CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

UNAIDS

CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV RESEARCH AND POLICY

Laboratory Science:

Sanctuary of Scientific & Clinical Research Discovery

African Society for Laboratory Medicine Conference, Cape Town

Salim S Abdool Karim

Director: CAPRISA
Chair: UNAIDS Scientific Expert Panel
Pro Vice-Chancellor (Research): University of KwaZulu-Natal
Professor of Clinical Epidemiology, Columbia University
Adjunct Professor of Medicine, Cornell University
Associate Member, Ragon Institute of MGH, MIT and Harvard

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

Ragon Institute of MGH, MIT and Harvard

Columbia University MAILMAN SCHOOL OF PUBLIC HEALTH

What has laboratory research contributed in the fight against HIV?

After all, we do not have a vaccine or cure yet !

Has laboratory science provided any significant new tools or technologies to the global AIDS response?

Discovery of HIV as the cause of AIDS using viral culture

1983

Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)

Abstract. *A retrovirus belonging to the family of recently discovered human T-cell leukemia viruses (HTLV), but clearly distinct from each previous isolate, has been*

Science AAAS

1984

Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS

Abstract. *Peripheral blood lymphocytes from patients with the acquired immunodeficiency syndrome (AIDS) or with signs or symptoms that frequently precede AIDS*

Science AAAS

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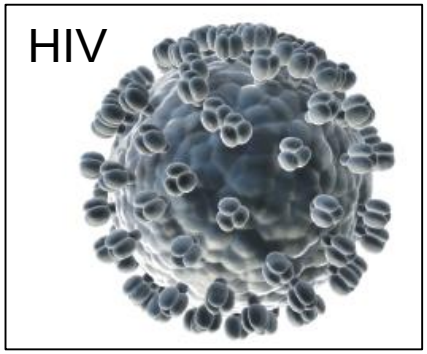
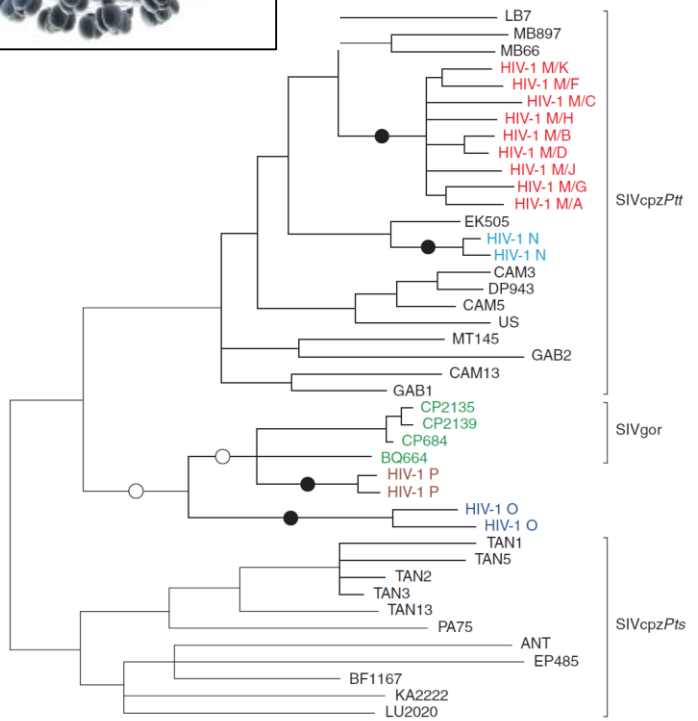
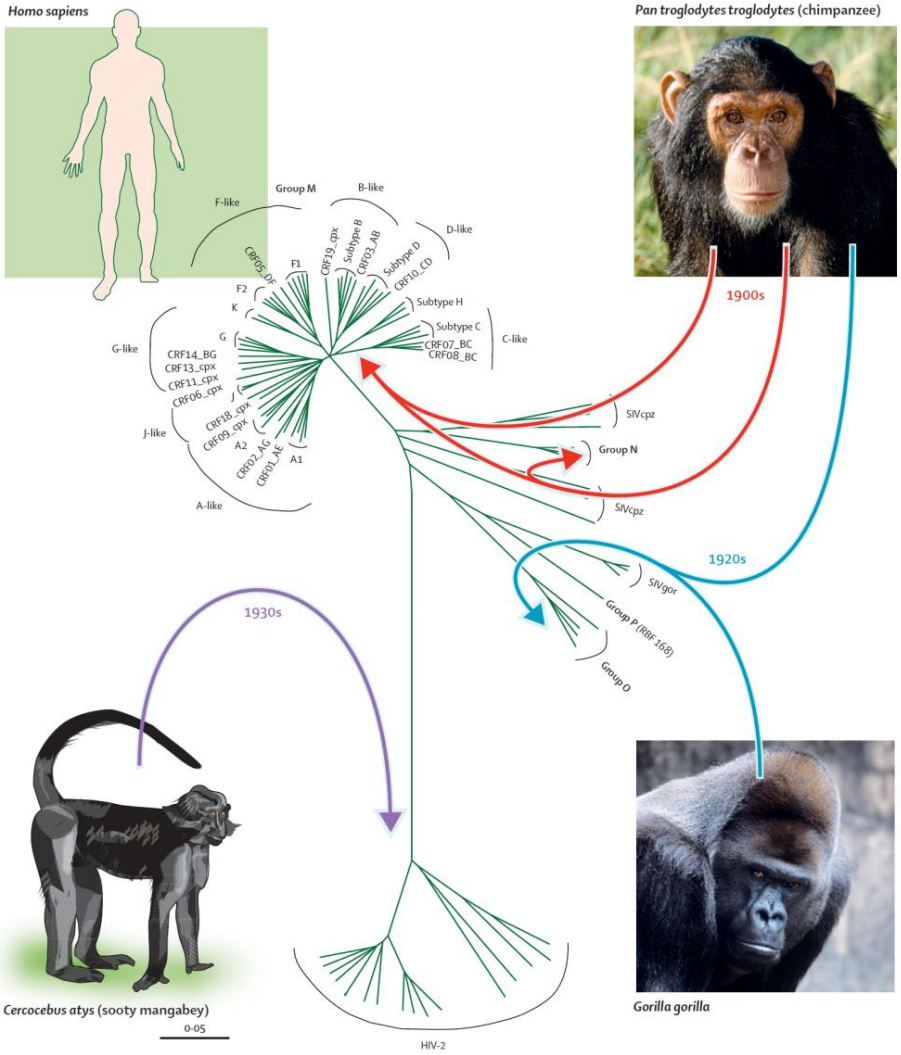
Discovery of origins of AIDS viruses by genetic sequencing of HIV & SIV







Source: *Tebit DM, et al. Lancet Infectious Diseases 2011; 11: 45–56*
Sharp PM, Hahn BH. Cold Spring Harb Perspect Med 2011;1:a006841

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Development of first HIV diagnostic tests through production of HIV antigens & ELISA platforms

- **1985: First HIV diagnostic tests, based on anti-HIV antibody detection in blood**
- **2002: First HIV rapid, point-of-care HIV test**

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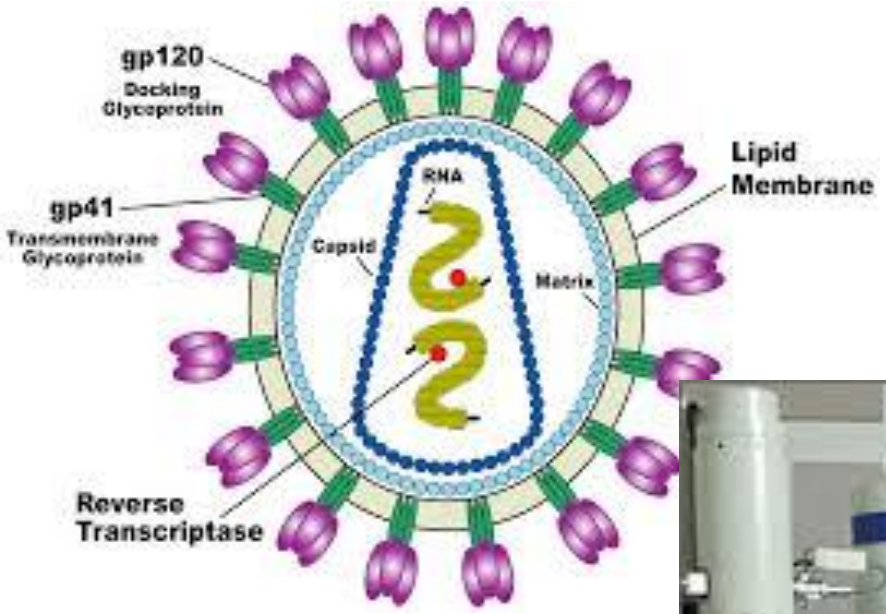
Discovery of the first AIDS treatment (AZT) through identification of viral reverse transcriptase within the structure of HIV



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Discovery of first ARV prevention of mother to child transmission by linking HIV diagnostics with (N)NRTIs

The NEW ENGLAND JOURNAL of MEDICINE

Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, PH.D., PAVEL KISELEV, PH.D., GWENDOLYN SCOTT, M.D., MARY JO O'SULLIVAN, M.D., RUSSELL VANDYKE, M.D., MOHAMMED BEY, M.D., WILLIAM SHEARER, M.D., PH.D., ROBERT L. JACOBSON, M.D., ELEANOR JIMENEZ, M.D., EDWARD O'NEILL, M.D., BRIGITTE BAZIN, M.D., JEAN-FRANÇOIS DELFRAISSY, M.D., MARY CULNANE, M.S., ROBERT COOMBS, M.D., PH.D., MARY ELKINS, M.S., JACK MOYE, M.D., PAMELA STRATTON, M.D., AND JAMES BALSLEY, M.D., PH.D., FOR THE PEDIATRIC AIDS CLINICAL TRIALS GROUP PROTOCOL 076 STUDY GROUP*

1994:
AZT reduced MTCT transmission by 67.5%

THE LANCET

Articles

Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial

1999:
NVP reduced HIV MTCT transmission by ~47% in a breastfeeding population

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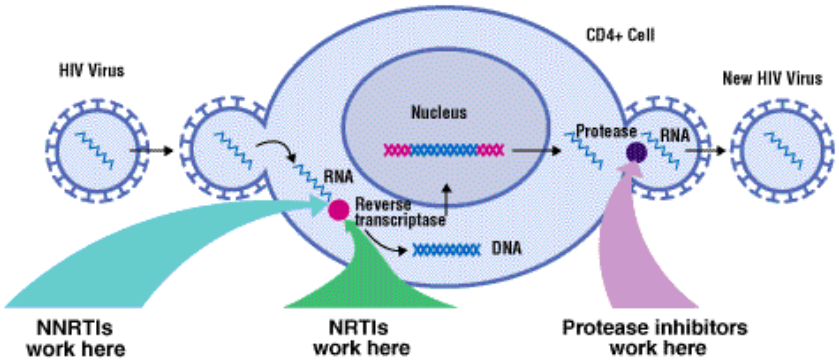
Discovery of "Highly Active AntiRetroviral Therapy" for AIDS when multiple drug targets identified in HIV

The NEW ENGLAND JOURNAL of MEDICINE

A TRIAL COMPARING NUCLEOSIDE MONOTHERAPY WITH COMBINATION THERAPY IN HIV-INFECTED ADULTS WITH CD4 CELL COUNTS FROM 200 TO 500 PER CUBIC MILLIMETER

SCOTT M. HAMMER, M.D., DAVID A. KATZENSTEIN, M.D., MICHAEL D. HUGHES, PH.D., HOLLY GUNDACKER, M.S., ROBERT T. SCHOOLEY, M.D., RICHARD H. HAUBRICH, M.D., W. KEITH HENRY, M.D., MICHAEL M. LEDERMAN, M.D., JOHN P. PHAIR, M.D., MANETTE NIU, M.D., MARTIN S. HIRSCH, M.D., AND THOMAS C. MERIGAN, M.D., FOR THE AIDS CLINICAL TRIALS GROUP STUDY 175 STUDY TEAM*

Highly active antiretroviral therapy (HAART)



Before ART After ART

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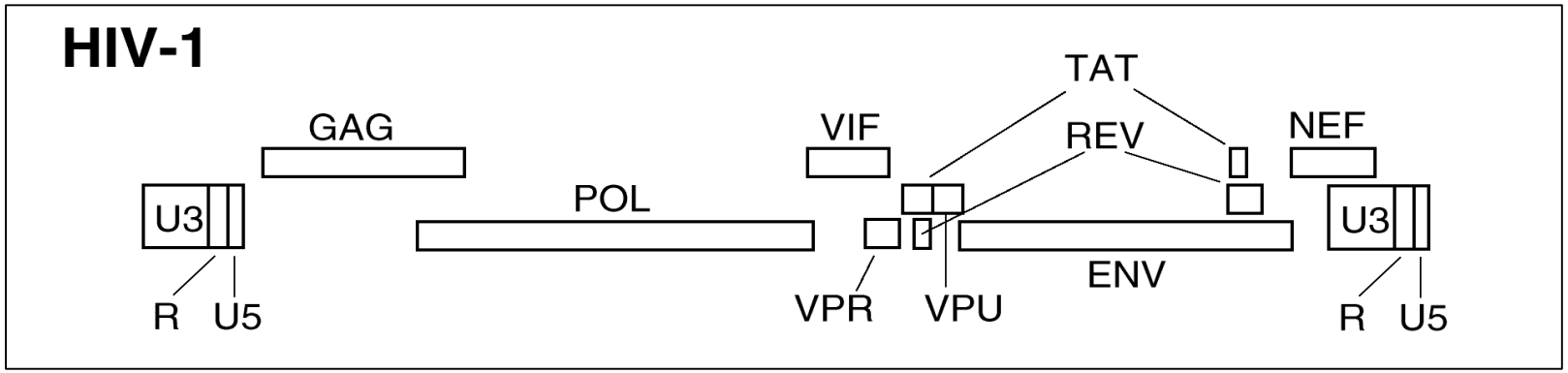
Discovery of the first effective HIV vaccine through the identification of target epitopes on the viral envelope

The NEW ENGLAND JOURNAL of MEDICINE

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

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.I Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

ALVAC-HIV and AIDSVAX B/E vaccine regimen reduced HIV incidence by 31.2% in Thailand



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Discovery of the first topical & oral ARV prophylaxis based on tenofovir levels in vaginal & anal mucosa

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

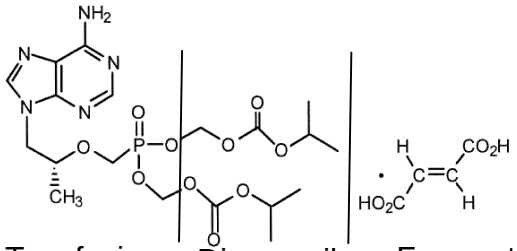
Quarraisha Abdool Karim,[1,2*†] Salim S. Abdool Karim,[1,2,3*] Janet A. Frohlich,[1] Anneke C. Grobler,[1] Cheryl Baxter,[1] Leila E. Mansoor,[1] Ayesha B. M. Kharsany,[1] Sengeziwe Sibeko,[1] Koleka P. Mlisana,[1] Zaheen Omar,[1] Tanuja N. Gengiah,[1] Silvia Maarschalk,[1] Natasha Arulappan,[1] Mukelisiwe Mlotshwa,[1] Lynn Morris,[4] Douglas Taylor,[5] on behalf of the CAPRISA 004 Trial Group‡

Science
AAAS

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc.,

IPREX
Global Communication



Tenofovir (prodrug) | Disoproxil (absorption) | Fumarate (formulation)

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Discovery that treatment is effective prevention through suppression of viral replication with triple ARVs

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

- 1763 discordant couples
- ART at CD4 up to 550 vs only <250
- 96% effective

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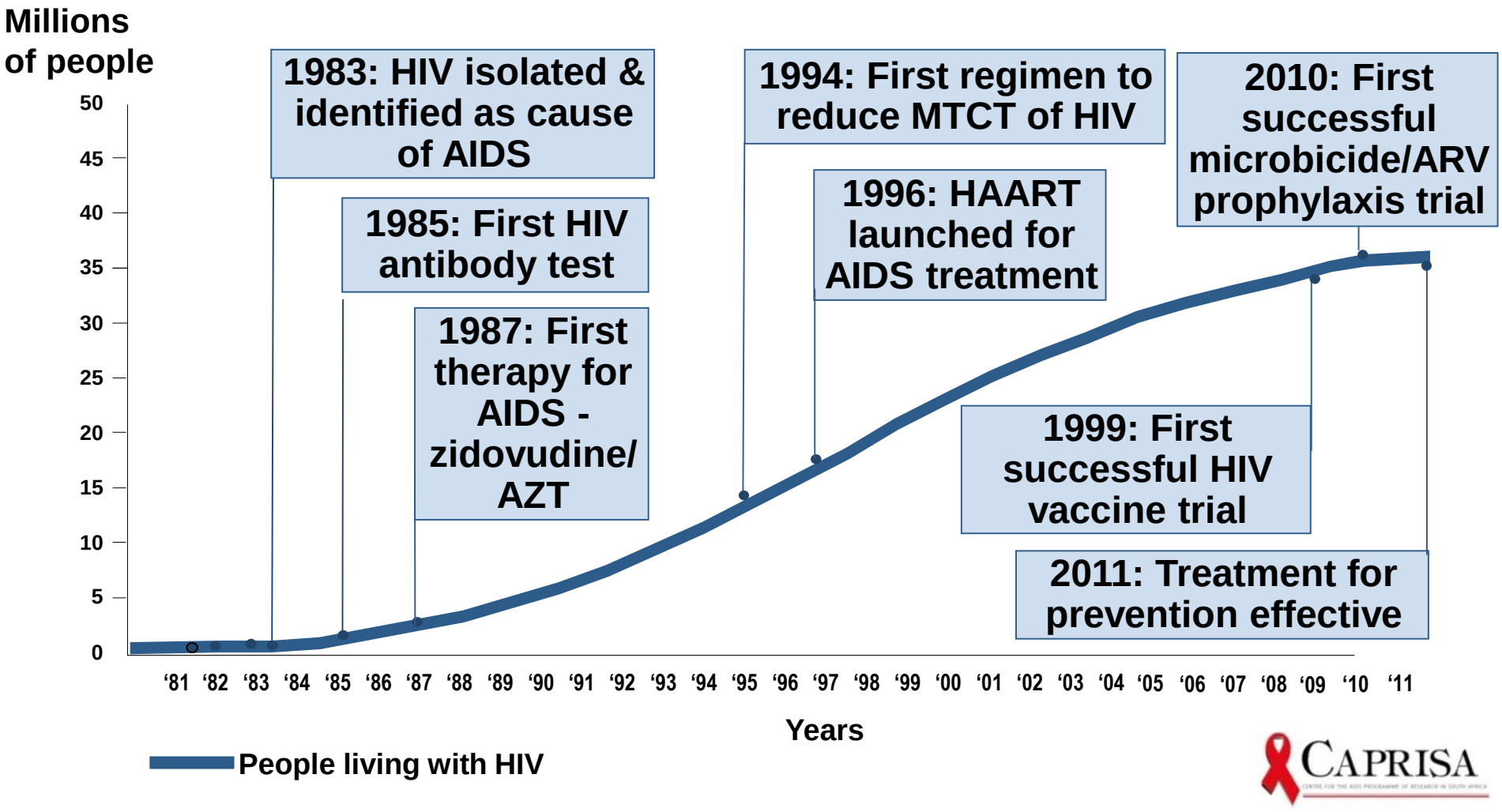
So, what has laboratory research contributed in the fight against HIV?

Almost everything!

Ten laboratory research discoveries over 30 years define today's HIV response



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Yet we face substantial challenges to laboratory science in Africa

- **Lack of political commitment to laboratory science**
- **Shortage of Lab training opportunities & scholarships**
- **High cost of purchasing & maintaining equipment**
- **High cost to import reagents & assay kits**
- **Emigration to overseas labs – brain drain**

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How can the science community rise to these challenges?

- **Each of us and our organisations has to rise to being strong ambassadors for laboratory research**
- **We have to continually balance competition and collaboration between our research laboratories**
- **Please keep reminding key decision-makers of the contributions by laboratory research**
- **We need to keep making new and important scientific contributions to the AIDS response**

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Some future directions in HIV laboratory science in Africa

Watch this space!

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Some future directions in HIV laboratory science in Africa

3 key laboratory research areas to watch

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Some future directions in HIV laboratory science in Africa

1. New applications of genetic epidemiology
2. New long-acting approaches to antiretroviral therapy & prophylaxis
3. New prevention strategies using broadly neutralising antibodies

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1. New applications of genetic epidemiology: Identifying patterns of transmission for tailored interventions

- **The general approach to HIV prevention of the past is no longer optimal or appropriate**
- **Need to use today's tools to take up the challenges of understanding HIV transmission – to enable targeted interventions (match epi & interventions)**
- **For example: Why is HIV continuing to spread so rapidly in young women in Africa?**

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HIV prevalence in school boys & girls in rural South Africa (Grades 9 & 10)

Age Group (years)	HIV Prevalence (2010) % (95% Confidence Interval)	
	Male (n=1252)	Female (n= 1423)
≤15	**1.0** (0.0 - 2.2)	**2.6** (1.2 - 4.0)
16-17	**1.1** (0.2 - 2.0)	**6.1** (2.6 - 9.6)
18-19	**1.5** (0 - 3.7)	**13.6** (9.0 - 18.1)
≥20	**1.8** (0 - 3.9)	**24.7** (6.3 - 43.1)

***Source**: Abdool Karim Q, et al Sex Transm Infect 2014*

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HIV incidence in 18-35 year women in this community:

9.1%

9.1 per 100 women-years
(95% CI: 7 - 12)

Source: *Abdool Karim Q et al, Science 2010*

HIV prevalence in young pregnant women in rural South Africa (2009-2012)

Age Group (Years)	HIV Prevalence (N=1029)
≤16	**8.4%**
17-18	**18.6%**
19-20	**25.4%**
21-22	**32.8%**
23-24	**44.8%**

Source*: Abdool Karim Q, 2014*

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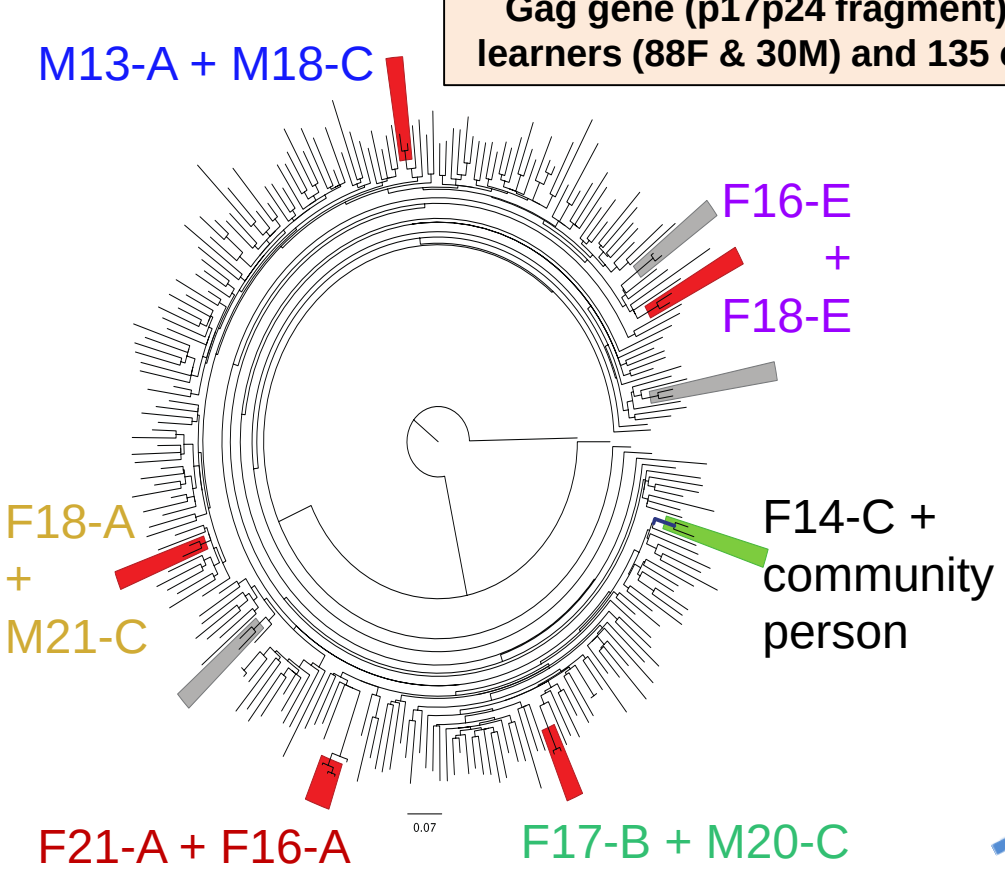
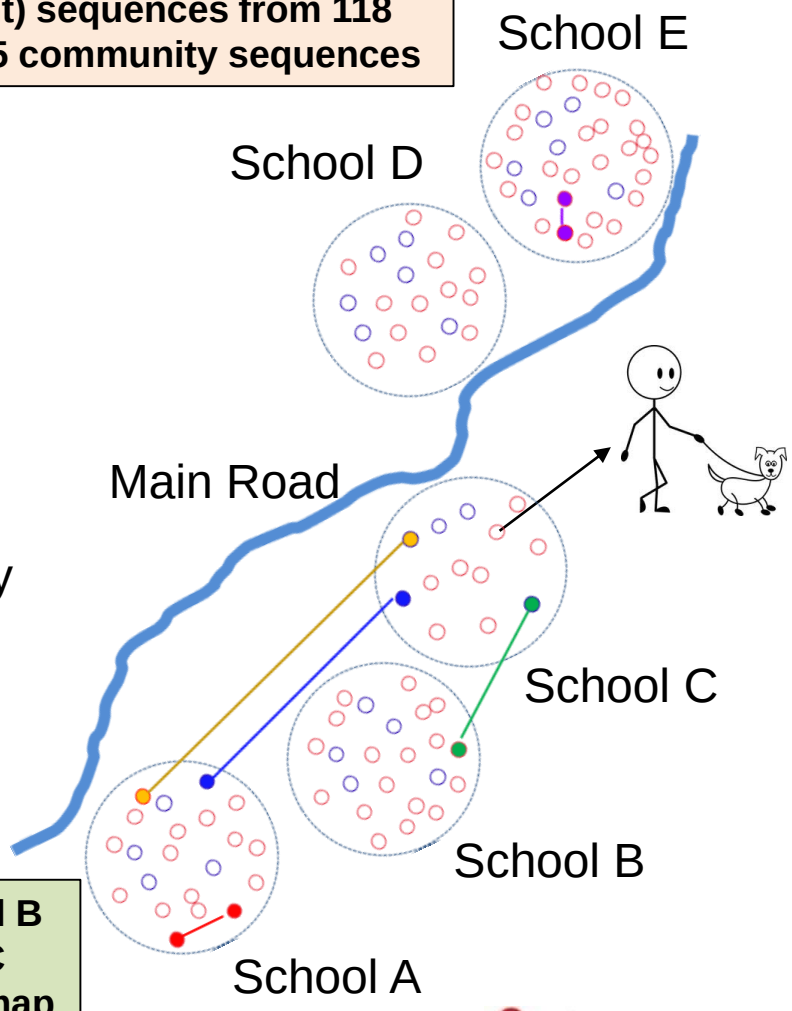
Gene sequencing & phylogenetic analysis to unravel HIV transmission

Gag gene (p17p24 fragment) sequences from 118 learners (88F & 30M) and 135 community sequences





F21-B = Female, 21 years, from School B
M20-C = Male, 20 years, from School C
Green colour = line linking cluster in map

Source: Kharsany et al. AIDS Research & Human Retroviruses 2014

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2. New approaches to enhancing ARV adherence for HIV treatment and prevention in women in Africa

- **Scale-up of AIDS treatment is rapid in Africa – goal is to put almost 25m HIV +ve people in Africa on ART**
- **Adherence to oral/topical ARV prophylaxis a challenge**
- **Health care delivery systems in several parts of Africa are dysfunctional – not able to reach many in need, provide quality care, maintain drug supply, monitor therapeutic response and maintain retention**
- **2 or 3-monthly injectable ARVs could help reduce health service burden eg. Rilpivirine and Cabotegravir**

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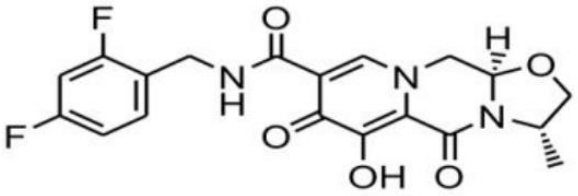
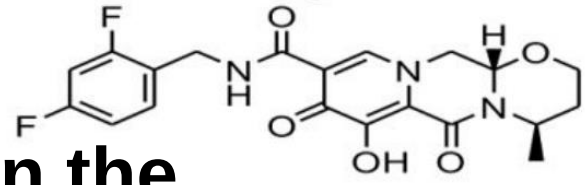
Prevent sub-optimal adherence through new long-acting antiretrovirals like Cabotegravir / GSK1265744LA

- **Integrase inhibitor – high genetic barrier to resistance**
- **Effective in suppressing viral load**
- **Half life: 21-50 days**
- **Administered as a 3-monthly injection**
- **Being studied for prevention in the HPTN 071 & CAPRISA 014 trials**

GSK1265744 (GSK744)



Dolutegravir



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3. New prevention strategies using broadly neutralizing antibodies

Evolution of an HIV glycan–dependent broadly neutralizing antibody epitope through immune escape

Penny L Moore[1,2], Elin S Gray[1], C Kurt Wibmer[1,2], Jinal N Bhiman[1,2], Molati Nonyane[1], Daniel J Sheward[3], Tandile Hermanus[1], Shringkhala Bajimaya[4], Nancy L Tumba[1], Melissa-Rose Abrahams[3], Bronwen E Lambson[1], Nthabeleng Ranchobe[1], Lihua Ping[5], Nobubelo Ngandu[3], Quarraisha Abdool Karim[6], Salim S Abdool Karim[6], Ronald I Swanstrom[5], Michael S Seaman[4], Carolyn Williamson[3] & Lynn Morris[1,2]

In 2012, we discovered of how humans can make broadly neutralising antibodies

Editorial in Nature Medicine accompanying our findings

A sweet surprise for HIV broadly neutralizing antibodies

nature medicine

Johannes P M Langedijk & Hanneke Schuitemaker

The production of cross-reactive neutralizing antibodies is the ultimate goal in HIV vaccine development, but no immunogen other than HIV itself has been able to elicit this type of humoral immunity. In natural HIV infections, these antibodies take several years to develop. A new study sheds light on what may be causing this delay in neutralizing antibody development (aaa–bbb).^

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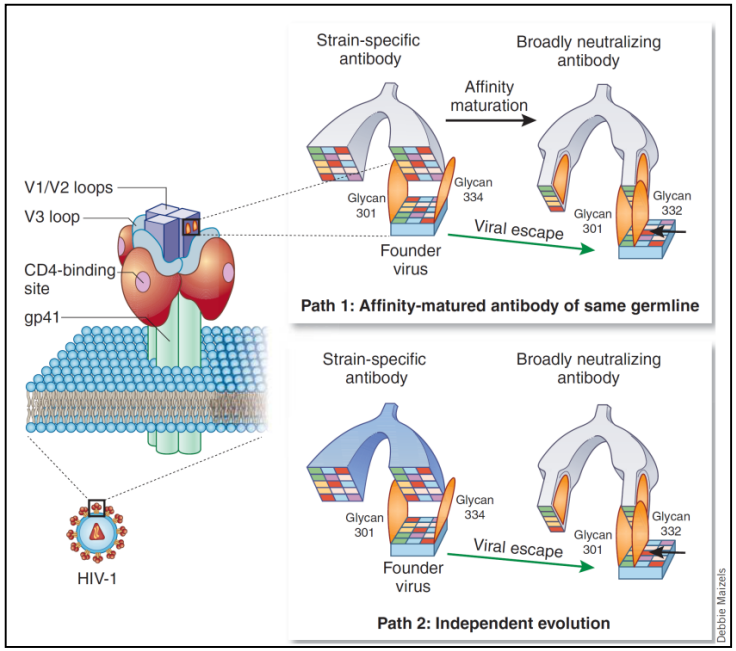
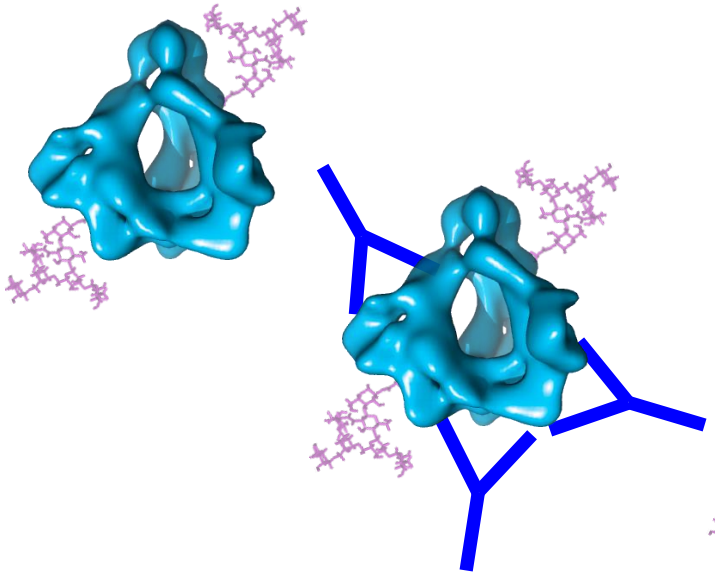
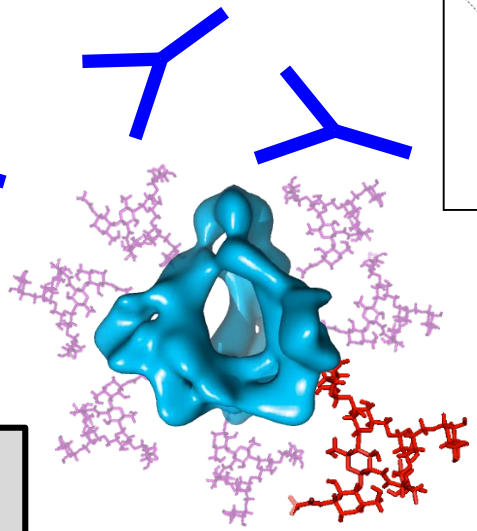
What did we show?



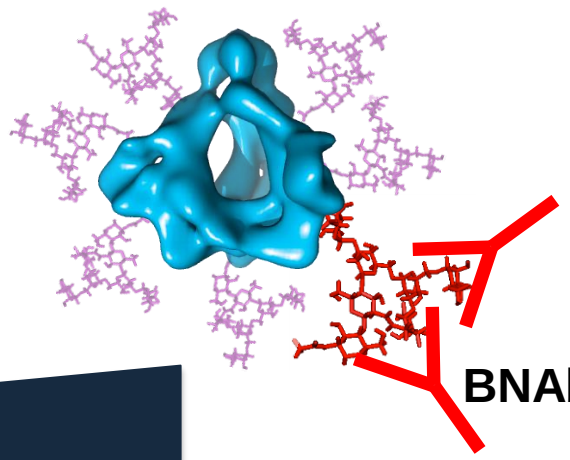


Strain-specific Ab

A woman from the CAPRISA 004 tenofovir gel trial developed a very unusual antibody that is able to kill about 88% of HIV strains from across the world



Glycan/sugar Moved 334 - 332



BNAb

years of infection

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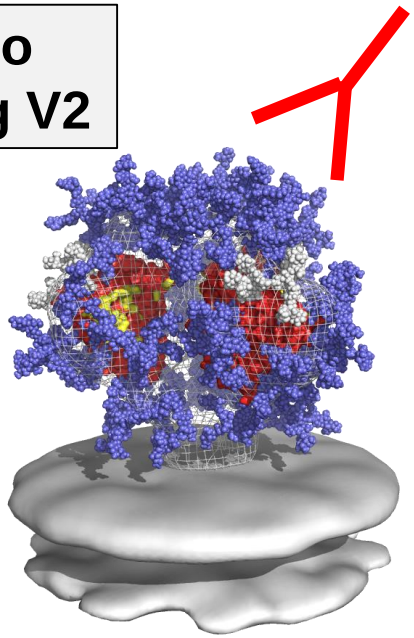
In 2013, we elucidated a pathway for V2-directed antibody development

Developmental pathway for potent V1V2–directed HIV–neutralizing antibodies

Nicole A. Doria-Rose[1]*, Chaim A. Schramm[2]*, Jason Gorman[1]*, Penny L. Moore[3,4,5]*, Jinal N. Bhiman[3,4], Brandon J. DeKosky[6], Michael J. Ernandes[1], Ivelin S. Georgiev[1], Helen J. Kim[7,8,9], Marie Pancera[1], Ryan P. Staupe[1], Han R. Altae-Tran[1], Robert T. Bailer[1], Ema T. Crooks[10], Albert Cupo[11], Aliaksandr Druz[1], Nigel J. Garrett[5], Kam H. Hoi[12], Rui Kong[1], Mark K. Louder[1], Nancy S. Longo[1], Krisha McKee[1], Molati Nonyane[3], Sijy O'Dell[1], Ryan S. Roark[1], Rebecca S. Rudicell[1], Stephen D. Schmidt[1], Daniel J. Sheward[13], Cinque Soto[1], Constantinos Kurt Wibmer[3,4], Yongping Yang[1], Zhenhai Zhang[2], NISC Comparative Sequencing Program†, James C. Mullikin[14,15], James M. Binley[10], Rogier W. Sanders[16], Ian A. Wilson[7,8,9,17], John P. Moore[11], Andrew B. Ward[7,8,9], George Georgiou[6,12,18], Carolyn Williamson[5,13], Salim S. Abdool Karim[5,19], Lynn Morris[3,4,5], Peter D. Kwong[1], Lawrence Shapiro[1,2] & John R. Mascola[1]

CAP256-VRC26.25 is a long-armed Ab - can reach to neutralize HIV through the sugar coating surrounding V2



- **Ultra-long CDRH3 ("long-arms")**
- **Highly potent antibody**
- **CAP256-VRC26.25 targets the V2 loop**
- **Monkey challenge studies in process**
- **Next - GMP manufacture for human trials**
- **Potential monthly injectable passive immunity**

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Conclusion

- **Laboratory Science:**

  Hotbed of Scientific & Clinical Research Discovery

- **Laboratory research has generated most of the HIV technologies in the global AIDS response today**
- **Laboratory research has the potential to make many more great contributions**
- **Continue promoting laboratory medicine through our high impact research results…**

…they are our most powerful advocates!

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