The Potential For Harnessing the Immune System to Control HIV

Gordon Dickinson, MD

Chief, Infectious Diseases, U Miami School of Medicine, and Co-Director, Special Immunology, Miami VA Medical Center

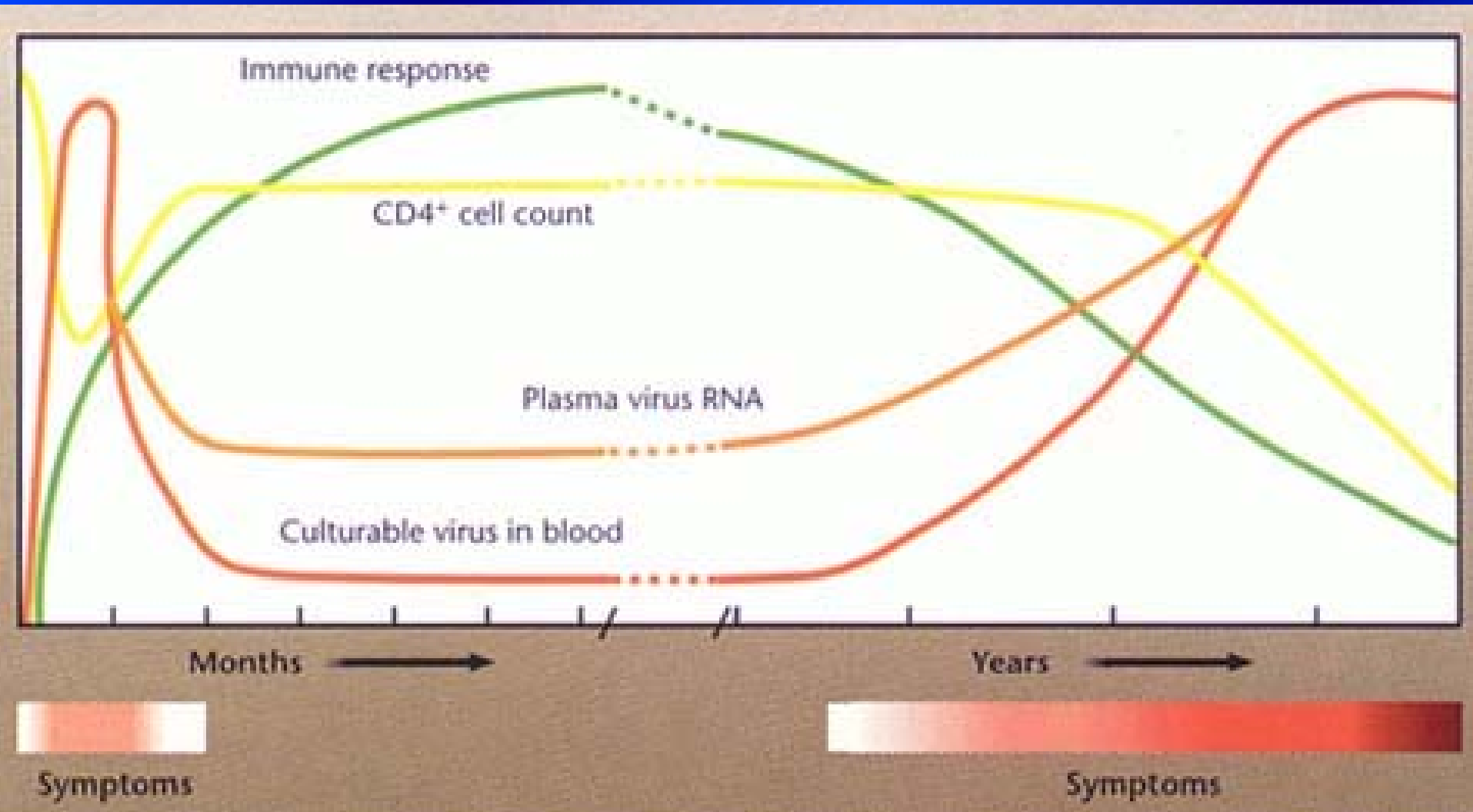
The Challenge of Antiretroviral Therapy -2006

- Adherence, or lack thereof
- Resistance
- Cost
- Drug interaction
- Toxicity
- Failure to restore immune function – treatment failure

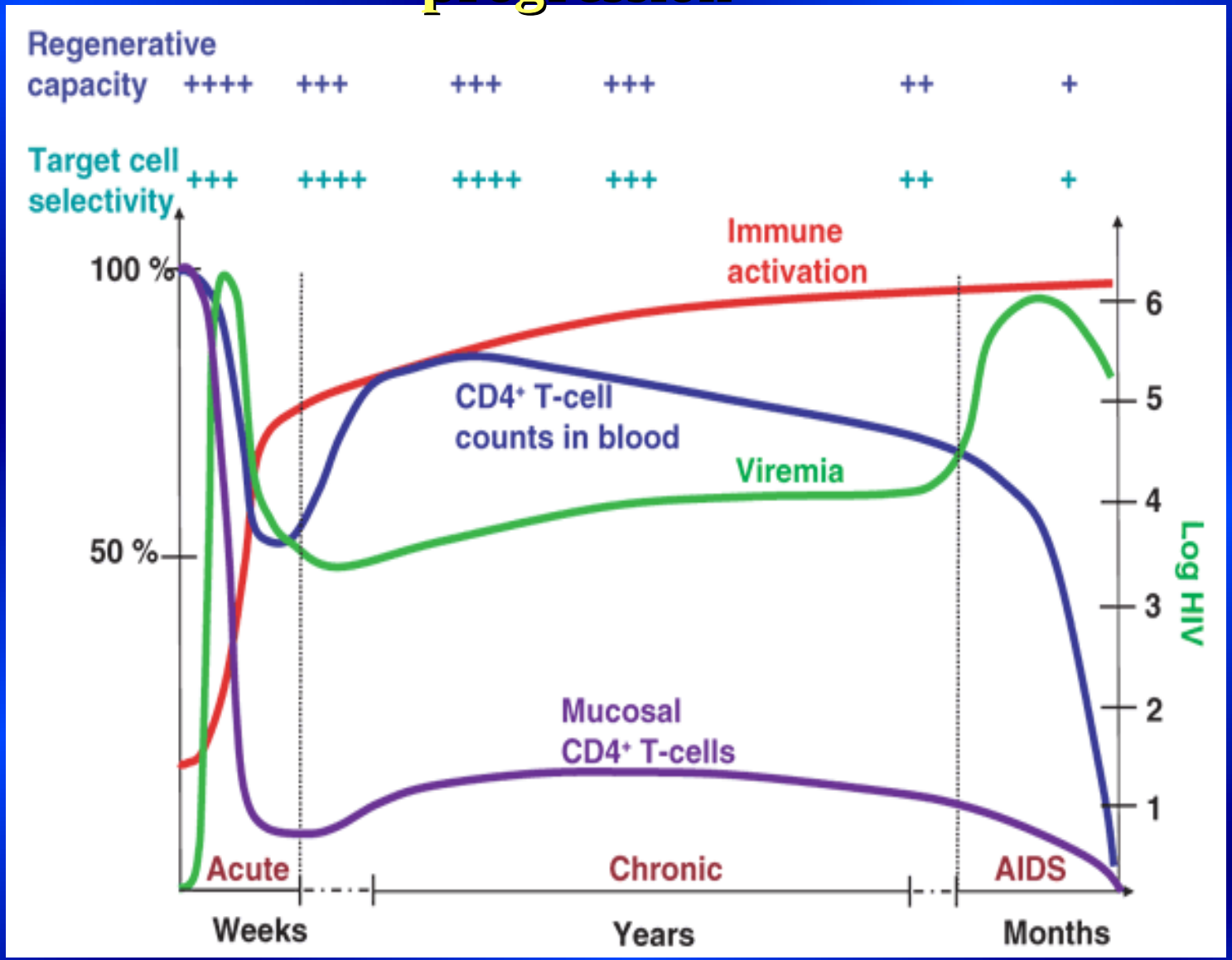
Objectives

- Review new paradigm of the pathogenesis of HIV disease.
- Review selected attempts to intervene with “immuno-modulators”.
- Vaccine development – is it all doom and gloom?

Traditional View of HIV Infection



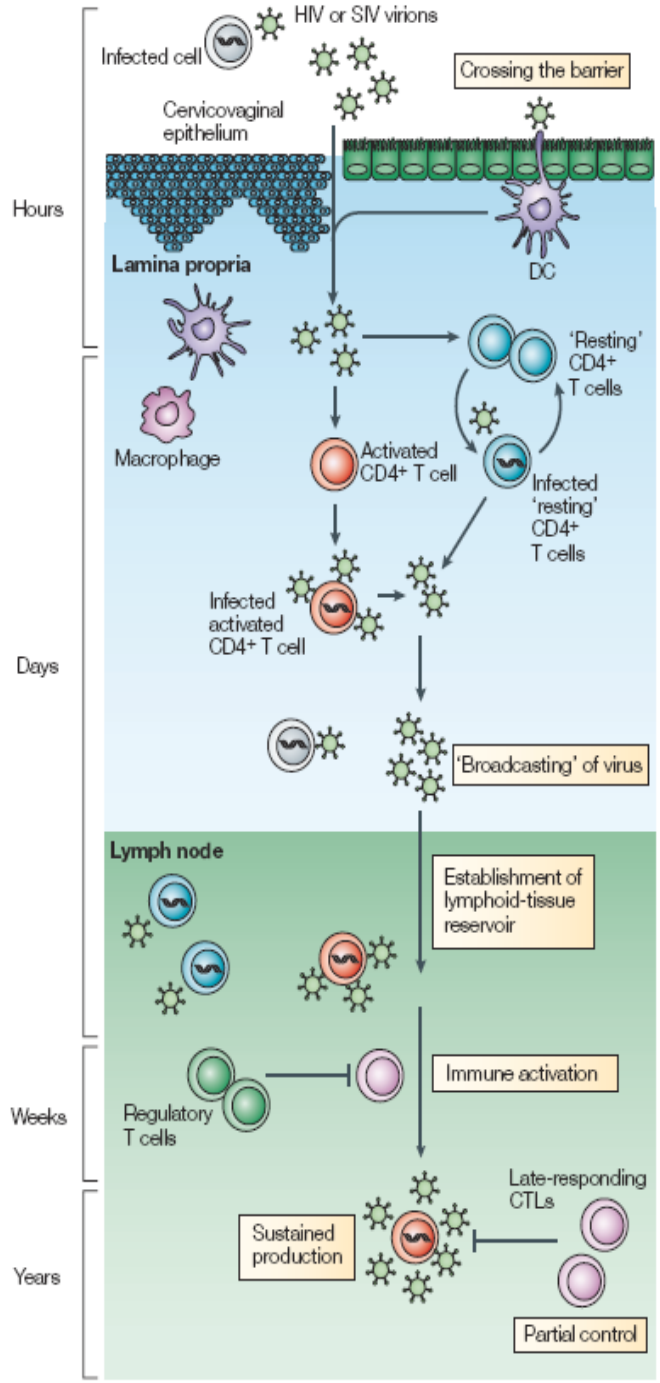
Quantitative and qualitative measures of HIV disease progression



Grossman et al: Nature Medicine **12**, 289 - 295 (2006)

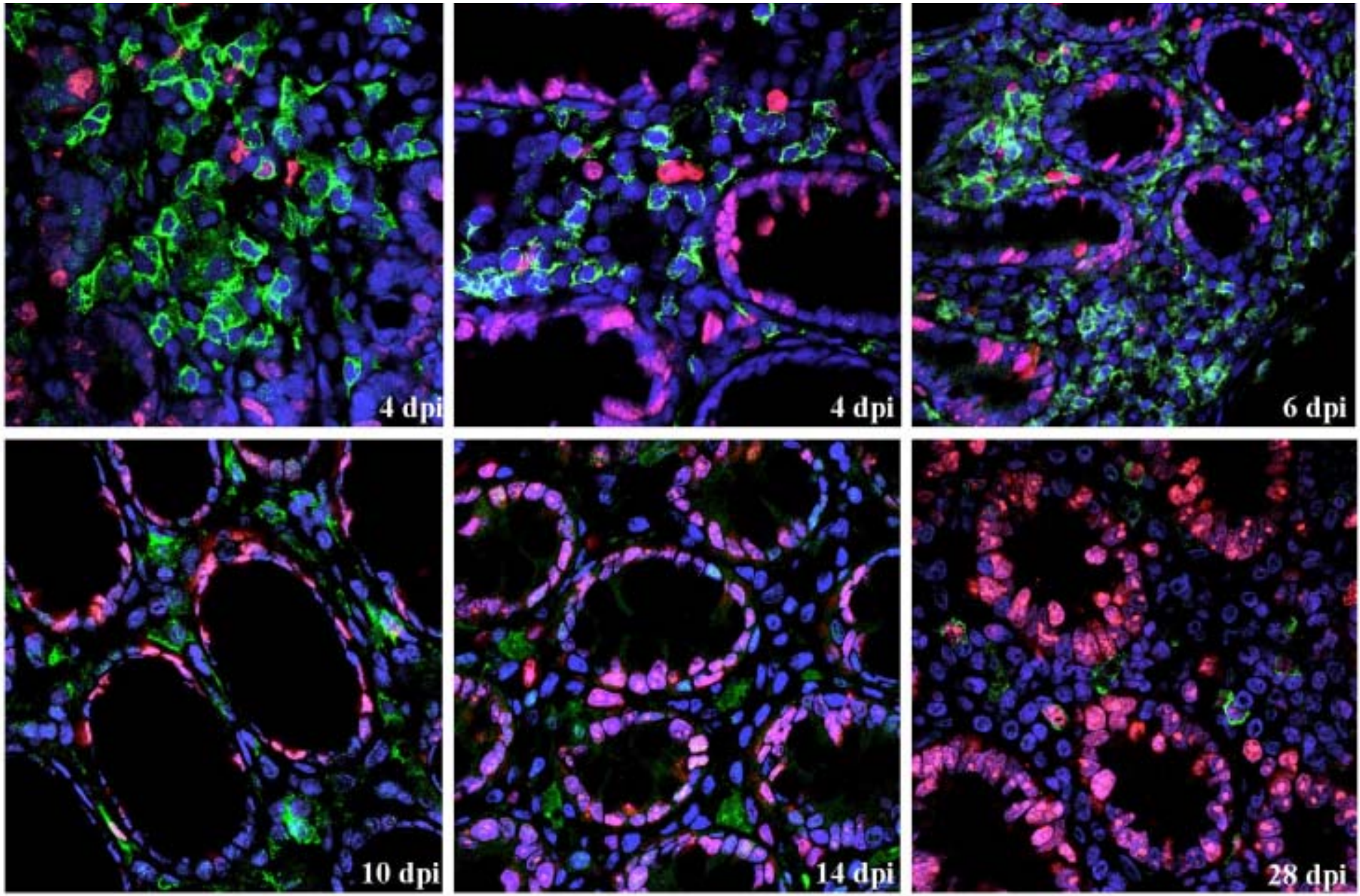
Initial events in Acute HIV Infection

- Infection established at point of entry predominantly in CCR5+ CD4 memory T cells
- Spreads to regional lymph nodes via DC and to the mucosal associated lymphoid tissue (MALT)
- Gastrointestinal tract is the most prominent early site of virus replication (1-3 weeks post infection)
- Widespread depletion of memory CD4 T cells that is only partially restored with later HAART



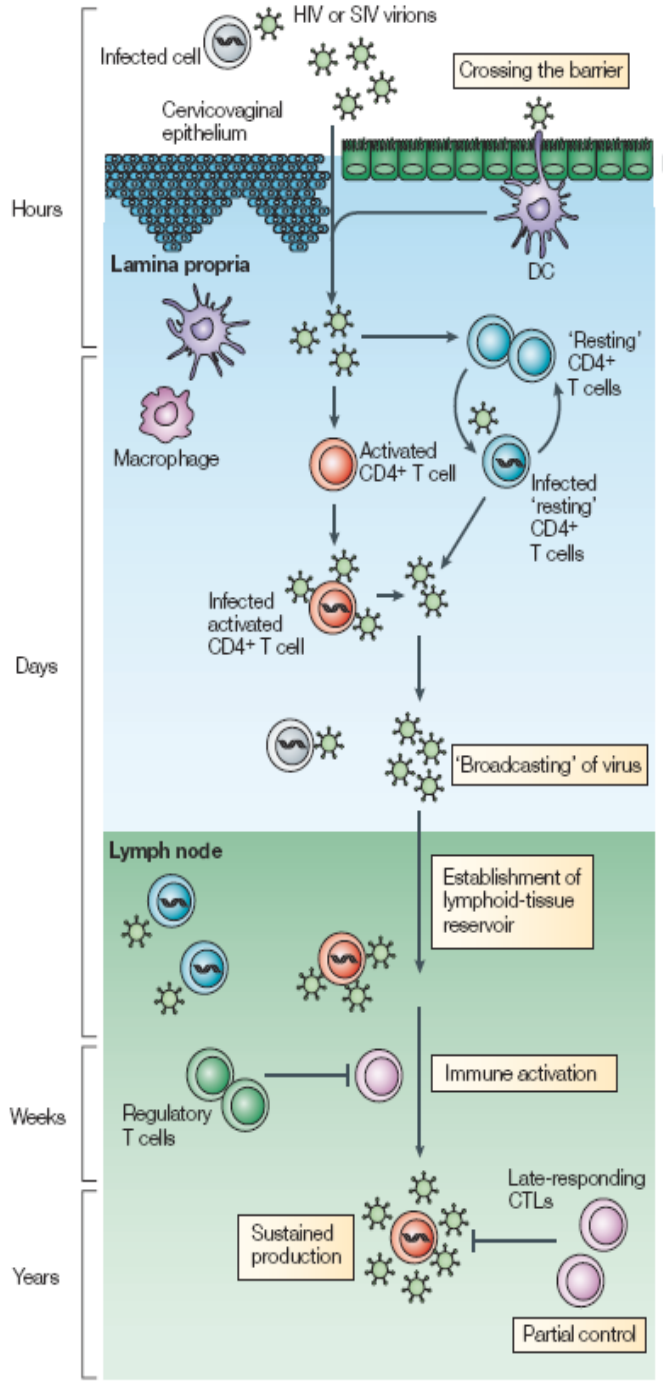
Peak Replication and Massive CD4 + T Cell Depletion in Gut Lamina Propria

(slide from A Haase)



Inability of the host to clear the infection: Why??

- Massive replication of virus in GALT and depletion of memory CD4+ T cells
- Antigen specific CD8 T cell immune response is “too little, too late”
- Premature induction of immunosuppressive regulatory T cells
- Establishment of a latent reservoir of HIV in resting memory CD4 T cells (integrated virus not visible to the immune system)- minimally affected by HAART



Summary: Initial events in Acute HIV Infection

- Infection established at point of entry predominantly in CCR5+ CD4 memory T cells
- Spreads to regional lymph nodes via DC and to the mucosal associated lymphoid tissue (MALT)
- Gastrointestinal tract is the most prominent early site of virus replication (1-3 weeks post infection)
- Widespread depletion of memory CD4 T cells that is only partially restored with later HAART
- Establishment of a latent reservoir of HIV in resting memory CD4 T cells (integrated virus not visible to the immune system)- minimally affected by HAART

Different course of SIV in two primate models

Sooty mangabey
(*Cercocebus atys*)

Location: Subsaharan western Africa Sierra Leone to Ghana

Slow or non-progression

Rhesus macaque
Macaca Mulatta

Location: Northern India and southern China

Rapid Progression

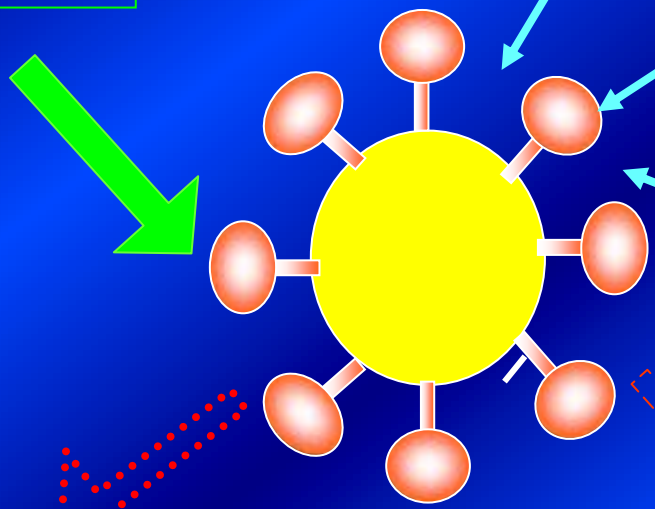
Approaches for More Effective Virologic Control and Immune Reconstitution in Chronic HIV Disease

Host: Immune Strategies to Attack HIV

New Antiretroviral Therapies (entry inhibitors)

Immune Based Therapies, Cytokines (IL-2); IL-15, IL-7, IL-21

Therapeutic Vaccines to boost HIV immunity



Blunt Host Immunity

Virus: Strategies for life-long persistence

The Immune System vs. HIV

- Monoclonal antibodies
- Cytokines
- Extracorporeal expansion
- Vaccination – Passive
- Vaccination – Therapeutic
- Vaccination - Preventive

Approaches to Immunotherapy of HIV infection

- **Down regulation – to stop the CD4 activation that propagates supports HIV replication.**
  - **TNX 355 - CD4 receptor blockade in HIV**
- **Up regulation**
  - **Use of cytokines to shift cytokine balance**
  - **Use of cytokines to assist immune reconstitution**
  - **Use of cytokines to help control chronic infections**

GM-CSF

- Placebo control trail suggests viral load reduction and CD4 increases in treated group.
- Promotes cytokine production from neutrophils.
- Decreases immune activation, and inflammation.
- Induces IL-2 production.

Role of Gamma Chain Cytokines

In peripheral lymphocyte expansion
In influencing innate immunity
In augmenting immune responses
(IL-2, IL-7, IL-15, IL-21)

Interleukin 2

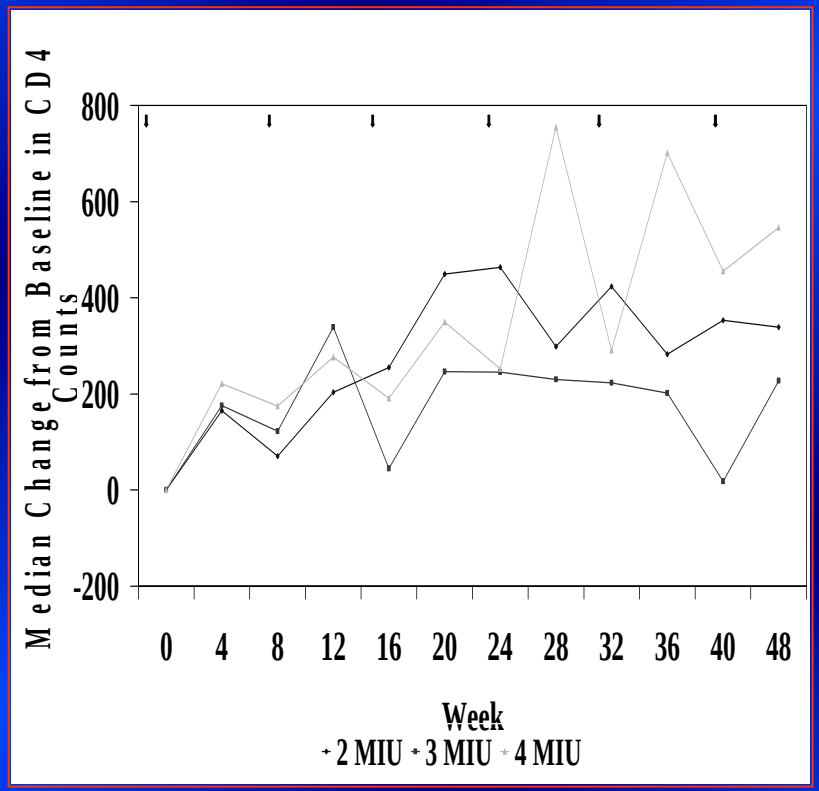
- Induces proliferation of CD4 and CD8+ cells.
- Increases activity of NK cells, Lymphokine activated killer cells (LAK).
- Causes expansion of existing CD4 clones.
- Indirectly induces IL-7,which in turn increased naïve cell production.

Interleukin 2

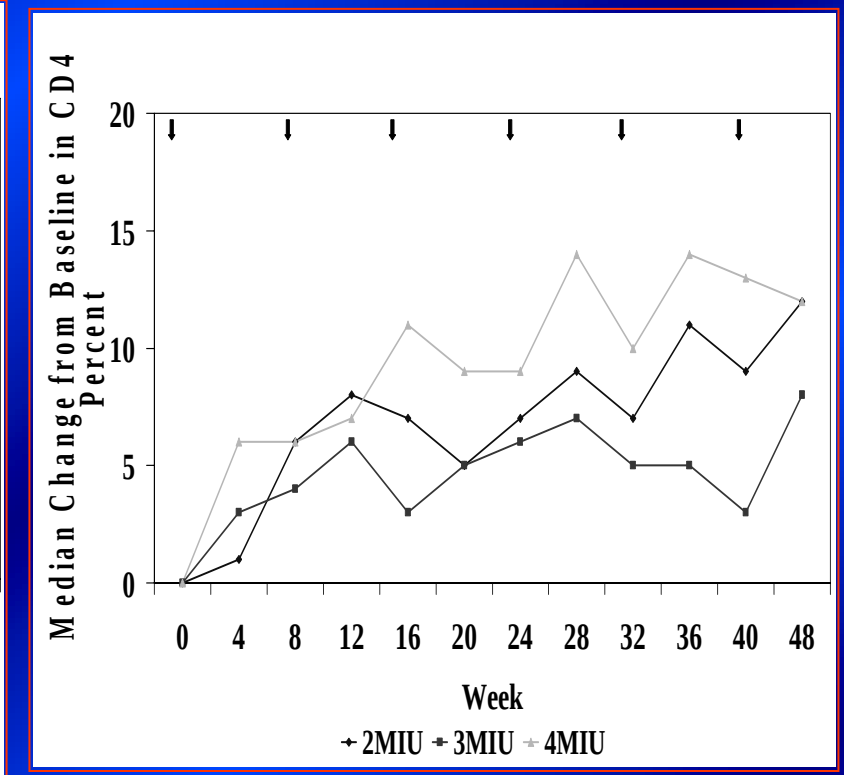
- Dramatic CD4 cell count increases without viral load increases in patients on antiretroviral therapy (CD4 counts <50–>350 cells/μL)
- Subcutaneous injections and continuous infusions used
- Dosages and frequency of administration vary
- Side effects include flulike symptoms, nausea, diarrhea, fever, and liver toxicity

PACTG 402: s/c IL-2 in children with low CD4
Median Change from Baseline for CD4

In absolute counts



in percentage



4miu

2miu

3miu

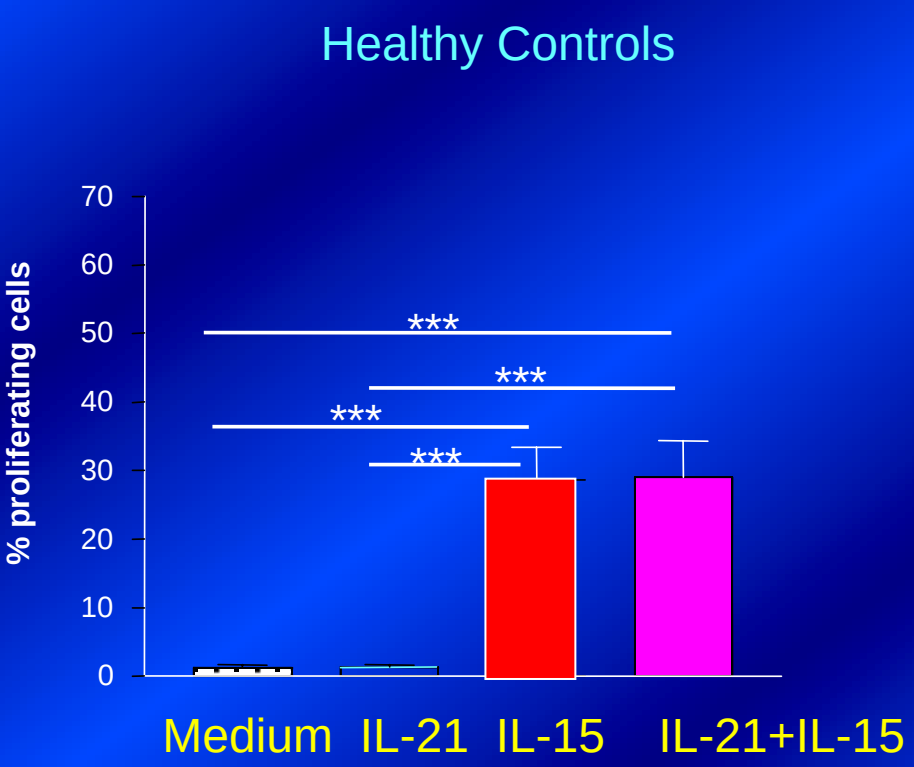
Problems with IL-2: Induction of T Regs

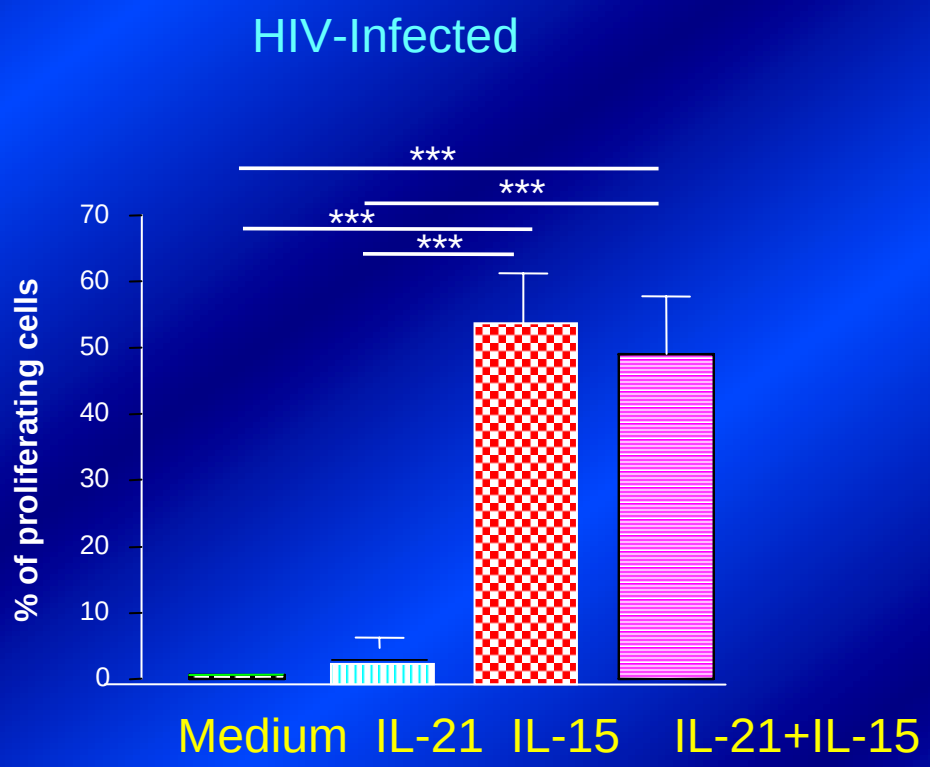
Pahwa et al, unpublished

Interleukin 12

- Greatly enhances cytotoxic T cells, NK cell function;
- Shifts cytokine pathways back to Th1
- Phase 1 trials underway - toxicity is a concern
- Toxicity may limit to ex vivo cell therapy setting

IL-15 induces CD8 T cell proliferation in healthy controls and HIV-infected individuals; IL-21 has no effect





IL-21 in HIV infection

- The predominant effect of IL-21 is to upregulate perforin in CD8 T cells and NK cells – not known why.
- Rapid onset, within 5 hours, and is long lasting (5 days).
- Unlike IL-15, IL-21 does not increase T cell activation or proliferation.
- The effect of IL-21 is more pronounced in HIV infected individuals than in observed in healthy controls.
- Cellular activation by IL-21 involves Stat 3 predominantly and Stat 5 in HIV+ patients.

Ex Vivo Cell Modification

- Cell expansion of polyclonal vs. oligoclonal vs. monclonal populations.
- Polyclonal - Studies by Klimas and Heberman using peripheral blood CTL's.
- Oligoclonal - Studies by Leiberman using CTl's stimulated with HIV peptides ex vivo.
- Monoclonal - Studies by Koenig using monoclonal CTL cell line, demonstrating in vivo resistance at 16 weeks.

Ex Vivo Cell Modification

- Lymph node vs. PBMC's
- Ohio State experience (Triozzi, Bressler, et al) using the principle that lymphnode cells have an advantage over PBMC's - antigen presentation, cytokines more antiviral, begin with lymph node cells. Ongoing trial in HIV positive viremic subjects.
- University of Miami - trial in HIV coinfected with Hepatitis B and/or C completed

Goals of Vaccination for HIV Infection

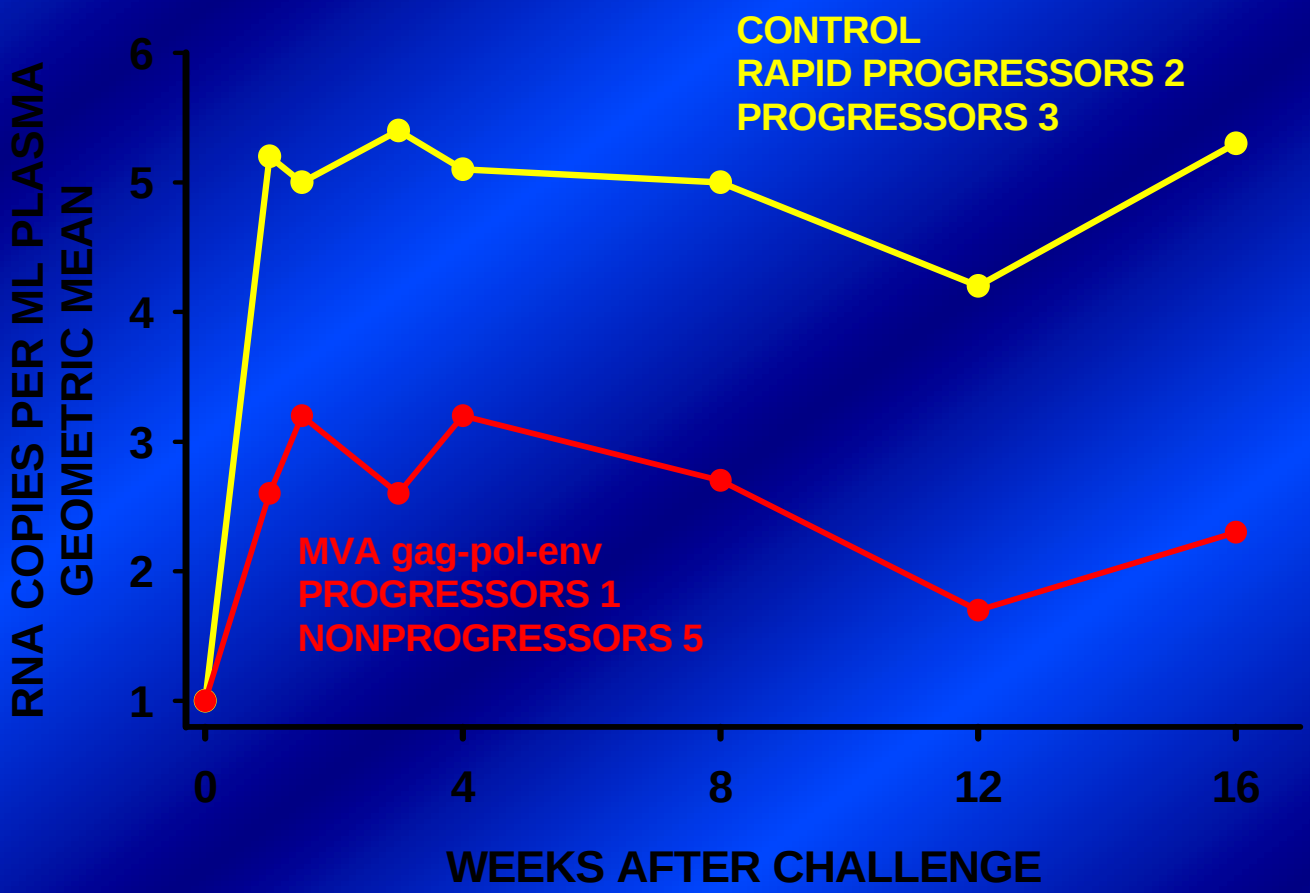
- Prevention
  - To prevent infection
  - To prevent disease
  - To prevent transmission
- Therapeutic
  - To prevent progressive disease….something natural infection [the ultimate vaccination] does not do.

Major Obstacles to Development of an HIV Vaccine - Biologic

- Extra-ordinary ability of the virus to elude host humoral and cellular immune responses.
  - Genetic diversity
  - Evasive properties of envelope proteins
- We do not know the correlates of immunity against this virus.
  - Discordance between measurable immune response and actual effect.

PROTECTION OF RHESUS MACAQUES AGAINST SIV SM E660 IV CHALLENGE BY RECOMBINANT VACCINIA (MVA) IMMUNIZATION

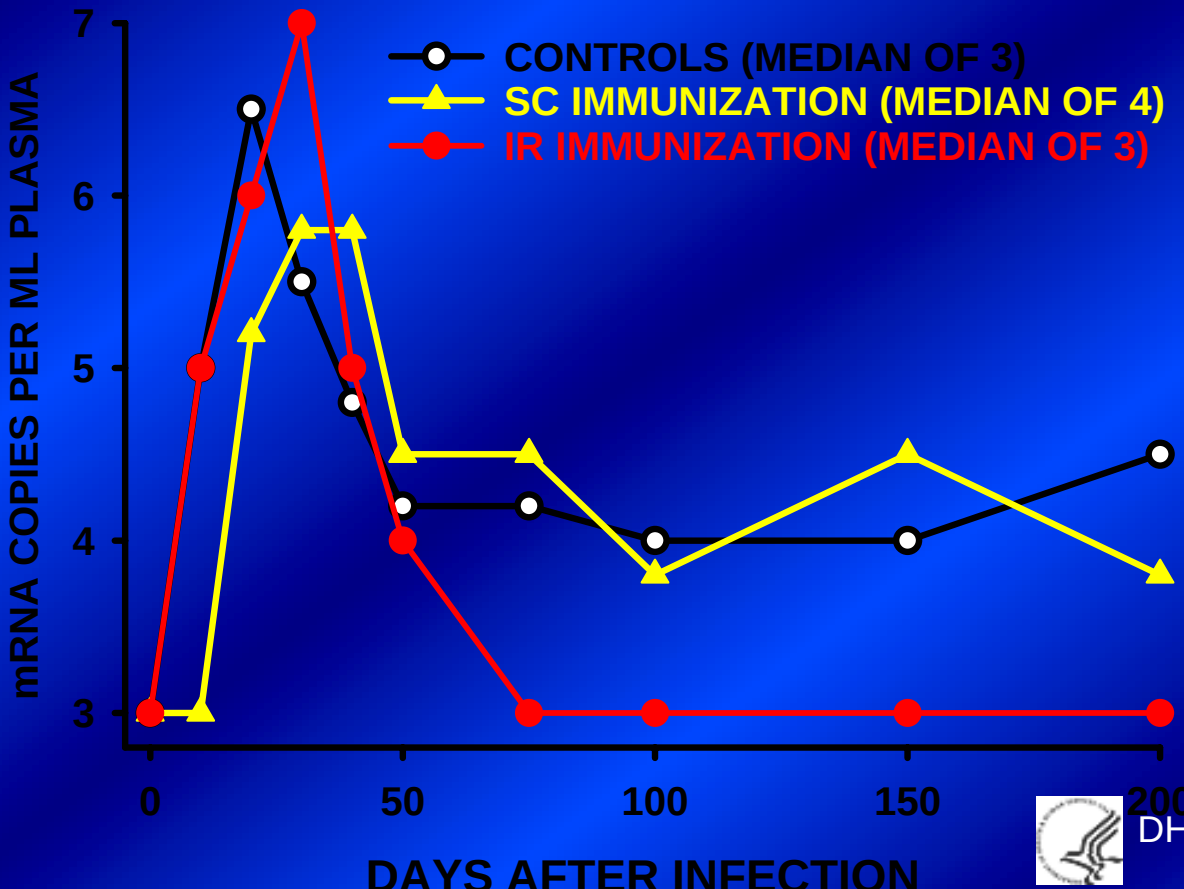
Ourmanov, J Virology, 2000, 74: 2740



DHHS/NIH/OD/OAR

MACAQUES IMMUNIZED SC OR IR WITH GAG/POL EPITOPE PEPTIDES PLUS ADJUVANT CHALLENGE: IR PATHOGENIC SHIV KU-2 10 WEEKS POST IMMUNIZATION

Belyakov et al, Nature Medicine 2001, 7: 1320



DHHS/NIH/OD/OAR

OFFICE OF AIDS RESEARCH

STATUS OF VACCINE CANDIDATES, MAR. 2006

PHASE I

Polyepitope CTL DNA (B) (Epimmune-NIH-HVTN)

MRK-Ad5 gag + ALVAC g/pr/e B (Merck-Aventis)

DNA + FPV multigene B (Australia-NIH)

VEEV-gag-C-2 Replicons (Alphavax-NIH-HVTN)

NYVAC-HIV C (EUROVACC)

AAV-gag C (CCRI-Targeted Genetics-IAVI- Europe, India)

DNA multigene C (ADARC-IAVI)

DNA gpe/beads B +/- oligo rgp140-V2 (Chiron-NIH-HVTN)

MVA and FP eg+rtn (Therion-HVTN-NIH)

Lipopetides* or ALVAC + Lipopeptides* (ANRS

PHASE I

Proteins rgp120 + tat/nef Fusion +Adj (GSK-NIH)

DNA gag*-A (MRC-IAVI-KAVI); MVA gag*-A (MRC-IAVI-KAVI); DNA + MVA-gag (MRC-IAVI-KAVI)

DNA gag or Adeno gag-B; DNA + Adeno gag B (Merck)

MVA nef (FIT BIOTECH)

DNA gag/pol-B (NIH-VRC)

Multi-env Vaccinia (St Jude)

MRK-Adeno 5 gag (Merck-HVTN-NIH)

DNA multigene B (Emory-GeoVax-CDC-NIH-HVTN)

DNA multigene/3 clade env (NIH-VRC) and
Ad5 multigene + 3 clade env (NIH-VRC)

DNA tat (ISS)

PHASE II

ALVAC g/pr/e* B + rgp120 (Aventis-NIH)

DNA gag* A + MVA gag* A (MRC-IAVI-KAVI-UVRI)

DNA gpn, ABCenv + Ad5gp, ABCenv (VRC-HVTN-NIH)

MercK-Ad5, g,p,n B Merck-HVTN-NIH

PHASE III

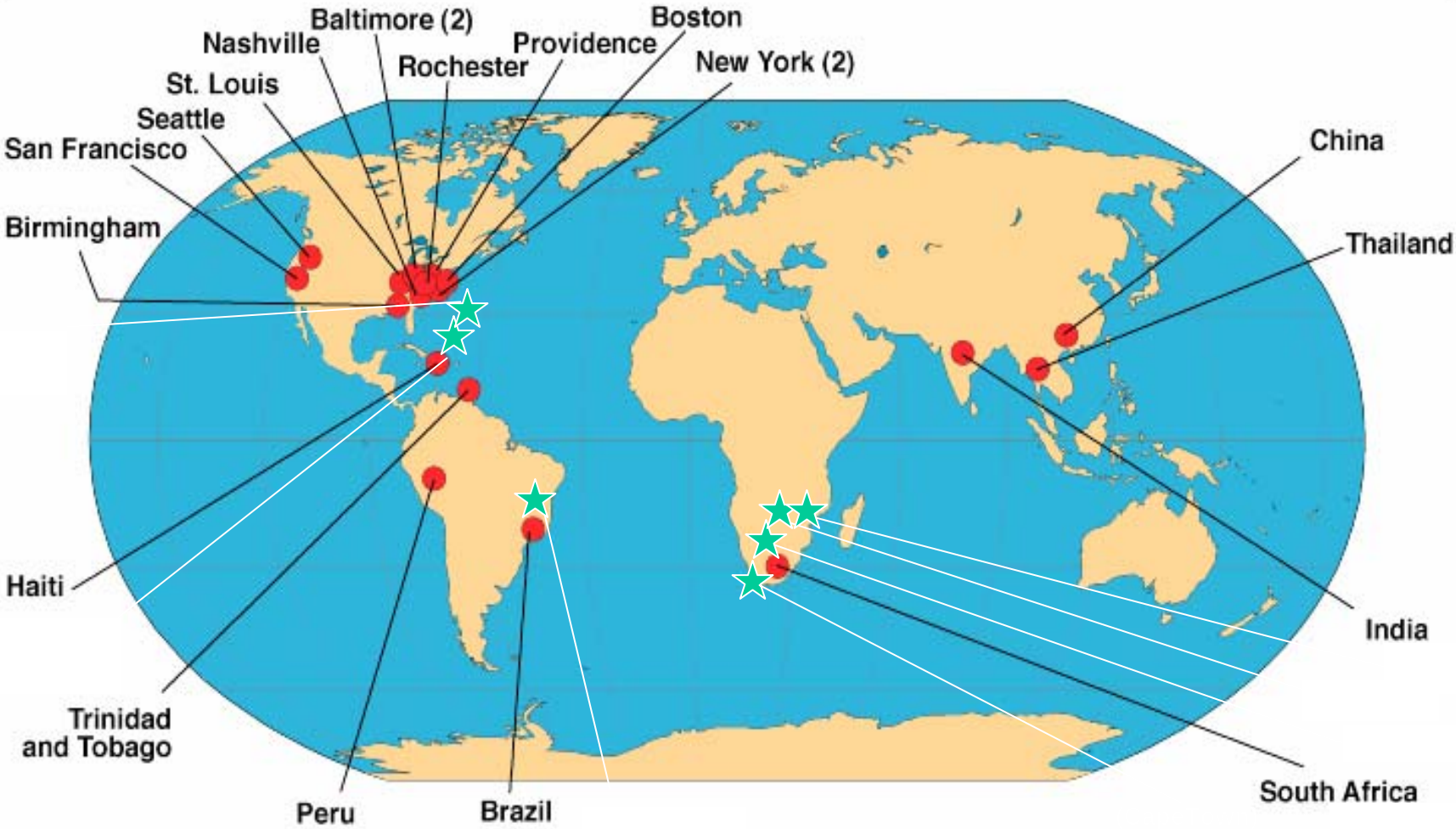
ALVAC g/pr/e* E + rgp120 (Thailand-DOD-NIH-Aventis-VaxGen)

CandidateAIDS Vaccines in Advanced (Phase II or III) Clinical Trials, Douek et al, Cell, Feb 2006

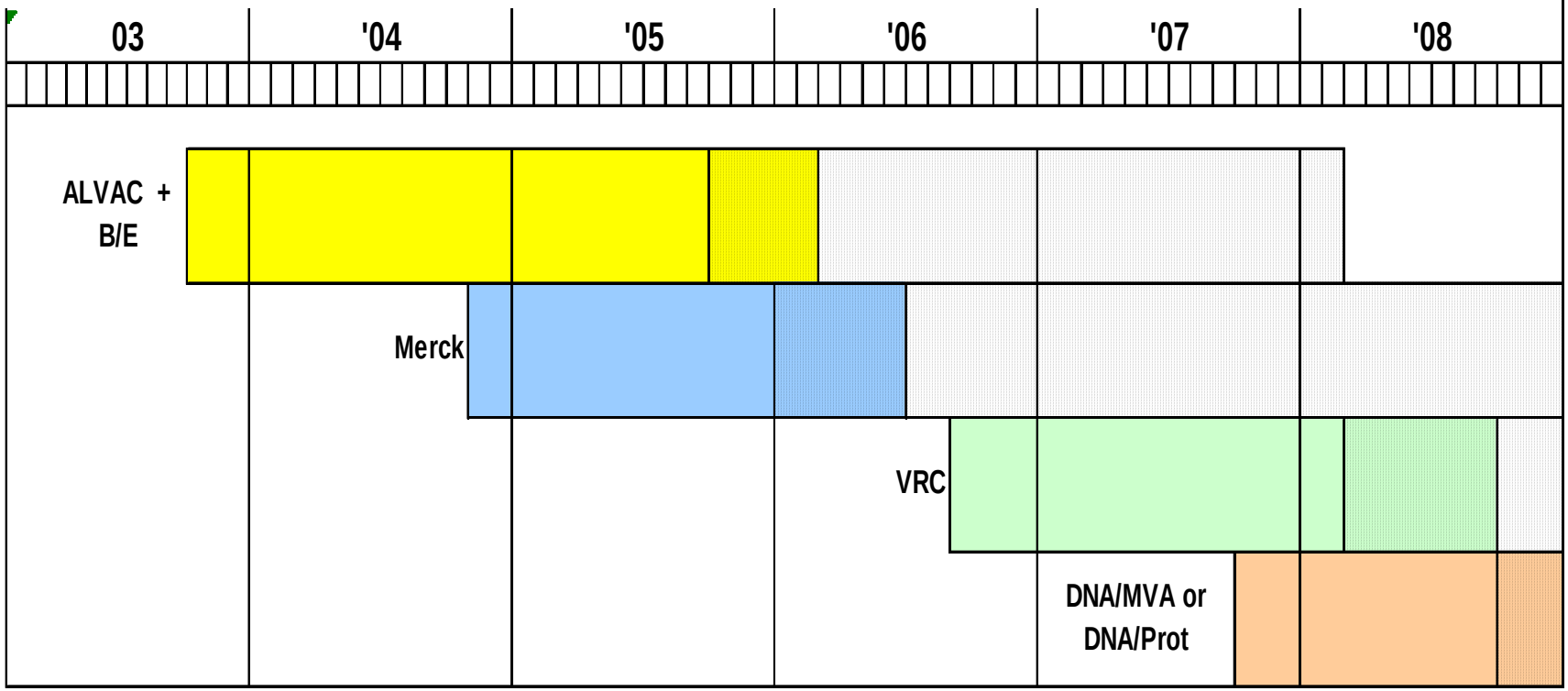
Vector	Insert (Clade)	Immune Profile	Manufacturer or Sponsor
Canary poxvirus +/- protein	Env (E) Gag/Pol(B), Env (B/E)	Cellular +/- humoral	Aventis/Vaxgen
rAd	Gag (B), Pol (B), Nef (B)	Cellular	Merck
DNA/rAd	Gag (B), Pol (B), Nef (B), Env (A,B,C)	Cellular +/- humoral	VRC, NIAID, NIH
AAV	Gag, PR, RT (C)	Cellular	IAVI
Lipopeptides	Gag, POL & Nef (B)	Cellular	ANRS

rAd - replication-defective adenovirus;AAV – adeno-associated virus; Env – envelope protein;Gag, group specific antigen; Nef, negative regulartory factor; Pol, polymerase, PR, protease, RT reverse transcriptase

NIAID HIV Vaccine Trials Network (HVTN)
Domestic and International Sites



Efficacy Trials – estimated timelines



Jorge Flores

Live Vaccination – vaccine protection against pathogenic SIV in Indian rhesus macaques,

adapted from Koff et al, Nature Immunology Jan 2006

Vaccine	Monkeys protected
Live attenuated: Δnef	59 of 63
Live attenuated: Δ3	12 of 12
Live attenuated: Δ5G	3 of 3
Live attenuated summary	74 of 78 (95%)
All other vaccine strategies	18 of 256 (7%)

WHAT TRANSLATES FROM ANIMAL MODELS TO HUMAN TRIALS

- Poxvirus vectors induce limited IFN gamma responses, but that does not correlate with protection in macaques, so we do not know if they will protect in humans.
- Responses to DNA vaccines for HIV env are better than to gag. DNA vaccines are much more immunogenic in mice >> than monkeys >> humans.
- Regulatory protein immunity appears to be important in acute infections and in some NHP vaccine studies, but phase I human trials are limited.

THE BIOLOGICAL BASIS OF AN AIDS VACCINE -Why so difficult to make?

BIOLOGICAL OBSTACLES

- Persistence of HIV and progression to AIDS
- Mechanisms of vaccine protection poorly understood

RESEARCH EXPERIENCE

- HIV envelope gp120 protein fails to induce broad neutralizing antibodies and fails to protect MSM
- Live attenuated SIVs protect but cause AIDS in NHP

IMPLICATION

- Immunobiological questions still unanswered

Challenges for Vaccine Efficacy Trials

- Identifying populations of individuals at risk of HIV infection:
  - In most behavioral risk categories youth are at highest risk of infection
- Enrolling individuals at risk of infection
  - Without risk of social harm,
  - While maintaining primary prevention programs
  - With highest ethical standards, and
  - With extensive consultation and education in the communities.

Summary

- Greatest immunologic damage occurs within weeks of infection.
- Immunotherapy for established infection may yet yield results.
- HIV vaccine: coming but not yet here.
- Continued progress in our understanding of the pathogenesis of HIV infection, and of our immune response.

Selected References

- Douek D, Kwong PD, Nabel GJ. The rational design of an AIDS vaccine. Cell 2006;124(feb):677-681.
- Haase AT. Perils at mucosal front lines for HIV and SIV and their hosts. Nature Reviews-Immunology. 2005 (Oct);5:783-792.
- Koff WC, Johnson PR, Watkins DI, et al. HIV vaccine design: insights from live attenuated SIV vaccines. Nature Immunology. 2006 (Jan);7:19-23.
- Mattapallil JJ, Douek DC, Hill B, Nishimura Y, Martin M, Roederer M. Massive infection and loss of memory CD4+ T cells in multiple tissues acute SIV infection. Nature. 2005 (April);434:1093-1097.