



Martin Delaney Collaboratory

Pediatric Adolescent Virus Elimination



**Elizabeth Glaser
Pediatric AIDS Foundation**
Fighting for an AIDS-free generation

www.pedaids.org

E2A: Approaching a Cure for Pediatric HIV

Cure research is here – Dr. Lynne Mofenson, EGPAF-Global

What is PAVE: A global landscape of the goals, the membership, and the trials occurring all over the world - Dr. Deborah Persaud, Johns Hopkins Bloomberg School of Public Health

Current trends in data: Broadly neutralizing antibodies and animal models – Dr. Mark Cotton, Tygerberg Children’s Hospital (TCH), Stellenbosch University (SU), South Africa

Informed and empowered: How youth feel about the movement toward cure – Josephine Nabukenya, EGPAF Board Member and Youth Advocate

Community Advocate: Reflections of a mother and long-time pediatric cure advocate – Martha Sichone-Cameron, EGPAF and Executive Director for International Community of Women Living with HIV (North America Region)

Discussion – moderated by Dr. Lynne Mofenson

Connecting

- Everyone is muted automatically, but all are welcomed to engage at any point during the webinar
- Feel free to ask questions through the Q&A box (bottom of screen) as they come to mind, we will get to all questions at the end
- This is being livestreamed/recorded and it will be shared
- If you have any connectivity issues, chat with Sarah Dennison-Johnson or Cosette Audi through the chat box, or email publications@pedaids.org





Pediatric Cure Research is Here

Lynne M Mofenson MD

Senior HIV Technical Advisor

Elizabeth Glaser Pediatric AIDS Foundation



Why is NOW the Time for Pediatric Cure?

What is New Since the Mississippi Baby?

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.

N Engl J Med 2013;369:1828-35.

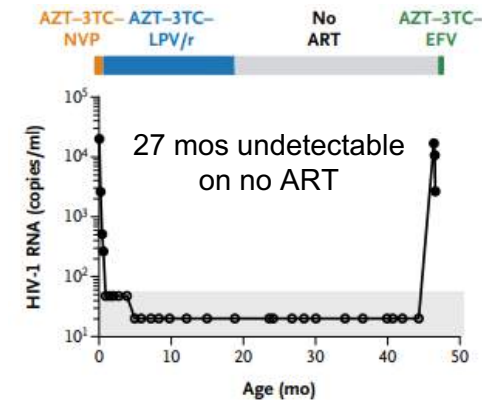


The NEW ENGLAND JOURNAL of MEDICINE

Viremic Relapse after HIV-1 Remission in a Perinatally Infected Child

Katherine Luzuriaga, M.D. et al.

N ENGL J MED 372;8 NEJM.ORG FEBRUARY 19, 2015



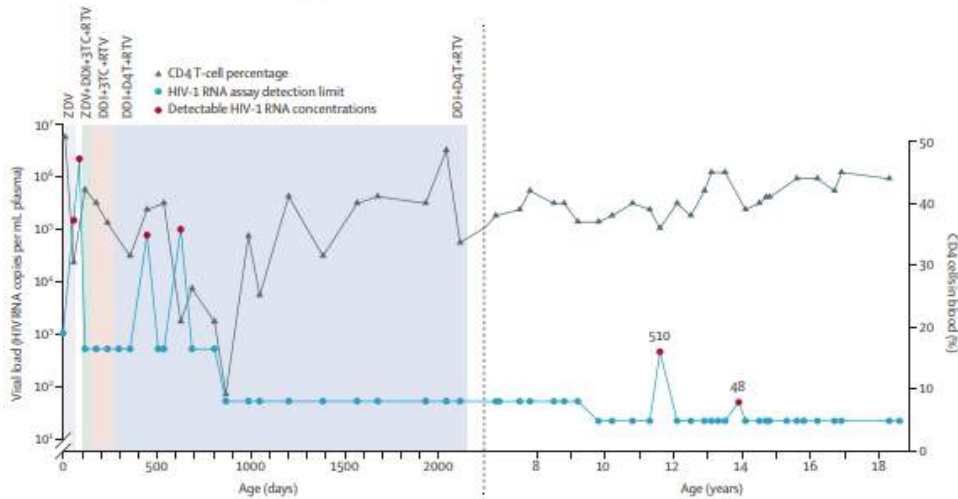
Several Additional Cases of HIV Remission With Very Early ART in Perinatal HIV Infection Have Been Reported

Lancet HIV 2016; 3: e49-54

HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report



Pierre Frange, Albert Foye, Véronique Avettand-Fenoël, Erianna Bellaton, Diane Descamps, Mathieu Angin, Annie David, Sophie Caillat-Zucman, Gilles Peytavin, Catherine Dollfus, Jerome Le Chenadec, Josiane Warszawski, Christine Rouzioux, Asier Sáez-Gnón, on behalf of the ANRS EPF-CO10 Pediatric Cohort and the ANRS EP47 VISCONTI study group



Hope of post-treatment control after perinatal infection?

Pages e6-e8. Rabie, Helena, and Cotton, Mark F.

Most adults and children with HIV require lifelong antiretroviral therapy (ART), although notable exceptions exist. Elite controllers, with a favourable genetic profile, do not need ART for many years, and post-treatment controllers, who began ART...

NATURE COMMUNICATIONS | (2019)10:412 |



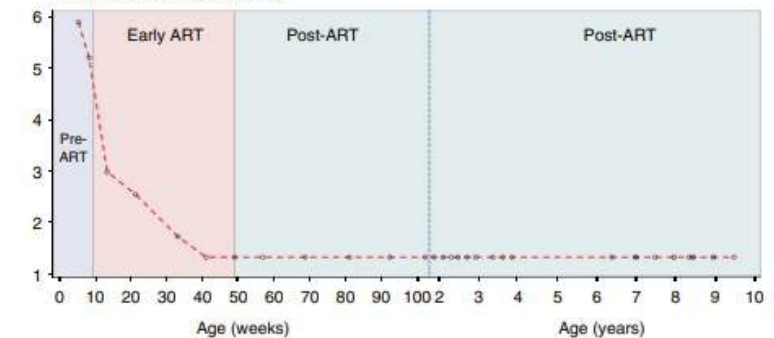
ARTICLE

<https://doi.org/10.1038/s41467-019-08351-0> OPEN

A child with perinatal HIV infection and long-term sustained virological control following antiretroviral treatment cessation

Avy Violari¹, Mark F. Cotton², Louise Kuhn³, Diana B. Schramm^{4,5}, Maria Paximadis^{4,5}, Shayne Loubser^{4,5}, Sharon Shalekoff^{4,5}, Bianca Da Costa Dias^{4,5}, Kennedy Otwombe¹, Afaaf Liberty¹, James McIntyre^{6,7}, Abdel Babiker⁸, Diana Gibb⁹ & Caroline T. Tiemessen^{4,5}

Viral load (log₁₀ copies per mL)



www.thelancet.com/hiv Vol 3 January 2016

Very Early ART – at Time of Diagnosis - is Now Standard of Care for Newly Diagnosed Infants and Children with HIV

→ Very early ART in infants is life-saving...

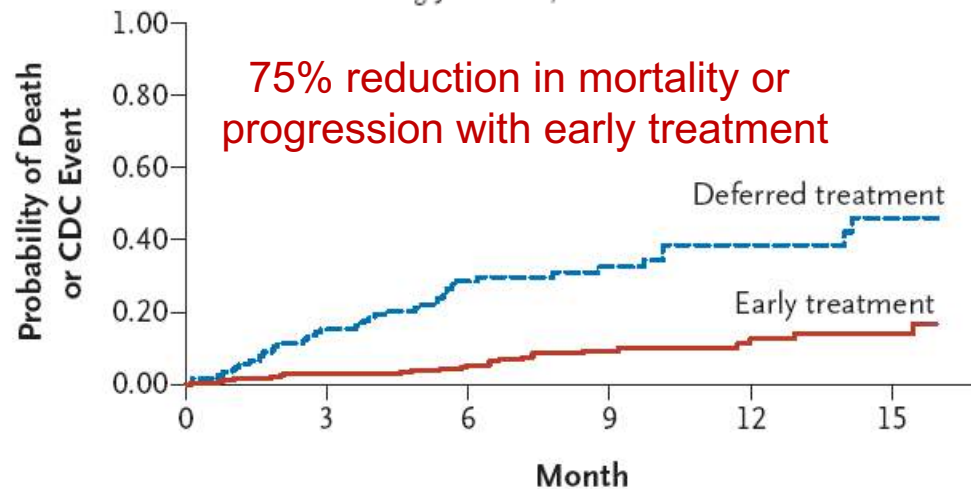
→ ...and is now recommended by WHO, US, and other guidelines

ORIGINAL ARTICLE

Early Antiretroviral Therapy and Mortality among HIV-Infected Infants

Avy Violari, F.C.Paed., Mark F. Cotton, M.Med., Ph.D., Diana M. Gibb, M.D., Abdel G. Babiker, Ph.D., Jan Steyn, M.Sc., Shabir A. Madhi, F.C.Paed., Ph.D., Patrick Jean-Philippe, M.D., and James A. McIntyre, F.R.C.O.G., for the CHER Study Team*

N Engl J Med 2008;359:2233-44.



4.4 When to start ART



Recommendations (2016)

ART should be initiated for all people living with HIV regardless of WHO clinical stage and at any CD4 cell count.

- Adults (*strong recommendation, moderate-certainty evidence*)
- Pregnant and breastfeeding women (*strong recommendation, moderate-certainty evidence*)
- Adolescents (*conditional recommendation, low-certainty evidence*)
- Children living with HIV one year old to less than 10 years old (*conditional recommendation, low-certainty evidence*)
- **Infants diagnosed in the first year of life (*strong recommendation, moderate-certainty evidence*).**

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3).

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection



Developed by the HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Panel's Recommendations

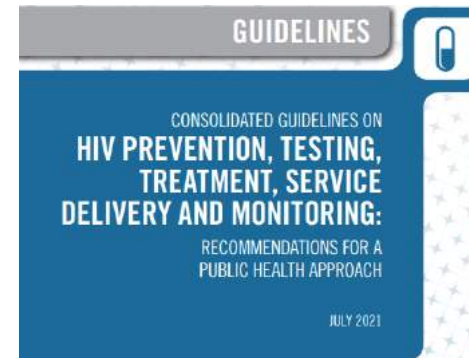
- Antiretroviral therapy (ART) should be initiated in all infants and children with HIV infection (**AI** for children aged <3 months, **AI*** for older children).
- **Rapid ART initiation (defined as initiating ART immediately or within days of diagnosis), accompanied by a discussion of the importance of adherence, and provision of subsequent adherence support is recommended for all children with HIV.**



HIV Diagnosis at Birth is Feasible and Being Implemented Even in Low-and-Middle Income Settings

→ Studies by EGPAF and others have shown point-of-care early infant diagnosis is feasible, acceptable, and cost-effective in LMIC...

→ ...and is now recommended for infant diagnosis by WHO



Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: an observational study in eight African countries



Flavia Bianchi¹, Jennifer Cohn², Emma Sacks, Rebecca Bailey, Jean-Francois Lemaire, Rhoderick Machekeano, on behalf of the EGPAF POC EID Study Team¹
Lancet HIV 2019; 6: e373-81

Bocke CE, et al. *Journal of the International AIDS Society* 2021; 24:e25677
<http://onlinelibrary.wiley.com/doi/10.1002/jia2.25677> | <https://doi.org/10.1002/jia2.25677>



Impact of Routine Point-of-Care Versus Laboratory Testing for Early Infant Diagnosis of HIV: Results From a Multicountry Stepped-Wedge Cluster-Randomized Controlled Trial

Emma Sacks, PhD,^{a,b,*} Jennifer Cohn, MD, MPH,^{c,*} Bernard Ochuka, MPH,^d Hauravi Mafaune, MPH,^e Admore Chudambuka, PhD,^f Collins Odhiambo, PhD,^{g,h} Rose Masaba, MD,ⁱ George Githuka, MBChB,^g Agnes Mahomva, MBChB, MPH,^h Angela Mushavi, MBChB, MMed,^h Jean-Francois Lemaire, MSc,^c Flavia Bianchi, MSc,^b and Rhoderick Machekeano, PhD, MPH^h

J Acquir Immune Defic Syndr • Volume 84, Supplement 1, July 1, 2020

RESEARCH ARTICLE

Point-of-care testing can achieve same-day diagnosis for infants and rapid ART initiation: results from government programmes across six African countries

Caroline E Bocke^{1,a}, Jessica Joseph^{1,a}, Melody Wang¹, Zelalem M Abate², Charles Atem³, Khady Diatou Coulibaly⁴, Adiou Kaborde⁵, Brianlin Klerman⁶, Leonard Kingwara⁷, Phisoan Mangwendza⁷, Talenda Maparo⁷, Rose Nadesge Mbaye⁸, Solomon Mukungungwa⁹, Catherine Nguju¹⁰, Divine Nzubuzantare¹, Marie Claire Okomo Assoumou¹¹, Yvensiach Reta¹, Barbara Wambugi⁶, Maria R Ricja¹, Trevor Peter¹, Naoko Doi¹, Lara Vojnovic², Shaikat Khan¹², and Jillian A Sacks¹

“We Need it the Same Day”: A Qualitative Study of Caregivers and Community Members’ Perspectives Toward the Use of Point-of-Care Early Infant Diagnosis

Leila Kutirayi, PhD,^a Bernard Ochuka, MPH,^a Hauravi Mafaune, MPH,^a Admore Chudambuka, MPH,^a Theresa Baffour, MPH,^a and Emma Sacks, PhD^a

J Acquir Immune Defic Syndr • Volume 84, Supplement 1, July 1, 2020

RESEARCH ARTICLE

The cost-effectiveness of scaling-up rapid point-of-care testing for early infant diagnosis of HIV in southern Zambia

Gatien De Broucker¹, Phillip P. Salvatore², Simon Mutembo³, Nkumbula Moyo⁴, Jane N. Mutanga⁵, Philip E. Thuma⁶, William J. Moss^{1,2}, Catherine G. Sutcliffe^{1,2,*}

PLOS ONE | <https://doi.org/10.1371/journal.pone.0248217> March 9, 2021



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HIV Treatment at Birth is Feasible and Being Implemented Even in Low-and-Middle Income Settings

→ HIV treatment of neonates is possible and being implemented...

→ ...and more potent antiretroviral drugs becoming available for newborns

Boeke CJ, et al. *Journal of the International AIDS Society* 2021; 24:e25677
<https://onlinelibrary.wiley.com/doi/10.1002/jia2.25677> | <https://doi.org/10.1002/jia2.25677>



RESEARCH ARTICLE

Point-of-care testing can achieve same-day diagnosis for infants and rapid ART initiation: results from government programmes across six African countries

Caroline F Boeke^{1*}, Jessica Joseph^{1*}, Melody Wang¹, Zetalem M Abate², Charles Atem³, Khady Diatou Coulibaly⁴, Adisu Kibede⁵, Brianan Kieman⁶, Leonard Kingwara⁷, Phibon Mangwendzi⁸, Tatenda Muparo⁹, Rose Nadege Mbatya¹⁰, Solomon Mukungunwa¹⁰, Catherine Ngu¹¹, Divine Nwabontare¹², Marie Claire Okomo Assoumou¹¹, Yemsiach Reta¹³, Barbara Wambugi¹⁴, Maria R Rijsa¹, Trevor Peter¹, Naoko Doi¹, Lara Vojnov¹, Shaikat Khan¹⁵ and Jillian A Sacks¹

Conclusions: Same-day diagnosis and treatment initiation for infants is possible with POC EID within routine government-led and -supported public sector healthcare facilities in resource-limited settings. Given that POC EID allows for rapid ART initiation, aligning to the World Health Organization's recommendation of ART initiation within seven days, its use in public sector programmes has the potential to reduce overall mortality for infants with HIV through early treatment initiation.

Clinical Infectious Diseases
 MAJOR ARTICLE



Safety and Efficacy of Starting Antiretroviral Therapy in the First Week of Life

Kenneth Mwaniki^{1*}, Chikako Ajikoh¹, Kara Bennett², Edmond V Capparelli³, Patrick Jean-Philippe⁴, Sikulile Moyo⁵, Terence Mohamed¹, Opone Belfrage⁶, Maureen Sabo⁷, Shalin Lockman^{1,8}, Joseph Makhele⁹, Mathias Lichtenfels¹⁰, Daniel R. Kaitoko¹¹, Michael D. Hughes¹², and Hugo L Shapiro¹³

Clinical Infectious Diseases[®] 2021;72(3):388-93



A Health Literate Patient-focused Approach to the Redesign of the Raltegravir (ISENTRRESS) Pediatric Kit and Instructions for Use

Alexander Mills, BSME,^{*} Laurie Myers, MBA,[†] Casey Raudenbush, MSN,[‡] David A. Vossen, BS,^{*} Hedy Teplitz, MD,[§] Yanna R. Miteva, MD,[¶] Suzanne Seeley, MS,^{||} Brenda Homony, MS,^{**} and Walter L. Straus, MD,[‡]

The Pediatric Infectious Disease Journal • Volume 41, Number 1, January 2022



CLINICAL SCIENCE

Optimizing Dolutedegravir Initiation in Neonates Using Population Pharmacokinetic Modeling and Simulation

Joseph Piscitelli, PharmD,^a Mina Nikanjam, MD, PhD,^a Brookie M. Best, PharmD,^a Edward Acosta, PharmD,^b Mark Mirochnick, MD,^c Diana F. Clarke, PharmD,^d Edmund V. Capparelli, PharmD,^a and Jeremiah D. Momper, PharmD, PhD^e

Clinical Infectious Diseases

MAJOR ARTICLE



ART Initiation for Infants Diagnosed With HIV Through Point of Care and Conventional Polymerase Chain Reaction Testing in Kenya: A Case Series

Catherine Weisler, MPH,^{*} May Maloba, KECHN/KRCHN, MS,[†] Kathy Goggins, PhD,^{‡,§} Shadrack Babu Kale, BA,[¶] Nicodemus Maosa, RCO,^{||} Elizabeth Muchoki,[¶] Melinda Brown, MSPH,^{**} Brad Gauvey, PNP, MPH,^{||} and Sarah Finocchiaro-Kessler, MPH, PhD[§]

The Pediatric Infectious Disease Journal • Volume 40, Number 4, April 2021

Clinical Infectious Diseases

BRIEF REPORT

Single Dose Abacavir Pharmacokinetics and Safety in Neonates Exposed to Human Immunodeficiency Virus (HIV)

Adrie Bekker,¹ Eric H. DeCloudt,² Gretchen Slade,³ Mark F. Cotton,⁴ Helena Rabie,¹ and Tim R. Cressley^{4,5}

CID 2021:72 (1 June) • BRIEF REPORT

Significant Patient Impact Observed Upon Implementation of Point-of-Care Early Infant Diagnosis Technologies in an Observational Study in Malawi

Reuben Mwenda,¹ Youyi Fong,² Turmon Majombo,² Emmanuel Saka,⁴ Daliso Midiani,¹ Christopher Mwase,² James Kandula,¹ Melody Wang,² Rachel Thomas,² Judith Sherman,⁴ and Lara Vojnov¹

Clinical Infectious Diseases[®] 2018;67(5):701-17

Conclusions. ART initiation rates were significantly improved with the implementation of same-day POC EID testing compared with referred, longer-turnaround laboratory-based testing.

Very Early Treatment Reduces the Viral Reservoir

The Journal of Infectious Diseases

MAJOR ARTICLE



Early Initiation of Antiretroviral Therapy Following In Utero HIV Infection Is Associated With Low Viral Reservoirs but Other Factors Determine Viral Rebound

Jane R. Miller,^{1,2,6} Nonnede Bange,² Viscicus A. Vieira,² Emily Alland,² Julia Roider,^{1,2,4,5} Maximilian Muenchhoff,^{5,7} Rowena Filia,² Kenneth Sprenger,² Vuyokazi Ntanzana,⁸ Isabella Fati,⁹ Mahendran Archary,⁹ Andreas Groll,¹⁰ Nasreen Ismail,¹¹ Maria C. Garcia-Guerrero,¹¹ Philippa C. Matthews,^{12,13,14} Thandi Ntungwa,^{1,4,15,16,17} Maria C. Paetats,¹⁸ Javier Martinez-Picado,^{19,20,21,22} and Philip Goulder,^{7,23,24}

JID 2021:224 (1 December) •

Payne et al. *AIDS Res Ther* (2021) 18(6)
<https://doi.org/10.1186/s12981-021-00389-1>

AIDS Research and Therapy

RESEARCH

Open Access

Early ART-initiation and longer ART duration reduces HIV-1 proviral DNA levels in children from the CHER trial

Helen Payne,^{1,5,6*} Man K. Chan,⁷ Sarah A. Watters,^{2,3} Kennedy Otwombe,⁴ Nei-Yuan Hsiao,⁶ Abdel Babiker,⁷ Avy Violari,⁴ Mark F. Cotton,⁵ Diana M. Gibb,⁷ and Nigel J. Klein,¹

Clinical Infectious Diseases

MAJOR ARTICLE



Continuous Prophylactic Antiretrovirals/Antiretroviral Therapy Since Birth Reduces Seeding and Persistence of the Viral Reservoir in Children Vertically Infected With Human Immunodeficiency Virus

Marta Massanella,^{1,2} Thanyawee Puthanakit,^{2,3,4} Louise Lape,⁵ Thidarat Japirai,⁶ Paradee Sawangsiadhi,⁶ Mark de Souza,⁷ Piyarat Sutarattiwong,⁸ Pepee Kasalanka,⁹ Thitiporn Barkind,⁹ Sagarat Kasjanavanit,⁹ Rukkaeya Chokphairikit,⁹ Rawiwan Hansudewechakul,¹⁰ Wittaya Petchchai,¹¹ Julie L. Mitchell,^{12,13} Merlin L. Robb,^{12,13} Lydie Trautman,^{14,15} Jintana Ananworanich,^{16,17,18} and Nicolas Chomont,¹⁹ for the RV175/HIVNET184 and RV45/HIVNET 299 Study Groups

CID 2021:73 (

Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE



The CARMA Study: Early Infant Antiretroviral Therapy—Timing Impacts on Total HIV-1 DNA Quantitation 12 Years Later

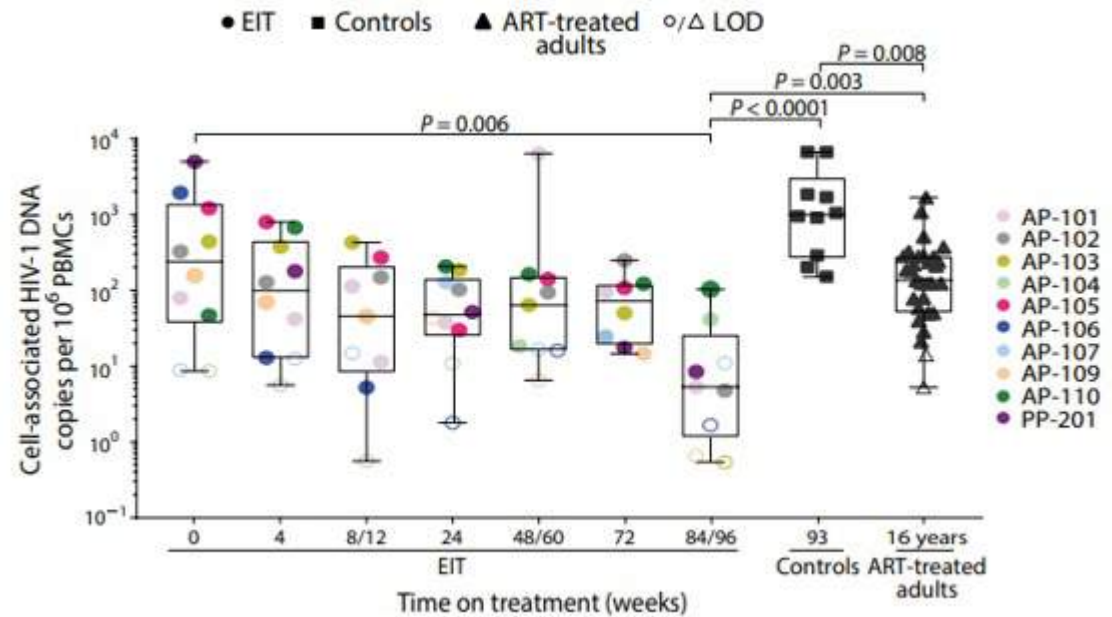
Caroline Foster,¹ Sara Dominguez-Rodriguez,^{2,3} Alfredo Tagarro,^{2,3} Triantafylia Gkouleli,⁴ Judith Heaney,^{2,4} Sarah Watters,¹ Alasdair Bamford,^{1,4} Katy Fidler,⁵ Marisa Navarro,⁶ Anita De Rossi,⁶ Paolo Palma,⁶ Eleni Nastouli,⁶ Paolo Rossi,⁶ Carlo Giaquinto,⁷ and Pablo Rojo,⁸ for the Early Treated Perinatally HIV Infected Individuals: Improving Children's Actual Life (EPIICAL) Consortium

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

Early antiretroviral therapy in neonates with HIV-1 infection restricts viral reservoir size and induces a distinct innate immune profile

Pilar Garcia-Broncano,¹ Shivaali Maddali,¹ Kevin B. Einkauf,^{1,2} Chenyang Jiang,^{1,2} Ce Gao,¹ Joshua Chevalier,^{1,2} Fatema Z. Chowdhury,¹ Kenneth Maswabi,³ Gbolahan Ajibola,³ Sikhulile Moyo,³ Terence Mohammed,³ Thabani Ncube,³ Joseph Makhema,³ Patrick Jean-Philippe,⁴ Xu G. Yu,^{1,2,5} Kathleen M. Powis,^{3,5,6,7} Shahin Lockman,^{2,3,5} Daniel R. Kuritzkes,^{2,5} Roger Shapiro,^{3,5,7} Mathias Lichterfeld,^{1,2,5*}



EIT: Early Infant Treatment study, diagnosed age <24 hours with FU through 96 wks
 Control: started ART at median age 4 months, blood samples at 93 weeks



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Immune Adjuncts to Treatment Are Being Studied in Neonates and in Infected Infants

The Journal of Infectious Diseases

MAJOR ARTICLE



The Journal of Infectious Diseases

MAJOR ARTICLE



Safety, Tolerability, and Pharmacokinetics of a Long-Acting Broadly Neutralizing Human Immunodeficiency Virus Type 1 (HIV-1) Monoclonal Antibody VRC01LS in HIV-1-Exposed Newborn Infants

Elizabeth J. McFarland,¹ Coleen K. Cunningham,^{2,3} Petronella Muresan,³ Edmund V. Capparelli,⁴ Charlotte Perlowski,⁵ Patricia Morgan,^{2,3} Betsy Smith,⁶ Rohan Hazra,⁷ Lynette Purdue,⁸ Paul A. Harding,⁹ Gerhard Theron,⁹ Hilda Mujuru,¹⁰ Allison Agwu,¹¹ Murli Purswani,¹² Mubeen H. Rathore,¹³ Britta Flach,¹⁴ Alison Taylor,¹⁴ Bob C. Lin,¹⁴ Adrian B. McDermott,¹⁴ John R. Mascola,¹⁴ and Barney S. Graham¹⁴, for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1112 Team

JID 2021:224 (1 December) • McFarland et al



Safety, Tolerability, and Pharmacokinetics of the Broadly Neutralizing Human Immunodeficiency Virus (HIV)-1 Monoclonal Antibody VRC01 in HIV-Exposed Newborn Infants

Coleen K. Cunningham,¹ Elizabeth J. McFarland,² R. Leavitt Morrison,³ Edmund V. Capparelli,⁴ Jeffrey T. Safrit,^{4,5} Lynne M. Mofenson,⁶ Bonnie Mathieson,^{6,8} Megan E. Valentine,⁷ Charlotte Perlowski,⁷ Betsy Smith,⁷ Rohan Hazra,⁷ Lynette Purdue,⁸ Petronella Muresan,^{8,11} Paul A. Harding,⁹ Tapiwa Mbengeranwa,¹⁰ Lisa-Gaye Robinson,¹⁰ Andrew Wiznia,¹⁴ Gerhard Theron,¹⁴ Bob Lin,¹⁴ Robert T. Baier,¹⁴ John R. Mascola,¹⁴ and Barney S. Graham¹⁴, for the IMPAACT P1112 team

JID 2020:222 (15 August) • Cunningham et al

EXTENDED SAFETY AND PK OF ANTI-HIV MONOCLONAL AB VRC07-523LS IN HIV EXPOSED INFANTS

00382

Coleen K. Cunningham¹, Edmund Capparelli², Elizabeth J. McFarland³, Petronella Muresan⁴, Charlotte Perlowski⁵, Dwight Yin⁶, Jack Moyer⁷, Sai Majji⁷, Lynette Purdue⁸, Paul A. Harding⁹, Adrian McDermott¹⁰, John R. Mascola¹⁰, Barney S. Graham¹⁰, for IMPAACT P1112 Team
¹UC Irvine, Irvine, CA; ²UC San Diego, San Diego, CA; ³U Colorado Anschutz Medical Campus, Aurora, CO; ⁴Statistical and Data Analysis Center/Frontier Science and Technology Research Foundation, Boston, MA; ⁵FHI 360, Durham, NC; ⁶NIAD, Bethesda, MD; ⁷NICHD, Bethesda, MD; ⁸NIAD, Baltimore, MD

SC VRC07-523LS is safe and well-tolerated when administered to neonates. VRC07-523LS, with its enhanced potency, rapid absorption, and slow elimination, can quickly achieve and maintain plasma levels >10 mcg/mL with dosing every 3 months.

TREATMENT WITH BROADLY NEUTRALIZING ANTIBODIES IN CHILDREN WITH HIV IN BOTSWANA

Roger L. Shapiro¹, Kenneth Maswabi², Gbolahan Ajibola², Michael Hughes¹, Molly Pretorius Holme¹, Kathleen M. Powis³, Sikhulile Moyo², Bryan S. Nelson¹, Marina Caskey⁴, Lucio Gama⁵, Patrick Jean-Philippe⁵, Dwight E. Yin⁵, Edmund Capparelli⁶, Daniel Kuntzkes⁷, Mathias Lichtenfeld⁸

- Recruited from Early Infant Treatment (EIT) cohort (all start ART <7 d)
- enrolled 28 EIT children at age 96 weeks and RNA <40 for ≥24 weeks prior to entry

Step 1: ART + dual bNAb (8-32 weeks)	Step2: Dual bNAbs alone (up to 24 weeks)	Step 3: bNAbs stopped and ART re-started
First 6 children: • 32 weeks of overlap while awaiting PK assessment of dual agent dosing	HIV RNA checked every 1-2 weeks	ART restarted if: • >400 copies/mL or • at 24 weeks
All subsequent children: • 8 weeks of overlap		

- Median age = 3.6 years (range 2.4, 5.6 years)
- Median CD4 count 1198 cells/mm³
- All were receiving lopinavir/ritonavir-based ART

- In this proof-of-concept study, dual bNAb treatment with VRC01LS and 10-1074 maintained viral suppression for 24 weeks in the absence of ART in 44% of children
- Newer bNAb combinations with greater breadth and potency, used in children with favorable pre-treatment characteristics and possibly with longer bNAb/ART overlap, may improve treatment success for this novel ART sparing strategy

Intravenous bNAb infusions every 4 weeks:

- VRC01LS: 30mg/kg IV load, 15 mg/kg IV every 4 weeks
- 10-1074: 30 mg/kg IV every 4 weeks



Elizabeth Glaser Pediatric AIDS Foundation
Fighting for an AIDS-free generation

Since the Mississippi baby first demonstrated that very early therapy can result in significant treatment-free remission of HIV:

- Very early diagnosis and treatment of infants has become standard of care globally
- Early treatment even with currently available lower potency regimens for neonates has been shown to significantly reduce the latent viral reservoir
- New more potent treatments are becoming available for neonates
- Immune adjuvants to treatment (bnAbs) have been shown safe in neonates and young infants

It is time to harness the changing treatment landscape of very early ART, take advantage of the unique viral and immune aspects of perinatal infection and the results from very early ART studies to accelerate research on assessing and optimizing immune-based strategies for remission and cure in children with HIV



**What is PAVE: A
global landscape of
the goals, the
membership, and
the trials occurring
all over the world**

- Dr. Deborah
Persaud, Johns Hopkins
University School of
Medicine



The Pediatric Adolescent Virus Elimination (PAVE) MDC

Deborah Persaud, MD

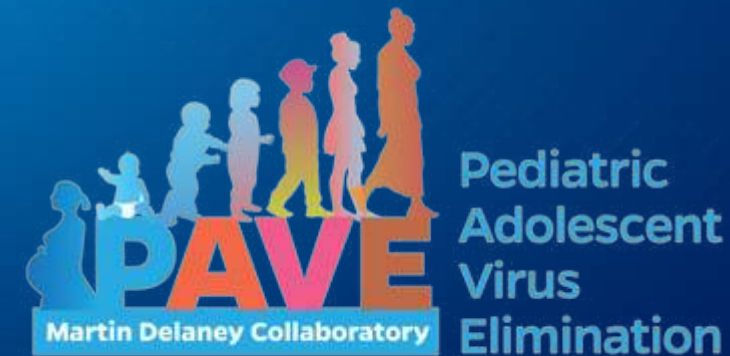
Johns Hopkins University School of Medicine

Ann Chahroudi, MD, PhD

Emory University

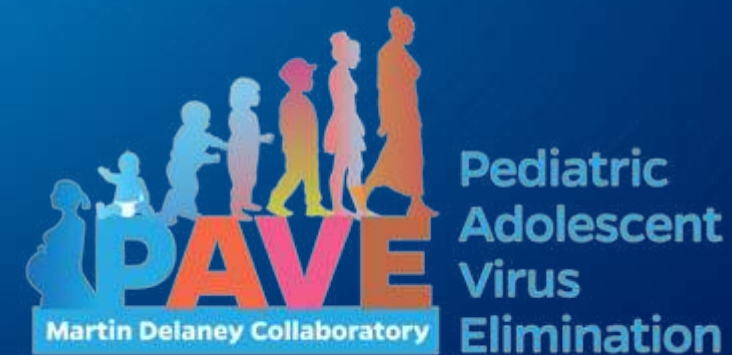
E2A Webinar

March 16th, 2022



A Tribute

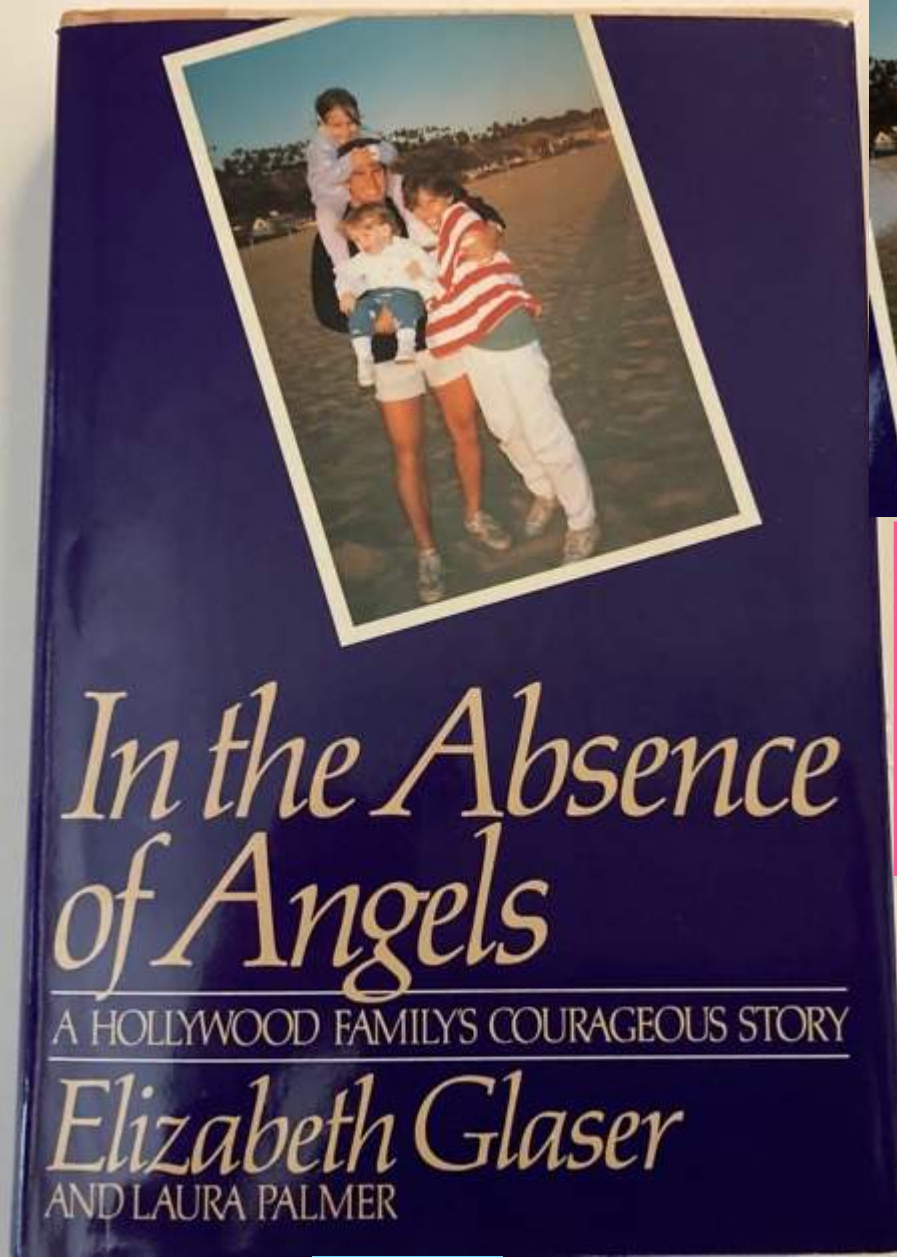
Elizabeth Glaser and the Foundation



A Tribute



ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION
www.pedais.org



So here we are, the all-American, happy beautiful family blown apart. It is as if a hurricane came through our house and nothing was spared except Paul. All the lights are out and nothing is in the right place. Who will straighten it out? I know I have to but I don't know where to begin. If I give up today and they find a cure for AIDS tomorrow, that would be tragic. I have to fight this war against time with every ounce of strength I have. Maybe this won't all end tragically. Maybe they will find a cure or at least a stabilizing drug.



2021

2005
GLASER PEDIATRIC AIDS FOUNDATION AWARD GOES TO HOPKINS SCIENTIST DEBORAH PERSAUD

2014



1991

HIV-1 Cure Research

- Current antiretroviral treatment (ART) is highly effective in sustaining HIV-1 replication to clinically undetectable plasma viral loads for years (decades).
- But, does not lead to virus eradication and cure
- Immediate establishment of HIV-1 infection in long-lived resting, memory CD4+ T cells
 - intact proviruses are non-expressed
 - cannot be targeted by conventional ART or host immune responses
 - can be reactivated to produce infectious virus
 - permitting a lifetime of viral persistence
 - rendering ART lifelong
- Discovery of effective immuno-therapeutics may circumvent lifelong ART, its toxicities and stigma (goal of HIV-1 remission and cure therapeutics)

The Latent HIV-1 Reservoir

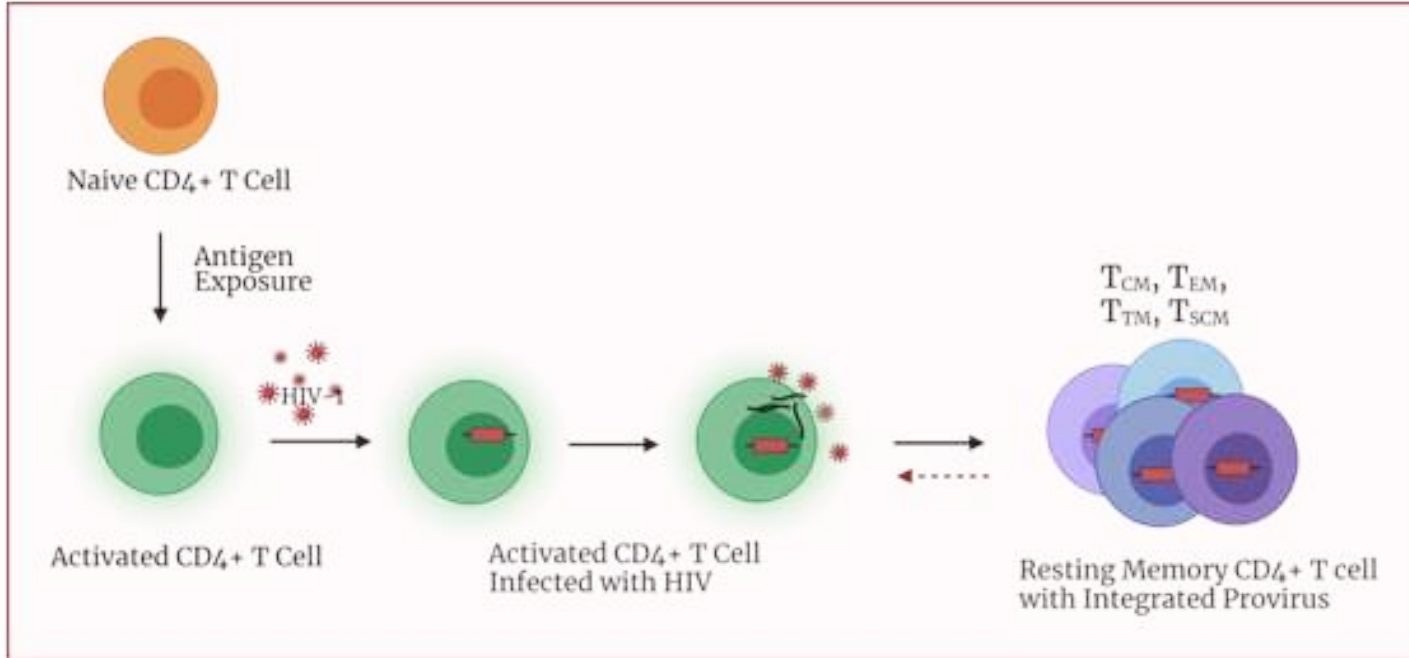
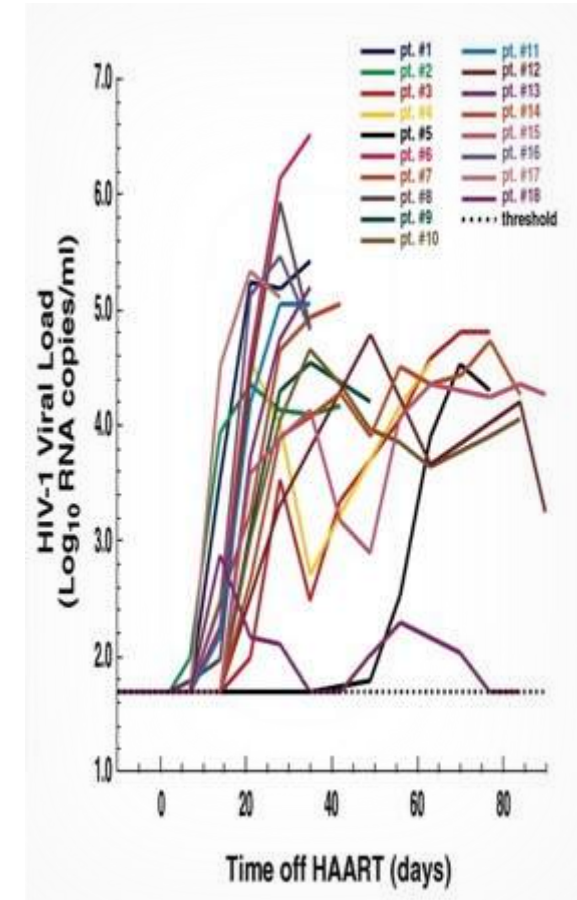


Figure created with Biorender.com

Finzi D et al Science 1997; Wong JK et al Science 1997; Chun TW et al PNAS 1997; Persaud D et al JCI 2000; Blankson J et al Ann Int, Med 2002; Chomont N et al. Nat Med 2009



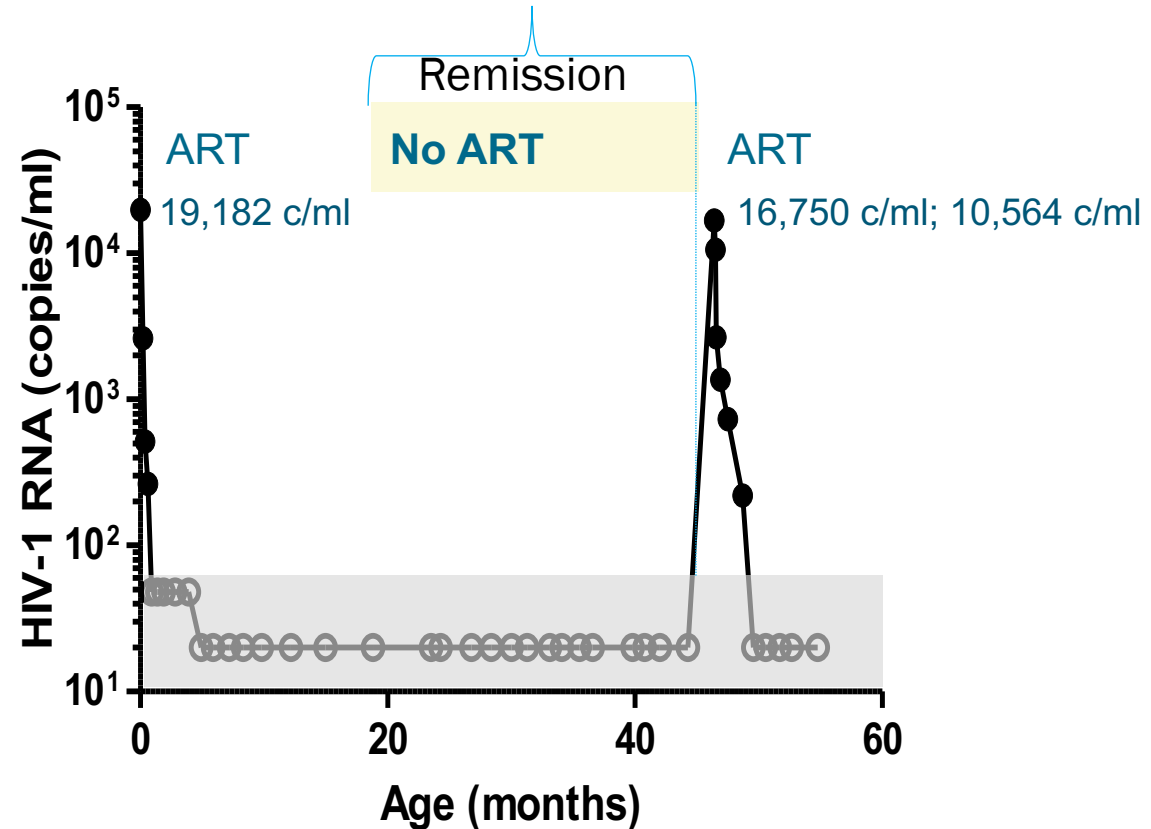
1999: ART for a median 2.2 years (mean rebound time 14 days)

Davey RT et al. PNAS 1999

Pediatric Case of ART-free Remission (2013)



“Mississippi Baby”
(2013; NEJM)



27 months of ART-free HIV Remission

PAVE: Pediatric Adolescent Virus Elimination Martin Delaney Collaboratory

Mission

To use cutting-edge science to establish a deep and broad understanding of the immunopathogenesis of pediatric HIV reservoirs, across the age spectrum,

AND

to demonstrate safety and efficacy of novel therapeutics to purge and control HIV/SIV reservoirs in nonhuman primates that will *pave* the way for future interventional human studies toward a lifetime of sustained HIV control off ART

Vision

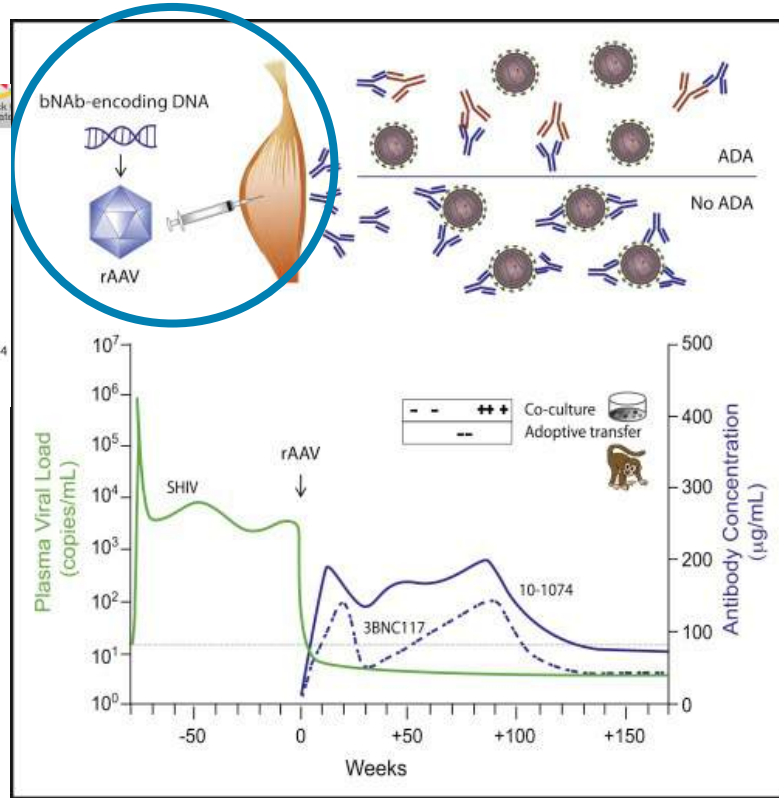
Sustained ART-free control of HIV replication in pediatric populations of different ages and ART durations will be possible with targeted approaches to eliminate reservoirs and/or combined with long-acting strategies to control viral rebound

Vector Technology for Delivery

Front. Immunol., 17 March 2020 | <https://doi.org/10.3389/fimmu.2020.00449>

Long-Term Delivery of an Anti-SIV Monoclonal Antibody With AAV

José M. Martínez-Navio^{1†}, Sebastian P. Fuchs^{1†}, Desiree E. Mendes¹, Eva G. Rakasz², Guangping Gao³, Jeffrey D. Lifson⁴ and Ronald C. Desrosiers^{1*}



The Miami Monkey

Presented at CROI 2020

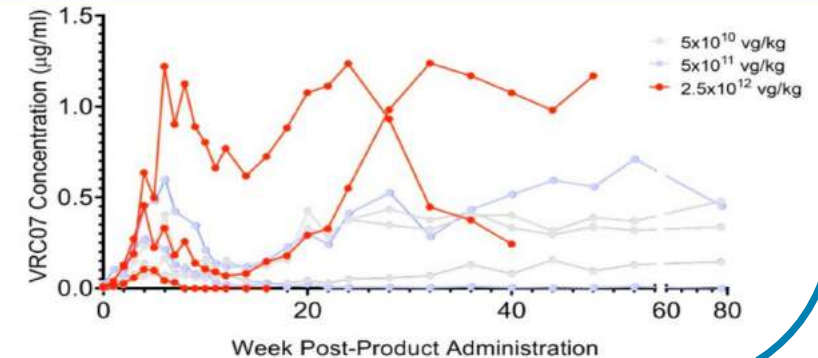
VRC 603

A Phase I Dose-Escalation Study of the Safety of **AAV8-VRC07** (VRC-HIVA070-00-GT) Recombinant AAV Vector Expressing VRC07 HIV-1 Neutralizing Antibody in Antiretroviral -Treated, HIV-1 Infected Adults With Controlled Viremia.

160 DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV8-MEDIATED GENE TRANSFER

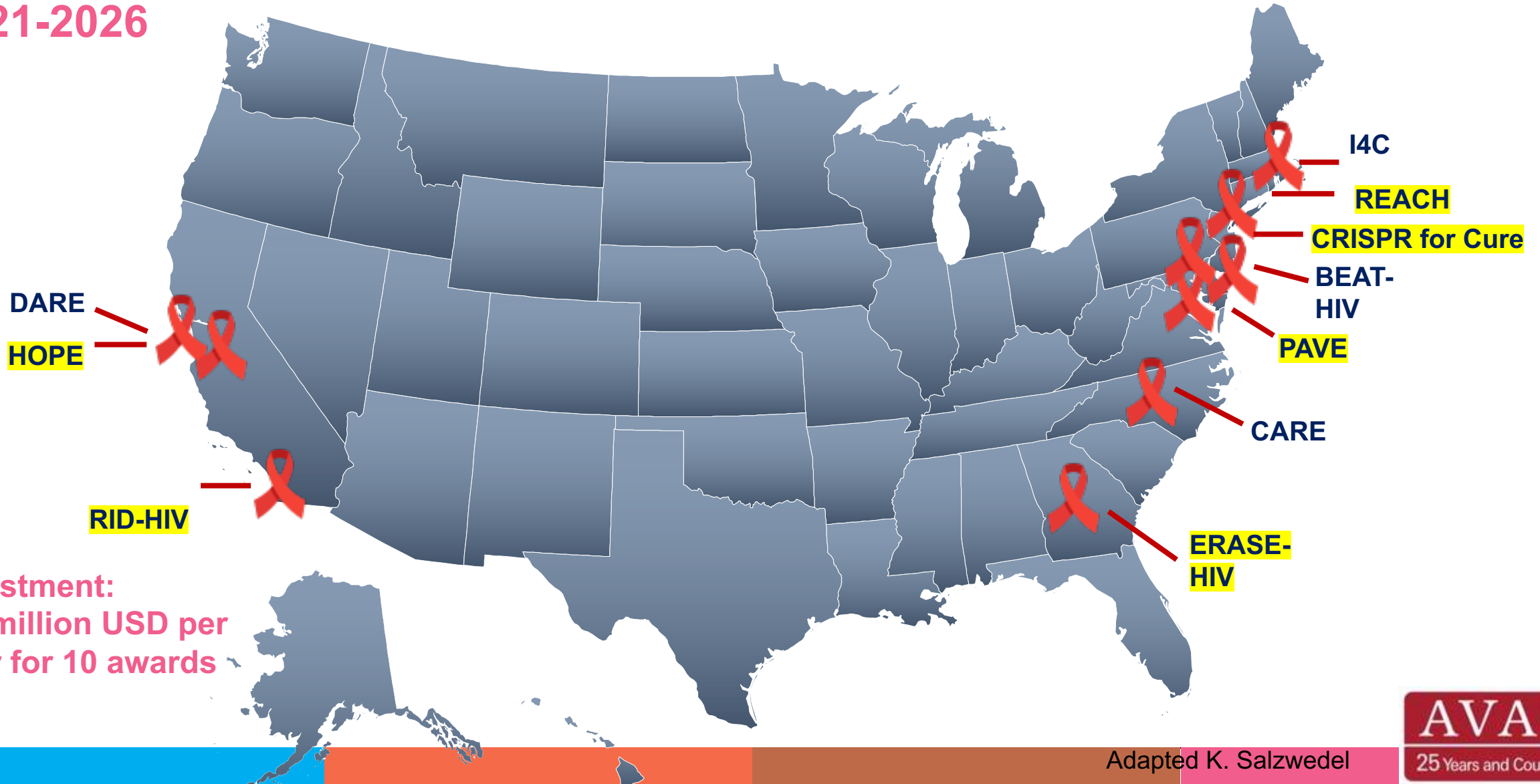
12:35 **Joseph P. Casazza**, Evan M. Cale, Sandeep Narपाला, Laura Novik, Galina V. Yamshchikov, Bob C. Lin, Janardan P. Pandey, Adrian McDermott, Mario R. Roederer, Alejandro Balazs, David Baltimore, Richard A. Koup, Julie E. Ledgerwood, John R. Mascola, for the VRC603 Team

Longitudinal Serum VRC07 Concentrations



Martin Delaney HIV Collaboratories

2021-2026



Investment:
53 million USD per
year for 10 awards

Adapted K. Salzwedel



PAVE MDC Team



• Oregon Primate Center/OHSU
Portland, OR
• Nancy Haigwood, PhD
• Ann Hessel, PhD

• University of Colorado
Boulder, CO
• Elizabeth McFarland, MD

• University of Kentucky
Lexington, KY
• Zachary Porterfield, MD

• University of Massachusetts
Worcester, MA
• Katherine Luzuriaga, MD

• Boston Children's Hospital (PVP)
Boston, MA
• Ofer Levy, MD, PhD

• Massachusetts General Hospital/ Ragon Institute
Boston, MA
• Mathias Lichterfeld, MD, PhD
• Roger Shapiro, MD
• Galit Alter, PhD

• National Institutes of Health
Bethesda, MD
• Mario Roederer, PhD
• Rick Koup, MD
• Joe Cassazaa, MD

• Johns Hopkins University
Baltimore, MD
• Deborah Persaud, MD
• Robert Siliciano, MD, PhD
• Janet Siliciano, PhD
• Francesco Simonetti, MD
• Adit Dhummakupt, PhD
• Winston Timp, PhD
• Alison Hill, PhD
• Allison Agwu, MD

• Weill Cornell Medical College
New York, NY
• Sallie Permar, MD, PhD

• Duke University
Durham, NC
• Genevieve Fouda, MD, PhD

• Emory University
Atlanta, GA
• Ann Chahroudi, MD, PhD
• Maud Mavigner, PhD

• Scripps Institute
Jupiter, FL
• Mauricio Martins, PhD
• Michael Farzan, PhD

• University of Miami
Miami, FL
• Savita Pahwa, MD
• Lesley deArmas, PhD

• Oxford University
Oxford, United Kingdom
• Philip Goulder, MA, FRCPCH,
Dphil, FMedSci

• Ospedale Pediatrico Bambino Gesù
Rome, Italy
• Paolo Palma, MD, PhD
• Nicola Cotugno, MDi

• Stellenbosch University
Stellenbosch, South Africa
• Mark Cotton, MD, PhD
• Barbara Laughton, MD
• Gert VanZyl, PhD
• Richard Glashoff, PhD

• University of the Witwatersrand
Johannesburg, South Africa
• Avy Violari, MD
• Caroline Tiemessen, PhD

• African Health Research Institute
Durban, South Africa
• Henrik Klooverpris, PhD



Project Goals

Aim 1: HIV-1 Reservoirs Biology

Define establishment & evolution of the HIV-1 latent reservoir in perinatal infection

Clinical cohorts & banked specimens

Aim 2: Eliciting HIV-1-specific Immunity

To enhance pediatric immunity & broadly neutralizing antibody (bNAb) delivery for HIV-1 post-ART control off ART

Human and infant NHP studies

Aim 3: Reservoir Elimination

Immune-targeted strategies to eliminate virus reservoirs

Infant NHP-pre-clinical testing

Aim 4: Quantifying HIV-1 Reservoirs and Immune Correlates

Optimize virologic, immunologic, & imaging methods to assess efficacy of HIV-1/S(H)IV cure interventions

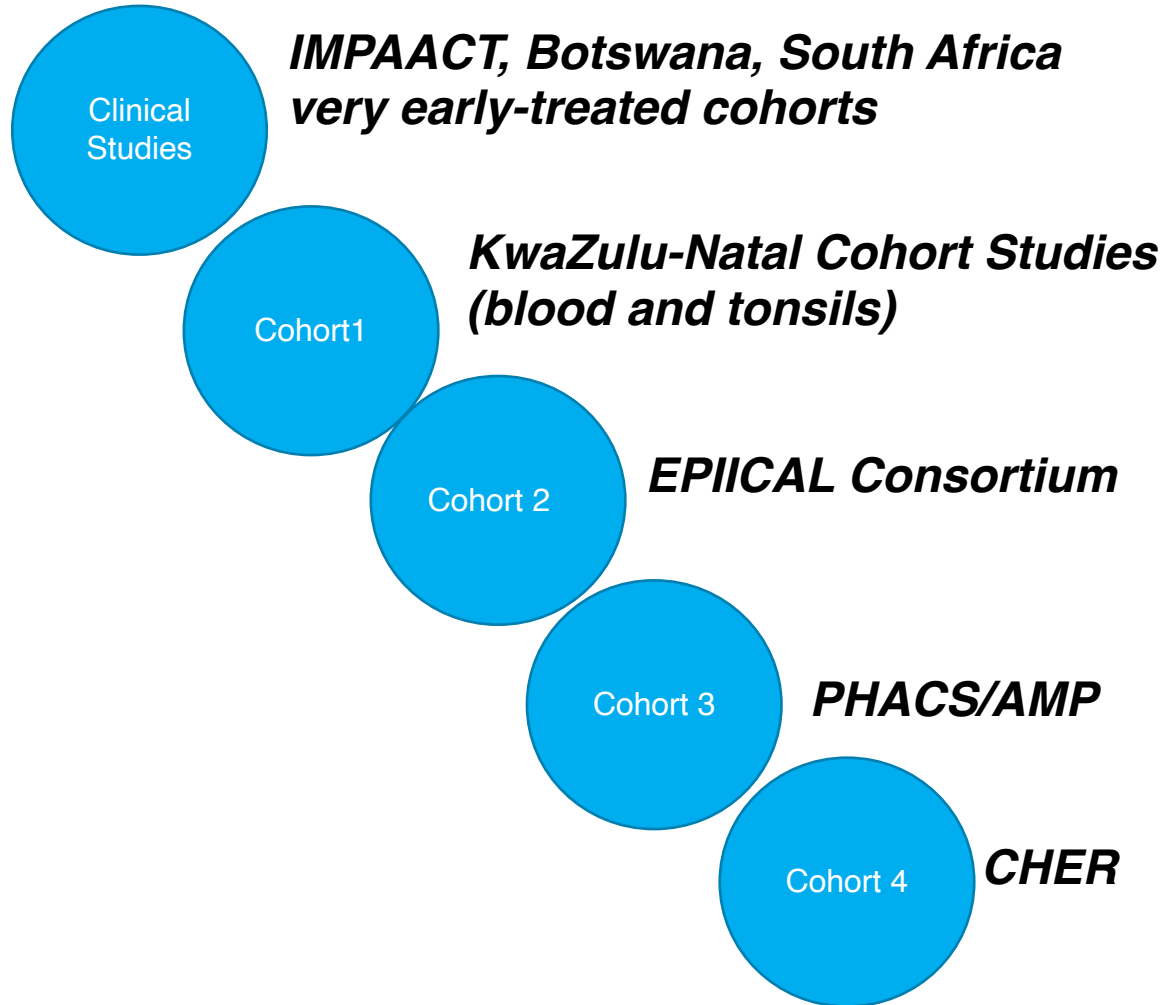
Human and infant NHP

Aim 5: Community Engagement

Foster community engagement in pediatric HIV-1 cure research

Community

Unique Clinical Cohorts & Biobanks





Optimization and validation
of Intact Proviral DNA Assay
for Non-subtype B HIV

Greg Laird, PhD



IL-15 Superagonist (N-803)

Jeff Safrit, PhD

Industry Partners



Combined TLR
4, 7, 8 adjuvants
(nanoparticles)

Jay Evans, PhD
Shannon Miller, PhD

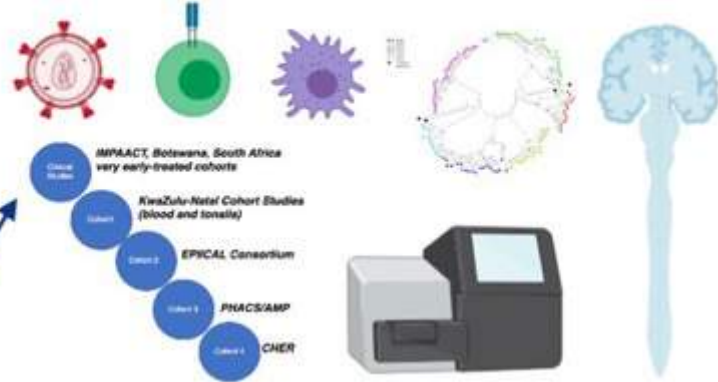


SMAC mimetic /
IAP inhibitors
EPIICAL Cohorts

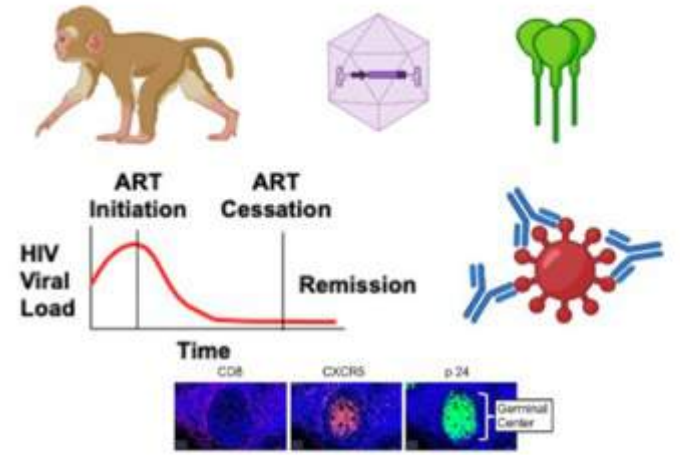
Jan Van Lunzen, MD
Heather Madsen, PhD

Scientific Agenda

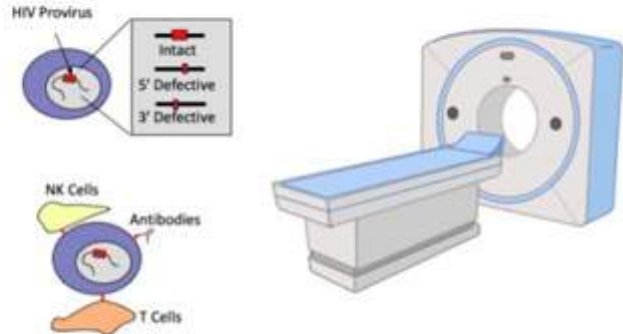
RF1: Basic Research on HIV Persistence



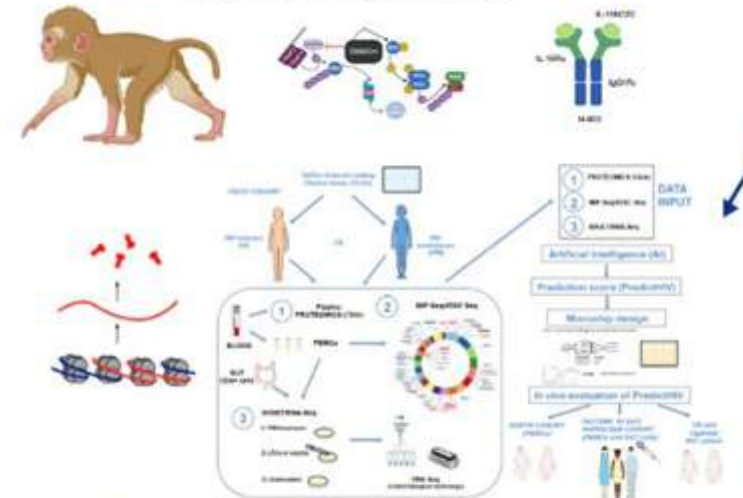
RF2: Control of Rebound



RF4: Assay Development, Optimization, Imaging



RF3: Eradication



Community Program

Industry Partners



Community Engagement





MPDs:
Deborah Persaud, MD
Ann Chahroudi, MD, PhD

Scientific Advisory Board

Executive Committee:
MPDs,
Haigwood,
Luzuriaga,
Goulder,
Safrit, Madsen

Community Advisory Board

Management and Operations:

- JHU Program Manager
- JHU administrative support
- JHU Statistical and Bioinformatics support
- Data sharing
- Network coordination

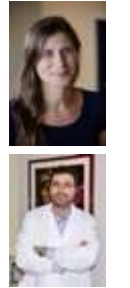
Research Focus 1
(Basic Research)
Director: Luzuriaga
AD: Lichterfeld



Research Focus 2
(Control of Rebound)
Director: Goulder
AD: Permar



Research Focus 3
(Eradication or inactivation)
Director: Chahroudi
AD: Palma



Research Focus 4
(Assays, Tools & imaging modalities)
Director: Persaud
AD: Pahwa



Industry Partnerships:
ImmunityBio
Inimmune
AcceleVirDx
ViiV

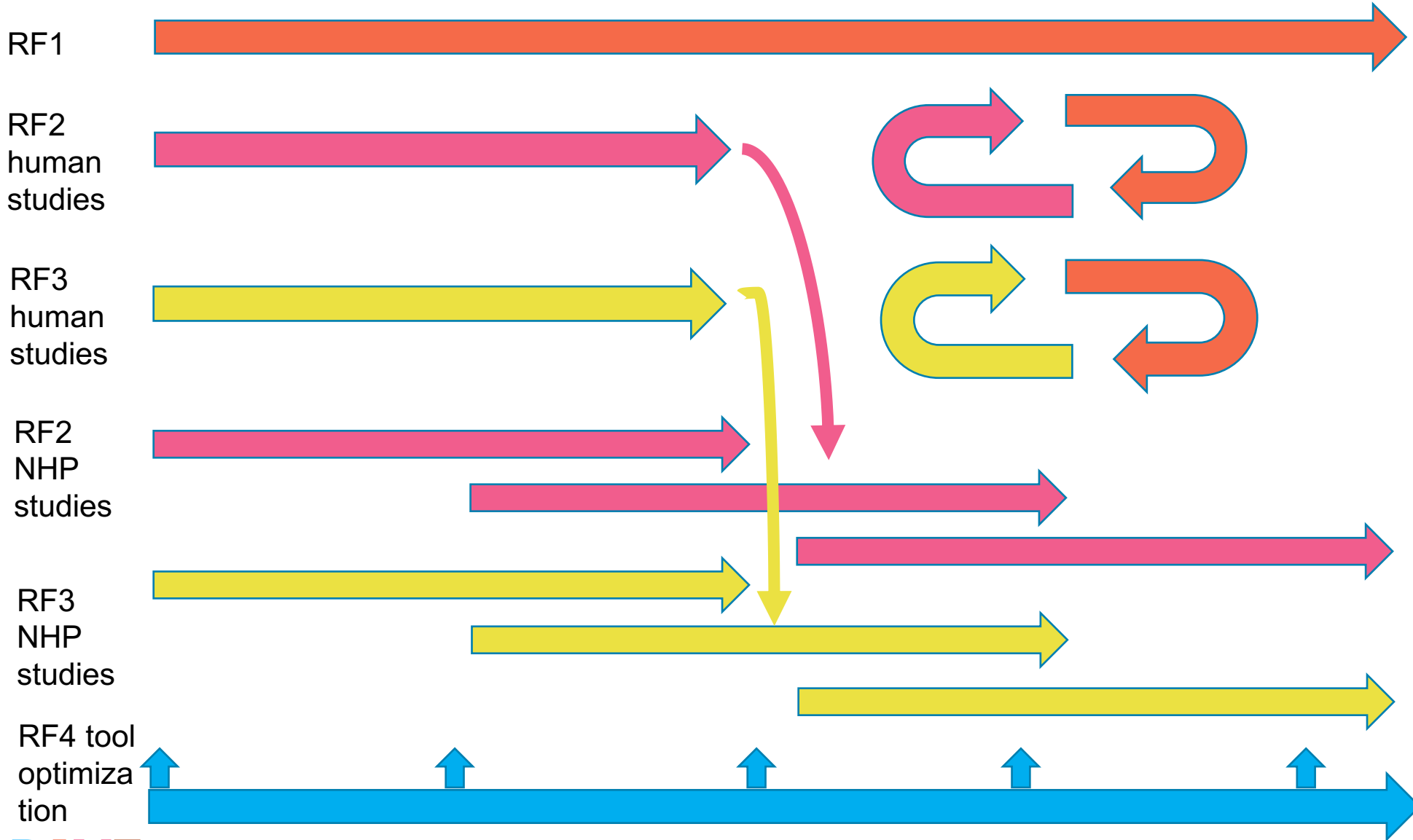
Community Program:
A. Agwu,
M. Cotton



Clinical Trial Networks, Consortium, and Cohorts

- IMPAACT** (S. Nachman)
- EPIICAL** (P. Palma, Paolo Rossi)
- P. Goulder, R. Shapiro, M. Cotton
PHACS/AMP (K. Patel)

Year 1 Year 2 Year 3 Year 4 Year 5

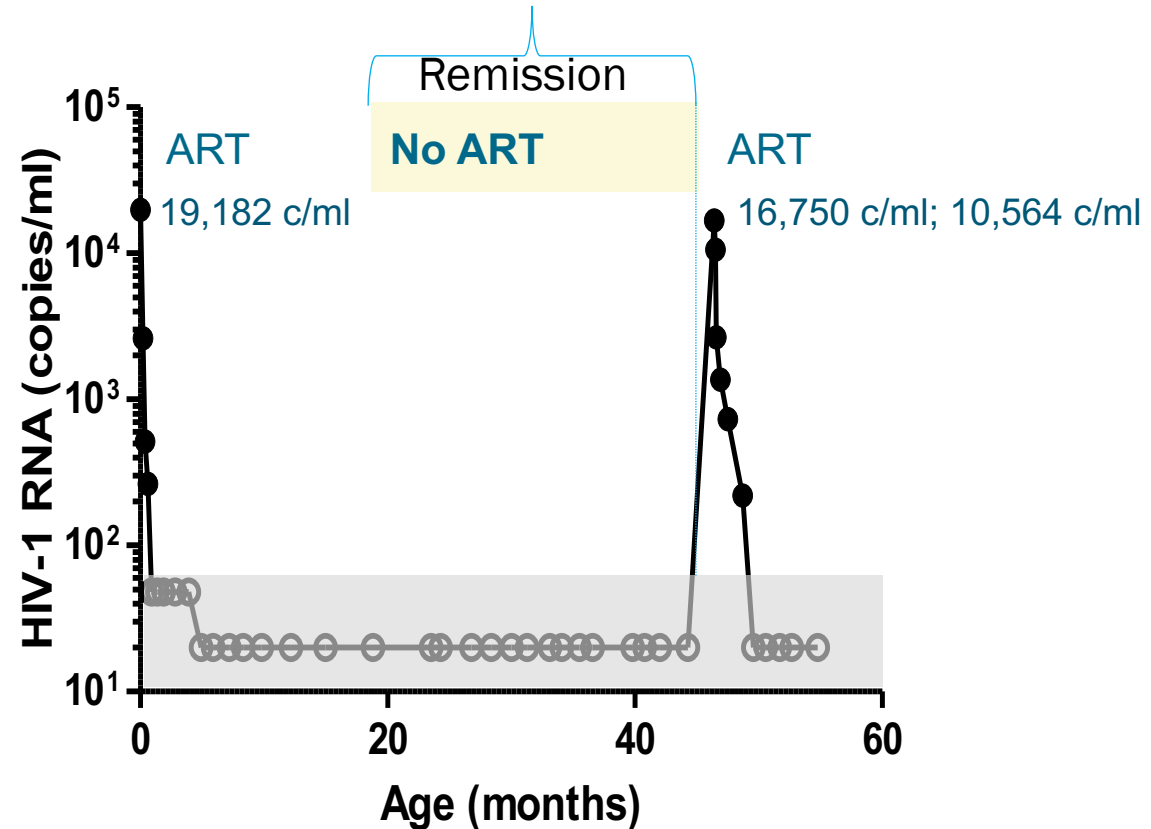


Inform development of clinical trials and biomarker studies to achieve and HIV remission and cure in perinatal infection

Pediatric Case of ART-free Remission (2013)



“Mississippi Baby”
(2013; NEJM)



27 months of ART-free HIV Remission

IMPAACT P1115: Accrual

32

460 infants enrolled in two cohorts at 30 sites in 11 countries between January 2015 and December 2017

Cohort 1

N=440 high-risk infants, initiated on pre-emptive ART within 48 hours of birth



34 of 36 diagnosed with *in utero* infection continued ART on-study

Cohort 2

N=20 infants diagnosed with *in utero* infection enrolled within 10 days of age and continued ART on-study (initiated NVP-based triple-ARV regimen within 48 hours of birth)

Very Early Treatment Reduces the Viral Reservoir

The Journal of Infectious Diseases

MAJOR ARTICLE



Early Initiation of Antiretroviral Therapy Following In Utero HIV Infection Is Associated With Low Viral Reservoirs but Other Factors Determine Viral Rebound

Jane R. Mills,^{1,2,3} Namande Banga,¹ Vitorias A. Vieira,⁴ Emily Alland,⁵ Julia Roider,^{1,2,3,6} Maximilian Muench,^{1,2} Rowena Fildes,¹ Kenneth Sprong,⁴ Vuyelisi Ntantana,¹ Isabelle Fati,¹ Maheshwar Anihara,¹ Andreas Groll,¹ Naveen Ismail,¹ Maria C. Garcia Guerrero,¹ Philippe C. Matthews,^{1,2,3,6} Thandi Ndlovu,^{1,2,3,6} Maria C. Prates,¹ Javier Martinez-Picado,^{1,2,3,6,7,8} and Philip Goulder,^{1,2,3,6}

JID 2021:224 (1 December)

Payne et al. *AIDS Res Ther* (2021) 18(6)
<https://doi.org/10.1186/s12961-021-00389-1>

AIDS Research and Therapy

RESEARCH

Open Access

Early ART-initiation and longer ART duration reduces HIV-1 proviral DNA levels in children from the CHER trial

Helen Payne,^{1,2,3} Man K. Chan,¹ Sarah A. Watters,^{1,2} Kennedy Orwombe,⁴ Nel-Yuan Hsiao,⁵ Abdel Babiker,⁶ Ayy Wolani,⁷ Mark F. Cotton,⁸ Diana M. Gibb,⁹ and Nigel J. Klein¹

Clinical Infectious Diseases

MAJOR ARTICLE



Continuous Prophylactic Antiretrovirals/Antiretroviral Therapy Since Birth Reduces Seeding and Persistence of the Viral Reservoir in Children Vertically Infected With Human Immunodeficiency Virus

Maria Mounie,^{1,2} Thompson Patissoke,^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000}

CID 2021:73 (1 August)

Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

The CARMA Study: Early Infant Antiretroviral Therapy—Timing Impacts on Total HIV-1 DNA Quantitation 12 Years Later

Caroline Foster,¹ Sara Dominguez-Rodriguez,^{1,2} Alfredo Tabora,^{1,2} Triantafylia Gkouleli,¹ Judith Heaney,^{1,2} Sarah Watters,¹ Alistair Bamford,^{1,2} Katy Fidler,¹ Marisa Navarro,¹ Anita De Rossi,¹ Paolo Palma,¹ Eleni Nestorou,¹ Paolo Rossi,¹ Carlo Giagaglia,¹ and Pablo Raju,¹ for the Early Treated Perinatally HIV Infected Individuals: Improving Children's Actual Life (EPICAL) Consortium

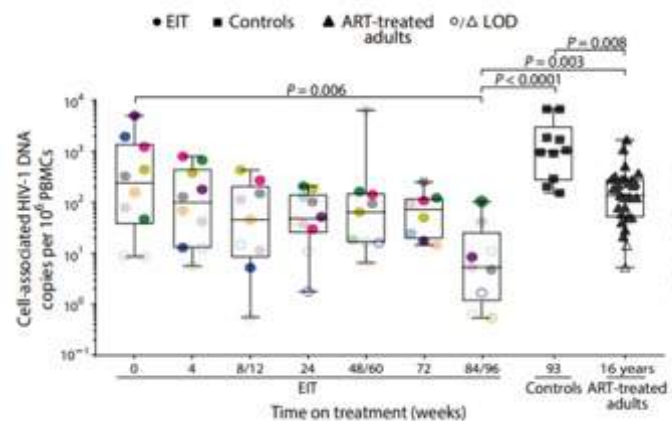


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

Early antiretroviral therapy in neonates with HIV-1 infection restricts viral reservoir size and induces a distinct innate immune profile

Pilar Garcia-Broncano,¹ Shivaali Maddali,¹ Kevin B. Einkauf,^{1,2} Chenyang Jiang,^{1,2}, Ce Gao,¹ Joshua Chevalier,^{1,2}, Fatema Z. Chowdhury,¹, Kenneth Maswabi,³, Gbolahan Ajibola,³, Sikhulile Moyo,³, Terence Mohammed,³, Thabani Ncube,³, Joseph Makhema,³, Patrick Jean-Philippe,⁴, Xu G. Yu,^{1,2,5}, Kathleen M. Powis,^{3,5,6,7}, Shahin Lockman,^{2,3,5}, Daniel R. Kuritzkes,^{2,5}, Roger Shapiro,^{3,5,7}, Mathias Lichterfeld,^{1,2,5*}



EIT: Early Infant Treatment study, diagnosed age <24 hours with FU through 96 wks
 Control: started ART at median age 4 months, blood samples at 93 weeks



Lynne Meryl Mofenson, MD



Why Focus on HIV-1 Cure

Dybul, Timothy Attoye, Solange Baptiste, Peter Cherutich, François Dabis, Steven G Deeks, Carl Dieffenbach, Brian Doehle,leen M Goodenow, Adam Jiang, Dominic Kempf, Sharon R Lewin, Murray M Lumpkin, Lauren Mathae, Joseph M McCune, Thumbi Ndung'u, s Nsubuga, Holly L Peay, John Pottage, Mitchell Warren, Izukanji Sikazwe, on behalf of the Sunnylands 2019 Working Group*

Effective curative interventions could:

Prevent new infections

Overcome the limitations of antiretroviral therapy

Combat stigma and discrimination

Provide a sustainable financial solution for the HIV-1 pandemic control

Dybul M. et al. Lancet HIV 2021

PAVE MDC Team



• Oregon Primate Center/OHSU
Portland, OR
• Nancy Haigwood, PhD
• Ann Hessel, PhD

• University of Colorado
Boulder, CO
• Elizabeth McFarland, MD

• University of Kentucky
Lexington, KY
• Zachary Porterfield, MD

• University of Massachusetts
Worcester, MA
• Katherine Luzuriaga, MD

• Boston Children's Hospital (PVP)
Boston, MA
• Ofer Levy, MD, PhD

• Massachusetts General Hospital/ Ragon Institute
Boston, MA
• Mathias Lichterfeld, MD, PhD
• Roger Shapiro, MD
• Galit Alter, PhD

• National Institutes of Health
Bethesda, MD
• Mario Roederer, PhD
• Rick Koup, MD
• Joe Cassazaa, MD

• Johns Hopkins University
Baltimore, MD
• Deborah Persaud, MD
• Robert Siliciano, MD, PhD
• Janet Siliciano, PhD
• Francesco Simonetti, MD
• Adit Dhummakupt, PhD
• Winston Timp, PhD
• Alison Hill, PhD
• Allison Agwu, MD

• Weill Cornell Medical College
New York, NY
• Sallie Permar, MD, PhD

• Duke University
Durham, NC
• Genevieve Fouda, MD, PhD

• Emory University
Atlanta, GA
• Ann Chahroudi, MD, PhD
• Maud Mavigner, PhD

• Scripps Institute
Jupiter, FL
• Mauricio Martins, PhD
• Michael Farzan, PhD

• University of Miami
Miami, FL
• Savita Pahwa, MD
• Lesley deArmas, PhD

• Oxford University
Oxford, United Kingdom
• Philip Goulder, MA, FRCPCH,
Dphil, FMedSci

• Ospedale Pediatrico Bambino Gesù
Rome, Italy
• Paolo Palma, MD, PhD
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• University of the Witwatersrand
Johannesburg, South Africa
• Avy Violari, MD
• Caroline Tiemessen, PhD

• African Health Research Institute
Durban, South Africa
• Henrik Klooverpris, PhD

Current trends in data: Broadly neutralizing antibodies and animal models

– Dr. Mark Cotton, Tygerberg Children's Hospital (TCH), Stellenbosch University (SU), South Africa



Broadly neutralizing antibodies against HIV-1 – a role in HIV-1 remission?

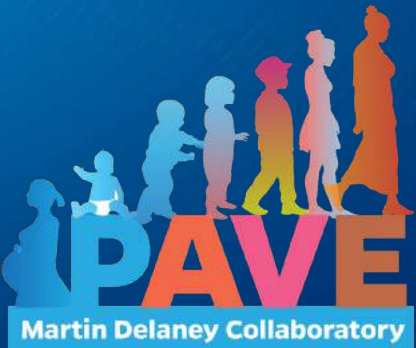
Mark Cotton

FAMCRU

Stellenbosch University

EGPAF Webinar

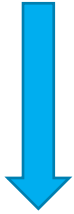
March 17, 2022



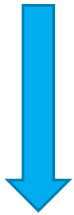
Pediatric
Adolescent
Virus
Elimination

HIV-1 entry into host cell

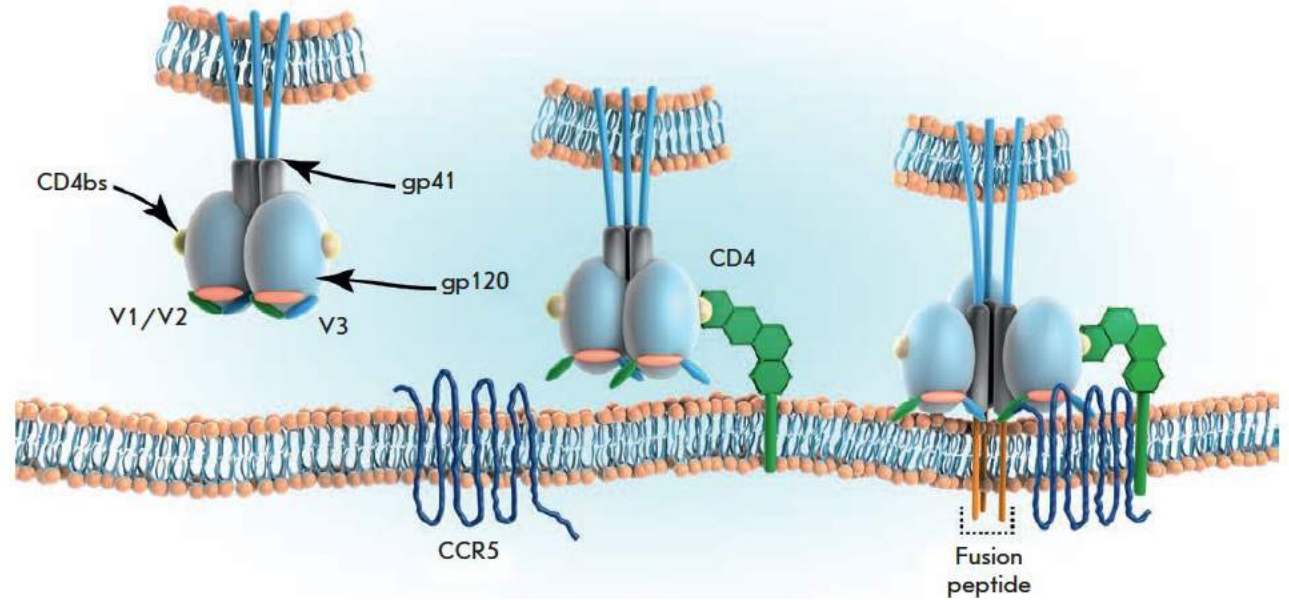
gp120 binds to CD4



V3, V1/V2 shift to expose CCR-5 / CXCR4 binding site



Viral fusion & entry



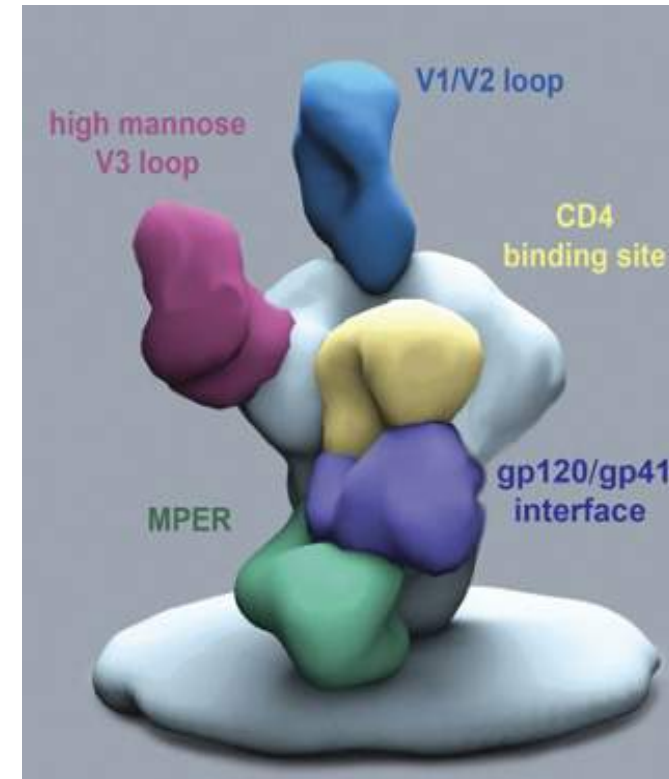
HIV env

- gp120 X3
- gp41 X3

How is HIV-1 envelope protected from Abs?

- Env spikes sparse (10 per virion)
- Intense glycosylation **hides conserved areas**
- Non-functional gp120 & gp41
 → Decoy Abs

MPER – membrane proximal external region



Gama L and Koup RA. Annual Review of Medicine Oct. 2017

1991 – 1st description of bNAbs

A large array of human monoclonal antibodies to type 1 human immunodeficiency virus from combinatorial libraries of asymptomatic seropositive individuals

(AIDS/antibody repertoires/passive immunization/filamentous phage/phage surface expression)

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Contributed by Richard A. Lerner, August 22, 1991

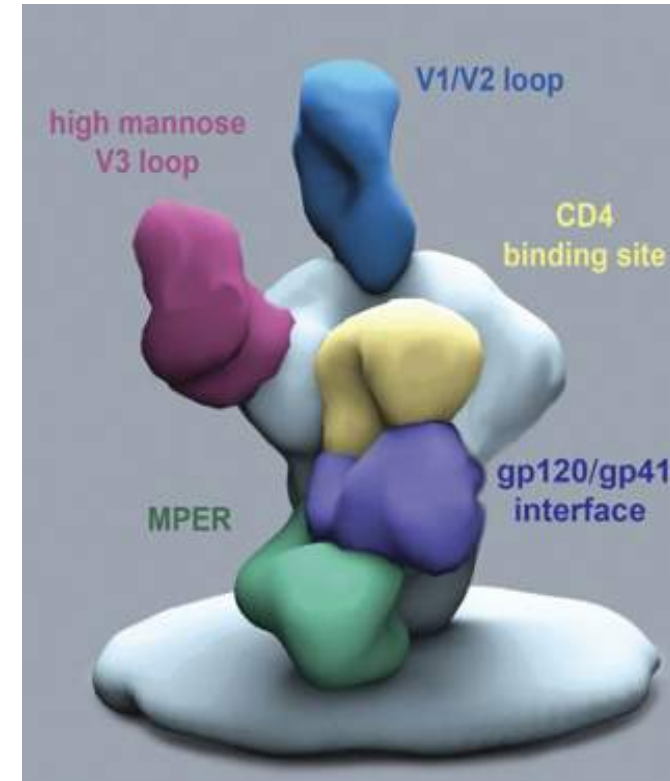
ABSTRACT A panel of human monoclonal antibody Fab fragments has been generated against the surface glycoprotein gp120 of type 1 human immunodeficiency virus (HIV) by antigen selection from a random combinatorial library expressed on the surface of filamentous phage. The library was prepared from 5 ml of bone marrow from an asymptomatic individual who has been HIV-positive for 6 years. The antibodies have high affinity for antigen (mostly with affinity constants of $>10^8 \text{ M}^{-1}$) and notable sequence diversity. Given appropriate donor selection, the methods described should allow the generation of antibodies for the evaluation of passive immunization as a therapy for AIDS.

numbers of monoclonal antibodies against the virus is unlikely to suffice. Third, it may be necessary to examine many antibodies to find rare but highly effective molecules. Antibodies could be rare either because they are present as minor components of typical responses or because they are present in only a few individuals.

Similarly, the study of large numbers of human antibodies should accelerate vaccine design. Recent vaccination data in nonhuman primates have shown the development of protective immunity against HIV-1 in chimpanzees vaccinated with recombinant gp120 (9) and against HIV-2 in cynomolgus monkeys vaccinated with whole killed virus (10). These

Where do bNAbs act?

1. V2-glycan site
2. V3-glycan epitope
3. Membrane proximal external region (MPER)
4. CD4 binding site (CD4bs)
5. gp120-gp41 interface, (includes fusion peptide)



Gama L and Koup RA. Annual Review of Medicine Oct. 2017

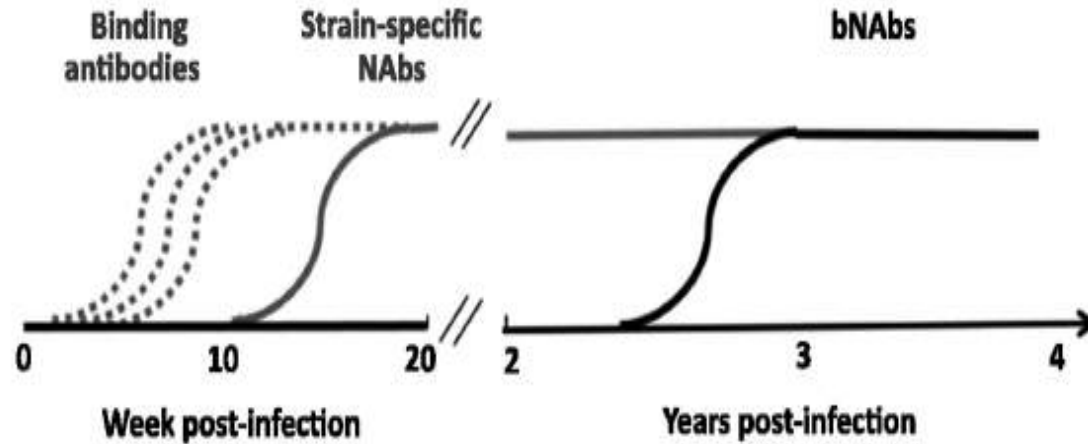
The rise of the bNAb against HIV

- 1st generation – phage display / B cell immortalization
- B cell culture & microneutralization
- B cells isolation by flow cytometry
- Long-acting – Fc Receptor adaptation
- Soluble recombinant Env trimers
- Deliver bNAb DNA through Adenovirus carriers – continued production

Study/Reference	Antibody Design	Year of Publication	Neutralization IC50 (1:100)	IC50 (1:100)	IC50 (1:100)	IC50 (1:100)
1st Generation	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
2nd Generation	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
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Study/Reference	Antibody Design	Year of Publication	Neutralization IC50 (1:100)	IC50 (1:100)	IC50 (1:100)	IC50 (1:100)
3rd Generation	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
4th Generation	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0
	10-1074 (V1-V2)	1992	100-1000 (100, 1000)	1.00 (100)	100	10.0

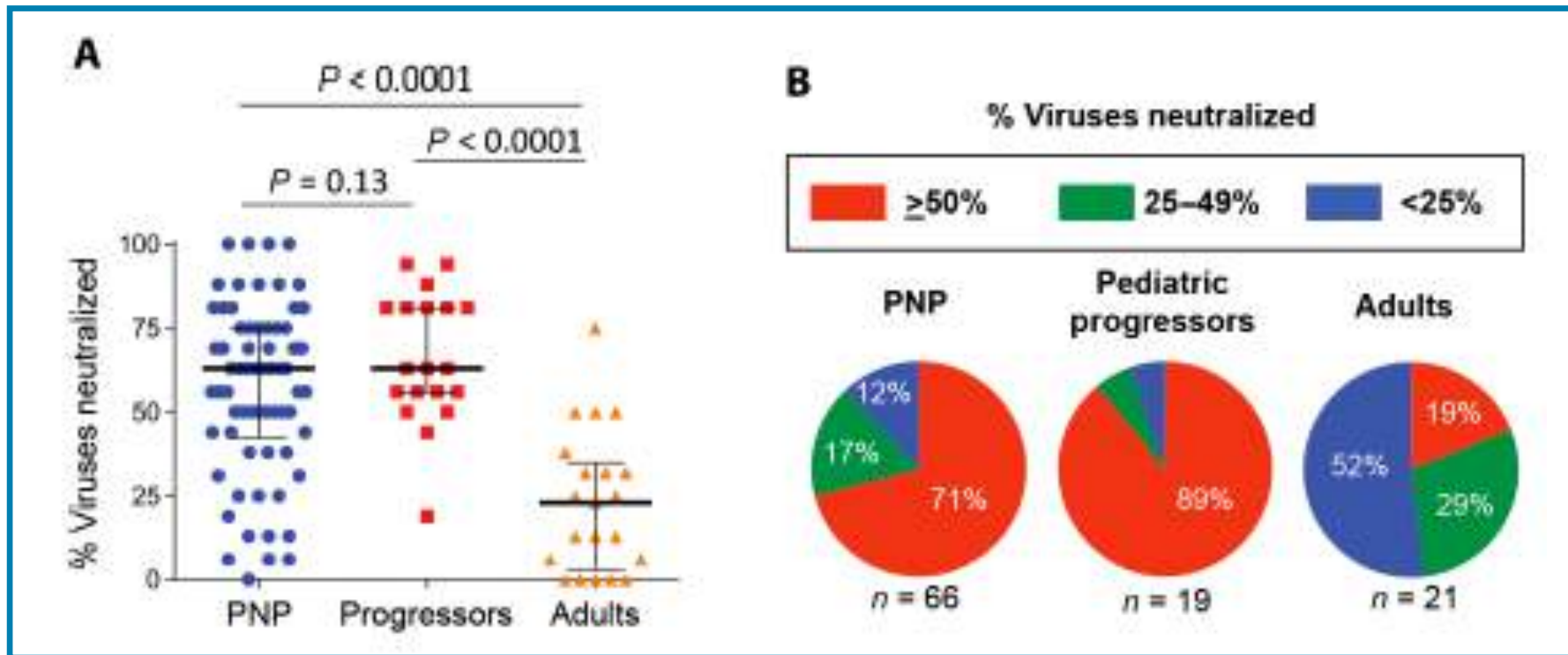
Timing of antibodies to HIV-1



bNAbs have no lasting benefits to their hosts

Moore PL. Curr HIV Res. 2018

bNAbs: Higher Prevalence in Pediatric than Adult HIV Infection



75% (64/85) pediatric & 19% adults with Abs neutralizing $\geq 50\%$ of 16-viruses panel ($p < 0.0001$)

High plasma viral load & years of exposure drive bNAb development

Potential roles for bNAbs in children

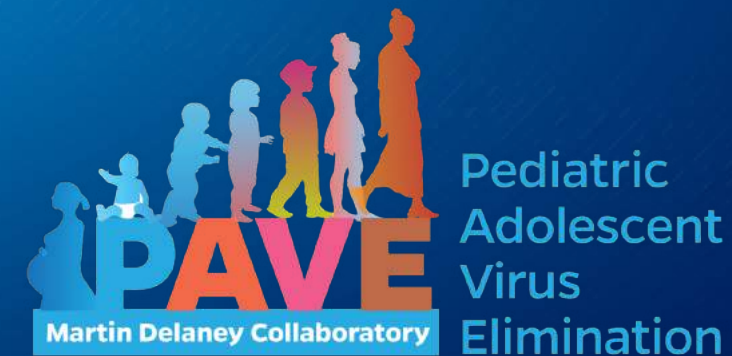
Treatment

- Suppress viraemia
- Control viraemia during ART interruption

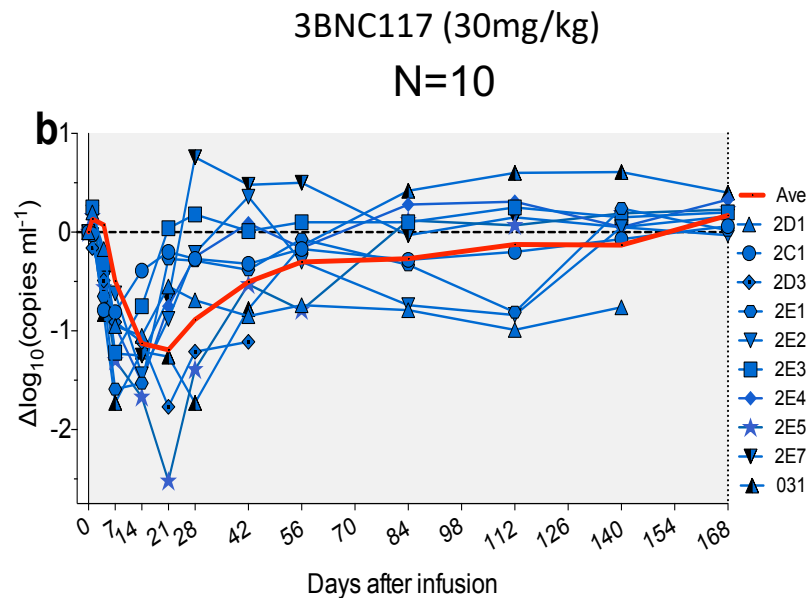
Prevention

- Vertical transmission including breastfeeding

Lessons Learned from bNAb trials in HIV+ Adults

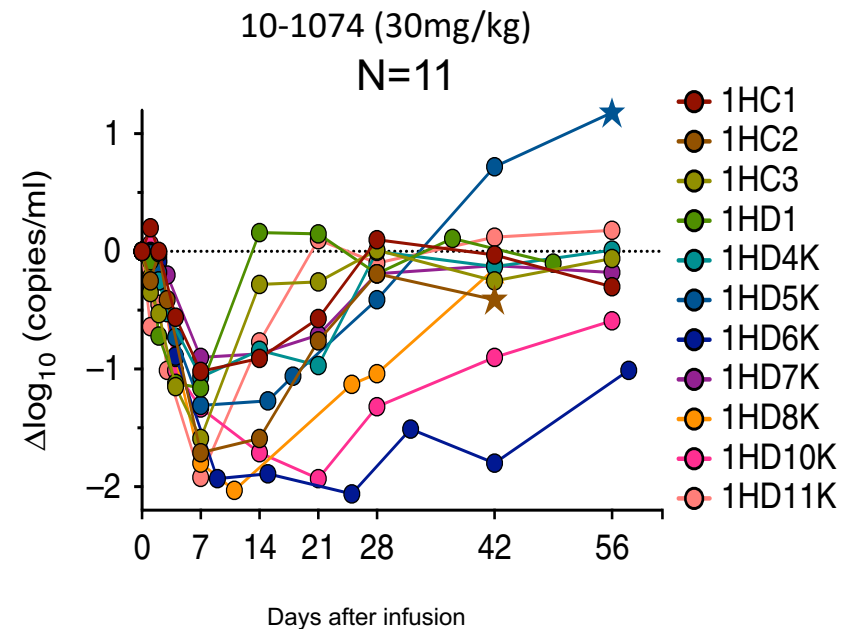


3BNC117 & 10-1074 Suppress HIV Viremia in Adults with chronic HIV



Mean VL 1.48 copies/ml decline >4 weeks

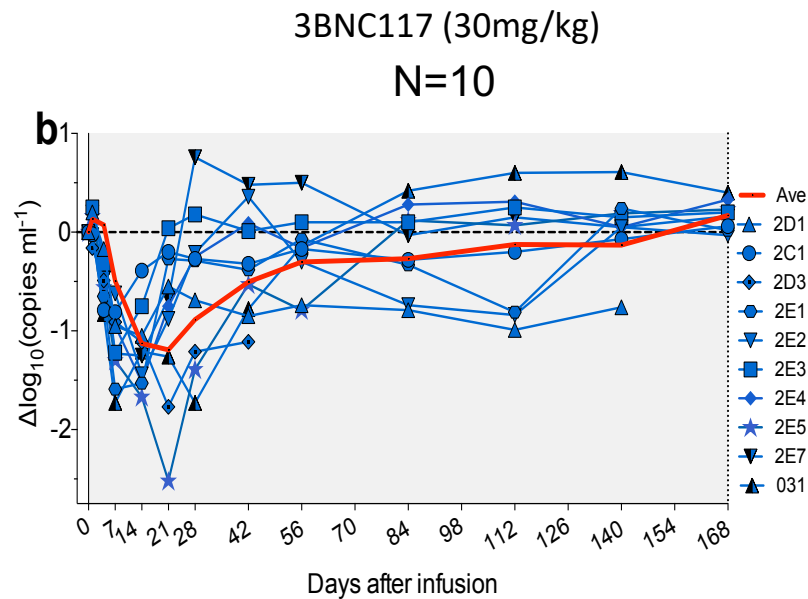
Caskey, Klein et al., Nature 2015



Mean VL decline 1.52 copies/ml >4W

Caskey, Schoofs et al., Nature Medicine 2017

3BNC117 & 10-1074 Suppress HIV Viremia in Adults with chronic HIV

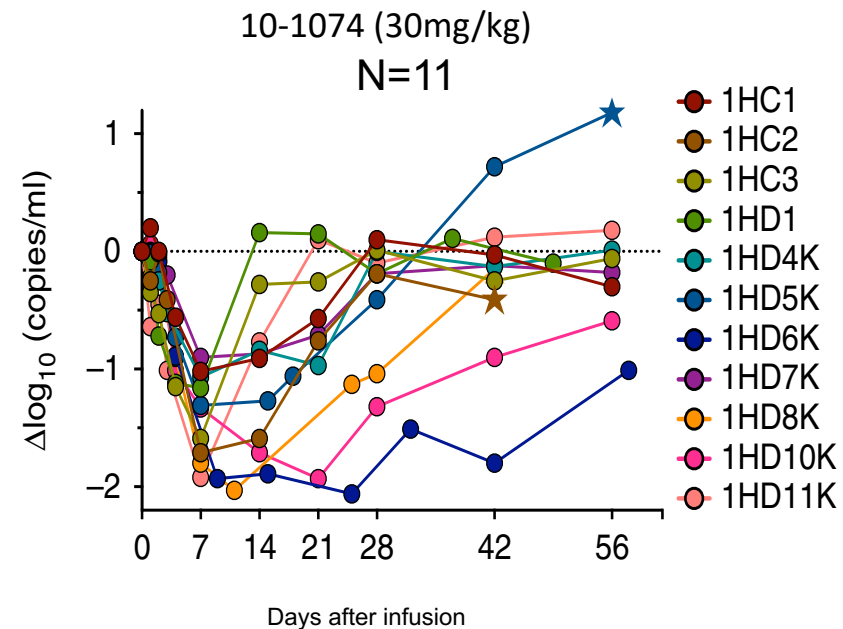


Mean VL 1.48 c

Caskey, Klein et al., Nature 2015

bNAbs resistance in rebounding virus

>4W

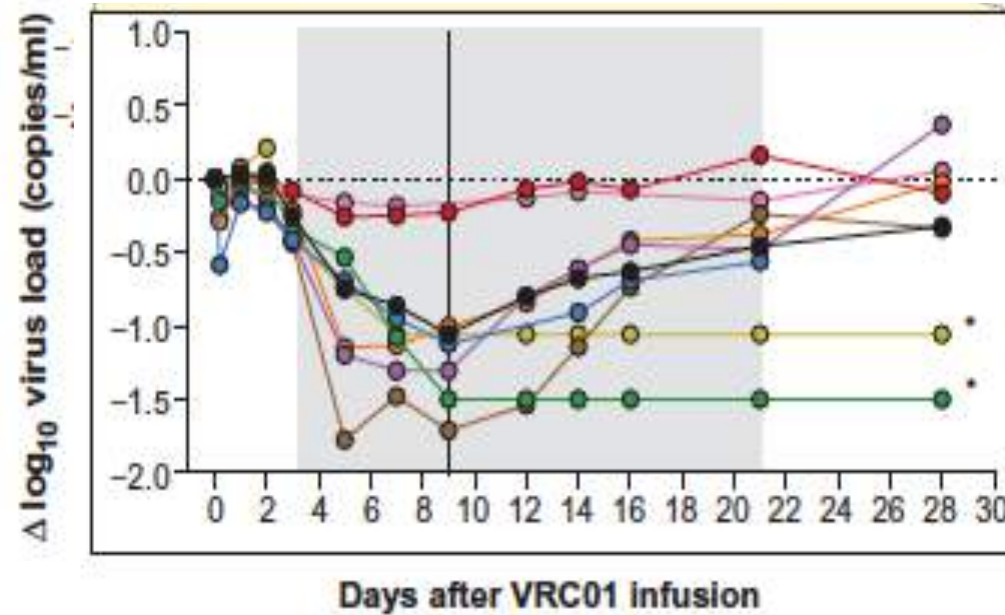


Caskey, Schoofs et al., Nature Medicine 2017

VRCO1 suppresses HIV Viremia in Adults with chronic HIV

VRCO1 (40mg/kg)

N=8



↓ 1.1-1.8 \log_{10} HIV RNA if susceptible

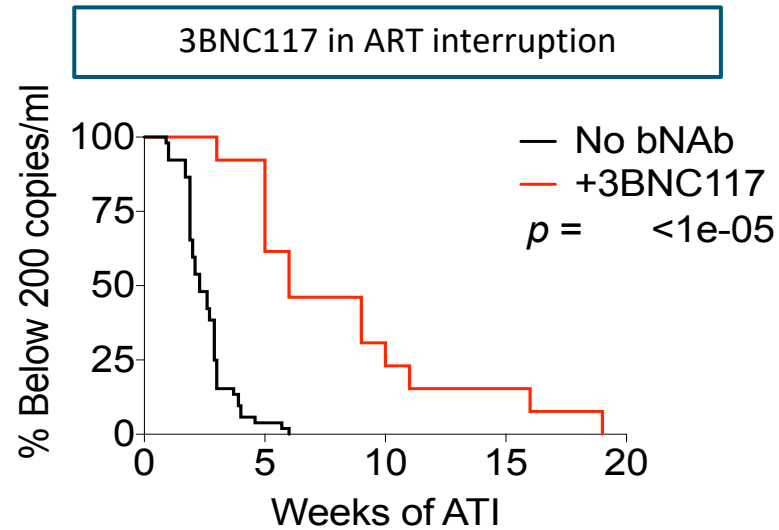
2/8 with pre-existing resistance

3BNC117 delays rebound during ART interruption (ATI)



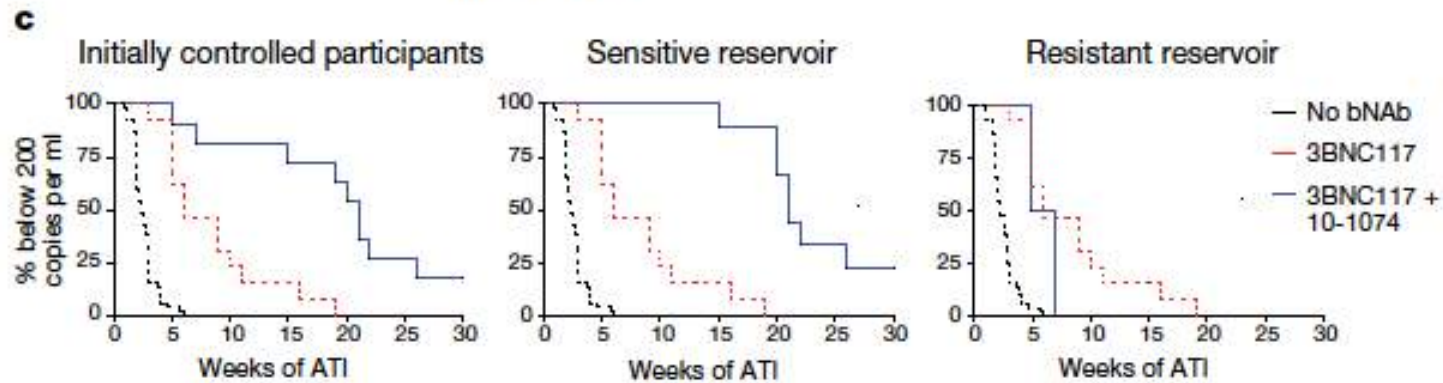
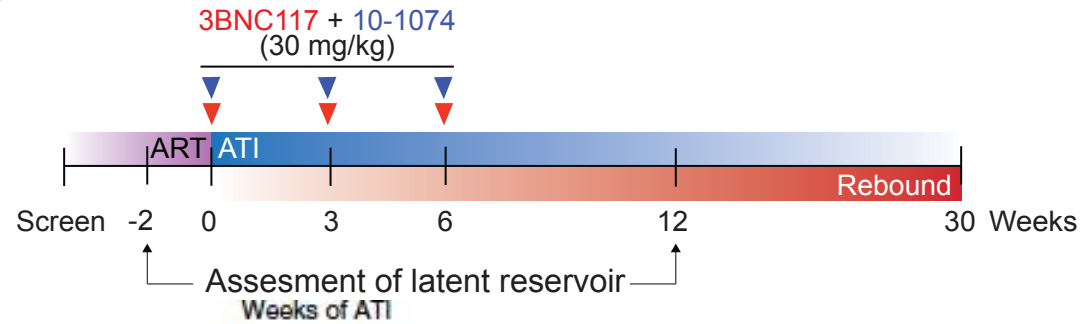
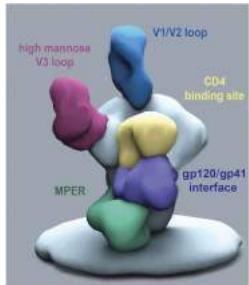
Delay in rebound vs # infusions

- None: – 2.6W
- X2: 5-9W
- X4: 19W



Individuals pre-screened; ATI-2 days after 1st 3BNC117 infusion

2 bNAbs: longer rebound delay than 1bNAb (ATI)



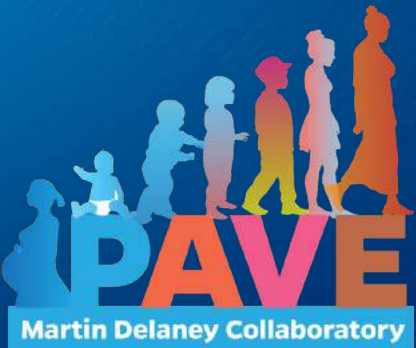
ATI-2 days after first infusion

2bNAbs delayed viral rebound for 5-30 weeks; median 21 weeks (Panel C)
(historic controls 2.3 weeks)

Vaccinal effect of bNAbs – added benefit

- 3BNC117 enhancement of humoral responses to Tier 2 viruses (Schoofs T, Klein F. et al., Science 2016)
- Nonhuman primates: early ART \leq 3 days of infection \rightarrow CD8-mediated control of SHIV infection (Nishimura et al. Cell Host Microbe 2017)

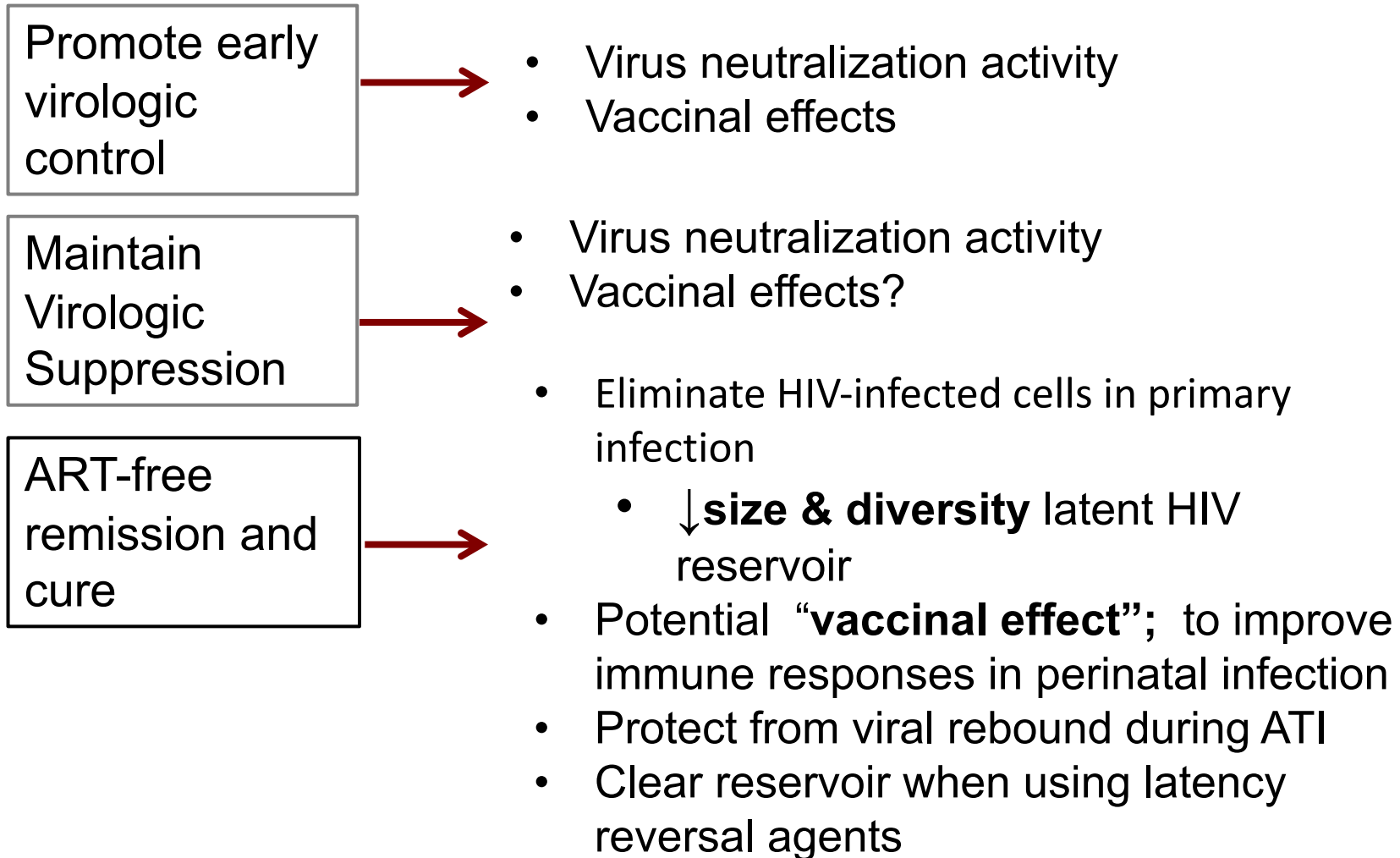
Pediatric bNAb Clinical Trial Therapeutic Landscape



Pediatric
Adolescent
Virus
Elimination

Martin Delaney Collaboratory

bNAbs for children



bNAb trials in children

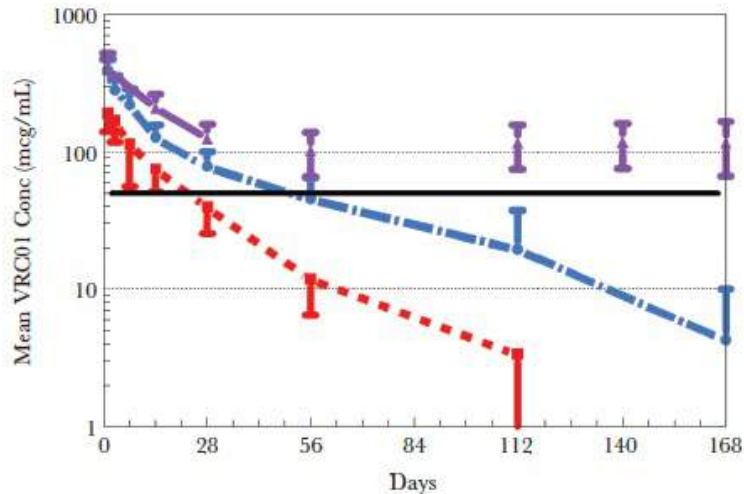
#	Study	Country	Intervention	Age at Intervention	Sample size (N)	Status
Primary HIV infection-Combination early ART + bNab						
1	IMPAACT 2008	Many	Early ART +/- VRCO1	Infants 72 hours-12 weeks	64	Complete
2	IMPAACT P1115 (Version 2.0)	Many	AZT/3TC/NVP/ Raltegravir +/- VRCO1	Neonates <48 hours	445 mother-infant pairs (45 HIV+ infants)	Enrolling
Maintenance Therapy in Suppressed Children						
3	UO1-Trial (Roger Shapiro)	Botswana	ART followed by 2 bNabs (VRCO1-LS and 10- 1074)	≥96 weeks ART suppressed	40	CROI 2022
4	UO1-Trial (Philip Goulder)	SA	ART followed by 2 bNabs (VRCO7523LS and CAP256)	2-9y ART suppressed	48	In development

Will VRCO1
reduce HIV
reservoir?

Will early
potent ART
+/- VRCO1
induce
remission?

1st bNAb study in infants

- VRC01 20→40mg/kg sc
- 40mg/kg monthly through breastfeeding
- Safe



2nd bNAb study in infants



EXTENDED SAFETY AND PK OF ANTI-HIV MONOCLONAL AB VRC07-523LS IN HIV EXPOSED INFANTS

00382

Coleen K. Cunningham¹, Edmund Capparelli², Elizabeth J. McFarland³, Petronella Muresan⁴, Charlotte Perłowski⁵, Dwight Yin⁶, Jack Moye⁷, Sai Majji⁷, Lynette Purdue⁸, Paul A. Harding³, Adrian McDermott⁶, John R. Mascola⁶, Barney S. Graham⁶, for IMPAACT P1112 Team
¹UC Irvine, Irvine, CA; ²UC San Diego, San Diego, CA; ³U Colorado Anschutz Medical Campus, Aurora, CO; ⁴Statistical and Data Analysis Center/Frontier Science and Technology Research Foundation, Boston, MA; ⁵FHI 360, Durham, NC; ⁶NIAID, Bethesda, MD; ⁷NICHD, Bethesda, MD; ⁸NIAID, Baltimore, MD

BACKGROUND

Vertical HIV transmission continues to occur due to barriers to antiretroviral therapy (ART). Prevention of infection might be improved with a potent, broadly neutralizing, monoclonal antibody (bNAb) administered to exposed infants. VRC07-523LS is 5-fold more potent and has a prolonged T_{1/2} compared to VRC01 and may provide protective levels over the duration of breastfeeding. This study was designed to determine safety and pharmacokinetic properties of VRC07-523LS in HIV-exposed infants.

METHODS

- Open label study of VRC07-523LS administered to HIV-exposed infants at increased risk of HIV

SC VRC07-523LS is safe and well-tolerated when administered to neonates. VRC07-523LS, with its enhanced potency, rapid absorption, and slow elimination, can quickly achieve and maintain plasma levels >10 mcg/mL with dosing every 3 months.

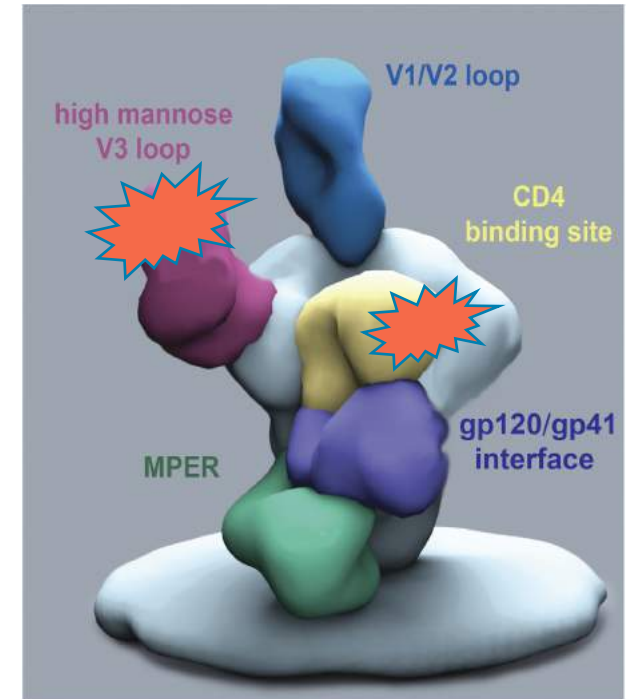
TABLE 3. Number of infants with local/systemic reactions reported after injection.

	Reaction	Grade ^a		Percent Resolved ≤ 24 hours
		1	2	
Cohort 1 N=11	Erythema	1	0	0
	Pain/tenderness	1	0	100
Cohort 2 Dose 1 N=11	Erythema	3	0	100
	Induration	2	3	80
	Edema	4	0	100
	Pain/tenderness	1	0	100
	Swelling	0	0	100

Tatelo trial – ‘the next thing’

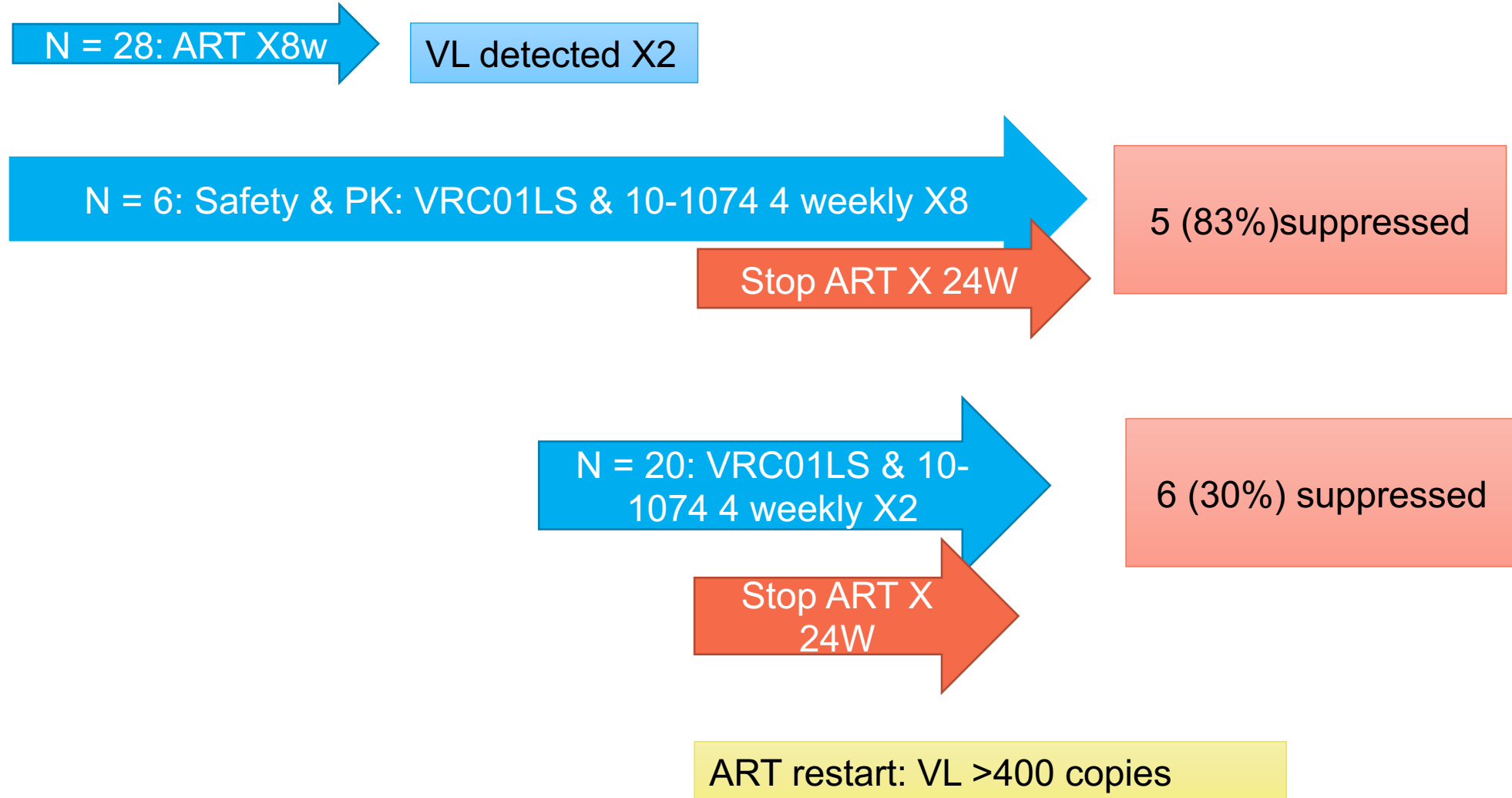
Treatment with broadly neutralising antibodies in children with HIV in Botswana

- N = 28
- ART (LPV-r) from ≤ 7 d
- VL <40 copies >24w at entry
- Median CD4 1198 cells/mL
- Age at entry – 2.4 to 5.6y
- Monitor X8w
- Add VRC01LS & 10-1074: weekly X4
- Stop ART for 24W
- Primary endpoint: # with undetectable VL at 24W



Roger Shapiro CROI 2022 abstract 32

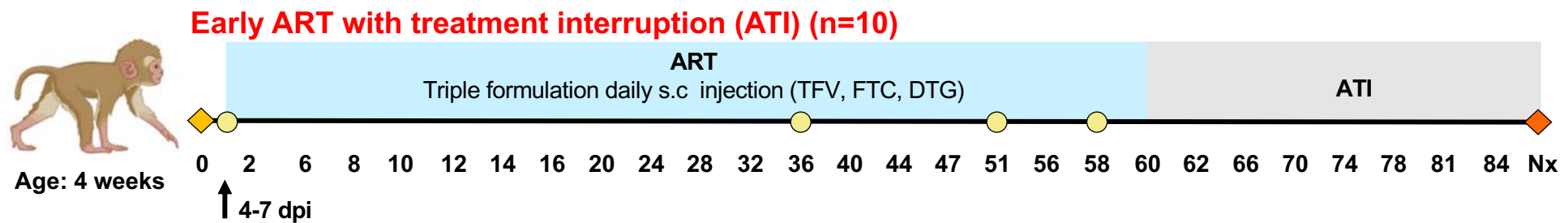
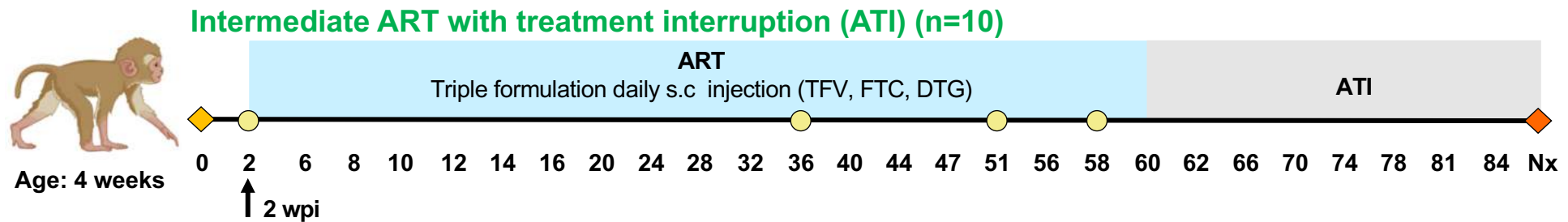
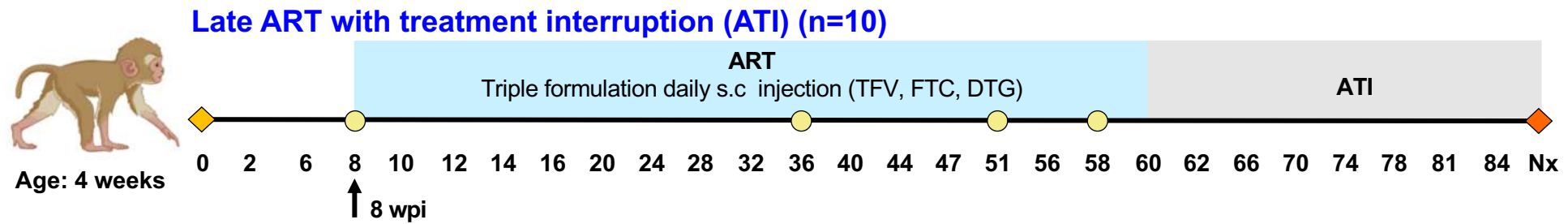
Tatelo Outcome



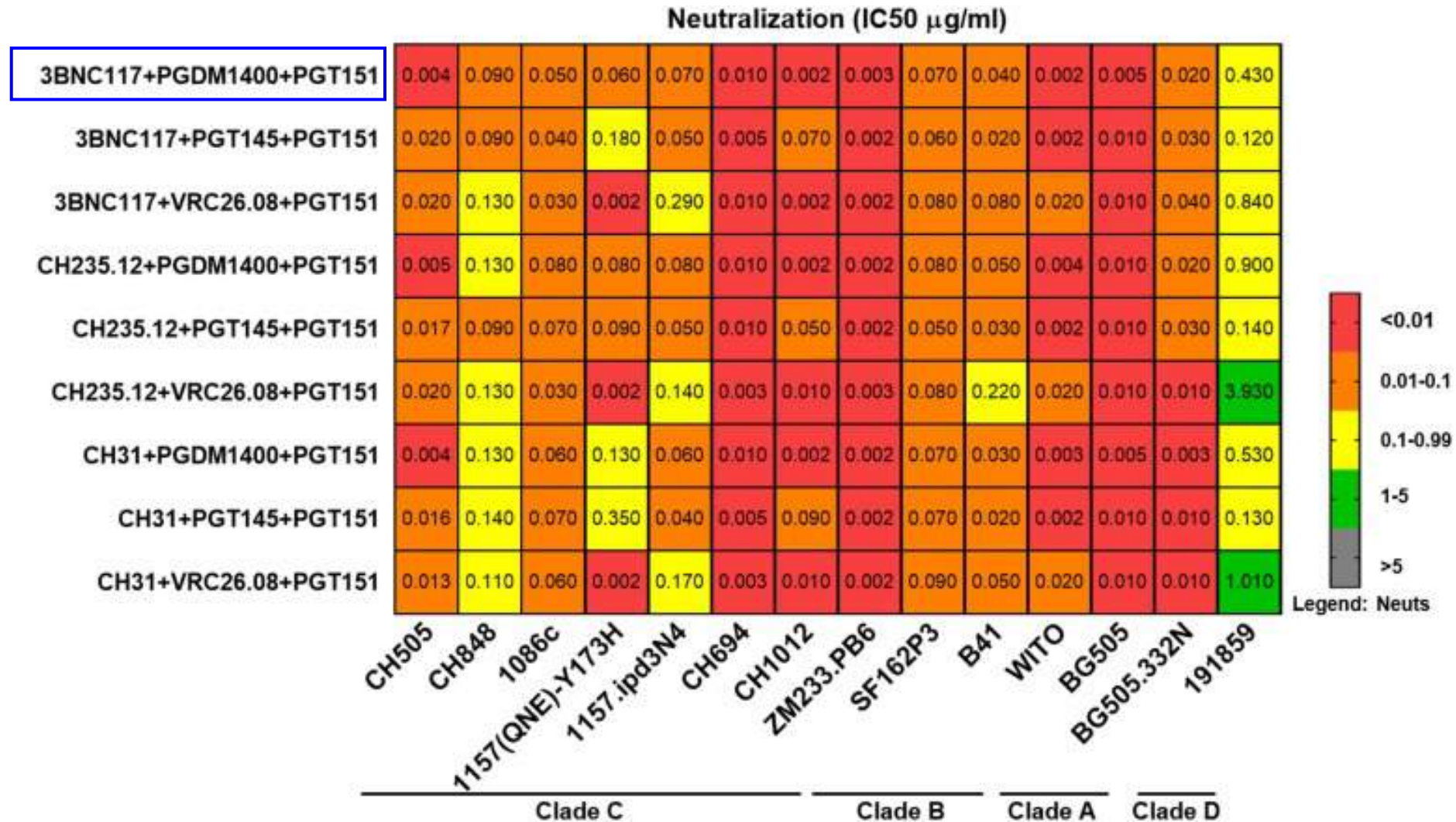
Rebound VL (HIV RNA copies/mL)

- Mean VL 17,400
- 4 with VL >100,000
 - 1 >10⁶
- All suppressed again on ART

Infant rhesus macaques SHIV infection model of HIV breastmilk transmission



Triple combination bNAbs demonstrate high neutralization potency and breadth against a cross clade SHIV panel



Acknowledgements

- Deborah Persaud
- IMPAACT investigators
- NHP work:
 - Sallie Permar
 - Genevieve Giny Fouda
 - Stella Berendam
- PAVE investigators

Informed and empowered: How youth feel about the movement toward cure

– Josephine Nabukenya,
EGPAF Board Member and
Youth Advocate



Community
Advocate:
Reflections of a
mother and long-
time pediatric cure
advocate

- Martha Sichone-Cameron,
EGPAF and Executive Director
for International Community of
Women Living with HIV



Q&A

We encourage all to participate!

- **We will prioritize questions coming in via the Q&A**
 - **Click the Q&A box** at the bottom of the screen, **type in your question(s) and hit send** – hosts will be notified and respond to your question.
 - We are also scanning the Facebook Livestream in case there are any additional questions
- We may not be able to get to all questions. If we are unable to get to your question, please email publications@pedaids.org with it. We will respond to all questions by the end of the day.



Elizabeth Glaser
Pediatric AIDS Foundation
Fighting for an AIDS-free generation