Bench to Bedside: Building Collaborations Towards an HIV Cure

Luis J. Montaner, D.V.M., M.Sc., D.Phil.

January 26, 2016

From Bench to Bus Stop: Building HIV Research Collaborations in Philadelphia

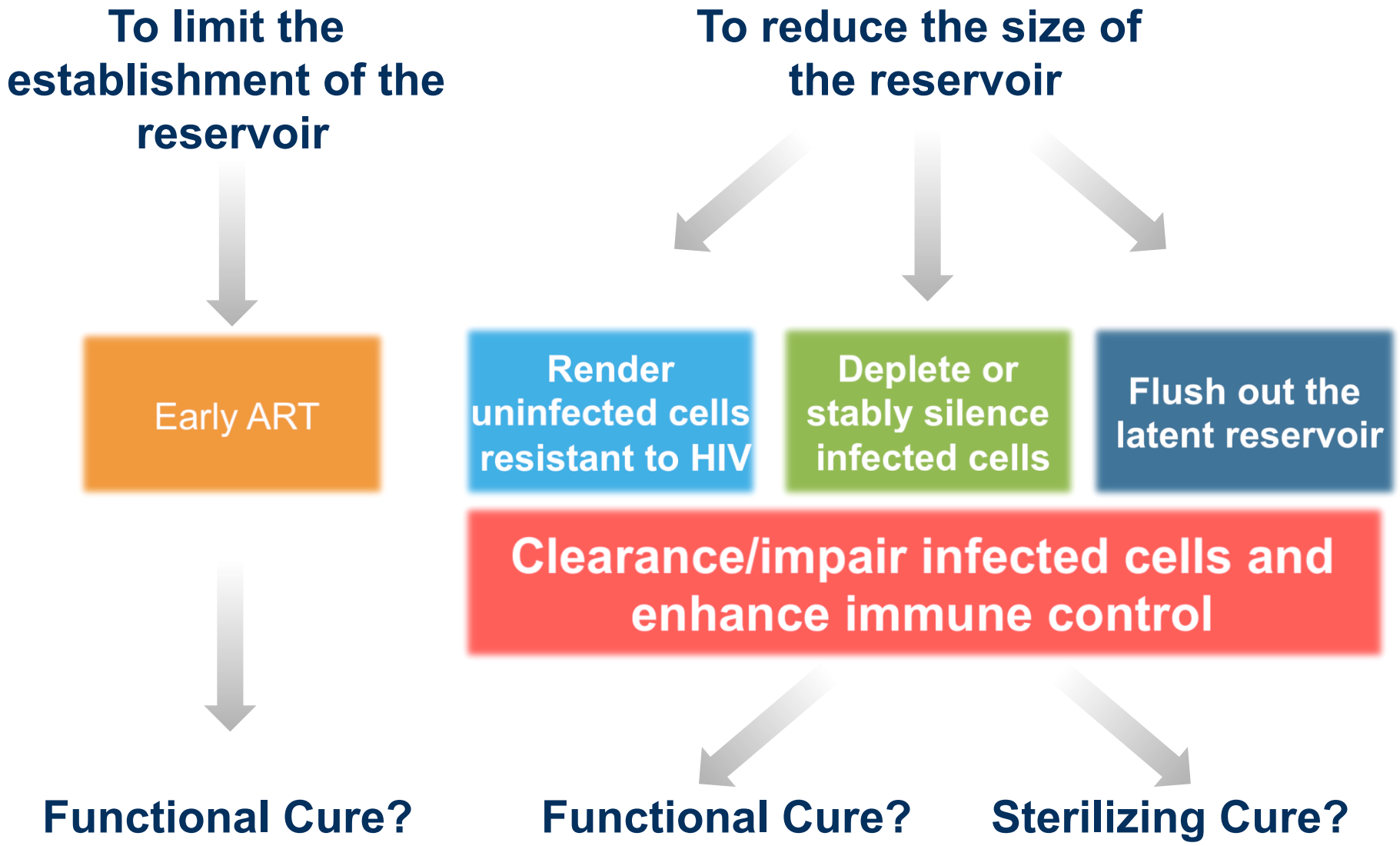
College of Physicians, Philadelphia

Outline

- ❑ **Conceptual overview of HIV cure research**
- ❑ **Our approach: Boost innate function**
- ❑ **Building Collaborative HIV Cure Teams**

What are the strategies for an HIV cure?

Cure strategies



Adapted - Courtesy of N. Chomont

Outline

- ❑ **Conceptual overview of HIV cure research**
- ❑ **Our approach: Boost innate function**
- ❑ **Building Collaborative HIV Cure Teams**

Type I IFNs

Type I (13 functional IFNA human genes) and several subtypes IFN-ε, ω, κ, δ, β.

Type II (only 1: IFN-γ)

Type III λ1 (IL-29), λ2 (IL-28A), λ3 (IL-28B) and λ4.

IFN-alpha increases NK response against autologous CD4 T cells infected cells

Lysis of HIV-1 Infected Autologous CD4+ Primary T cells by Interferon-alpha Activated NK cells Requires NKp46 and NKG2D.

Tomescu, C, Mavilio, D, Montaner, LJ.
AIDS 2015 29: 1767-73. PMID: 26372382

Retention of viability, cytotoxicity, and response to IL-2, IL-15, or IFN-alpha by human NK cells after CD107a degranulation.

Tomescu C, Chehimi J, Maino VC, Montaner LJ.
J Leukoc Biol. 2009 May;85(5):871-6. PMID: 19237639

NK cell lysis of HIV-1-infected autologous CD4 primary T cells: requirement for IFN-mediated NK activation by plasmacytoid dendritic cells.

Tomescu C, Chehimi J, Maino VC, Montaner LJ.
J Immunol. 2007 Aug 15;179(4):2097-104. PMID: 17675468

Cellular
Innate

PDC or NK as correlate of HIV control with Adaptive Anti-HIV Response

Immune
Adaptive

Plasmacytoid dendritic cell and functional HIV Gag p55-specific T cells before treatment interruption can inform set-point plasma HIV viral load after treatment interruption in chronically suppressed HIV-1(+) patients.

Immunology. 2015 Jul;145(3):380-90. PMID: 25684333

A correlate of HIV-1 control consisting of both innate and adaptive immune parameters best predicts viral load by multivariable analysis in HIV-1 infected viremic controllers and chronically-infected non-controllers.

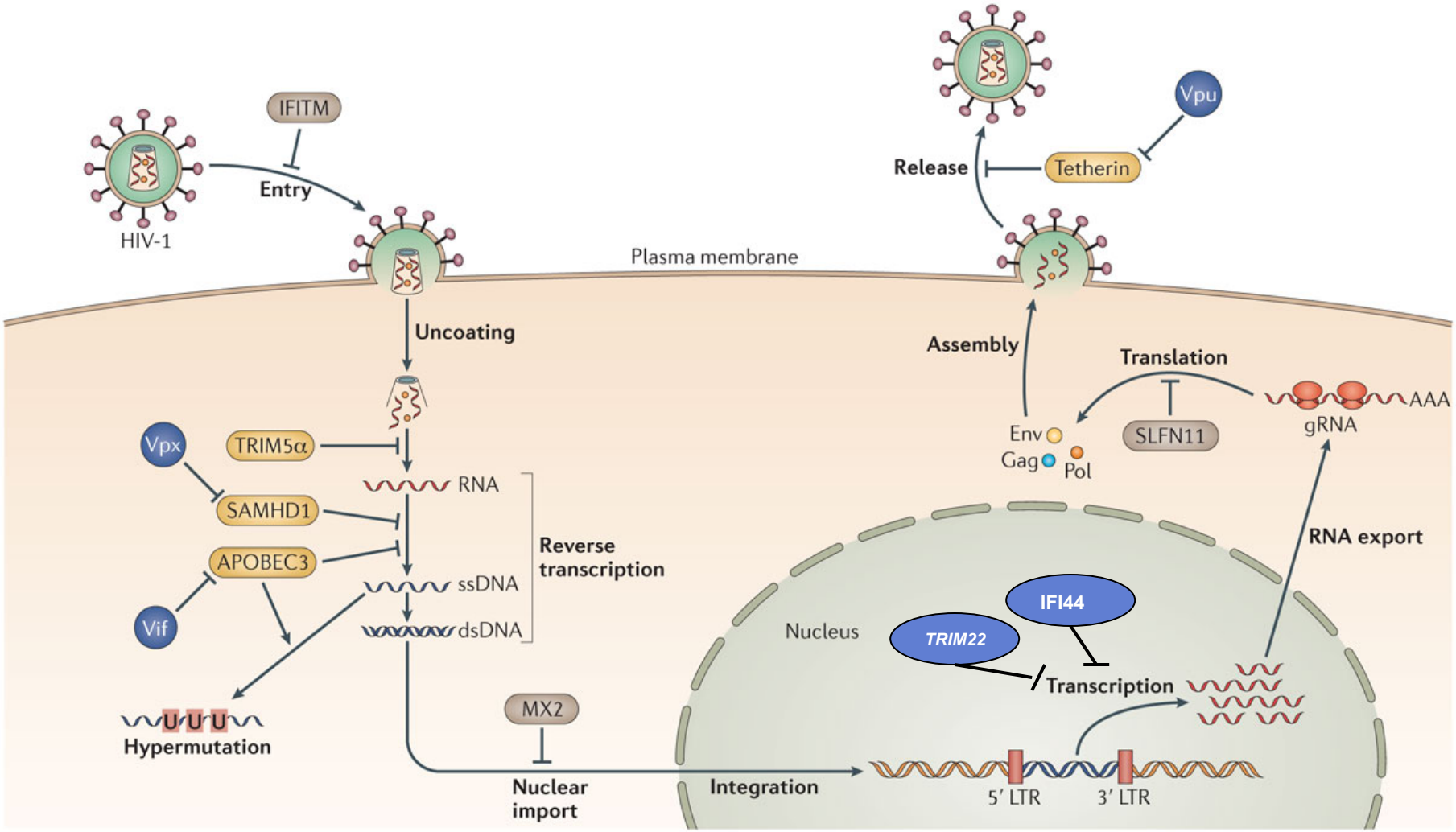
PLoS One. 2014 Jul 31;9(7):e103209. PMID: 25078947

Impact of protective killer inhibitory receptor/human leukocyte antigen genotypes on natural killer cell and T-cell function in HIV-1-infected controllers.

AIDS. 2012 Sep 24;26(15):1869-78. PMID: 22874514

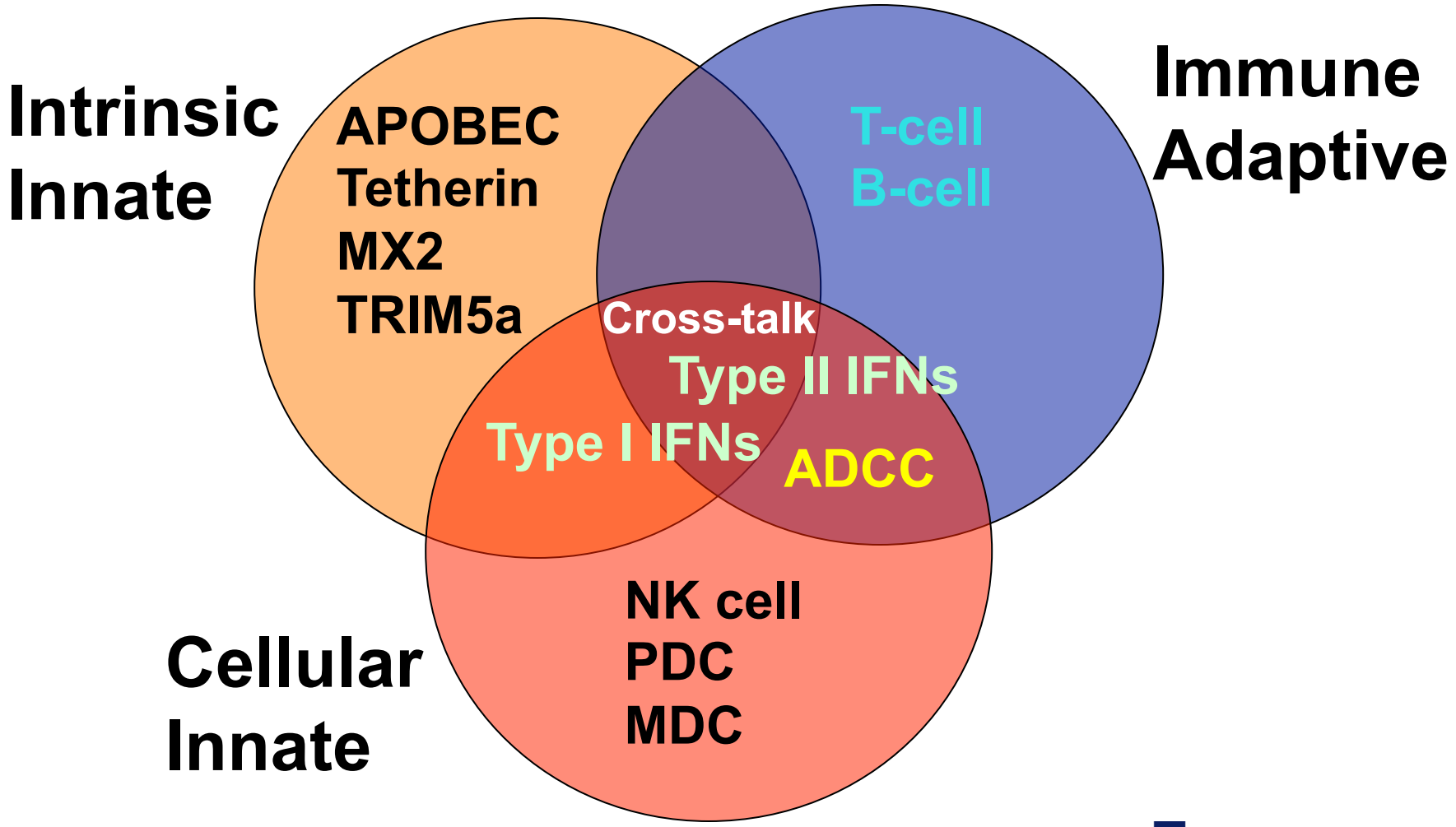
Cellular
Innate

Type I Interferon Modulation of Host Intrinsic HIV Resistance Factors



Nature Reviews Microbiology 13, 403–413 (2015)

Interferon regulation includes multiple arms of the antiviral response



Azzoni L, Foulkes AS, Papassavvas E, Mexas AM, Lynn KM, Mounzer K, Tebas P, Jacobson JM, Frank I, Busch MP, Deeks SG, Carrington M, O'Doherty U, Kostman J, Montaner LJ. Pegulated Interferon Alfa-2A Monotherapy Results in Suppression of HIV Type I Replication and Decreased Cell-Associated HIV DNA Integration. JID. 2013; 207:213-222.

Pegylated Interferon Alfa-2a Monotherapy Results in Suppression of HIV Type 1 Replication and Decreased Cell-Associated HIV DNA Integration

Livio Azzoni,[1] Andrea S. Foulkes,[2] Emmanouil Papasavvas,[1] Angela M. Mexas,[3] Kenneth M. Lynn,[1,4] Karam Mounzer,[5] Pablo Tebas,[4] Jeffrey M. Jacobson,[6] Ian Frank,[4] Michael P. Busch,[7,7a] Steven G. Deeks,[8] Mary Carrington,[9,9a] Una O'Doherty,[3] Jay Kostman,[4] and Luis J. Montaner[1]

[1]HIV-1 Immunopathogenesis Laboratory, The Wistar Institute, [2]Division of Biostatistics and Epidemiology, University of Massachusetts, Amherst, [3]Department of Pathology and Laboratory Medicine and [4]Department of Medicine, School of Medicine, University of Pennsylvania, [5]Jonathan Lax Treatment Center, Philadelphia FIGHT, and [6]Department of Medicine, Drexel University, Philadelphia, Pennsylvania; [7]Blood Systems Research Institute and [7a]Department of Laboratory Medicine and [8]Department of Medicine, University of California–San Francisco, San Francisco, California; and [9]Laboratory of Experimental Immunology, AIC Frederick, NCI Frederick, Frederick, Maryland and [9a]Ragon Institute of MGH, MIT and Harvard, Boston, Massachusetts

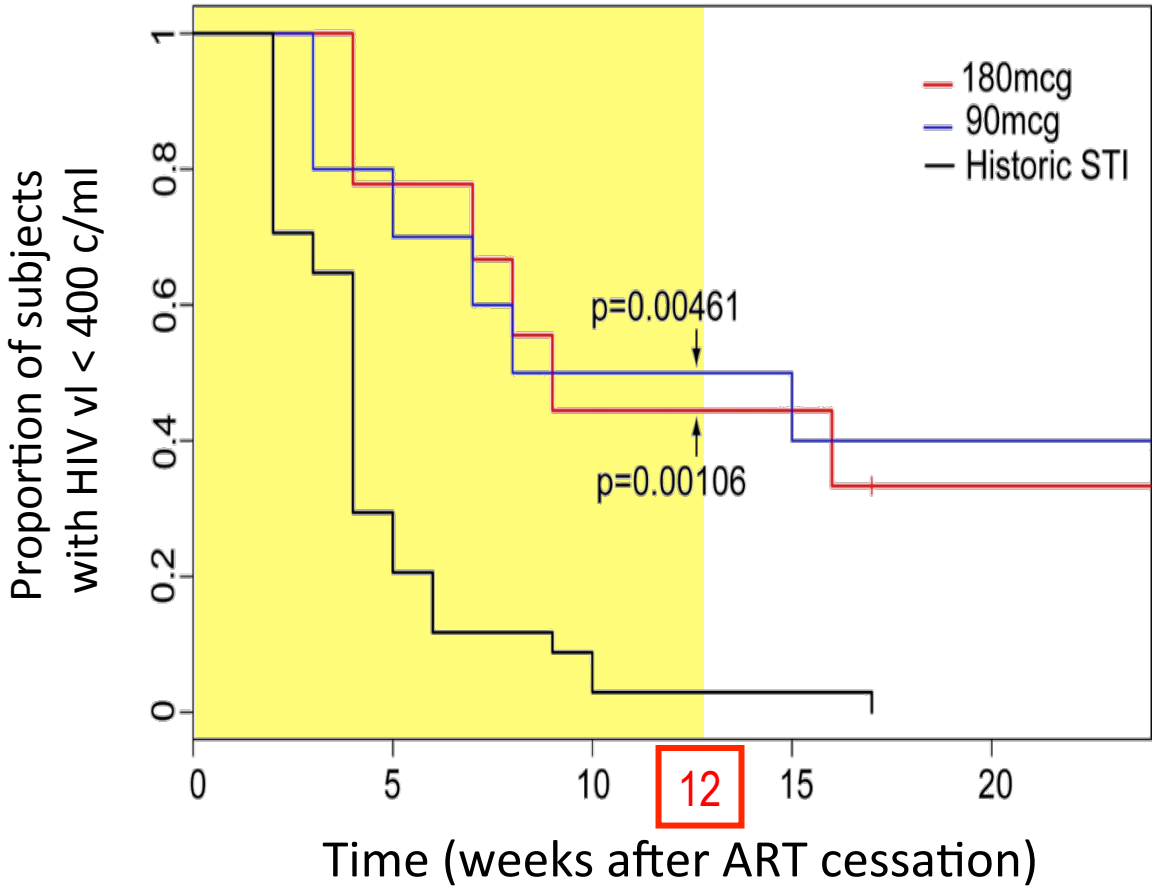
(See the editorial commentary by McNamara and Collins, on pages 201–3.)

Background. Antiretroviral therapy (ART)–mediated immune reconstitution fails to restore the capacity of the immune system to spontaneously control human immunodeficiency virus (HIV) replication.

Methods. A total of 23 HIV type 1 (HIV-1)–infected, virologically suppressed subjects receiving ART ($CD4^+$ T-cell count, >450 cells/μL) were randomly assigned to have 180 μg/week (for arm A) or 90 μg/week (for arm B) of pegylated (Peg) interferon alfa-2a added to their current ART regimen. After 5 weeks, ART was interrupted, and Peg–interferon alfa-2a was continued for up to 12 weeks (the primary end point), with an option to continue to 24 weeks. End points included virologic failure (viral load, ≥400 copies/mL) and adverse events. Residual viral load and HIV-1 DNA integration were also assessed.

Results. At week 12 of Peg–interferon alfa-2a monotherapy, viral suppression was observed in 9 of 20 subjects (45%), a significantly greater proportion than expected (arm A, $P = .0088$; arm B, $P = .0010$; combined arms, $P < .0001$). Over 24 weeks, both arms had lower proportions of subjects who had viral load, compared with the proportion of subjects in a historical control group (arm A, $P = .0046$; arm B, $P = .0011$). Subjects who had a

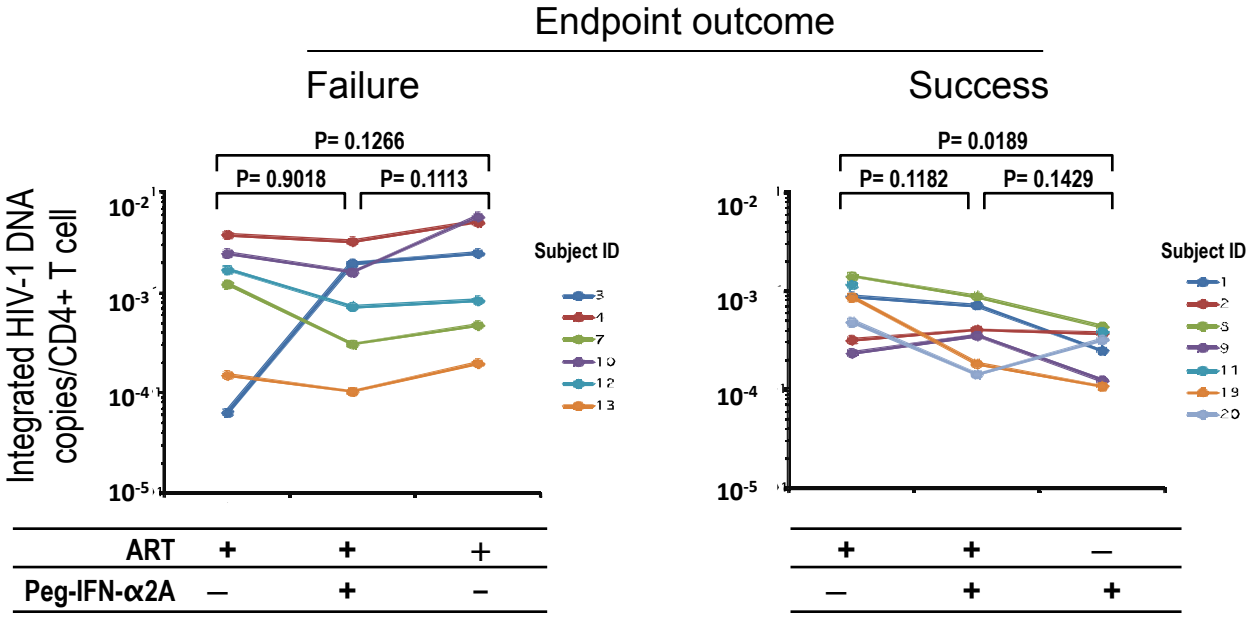
NCT00594880: Primary analysis



Conclusions

Compared to an anticipated rate of 9%, a significant proportion (45%) of immune-reconstituted subjects receiving peg-IFN-α2a monotherapy in the absence of ART maintains viral control.

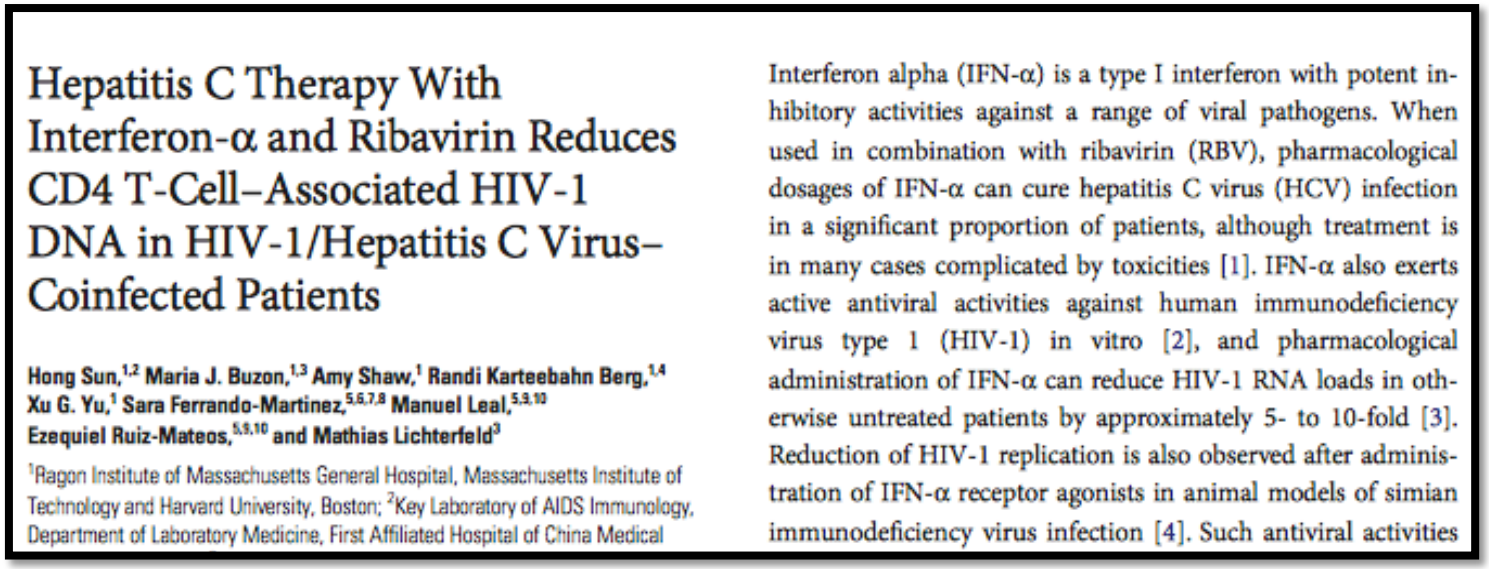
Mechanism: IFN-alpha anti-HIV-1 Therapy



Evidence for HIV-1 control response to be associated with decreased peripheral CD4 T-cell HIV integration levels (i.e., viral integrated reservoir).

3 independent studies (2013-2015) support the finding that PegIFN-α can decrease amount of CD4 T cell HIV DNA

Sun H, Buzon MJ, Shaw A, Barteebahn Berg R, Yu XG, Ferrando-Martinez S, Leal M, Ruiz-Mateos E, Lichterfeld M. JID. 2014; 209:1315-1320.



Hepatitis C Therapy With Interferon-α and Ribavirin Reduces CD4 T-Cell–Associated HIV-1 DNA in HIV-1/Hepatitis C Virus–Coinfected Patients

Hong Sun,[1,2] Maria J. Buzon,[1,3] Amy Shaw,[1] Randi Karteebahn Berg,[1,4] Xu G. Yu,[1] Sara Ferrando-Martinez,[5,6,7,8] Manuel Leal,[5,9,10] Ezequiel Ruiz-Mateos,[5,9,10] and Mathias Lichterfeld[3]

[1]Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard University, Boston; [2]Key Laboratory of AIDS Immunology, Department of Laboratory Medicine, First Affiliated Hospital of China Medical

Interferon alpha (IFN-α) is a type I interferon with potent inhibitory activities against a range of viral pathogens. When used in combination with ribavirin (RBV), pharmacological dosages of IFN-α can cure hepatitis C virus (HCV) infection in a significant proportion of patients, although treatment is in many cases complicated by toxicities [1]. IFN-α also exerts active antiviral activities against human immunodeficiency virus type 1 (HIV-1) in vitro [2], and pharmacological administration of IFN-α can reduce HIV-1 RNA loads in otherwise untreated patients by approximately 5- to 10-fold [3]. Reduction of HIV-1 replication is also observed after administration of IFN-α receptor agonists in animal models of simian immunodeficiency virus infection [4]. Such antiviral activities

Jiao Y-M, Weng W-J, Gao Q-S, Zhu W-J, Cai W-P, Li L-H, Li H-J, Gao Y-Q, Wu H. Hepatitis C therapy with interferon-α and ribavirin reduced the CD4 cell count and the total 2LTR circular and integrated HIV-1 DNA in HIV/HCV co-infected patients. Antiviral Research. 2015; 118:118-122.

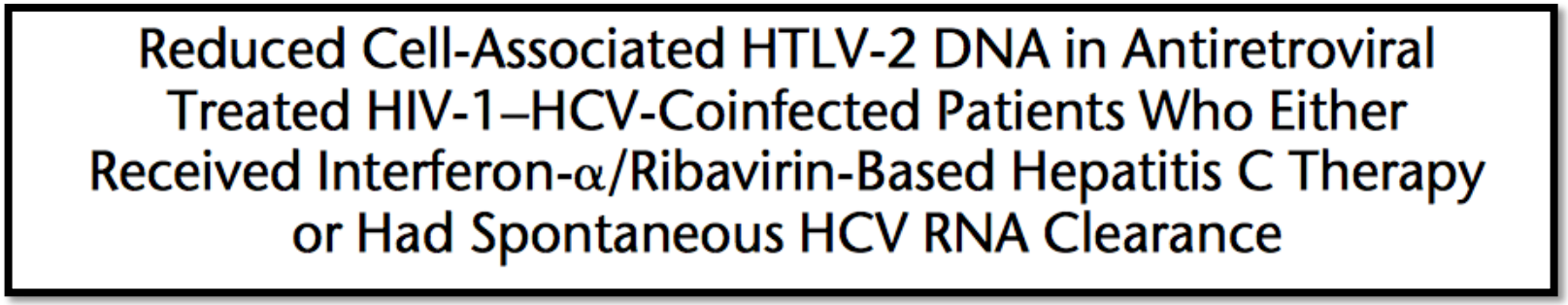
Hepatitis C therapy with interferon-α and ribavirin reduces the CD4 cell count and the total, 2LTR circular and integrated HIV-1 DNA in HIV/HCV co-infected patients

CrossMark

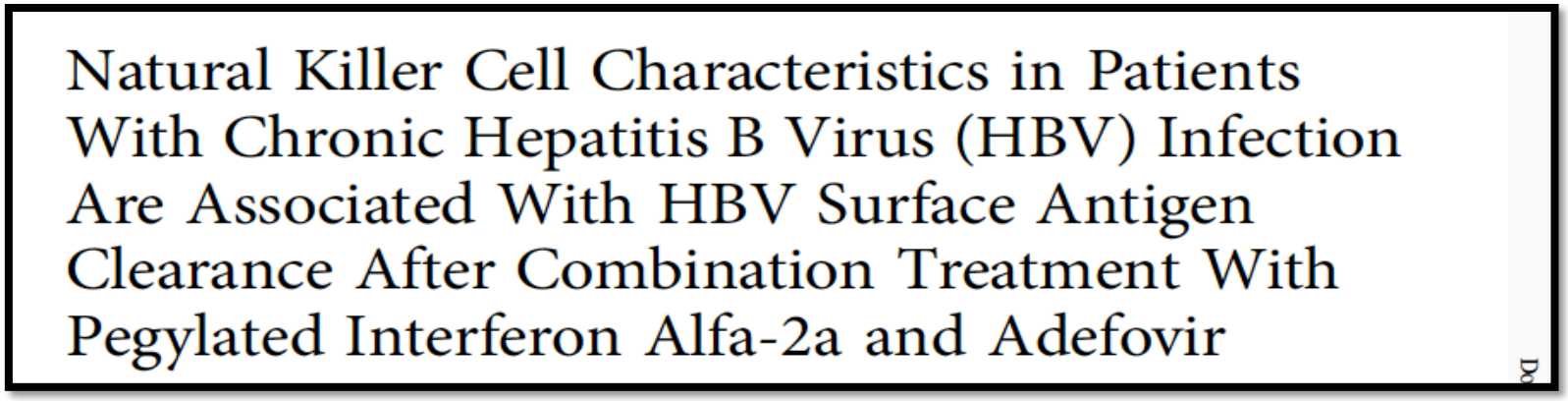
Yan-mei Jiao [a,1], Wen-jia Weng [a,1], Quan-sheng Gao [b,1], Wei-jun Zhu [c], Wei-ping Cai [d], Ling-hua Li [d], Hong-jun Li [a,*], Yan-qing Gao [a,*], Hao Wu [a,*]

[a] Beijing You'an Hospital, Capital Medical University, Xi Tou Tiao, Youanmen Wai, Fengtai District, Beijing 100069, China
[b] Laboratory of the Animal Center, Academy of Military Medical Sciences, No. 27 Taiping Road, Haidian District, Beijing 100850, China
[c] MOH Key Laboratory of Systems Biology of Pathogens and AIDS Research Center, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[d] Guangzhou Eighth People's Hospital, No. 627 Dongfeng East Road, Guangzhou 510060, China

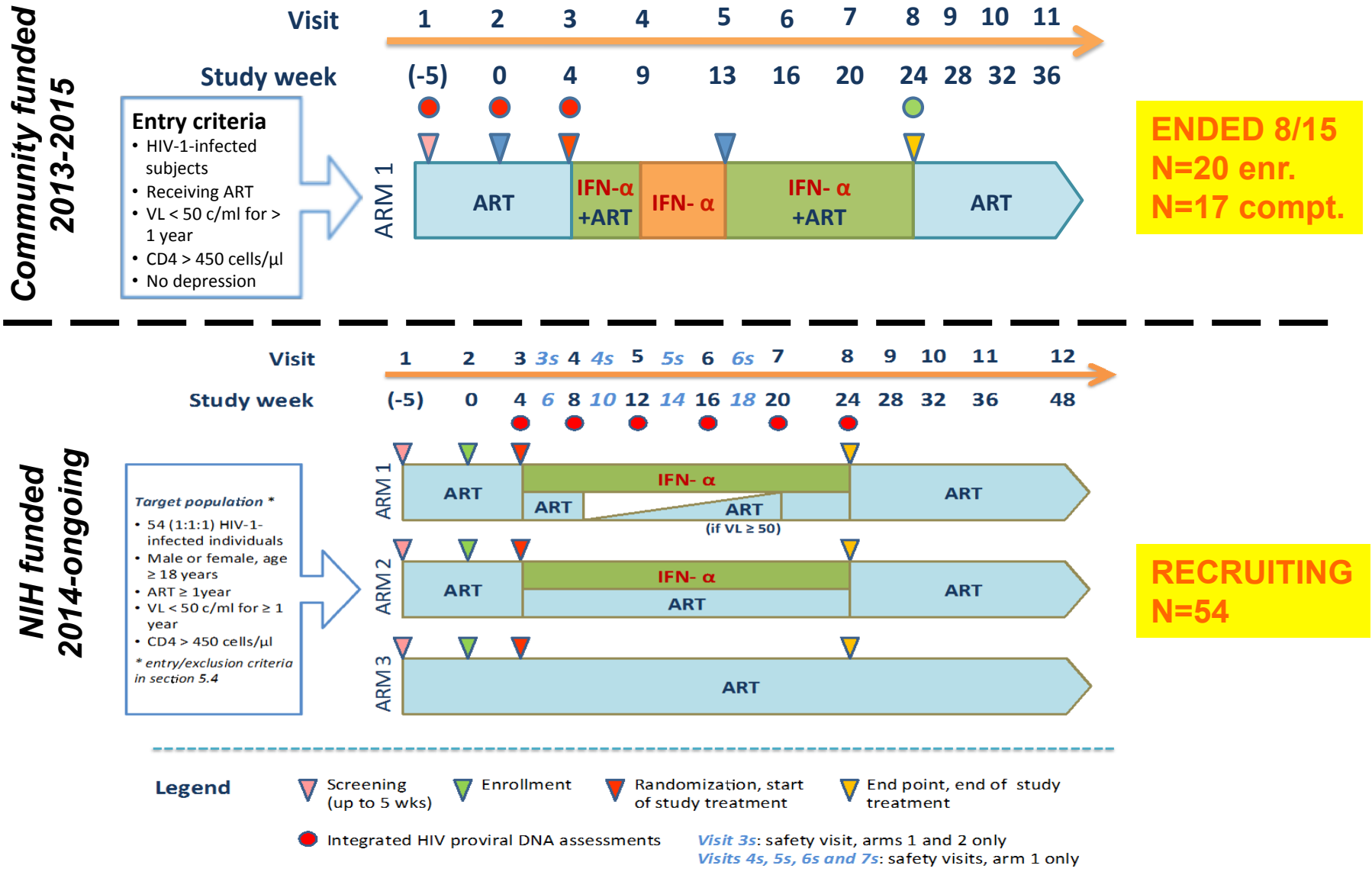
Abad-Fernández M, Dronda F, Moreno A, Casado JL, Pérez-Elias M-J, Quereda C, Moreno S, Vallejo A. Reduced Cell-Associated HTLV-2 DNA in Antiretroviral Treated HIV-1-HCV-Coinfected Patients Who Either Received Interferon-α/ Rivavirin-Based Hepatitis C Therapy or Had Spontaneous HCV RNA Clearance. J Acquir Infect Dis. 2015; 69:286-290.



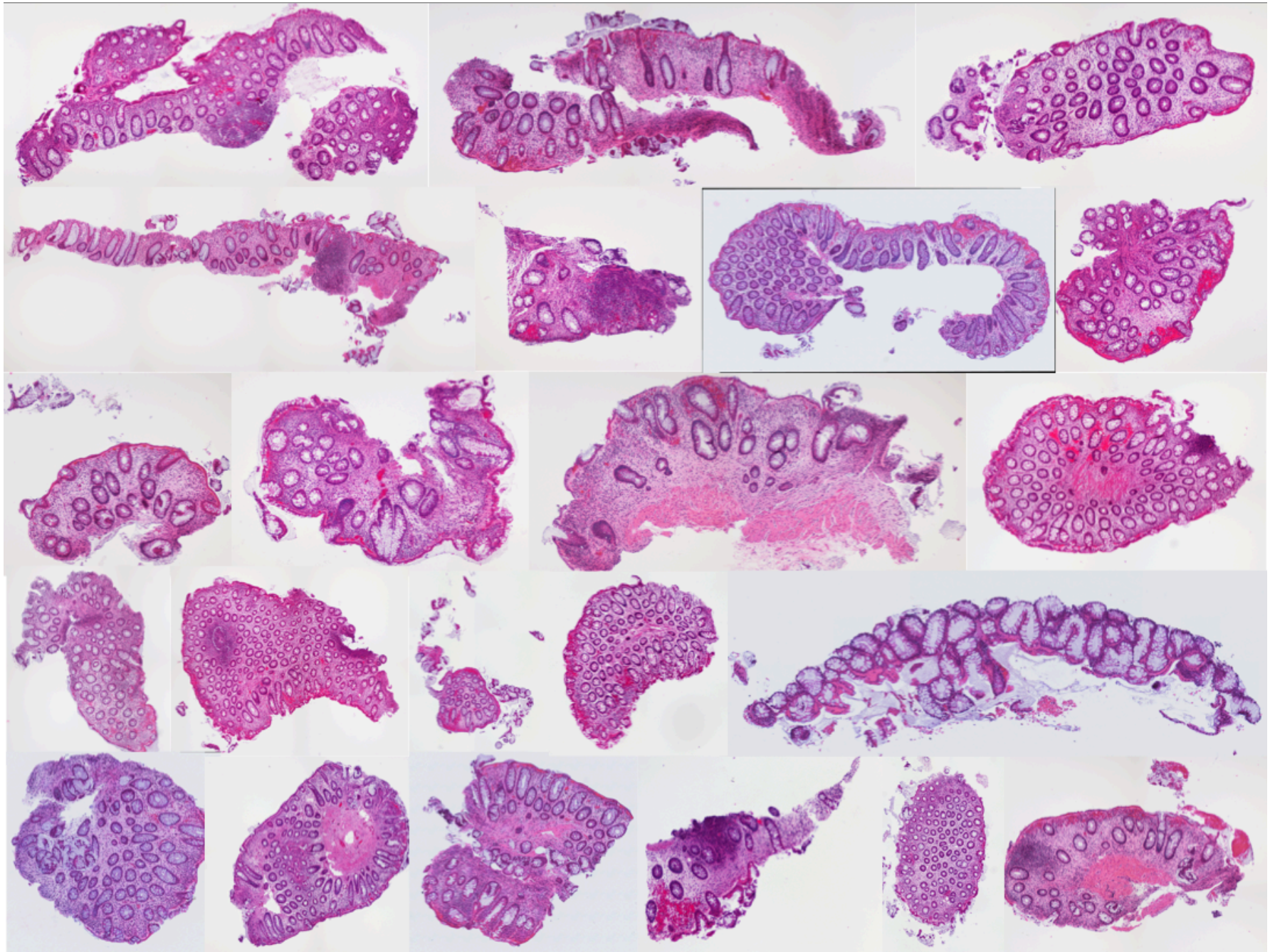
Stelma F, de Niet A, Plat-Sinnige JT, Jansen L, Takkenberg RB, Reesink HW, Kootstra NA, van Leeuwen EMM. Natural Killer Cell Characteristics in Patients with Chronic Hepatitis B Virus (HBV) Infection are Associated with HBV Surface Antigen Clearance After Combination Treatment with Pegylated Interferon Alfa-2a and Adefovir. JID. 2015; 212:1041-1051.



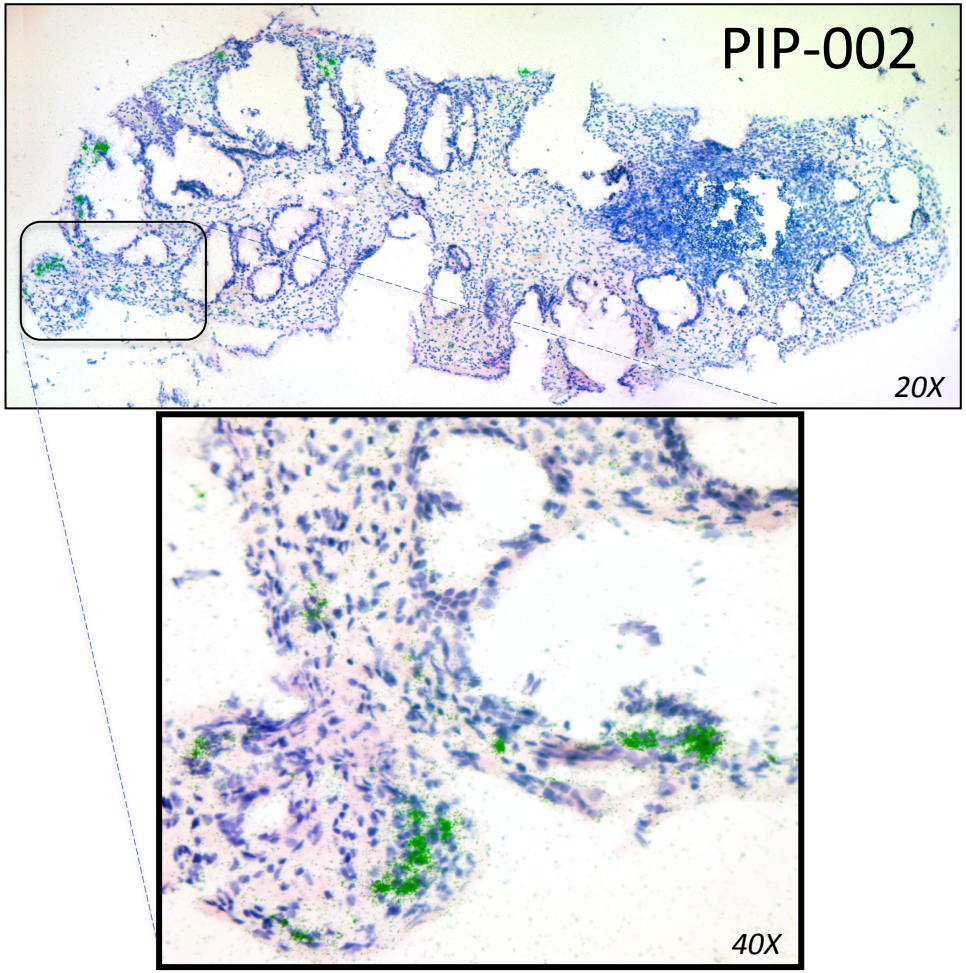
NCT01935089 and NCT00594880



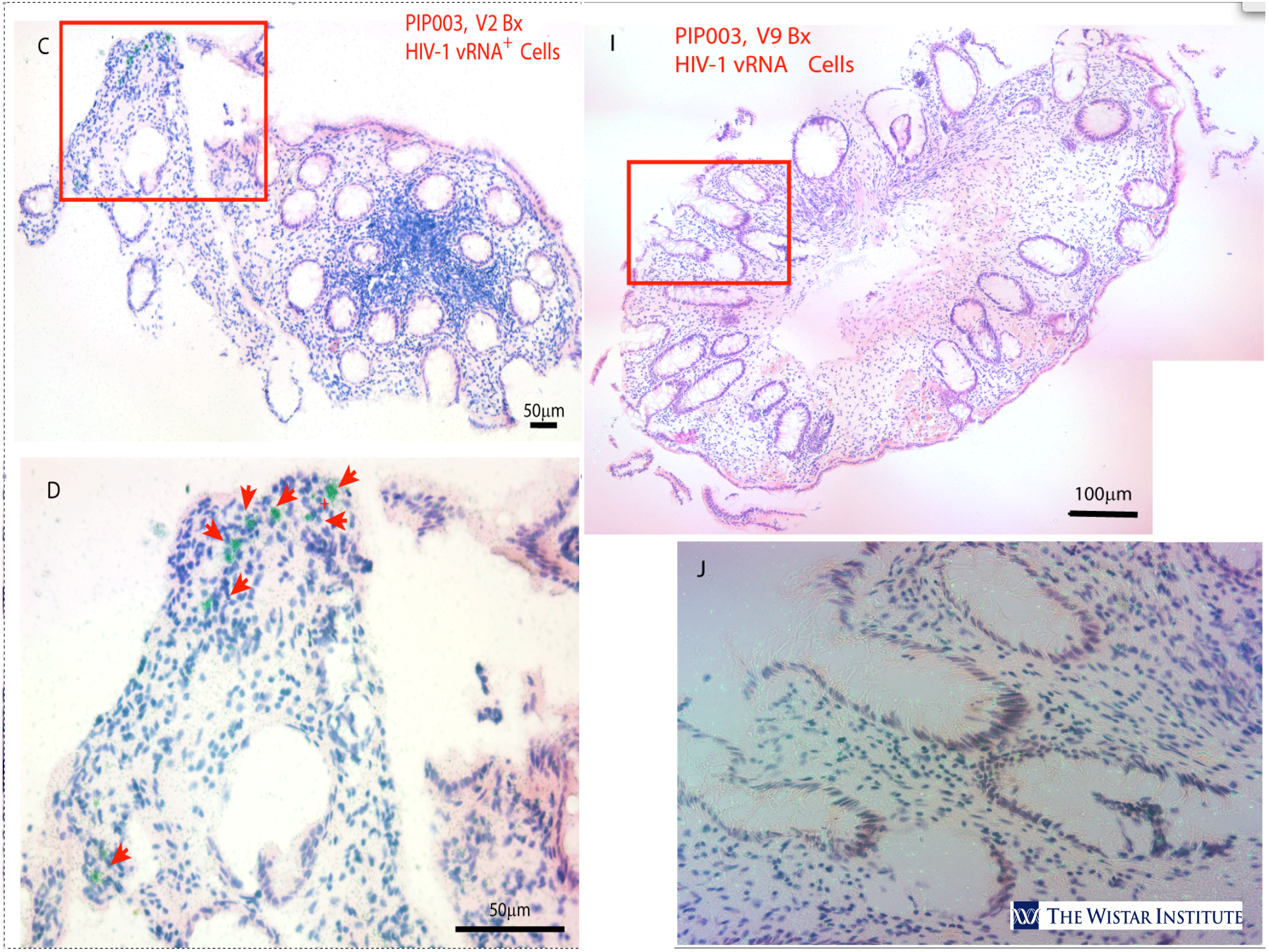
THE WISTAR INSTITUTE



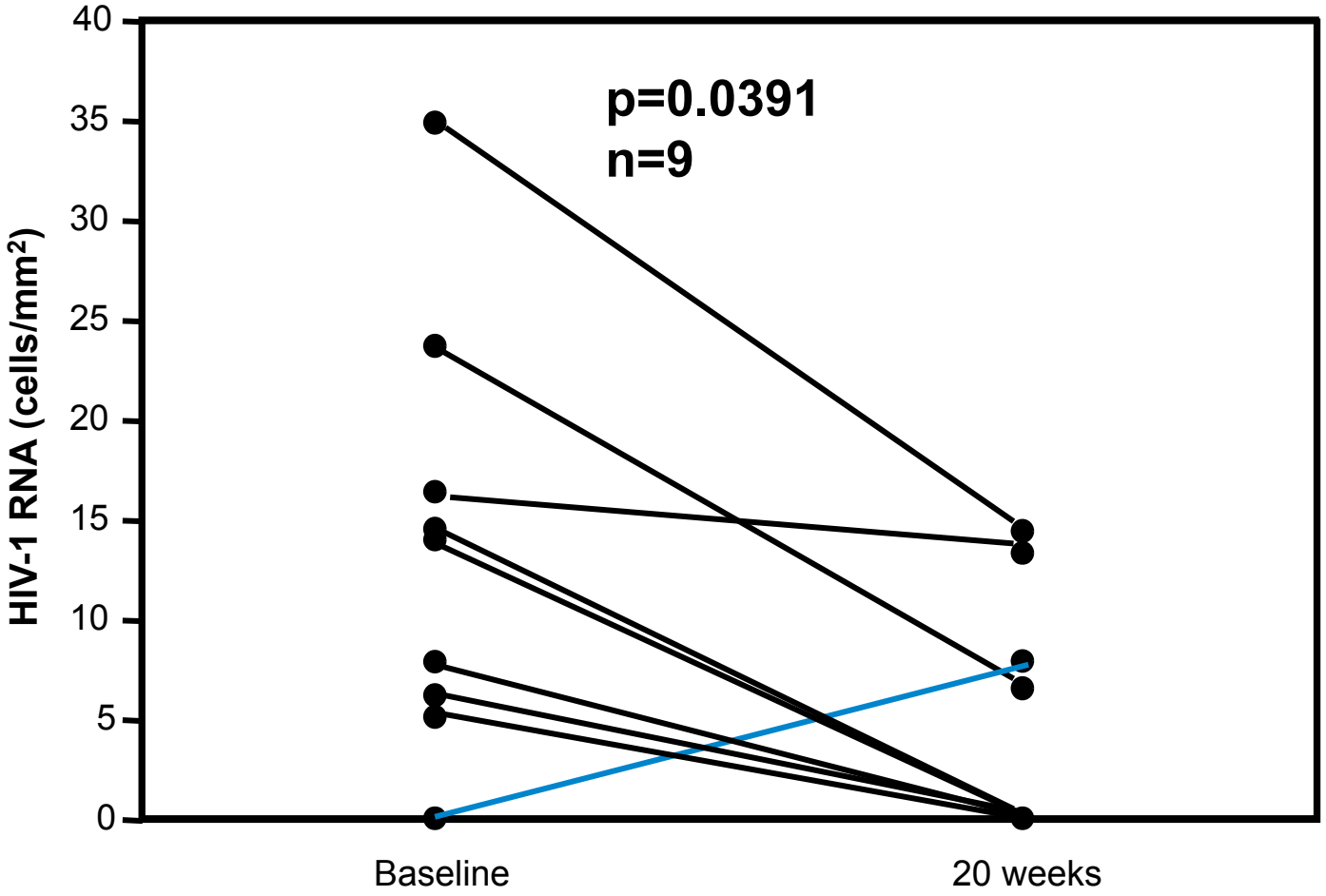
HIV RNA quantification in rectal tissue on long-term ART suppressed



Patient number	V2-Semi -quantification	V2-vRNA+ cells	V2-Area(mm2)	V2-vRNA+ cells/mm2
PIP 002	Positive	18	1.289306	13.96099917


C
PIP003, V2 Bx
HIV-1 vRNA+ Cells
50µm
D
50µm
I
PIP003, V9 Bx
HIV-1 vRNA Cells
100µm
J
THE WISTAR INSTITUTE

Peg-IFN-α2b+ ART together with ART interruption decreased rectal HIV RNA levels



8 or 8 with detectable RNA at baseline dropped HIV-1 RNA

1 patient with negative HIV-1 RNA at baseline showed positive HIV-1 RNA at end

Clinical implications to cure efforts

- **IFN-alpha immunotherapy can reduce HIV DNA levels beyond ART. Added data on inducible reservoir pending.**
- **IFN-alpha may be first immunotherapy to potentiate ART by reducing HIV RNA expression beyond ART.**
- **IFN-alpha immunotherapy is well tolerated.**
- **IFN-alpha may provide a tool to boost innate anti-viral preassure and/or clearance of HIV in cure strategies.**

Outline

- **Conceptual overview of HIV cure research**
- **Our approach: Boost innate function**
- **Building Collaborative HIV Cure Teams**
  - BEAT-HIV: Delaney Collaborative to cure HIV-1 Infection by combination immunotherapy


BEAT
HIV
Collaborative
Intrinsic
ΔCCR5
T-cell
CAR
NK Cell
ADCC
Antibody

BEAT-HIV:
Initial Research Foci

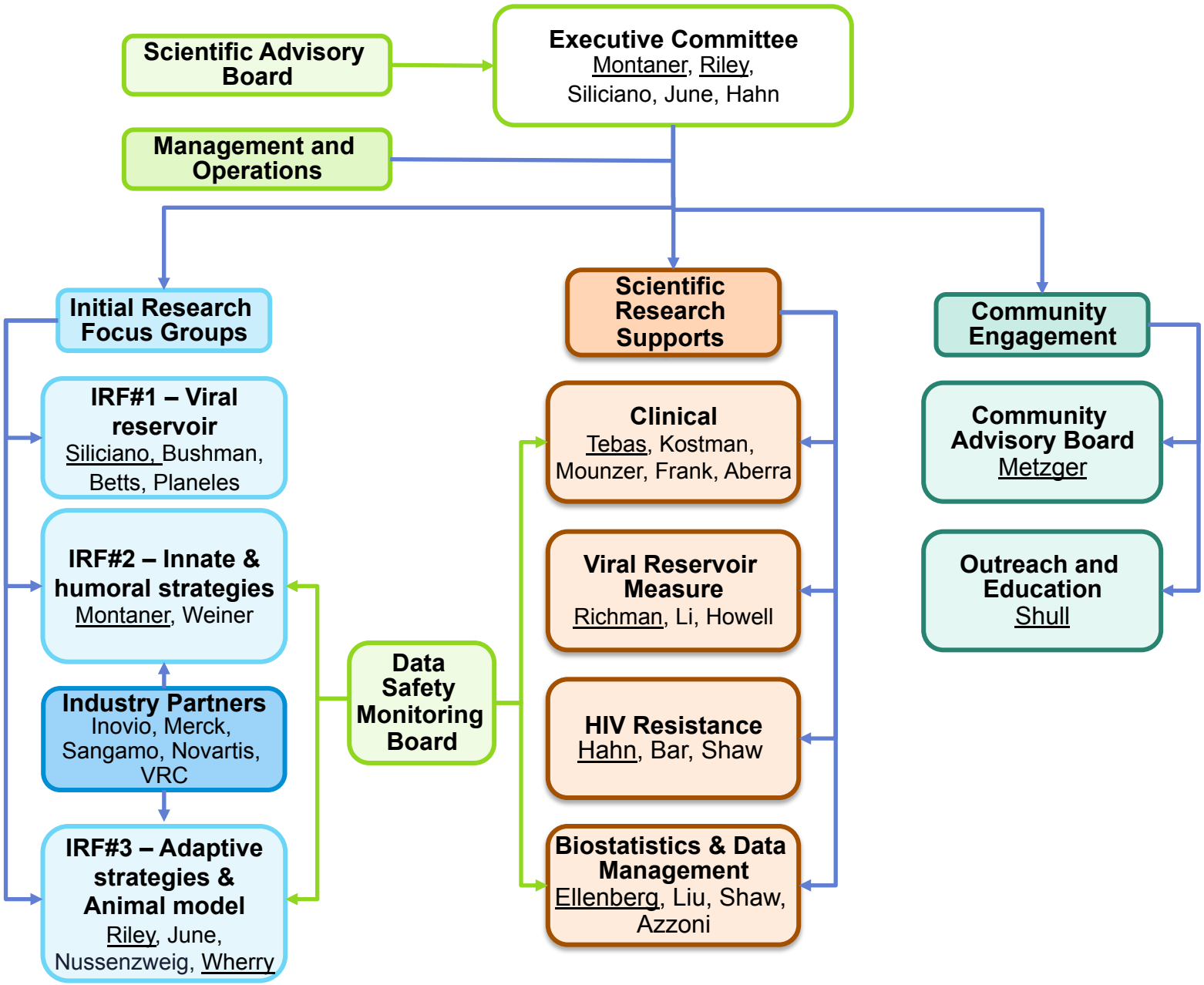
- Determining the frequency, reactivation potential of tissue or stem cell compartments (stem cells, lymph, rectal), containing active versus latent HIV reservoirs (replication incompetent and competent) in order to define the susceptibility for targeting by immunotherapy .
- Determining how best to develop and optimize a strategy for type-I interferon-induced antiviral responses and/or broadly neutralizing antibodies in order to control and eradicate HIV following ART interruption before combining with adaptive anti-HIV strategies.
- Determining how best to develop a strategy for the generation and infusion of CCR5 disrupted T-cells expressing HIV-1-specific CARs in order to control and eradicate HIV following ART interruption before combining with type-I interferon or neutralizing antibody strategies.

BEAT HIV Collaborative

- 3 Initial Research Foci
- 4 Scientific Research Support Groups
- Management and Administration (Wistar)
- Community engagement (UPENN & Philadelphia FIGHT)
- 35 Key Personnel:
  - **MPIs: Montaner, Riley**; Aberra, Azzoni, Bar, Betts, Bushman, Caskey, Ellenberg, Frank, Hahn, Howell, Jadlowsky, June, Shull, J. Siliciano, R. Siliciano, Kostman, Li, Liu, Metzger, Mounzer, Nussenzweig, Papasavvas, Planelles, Richman, Schlesinger, G. Shaw, P. Shaw, Showe, Strain, Tebas, Tomescu, Weiner, Wherry.
- 8 collaborating institutions:
  - **Wistar, UPENN**, John Hopkins U., Rockefeller U., U. Utah, **Philadelphia FIGHT**, Veterans Medical Research Foundation, U. Nebraska.
- 3 Industry partners & 1 Government partner
  - Merck, Sangamo, Inovio, VRC

BEAT HIV Collaborative

BEAT-HIV: Organizational and Leadership Structure



Clinical Study Team

Clinical Site Investigator

Jay Kostman, John Bell Health Center, Philadelphia FIGHT, Philadelphia, PA

Karam Mounzer, Jonathan Lax Clinic, Philadelphia FIGHT, Philadelphia PA

Pablo Tebas, Hospital of the University of PA , Philadelphia, PA

Ian Frank, Hospital of the University of PA , Philadelphia, PA

Jeffery M. Jacobson
Drexel Univ. School of Medicine, Philadelphia, PA

Clinical coordinators

Kenneth Lynn
Angela Kapalko,
Kyle Richards
Linden Lalley-Chareczko

Genentech/Roche
Merck

DAIDS

Daniella Livnat, Program Officer
Tia Morton, Program Officer
Larry Fox, Clinical Officer
Marjorie Dehlinger, Clinical Officer
Eileen Poiliot, Clinical Site Specialist

Acknowledgments

THE WISTAR INSTITUTE

Shaheed Abdulhaqq
Livio Azzoni
Jihed Chehimi
Jennifer Dubin
Betsy Gekonge
Agnes Mackiewicz
Sean Patro
Emmanouil Papasavvas
Maria Picone
Griffin Reynolds
Brian Ross
Costin Tomescu

Acknowledgments

The Wistar Institute
L. Showe
N. Dawany
Jeffrey Faust
Phlebotomy Unit

U. Mass
Andrea Foulkes

NCI
Mary Carrington
Fuh-Mei Duh
Maureen P. Martin

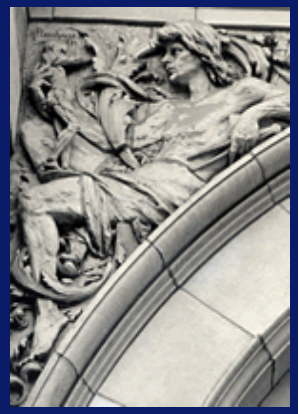
University of Pennsylvania
Una O'Doherty
Angela Mexas
Susan Ellenberg
CFAR Cores

BD BioSciences
Skip Maino
Maria Suni

Jonathan Lax Immune Disorder Clinic
Angela Kapalko
Karam Mounzer
Jane Shull
& Clinical Research Staff

University of Nebraska
Qingsheng Li

NIAID, NIH
The Philadelphia Foundation
Commonwealth of Pennsylvania
Genentech/Roche
Merck



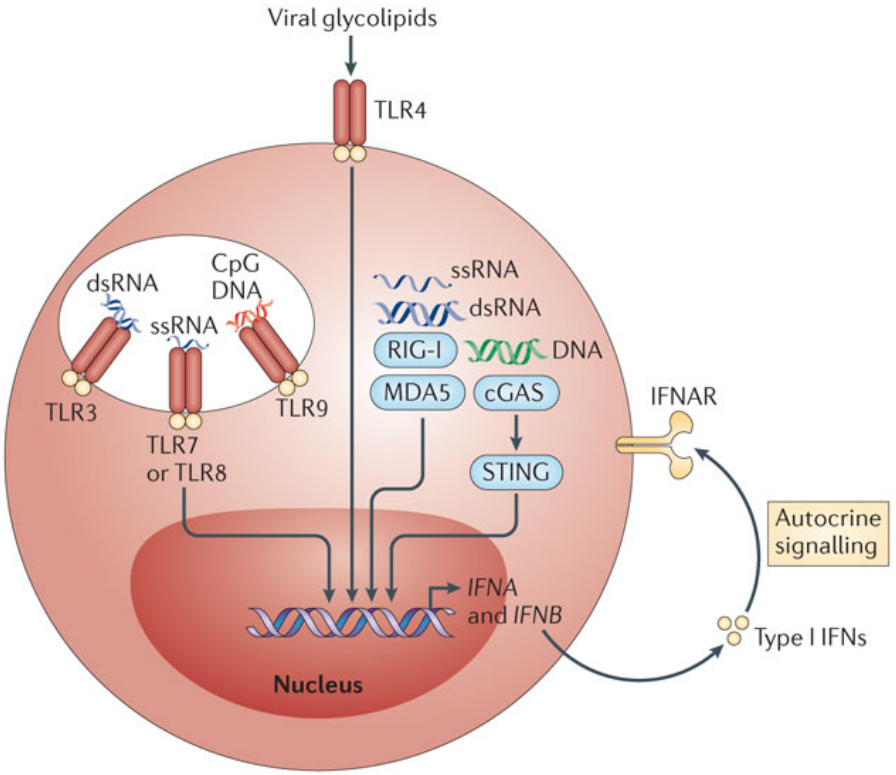
THE WISTAR INSTITUTE

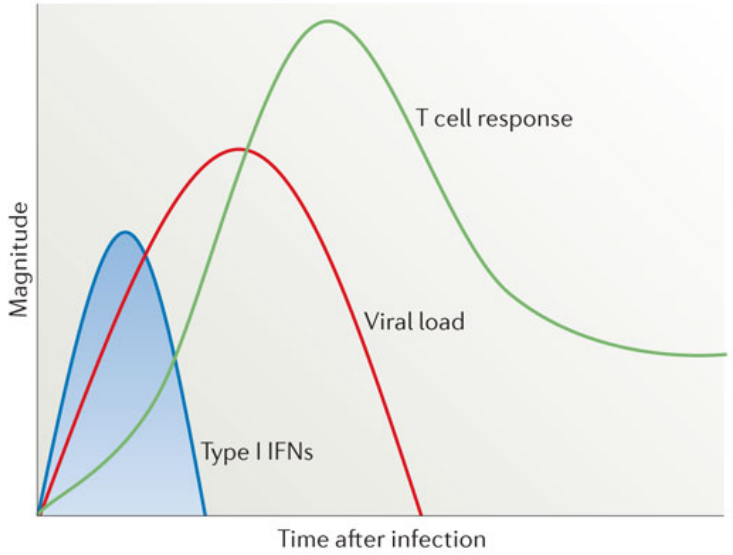
THANK YOU!

NCT00594880: Baseline characteristics

	180mcg-dose arm (n=12)	90mcg-dose arm (n=11)	p value
Age (years)			0.484
mean (sd)	44.8(6.8)	42.2(10.3)	
median(25%,75% quartiles)	45.5(42.8,48.5)	44(32,49.5)	
CD4 T cell count (cells/ mm^3)			
mean (sd)	962(352.8)	814.5(333.5)	0.315
median (25%,75% quartiles)	945(714.8,1210.8)	829(581.5,891.5)	
Gender			0.59
female	3(25%)	1(9.1%)	
male	9(75%)	10(90.9%)	
Race			0.214
African American	9(75%)	5(45.5%)	
Caucasian	3(25%)	6(54.5%)	
IL28 Genotype			1
CC	5(41.7%)	4(36.4%)	
CT	4(33.3%)	5(45.5%)	
TT	3(25%)	2(18.2%)	

Type I Interferons are early antiviral products following viral infection

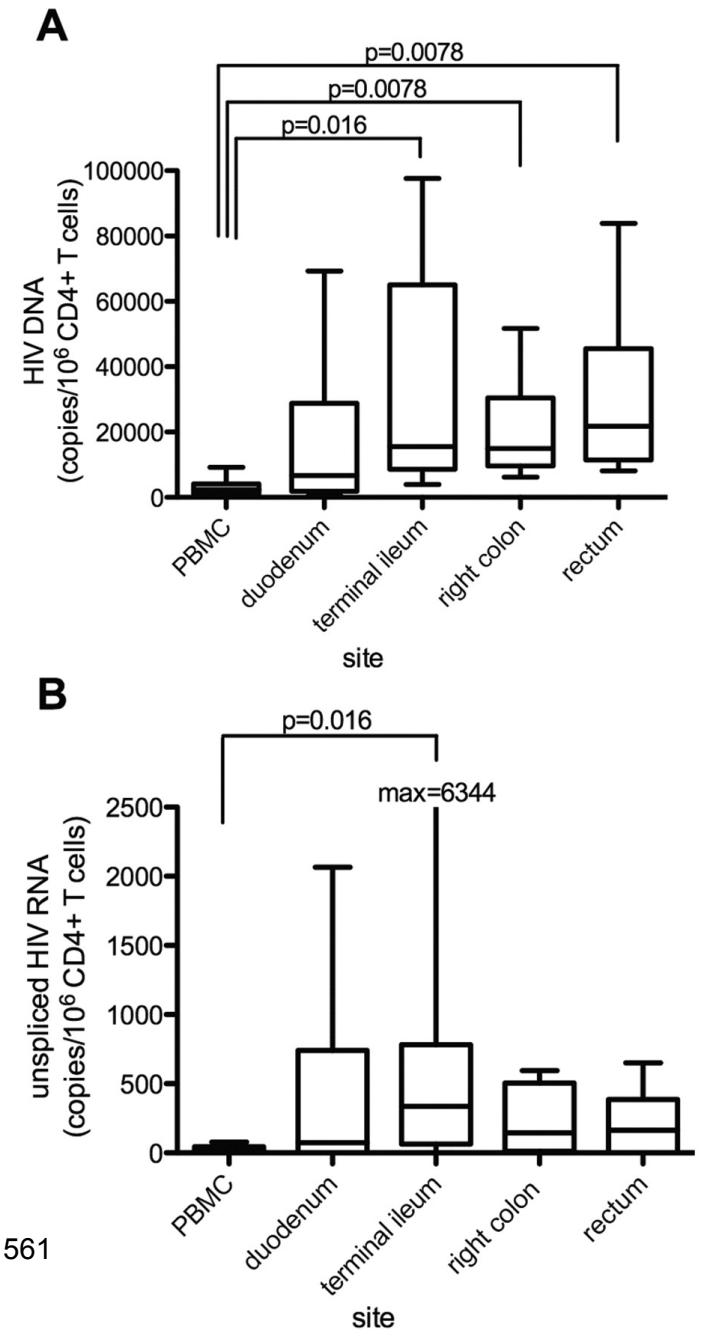




Nature Reviews | Immunology

Crouse J, Kalinke U, and Oxenius A. Regulation of antiviral T cell responses by type I interferons. Nature Reviews Immunology 2015;15(231–242).

The Journal of Infectious Diseases



Yukl S A et al. J Infect Dis. 2010;202:1553-1561