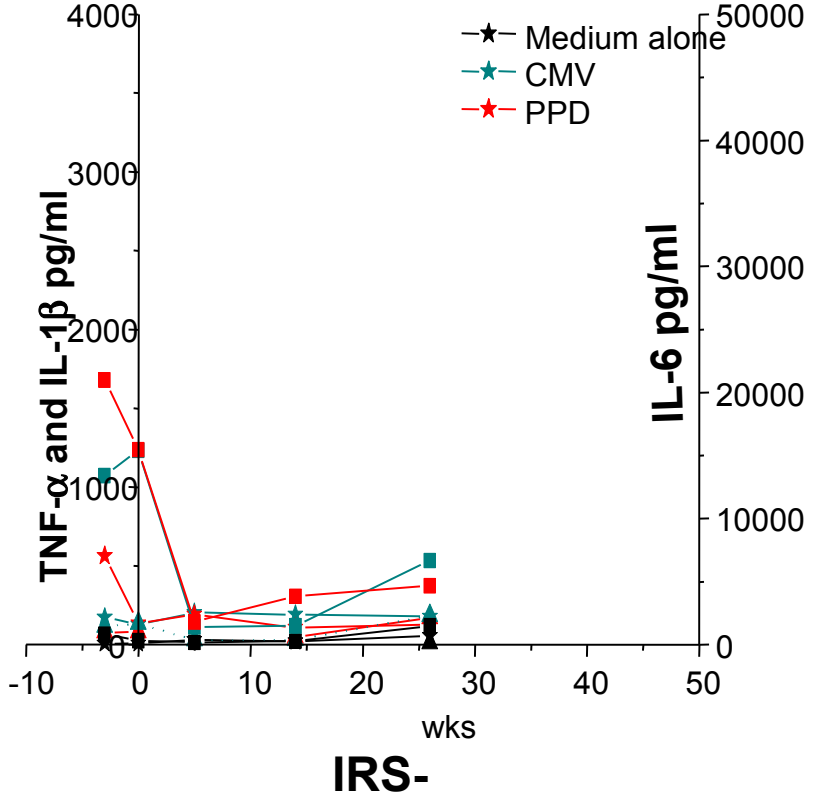
TB-IRS: Acute Exacerbation of a Th1 response to tuberculin but not to live TB (ELISpot IFN-γ) (Bourgarit, AIDS 2006)



- N IFN-g producing T cells to PPD significantly stronger in IRS +
- No or weak response to to live TB-associated antigens: ESAT-6, CFP-10, 85B
- Mediated by CD4 T cells: up to 35% of circulating CD4 T cells

ANRS EP-21: PARADOX-TB :
Non PPD-specific pro-inflammatory cytokine storm during IRS





Multiplex Detection of cytokines –Chemokines in culture supernatants (Chimioluminescence)

=> Intense inflammatory response both Ag-specific (PPD) and non specific: cytokines **:TNF-a, IL-6, IL-10**
chemokines: **RANTES, MCP1..**

Bourgarit et al. AIDS, 2006

Paradox-TB: A prospective study of the Immune Restoration Syndrome associated with TB in HIV infection

- **A frequent syndrome :**
  - in 40% (9/22) TB-HIV co-infected patients with severe CD4 defects and rapid CD4 restoration within 3 months after treatment initiation
- **A brutal explosion of tuberculin-specific T cells**
  - Poorly or undetectable at baseline,
  - Rapidly restored and exacerbated, within a month
  - **Mediated by activated CD4 Th1 cells + γδ T cells**
  - with specific release of Th1 cytokines and pro-Th1 chemokines

    but without deregulated Th2 response
  - Directed against Antigens present in tuberculin
  - **Associated to an acute non-specific inflammatory response**

Bourgarit et al. AIDS, 2006

Immune Restoration Syndrome associated with TB in HIV infection

- **Paradox-TB : Pending Questions > BK-VIR-IS**
  - Clonality of the response?
  - Antigens involved? And role of γ-δ T cells?
  - Role of regulatory T cells ?
  - Individual susceptibility?
    - Why only 40% IRs if this corresponds to a physiological restoration of tuberculin specific T cells?
      - Strains ?
      - Host Genetic Predisposition?
        - » HLA
        - » Other Genes: Th1 pathways…,

Bourgarit et al. AIDS, 2006

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Baakili A, Béglé A-M, Besse F, Bollens D, Bouchaud O, Bursachi P, Cadranel J, Camuset J, Chakvetadze C, Delgado J, Diemer M , Dupont B, Elmarsafy S, Fain O, Fonquernie L, Furco A, Girard P-M, Grillot-Courvalin C, Guignet A, Guilleminot MC, Herrmann J-L, Jeantils V, Grivois JF, Joly V, Jouis V, Klutse P, Lacombe K, Lahoulou R, Lavolé A, Lefebvre B, Lefort A, Letellier E, Lortholary O, Metro A TrumeauM, Meynard J-L, Meyohas M-C, Molina J-M, Obenga G , Parrinello M, Pelet O, Pintado C, Ponscarme D, Rami A, Rozenbaum W, Sahli H, Sellier P, Slama L, Courtial S, Tubiana R, Stirnemann J, Tassi S , Taulera O, Touitou H , Vacher I,., Vincent F, Yeni P