The 'London Patient' goes into HIV remission

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

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

Is The End In Sight: Prevention vs Cure
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
Bethesda, MD, USA
Disclosure: None

Editorial

Ending the HIV Epidemic
A Plan for the United States

AS Fauci, RR Redfield, G Sigounas, MD Weahkee, and BP Giroir
No More Excuses. We Have the Tools to End the HIV/AIDS Pandemic.

Anthony S. Fauci
"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.
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
### The situation before 2008

#### Risk of transmission in partnerships

<table>
<thead>
<tr>
<th>HIV-1 RNA copies/ml</th>
<th>No. of studies</th>
<th>No. of events</th>
<th>No. of person years</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;400</td>
<td>2</td>
<td>0</td>
<td>291</td>
<td>0 (0–1.27)</td>
</tr>
<tr>
<td>≥400</td>
<td>1</td>
<td>0</td>
<td>52</td>
<td>0 (0–5.79)</td>
</tr>
<tr>
<td>All studies</td>
<td>5</td>
<td>5</td>
<td>1098</td>
<td>0.46 (0.19–1.09)</td>
</tr>
</tbody>
</table>

### Attia, AIDS, 2009

- Rate per 100 person-years
- Infektionstransmission / Spitalhygiene
Limited evidence from partner studies

Evidence < 2008

Transmission risk / 100 py

2008 2010 2012 2014 2016 2018

upper 95% CI
transmission risk
Zero events, increasing number of observations

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

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event/person years</th>
<th>Rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melo 2008</td>
<td>0 / 90</td>
<td>0.00</td>
<td>0.00</td>
<td>4.02</td>
</tr>
<tr>
<td>Del Romero 2010</td>
<td>0 / 492</td>
<td>0.00</td>
<td>0.00</td>
<td>0.75</td>
</tr>
<tr>
<td>Reynolds 2011</td>
<td>0 / 53</td>
<td>0.00</td>
<td>0.00</td>
<td>6.72</td>
</tr>
<tr>
<td>Donnell 2010</td>
<td>0 / 273</td>
<td>0.00</td>
<td>0.00</td>
<td>1.34</td>
</tr>
<tr>
<td>Apondi 2011</td>
<td>0 / 185</td>
<td>0.00</td>
<td>0.00</td>
<td>1.97</td>
</tr>
<tr>
<td>Cohen 2011</td>
<td>0 / 1145</td>
<td>0.00</td>
<td>0.00</td>
<td>0.33</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.14</td>
</tr>
<tr>
<td>add PARTNER &amp; Opposite Attract</td>
<td>0 / 4063</td>
<td>0.00</td>
<td>0.00</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Loutfy 2013, PLOS One; Rodger Lancet 2019 in press; Bavinton Lancet HIV, 2018
Time supports the validity of the Swiss statement

Continued absence of evidence increases certainty

```
<table>
<thead>
<tr>
<th>Year</th>
<th>Transmission Risk / 100 py</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>1.3</td>
</tr>
<tr>
<td>2010</td>
<td>0.7</td>
</tr>
<tr>
<td>2012</td>
<td>0.26</td>
</tr>
<tr>
<td>2014</td>
<td>0.84</td>
</tr>
<tr>
<td>2016</td>
<td>0.46</td>
</tr>
<tr>
<td>2018</td>
<td>0.23</td>
</tr>
<tr>
<td>2020</td>
<td>0.44</td>
</tr>
</tbody>
</table>
```

«Swiss statement» 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
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?
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 cpm²
- 18% of infants lost to follow-up, transferred or died
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

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!
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
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**

<table>
<thead>
<tr>
<th></th>
<th>F/TAF (n=2694)</th>
<th>F/TDF (n=2693)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Incidence</td>
<td>0.16 infections</td>
<td>0.34 infections</td>
</tr>
<tr>
<td></td>
<td>4370 PY</td>
<td>4386 PY</td>
</tr>
</tbody>
</table>

HIV Incidence Rate/100 PY

- **F/TAF** 0.16
- **F/TDF** 0.34

Incidence Rate Ratio [95% CI]

- **Favors F/TAF** 0.19
- **Favors F/TDF** 1.15

**Noninferiority**

RR = 1, no difference

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])

### Participants, n

<table>
<thead>
<tr>
<th>TFV-DP in DBS medium/high</th>
<th>TFV-DP in DBS low</th>
<th>Suspected baseline infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>F/TAF n=7</th>
<th>F/TDF n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance genotyped*</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Resistance to study drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTC</td>
<td>0</td>
<td>4†</td>
</tr>
<tr>
<td>TFV</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*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

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]

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

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

Overall in SF
- 94% diagnosed
- 81% retained (≥1 lab tests)
- 92% suppressed
Effects of PrEP on Drug Resistance and Acute HIV Infection in New York City Surveillance Population

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

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

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

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]

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
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

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

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

<table>
<thead>
<tr>
<th>Resistance Mutation Analysis, %</th>
<th>PrEP Users (n = 91)</th>
<th>Never-Users (n = 3594)</th>
<th>All Patients (N = 3685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype data available</td>
<td>75</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Resistance mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M184I/V/IV/MV</td>
<td>29</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>K65R</td>
<td>0</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Acute HIV infection</td>
<td>33</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

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\%)\(^2\)

![Pie chart showing negative NAAT prevalence and timing relative to PrEP initiation (n = 91).](chart.png)

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 homozygous CCR5-d32 mutation
Cellular HIV-1 DNA Reservoir Measurements

Hematological treatment

- LACE
- αCD52
- MTX
- CsA

Time after allo-HSCT (Days)

- qPCR <0.65 LTR copies/ million CD4 cells
- qPCR <0.69 Gag copies/ million CD4 cells
- ddPCR LTR: 7/8 negative and 1 low level pos

Bosman, Nijhuis et al JIAS 2018
‘The London Patient’

- Homozygous for wild type CCR5
- Infection with R5 using virus
- Hodgkin Lymphoma
- Single HSCT
- No irradiation
- Reduced intensity conditioning
- T cell depletion with aCD52
- Mild GVH
- 100% T cell donor chimerism

Timothy Brown

- Heterozygous for $\Delta 32$
- Infection with R5 using virus
- Acute Myelogenous Leukemia
- Two HSCT
- Total Body Irradiation
- Full intensity conditioning
- T cell depletion with ATG
- Mild GVH
- 100% T cell donor chimerism
Patient No More

Timothy Brown—aka “the Berlin Patient”—is the man who once had HIV.

Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation
Kristina Allers et al. 2011
117: 2792-2799

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 Hutter, MD et al N ENGL J MED 2009; 360: 692-698 Feb 2009

Summary

• HSCT with Δ 32 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

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

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

Evidence for the cure of HIV infection by CCR5 Delta32/Delta32 stem cell transplantation
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