

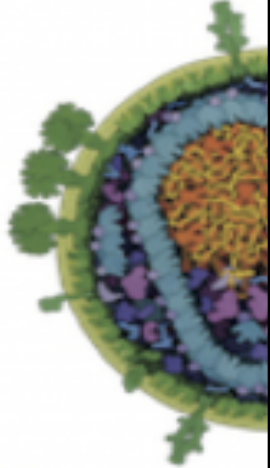
# Sustained HIV-1 remission following homozygous CCR5 delta-32 allogeneic haemopoetic stem cell transplantation

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# “The London patient”

CROI 2019



## HIV-1 remission following CCR5 $\Delta$ 32/ $\Delta$ 32 haematopoietic stem-cell transplantation

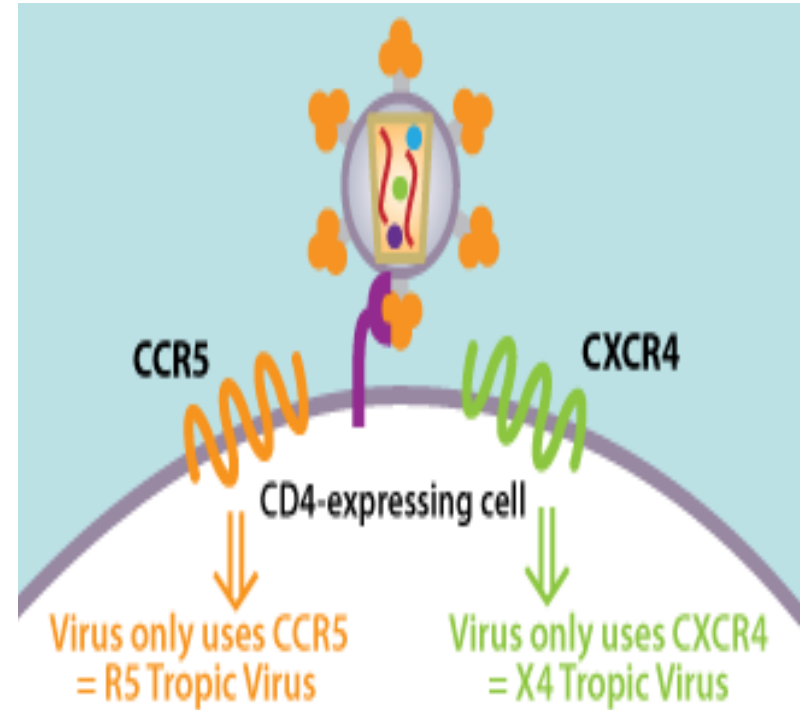
Ravindra K. Gupta , Sultan Abdul-Jawad, Laura E. McCoy, Hoi Ping Mok, Dimitra Peppas, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M. J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew J. Innes, Luke Muir, Laura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

Conference on Retroviral  
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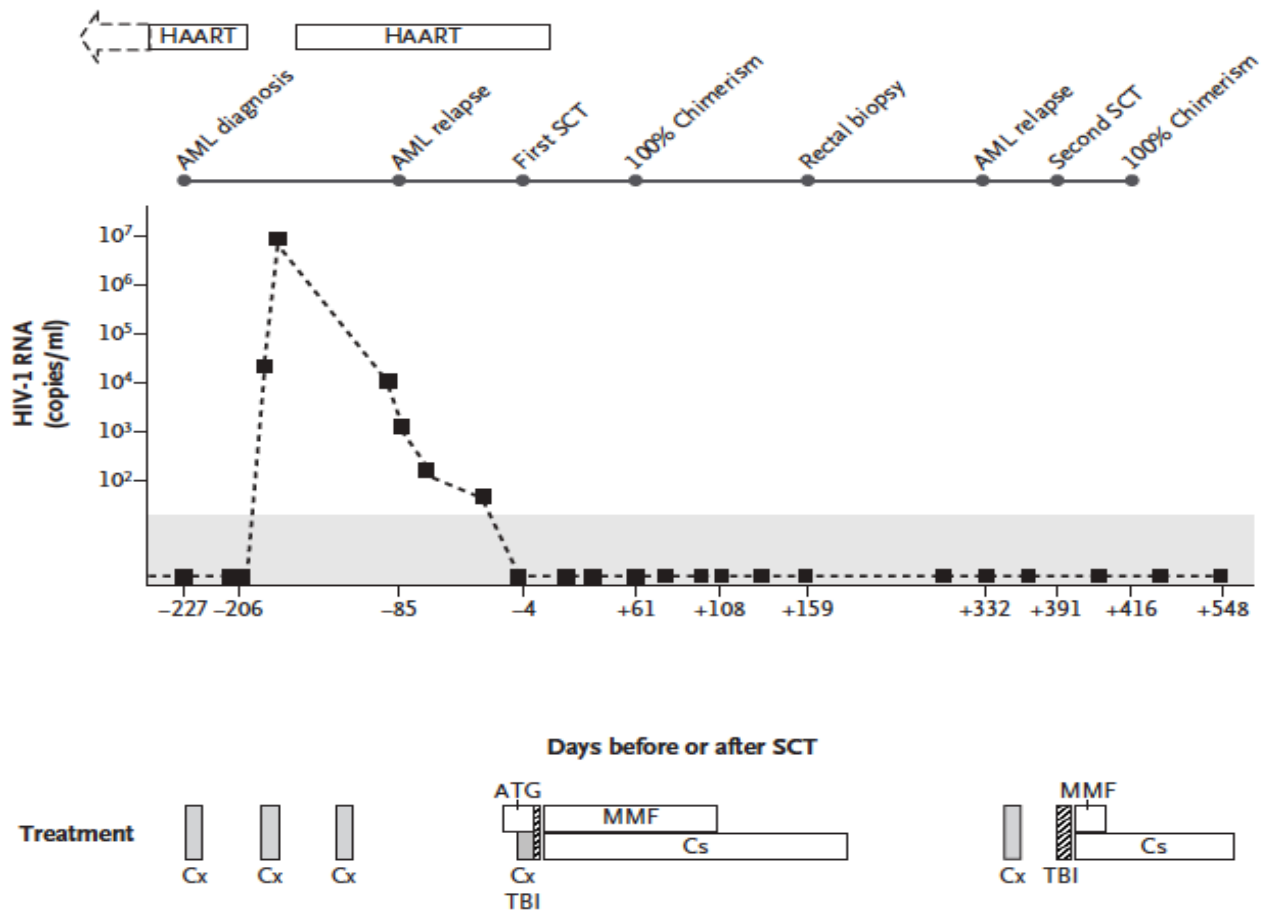
# HIV-1 & CCR5 as a target for remission

- CCR5 is the main co-receptor for HIV entry into CD4+ target cells
- $\Delta 32$  mutation = 32bp CCR5 deletion, preventing expression.
- 1% of Europeans are  $\Delta 32$  homozygous & resistant to R5 HIV-1



# Allo-HSCT cure possible with $\Delta 32/\Delta 32$ donor

“The Berlin patient”



# “The Berlin Patient”: mechanism NOT understood

- Off-ART for >8 years with no viral rebound:
  - chemotherapy regimen
  - need for 2 rounds of treatment
  - role of whole body irradiation
  - graft vs host disease (GVHD)
  - unmeasured patient specific factors

# “The London patient”

**2015:**

5 day ART interruption; VL 1500

M184V + K65R + E157Q

Switched to RPV + DTG + 3TC

VL suppressed subsequently

# Allogeneic Stem Cell Transplantation

- **LACE conditioning:** lomustine, cyclophosphamide, cytarabine and etoposide
- **13<sup>th</sup> May 2016 day 0:** underwent stem cell infusion
  - Gram negative sepsis
  - Dental abscess
  - **Day 31:** discharged
  - **Day 77:** colitis ?GVHD on gut biopsy
  - **Day 85:** CMV & EBV reactivation; treated with Ganciclovir & Rituximab

LOD  
<1c/mL



VL (Copies/ml plasma)

10,000  
1,000  
100  
10

TDF+FTC  
+RAL  
RPV+3TC+DTG

-215 -141 -27 0 +29+77+150 +424 +510 +1028

TIME POST HSCT (days)

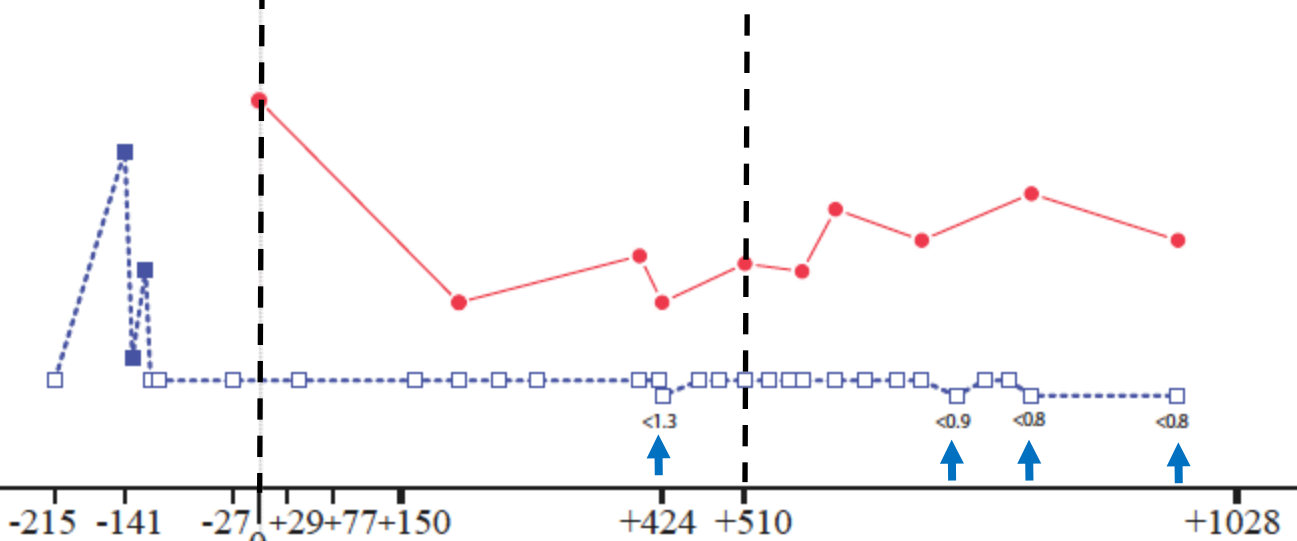
Allo-HSCT (May 2016)  
100% Chimerism  
Mild gut GvHD  
Stop CsA

Written  
informed  
consent



STOP cART (Sept 2017)  
PET CT: lymphoma  
remission Dec 2017

18 months off cART  
(Feb 2019)

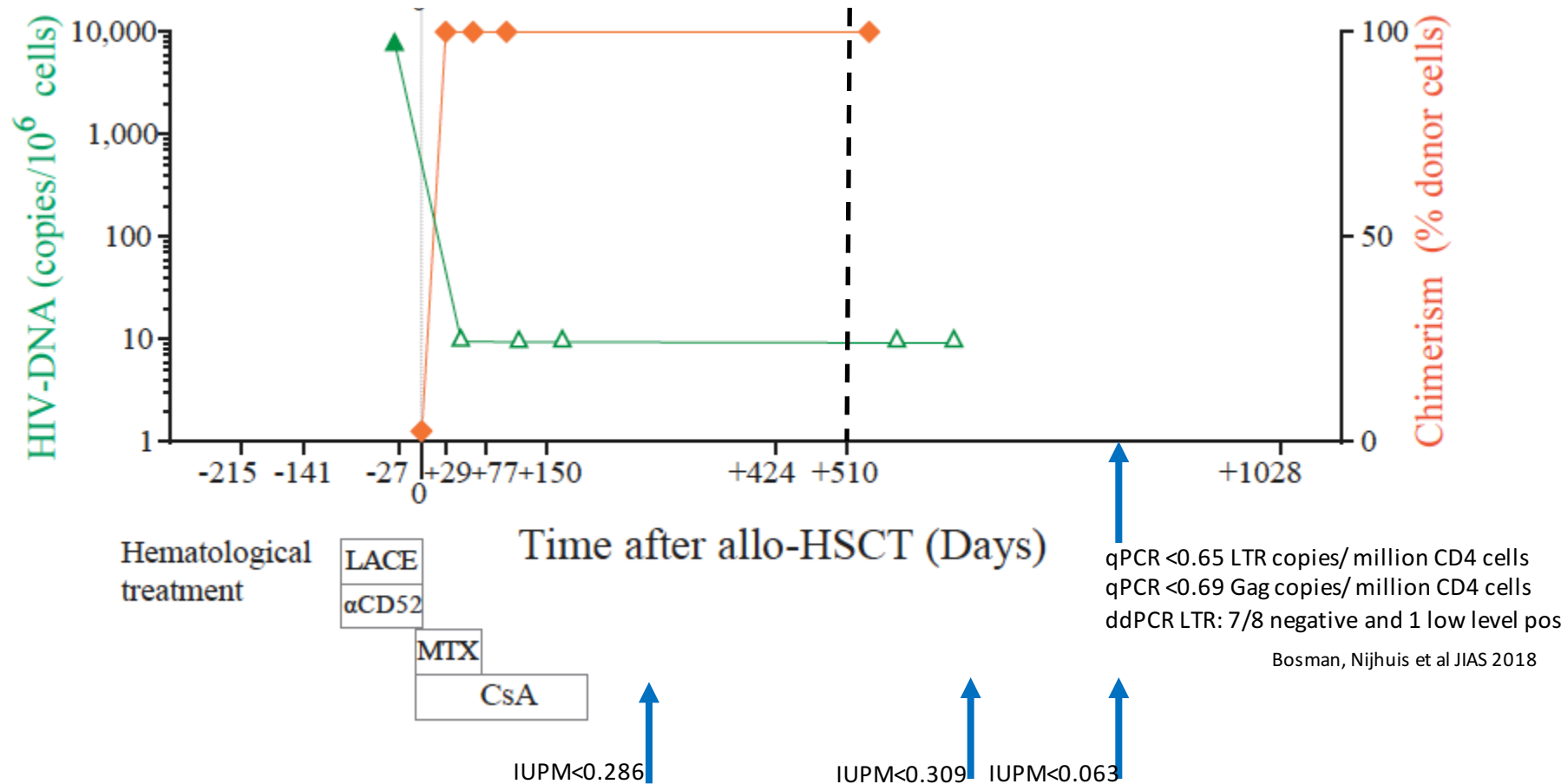


CD4 count (cells/μL)

600  
400  
200  
0



# Cellular HIV-1 DNA reservoir measurements



# Additional investigations

- **Lymphoma & HSCT**

- 100% chimerism; CT/PET remission +120 & +365 days

- **Tropism**

- Pre-HSCT virus CCR5-tropic by genotypic & phenotypic assay
- Host CCR5wt/wt pre-HSCT,  $\Delta 32/\Delta 32$  post-transplant
- Loss of CCR5 expression on CD4 and CD8 T cells
- Circulating CD4 cells susceptible to CXCR4-tropic HIV-1 but not to CCR5-tropic HIV-1

# Additional investigations

- **Drug concentrations**

- Undetectable plasma TDF, 3TC and DTG at day +648
- Undetectable plasma panel of all available ARVs day +973

- **HIV-DNA**

- Total HIV-1 DNA in CD4+ cells undetectable by ultra-sensitive qPCR in all replicates & in 7/8 replicates of the ultra-sensitive HIV-1 LTR ddPCR
- Persistently undetectable whole blood DNA/RNA by SAMBA

# Additional investigations

- **Quantitative viral outgrowth assays**
  - Undetectable on days +217 (on ART) & days +678 and +876 (off ART) = reservoir estimation  $<0.029$  IUPM
- **Immunology**
  - Loss of antibody responses to a range of HIV-1 antigens
  - Loss of HIV-1 specific T-cell responses

**IUPM = infectious units per million**

# Comparison of the two cases

## 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

## The “Berlin patient”

- 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

# Conclusion

- Second proven case of sustained HIV-1 remission
- Additional investigation may include GI & CNS assessment
- Virological monitoring continues

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London



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# Acknowledgements

- **“The London patient”**



**Thank you!**



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