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Research Institute

Impact of the HIV Epidemic on the Blood Supply System and Responses to Potential Transfusion Transmitted Emerging Infections Diseases

Michael Busch, MD, PhD

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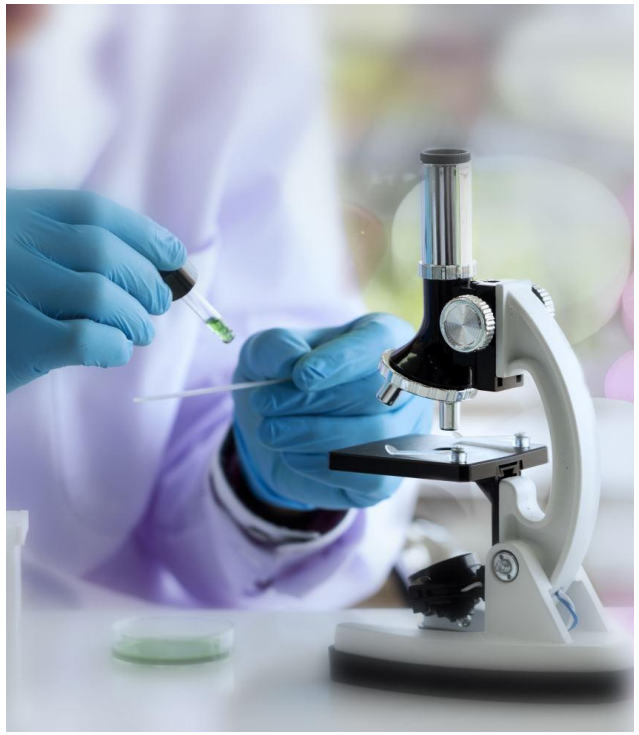
Vitalant Research Institute



The Vitalant Research Institute (VRI) is dedicated to advancing blood safety and efficacy world-wide through scientific research, education and the promotion of evidence-based policies, and to contributes to discovery and translational research based on global blood donor surveillance and pathogenesis studies.

The **Vitalant Innovation Center (VIC)** extends and focuses programs within VRI and the Vitalant Blood Services Division (BSD) to knit together discovery and translational science with implementation

History of Vitalant Research Institute

1959

Irwin Memorial Blood Center Research and Scientific Services

Research Program established by Herb Perkins

1986

Mike Busch joins Irwin Scientific Services

1998

Blood Centers of the Pacific & affiliation with Blood Systems Inc.

Blood Centers of the Pacific

2004

Blood Systems Research Institute (BSRI) founded

Blood Systems Research Institute

2016

BSRI Denver opened

2018

Renamed Vitalant Research Institute (VRI)

vitalant Research Institute

2021

Vitalant Innovation Center (VIC) opened in Denver

vitalant Innovation Center

2022

VRI new facility in SF opened

Brian Custer becomes Director

Major Research Programs

2020s

2021 – SARS-CoV-2 Options to EQAPOL
2021 – Transfusion-Transmissible Infections Monitoring System (TTIMS)
2020 – SARS-CoV-2 Supplement to REDS-IV-Pediatric
2020 – National SARS-CoV-2 Seroincidence Studies in Blood Donors & Research Donor Cohort Studies
2020 – Assessing Donor Variability and New Concepts in Eligibility (ADVANCE) Study
2022 – Innate Sensing of the Cell-Free DNA & the Interferon-Mediated Control of HIV *in Vivo*
2022 – Hematopoietic & Immune Development in the Human Chorion
2021 – ACTIV Integration of Host-targeting Therapies for COVID-19 Administrative Coordinating Center (C3PO)
2020 – Transfusion-Related Immunomodulation Influences Infectious Disease Outcomes

2010s

2014 – Multiplex treatment-Outcomes Test fir Chagas Disease
2014 – Chikungunya Seroprevalence Study in Puerto Rico Following a 2014 Outbreak
2014 – Validation of Ultra-Sensitive Assays for Quantifying HIV Persistence (RAVEN)
2012 – HIV Incidence Testing using Multiple Biological Specimens (CEPHIA)
2012 – Screening and Confirmatory Testing for Human Babesia-SBIR Phase II
2011 – Recipient Epidemiology and Donor Evaluation Study-III – Central Laboratory
2010 – Impact of Early Antiretroviral Therapy on HIV Persistence and Inflammation
2010 – External Quality Assurance Program Oversight (EQAPOL)
2019 – The Impact of Illness and Medical Treatments on the Alloantibody Response to Platelet Transfusion
2019 – NIAID Virology Quality Assurance (VQA)
2018 – REDS-IV-Pediatric
2017 – RedeS
2016 – ZIKV Supplement to REDS-III
2016 – amfAR Institute for HIV Cure Research

2000s

2004 – Acute HCV Infection in Injection Drug Users
2004 – Natural History & Pathogenesis of WNV in Viremic Blood Donors
2003 – Natural History of Acute and Chronic HCV in Blood Donors
2002 – Immunologic and Virologic Features of Early HIV Infection (OPTIONS)
2009 – Viral/immune Parameters of Dengue and WNV in Donors
2006 – Mechanisms and Clinical Effects of Microchimerism in Transfused Trauma Patients
2004 – Retrovirus Epidemiology Donors Study, Part II (REDS-II)

1990s

1999 – Pathophysiology of HTLV-I and HTLV-II Infection "HOST"
1996 – Donor Leucocyte Activation/Proliferation Post-Transfusion
1994 – Viral Activation in Transfusion Study, VATS
1992 – Impact of Homologous Blood Transfusion on HIV Replication and Disease in vivo (AABB NBF)
1992 – HIV Diversity/Pathogenesis in Donor/Recipient Clusters

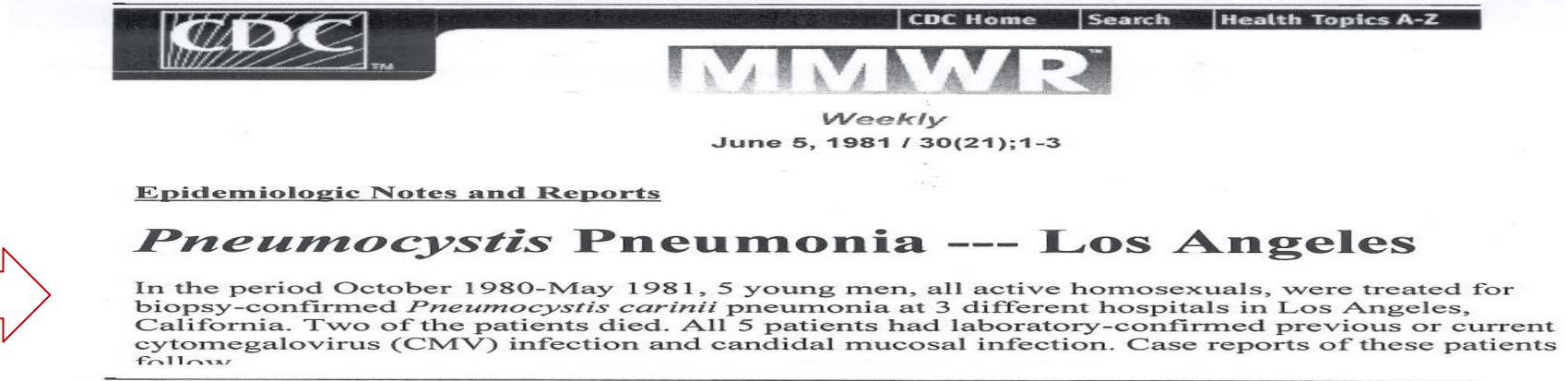
1980s

1987 – AIDS Epidemiologic Study of Blood Donors
1986 – Transfusion-Related Viral Infections and Immune Response
1986 – Effectiveness of HIV-1 Screening
1986 – Development/Evaluation of New Screening Tests for HTLV-III HIV-1 Antibodies/Antigens/Nucleic Acids
1984 – Transfusion Safety Study (TSS)
1989 – Retrovirus Epidemiology Donor Study, REDS-I
1988 – Removal/Inactivation of Viruses in Blood
1988 – Natural History of AIDS in Homosexual Man ("San Francisco Men's Health Study")
1987 – Epidemiologic Study of Heterosexual Transmission of HIV from Persons with Transfusion-Associated Infections ("Partner Study")

Outline

- Discovery of TT-HIV and pre-screening risk
- Progressive improvements of HIV serological and NAT systems/assays for donor screening
- Molecular surveillance and breakthrough infections
- Implications for advancing HIV diagnostics and staging
- Implications for HIV surveillance & pathogenesis
- Response to Emerging Infectious Diseases

June 5, 1981



CDC Home | Search | Health Topics A-Z

MMWR

Weekly

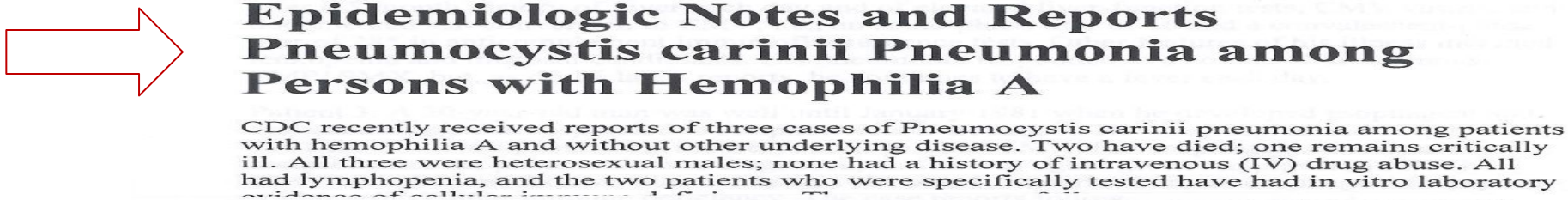
June 5, 1981 / 30(21);1-3

Epidemiologic Notes and Reports

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

July 16, 1982



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MMWR

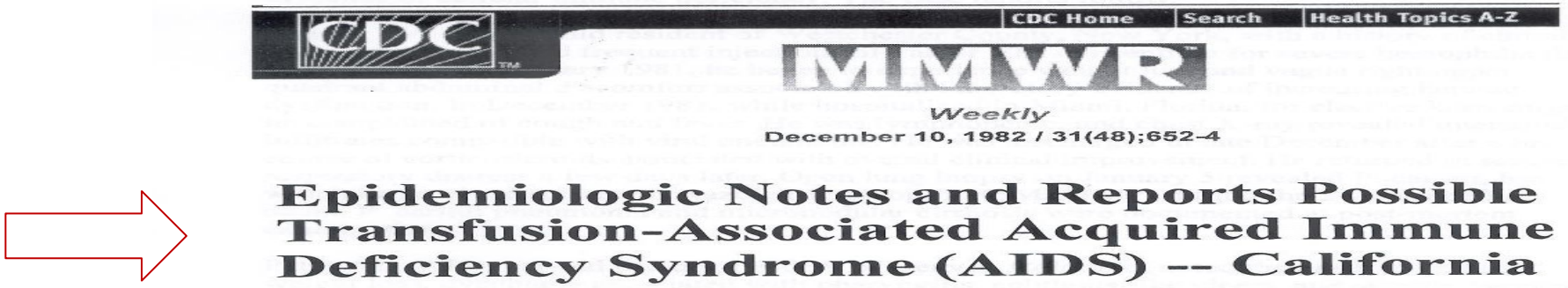
Weekly

July 16, 1982 / 31(27);365-7

Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among Persons with Hemophilia A

CDC recently received reports of three cases of Pneumocystis carinii pneumonia among patients with hemophilia A and without other underlying disease. Two have died; one remains critically ill. All three were heterosexual males; none had a history of intravenous (IV) drug abuse. All had lymphopenia, and the two patients who were specifically tested have had in vitro laboratory

Dec 10, 1982



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MMWR

Weekly

December 10, 1982 / 31(48);652-4

Epidemiologic Notes and Reports Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) -- California

"This report and continuing reports of AIDS among persons with hemophilia A raise serious questions about the possible transmission of AIDS through blood and blood products."

Workgroup to Identify Opportunities for Prevention of Acquired Immune Deficiency Syndrome

January 4, 1983, CDC, Atlanta

isease detectives puzzle over problem of control

$4,000, from 1-A
rom being stigmatized.
emophiliac associations
o avoid increasing the cost
d products or interrupting
pply.
blood-processing companies
blood banks wanted to avoid
bering the blood-collecting
s with additional costly tests.
CDC was mainly interested in
ng the dangers to public health
alarming society, regardless of
special interests got hurt. Or at
that was the ideal.

•

he meeting started promptly at
Tuesday morning in Auditorium
which was the smaller of the
C's two auditoriums but still quite
ge. The room was half filled by
ur long tables arranged in a
uare, so there was no head table
nd all 38 people sitting around the
quare were of ostensibly equal im-
portance.

About 150 observers crowded the remaining half of the room, occupying all the folding chairs and standing at the rear.

Most of the discussions and arguments would come that afternoon. The morning would be spent listening to the latest grim details of the epidemic. The disease in question was called Acquired Immune Deficiency Syndrome (AIDS) because it impaired its victims' immune system, leaving them hopelessly vulnerable to infections.

"We now have 881 cases," said Dr. Harold Jaffe, addressing the gathering from in front of a large movie screen that displayed the figures. "Fifty-nine percent of cases have been reported since January of last year."

As is customary at medical gatherings, Jaffe, a member of the AIDS task force, spoke in almost a monotone, with no display of emotion or other sign of the frightening nature of his data. He neglected to point out that the number of cases was continuing to double every six months.

Most of the victims, 74.6 percent, were gay, Jaffe said. No one knew why. The only clue was that the homosexuals who had AIDS were unusually promiscuous. They had had sex with an average of 61 different partners each year, as compared

Meeting at the Centers for Disease Control are epidemiologists and blood specialists concerned with the AIDS epidemic and worried about U.S. blood supplies

The danger to hemophiliacs — which was the main reason the meeting had been called — was addressed by Dr. Bruce L. Evatt, who had represented the CDC at a similar emergen-

under investigation. Eight of the 10 victims were dead, he said. In only six months, AIDS had become the second leading cause of death for hemophiliacs, second only to uncon-

Blood banks and commercial processors could stop using blood from high-risk groups, primarily homosexuals. Or, they could test the blood after they get it, to see whether

The New England
Journal of Medicine

Volume 310 JANUARY 12, 1984 Number 2

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) ASSOCIATED WITH TRANSFUSIONS

JAMES W. CURRAN, M.D., DALE N. LAWRENCE, M.D., HAROLD JAFFE, M.D., JONATHAN E. KAPLAN, M.D., LAWRENCE D. ZYLA, M.P.H., MARY CHAMBERLAND, M.D., ROBERT WEINSTEIN, M.D., KUNG-JONG LUI, PH.D., LAWRENCE B. SCHONBERGER, M.D., THOMAS J. SPIRA, M.D., W. JAMES ALEXANDER, M.D., GARY SWINGER, D.V.M., ARTHUR AMMANN, M.D., STEVEN SOLOMON, M.D., DAVID AUERBACH, M.D., DONNA MILDVAN, M.D., RAND STONEBURNER, M.D., JANINE M. JASON, M.D., HARRY W. HAVERKOS, M.D., AND BRUCE L. EVATT, M.D.

Transfusion Safety Study (TSS)

Rate of Transmission and Factors Influencing Human Immunodeficiency Virus Type 1 Transmission by Blood Transfusion and Pathogenesis

200,000 donor samples were saved in 1984 prior to HIV Ab testing
0.23% of repository samples test positive HIV on 1st gen Ab assays
91% of recipients of HIV-1 antibody positive transfusions were infected

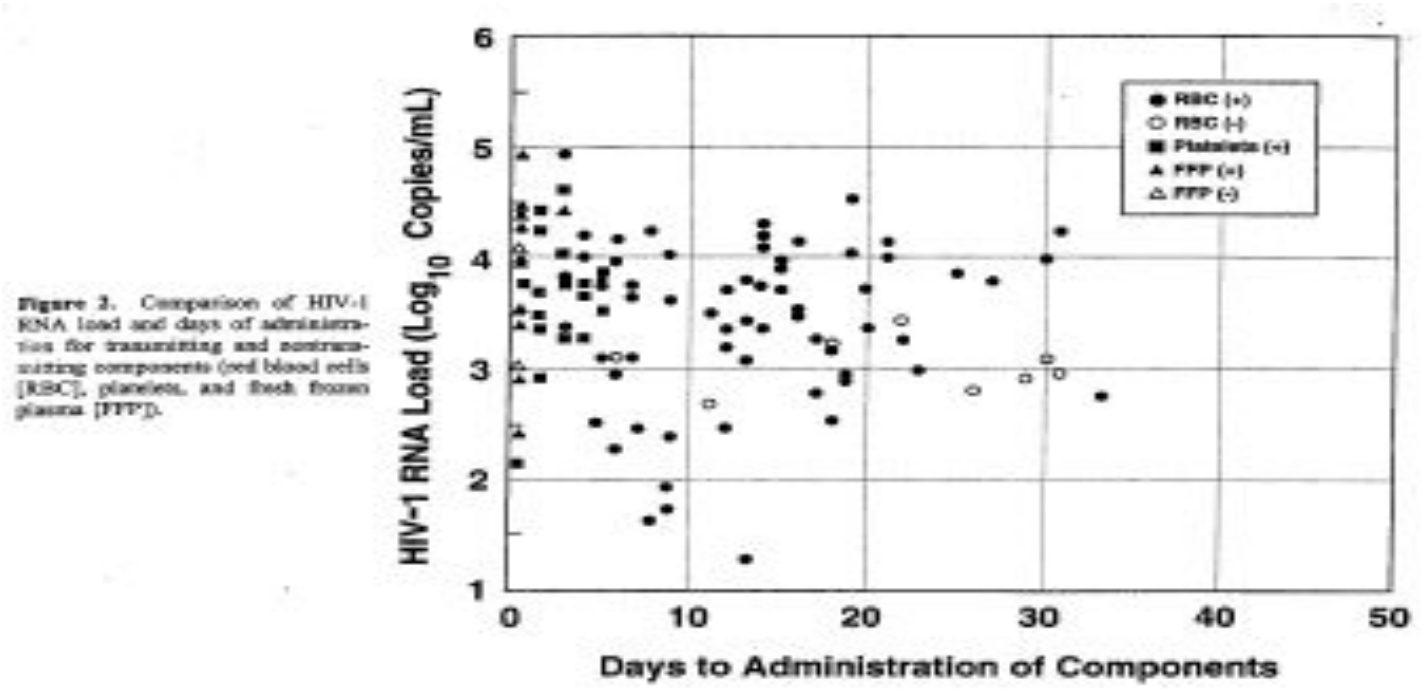
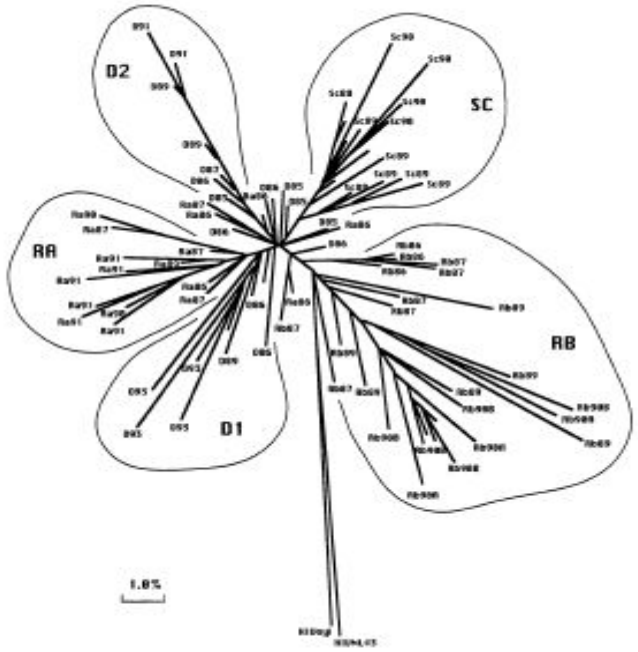


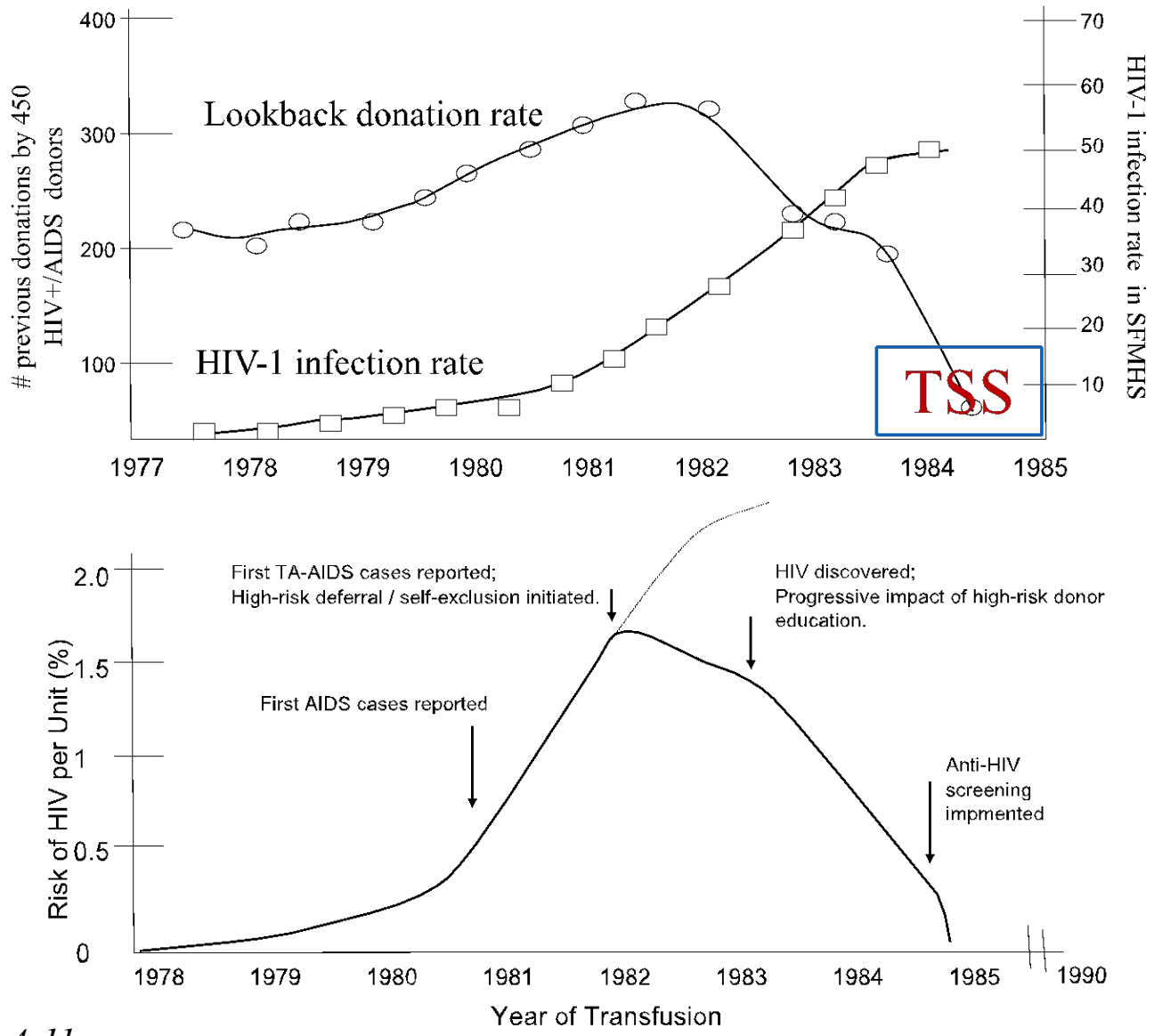
Figure 3. Comparison of HIV-1 RNA load and days of administration for transmitting and nontransmitting components (red blood cells [RBC], platelets, and fresh frozen plasma [FFP]).



Independent evolution of HIV quasispecies in linked donors and recipients

Donegan et al Ann Intern Med 113:733–739, 1990
Busch et al. JID 174: 26 - 33, 1996
Diaz et al. AIDS 11: 415 - 422, 1997

Risk of HIV Transmission by Blood Transfusions Before the Implementation of HIV-1 Antibody Screening



Busch et al. Transfusion 1991; 3: 4-11

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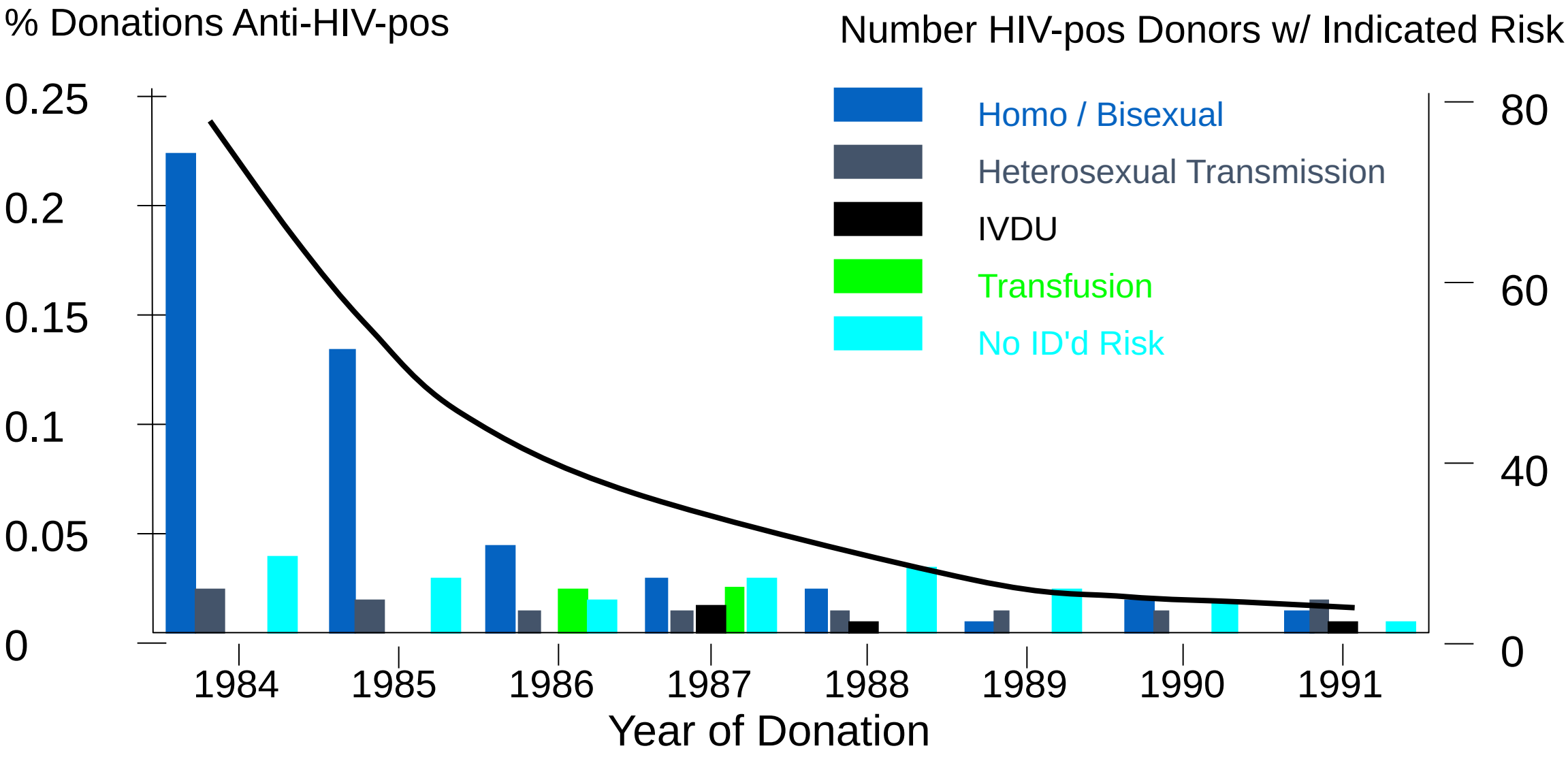
Rate and risk factors of HIV-infected donors in SF



Busch MP. *Retroviruses and Blood Transfusions: The Lessons Learned and the Challenge Yet Ahead. Blood Safety: Current Challenges. Transfusion 1992*

TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) BY BLOOD TRANSFUSIONS SCREENED AS NEGATIVE FOR HIV ANTIBODY

JOHN W. WARD, M.D., SCOTT D. HOLMBERG, M.D., JAMES R. ALLEN, M.D., DAVID L. COHN, M.D., SARA E. CRITCHLEY, M.S.N., STEVEN H. KLEINMAN, M.D., BRUCE A. LENES, M.D., OTTO RAVENHOLT, M.D., M.P.H., JACQUALYN R. DAVIS, MT(ASCP), M. GERALD QUINN, M.D., AND HAROLD W. JAFFE, M.D.

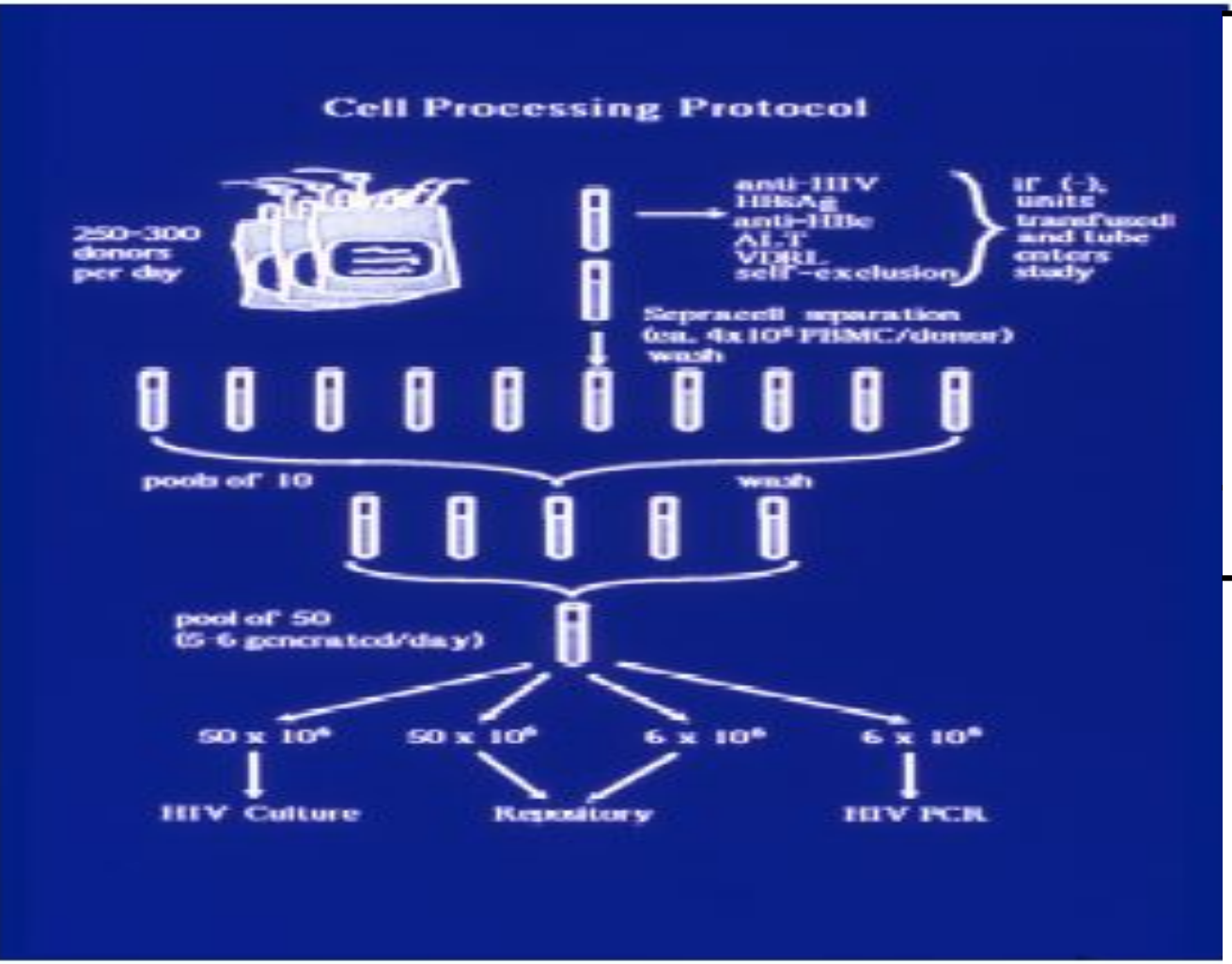
Table 1. Cases of HIV Transmitted by Screened Blood Investigated March 1985 to October 1987, United States.

DONOR (NO./AGE/SEX)	MODE OF HIV TRANSMISSION TO DONOR	PUTATIVE PERIOD FROM INFECTION OF DONOR TO DONATION	ACUTE RETROVIRAL SYNDROME	RECIPIENT (NO./AGE/SEX)	TYPE OF COMPONENT RECEIVED*
1/31/M†	Homosexual	<12 wk	No	1/60/M	Platelets
				2/57/M	RBC
2/28/F	Heterosexual	<14 wk	No	3/46/M	RBC
				4/61/F	Cryo
3/20/M	Homosexual	<16 wk	No	5/<1/F	Platelets
				6/55/M	FFP
4/34/M	Homosexual	Unknown	No	7/71/F	RBC
				8/45/M	Platelets
5/39/M	Unknown	<16 wk	Yes	9/71/F	RBC
				10/56/M	RBC
6/20/M	Homosexual	Unknown	No	11/71/F	RBC
7/34/M	Homosexual	<12 wk	Yes	12/66/F	RBC
				13/57/M	FFP

*RBC denotes red cells, Cryo cryoprecipitate, and FFP fresh-frozen plasma.

†As described in reference 8.

HIV Culture and PCR of Pools of PBMCs from 75,000 Seronegative SF Blood Donations

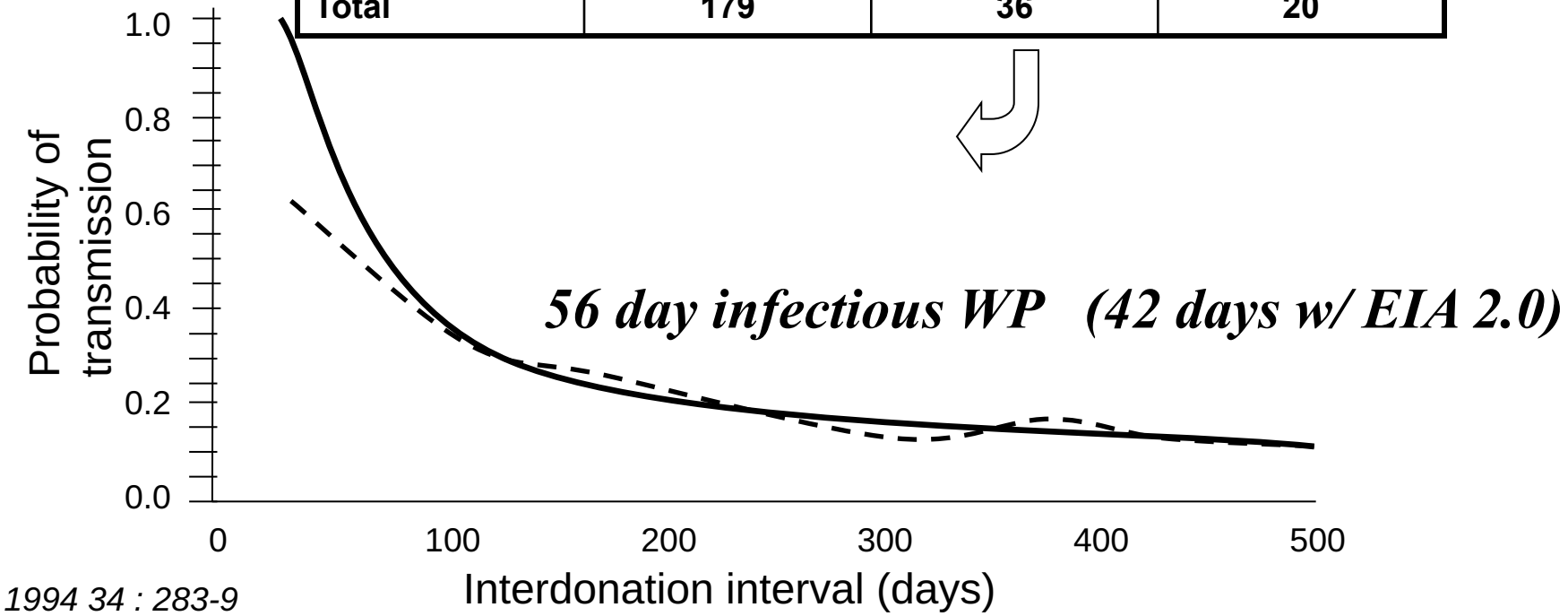


Status of Pool	No.	(%)
Available for culture	1,530	
Contaminated by bacteria	94	(6.1)
Completed culture	1,436	(93.9)
Positive for HIV-1		
Initially *	11	(0.7)
Confirmed †	**1**	(0.07)
Available for PCR	873	
Reactive		
Initially *	55	(6.3)
Repeatedly †	21	(2.4)
Confirmed	**1**	(0.11)

Busch … Vyas. N Engl J Med 325, 1991

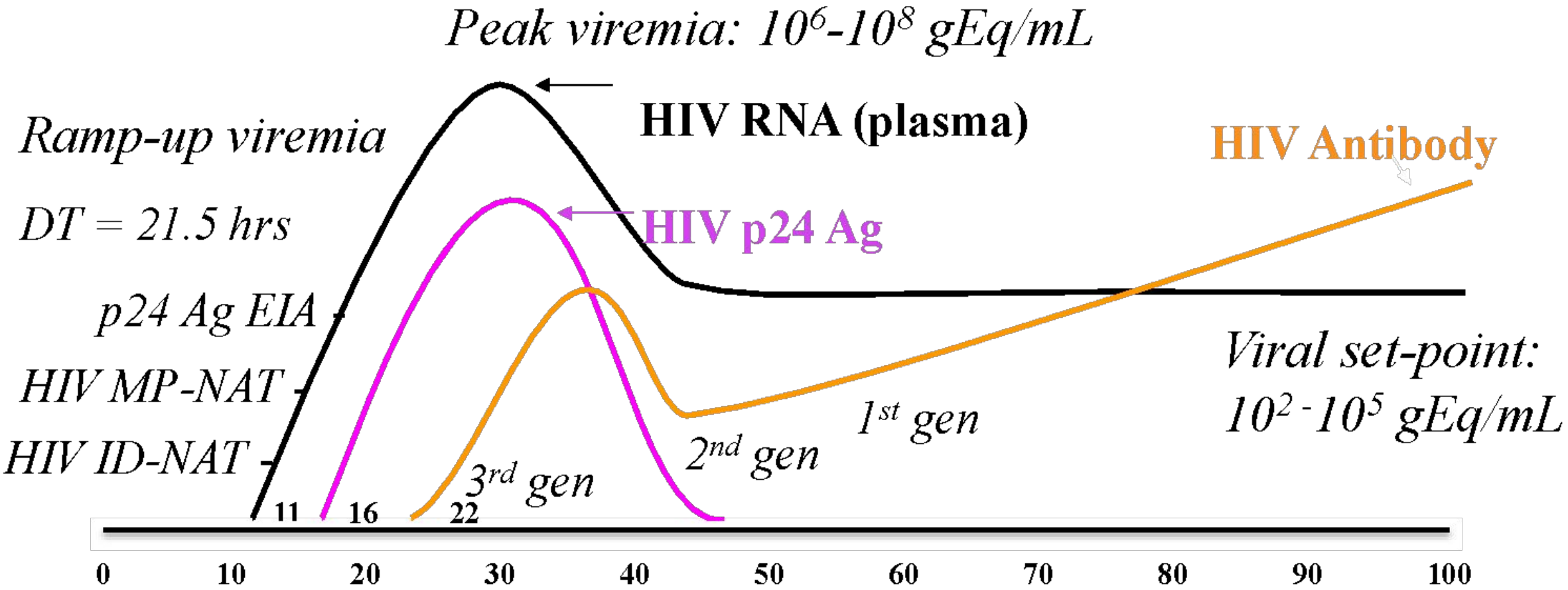
HIV-1 transmission by transfusion of blood from SC donors according to the inter-donation interval

Interdonation interval (days)	Total	HIV-1 transmission	
		Number	Percentage
45 - 90	17	13	76
91 - 180	29	8	28
181 - 360	48	9	19
361 - 540	39	5	13
541 - 720	14	0	0
> 720	32	1	3
Total	179	36	20



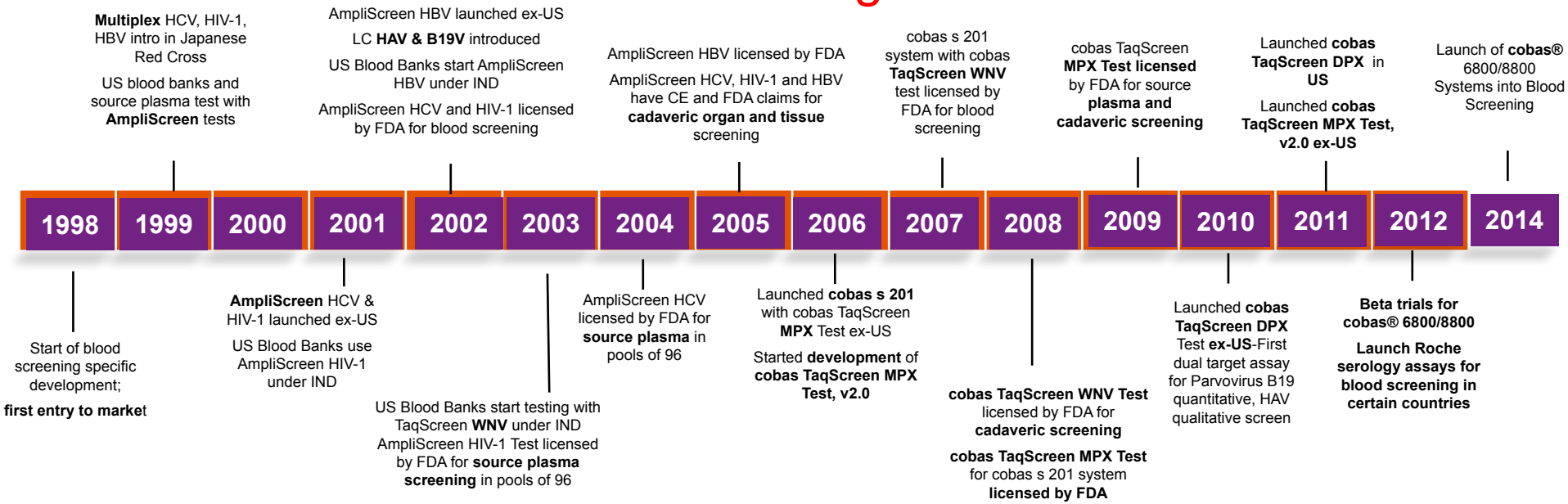
Petersen et al. Transf. 1994 34 : 283-9

HIV Viremia and Seroconversion during Acute Infection

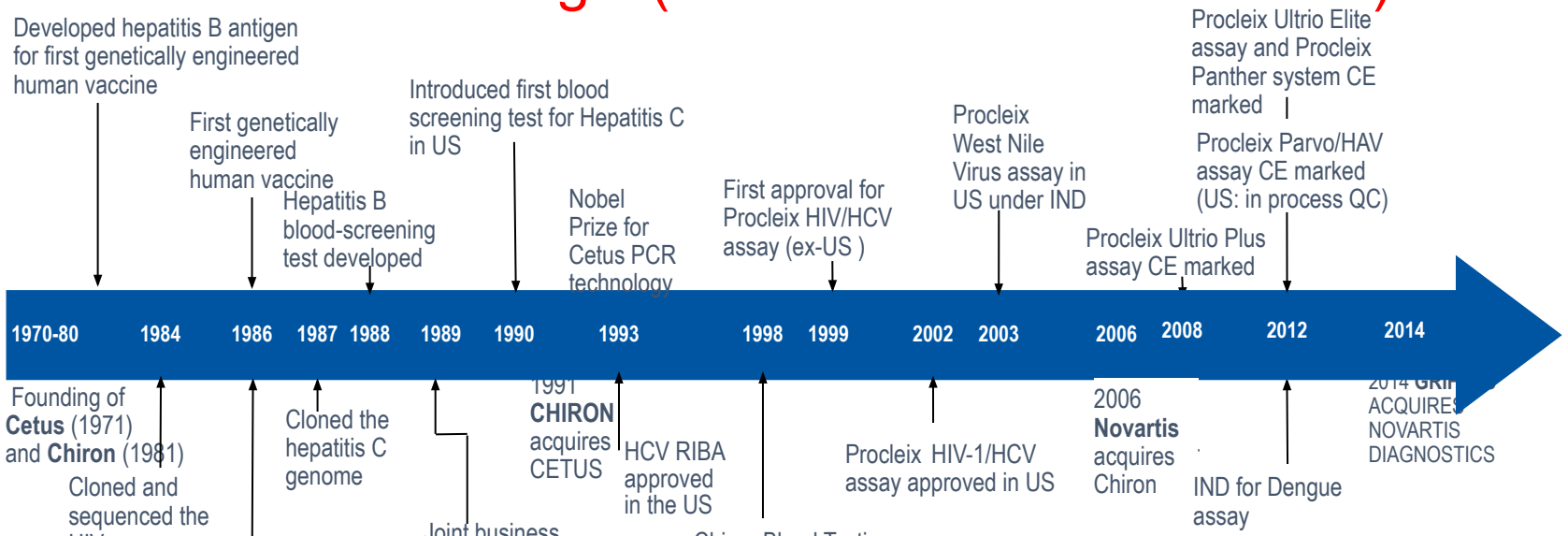


Transfusion. 2022;62:1334–1339.

Roche Diagnostics



Grifols/Holgic (Chiron/Novatis/Gen-Probe)



INTERNATIONAL FORUM

DOI: 10.1111/j.1423-0410.2011.01506.x
Vox Sanguinis

International survey on NAT testing of blood donations: expanding implementation and yield from 1999 to 2009

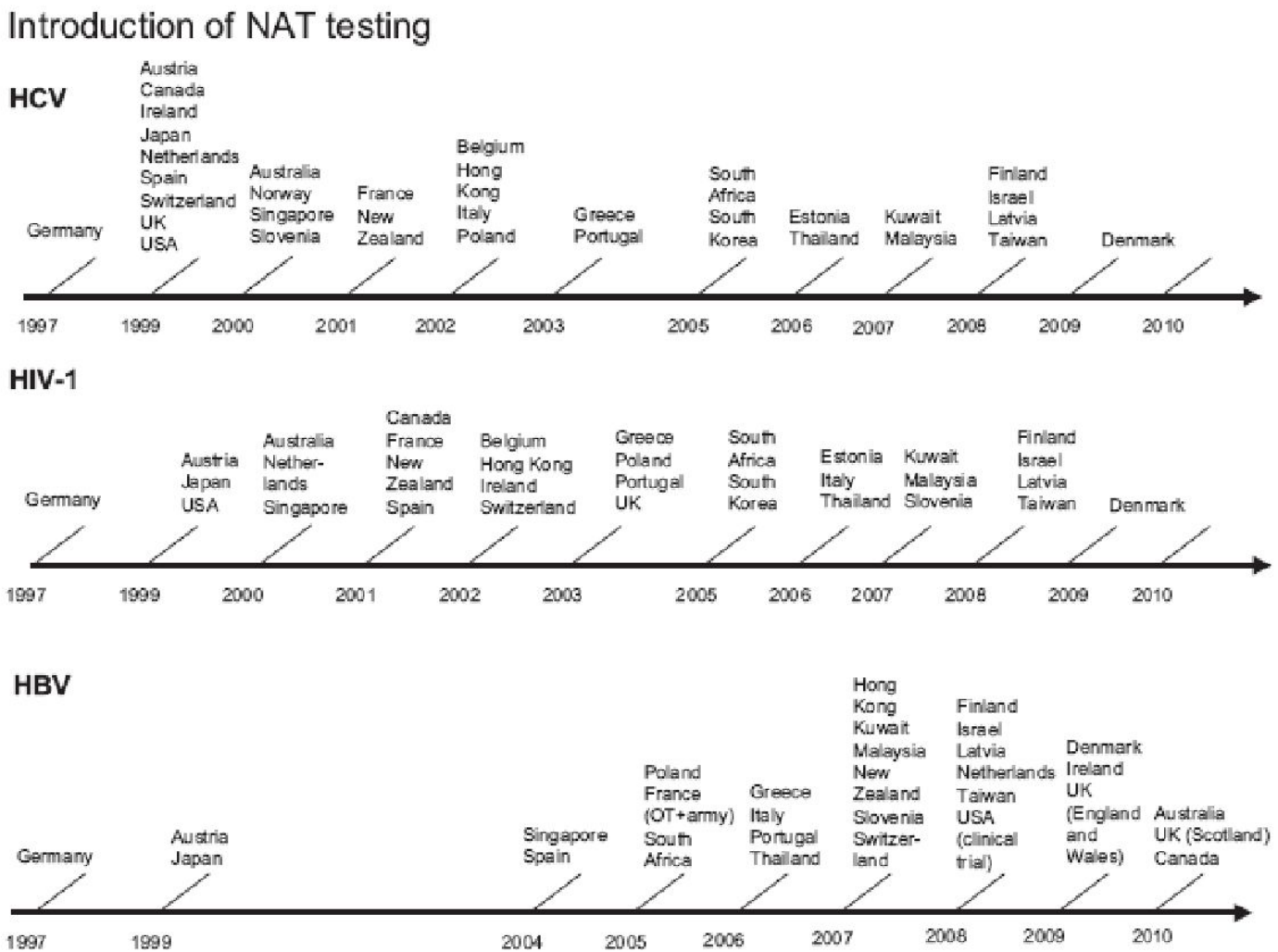
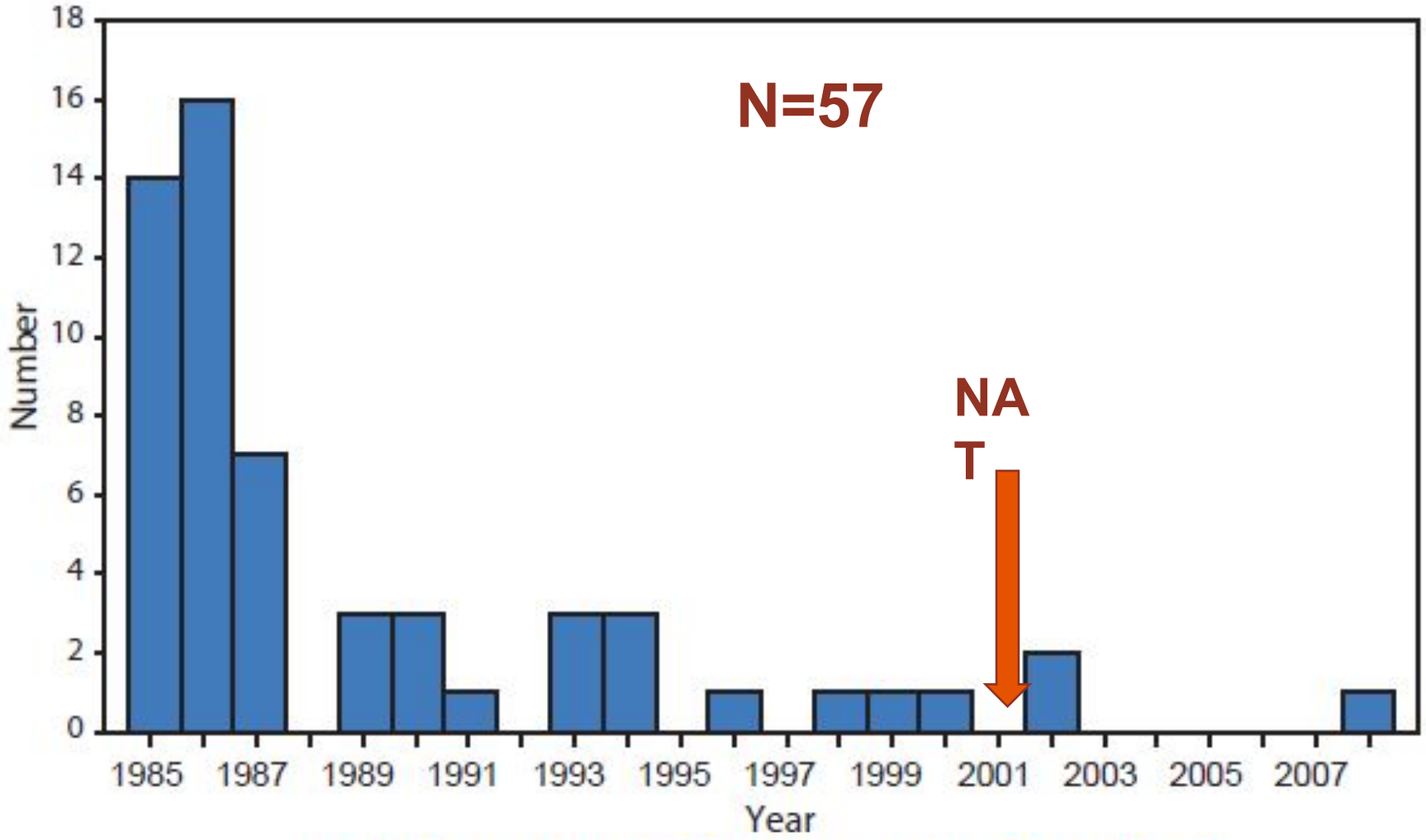


FIGURE 2. Number of cases of transfusion-transmitted HIV infection from contaminated blood products, by transfusion year — United States, 1985–2008



MMWR / October 22, 2010 / Vol. 59 / No. 41

JOURNAL OF VIROLOGY, Apr. 2009, p. 3288–3297 Vol. 83, No. 7
0022-538X/09/$08.00+0 doi:10.1128/JVI.02423-08

High Specific Infectivity of Plasma Virus from the Pre-Ramp-Up and Ramp-Up Stages of Acute Simian Immunodeficiency Virus Infection▽

Zhong-Min Ma,[1,2] Mars Stone,[1,2] Mike Piatak, Jr.,[3] Becky Schweighardt,[4] Nancy L. Haigwood,[5] David Montefiori,[6] Jeffrey D. Lifson,[3] Michael P. Busch,[7,8] and Christopher J. Miller[1,2,9]*

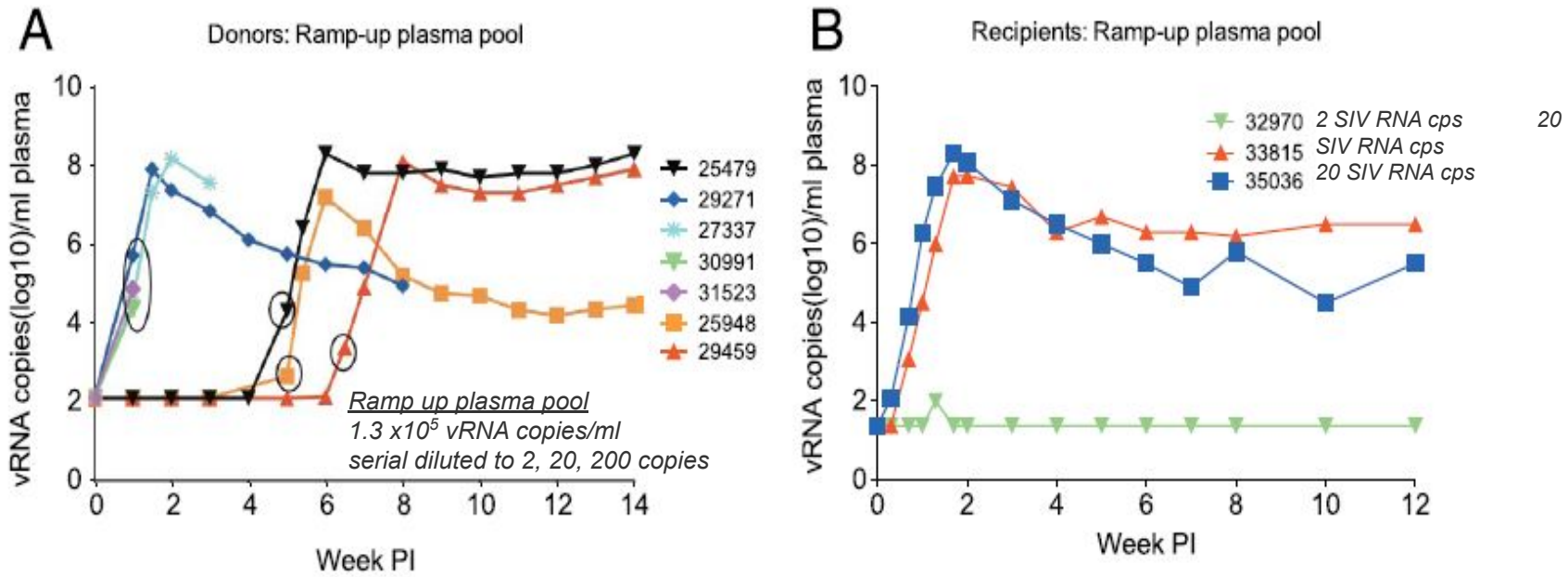
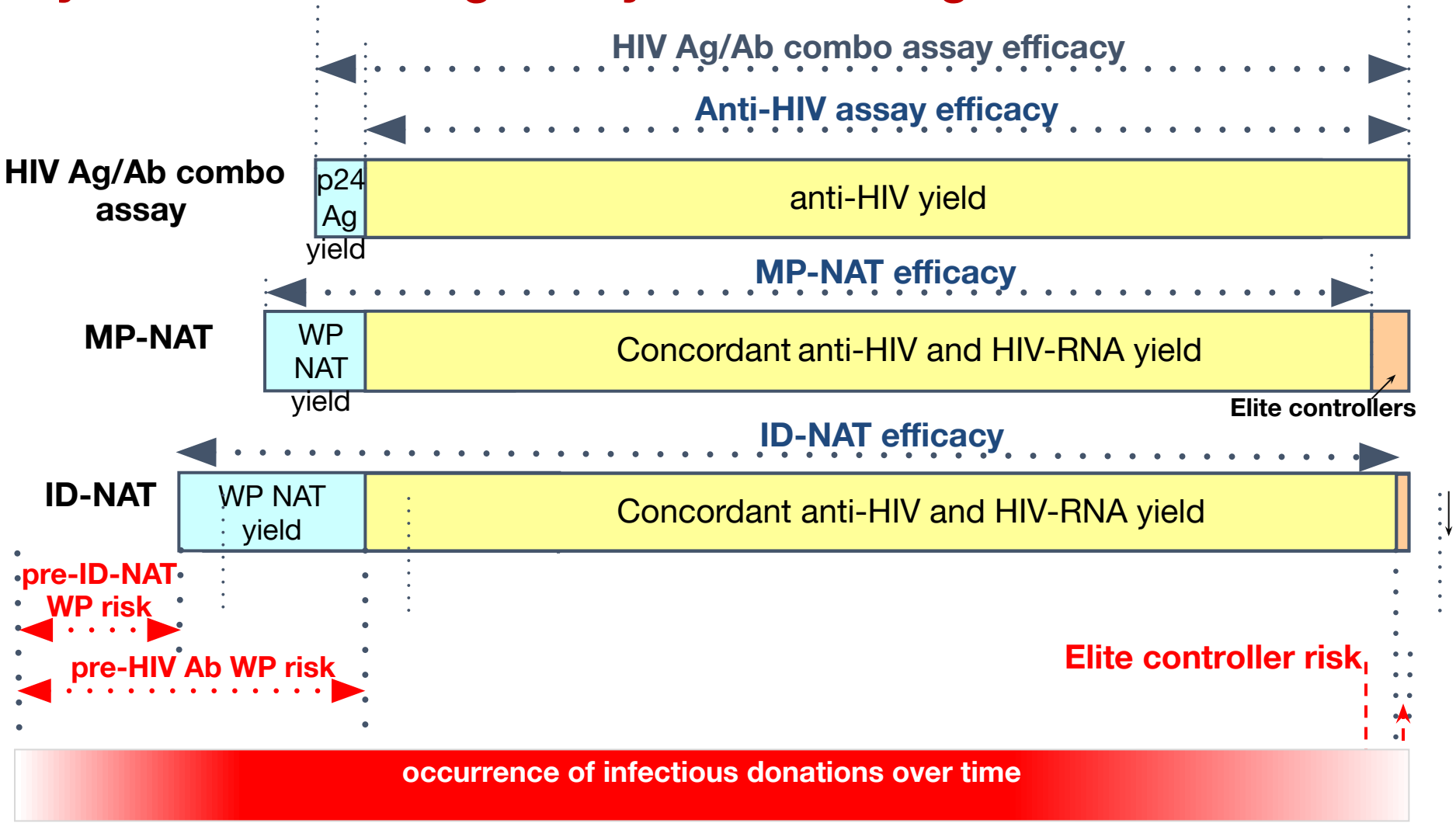


FIG. 3. vRNA$^+$ plasma samples used to produce the ramp-up-stage plasma pool and outcome of challenge of recipient animals with the serially diluted ramp-up-stage plasma pool. (A) Plasma vRNA levels in donor animals that were vaginally inoculated twice in one day with 10^5 $TCID_{50}$ of SIVmac251 or weekly from 0 to 13 weeks with 10^3 $TCID_{50}$ of SIVmac251 until infection was detected. Each sample used to make up the ramp-up-stage pool is circled. (B) Plasma vRNA levels in SIV-naïve recipient animals after i.v. infusion of the ramp-up-stage plasma pool. While 1 animal inoculated i.v. with 2 SIV RNA copies (animal 32970) did not become infected, 2 of 2 animals inoculated i.v. with 20 SIV RNA copies (animals 33815 and 35036) did become infected. These two animals had a typical pattern of viremia after the plasma transfer.

Macaque ID_{50} = 1-10 SIV virions / inocula

Efficacy of HIV Screening Assays and Closing Infectious Window Period

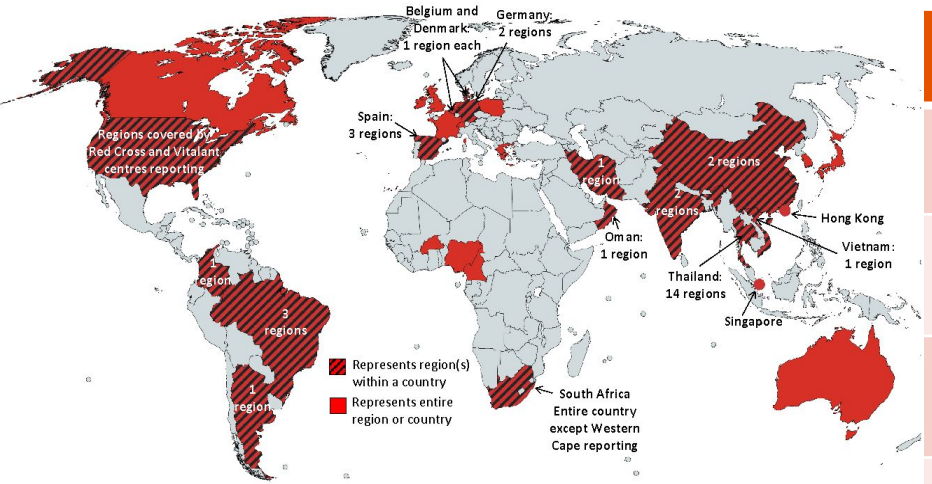


Bruhn et al. Transfusion 2013:53:2399-2412

P228

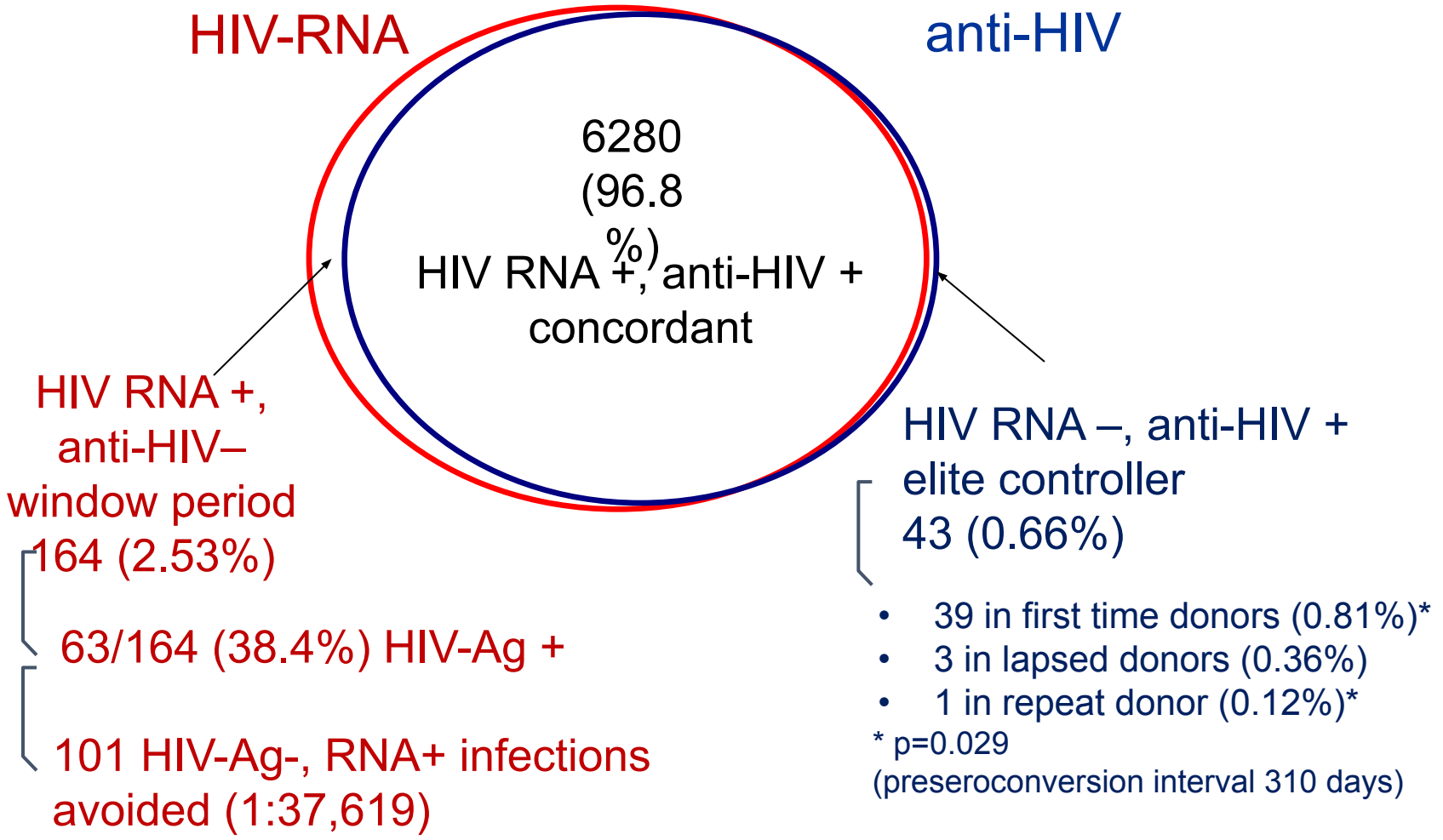
Global Nucleic Acid Amplification Testing (NAT) Use and Confirmatory Testing Approaches in Blood Donor Screening

HM Faddy[1,2], J Acutt[1], MM Dean[1,2], C Osiowy[3], Clive Seed[4], Brian Custer[5], Michael Busch[5], Susan Stramer[6]
on behalf of the Virology and SRAP subgroups of the ISBT WP on TTID.



	HIV-1	HCV	HBV	HEV	WNV	ZIKV
No. tested	517,547,384	540,392,660	370,188,565	7,721,980	140,202,921	19,301,071
NAT positive	32,914	74,945	67,895	1,763	3,143	589
First time^	61%	80%	75%	91%	13%	14%
Repeat^	39%	20%	25%	9%	87%	86%
NAT yield*	1,155 2.2/million	1,121 2.07/million	14,376 39/million	228/million	22/million	30/million
First time^	24%	36%	29%	-	-	-
Repeat^	76%	64%	71%	-	-	-

HIV infections in five years of ID-NAT screening of 3,799,509 donations in South Africa (SANBS)



Vermeulen M et al, (SANBS, Johannesburg, South Africa)

HIV is back in the blood safety spotlight

June 2019

Ending the HIV Epidemic: A Plan for America

HHS is proposing a once-in-a-generation opportunity to eliminate new HIV infections in our nation. The multi-year program will infuse 48 counties, Washington, D.C., San Juan, Puerto Rico, as well as 7 states that have a substantial rural HIV burden with the additional expertise, technology, and resources needed to end the HIV epidemic in the United States. Our four strategies – diagnose, treat, protect, and respond – will be implemented across the entire U.S. within 10 years.

GOAL:

75% reduction in new HIV infections in 5 years and at least **90%** reduction in 10 years.

HHS will work with each community to establish local teams on the ground to tailor and implement strategies to:

- **Diagnose** all people with HIV as early as possible.
- **Treat** people with HIV rapidly and effectively to reach sustained viral suppression.
- **Prevent** new HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs).
- **Respond** quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.

The Initiative will target our resources to the 48 highest burden counties, Washington, D.C., San Juan, Puerto Rico, and 7 states with a substantial rural HIV burden.

Geographical Selection:
Data on burden of HIV in the US shows areas where HIV transmission occurs more frequently. More than 50% of new HIV diagnoses* occurred in only 48 counties, Washington, D.C., and San Juan, Puerto Rico. In addition, 7 states have a substantial rural burden – with over 75 cases and 10% or more of their diagnoses in rural areas.

*2016-2017 data

Ending the HIV Epidemic | www.HIV.gov

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hivma
hiv medicine association

UNDETECTABLE = UNTRANSMITTABLE

In 2017, HIVMA endorsed the *U=U Consensus Statement*, saying definitively that when a person living with HIV has an undetectable viral load, they will not transmit HIV.

The science is clear.

- **HPTN 052**
- **PARTNER**
- **Opposites Attract**
- **PARTNER 2**

Combined data from 2008-2016 show that **there were ZERO linked HIV transmissions** after more than **a hundred thousand condom-less sex acts** within both heterosexual and male-male serodiscordant couples where the partner living with HIV had a **durably undetectable viral load**.

But the need remains great.

- Only **11%** of young adults 18-30 believe that ART is "very effective" in preventing HIV.
- Only **50%** of people living with HIV are engaged in care and virally suppressed.

*"The body of scientific evidence to-date has established that there is **effectively no risk of sexual transmission of HIV** when the partner living with HIV has a durably undetectable viral load, **validating the U=U message of HIV treatment as prevention.**"*

Anthony S. Fauci, MD
July 2018

www.HIVMA.org | Oct. 2018 | #UequalsU

HIV Diagnosis

Elliott T et al. *Journal of the International AIDS Society* 2019, **22**:e25419
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25419/full | https://doi.org/10.1002/jia2.25419

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

REVIEW

Challenges of HIV diagnosis and management in the context of pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), test and start and acute HIV infection: a scoping review

Tamara Elliott[1,2], Eduard J Sanders[3,4], Meg Doherty[5], Thumbi Ndung'u[6,7,8,9], Myron Cohen[10], Pragna Patel[11], Gus Cairns[12,13], Sarah E Rutstein[10], Jintanat Ananworanich[14,15], Colin Brown[16,17] and Sarah Fidler[1,18,§]

Discussion: Missed acute HIV infection prevents people living with HIV (PLHIV) from accessing early treatment, increases likelihood of onward transmission, and allows for inappropriate initiation or continuation of PrEP, which may result in HIV drug resistance. While immediate ART is recommended for all PLHIV, studies have shown that starting ART in the setting of acute HIV infection may result in a delayed or complete absence of development of HIV-specific antibodies, posing a diagnostic challenge that is particularly pertinent to resource-limited, high HIV burden settings where HIV-antibody POCTs are standard of care. Similarly, ART used as PrEP or PEP may supress HIV RNA viral load, complicating current HIV testing algorithms in resource-wealthy settings where viral detection is included. As rollout of PrEP continues, HIV testing algorithms may need to be modified.

Conclusions: With increasing use of PrEP and ART in acute infection we anticipate diagnostic challenges using currently available HIV testing strategies. Research and surveillance are needed to determine the most appropriate assays and optimal testing algorithms that are accurate, affordable and sustainable.

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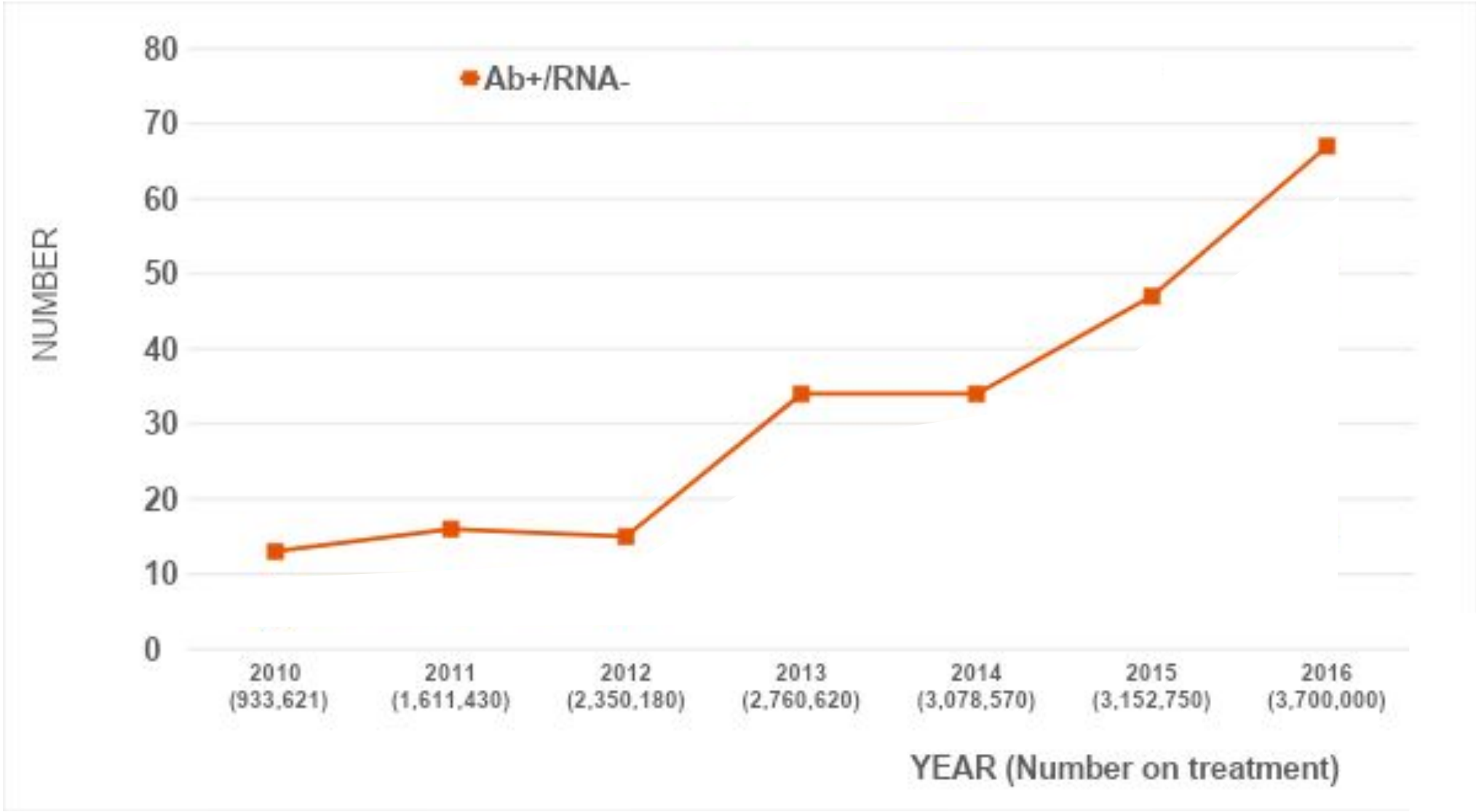
Discovery of "False Elite Controllers": HIV Antibody-Positive RNA-Negative Blood Donors Found to be on Antiretroviral Treatment - REDS-III South Africa



Sykes et al. J Infect Dis. 2019 Apr 5. pii: jiz145. doi: 10.1093/infdis/jiz145.

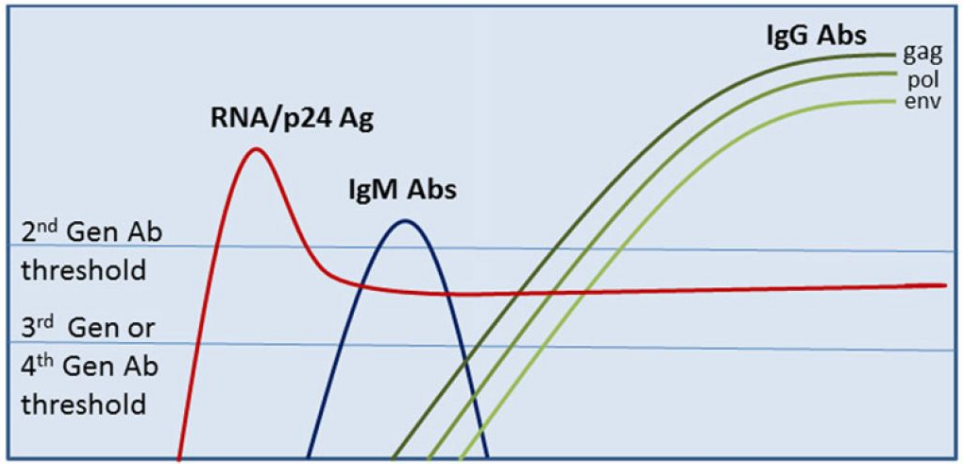
HIV infection progression

Timing Is Everything: Shortcomings of Current HIV Diagnostics in the Early Treatment Era

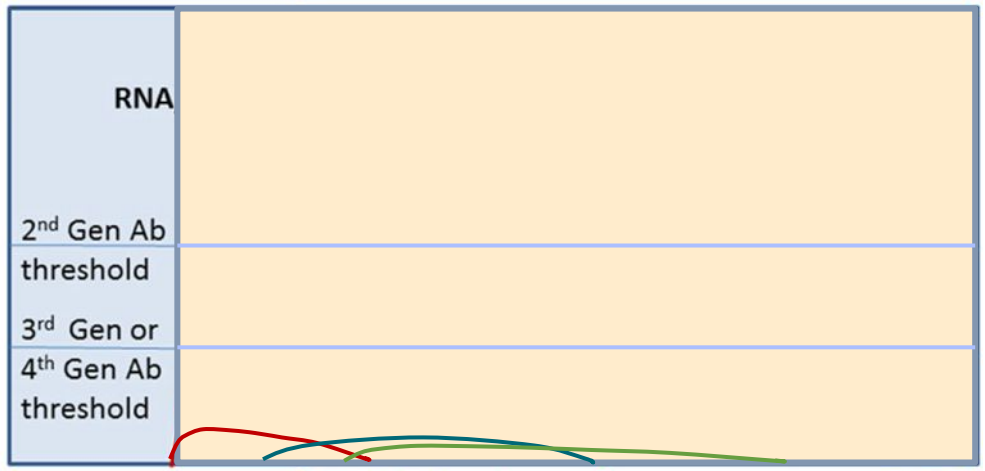
Sheila M. Keating, Christopher D. Pilcher, and Michael P. Busch

Blood Systems Research Institute and Departments of Medicine and Laboratory Medicine, University of California, San Francisco

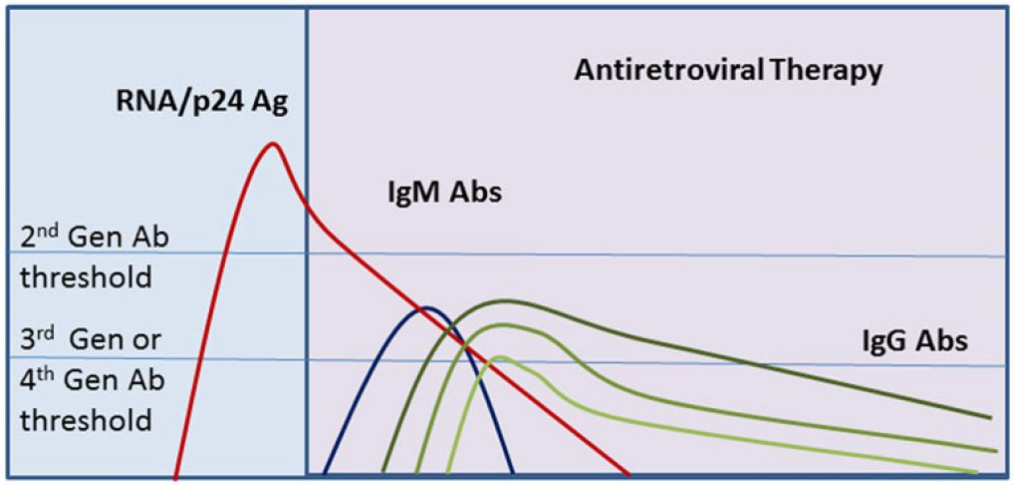
Without ART



PrEP Breakthrough?



With Early ART



- What happens to HIV progression and detection for someone taking PrEP or PEP if there is a breakthrough rather than aborted infection?
- How will the biomarkers of infection be altered?
- Can we detect those markers using blood screening assays?

CID 2016:63 (15 August)

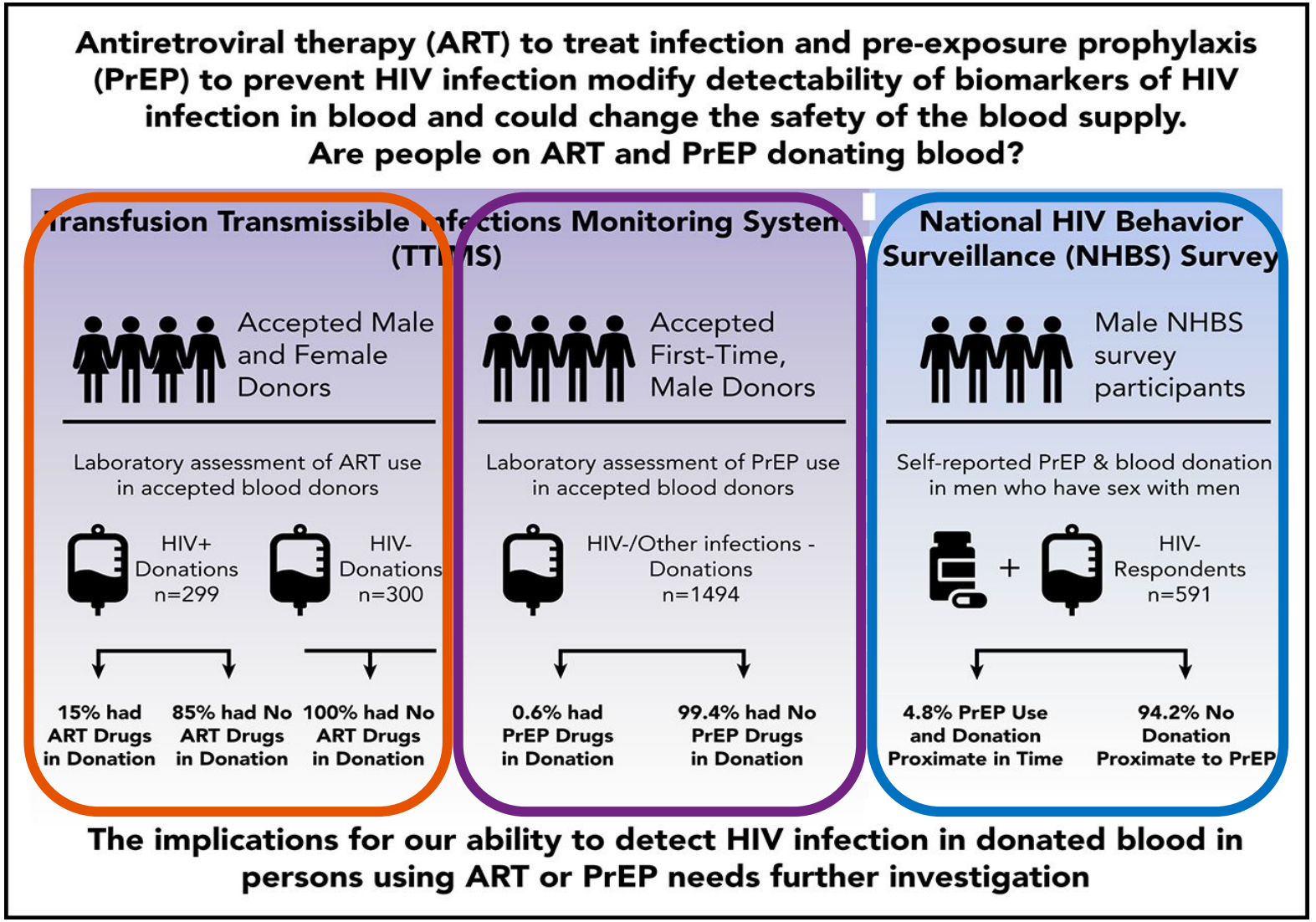
vitalant Research Institute

HIV antiretroviral therapy and prevention use in US blood donors: a new blood safety concern

Brian Custer,[1,2] Claire Quiner,[1,3] Richard Haaland,[4] Amy Martin,[4] Mars Stone,[1,2] Rita Reik,[5] Whitney R. Steele,[6] Debra Kessler,[7] Phillip C. Williamson,[8] Steven A. Anderson,[9] Alan E. Williams,[9] Henry F. Raymond,[10] Willi McFarland,[11] William T. Robinson,[12,13] Sara Glick,[14] Kwa Sey,[15] C. David Melton,[16] Simone A. Glynn,[17] Susan L. Stramer,[18] and Michael P. Busch,[1,2] for the Transfusion-Transmissible Infections Monitoring System

Samples for ART testing collected during period of 9/2015 – 12/2017

Samples for PrEP testing collected during period of 9/2018 – 5/2019



Transfusion Transmissible Infections Monitoring System

ART Use in U.S. Blood Donors

HIV Blood Screening Results	HIV-positive donors at TTIMS blood centers during period*	Samples tested for ARVs	ARVs detected n (%)	Estimated days since last ARV dose		
				1 day ago n (row %)	2 days ago n (row %)	3 days ago n (row %)
HIV Negative	-	300	0			
HIV Positive	463	299	46 (15.4)**	31 (67.4)	12 (26.1)	3 (6.5)
NAT yield (NAT reactive, serology non-reactive	11	0	-	-	-	-
NAT and serology reactive	398	252	5 (2.0)	4 (80.0)	1 (20.0)	0
Serology reactive	54	47	41 (87.3)	27 (65.9)	11 (26.8)	3 (7.3)

September 2015 through December 2017

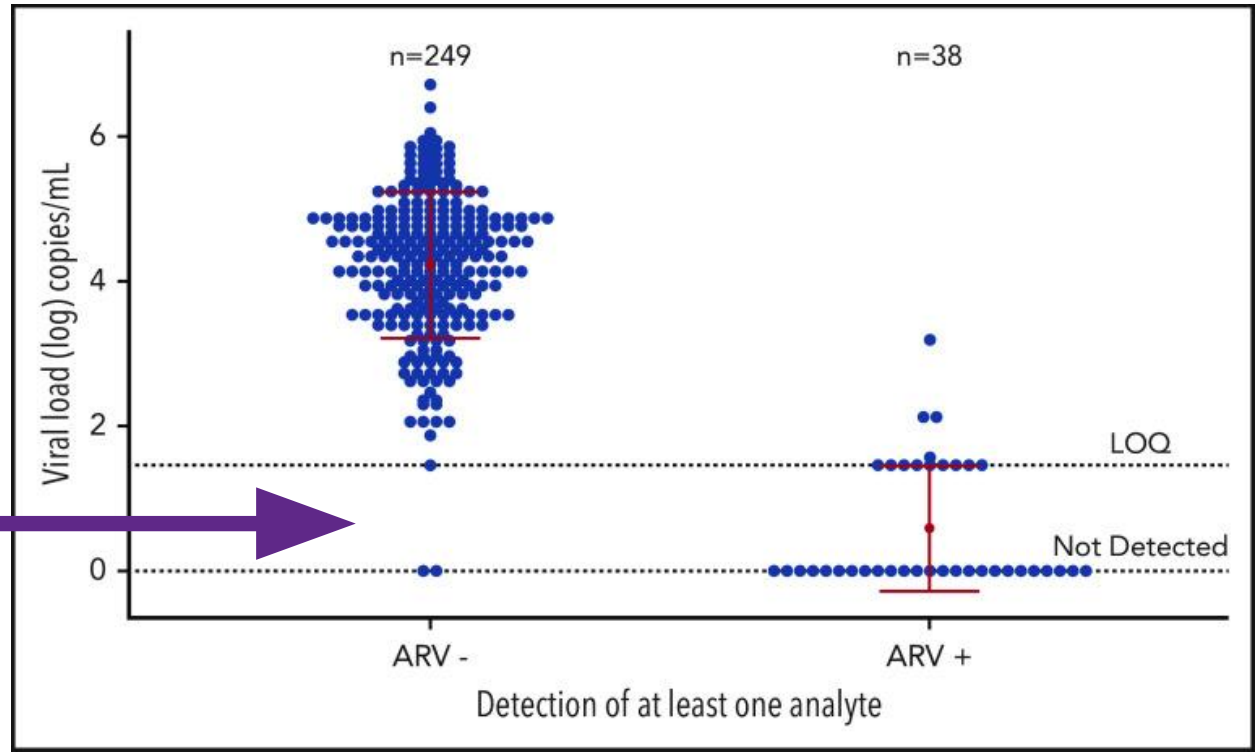
** 95% Confidence Interval 11.5 – 20.0%

Blood. 2020 Sep 10;136(11):1351-1358. doi: 10.1182/blood.2020006890.

Transfusion Transmissible Infections Monitoring System

Key concern about PrEP/PEP #1: Viral nucleic acid levels may be suppressed

Not detected but Infectious ?



A comparison of HIV RNA concentrations in ARV-negative and ARV-positive donations from HIV-positive persons with and without evidence of ART use at the time of blood donation from 299 HIV-positive voluntary blood donations collected in the US from September 2015 through December 2017.
Thirteen ARV drug analytes (raltegravir, tenofovir [TFV], abacavir, ritonavir, lamivudine, efavirenz, emtricitabine [FTC], elvitegravir, dolutegravir, cobicistat, etravirine, darunavir, and rilpivirine) were simultaneously measured.

Custer B et al. HIV antiretroviral therapy and prevention use in US blood donors: a new blood safety concern. *Blood*. 2020;136(11):1351-1358. doi:10.1182/blood.2020006890
Saeed S et al. Evaluation of a pre-exposure prophylaxis (PrEP)/post-exposure prophylaxis (PEP) deferral policy among blood donors. Transfusion. 2021 Jun;61(6):1684-1689. doi: 10.1111/trf.16349. Epub 2021 Mar 16. PMID: 33724472.

Update on ARV Use in U.S. Blood Donors (9/2015 – 6/2022)

HIV screening results	ARV detection by HIV testing classification			
	ARVs Not Detected N (%)	Median HIV VL (IQR)*	ARVs Detected N (%)	Median HIV VL (IQR)*
NAT Only	10 (100)	-	0	-
Concordant Positive	665 (95.3)	22855 (4948-81691)	33 (4.7)	299 (57-11388)
Low-level RNA NAT Confirmed	5 (9.6)	39 (21-75)	47 (90.4)	21 (0-21)
Unresolved Potential Controller	12 (14.8)	21 (16-28)	69 (85.2)	0
Serology Confirmed Positive	1 (11.1)	-	8 (88.9)	0 (0-16)
Serology Repeat Reactive	5 (26.3)	-	14 (73.7)	-
Total	698 (80.3)	21383 (4198-80822)	171 (19.7)	11 (0-38)

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2017) 112, 473–476
SHORT REPORT
© 2017 International Society of Blood Transfusion
DOI: 10.1111/vox.12516

Blood safety implications of donors using HIV pre-exposure prophylaxis

C. R. Seed,[1] H. Yang[2] & J. F. Lee[1]
[1]Australian Red Cross Blood Service, Perth, WA, Australia
[2]Australian Red Cross Blood Service, Sydney, NSW, Australia

A donor using PrEP may unknowingly become HIV infected with a breakthrough infection

Suppressed viral replication resulting in a virus level undetectable by the most sensitive HIV NAT.

False negative' results on HIV serological IAs, including 4th generation HIV Ab/Ag combo immunoaasays.

Blood components derived from such donations with large volumes of plasma could contain levels of HIV above the putative infectious threshold for transmission by blood.

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2021) 116, 379–387
© 2020 International Society of Blood Transfusion
DOI: 10.1111/vox.13011

ORIGINAL PAPER

Effect of HIV pre-exposure prophylaxis (PrEP) on detection of early infection and its impact on the appropriate post-PrEP deferral period

Clive R. Seed,[1] Claire E. Styles,[1] Veronica C. Hoad,[1] Hung Yang,[2] Michael J. Thomas[3,4] & Iain B. Gosbell[2,5]
[1]Australian Red Cross Lifeblood, Perth, Australia
[2]Australian Red Cross Lifeblood, Sydney, Australia
[3]Australian Red Cross Lifeblood, Brisbane, Australia
[4]University of Queensland, Brisbane, Australia
[5]School of Me

- Three study groups were compared; those taking oral daily tenofovir disoproxil fumarate (TDF) or FTC/TDF ('PrEP as randomized'), a subset of these who had detectable TDF concentrations in plasma in any sample during the seroconversion period ('PrEP as treated') and a 'Placebo' group.
- PrEP slows the progression of seroconversion.

Table 2 Modelled cumulative time from Fiebig stage 1 to reach next Fiebig stages among seroconverters in the Partners PrEP study

		Estimated mean time to reach (days)	
Fiebig stage	**Defined as first appearance of:**	**PrEP as treated (N = 21)**	**Placebo (N = 65)**
2	p24 antigen	10	3
3	Antibody (rapid test)	16	9
4	WB indeterminate	19	10
5	WB positive without p31 band	28	17
6	WB complete	80	49

WB, western blot.

Received: 28 July 2021 | Revised: 21 September 2021 | Accepted: 23 September 2021

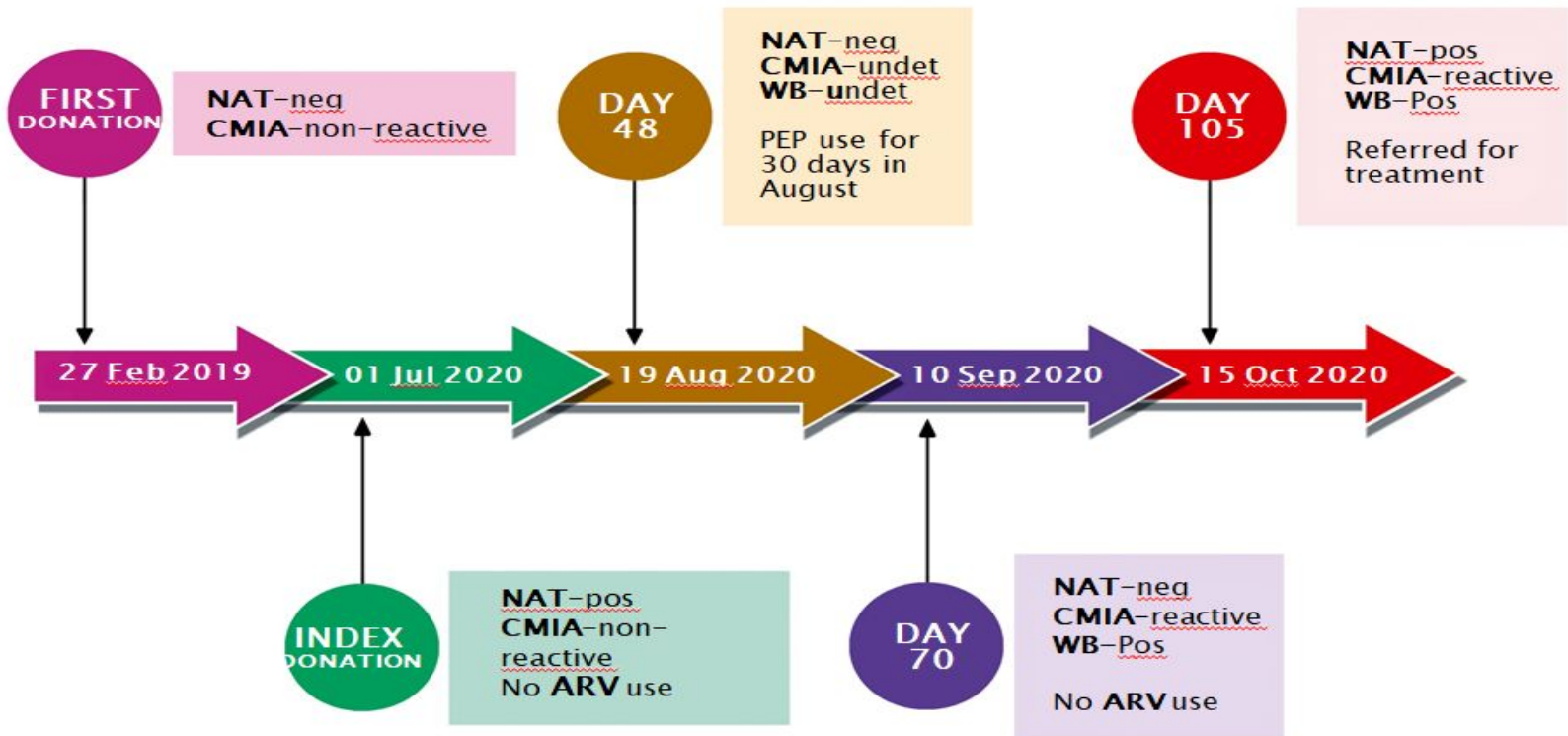
DOI: 10.1111/trf.16698

CASE REPORT

TRANSFUSION

Influence of unreported HIV prophylaxis on the kinetics of post-blood donation HIV seroconversion

Anna S. Nishiya[1,2] | Nanci A. Salles[1] | Cesar de Almeida-Neto[1,4] | Steven S. Witkin[3,5] | Suzete C. Ferreira[1,2] | Fátima A. H. Nogueira[1] | Tila Facincani[1] | Vanderson Rocha[1,2,4,6] | Alfredo Mendrone-Jr[1,2]



Long-acting early viral inhibition (LEVI)

Comparison of acute HIV infection (AHI) to infections that occur in the setting of long-acting early viral inhibition (LEVI)

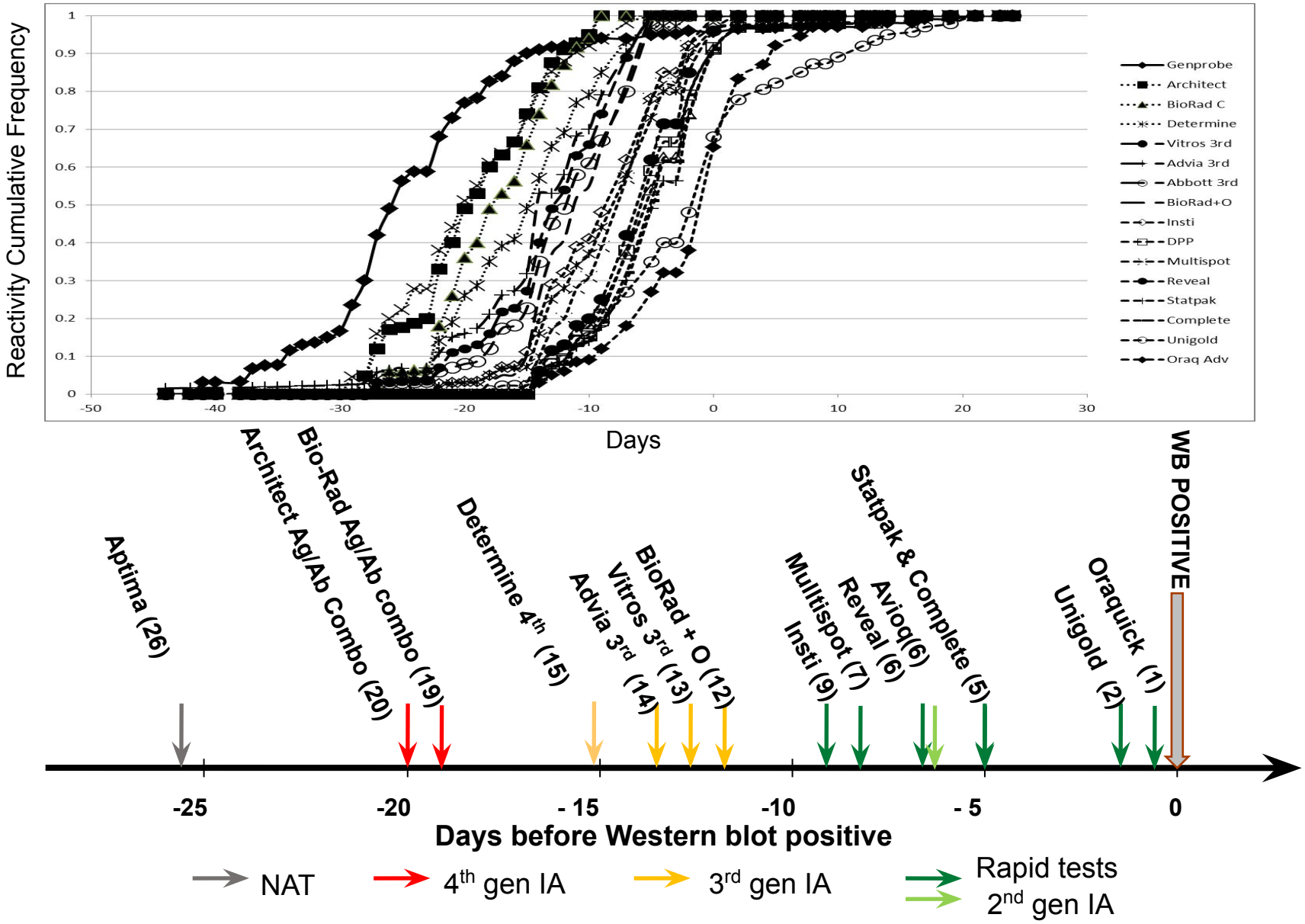
	AHI	LEVI
Cause	Phase of natural HIV infection	Long-acting anti-viral PrEP agent (prototype: CAB-LA)
Onset	New infection	Infection during PrEP Initiation of PrEP agent during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Minimal, variable, often no symptoms reported
Detection	Ag/Ab assay, RNA assays (including less sensitive POC and pooled tests), DNA assays, total nucleic acid assays	Ultrasensitive RNA assay (often low or undetectable RNA, low/undetectable DNA, diminished/delayed Ab production)
Assay reversion	Rare	Common for many test types
Duration	1-2 weeks (until Ab detection)	Months (until viral breakthrough, drug clearance, or ART start); can persist months after the anti-viral agent is discontinued
Transmission	Very likely	Unlikely (except possibly through blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when viral load is low)

Marzinke, JID 2021; 224:1581
Eshleman, JID 2022; 225:1749
Eshleman, JID 2022; 226:2170
Marzinke, AAC 2023; In Press

Impact of TM Research on HIV Diagnostics and Staging of Infection

- Developed concept of infectious pre-SC window phase (WP) and Incidence-WP model to project yield of enhanced testing that shorten the diagnostic WP
- Analyzed plasma donor SC panels to establish HIV replication dynamics (doubling time during “ramp-up viremia”) and Fiebig staging classification system (eclipse phase through complete SC) now widely employed to classify newly diagnosed persons
- Diagnostic utility of improved serological (2^{nd}-4^{th} generation) assays and mini-pool relative to individual sample NAT in donor and diagnostic settings
- Contributing NAT yield and early SC donation plasma to evaluations of enhanced diagnostic and VL assays and to NIAID EQAPOL program

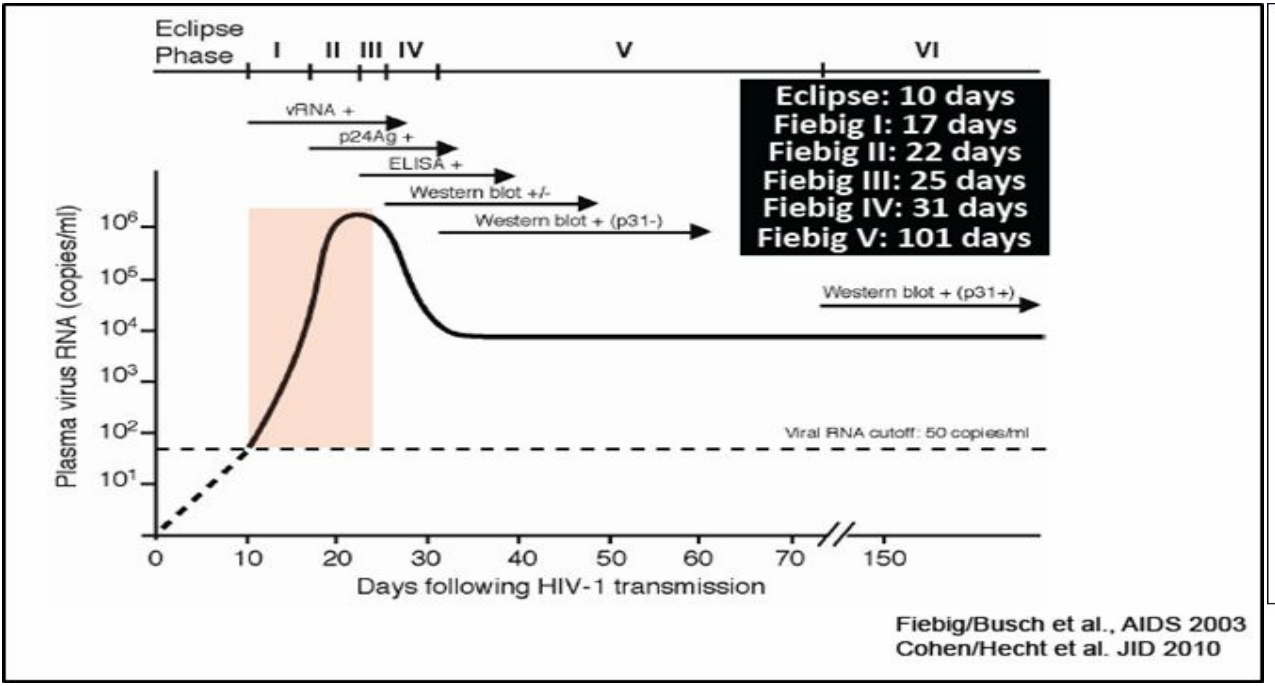
Data from 17 pasma that progressed from antibody negative/ NAT positive to WB positive used to construct a relative sequence of reactivity timeline



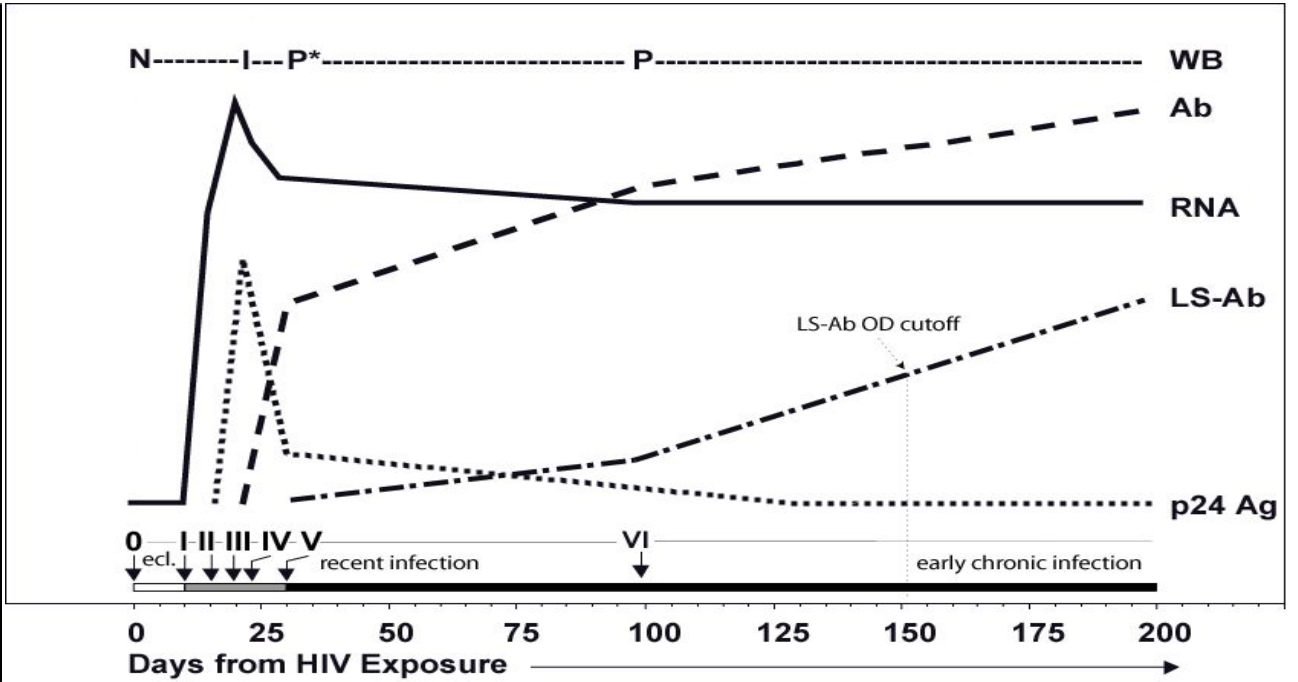
Adapted from Owen et al J Clin Micro 2008 and Masciotra et al J Clin Virol 2011,2013

Long term impact of blood donor HIV studies

Fiebig Stages of HIV Infection



Development of HIV Incidence Assays



Janssen RS, Satten GA, Stramer SL, …, Busch MP. New Testing Strategy to Detect Early HIV-1 Infection for Use in Incidence Estimates and for Clinical and Prevention Purposes. JAMA, 280(1):42-48, 1998.

Busch MP, Pilcher CD, Mastro TD, et al,. Beyond Detuning: Ten Years of Progress and New Challenges in the Development and Application of Assays for HIV Incidence Estimation from Surveys. AIDS 24(18):2763-2771, 2010

The Journal of Infectious Diseases

MAJOR ARTICLE

HIV Antibody Level as a Marker of HIV Persistence and Low-Level Viral Replication

Sheila M. Keating,[1,2] Christopher D. Pilcher,[3,a] Vivek Jain,[3] Mila Lebedeva,[1] Dylan Hampton,[1] Mohamed Abdel-Mohsen,[4] Xutao Deng,[1] Gary Murphy,[5] Alex Welte,[6] Shelley N. Facente,[3] Frederick Hecht,[3] Steven G. Deeks,[3] Satish K. Pillai,[1,2] and Michael P. Busch[1,2,a]

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

vitalant Research Institute

Impact of TM Research on HIV Pathogenesis Research

- Studied clusters of HIV infected donors and recipients contributed to understanding of HIV quasispecies, bottleneck of transmission and rates and viral and immune correlates of quasispecies evolution

- Plasma donor panels studied in collaboration with CHAVI established the concept of transmitted/founder (T/F) viruses and subsequent evolution of HIV and mechanisms driving evolution

- Characterizing evolution of T/F viruses over time in acutely infected donors in US, SA and Brazil to corroborate recent evidence for directional evolution of HIV toward viruses that resist neutralizing Abs and may be more pathogenic

- Enrolling and following cohorts of acutely infected donors in US, SA, Brazil to

PNAS

Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection

Brandon F. Keele[a], Elena E. Giorgi[b,c], Jesus F. Salazar-Gonzalez[a], Julie M. Decker[a], Kimmy T. Pham[a], Maria G. Salazar[a], Chuanxi Sun[a], Truman Grayson[a], Shuyi Wang[a], Hui Li[a], Xiping Wei[a], Chunlai Jiang[d], Jennifer L. Kirchherr[d], Feng Gao[d], Jaffery A. Anderson[e], Li-Hua Ping[f], Ronald Swanstrom[f], Georgia D. Tomaras[g], William A. Blattner[h], Paul A. Goepfert[a], J. Michael Kilby[a], Michael S. Saag[a], Eric L. Delwart[i], Michael P. Busch[j], Myron S. Cohen[e], David C. Montefiori[g], Barton F. Haynes[d], Brian Gaschen[b], Gayathri S. Athreya[b], Ha Y. Lee[a], Natasha Wood[k], Cathal Seoighe[k], Alan S. Perelson[b], Tanmoy Bhattacharya[b,l], Bette T. Korber[b,l], Beatrice H. Hahn[a,m], and George M. Shaw[a,m,n]

Review

Modeling sequence evolution in acute HIV-1 infection

Ha Youn Lee [a,b,1], Elena E. Giorgi [a,c,1], Brandon F. Keele [d], Brian Gaschen [a], Gayathri S. Athreya [a], Jesus F. Salazar-Gonzalez [d], Kimmy T. Pham [d], Paul A. Goepfert [d], J. Michael Kilby [d,2], Michael S. Saag [d], Eric L. Delwart [e], Michael P. Busch [e], Beatrice H. Hahn [d], George M. Shaw [d], Bette T. Korber [a,f], Tanmoy Bhattacharya [a,f], Alan S. Perelson [a,*]

Journal of Theoretical Biology 261 (2009) 341–360

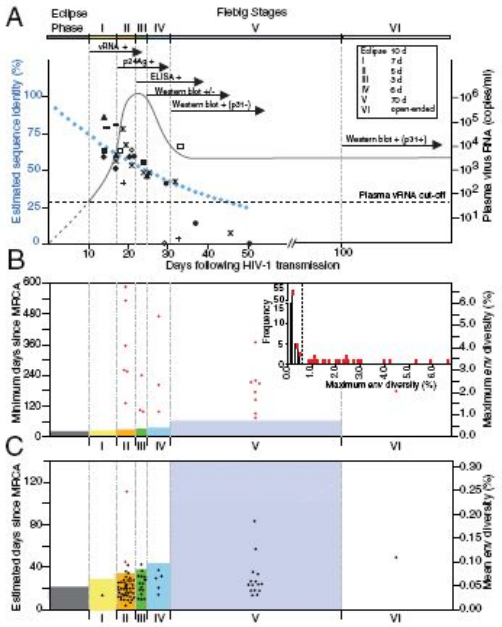


Fig. 1. HIV-1 *env* diversity in relation to Fiebig stage. (*A*) Fiebig stages (28)

Published June 1, 2009

JEM ARTICLE

The first T cell response to transmitted/ founder virus contributes to the control of acute viremia in HIV-1 infection

Published June 1, 2009

JEM ARTICLE

Genetic identity, biological phenotype, and evolutionary pathways of transmitted/founder viruses in acute and early HIV-1 infection

OPEN ACCESS Freely available online PLoS PATHOGENS

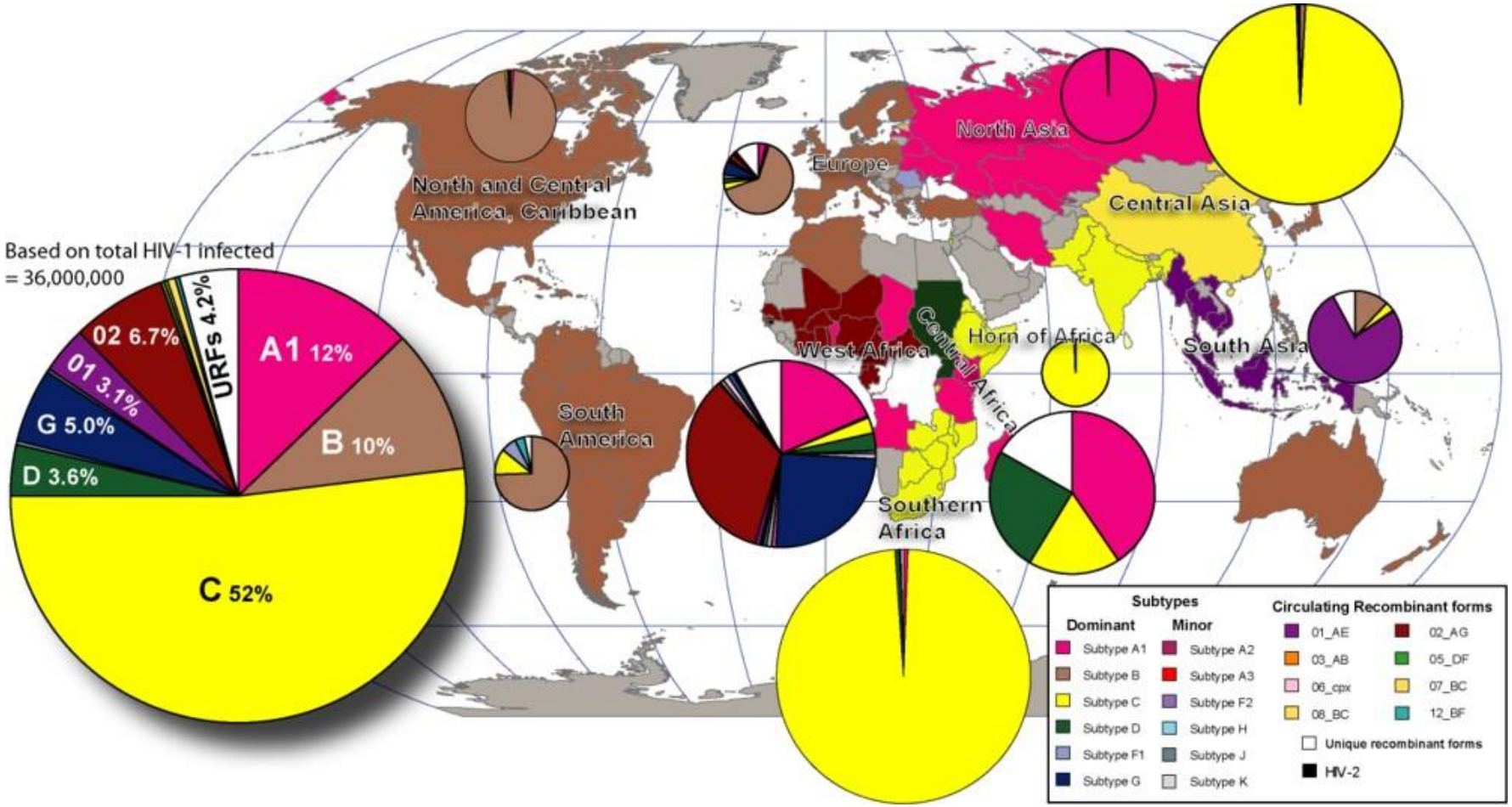
Whole Genome Deep Sequencing of HIV-1 Reveals the Impact of Early Minor Variants Upon Immune Recognition During Acute Infection

March 2012 | Volume 8 | Issue 3 | e1002529

Table 1
Fiebig stage classification for sub-stages of HIV-1 primary infection, and the average and cumulative duration of each phase.

Stage	Duration of each phase (days)	Cumulative duration (days)
Eclipse	10 (7,21)	10 (7,21)
I (vRNA+)	7 (5,10)	17 (13,28)
II (p24Ag+)	5 (4,8)	22 (18,34)
III (ELISA+)	3 (2,5)	25 (22,37)
IV (Western Blot ±)	6 (4,8)	31 (27,43)
V (Western Blot +, p31−)	70 (40,122)	101 (71,154)
VI (Western Blot +, p31+)	Open-ended	

Geographical distribution of HIV clades



Global distribution of HIV genotypes

At http://www.hiv.lanl.gov.

Molecular surveillance of HIV, HCV, and HBV in blood donors

- Major risk of TTV is from donations during acute infection WP (incident infections); testing errors, viral variants and immunosilent infections are minor contributors
- Combined NAT and serological screening, supplemented by novel serological test strategies (e.g., detuned EIAs), identifies incident cases and test errors
- Systematic program for genetic characterization of viral genomes in donors with incident infections
  - monitor circulating strains of viruses transmitted to donor population, and this within “low risk” general population
  - detect rare variants, including vaccine and drug escape mutants, that may be increasing in U.S. population

Surveillance of the Genetic Variation in Incident HIV, HCV, and HBV Infections in Blood and Plasma Donors: Implications for Blood Safety, Diagnostics, Treatment, and Molecular Epidemiology

Eric Delwart,[1]* Mary C. Kuhns,[2] and Michael P. Busch[1]

Journal of Medical Virology 78:S30–S35 (2006)

Human immunodeficiency virus type 1 incidence among blood donors in France, 1992 through 2006: use of an immunoassay to identify recent infections

TRANSFUSION 2008;48:1567-1575.

Josiane Pillonel, Francis Barin, Syria Laperche, Pascale Bernillon, Stéphane Le Vu, Sylvie Brunet, Damien Thierry, Jean-Claude Desenclos, for the "Transfusion-Transmissible Agents Working Group" of the French Society of Blood Transfusion

Genetic Diversity of Recently Acquired and Prevalent HIV, Hepatitis B Virus, and Hepatitis C Virus Infections in US Blood Donors

The Journal of Infectious Diseases

Eric Delwart,[1,2] Elizabeth Slikas,[1] Susan L. Stramer,[3] Hany Kamel,[4] Debra Kessler,[5] David Krysztof,[3] Leslie H. Tobler,[1] Danielle M. Carrick,[6] Whitney Steele,[6] Deborah Todd,[6] David J. Wright,[6] Steven H. Kleinman,[6,7] and Michael P. Busch[1,2] for the NHLBI-REDS-II Study Group

The human immunodeficiency virus-1 genotype diversity and drug resistance mutations profile of volunteer blood donors from Chinese blood centers

TRANSFUSION 2012;52:1041-1049.

Peibin Zeng, Jingxing Wang, Yi Huang, Xiaoming Guo, Julin Li, Guoxin Wen, Tonghan Yang, Zhongqiao Yun, Miao He, Yu Liu, Yuzhe Yuan, Jane Schulmann, Simone Glynn, Paul Ness, J. Brooks Jackson, and Hua Shan, for the NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II), International Component

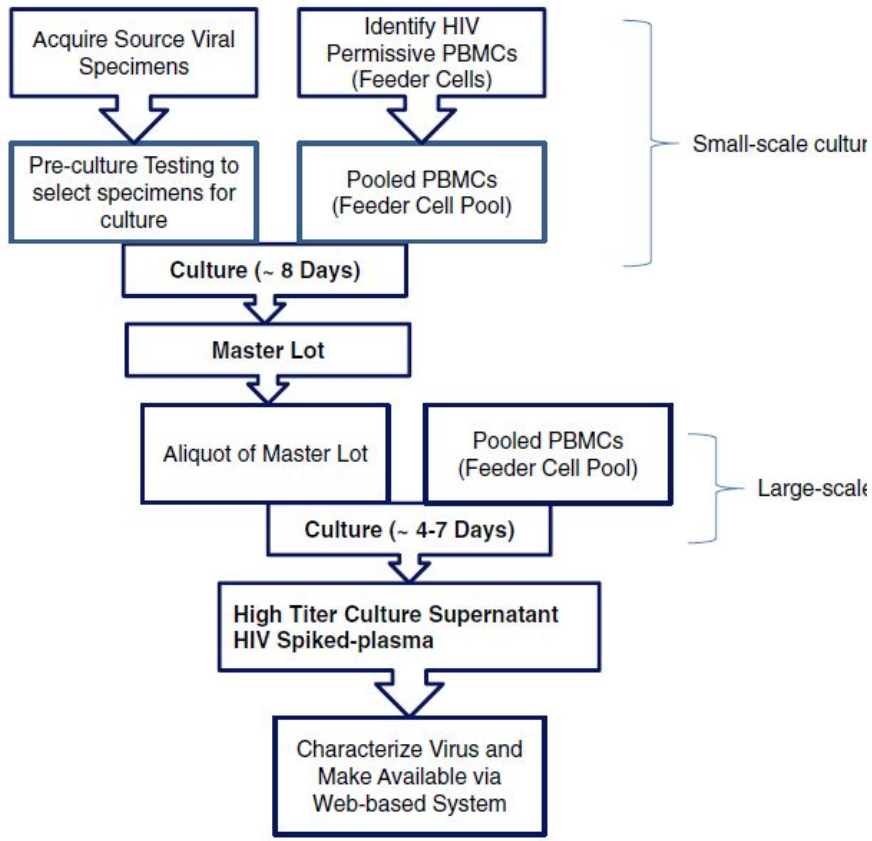
HIV genotypes and primary drug resistance among HIV seropositive blood donors in Brazil

JAIDS 63(3):387-392, 2013.

Alencar CS[1,2], Sabino EC[3], Carvalho SMF[4], Leao S[5], Carneiro- Proietti AB[6], Capuani L[7], Oliveira CL[8], Carrick D[9], Birch RJ[9], Gonçalez TT[10], Keating S[10], Swanson P[11], Hackett JJr[11] and Busch MP[10], for the NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II), International Component

Development of a contemporary globally diverse HIV viral panel by the EQAPOL program

Ana M. Sanchez [a], C. Todd DeMarco [a], Bhavna Hora [a], Sarah Keinonen [a], Yue Chen [a], Christie Brinkley [a], Mars Stone [b], Leslie Tobler [b], Sheila Keating [b], Marco Schito [c], Michael P. Busch [b], Feng Gao [a,*], Thomas N. Denny [a]



Characterization of expanded viruses in EQAPOL Viral Diversity panel.

Sample name	Fiebig stage	Donation year	Country of origin	Source GenBank	HIV subtype	Coreceptor usage	GenBank
DEMA106ES002	ND	2006	Spain[a]	FJ670523	A1	CCR5	JX140651
DEMA105TZ001	ND (CHI)	2005	Tanzania[a]	FJ670519	A1	CXCR4	JX140650
DEMA07UG005	IV	2007	Uganda[b]	JX236676	A1	CCR5	KC596070
DEMA03RW001	III	2003	Rwanda[b]	JX236678	A1	CCR5	KF716499
DEMA03UG002	IV	2003	Uganda[b]	JX236669	A1	CCR5	KF716500
DEMA11KE001	IV	2011	Kenya[c]	KC018749	A1	CCR5	KC018749
DEMA110UG001	VI	2010	Uganda[c]	KC019075	A1	CCR5	KF859745
DEMB09BO001	ND (AHI)	2009	Bolivia[a]	KC112996, KC112997	B	CCR5	JX140656
DEMB10CN002	ND (CHI)	2010	China[d]	None	B	CCR5	JX140658
DEMB05FR001	II/III	2005	France[e]	None	B	CCR5	JX140652
DEMB08FR002	II/III	2008	France[f]	None	B	CCR5	JX140654
DEMBXXDE001	I/II	UNK	Germany[e]	None	B	CCR5	KC596067
DEMB03JP004	I/I	2003	Japan[f]	None	B	CCR5	KC473846
DEMBXXPL001	II	UNK	Poland[e]	JN687774, JN687691	B	CCR5	KC596069
DEMB08ES001	ND (AHI)	2008	Spain[a]	FJ670531	B	CCR5	JX140653
DEMB08UY001	ND (AHI)	2008	Uruguay[a]	GU362886	B	CCR5	JX140655
DEMB09US002	I/II	2009	USA[f]	None	B	CCR5	JX140657
DEMB10VE001	ND (AHI)	2010	Venezuela[a]	KC113011, KC113010	B	CCR5	JX140659
DEMB10ES002	ND (AHI)	2010	Spain[a]	KC113004	B	CCR5	KC473842
DEMB09CN002	ND (CHI)	2009	China[d]	None	B	CCR5	KC596066
DEMB10US001	I/II	2010	USA[f]	None	B	CCR5	KC473825
DEMB11US006	I/II	2011	USA[f]	None	B	CCR5	KC473833
DEMB10US007	I/II	2010	USA[f]	None	B	CCR5	KC473828
DEMB10US011	VI	2010	USA[f]	None	B	CCR5	KC473830
DEMB11US002	VI	2011	USA[f]	None	B	CCR5	KC473831
DEMB10ES003	ND (AHI)	2010	Spain[a]	KC113005	B	CCR5	KC473843
DEMB09ES007	ND (AHI)	2009	Spain[a]	KC112998, KC112999	B	CCR5	KC473841
DEMB10US003	VI	2010	USA[f]	None	B	CCR5	KC473826
DEMB11US015	VI	2011	USA[f]	None	B	CCR5	KC473835
DEMB10US004	VI	2010	USA[f]	None	B	CCR5	KC473827
DEMB11US004	VI	2011	USA[f]	None	B	CCR5	KC473832
DEMB11US011	V	2011	USA[f]	None	B	CCR5	KC473834
DEMB10US009	VI	2010	USA[f]	None	B	CCR5	KC473829
DEMB09US003	I/II	2009	USA[f]	None	B	CCR5	KC473824
DEMB11FR001	I/II	2011	France[f]	None	B	CCR5	KF716496
DEMC07AO001	ND	2007	Angola[a]	EU884500	C	CCR5	JX140662
DEMC07BR003	VI	2007	Brazil[e]	JN687737, JN687655	C	CCR5	JX140663
DEMC08NG001	ND	2008	Nigeria[a]	EU786681	C	CCR5	JX140665
DEMC07ZA011	II	2007	South Africa[a]	JN687618-JN687627, JN687694-JN687703, JN687778-JN687798	C	CCR5	JX140664
DEMC08ZA011	II	2008	South Africa[a]	JN687724, JN687641	C	CCR5	JX140666
DEMC09ZA008	IND	2009	South Africa[f]	None	C	CCR5	JX140667
DEMC09ZA009	I/II	2009	South Africa[f]	None	C	CCR5	JX140668
DEMC10ZA001	I/II	2010	South Africa[f]	None	C	CCR5	JX140669
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DE00210CM013	ND	2010	Cameroon[g]	JN864054	CRF02_AG and URF_01A1G	CCR5	KF859739 KF859740
DE00109CN003	IV	2009	China[d]	JX960615	CRF01_AE	CCR5	KC596061
DE00109CN004	IV	2009	China[d]	JX960618	CRF01_AE	CCR5	KC596062
DE00110CN001	IV	2010	China[d]	JX960610	CRF01_AE	CCR5	KC596063
DE00111CN003	ND (CHI)	2011	China[d]	JX960600	CRF01_AE	CCR5	KC596065
DE00111CN002	IV	2011	China[d]	None	CRF01_AE	CCR5	KC596064
DE00206AO001	ND (RHI)	2006	Angola[a]	EU884501	CRF02_AG	CCR5	JX140645
DE00208CM004	VI	2008	Cameroon[g]	None	CRF02_AG	CCR5	JX140647
DE00208CM001	VI	2008	Cameroon[g]	None	CRF02_AG	CCR5	JX140646
DE00400GR002	ND	2000	Greece[e]	JN687744, JN687745, JN687660, JN687661	CRF04_CPX	CCR5/CXCR4	JX140648
DE01405BR001	ND	2005	Brazil[a]	FJ670522	CRF14_BG	CCR5/CXCR4	JX140649
DE01405ES002	ND (CHI)	2005	Spain[a]	FJ670528	CRF14_BG	CCR5/CXCR4	KC473837
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DE02210CM014	ND	2010	Cameroon[g]	JN864059	CRF22_01A1	CCR5	KF716463
DE02210CM010	ND	2010	Cameroon[g]	JN864050	CRF22_01A1	CCR5	KF716460
DE02408ES002	ND (RHI)	2008	Spain[a]	FJ670526	CRF24_BG	CCR5	KC473838
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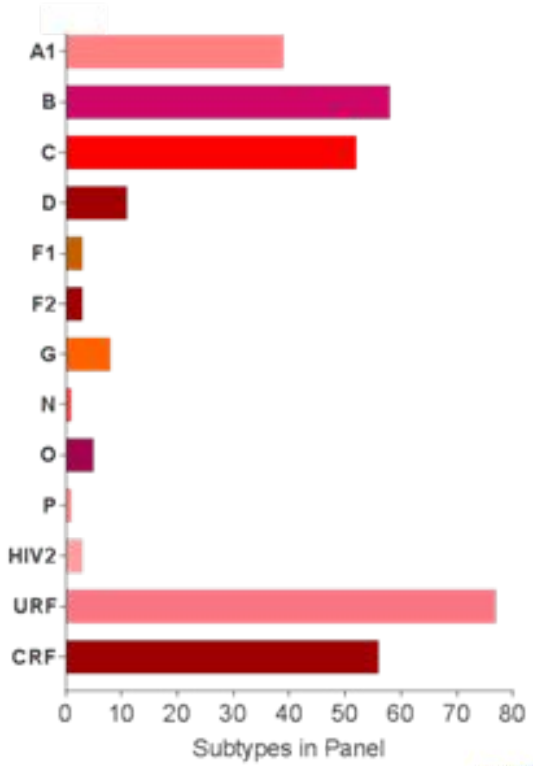
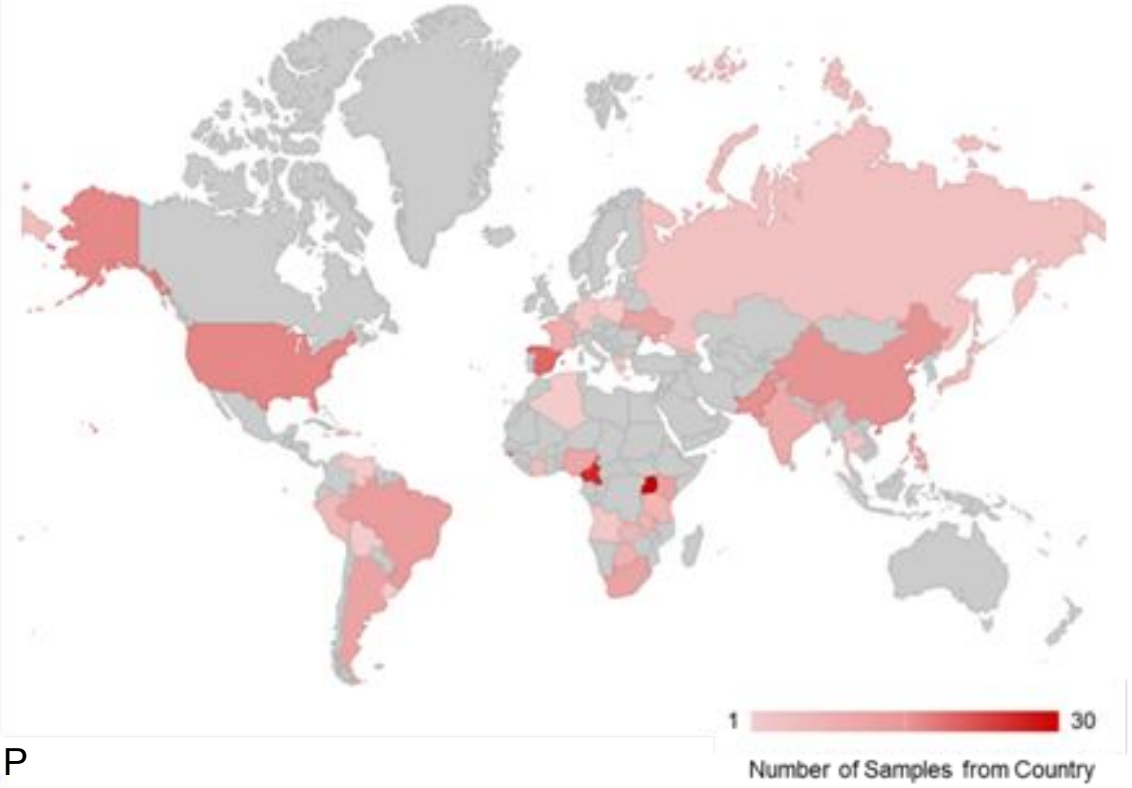
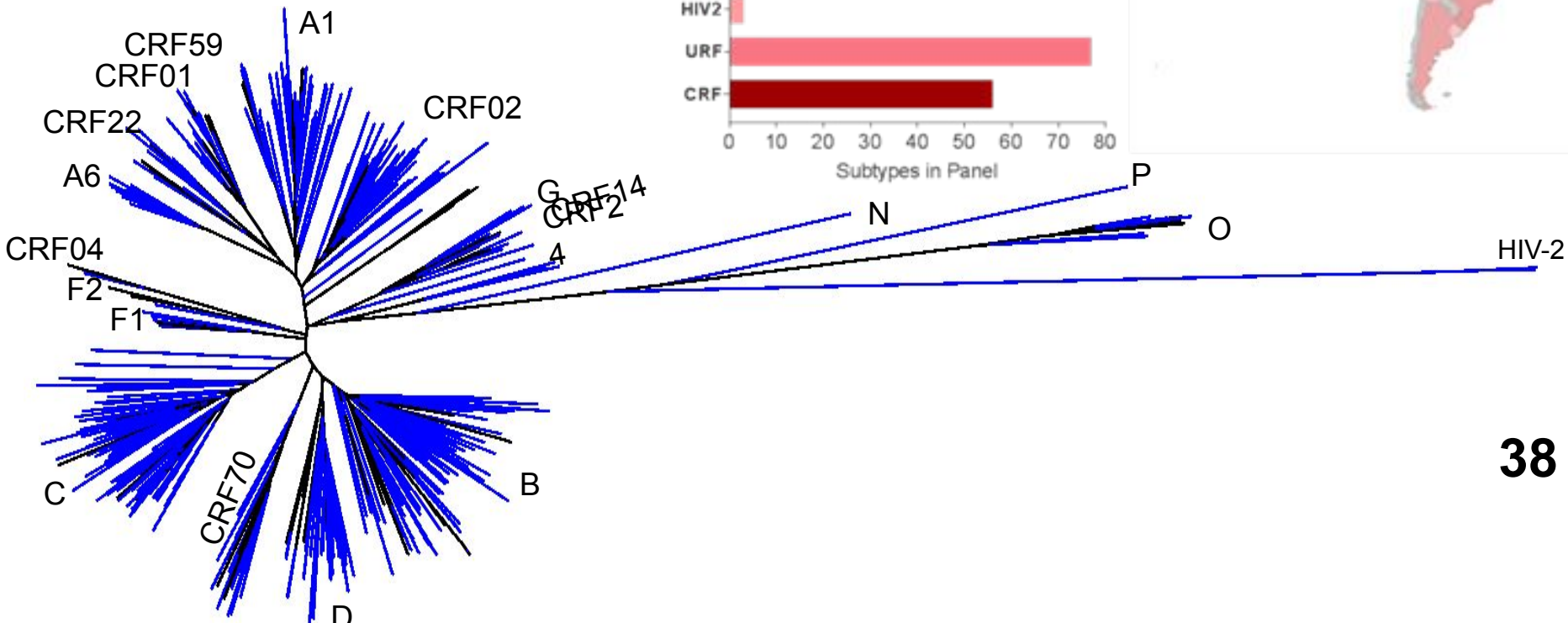
DEMD10CM009	VI	2010	Cameroon[g]	None	D	CCR5/CXCR4	JX140670
DEMD07UG002	II	2007	Uganda[b]	JX236670	D	CCR5	KC596071
DEMD08UG001	I	2008	Uganda[b]	JX236672	D	CCR5	KC596072
DEMD07UG007	I	2007	Uganda[b]	JX236673	D	CCR5	KF716503
DEMD07UG001	IV	2007	Uganda[b]	JX236679	D	Pending	KF716502
DEMD05UG001	II	2005	Uganda[b]	JX236668	D	CCR5	KF716501
DEMD11KE003	IV	2011	Kenya[c]	KC018957	D	Pending	KF716476
DEMD10UG004	VI	2010	Uganda[c]	KC018740	D	CCR5/CXCR4	KF716479

Journal of Immunological Methods

Geographic and Phylogenetic Diversity of EQAPOL Panel







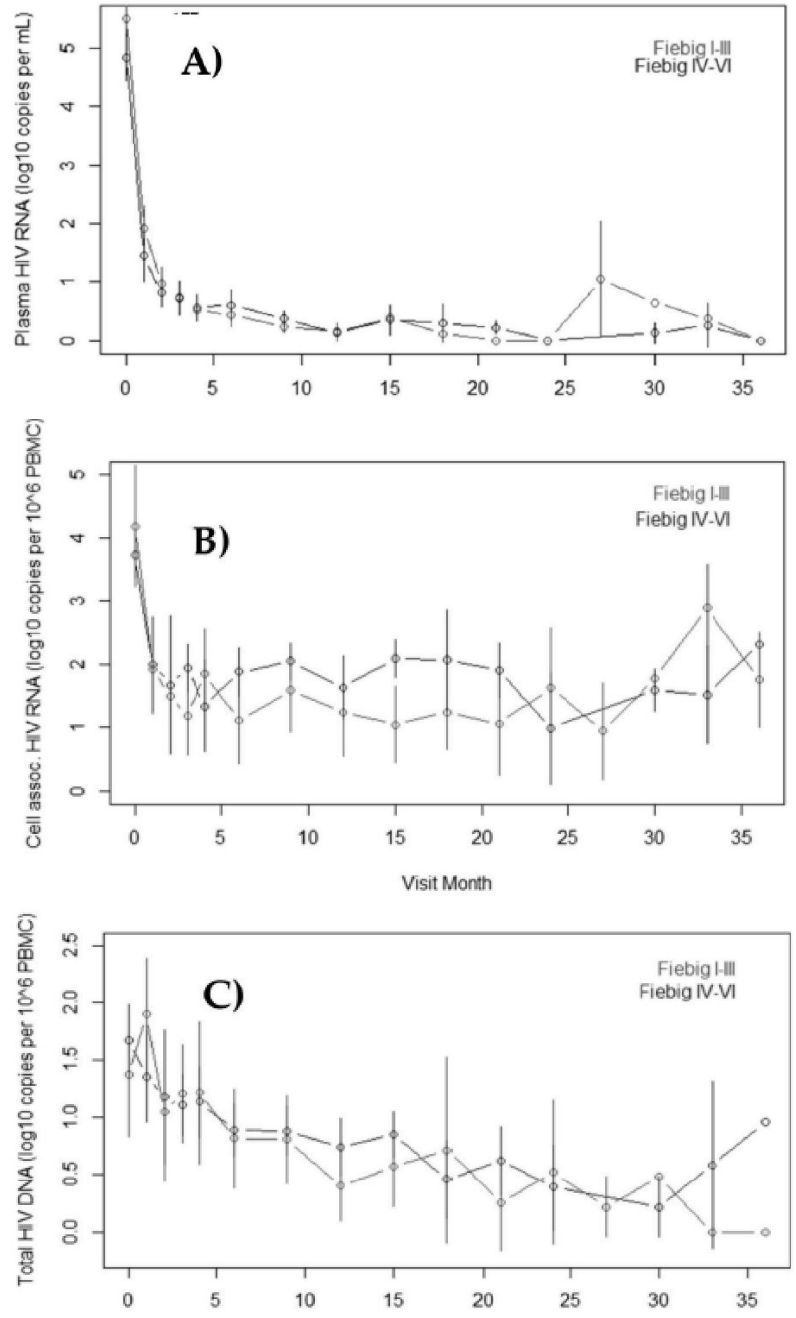
38 Countries

Blood Center Testing Allows the Detection and Rapid Treatment of Acute and Recent HIV Infection

Karin van den Berg [1], Marion Vermeulen [1], Sonia Bakkour [2,3], Mars Stone [2,3], Genevieve Jacobs [1], Cynthia Nyoni [1], Coreen Barker [4], Christopher McClure [5], Darryl Creel [5], Eduard Grebe [2,6], Nareg Roubinian [2,3,7], Ute Jentsch [1], Brian Custer [2,3], Michael P. Busch [2,3], Edward L. Murphy [2,3,8,*] and on behalf of the Recipient Epidemiology and Donor Evaluation Study (REDS)-III South Africa International Program [†]

Table 1. Characteristics of the study population, by Fiebig stage at time of treatment initiation and in the untreated HIV comparison group. Numerical variables are presented as median (interquartile range (IQR)) and categorical variables as n (%).

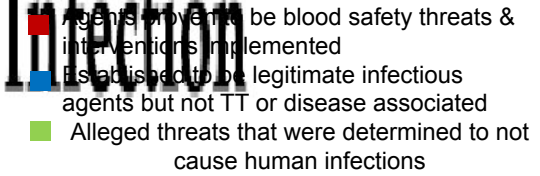
Variable	Fiebig I–III (n = 18)	Fiebig IV–VI (n = 45)	Elite Controllers (N = 11)	Untreated HIV cases (n = 100)
Age (median)	29 (20)	26 (10)	34 (13)	27 (9)
Female	13 (72%)	32 (71%)	9 (82%)	75 (75%)
Population group *				
African	16 (89%)	40 (89%)	11(100%)	94 (94%)
Other	2 (11%)	4 (11%)	0	6 (6%)
Geographic region				
Egoli (Johannesburg region)	7 (39%)	17 (38%)	3 (27%)	28 (28%)
Other region (KwaZulu-Natal, Mpumalanga, Northern, Eastern cape)	11 (61%)	28 (62%)	8 (73%)	72 (72%)



Viruses **2022**, *14*, 2326. https://doi.org/10.3390/v14112326

Risks of major transfusion-transmitted viral infections and emerging infectious agents of concern to blood safety

Blood Center Testing Allows the Detection and Rapid Treatment of Acute and Recent HIV Infection

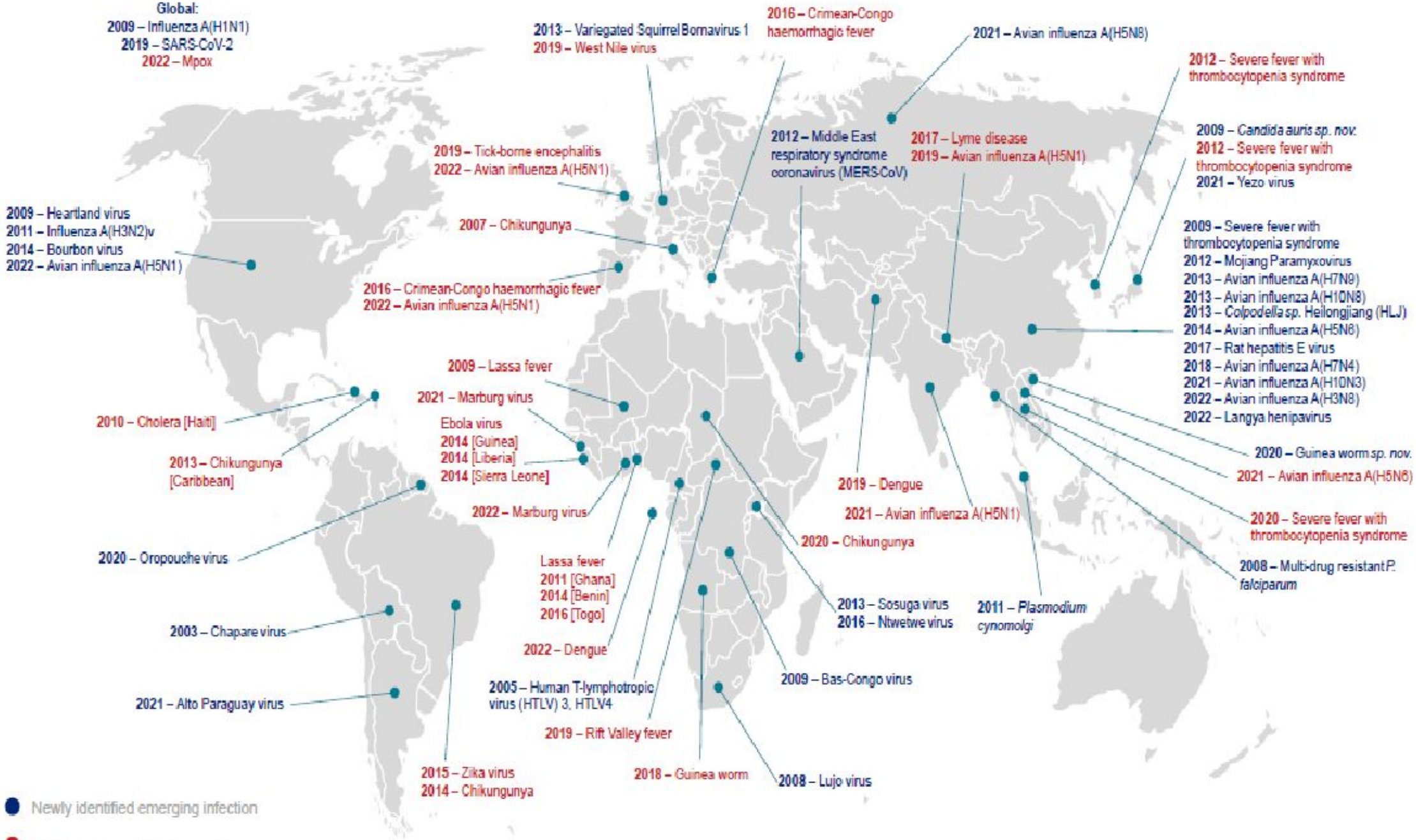


Karin van den Berg [1], Marion Vermeulen [1], Sonia Bakkour [2,3], Mars Stone [2,3], Genevieve Jacobs [1], Cynthia Nyoni [1], Coreen Barker [4], Christopher McClure [5], Darryl Creel [5], Eduard Grebe [2,6], Nareg Roubinian [2,3,7], Ute Jentsch [1], Brian Custer [2,3], Michael P. Busch [2,3], Edward L. Murphy [2,3,8,*] and on behalf of the Recipient Epidemiology and Donor Evaluation Study (REDS)-III South Africa International Program [†]

Busch MP, Bloch EA, Kleinman S. Prevention of Transfusion Transmitted Infections. Blood 2019

vitalant Research Institute

Global map of emerging infections since 2003



Evaluating EID threats to blood safety

3 basic questions need to be answered:

Is it in the blood supply?

- Measure the agent in donors during epidemics (RNA, Ag, Abs, infectivity)
- Estimation of donor risks: prevalence, incidence, durations of detection
- Estimation of blood component risks
  - Temperature, preparation, storage duration effects on infectivity?
  - Is antibody in the infected donor or co-transfused components protective?

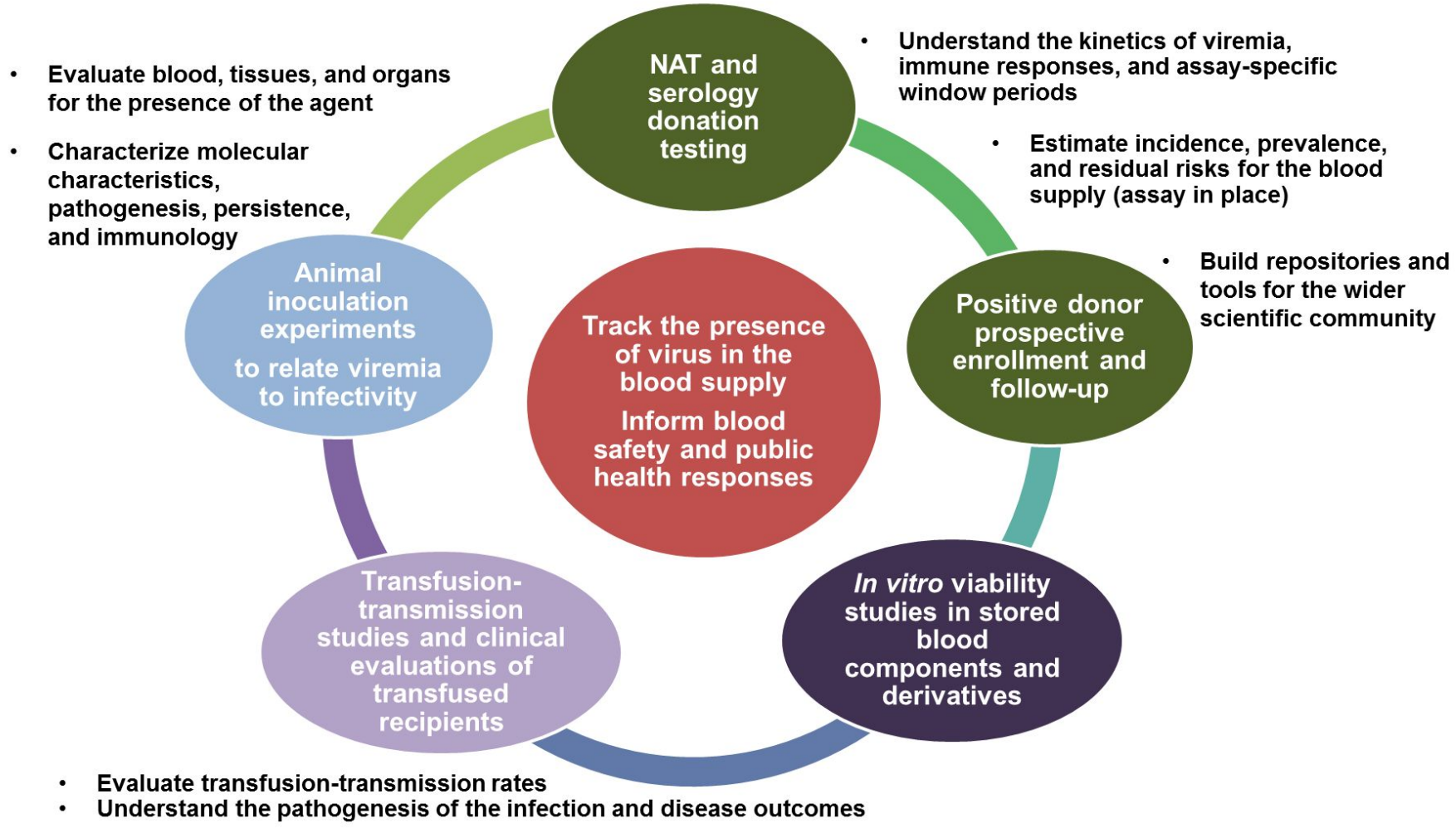
Is it transfusion-transmitted and what is the risk?

- Is transmission risk dependent on stage of infection or VL in the donor/component
- Do recipient antibodies from prior infection protect from TT

If transfusion-transmitted, does it have a clinical impact in transfused recipients?

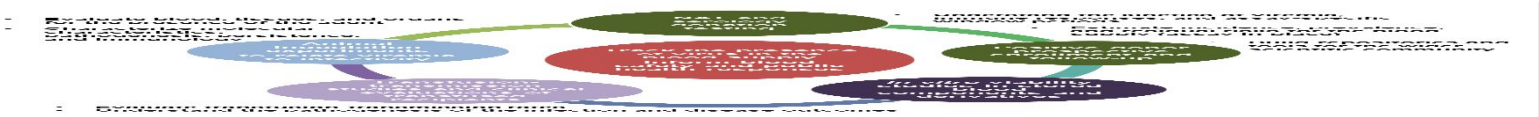
- Is TT disease more or less severe than usual routes of infection

Assessing the risk of transfusion-transmission for newly discovered pathogens



Lanteri et al, Transfusion 2016

vitalant Research Institute



Donation archives and prospective donor-recipient repositories: indispensable tools for monitoring blood safety

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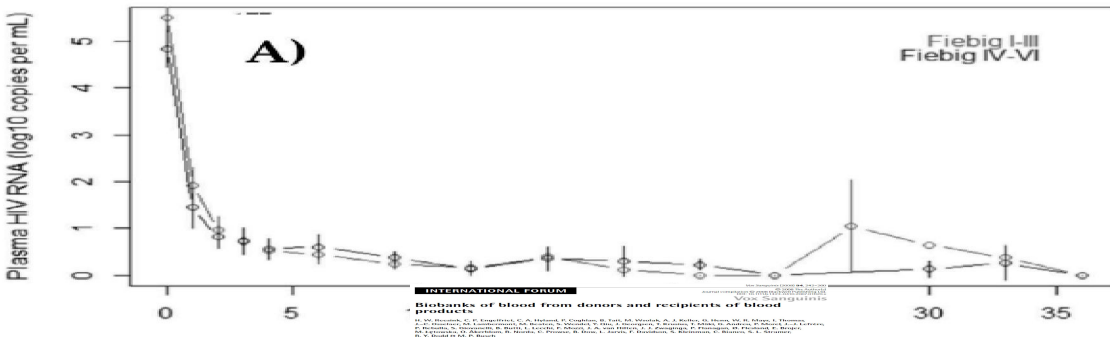
TABLE 1. Donation and donor-recipient repositories established for research purposes

Country	Name of study	Funding agency	Time frame of funding	Samples type	Number of samples	Number of original articles	Time frame of publications
USA	HEART	NIH Clinical Center	1968-1997	Donor-recipient	29,055 donations, 3,429 recipients	73	1970-2005
	TTVS	NHLBI	1974-1979	Donor-recipient	5,655 donations, 1,533 recipients	14	1978-1984
	TSS	NHLBI	1984-1985	Donations	201,212	27	1990-2003
	FACTS	NHLBI	1985-1991	Recipients	11,494	9	1989-2004
	REDS GSR/GLPR	NHLBI	1991-1994	Donations	508,151 (GSR)/ 147,915 (GLPR)	17	1993-2006
	VATS	NHLBI	1995-1999	Donor-recipient	3,864 donations, 531 recipients	26	2001-2003
	REDS RADAR	NHLBI	2003-2005	Donor-recipient	13,201 donations, 3,574 recipients	2	
	TRIPS	NIH Clinical Center/NHLBI	2002-ongoing	Donor-recipient	4,401 donations, 8,771 recipients	1	
The Netherlands		Internal	1985-1990	Donor-recipient	5,000 donations, 1,000 recipients	15	1989-2006
UK	TTISG	NHS	1991	Donor-recipient	21,923 donations, 5,579 recipients	2	1999-2000
Italy	Cooleycare	Italian NIH	1989-2002	Recipients	1,481	8	1990-2004
EU	BOTIA	EU	2006-2008	Donor-recipient	30,000 pairs		



Viruses 2022, 14, 2326. https://doi.org/10.3390/v14112326

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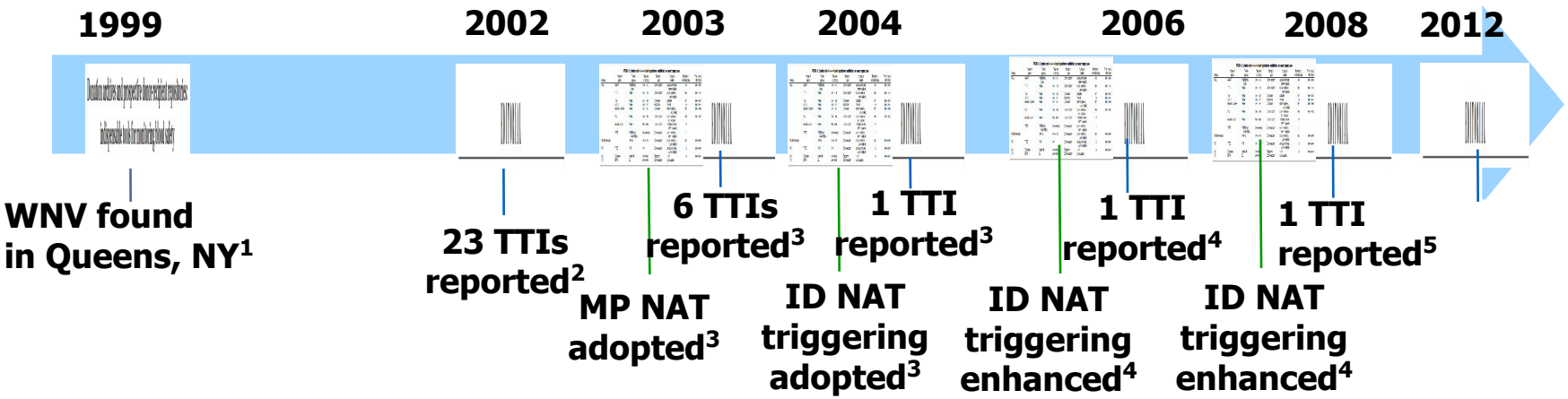
U.S. WNV blood donor screening timeline



All transfusion-transmitted infections (TTIs) traced to WNV RNA(+) / Antibody(-) transfusions, except for 2013 case in which donation had very low VL with IgM and IgG

[1]Lanciotti, RT, Roehrig JT, Deubel V, Smith J, Parker M, Steele K, et al. Science, 1999

[2]Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, Stramer SL, Stobierski MG et al. *N Engl J Med.* 2003

[3]Busch MP, Caglioti S, Robertson EF, McAuley, JD, Tobler LH, Kamel H et al. *New England J Med,* 2005

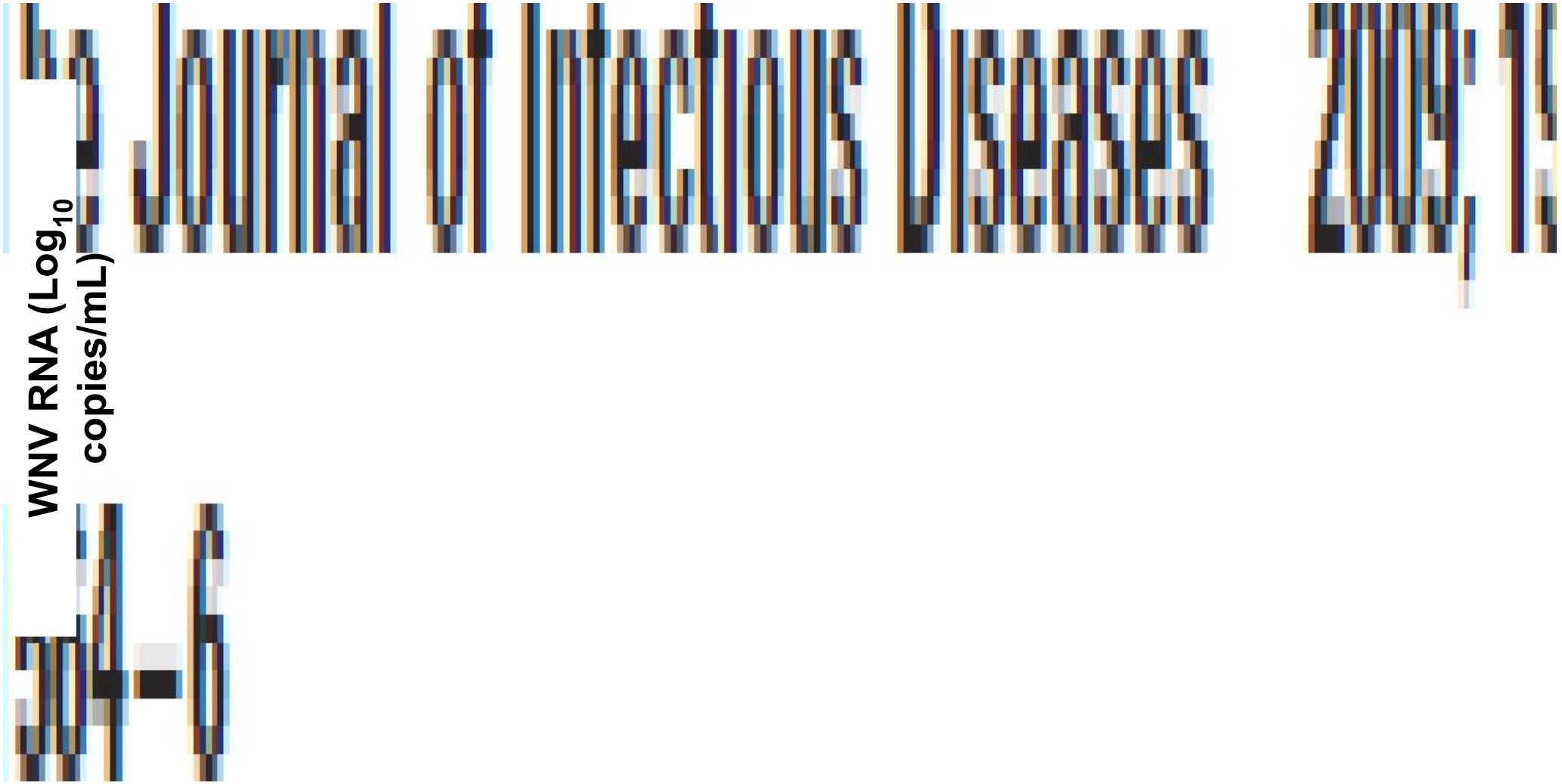
Stramer SL, Fang CT, Foster GA, Wagner AG, Brodsky JP, Dodd RY. *N Engl J Med.* 2005

[4]Kleinman SH, Williams JD, Robertson G, Caglioti S, Williams RC, Spizman R et al. *Transfusion.* 2009

[5]Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report.* 2009

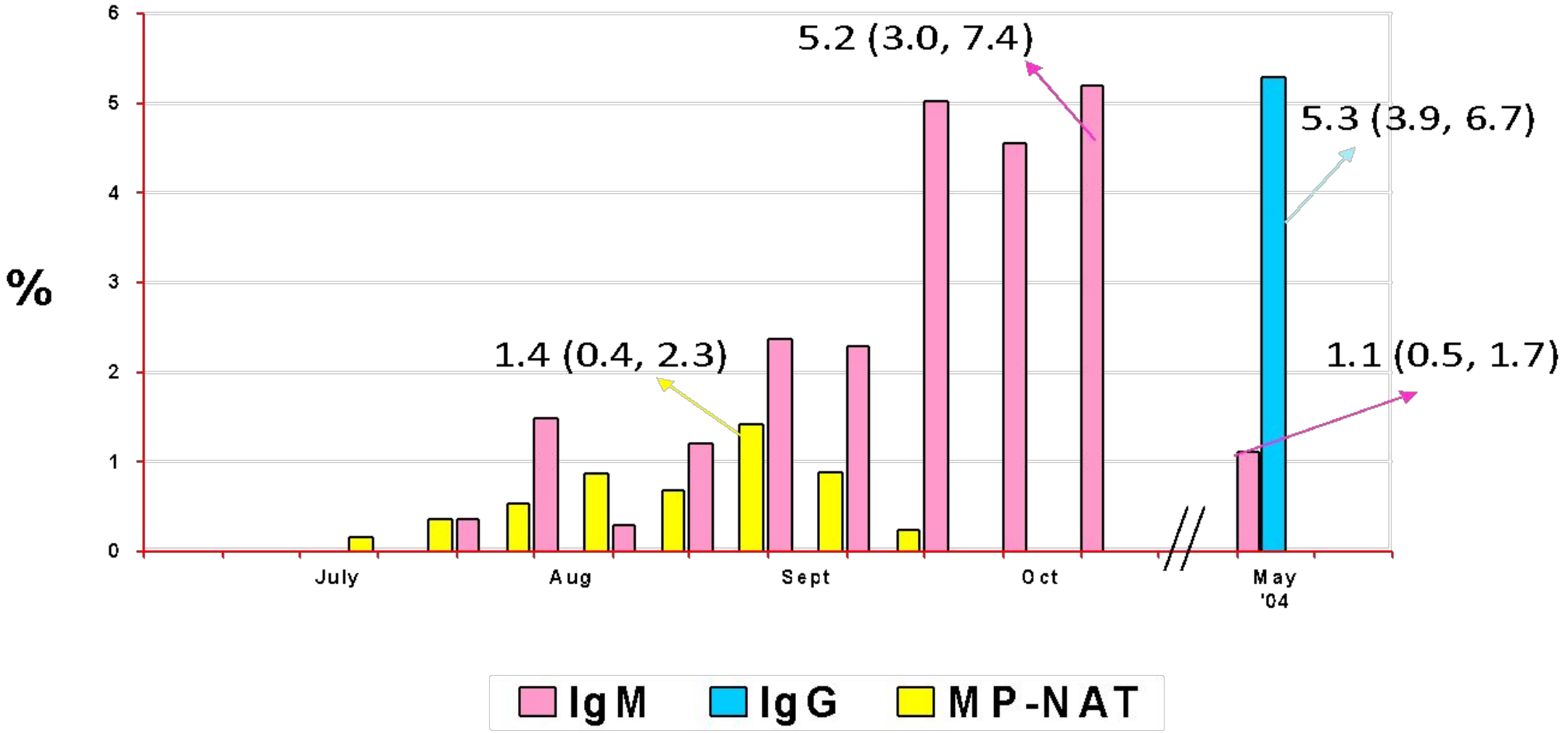
[6]Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report.* 2013

Window Periods for acute WNV infection parameters, and need for targeted ID-NAT



Busch et al, JID, 2008

WNV MP NAT yield relative to IgM and IgG seroprevalence rates
North Dakota, 2003

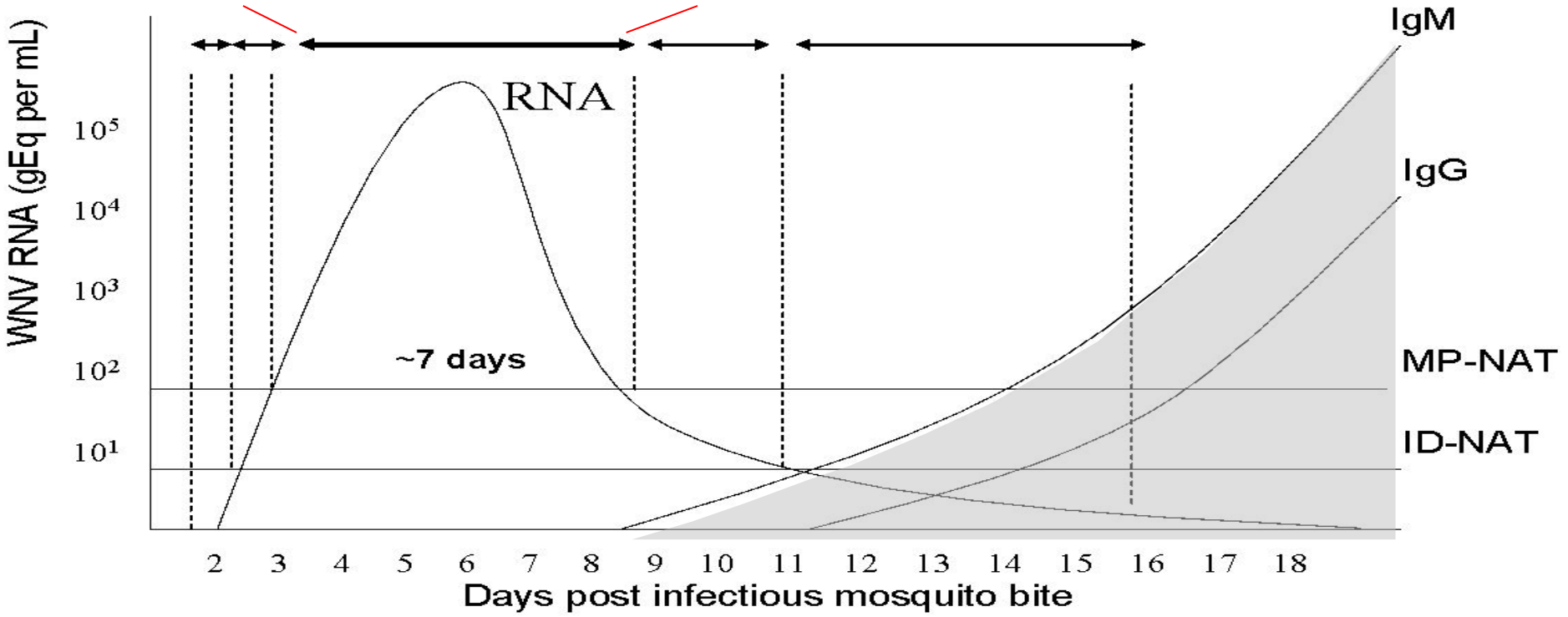


Busch et al, EID, 2006

Derivation of $T_{MP\text{-}NAT}$ from period-specific MP-NAT yield and peak IgM prevalence rates

Stage-I	Stage-II	Stage-III	Stage-IV	Stage-V
IDNAT+/- MPNAT- IgM-	IDNAT+ MPNAT- IgM-	MPNAT+ IgM-	IDNAT+ MPNAT- IgM+	IDNAT +/- MPNAT- IgM+/IgG+

6.9 day (95% CI, 3.0 -10.7)



Busch et al, EID, 2006

State-specific WNV infection rates (per 1000) in 2003, projected from MP-NAT yield and T_{MP-NAT}

- Highest infection rates in Nebraska (4.9%), Colorado (4.3%), North Dakota (4.1%), South Dakota (4.0%), Wyoming (3.5%) and Kansas (2.1%)
- Nationally, 735,000 persons (95% CI 583,000-887,000) infected with WNV in 2003

Busch et al, EID, 2006

Estimated cumulative incidence of West Nile virus infection in US adults, 1999–2010

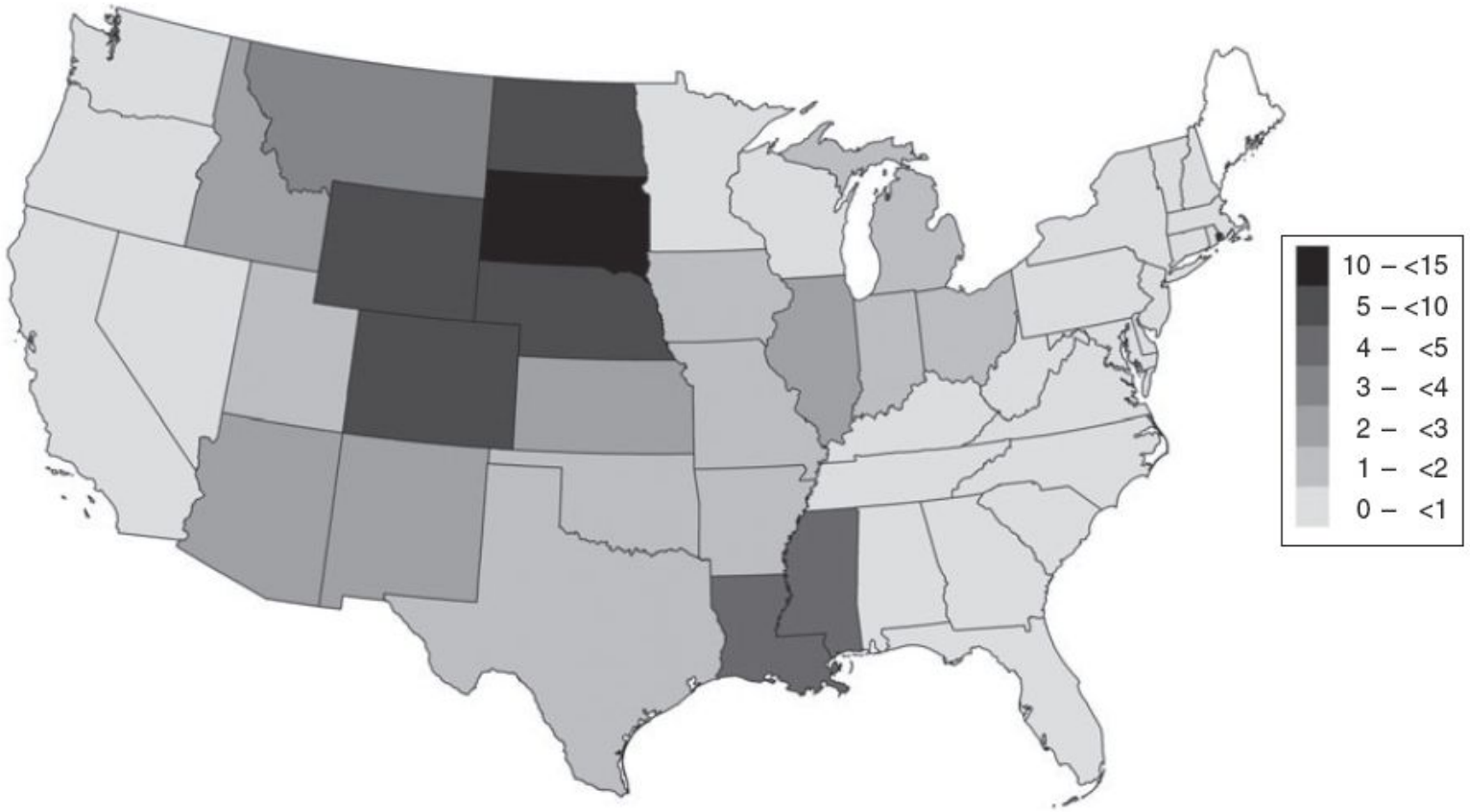
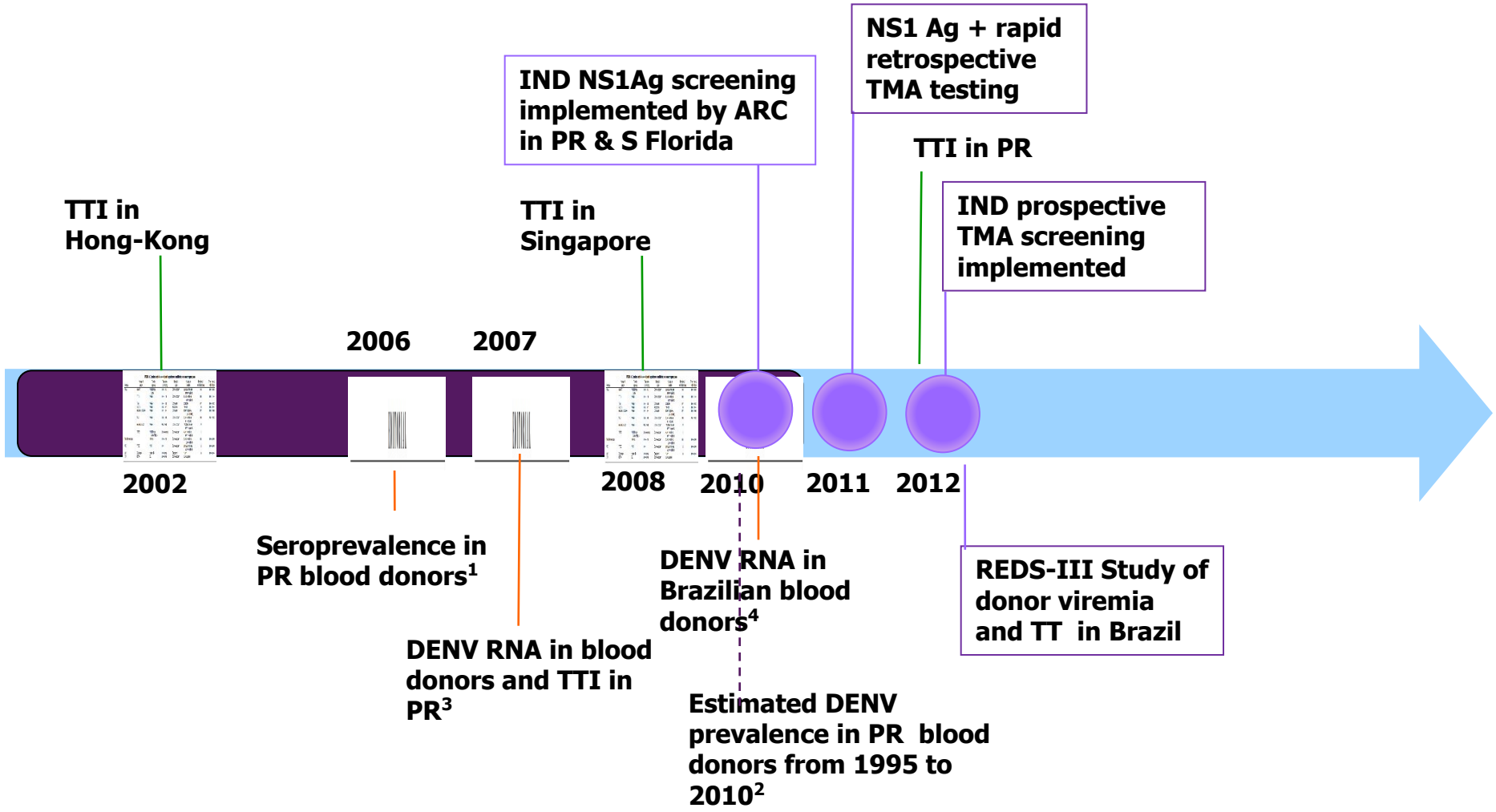


Fig. 1. Estimated cumulative incidence of West Nile virus infection (per cent of population infected) in US adults aged ⩾16 years, 1999–2010.

~2.8 million infected and 780,000 developed clinical disease in US by 2012

Petersen et al. Epid Infect 2012

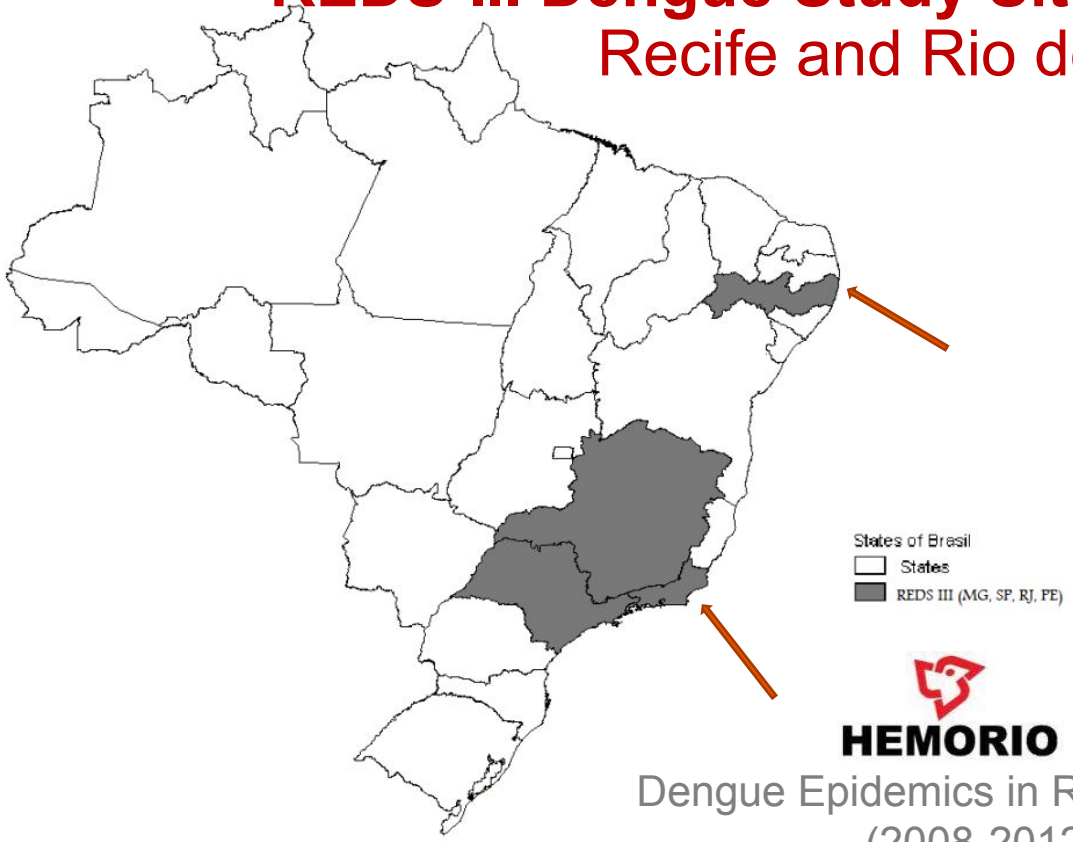
Evaluating the risk for dengue transfusion-transmission in Puerto Rico and Brazil



[1] Mohammed H., Tomashek K.M., Stramer S.L., Hunsperger E., *Transfusion August 2012*
[2] Petersen L.R, Tomashek K.M., Biggerstaff B.J., *Transfusion August 201*
[3] Stramer S.L., Linnen J.M., Carrick J.M., et, *Transfusion August 2012*
[4] Dias L.L., Amarilla A.A., Poloni T.R., Covas D.T., Aquino V.H., Figueiredo L.T.M., *Transfusion August 2012*

REDS-III Dengue Study Sites and Epidemic Activity

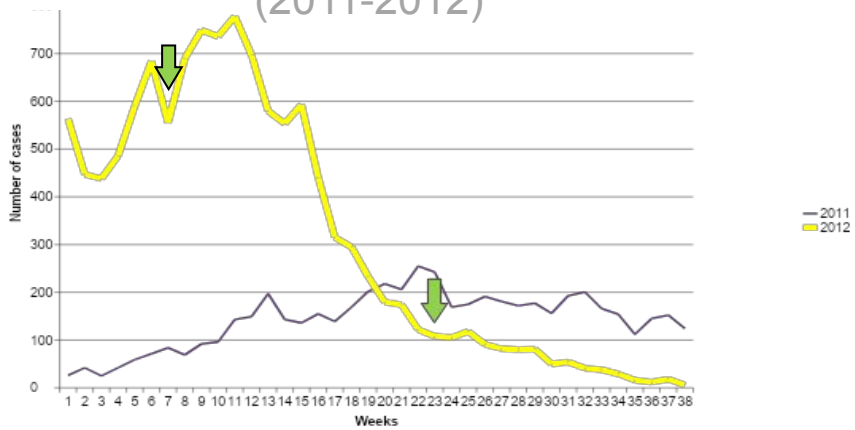
Recife and Rio de Janeiro, 2012



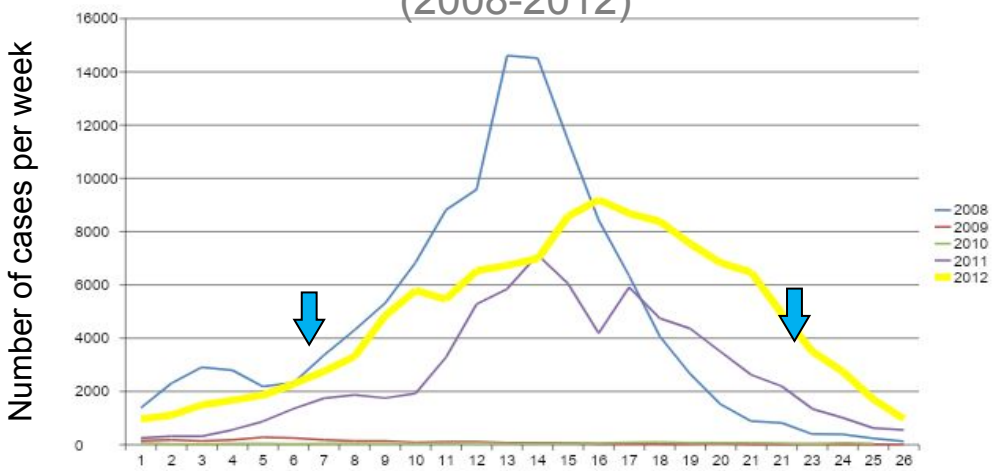
HEMORIO

Fundação HEMOPE

Dengue Epidemics in Recife (2011-2012)



Dengue Epidemics in Rio de Janeiro (2008-2012)

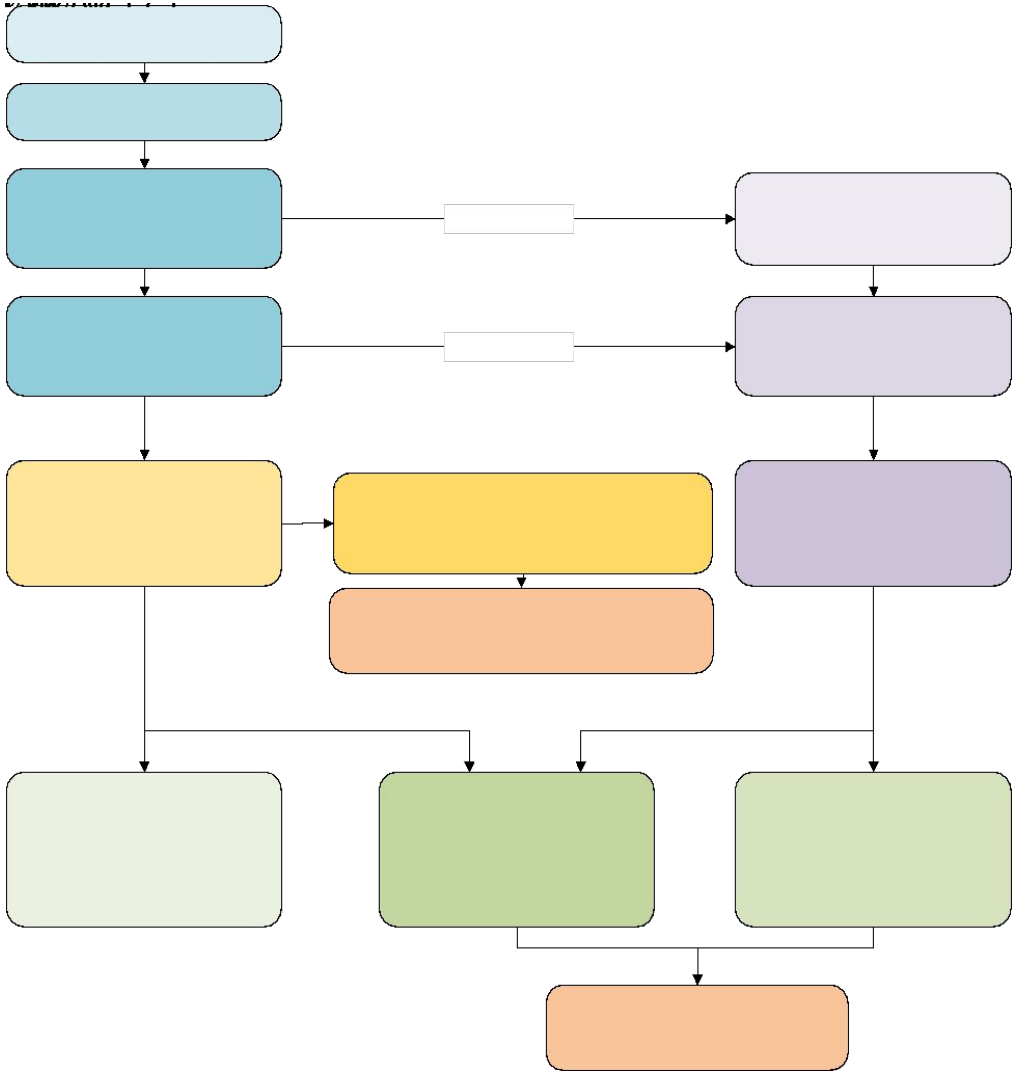


J Infect Dis. 2016 Mar 1;213(5):694-702
J Infect Dis. 2016 Jul 1;214(1):49-54.
Sci Rep. 2017 Nov 9;7(1):15216.

REDS-III

Dengue Transfusion-Transmission Study in Brazil 2012 Rio de Janeiro and Recife

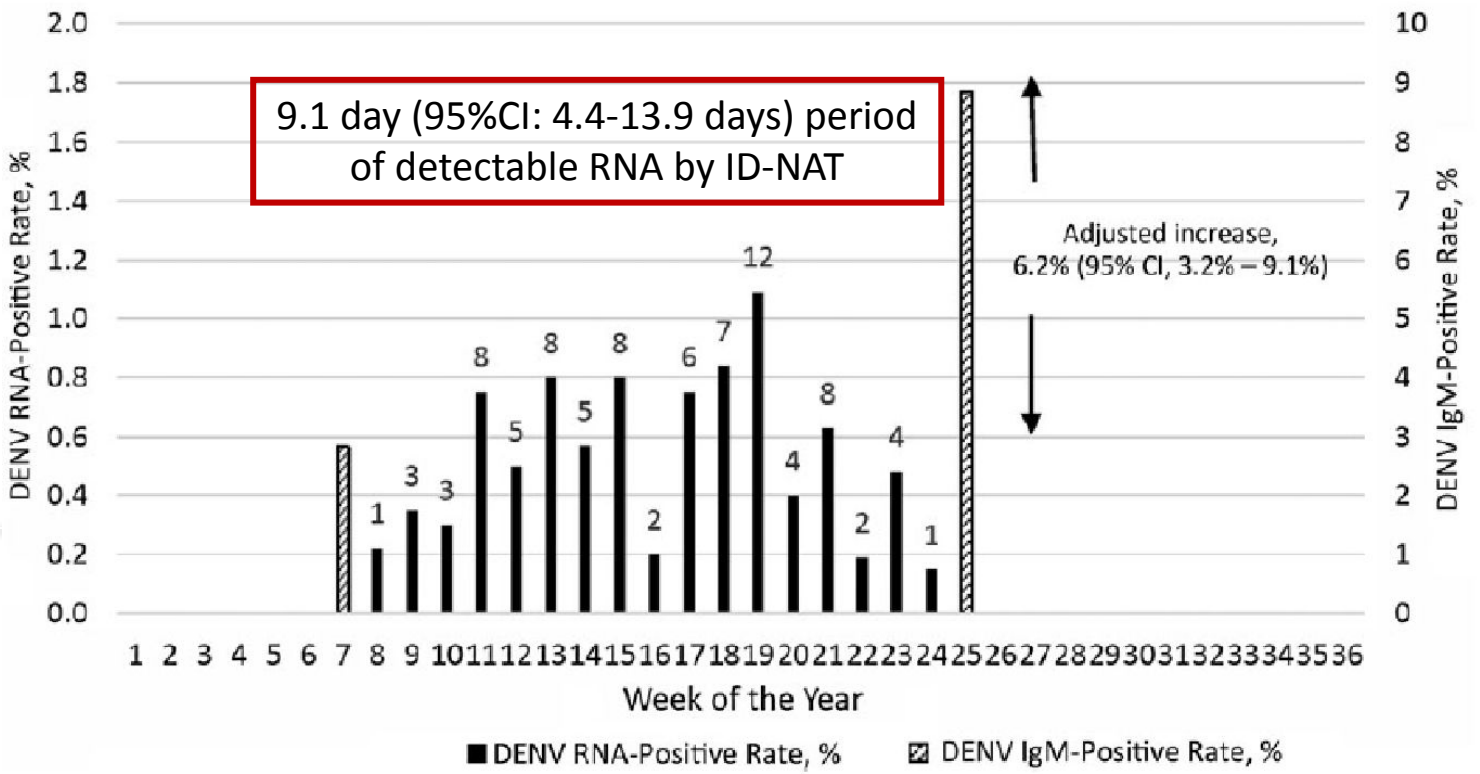
- **DENV-4 viremia confirmed in 0.51% of donors in Rio de Janeiro and 0.80% in Recife**
- **Estimated rate of transfusion transmission 37.5% (95% CI 15–64%)**
- **Symptomatic infection, severity and death not different between TT and mosquito acquired infections and uninfected control patients**



J Infect Dis. 2016 Mar 1;213(5):694-702
J Infect Dis. 2016 Jul 1;214(1):49-54.
Sci Rep. 2017 Nov 9;7(1):15216.

Duration of Dengue Viremia in Blood Donors and Relationships Between Donor Viremia, Infection Incidence and Clinical Case Reports During a Large Epidemic

Michael P. Busch,[1,2] Ester C. Sabino,[6] Donald Brambilla,[5] Maria Esther Lopes,[7] Ligia Capuani,[6] Dhuly Chowdhury,[5] Christopher McClure,[5] Jeffrey M. Linnen,[3] Harry Prince,[4,a] Graham Simmons,[1,2] Tzong-Hae Lee,[1] Steven Kleinman,[5] and Brian Custer[1,2]; for the International Component of the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)[b]



1 case of clinical dengue diagnosed for every 3 infections
853 cases of reported clinical disease per NAT yield donation

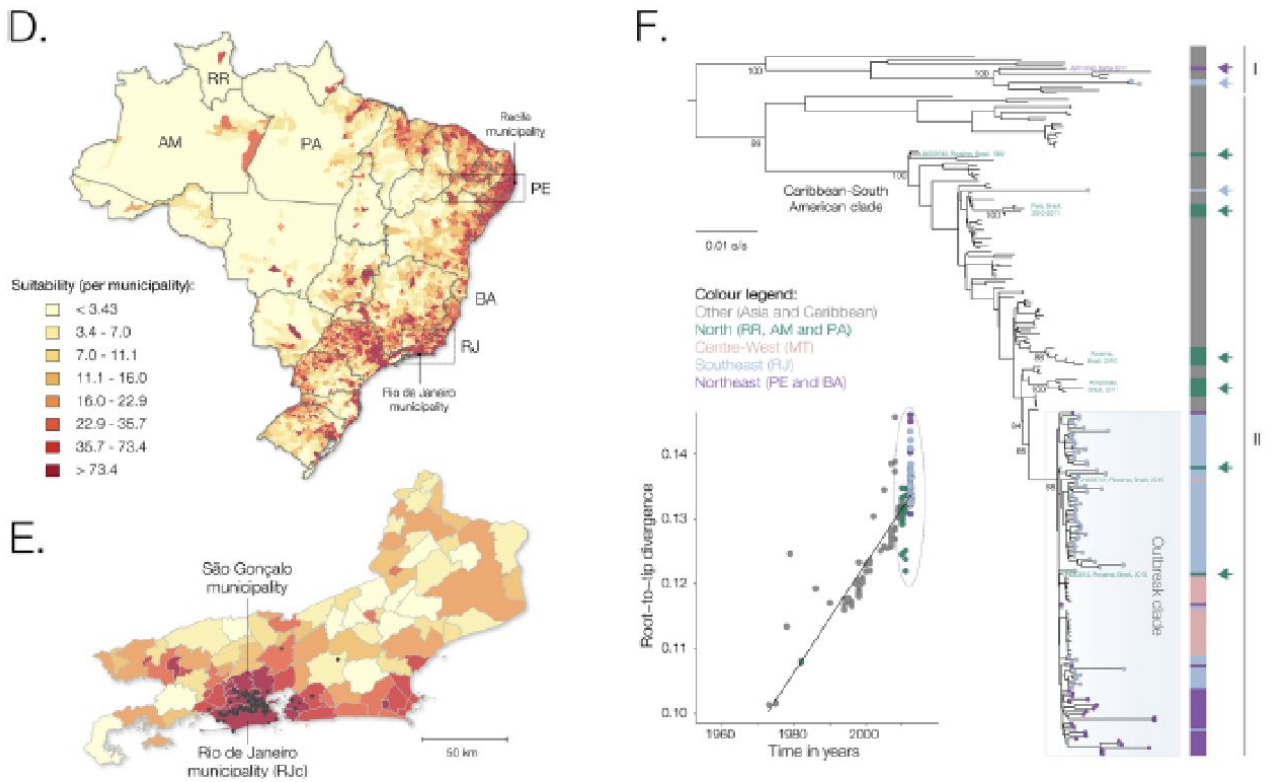
JID 2016

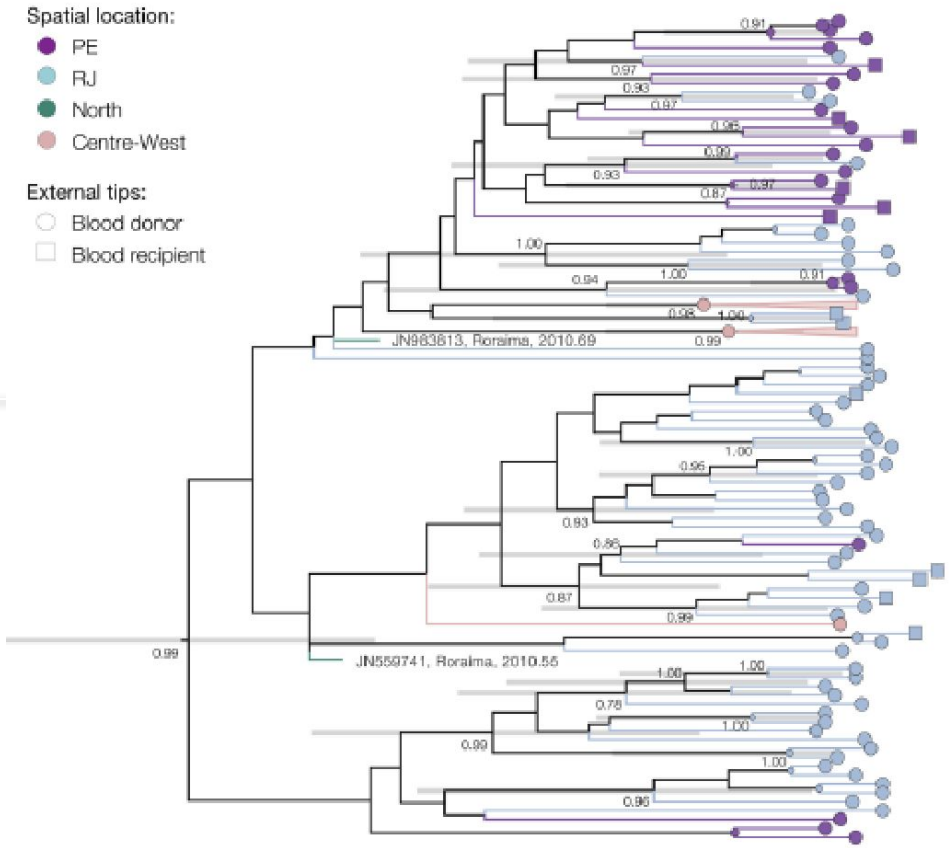
Genomic and epidemiological characterisation of a dengue virus outbreak among blood donors in Brazil

SCIENTIFIC REPORTS | 7: 15216 | DOI:10.1038/s41598-017-15152-8

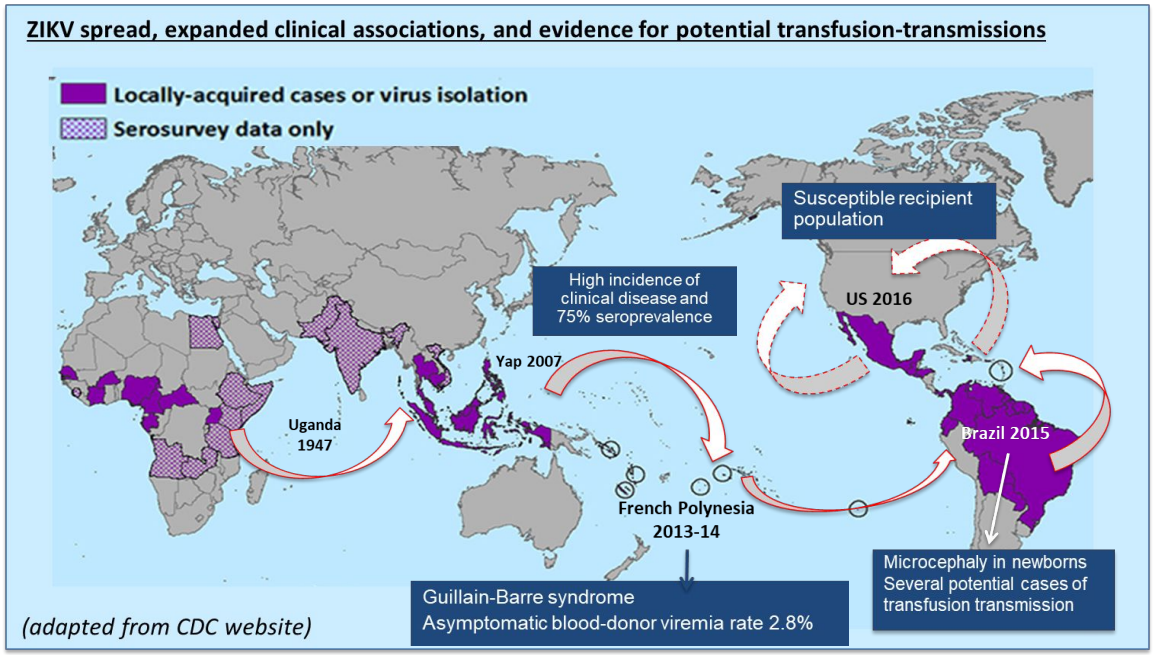
Nuno R. Faria[1], Antonio Charlys da Costa[2,3], José Lourenço[1], Paula Loureiro[4], Maria Esther Lopes[5], Roberto Ribeiro[2,3], Cecilia Salete Alencar[6], Moritz U. G. Kraemer[1], Christian J. Villabona-Arenas[7], Chieh-Hsi Wu[8], Julien Thézé[1], Kamran Khan[9,10], Shannon E. Brent[9], Camila Romano[2], Eric Delwart[11,12], Brian Custer[11,12], Michael P. Busch[11,12], Oliver G. Pybus[1], Ester C. Sabino[2,3] & NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)*

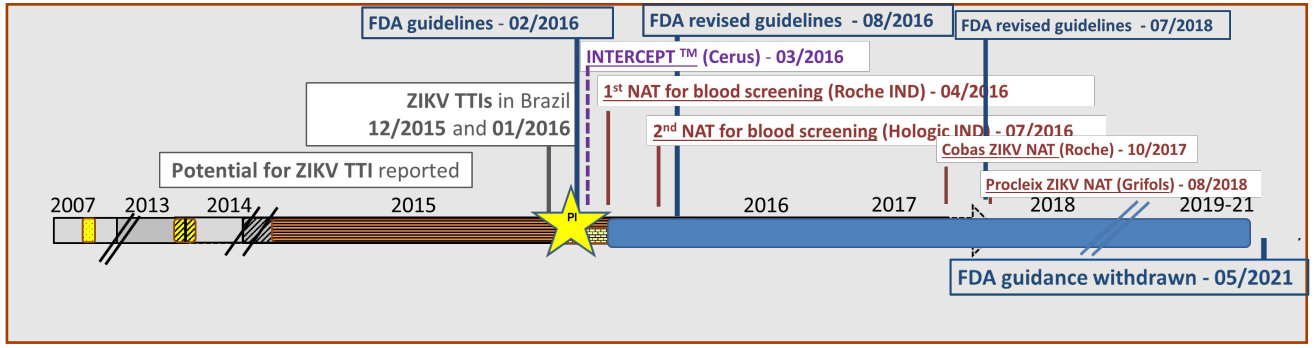
Outbreaks caused by Dengue, Zika and Chikungunya viruses can spread rapidly in immunologically naïve populations. By analysing 92 newly generated viral genome sequences from blood donors and recipients, we assess the dynamics of dengue virus serotype 4 during the 2012 outbreak in Rio de Janeiro. Phylogenetic analysis indicates that the outbreak was caused by genotype II, although two isolates of genotype I were also detected for the first time in Rio de Janeiro. Evolutionary analysis and modelling estimates are congruent, indicating a reproduction number above 1 between January and June, and at least two thirds of infections being unnoticed. Modelling analysis suggests that viral transmission started in early January, which is consistent with multiple introductions, most likely from the northern states of Brazil, and with an increase in within-country air travel to Rio de Janeiro. The combination of genetic and epidemiological data from blood donor banks may be useful to anticipate epidemic spread of arboviruses.





Zika Virus – Lessons Learned





U.S. (2015-2021):

- Development of research assays

  - Pathogen reduction in Puerto Rico
  - ZIKV screening under IND then licensed

✔ ZIKV outbreak waned down

✔ Risk mitigation strategies discontinued

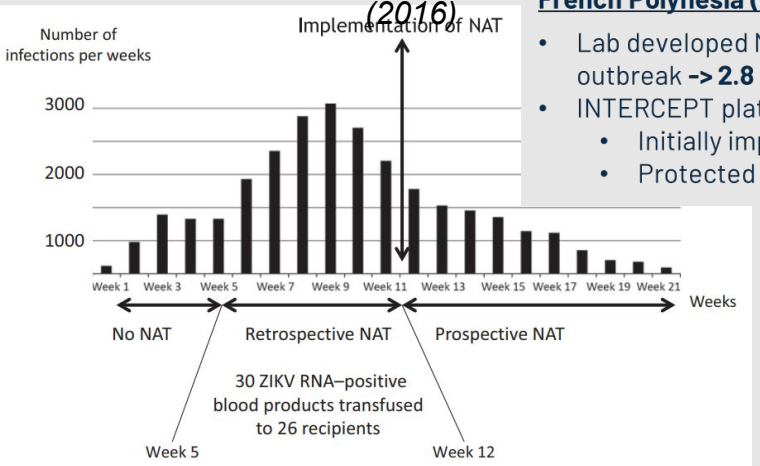
Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components

Guidance for Industry

1. Test all donations collected in the US and its territories with an investigational individual donor nucleic acid test (ID-NAT) for ZIKV under an investigational new drug application (IND), or when available, a licensed test *or*
2. **Implement pathogen reduction technology for platelets and plasma using an FDA-approved pathogen reduction device** as specified in the Instructions for Use of the device. If an FDA-approved pathogen reduction device becomes available for Whole Blood or red blood cells, you may implement pathogen reduction technology for such products rather than testing the donations as described in section IV.A.1.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2018

Musso ISBT Science Series (2016)

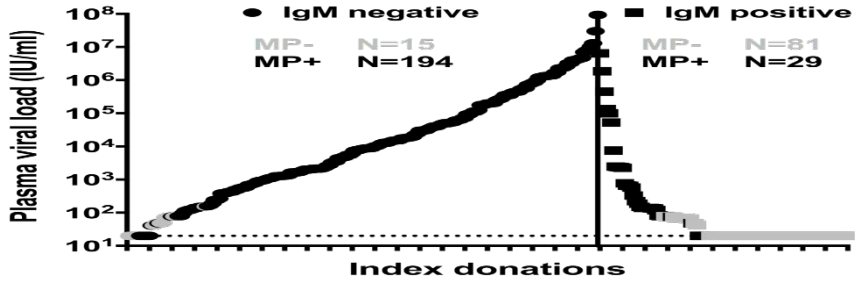


French Polynesia (2013/2014):

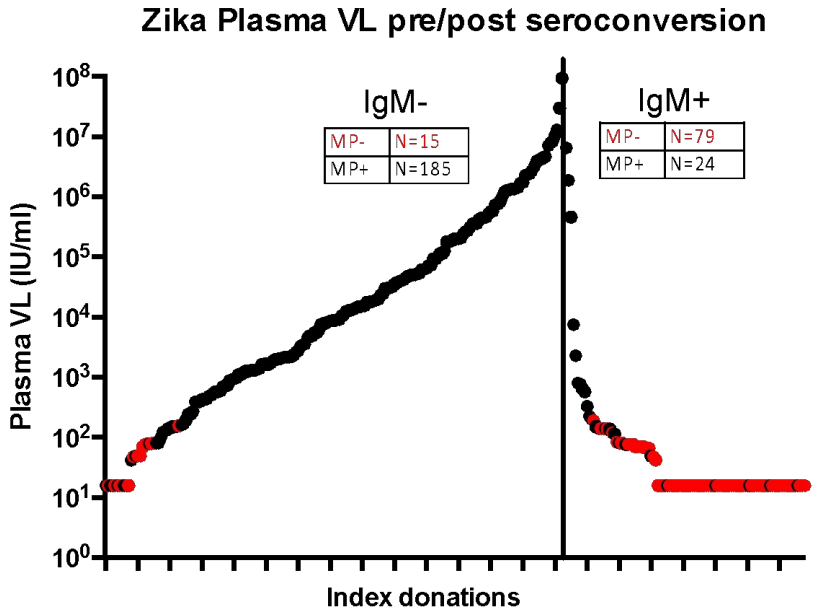
- Lab developed NAT assay implemented week 12 of the outbreak **-> 2.8 % of blood donors tested ZIKV RNA+**
- INTERCEPT platelets were in routine use since 2010
  - Initially implemented to prevent DENV/CHIKV
  - Protected platelet recipients for 12 weeks

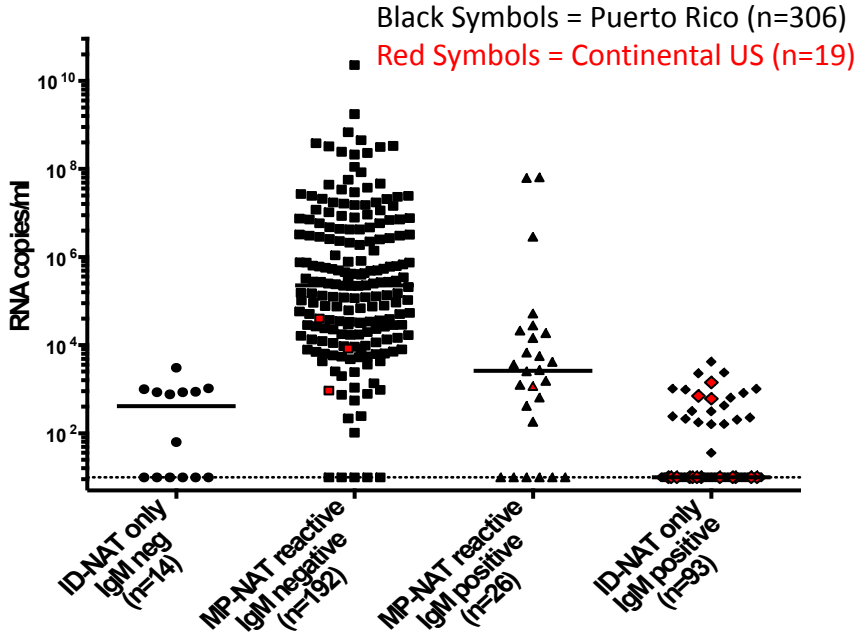
Brazil (2015):

- GBS + Congenital syndromes
- **ZIKV TTI cases**



Staging ZIKV NAT yield cases and application to Incidence Estimation





viremia duration of 9.9 days (SD ± 3.9)

Use of Blood Donor Screening Data to Estimate Zika Virus Incidence, Puerto Rico, April–August 2016

Michelle S. Chevalier, Brad J. Biggerstaff, Sridhar V. Basavaraju, M. Cheryl Bañez Ocfemia, Jose O. Alsina, Consuelo Climent-Peris, Robin R. Moseley, Koo-Whang Chung, Brenda Rivera-García, Melissa Bello-Pagán, Lisa L. Pate, Susan A. Galel, Phillip Williamson, Matthew J. Kuehnert

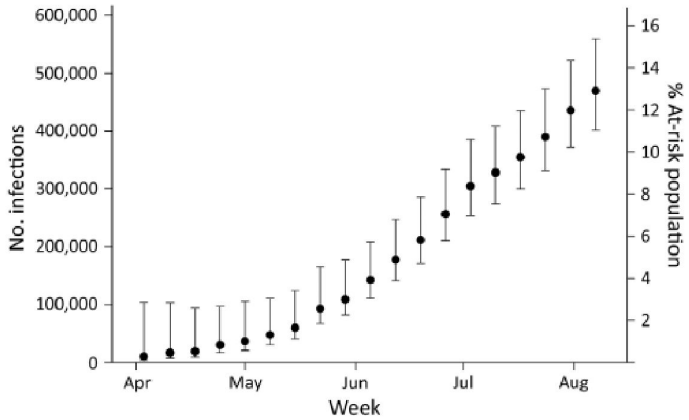
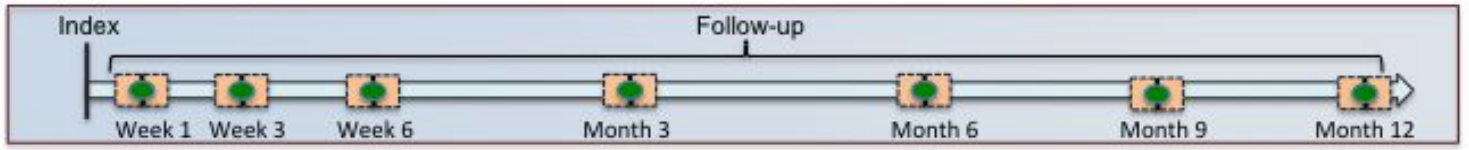


Figure 2. Cumulative weekly estimates of the number and percentage of at-risk population with incident Zika virus infections

Williamson et al., Lancet ID 2021

Chevalier et al.. EID 2017

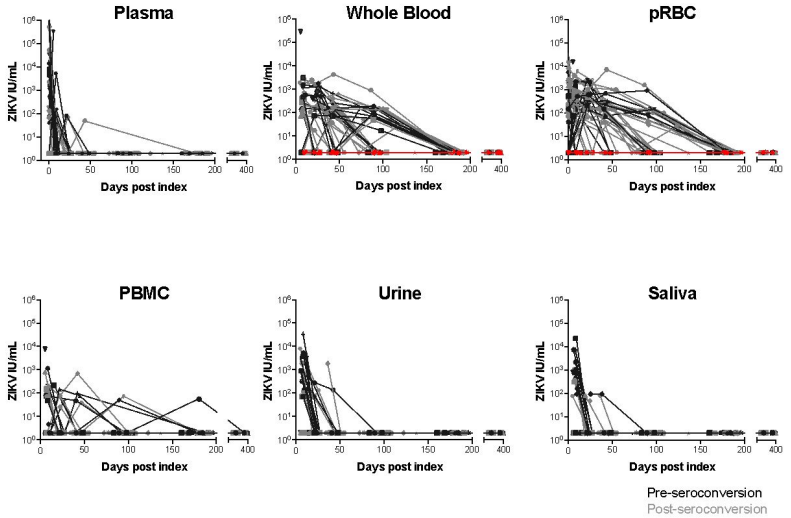
Natural History Cohort of Zika Virus RNA+ Blood Donors



Enrollment per site		
BSSM (PR)	OneBlood	BSI
45	9	2

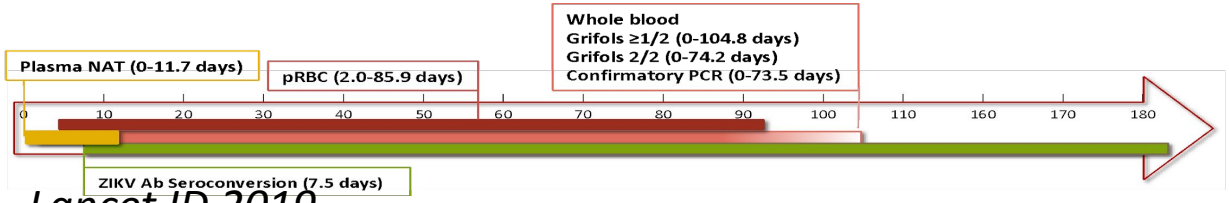
Objectives:

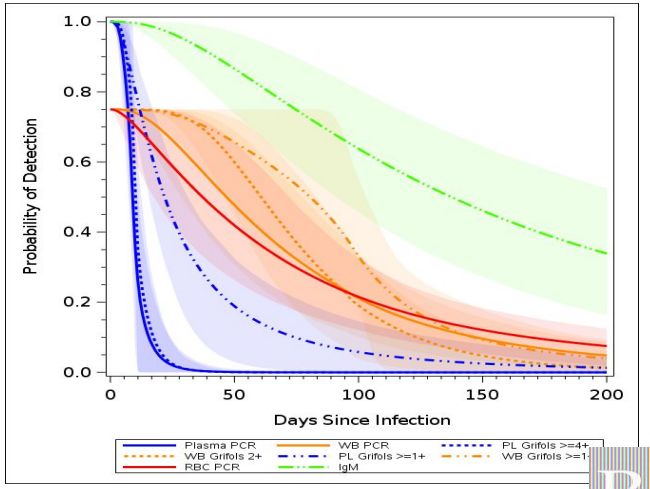
- Evolution of viral and immunological markers over time
- Distribution and compartmentalization in blood and body fluids
- Evaluate the viral and immune mechanisms leading to viral clearance or clinical pathogenesis
- Evaluate clinical outcomes post donation
- Shared samples with 40 government, academic and commercial laboratories
  - Characterize the performance of existing and future assays and provide standards for assay development



Compartment	Assay	Interval*	Mean (CI) days
serum	MAC ELISA IgM	IgM detection	7.7 (6.1, 9.2)
RBC	BSRI PCR	RNA detection	2.0 (0.8, 3.3)
plasma	Grifols ≥1/8 pos	RNA clearance	34.8 (19.9, 56.2)
plasma	Grifols ≥4/8 pos	RNA clearance	11.1 (9.2, 14.4)
plasma	BSRI PCR	RNA clearance	9.9 (8.1, 12.0)
RBC	BSRI PCR	RNA clearance	85.9 (58.4,109.6)
WB	Grifols ≥1/2 pos	RNA clearance	104.8 (76.7, 129.9)
WB	Grifols 2/2 pos	RNA clearance	74.2 (43.8, 104.9)
WB	BSRI PCR	RNA clearance	73.5 (39.8, 107.5)

* Since plasma NAT detectable infection





Stone et al., Lancet ID 2019

Surveillance for Zika, Chikungunya, and Dengue Virus Incidence and RNAemia in Blood Donors at 4 Brazilian Blood Centers During 2016–2019

Brian Custer,[1,2] Eduard Grebe,[1,2,3] Renata Buccheri,[1] Sonia Bakkour,[1,2] Mars Stone,[1,2] Ligia Capuani,[4] Cecilia Alencar,[5] Luiz Amorim,[6] Paula Loureiro,[7,8] Anna Barbara Carneiro-Proietti,[9] Alfredo Mendrone-Junior,[10] Thelma Gonçalez,[1] Kui Gao,[11] Kristin W. Livezey,[11] Jeffrey M. Linnen,[11] Don Brambilla,[12] Chris McClure,[12] Michael P. Busch,[1,2] and Ester C. Sabino,[4] for the Recipient Epidemiology and Donor Evaluation Study (REDS-III) International Component Brazil

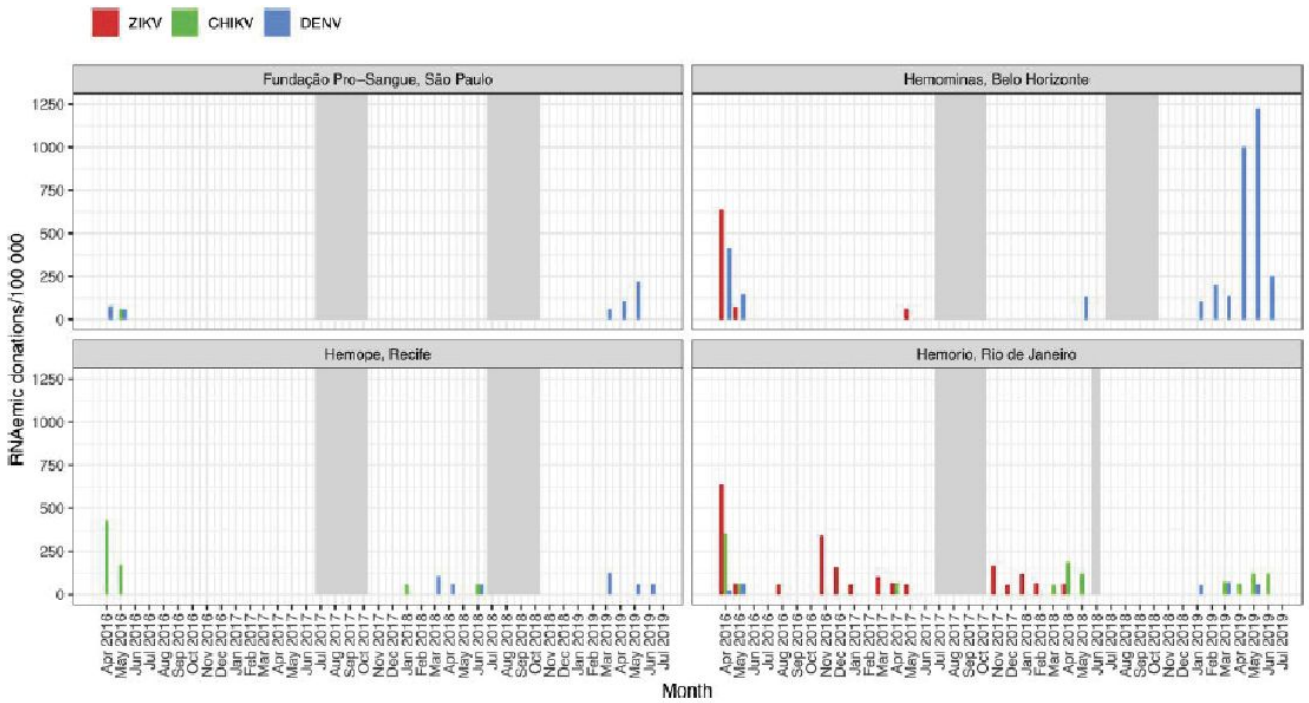


Figure 1. Prevalence of RNAemic donations by month in 4 blood centers. Minipool samples from the months shown in gray were not tested. Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus; ZIKV, Zika virus.

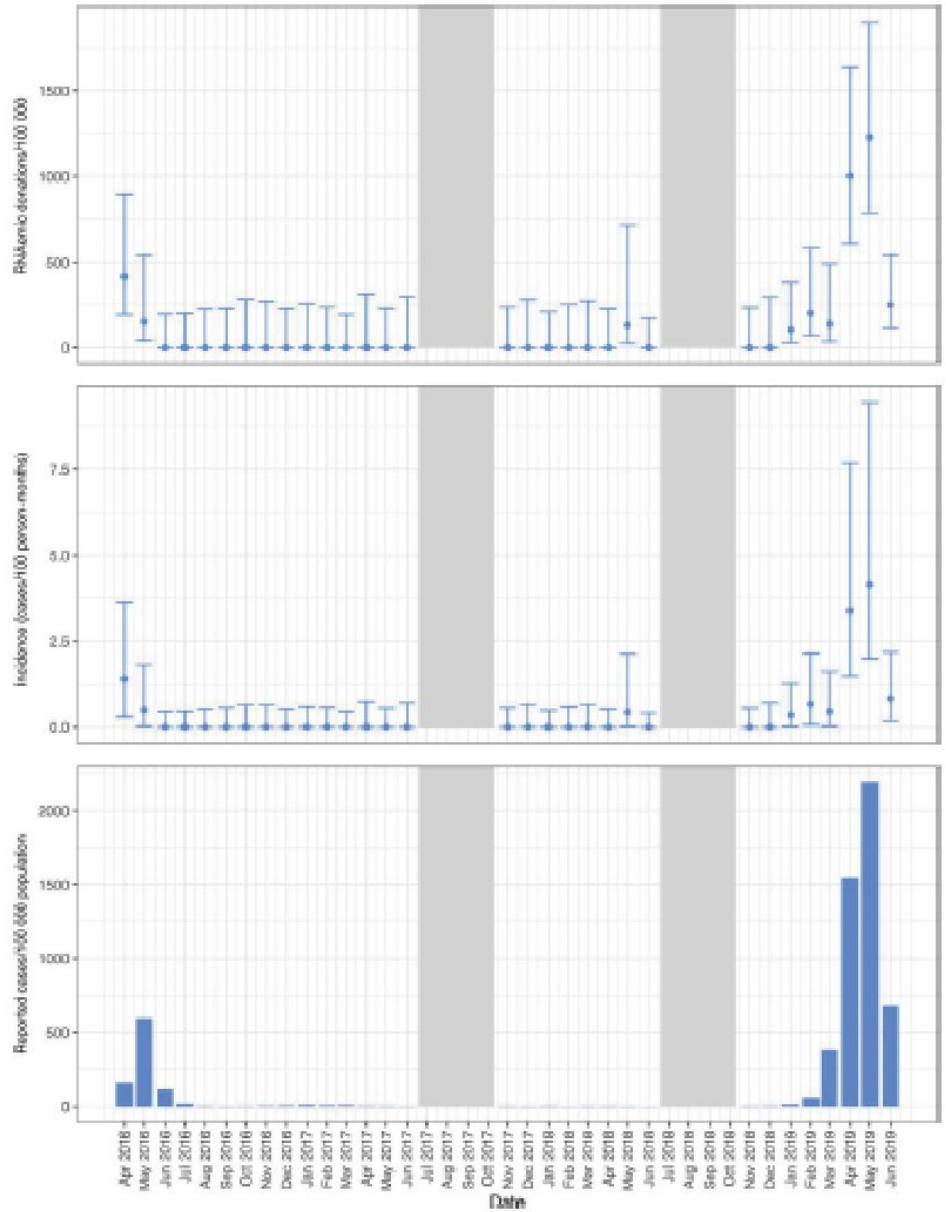


Figure 5. Prevalence of RNAemic donations and donor incidence rates at Hemominas and reported case rates of dengue virus infections by month in Belo Horizonte. Minipool samples from the months shown in gray were not tested.

Conclusions

- Progressive improvements in HIV screening assays have virtually (but not completely) eliminated TT-HIV (and HBV and HCV) infections
- Molecular characterization of NAT yield cases and surveillance for early-ART and PrEP breakthrough HIV infections contribute to HIV epidemic surveillance
- Advances in HIV donor testing and blood donor based research studies have contributed to HIV diagnostics, pathogenesis and cure research and public health surveillance
- Further opportunities to cross-fertilize transfusion medicine and HIV research and EID surveillance include:
  - establishing a global program to characterize incident infections in donors (risk factors, clades, resistance profiles) to help monitor the pulse of TT viral epidemic
  - referral of acutely infected donors to research programs for longitudinal studies focused on understanding the progressive stages of infections and responses to interventions
  - Rapid response with blood donor and recipient based studies to understand infection dynamics and clinical significance of EIDs for transfusion safety and epidemic potential