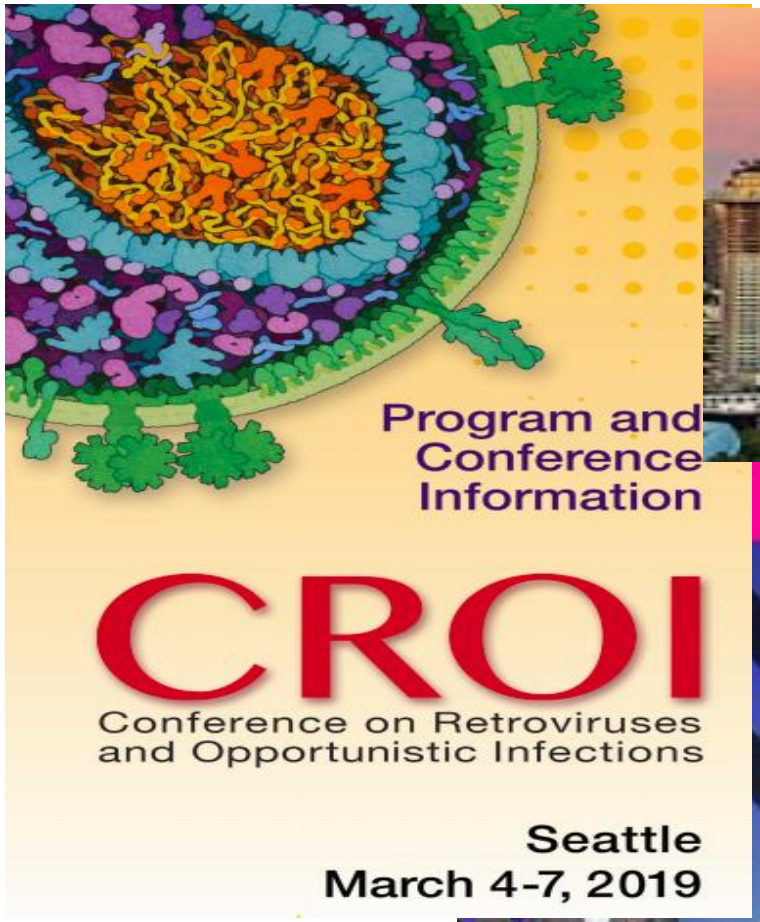
Is The End In Sight: Prevention vs Cure



HIV patient in Dusseldorf could be third person 'cured' of virus after bone marrow transplant

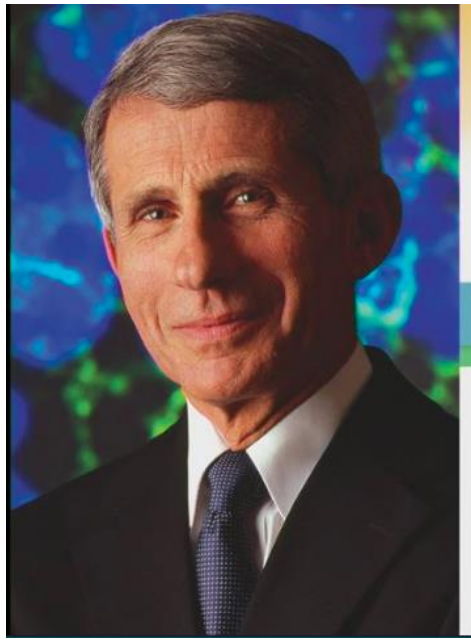
The 'London Patient' goes into HIV remission

Indira Brar, MD
Senior Staff Infectious Diseases, Henry Ford Health System, Detroit

The Washington Post

February 5, 2019

Trump Announces Goal of Ending HIV/AIDS Epidemic by End of Next Decade



ENDING THE HIV EPIDEMIC: A PLAN FOR THE UNITED STATES

SPECIAL PRESENTATION

ANTHONY S. FAUCI

National Institute of Allergy and Infectious Diseases,
National Institute of Health,
US Department of Health and Human Services

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Disclosure: None

CROI 2019

JAMA

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Published online February 7, 2019

Editorial

Ending the HIV Epidemic A Plan for the United States

AS Fauci, RR Redfield, G Sigounas, MD Weahkee, and BP Giroir

The Washington Post

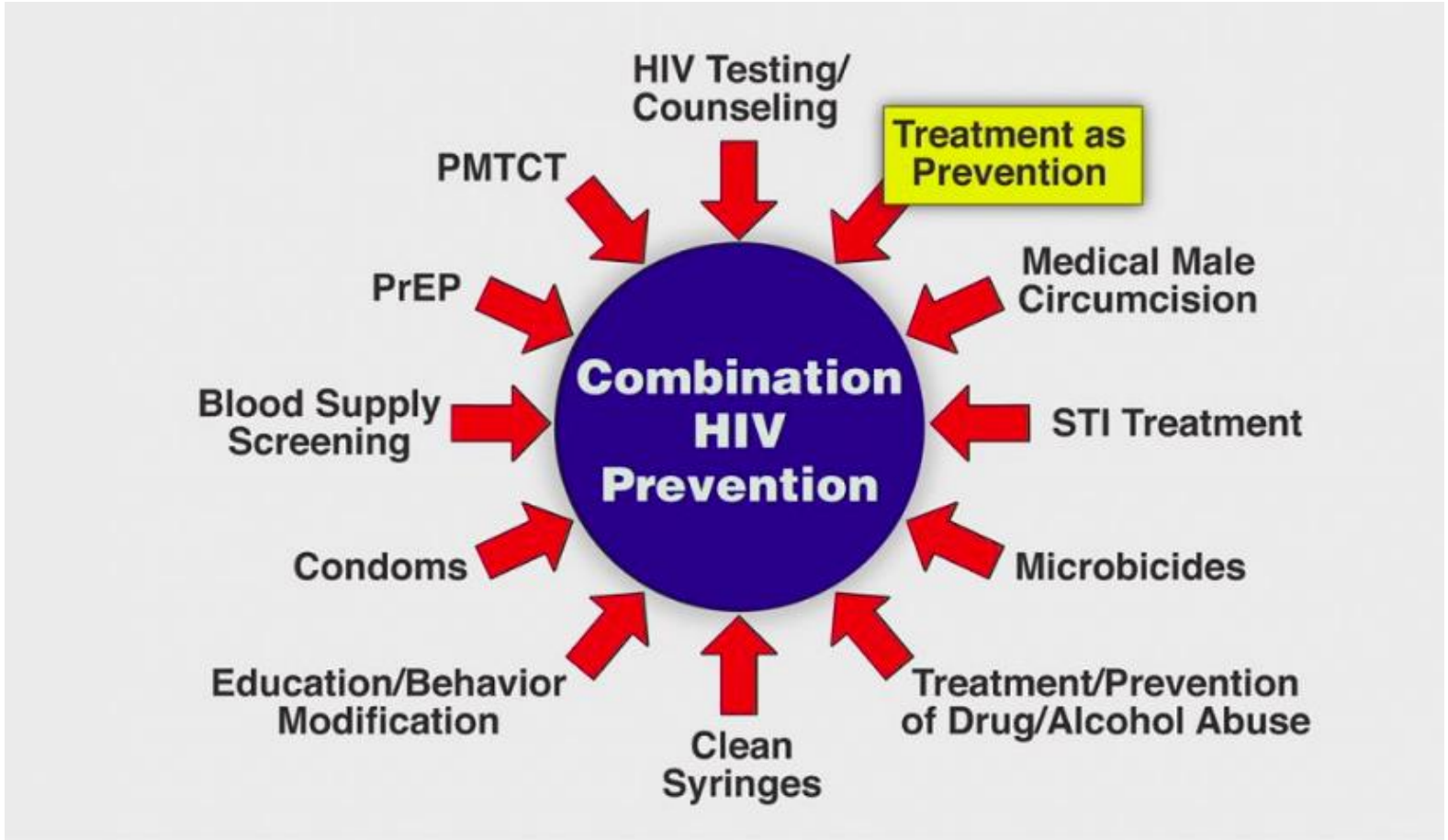
January 10, 2016

OPINIONS

No More Excuses. We Have the Tools to End the HIV/AIDS Pandemic.

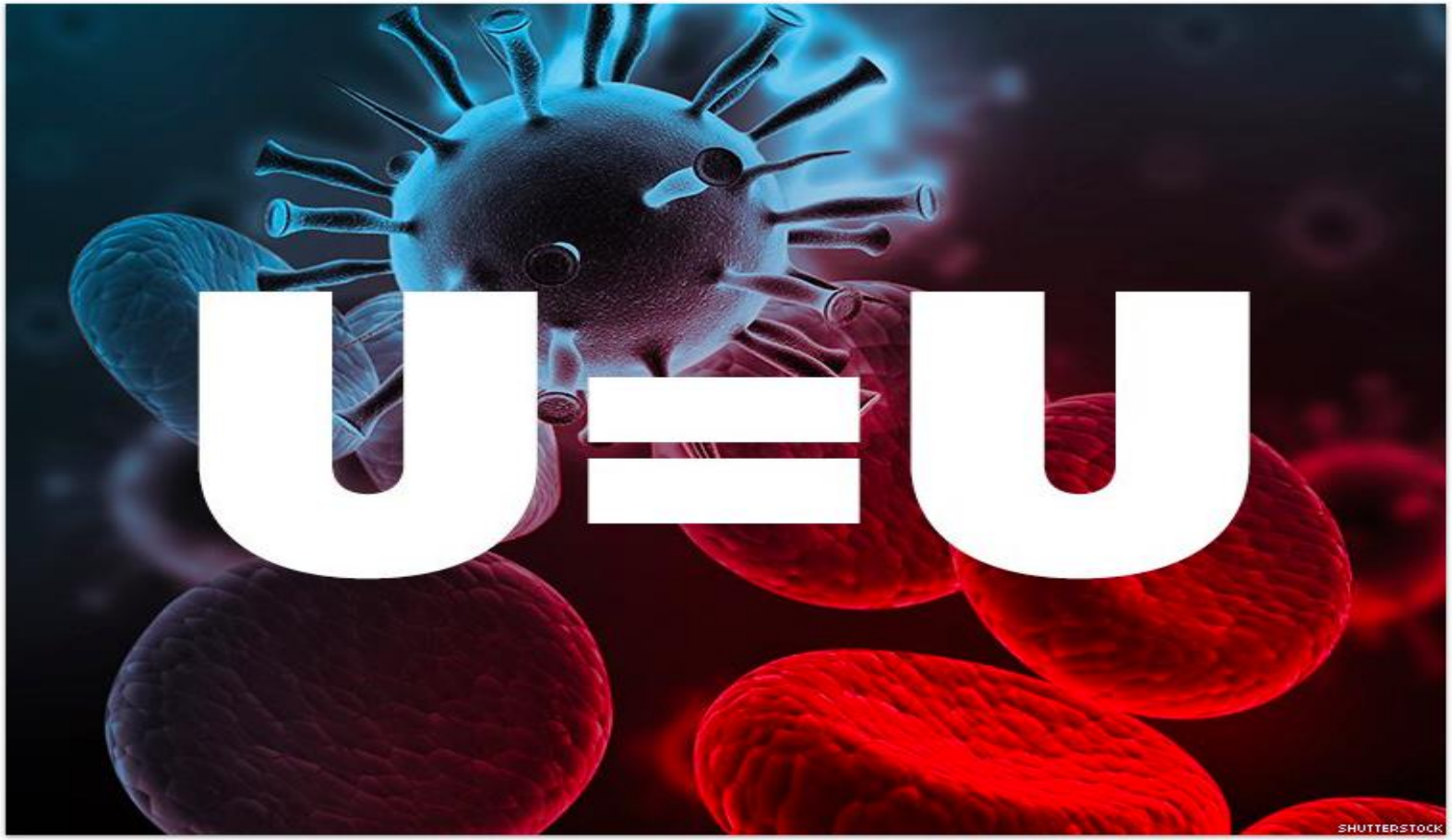
Anthony S. Fauci

Ending the HIV Epidemic:
Fauci; CROI 2019


HIV Testing/
Counseling
PMTCT
Treatment as
Prevention
PrEP
Medical Male
Circumcision
Combination
HIV
Prevention
Blood Supply
Screening
STI Treatment
Condoms
Microbicides
Education/Behavior
Modification
Clean
Syringes
Treatment/Prevention
of Drug/Alcohol Abuse

September 2017

BREAKING: CDC Officially Admits People With HIV Who Are Undetectable Can't Transmit HIV



In a historic letter, the Centers for Disease Control and Prevention support the science behind "Undetectable Equals Untransmittable."

"Across **three different studies**, including thousands of couples and **many thousand acts of sex without a condom** or pre-exposure prophylaxis (PrEP)," the statement continues, "**no HIV transmissions to an HIV-negative partner were observed when the HIV-positive person was virally suppressed.**

The CDC officially backing the science behind the campaign is another key step towards U=U being the most important message of 2017 in the fight against HIV.

The Swiss Statement - 30.1.08

EKAF — WEITERE ORGANISATIONEN UND INSTITUTIONEN

An HIV-infected individual

- without additional STD and
- on an anti-retroviral therapy (ART) with
- completely suppressed viremia

➔is sexually **non-infectious**, thus,
cannot pass on HIV through *sexual contact*

Therapie (ART) mit vollständig supprimierter

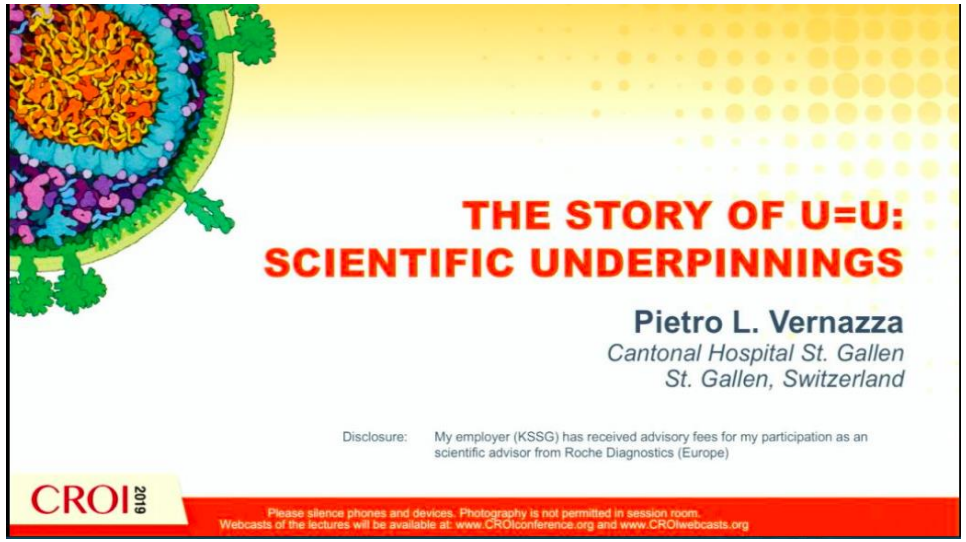
In 2019 The Swiss Concluded

Summary

- So far: **not a single documented case** of transmission during cART
- Continued **absence of evidence** is evidence
- All prospective studies evaluating the risk found **zero risk**!
- Even if risk is not zero, it is **< 1:1000 PY**

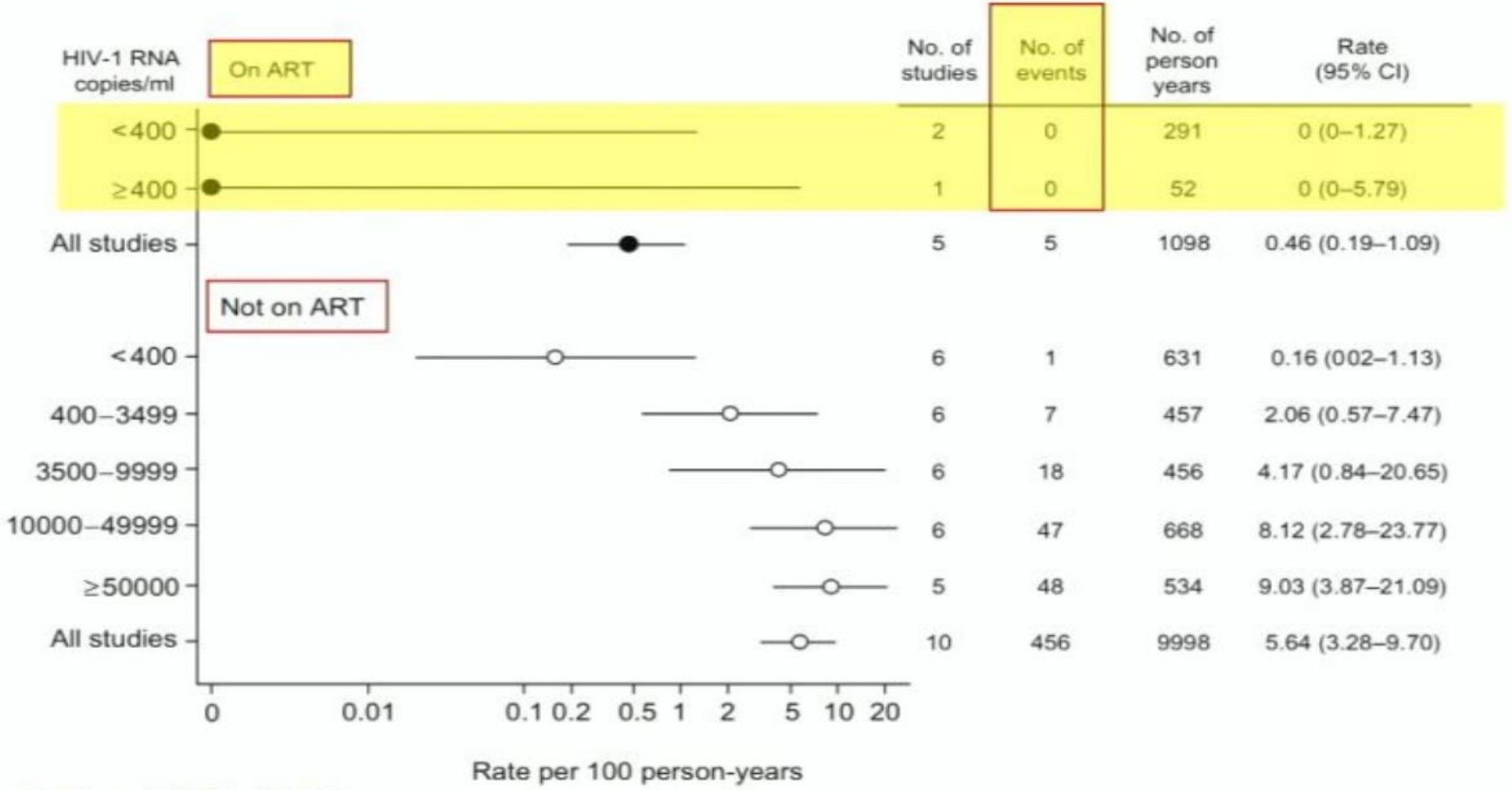
Infektiologie / Spitalhygiene

Kantonsspital St.Gallen



The situation before 2008

Risk of transmission in partnerships

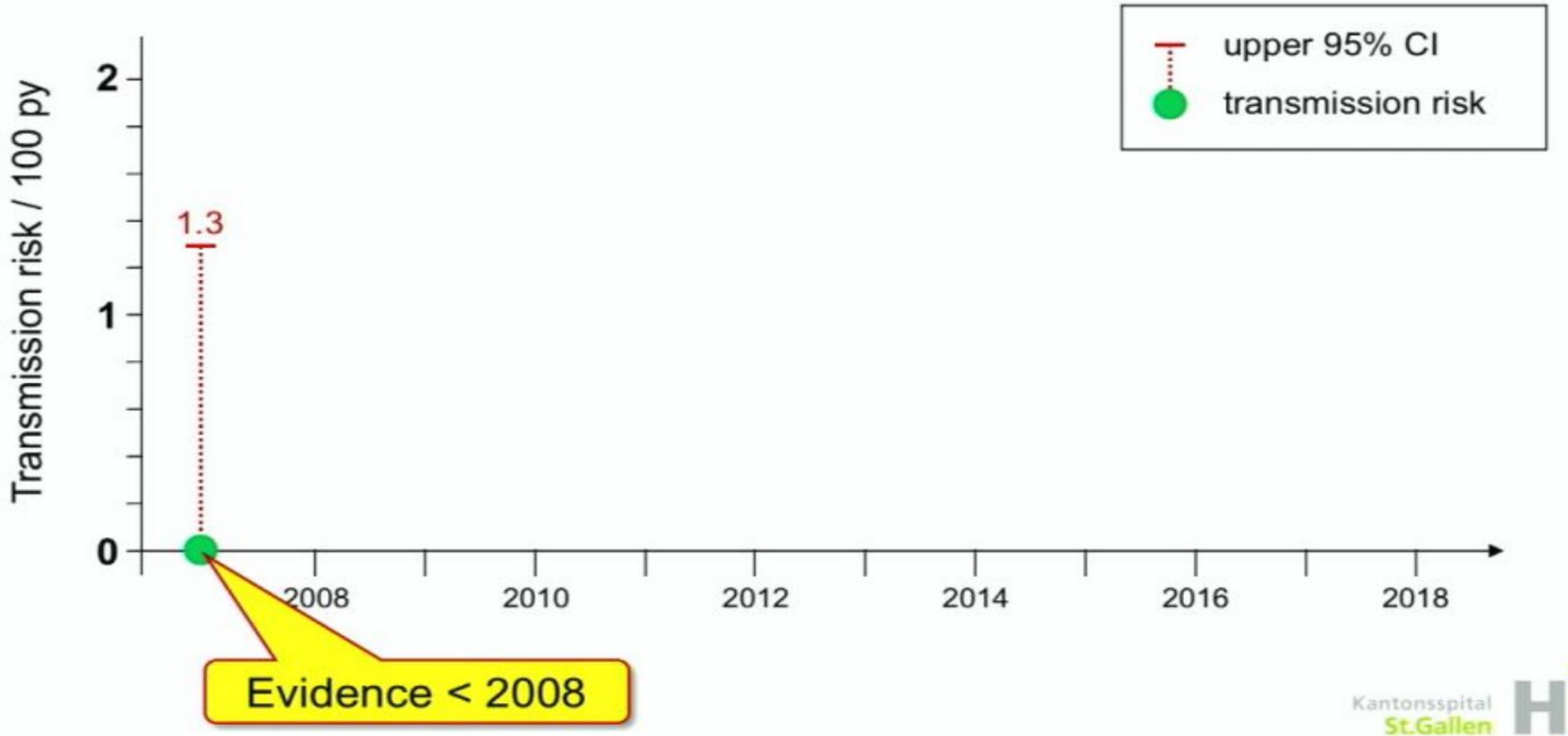


	No. of studies	No. of events	No. of person years	Rate (95% CI)
On ART				
<400	2	0	291	0 (0–1.27)
≥400	1	0	52	0 (0–5.79)
All studies	5	5	1098	0.46 (0.19–1.09)
Not on ART				
<400	6	1	631	0.16 (002–1.13)
400–3499	6	7	457	2.06 (0.57–7.47)
3500–9999	6	18	456	4.17 (0.84–20.65)
10000–49999	6	47	668	8.12 (2.78–23.77)
≥50000	5	48	534	9.03 (3.87–21.09)
All studies	10	456	9998	5.64 (3.28–9.70)

Attia, AIDS, 2009

THE STORY OF U=U: SCIENTIFIC UNDERPINNINGS (ABSTRACT 116)
Pietro L. Vernazza. CROI 2019

Limited evidence from partner studies



Infektiologie / Spitalhygiene

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THE STORY OF U=U: SCIENTIFIC UNDERPINNINGS (ABSTRACT 116)
Pietro L. Vernazza. CROI 2019

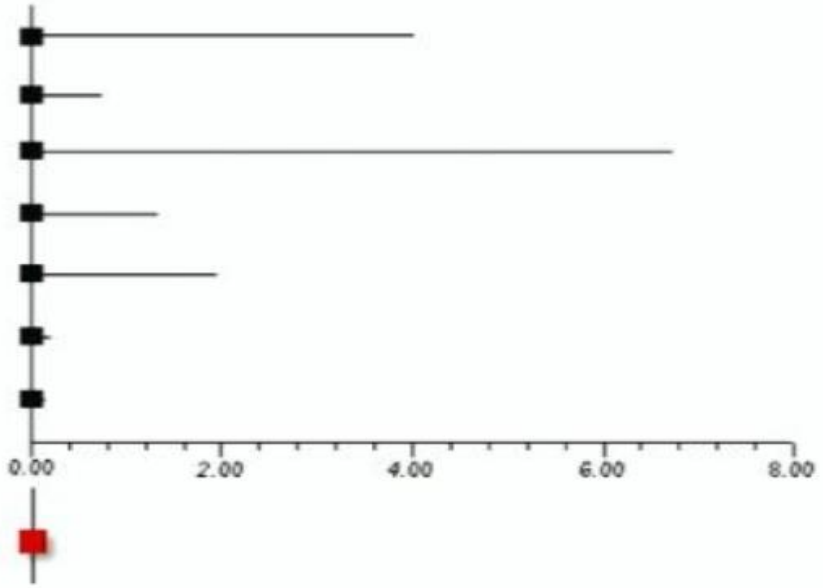
Zero events, increasing number of observations

Forest plot of HIV transmission rates per 100 person-years, excluding unconfirmed viral loads

Study name	Event / person years	Rate	Lower limit	Upper limit
Melo 2008	0 / 90	0.00	0.00	4.02
Del Romero 2010	0 / 492	0.00	0.00	0.75
Reynolds 2011	0 / 53	0.00	0.00	6.72
Donnell 2010	0 / 273	0.00	0.00	1.34
Apondi 2011	0 / 185	0.00	0.00	1.97
Cohen 2011	0 / 1145	0.00	0.00	0.33
Total		0.00	0.00	0.14
add PARTNER & Opposite Attract	0/4063	0.00	0.00	**0.07**

Statistics for each study

Rate per 100 person-years and 95% CI



Loutfy 2013, PLOS One; Rodger Lancet 2019 in press; Bavinton Lancet HIV, 2018

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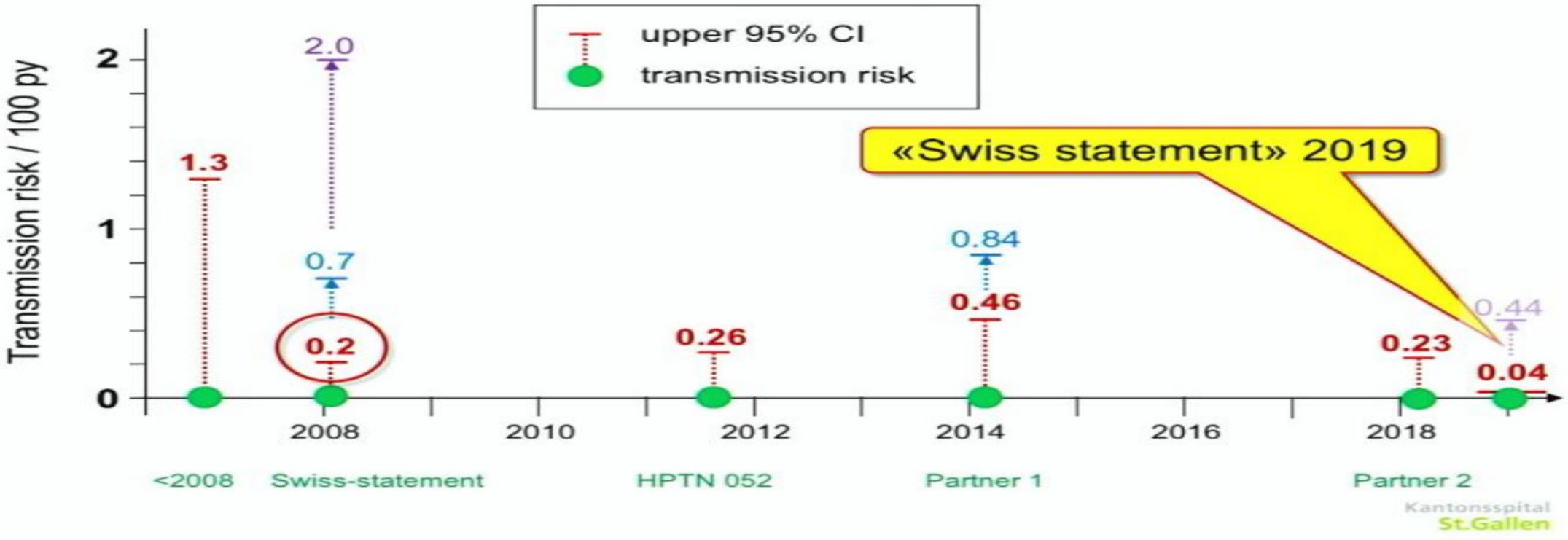
Infektiologie / Spitalhygiene

Time supports the validity of the Swiss statement

Continued absence of evidence increases certainty



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THE STORY OF U=U: SCIENTIFIC UNDERPINNINGS (ABSTRACT 116)
Pietro L. Vernazza. CROI 2019

Summary

- So far: **not a single documented case** of transmission during cART
- Continued **absence of evidence** is evidence
- All prospective studies evaluating the risk found **zero risk**!
- Even if risk is not zero, it is **< 1:1000 PY**

DOES U=U APPLY EQUALLY TO:

- Occupational exposure?
- Breastfeeding?
- Needle sharing?
- Biological plausibility and likelihood are strong but data are limited

CARING FOR U: CLINICAL CONUNDRUMS (ABSTRACT 117)
Nneka Nwokolo. CROI 2019

CONUNDRUM 3 - BREASTFEEDING

- Woman on effective ART for several years
- VL <40 copies/ml
- Asks if she can breastfeed her newborn baby
- Is risk of transmission different in woman with long term viral suppression compared to one with shorter duration of suppression?

CARING FOR U: CLINICAL CONUNDRUMS (ABSTRACT 117)
Nneka Nwokolo. CROI 2019

BREASTFEEDING (I)

PROMISE study

- 2431 mother-infant pairs randomised to maternal ART or infant prophylaxis with nevirapine during breastfeeding
- Infants in ART arm also received daily nevirapine prophylaxis for six weeks
- 2 infants infected with maternal VL <40 copies/ml
- Transmission rate 0.3% at 6/12; 0.6% at 12/12

BREASTFEEDING (II)

- 2017 meta analysis of post natal HIV transmission – no studies show zero infections (1.1% at 6/12 and 2.9% at 12/12)[1]
- HOWEVER, 2018 Tanzanian study showed no transmissions to infants of mothers on ART with VL <1000 cpm[2]
- 18% of infants lost to follow-up, transferred or died

CARING FOR U: CLINICAL CONUNDRUMS (ABSTRACT 117)
Nneka Nwokolo. CROI 2019

TRANSMISSION: POSSIBLE EXPLANATIONS

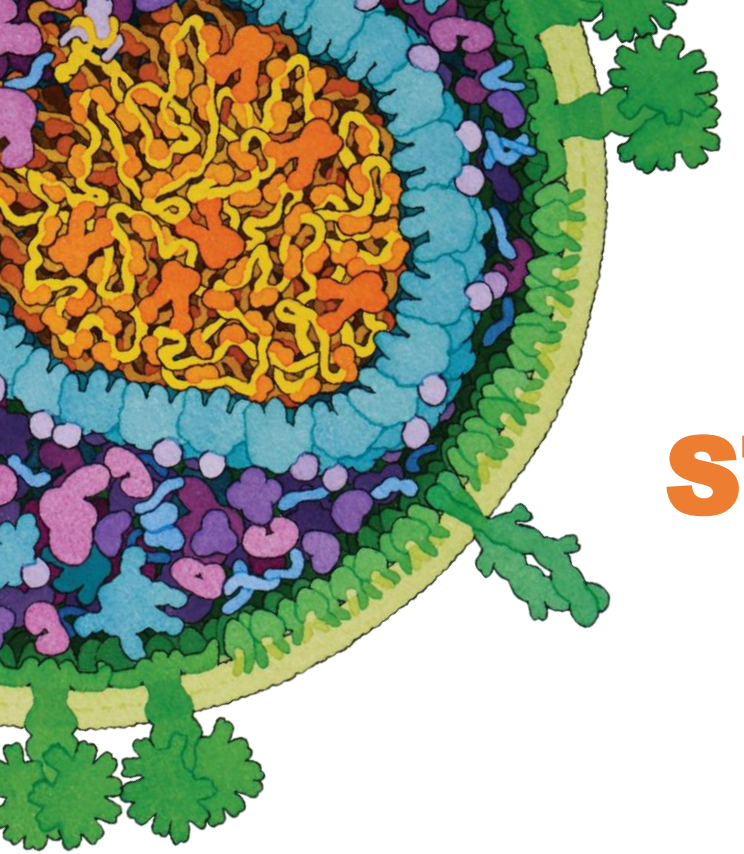
- Transmission from cell associated virus in breast milk (greater exposure to infected cells from milk than from sexual fluid – equivalent of >150L over 6/12)
- Immune activation in breast milk – 10 x greater HIV replication in milk vs. blood; latently infected CD4 cells subject to potential activation

1. Serghides L, R4P Madrid October 2018
http://webcasts.hivr4p.org/console/player/40493mediaType=slideVideo&&crd_fl=0&ssmsrq=1550362754479&ctms=5000&csmsrq=5127,
2. Waitt et al. Lancet HIV 2018

TRANSMISSION: POSSIBLE EXPLANATIONS (II)

- Breast inflammation (mastitis, abscess, engorgement)
- Immune vulnerability of infant gut
- Transmission before maternal viral load undetectable
- Possible poor adherence – adherence difficult in post-partum period!

CARING FOR U: CLINICAL CONUNDRUMS (ABSTRACT 117)
Nneka Nwokolo. CROI 2019



THE PHASE 3 DISCOVER STUDY: DAILY F/TAF OR F/TDF FOR HIV PREEXPOSURE PROPHYLAXIS

Brad Hare

Kaiser Permanente San Francisco Medical Center
San Francisco, CA, USA

Disclosure: Nothing to Disclose

Background

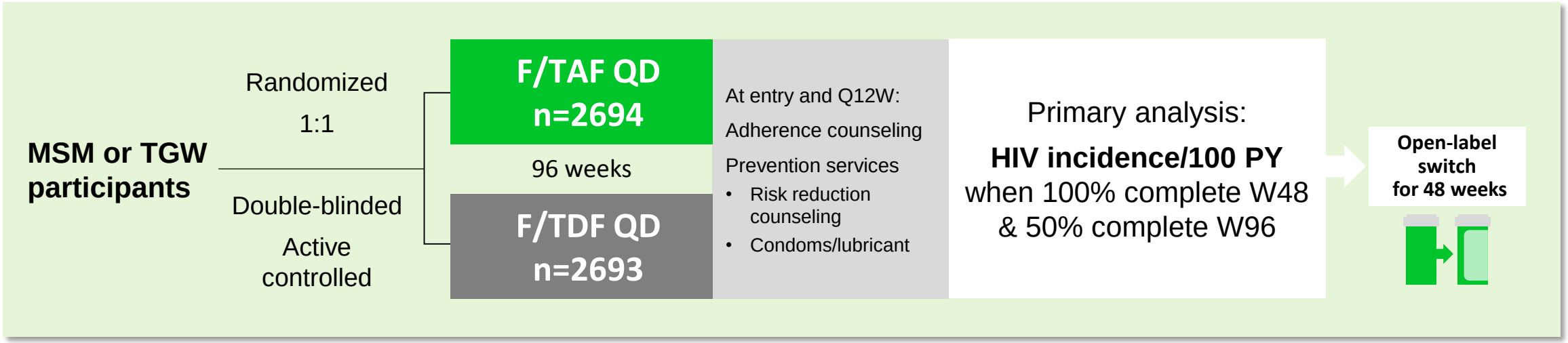
- F/TDF is the only approved drug for HIV pre-exposure prophylaxis (PrEP)

- The Phase 3 DISCOVER study evaluated the efficacy and safety of F/TAF for PrEP among cis-MSM and TGW at high risk of HIV infection

F (or FTC)/TDF, emtricitabine/tenofovir (TFV) disoproxil fumarate; F (or FTC)/TAF, emtricitabine/tenofovir alafenamide; MSM, men who have sex with men; PBMC, peripheral blood mononuclear cells; TFV-DP, TFV-diphosphate; TGW, transgender women.

1. Sullivan IAC 2018. 2. Grulich Lancet HIV 2018. 3. Ruane JAIDS 2013. 4. Custodio EACS 2017. 5. Sax Lancet 2015. 6. Gupta AIDS 2019.

DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP



Eligibility required high sexual risk of HIV

- 2+ episodes condomless anal sex in past 12W **or** rectal gonorrhea/ chlamydia, syphilis in past 24W
- HIV & HBV negative, eGFR ≥60 mL/min
- Prior use of PrEP allowed

Study conducted in NA, EU in cities/sites with high HIV incidence

- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%

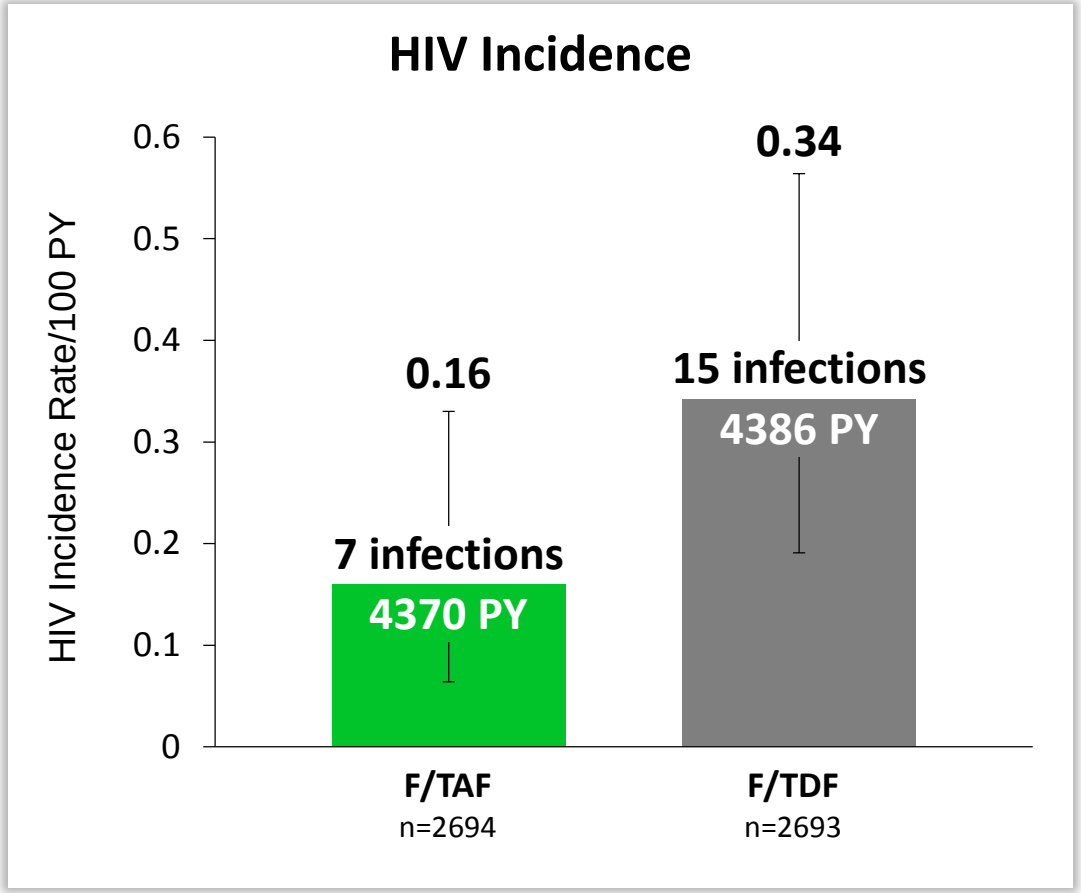
Primary efficacy endpoint: HIV incidence

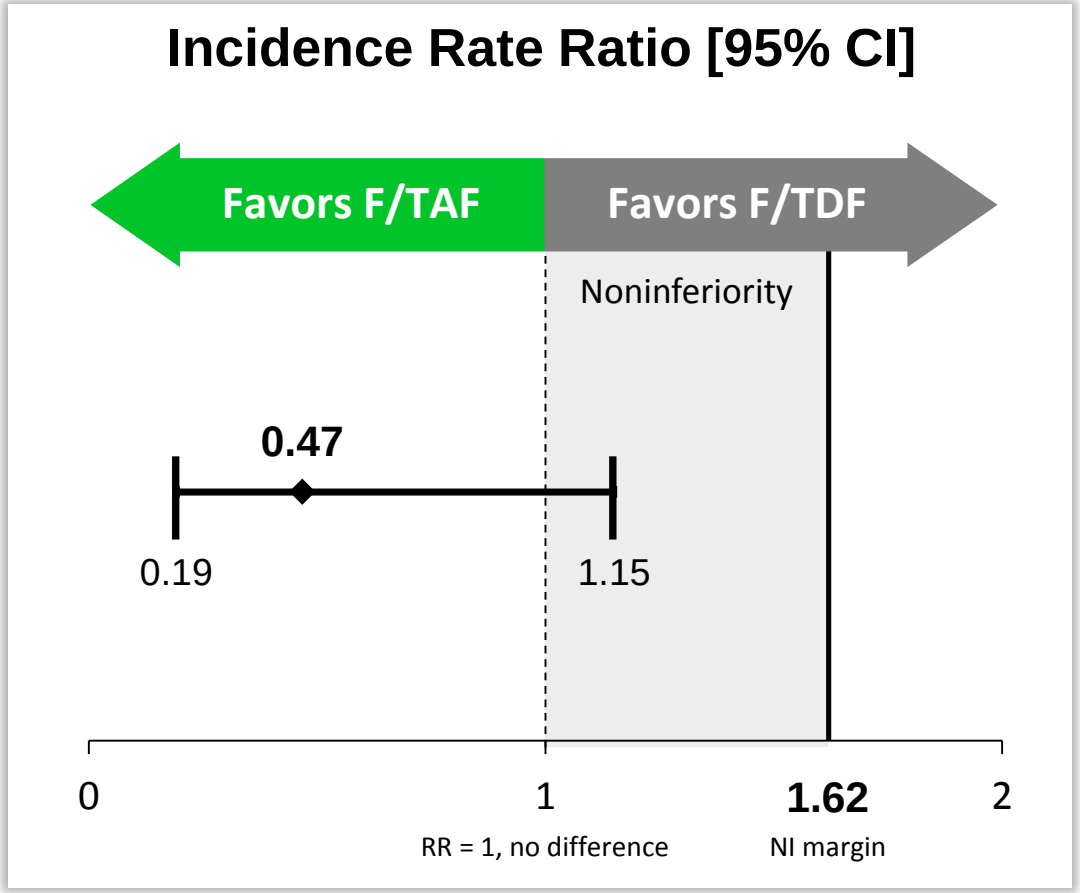
- Evaluated by rate ratio with noninferiority (NI) margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg. eGFR, estimated glomerular filtration rate.

DISCOVER Primary Endpoint Analysis: HIV Incidence

22 HIV infections in 8756 PY of follow-up

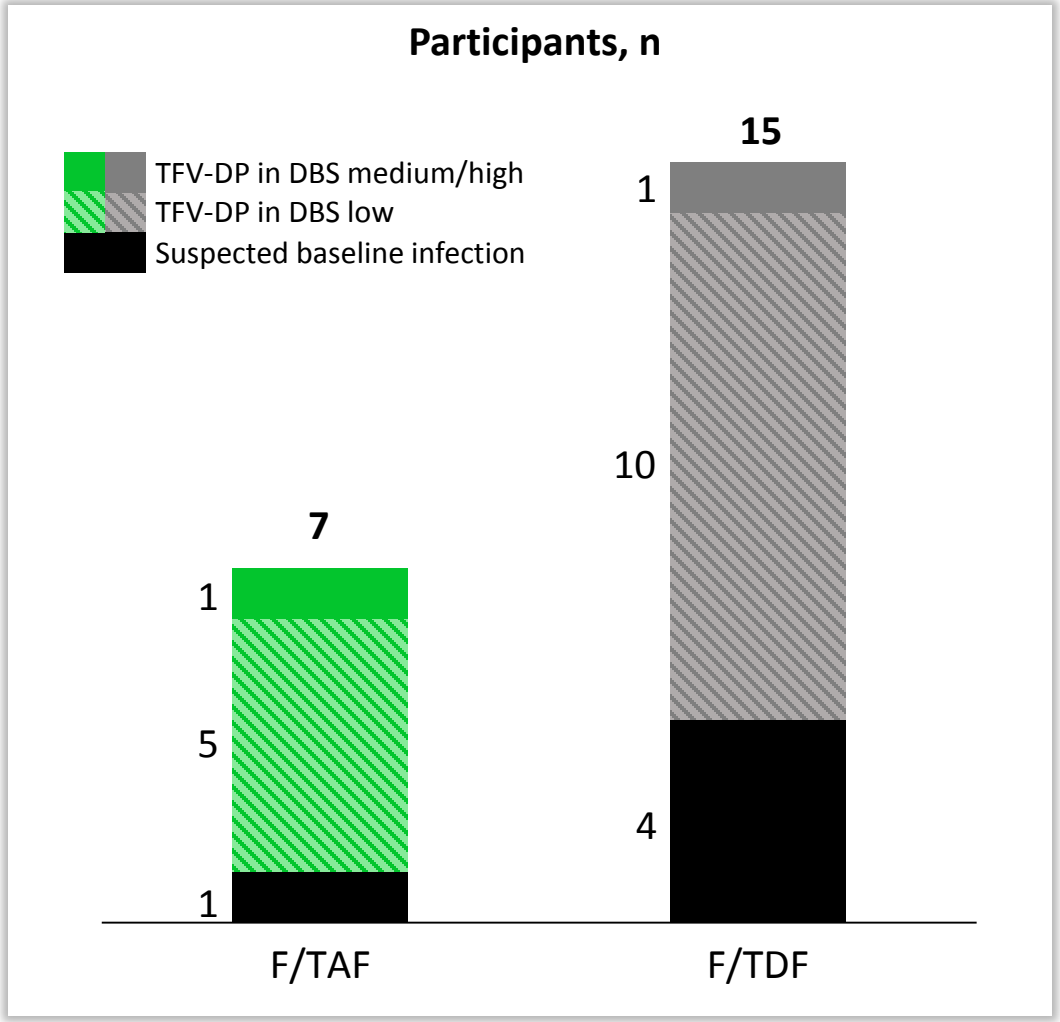




F/TAF is noninferior to F/TDF for HIV prevention

CI, confidence interval; RR, rate ratio.

DISCOVER Adherence and Resistance Analyses of HIV Infections

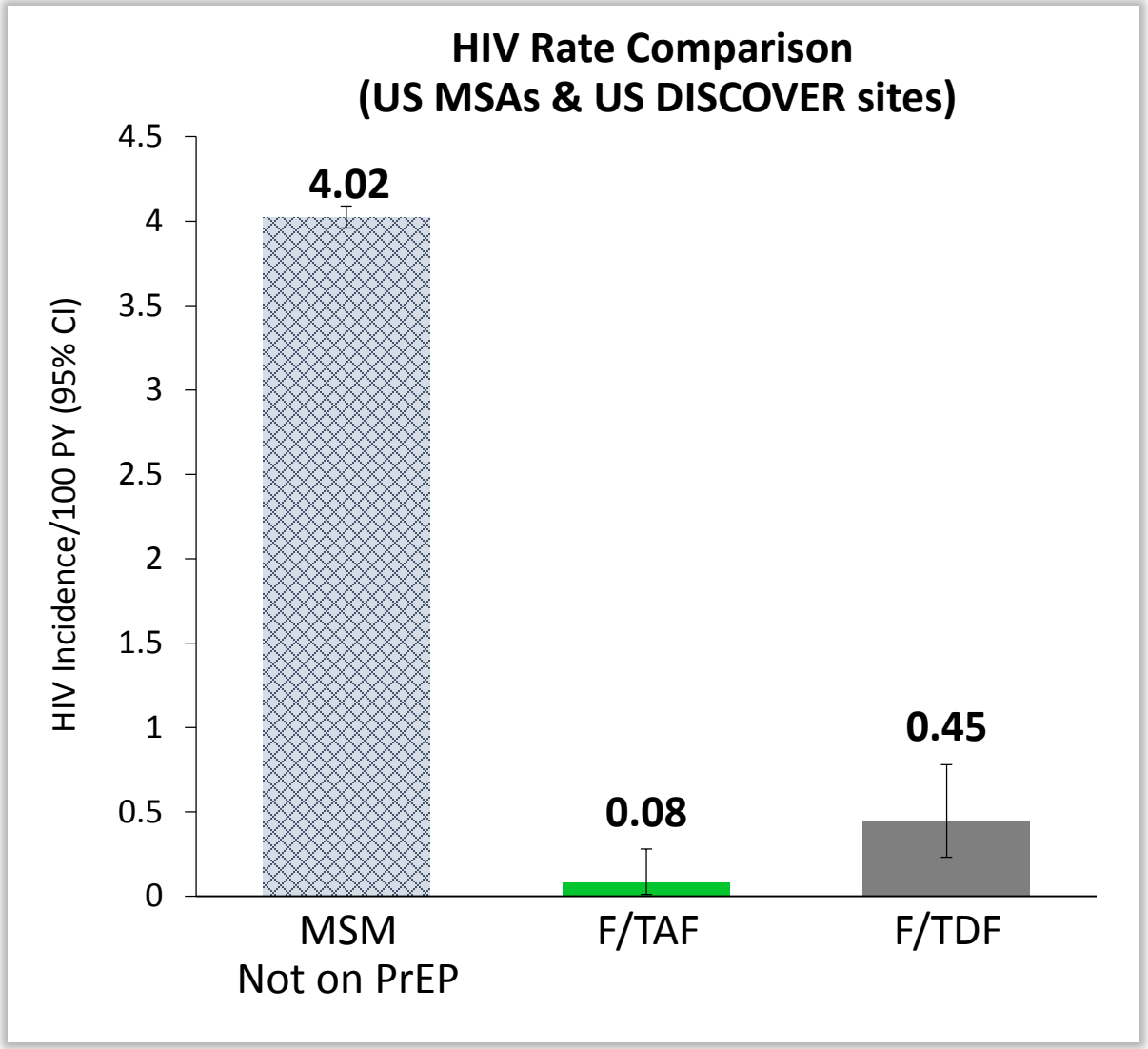


- 7 F/TAF infections: 1 suspected baseline infection, 5 low levels of TFV-DP in DBS,1 medium level
- 15 F/TDF infections: 4 suspected baseline infections, 10 low levels of TFV-DP in DBS, 1 high level
- In a sensitivity analysis that excluded suspected baseline infections, noninferiority was maintained (0.55 [0.20, 1.48])

n	F/TAF n=7	F/TDF n=15
Resistance genotyped*	6	13
Resistance to study drugs		
FTC	0	4†
TFV	0	0

*3 samples could not be amplified; †All 4 participants with resistance were suspected baseline infections.

Comparing DISCOVER Results to HIV Infection Rate In MSM at HIV Risk but Not on PrEP



- In the absence of placebo control, we sought to contextualize the HIV incidence rates in DISCOVER to the rate in MSM not on PrEP
- Using CDC-reported HIV surveillance data, calculated background infection rate for MSM at HIV infection risk* in US metropolitan statistical areas (MSAs) that overlapped with DISCOVER sites[1]
- HIV infection rate for MSM not on PrEP in 2016:
  - 4.02/100 PY 95%CI [3.96, 4.09]
- HIV incidence rates in US DISCOVER sites:
  - F/TAF = 0.08/100 95%CI [0.01, 0.28]
  - F/TDF = 0.45/100 95%CI [0.23, 0.78]

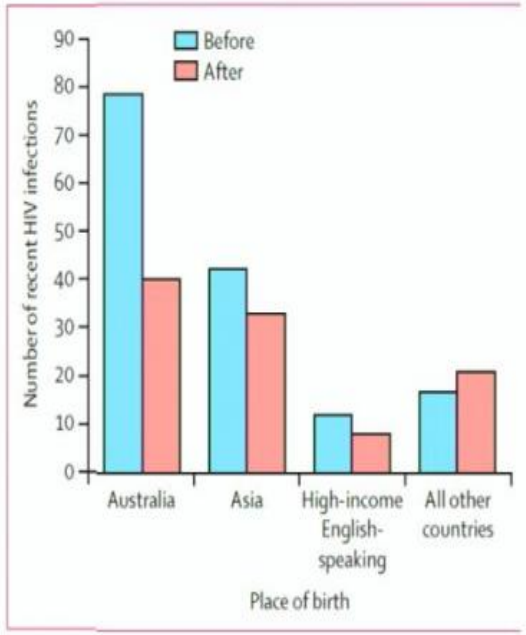
*CDC-defined persons with an indication for PrEP use (Smith Ann Epidemiol 2018). 1. Mera JIAS 2019, under review.

Conclusions

- F/TAF was noninferior to F/TDF in preventing HIV infection in high-risk cis-MSM and TGW
  - F/TAF HIV incidence was 0.16/100 PY, and F/TDF HIV incidence was 0.34/100 PY
  - The majority of HIV infections occurred prior to study entry or in participants with low or undetectable drug levels
- F/TAF is an effective and safer option for PrEP in cis-MSM and TGW at risk for HIV infection

Decrease in HIV Infection with Introduction of PreP

Decline in recent HIV infections in the 12 months after PrEP implementation, NSW (2016-2018)



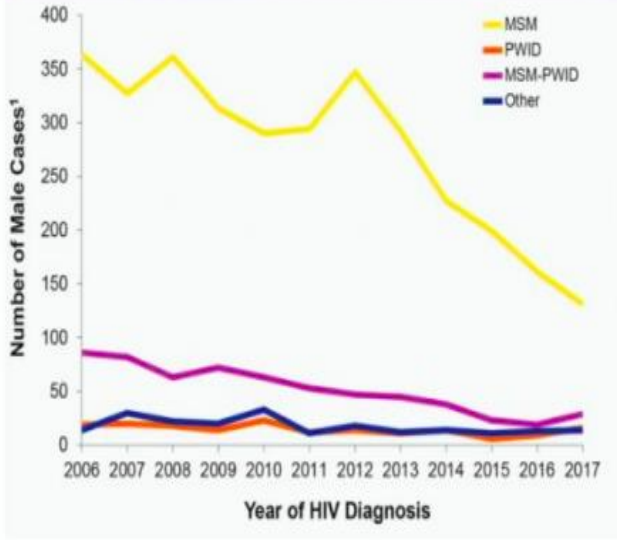
- 50% decline in new HIV infections (acquired in last 12 months) in Australian-born MSM within 12 months of meeting PrEP implementation targets
- 2018 saw the lowest ever number of HIV diagnoses reported in NSW

21

A Grulich et al, Lancet HIV 2018, 5, e629-e637

Declining HIV diagnoses in the US (3): San Francisco

Figure 2.4 Number of men newly diagnosed with HIV by transmission category, 2006-2017, San Francisco



Overall in SF
- 94% diagnosed
- 81% retained (≥1 lab tests)
- 92% suppressed

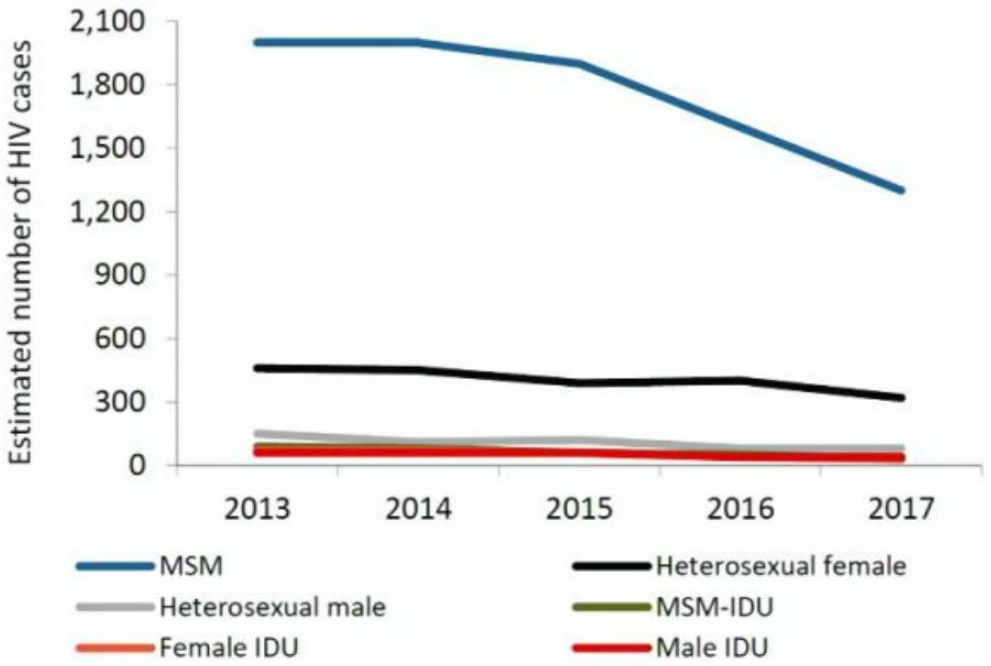
35

MORE THAN U: MAXIMIZING POPULATION-LEVEL EFFECTS OF U=U (ABSTRACT 119)
Andrew E Grulich. CROI 2019

Effects of PrEP on Drug Resistance and Acute HIV Infection in New York City Surveillance Population

Declining HIV diagnoses in the US (1): New York City

FIGURE 10.2: Trends in estimated incident HIV infections[1] by sex at birth and transmission risk, NYC 2013-2017[2]



Overall in NYC
- 93% diagnosed
- 86% treated
- 93% suppressed

New York City Annual Surveillance Report 2017

IMPACT OF PREP ON DRUG RESISTANCE AND ACUTE HIV INFECTION, NEW YORK CITY, 2015-2017 (ABSTRACT 107)
Kavita Misra. CROI 2019

PrEP Surveillance Study: Background

- PrEP use has increased for both sexes in NYC, with largest increase in men[1]
  - Self-reported use among MSM increased from 2% in 2012 to 28% in 2016[2]
  - Self-reported use among sex and needle-sharing partners of HIV-infected individuals increased from 11% in 2016 to 21% in 2018[3]
- Prescribing PrEP to individuals with undetected HIV infection may increase risk of developing drug resistance[4]
- Study used surveillance data to identify drug resistance to PrEP medications in recently HIV-diagnosed individuals (ie, < 12 months) with history of PrEP use prediagnosis[5]

1. Salcuni. IDWeek 2017. Abstr 898. 2. Myers. Am J Public Health. 2018;108(Suppl 4):S251.
3. Misra. JAIDS. 2017;76:132. 4. Parikh. Curr Opin HIV AIDS. 2016;11:49. 5. Misra. CROI 2019. Abstr 107.

PrEP Surveillance Study: Study Design

- Objectives
  - Determine rate of resistance to PrEP ARVs in persons with prediagnosis PrEP use
  - Compare PrEP users vs never-users regarding resistance to PrEP drugs and AHI
  - Determine frequency and timing of negative NAAT prior to PrEP initiation in PrEP users
- Data sources
  - PrEP use: HIV partner services, medical provider report forms, NYC surveillance field investigation
  - Drug resistance, HIV NAAT, and AHI: NYC surveillance registry and laboratory database

Misra. CROI 2019. Abstr 107.

PrEP Surveillance Study: Patient Characteristics

- Of **3685** patients diagnosed with HIV in past 12 mos and referred for partner services in NYC, **n = 91 (2%) used PrEP prior to diagnosis**
  - Median duration of PrEP prior to HIV diagnosis: 106 days (IQR: 214)
  - Median duration from PrEP initiation to HIV diagnosis: 250 days (IQR: 395)
- Higher rates of PrEP use among individuals who were younger (< 30 yrs), cis-men, white, and MSM

Characteristic, %	PrEP Users (n = 91)	Never-Users (n = 3594)
Aged < 30/≥ 30 yrs	58/42	37/63
Gender		
Cis-women	2	21
Cis-men	92	76
Transgender: MTF	5	3
Race/ethnicity		
▪ Black	23	46
▪ Hispanic	27	32
▪ White	41	14
▪ Other	9	7
Transmission risk		
▪ **Heterosexual**	**3**	**28**
▪ **IDU**	**2**	**3**
▪ **MSM**	**89**	**66**
▪ **Transgender sex**	**6**	**3**

Misra. CROI 2019. Abstr 107.

PrEP Surveillance Study: Resistance Mutations, Acute HIV Infection

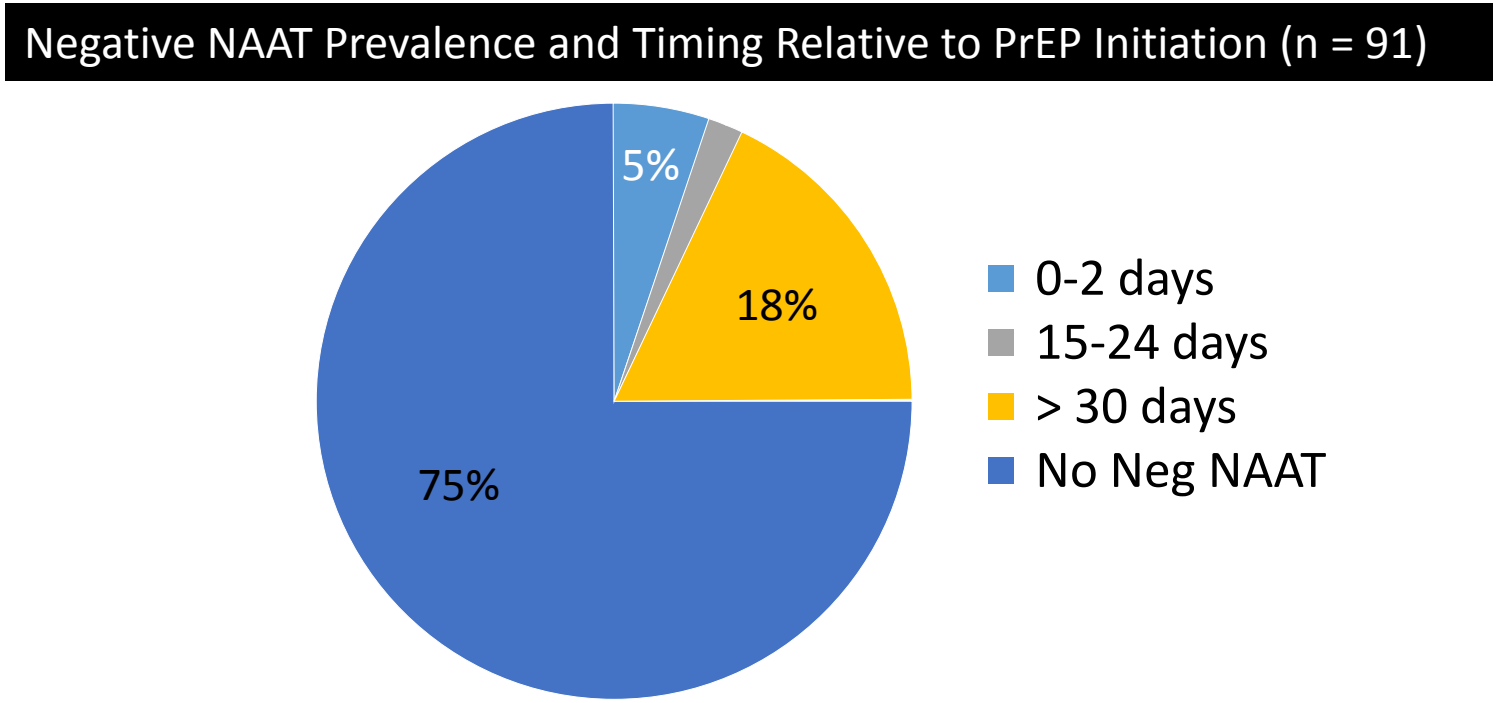
- Identification of FTC but not TDF resistance mutations more common among PrEP users vs never-users
  - K65R identified in 4 individuals, all never-users
- Diagnosis with acute HIV infection more common among PrEP users vs never-users

Resistance Mutation Analysis, %	PrEP Users (n = 91)	Never-Users (n = 3594)	All Patients (N = 3685)
Genotype data available	75	63	63
Resistance mutations			
M184I/V/IV/MV	**29**	**2**	**3**
K65R	**0**	**< 1**	**< 1**
Acute HIV infection	33	9	10

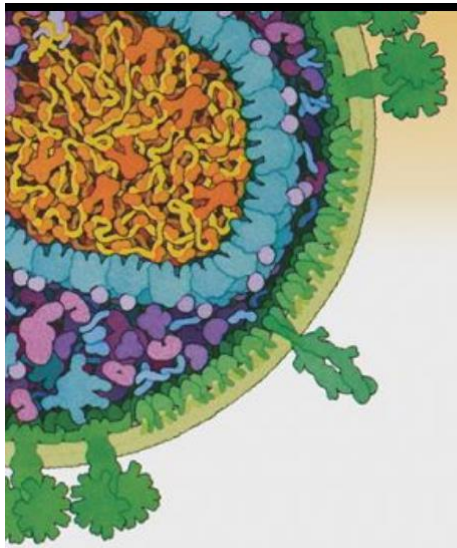
Misra. CROI 2019. Abstr 107

PrEP Surveillance Study: Negative NAAT

- NY state requires NAAT in persons symptomatic for AHI or with negative antibody test who report potential exposures within past 3 mos[1]
- Negative NAAT results within window of 0-2 days before PrEP initiation occurred in 5 out of 91 PrEP users (5%)[2]



1. New York State Department of Health AIDS Institute. Updated December 2018. 2. Misra. CROI 2019. Abstr 107. Reproduced with permission.



SUSTAINED HIV-1 REMISSION FOLLOWING HOMOZYGOUS CCR5 DELTA32 ALLOGENIC HSCT

Ravindra K. Gupta
University College London
London, United Kingdom

Disclosure: Self: Research grant/grant pending from Wellcome Trust; consulting or advisor fees from ViiV Healthcare, Inc.; speaker's bureau for Gilead Sciences

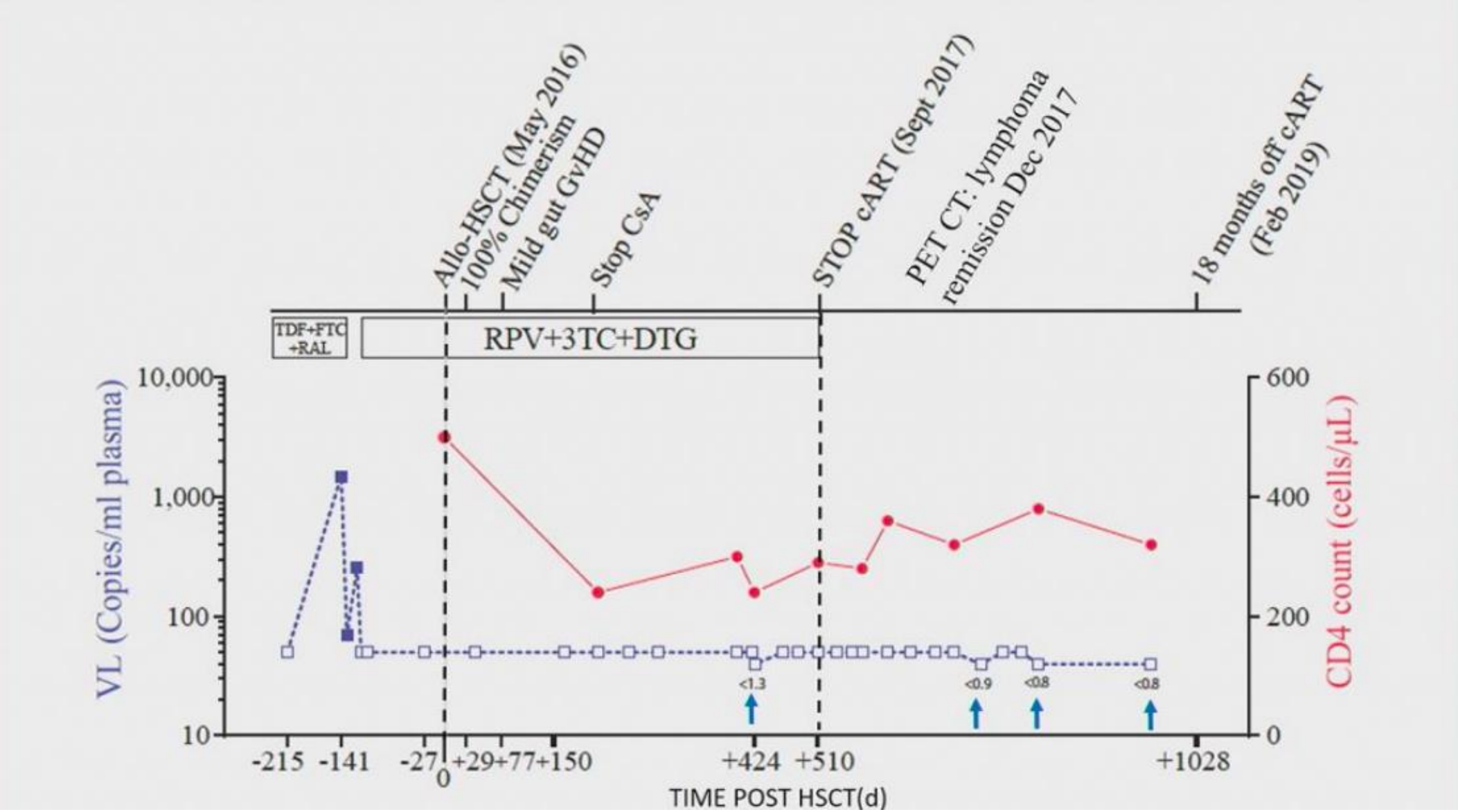
Case History

- **HIV-1 Diagnosis 2003**
- **2013:** Stage IVb Hodgkin lymphoma

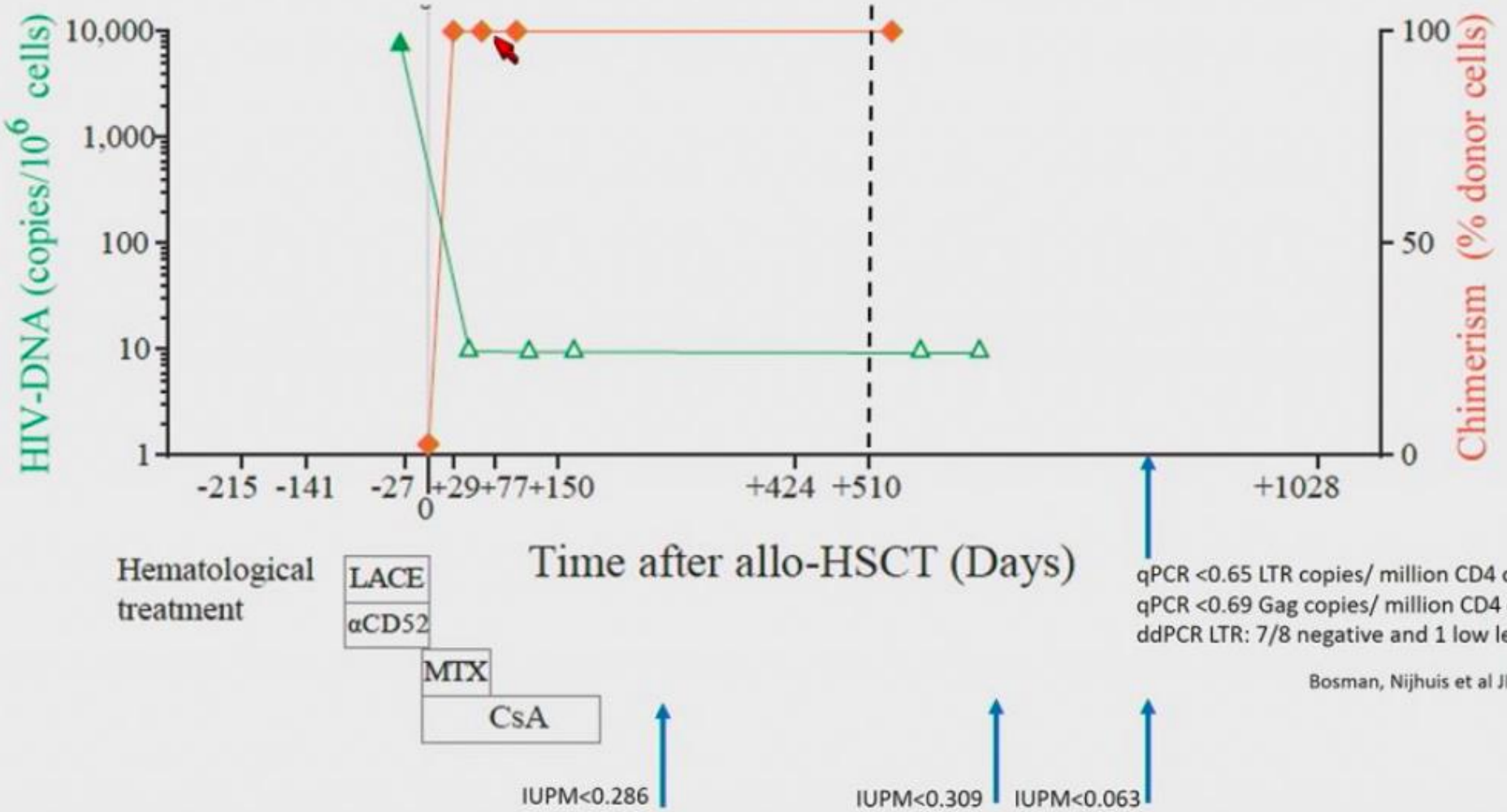
  Atripla initiated. Viral suppression achieved

  Switch to TDF/FTC/Raltegravir (ABVD chemo)

- Failed multiple lines of chemotherapy and mobilisation for auto SCT
- Donor registry search for allo HSCT
  - Unrelated 9/10 HLA high-resolution match.
  - Donor homozoygous CCR5-d32 mutation


Allo-HSCT (May 2016)
100% Chimerism
Mild gut GvHD
Stop CsA
STOP cART (Sept 2017)
PET CT: lymphoma remission Dec 2017
18 months off cART (Feb 2019)
TDF+FTC +RAL
RPV+3TC+DTG
VL (Copies/ml plasma)
10,000
1,000
100
10
CD4 count (cells/µL)
600
400
200
0
<1.3
<0.9
<0.8
<0.8
-215
-141
-27
0
+29+77+150
+424
+510
+1028
TIME POST HSCT(d)

Cellular HIV-1 DNA Reservoir Measurements



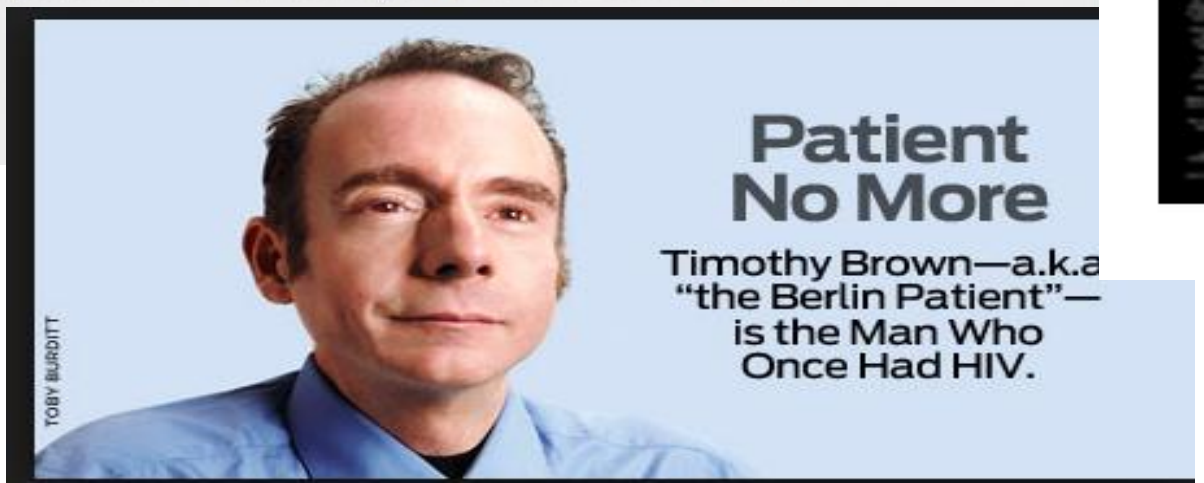
'The London Patient'	*Timothy Brown*
• Homozygous for wild type CCR5	• Heterozygous for ∆32
• Infection with R5 using virus	• Infection with R5 using virus
• Hodgkin Lymphoma	• Acute Myelogenous Leukemia
• Single HSCT	• Two HSCT
• No irradiation	• Total Body Irradiation
• Reduced intensity conditioning	• Full intensity conditioning
• T cell depletion with aCD52	• T cell depletion with ATG
• Mild GVH	• Mild GVH
• 100% T cell donor chimerism	• 100% T cell donor chimerism

Summary

- HSCT with Δ32 homozygous donor
- 18 months remission with no viral rebound after HSCT
- Adaptive Immune responses declining or absent post transplant

This case reaffirms CCR5 as a candidate for remission approaches

Please see poster 394 Wednesday on a further case of HSCT



nature Accelerated Article Preview

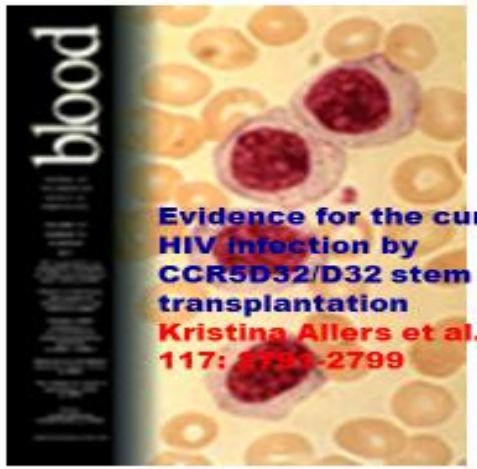
LETTER
doi:10.1038/s41586-019-1027-4

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

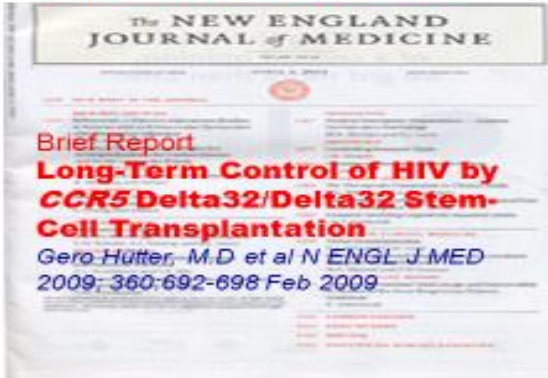
Ravindra K Gupta, Sultan Abdul-jawad, Laura E McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M.J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew Innes, Luke Muir, Laura Waters, John Frater, Andrew ML Lever, SG Edwards, Ian H Gabriel & Eduardo Olavarria

The New York Times

New Hope of a Cure for H.I.V.

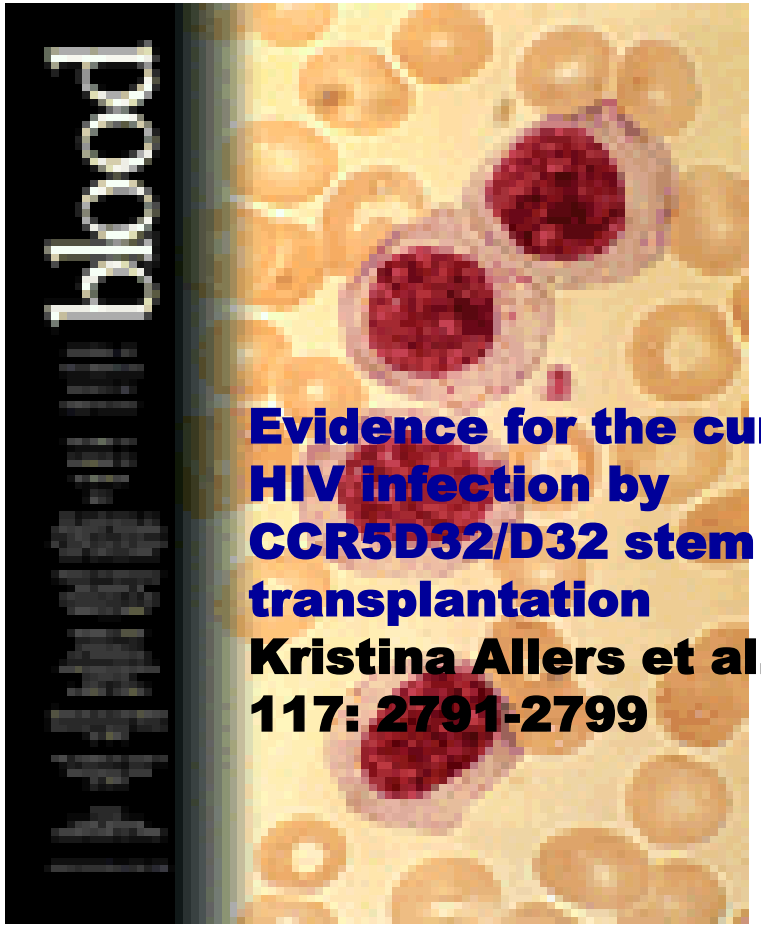


from Stem Cell Transplant



The New York Times

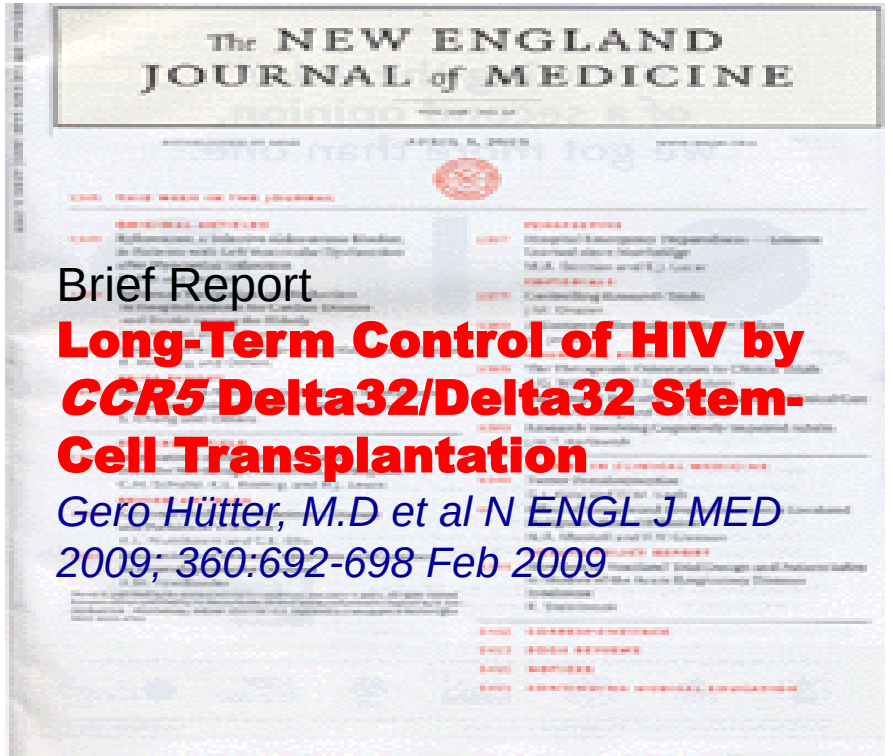
New Hope of a Cure for H.I.V.



Evidence for the cure of HIV infection by CCR5D32/D32 stem cell transplantation

Kristina Allers et al. 2011 117: 2791-2799

The Berlin Patient Becomes First Human Cured of AIDS from Stem Cell Transplant



Brief Report

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D et al N ENGL J MED 2009; 360:692-698 Feb 2009