





# An HIV cure : why, how and for whom ?



Nicolas Dauby CHU Saint-Pierre BREACH Spring Meeting 23/05/2024



Respect Innovation Engagement Solidarity Quality

# Disclaimer

I am not involved in HIV cure research

I will only cover studies in humans

I have only 20 minutes

# Why do we need a HIV cure ?



## Keith Haring, "Unfinished Painting," 1989

# Dramatic impact of ART on the lives of PLWH





## HIV is a chronic condition

### Lifelong treatment

- Daily pill
- Bi-monthly injections

Cost of treatment

Side effect of treatment

Stigma

### **Co-morbidity**

Immune activation

### Cancers (subgroup of patients)

Poorer/attenuate response to vaccines

### To cure : part of our mission as physician

RAPHAËL GAILLARD

L'homme augmenté "Soigner, c'est chercher à libérer le patient des chaînes qui l'entravent, pour restaurer le silence des organes et laisser libre cours à l'être que la maladie prédendait rabaisser au rang d'une machine, en panne ou rongée de l'intérieur"

# Why a cure ? Lessons from patients cured from Hepatitis C

Richmond et al. Hepatology, Medicine and Policy (2018) 3:8 https://doi.org/10.1186/s41124-018-0036-5 Hepatology, Medicine and Policy

#### RESEARCH

CrossMark

**Open Access** 

Achieving a hepatitis C cure: a qualitative exploration of the experiences and meanings of achieving a hepatitis C cure using the direct acting antivirals in Australia

Jacqueline A. Richmond<sup>1,2,3\*</sup>, Jeanne Ellard<sup>4</sup>, Jack Wallace<sup>1,2</sup>, Rachel Thorpe<sup>1</sup>, Peter Higgs<sup>2,5</sup>, Margaret Hellard<sup>2,6,7</sup> and Alexander Thompson<sup>8,9</sup>

### Breaking a connection from the past

It's like the last mark ... is now gone. All the rest is just memories that I don't have to think about (Participant 6, male).

### Feeling normal

I love not being infectious... That for me has probably been the biggest thing – not having to feel guilty every time I had a blood test done that I might infect somebody, going to the dentist is nowhere near as stressful (Participant 17, female).

# Meaning of cure for patients living with HIV in the US Cure meant....

### WHAT DOES A 'CURE FOR HIV' LOOK LIKE?

397 PEOPLE LIVING WITH HIV IN THE U.S. SURVEYED. (RESULTS EXCEED 100% BECAUSE RESPONDENTS WERE ALLOWED TO SELECT MORE THAN ONE ANSWER.)



Other :

"A life free of SECRETS, STIGMA and MEDICATIONS"

*"Freedom to go on vacations without medications"* 

*"Dead virus that cannot reproduce"* 

https://www.positivelyaware.com/articles/what-does-hiv-cure-mean-you

# Perceptions on HIV cure research in Ghana



### Bonney J Viral Eradication 2021

A cure For whom ?

# Patients aging with HIV are increasing in care



DEPUIS 40 ANS, AIDES LUTTE POUR LA SANTÉ ET LES DROITS DES PERSONNES SÉROPOSITIVES. **CONTINUONS ENSEMBLE.** 



### PWHIV 50+ in care



Dominique Van Beckoven, Sciensano BREACH Meeting 2023

# Adolescent girls and young women are disproportionately affected by new HIV infections (UNAIDS)

2300

12 200

2800

9400

4000

Figure 1.5 Change in number of new HIV infections, 2010–2022, and number of new HIV infections, 2022, among adolescents and young people (aged 15-24 years), by sex, selected countries, eastern and southern Africa







Adolescent boys and young men (15–24 years)

### HIV cure-related clinical research participants demographic, 15 March 2024 (142 clinical trials/observational studies)

Total # of participants	6982			
Total from studies reporting sex and gender	6960			
Female	1241 (18.1%)			
Male	5541 (80.8%)			
Transgender women	30 (0.4%)			
Transgender men	3 (0.04%)			
Transgender (not identified)	3 (0.04%)*			
Non-binary or gender non-conforming	11 (0.2%)**			
Missing/not reported	36 (0.5%)			
Total from studies reporting race/ethnicity	4928			
Asian	300 (6.1%)			
Black	904 (18.3%)			
Hispanic	348 (7.1%)***			
White	3046 (61.8%)			
Native American/Native Hawaiian, American	15 (0.3%)			
Indian/Alaskan Native				
Pacific Islander	2 (0.04%)			
Indigenous Australian	1 (0.02%)			
More than one race/ethnicity	166 (3.4%)			
Other/unknown/not reported	311 (6.3%)			



### **Treatment Action Group**



# How to reach a cure ?



*HIV "sterilizing" cure* : complete elimination of all HIV-infected cells from the body

examples : HCV, syphilis, tuberculosis

HIV "functionnal" cure : facilitation of long term control

*Contradiction / oxymoron* : virus is still persistent, infected cells are not eliminated

Other wording : "remission" (≠ cure), "durable suppression"

Session tomorrow : post treatment controllers, block and lock

### The quest for a sterilizing cure : "Shock and kill" Draining the reservoir using latency reversing agents (LRA)



### First step for shock & kill : "shock" with LRA have failed in vivo

The Journal of Infectious Diseases



### A Phase 1/2 Randomized, Placebo-Controlled Trial of Romidespin in Persons With HIV-1 on Suppressive Antiretroviral Therapy

Deborah K. McMahon, <sup>1</sup> Lu Zheng,<sup>2</sup> Joshua C. Cyktor,<sup>1</sup> Evgenia Aga,<sup>2</sup> Bernard J. Macatangay,<sup>1</sup> Catherine Godfrey,<sup>3,®</sup> Michael Para,<sup>4</sup> Ronald T. Mitsuyasu,<sup>5</sup> Joseph Hesselgesser,<sup>6</sup> Joan Dragavon,<sup>7</sup> Curtis Dobrowolski,<sup>8</sup> Jonathan Karn,<sup>8</sup> Edward P. Acosta,<sup>9</sup> Rajesh T. Gandhi,<sup>10</sup> and John W. Mellors,<sup>1</sup> for the ACTG A5315 Team

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Henning Gruell\*, Jesper D Gunst\*, Yehuda Z Cohen\*, Marie H Pahus, Jakob J Malin, Martin Platten, Katrina G Millard, Martin Tolstrup, R Brad Jones, Winnifer D Conce Alberto, Julio C C Lorenzi, Thiago Y Oliveira, Tim Kümmerle, Isabelle Suárez, Cecilia Unson-O'Brien, Lilian Nogueira, Rikke Olesen, Lars Østergaard, Henrik Nielsen, Clara Lehmann, Michel C Nussenzweig, Gerd Fätkenheuer, Florian Klein, Marina Caskey, Ole S Søgaard



Romidepsin, one of the LRA with the most potent activity ex vivo has no impact on the reservoir in vivo

# CRISPR editing using EBT-101 is safe but does not prevent HIV viral rebound



# CRISPR editing using EBT-101 is safe but does not prevent HIV viral rebound





AE, adverse event; ART, antiretroviral therapy; HIV-1, immunodeficiency virus type 1

### CRISPR editing using EBT-101 is safe but does not prevent HIV viral rebound



#### Cure for HIV could be months away as first three patients are injected with new CRISPR therapy that seeks and destroys lingering pieces of virus

- HIV went from certain death sentence to chronic disease people can live with
- CRISPR uses enzyme to cut large sections of HIV DNA, eliminating it from cells
- READ MORE: Researchers make breakthrough in fight against HIV using CRISPR



AE, adverse event; ART, antiretroviral therapy; HIV-1, immunodeficiency virus type 1

# CRISPR editing using EBT-101 is safe but does not prevent HIV viral rebound



new CRISPR therapy that seeks and destroys lingering pieces of virus

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AE, adverse event; ART, antiretroviral therapy; HIV-1, immunodeficiency virus type 1



#### News

Abou

#### The search for a cure

# CRISPR gene therapy EBT-101 does not prevent HIV viral rebound

Liz Highleyman 14 May 2024 Estimated reading time 6 minutes



# "Natural" resistance toward HIV-1 in individuals with CCR5 co-receptor polymorphism ( $\Delta 32/\Delta 32$ )



# "Natural" resistance toward HIV-1 in individuals with CCR5 co-receptor polymorphism ( $\Delta 32/\Delta 32$ )



### Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene

Michel Samson\*, Frédérick Libert\*, Benjamin J. Doranz†, Joseph Rucker†, Corinne Liesnard‡, Claire-Michèle Farber§, Sentob Saragosti||, Claudine Lapouméroulie¶, Jacqueline Cognaux#, Christine Forceille#, Gaetan Muyldermans#, Chris Verhofstede#, Guy Burtonboy#, Michel Georges☆, Tsuneo Imai\*\*, Shalini Rana††, Yanji Yi††, Robert J. Smyth††, Ronald G. Collman††, Robert W. Doms†, Gilbert Vassart\*‡‡ & Marc Parmentier\*

\* IRIBHN and Services de ‡‡ Génétique Médicale, ‡ Virologie and § Immunodéficiences, Université Libre de Bruxelles, Campus Erasme, 808 route de Lennik, B-1070 Bruxelles, Belgium



TABLE 1	Genotype and allele frequencies of CCR-5 and $\Delta ccr\text{-}5$ in cohorts of Caucasians							
	Seronegative			Seropositive				
	Number	Frequency	s.e.	Number	Frequency	s.e.	χ <sup>2</sup>	
Genotypes CCR-5/CCR-5 CCR-5/Δccr-5 Δccr-5/Δccr-5 Total	582 114 8 704	0.827 0.162 0.011 1.000	0.014 0.014 0.004	645 78 0 723	0.892 0.108 0.000 1.000	0.012 0.012 <0.001	1 degree of freedom 12.7 P < 0.0005	
Alleles CCR-5 ∆ccr-5 Total	1278 130 1408	0.908 0.092 1.000	0.008 0.008	1368 78 1446	0.946 0.054 1.000	0.006 0.006	1 degree of freedom 15.1 P < 0.0005	

Cases of HIV cures following hematopoietic stem cell CCR5  $\Delta$ 32/ $\Delta$ 32 transplant : a proof of concept for gene therapy







« Berlin patient »
Timothy Brown
Acute Leukemia
Two HSC
transplants
CCR5 Δ32/Δ32
(2007-2008)

« London patient » Adam Castallejo «New York patient » Acute Leukemia CCR5  $\Delta$ 32/ $\Delta$ 32 cord blood transplant in 2017





Paul Edmonds, 68 years Acute Leukemia CCR5 Δ32/Δ32 transplant in 2019

### Resurgence of HIV infection after CCR5 wild type stem cell transplant Reduction of the reservoir delays HIV rebound but is not sufficient for cure

#### **Annals of Internal Medicine**

### Original Research

### Antiretroviral-Free HIV-1 Remission and Viral Rebound After Allogeneic Stem Cell Transplantation

#### **Report of 2 Cases**

Timothy J. Henrich, MD; Emily Hanhauser, BS; Francisco M. Marty, MD; Michael N. Sirignano, BS; Sheila Keating, PhD; Tzong-Hae Lee, MD, PhD; Yvonne P. Robles, BA; Benjamin T. Davis, MD; Jonathan Z. Li, MD; Andrea Heisey, BS; Alison L. Hill, PhD; Michael P. Busch, MD, PhD; Philippe Armand, MD, PhD; Robert J. Soiffer, MD; Marcus Altfeld, MD, PhD; and Daniel R. Kuritzkes, MD

#### RESEARCH ARTICLE

Extensive virologic and immunologic characterization in an HIV-infected individual following allogeneic stem cell transplant and analytic cessation of antiretroviral therapy: A case study

Nathan W. Cummins<sup>1</sup><sup>e</sup>, Stacey Rizza<sup>1</sup><sup>e</sup>, Mark R. Litzow<sup>2</sup>, Stephane Hua<sup>3</sup>, Guinevere Q. Lee<sup>3</sup>, Kevin Einkauf<sup>3</sup>, Tae-Wook Chun<sup>4</sup>, Frank Rhame<sup>5,6</sup>, Jason V. Baker<sup>7</sup>, Michael P. Busch<sup>8,9</sup>, Nicolas Chomont<sup>10,11</sup>, Patrick G. Dean<sup>12</sup>, Rémi Fromentin<sup>10,11</sup>, Ashley T. Haase<sup>6</sup>, Dylan Hampton<sup>8</sup>, Sheila M. Keating<sup>8,9</sup>, Steven M. Lada<sup>13,14</sup>, Tzong-Hae Lee<sup>8</sup>, Sekar Natesampillai<sup>1</sup>, Douglas D. Richman<sup>13,14</sup>, Timothy W. Schacker<sup>15</sup>, Stephen Wietgrefe<sup>6</sup>, Xu G. Yu<sup>3,16</sup>, Joseph D. Yao<sup>17</sup>, John Zeuli<sup>1</sup>, Mathias Lichterfeld<sup>3,16</sup>, Andrew D. Badley<sup>1</sup>\*

Two patients who underwent HSCT from CCR5 wild type donors

No detection of HIV from blood and rectal mucosa

Rebound after ART interruption (2,8 and 7,4 months)

One patients who underwent HSCT from CCR5 wild type donors

No detection of HIV from blood and rectal mucosa

Rebound after ART interruption (7,9 months)

Resurgence of HIV infection after CCR5 wild type stem cell transplant Reduction of the reservoir delays HIV rebound but is not sufficient for cure



Allogeneic hematopoietic stem cell transplant from CCR5 ( $\Delta 32/\Delta 32$ ) is not a scalable strategy for HIV Cure

- High risk procedure
  - Graft versus host disease
  - Infections
- Limited number of compatible donors
- Important regional variation in CCR5 polymorphism
  - Ethiopia 0%



### Infusion of CCR5-edited CD4+ T cells A possible role in delayed viral rebound related to increased of HIVspecific CD8 T cells



0

Time since ATI (weeks)

6

10

8

12

Percentage of CCR5-disrupted alleles in CD4\* T cells present in the peripheral blood at the indicated time after initiation of the ATI. <sup>A</sup>P values were calculated using the Kruskal-Wallis test for differences between the 3 treatment groups. <sup>IP</sup> values for cohort 3 by LR analysis. <sup>C</sup>Twelve- and 16-week values may not be comparable, as the length of ATI was different for each group. <sup>IC</sup>Cohort 1: 24-week data are missing for 1 person; for 16-week ATI AUC, the missing 24-week value was imputed as the 16-week value. <sup>E</sup>Because of the variability in visit windows, the AUC was normalized by dividing by the actual length of the 16-week ATI AUC/(time between 16-week ATI visits).

9.4 (6.5, 15.5)

12.9 (11.0, 20.8)

11.6 (9.1, 15.0)

10.9 (9.7, 16.4)

13.3 (12.1, 19.5)

27.2 (19.5, 28.2)

25.2 (18.2, 26.2)

14.2 (13.5, 22.0)

0.33

0.10

0.03

0.19

0.17

0.04

0.06

7.7 (4.7, 11.9)

11.5 (8.2, 14.8)

10.3 (7.1, 14.0)

7.3 (4.6, 11.0)

16 weeks<sup>CO</sup>

4-week peak

4-week mean

16-week ATI mean value<sup>£</sup>

12.1 (7.0, 16.5)

17.4 (11.8, 26.2)

15.8 (10.5, 20.8)

12.6 (9.7, 17.1)

#### Tebas JCI 2021

Importance of the immune system in the control of HIV Selected cases with implication for (functional) cure

### Effective control of HIV w/o ART

- Elite controllers
- 20-40% have specific alleles
- Post-treatment controllers

(see session tomorrow)

### Effective eradication of HIV w/o ART

### Esperanzah patient

• Elite controller profile (CCR5 WT)



- After ART interruption
  - Only 7 defective proviral DNA sequences
  - Mutations detected (previous replication)
  - CD4+/CD8+ p24 specific responses
  - Patients'cells are able to grow HIV-1

Original Research | 16 November 2021

#### A Possible Sterilizing Cure of HIV-1 Infection Without Stem Cell Transplantation

Authors: Gabriela Turk, PhD , Kyra Seiger, BSc , Xiaodong Lian, PhD , Weiwei Sun, PhD, Elizabeth M. Parsons, BSc , Ce Gao, PhD , Velizaveta Rassadkina, BSc , Maria Laura Polo, PhD, Alejandro Czernikier, MSc, Yanina Ghiglione, PhD, Alejandra Vellicce, MD, Joseph Varriale, MSc , Jun Lai, MSc, Yuko Yuki, DDM, Maureen Martin, MD , Ajantha Rhodes, BSc, Sharon R. Lewin, PhD , Bruce D. Walker, MD, Mary Carrington, PhD , Robert Siliciano, MD, Janet Siliciano, PhD, Mathias Lichterfeld, MD, PhD, Natalia Laufer, MD, PhD , and Xu G. Yu, MD, MSc SHOW FEWER | <u>AUTHOR, ARTICLE, & DISCLOSURE INFORMATION</u>

# Romuald or Patient de Genève

- Diagnosed HIV in 1990, continuous suppressive ART since 2005
- Diagnosed with biphenotypic sarcoma in 2018
  - Chemotherapy
  - Allogenic hematopoietic stem cell transplant from an HLAmatched wild-type CCR5 donor
- Acute hepatic GVHD 8 months after HSCT, treated with corticosteroid/calcineurin inhibitors
- Chronic hepatic GVHD treated by **ruxolitinib**
- No evidence of HIV-1 RNA rebound,
- No viral amplification in cell culture
- No development of HIV T-cell specific responses
- Decline of HIV-1 IgG

ART discontinued in november 2021



## Geneva patient : "HIV cure" despite CCR5 wild type Hypothesis

- Graft versus host disease role in elimination of HIV-infected cells ?
- Role of NK cells in control of HIV ?
- Ruxolitinib role in the modification of activation treshold of infected cells (reservoir replenishment)?

## Ruxolitinib : an unexpected game changer ? Ruxolitinib mediates reservoir decay among PLWH with high baseline reservoir

JAK1/2 inhibitor approved for GVHD treatment

• JAK-STAT pathway involved in pro-HIV-events





. Reece MD, Zhang Z, Pereira-Ribeiro S, et al. Ruxolitinib-mediated HIV-1 reservoir decay in A5336 phase 2a trial. IAS 2023, July 23-26, 2023. Brisbane.

# What would be acceptable as an intervention ? Insights from PLWH in Ghana





### WHY?

An HIV cure is a desirable objective both for the patients and the physicians

### FOR WHOM ?

Should be scalable and accepted to all/a majority of PLWH, irrespective of age, ethnicity and place of residence

### **HOW** ?

We are still far from a scalable, safe and efficient cure

Possibly need a combination of different strategies that include reservoir reduction and reinforcement of anti HIV immunity