BMT CTN Protocol 0903 and the Search for a CCR5Δ32 Donor

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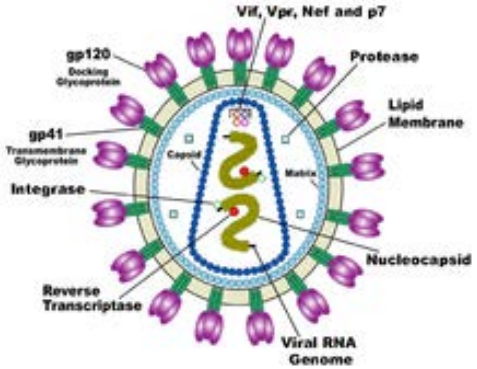


HIV

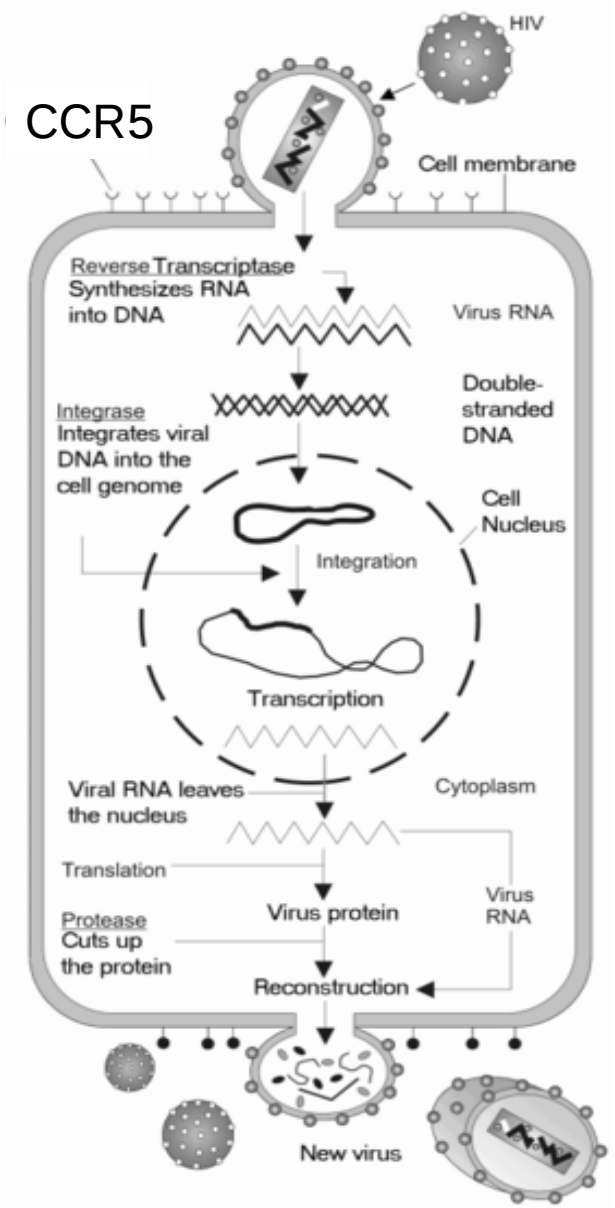
- **Human Immunodeficiency Virus** is a lentivirus (a slowly replicating retrovirus): positive sense RNA
- Preferentially infected CD4+ T cells (T-helper cells) as well as macrophages and dendritic cells
- Without treatment, progressive loss of CD4+ cells occurs, leading to cellular immunity defects and profound immunodeficiency
- "AIDS" is defined by the occurrence of various illnesses that represent the deteriorated state of the infected individual's immune function
  - Opportunistic infections
  - Malignancies (some virally driven; immune surveillance)

HIV Lifecycle and Treatment

Drug targets occur at various points in the viral life cycle

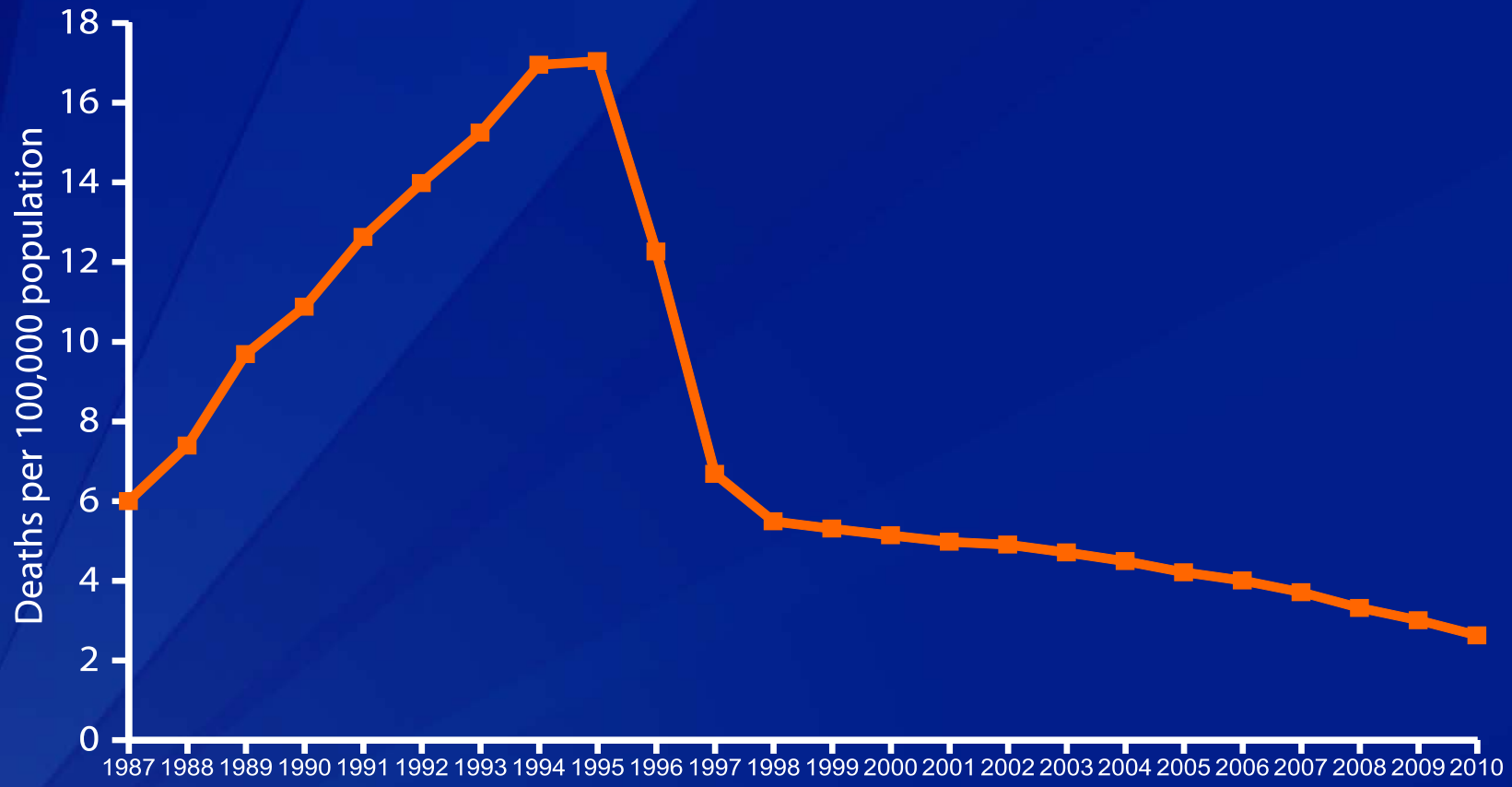
Combination ARV therapy is required to avoid development of rapid resistance

Long term viral control is now possible with combination ARV therapy



From: “HIV” in Wikipedia

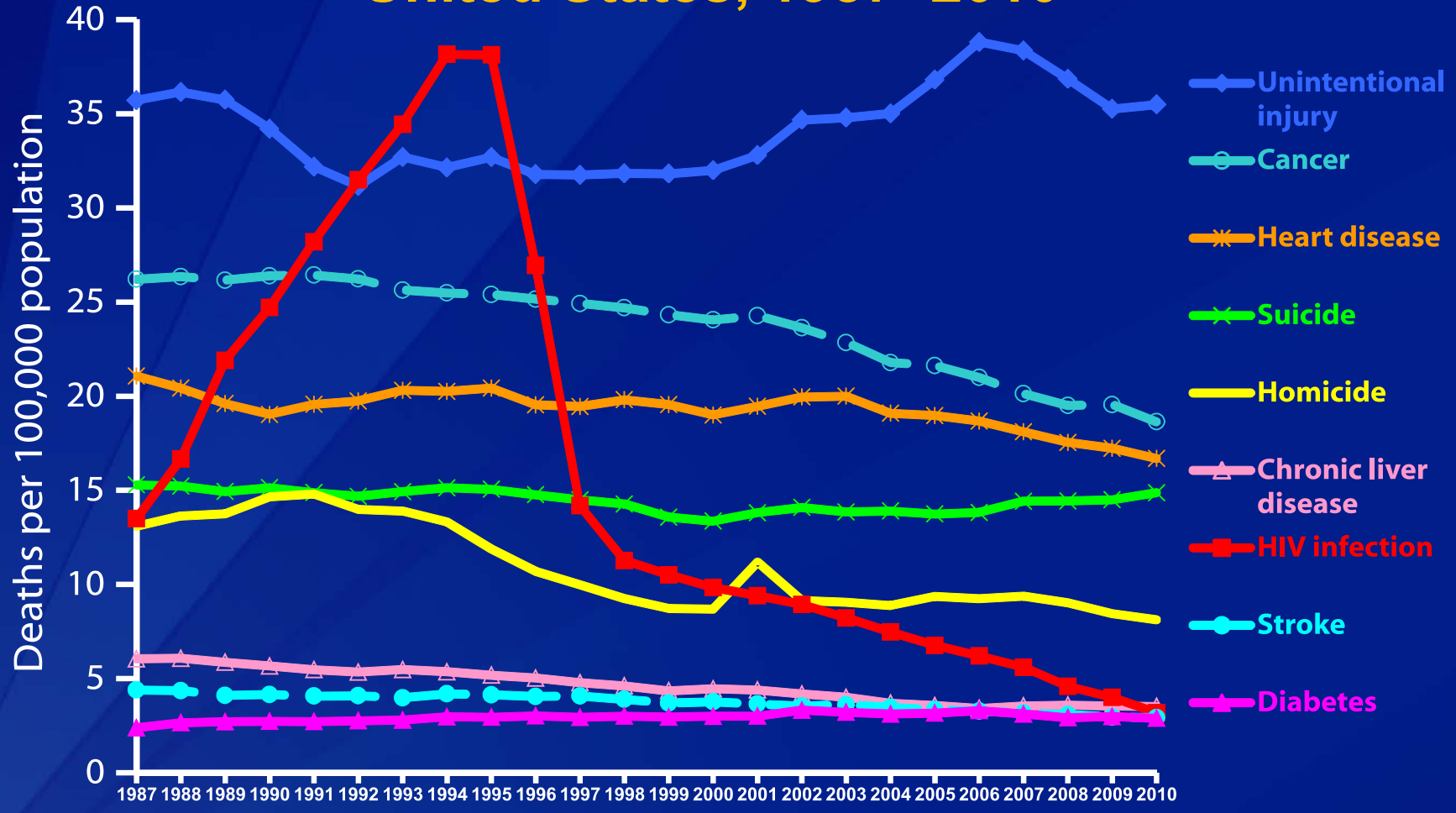
Trends in Annual Age-Adjusted* Rate of Death Due to HIV Infection, United States, 1987–2010



Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.

*Standard: age distribution of 2000 US population

Trends in Annual Rates of Death due to the 9 Leading Causes among Persons 25–44 Years Old, United States, 1987–2010



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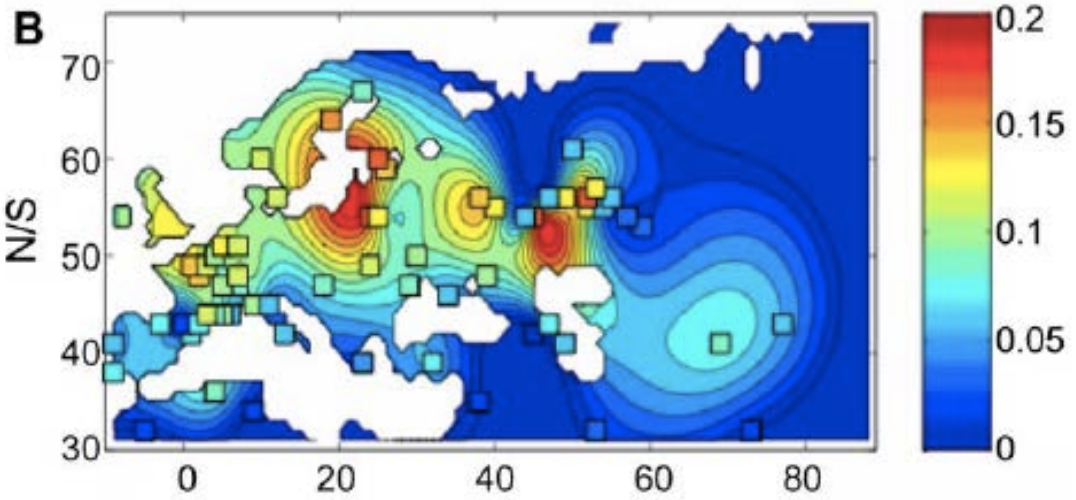
CCR5Δ32



From Galvani *et al*., *Microbes Inf* 2005

- HIV typically uses the chemokine receptor CCR5 to enter cells, perpetuate infection
- CCRΔ32 homozygosity: 1% in N Europe, essentially non-existent outside Europe

Big News...

The NEW ENGLAND JOURNAL of MEDICINE

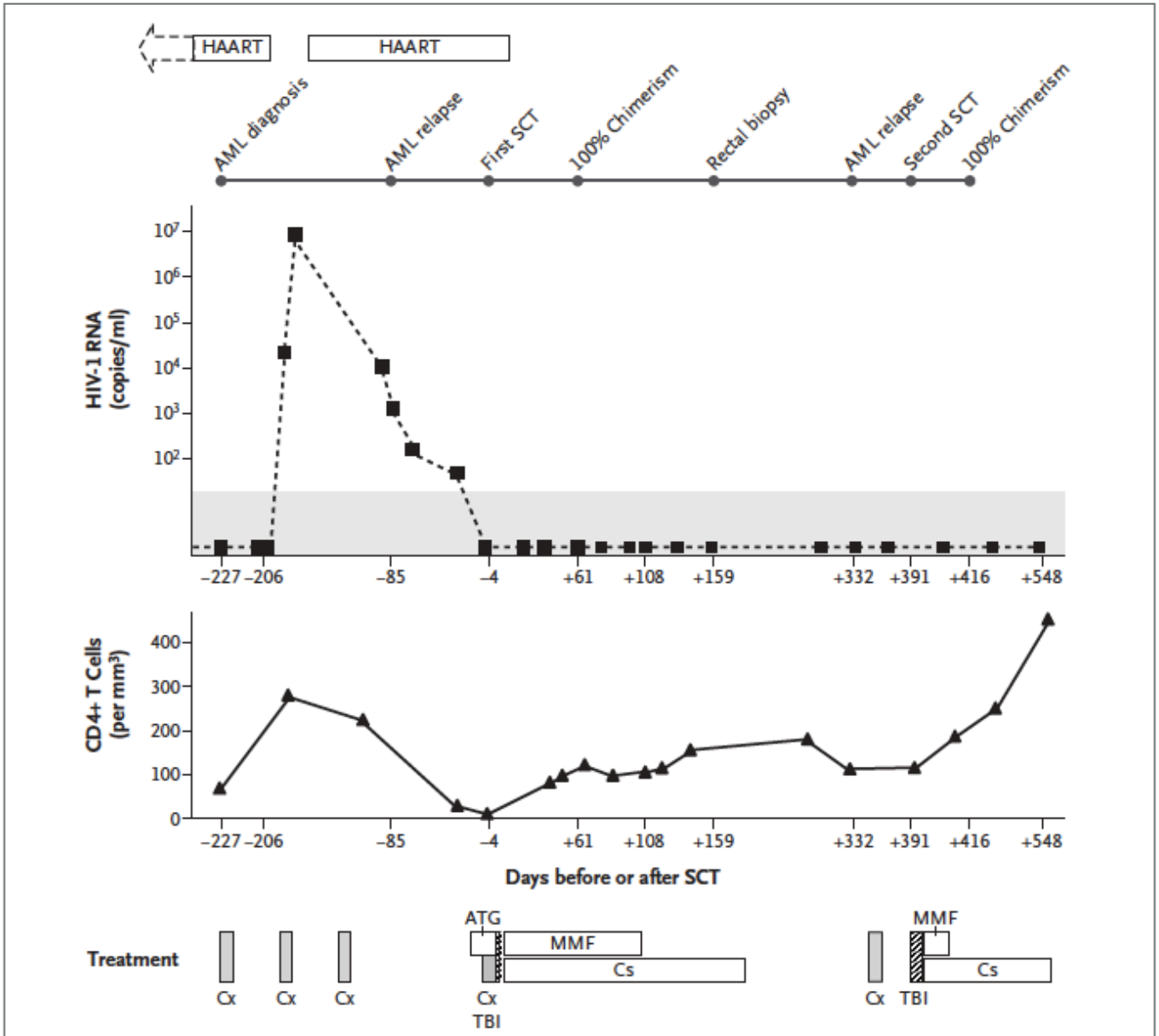
BRIEF REPORT

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

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

Case Summary

- 40 y/o man diagnosed with AML
- Previous dx of HIV infection x 10 yrs, on HAART (emtricitabine, efavirenz, tenofovir x 4 yrs); no HIV-related illnesses
- HAART stopped during induction chemo for liver tox: rebound HIV VL 6.9 x 10^6 then well-controlled to ND after resuming
- Relapse-> alloHCT using CCR5Δ32 +/+ donor
- Relapse at day 332-> reinduction, second transplant; remains in remission to present


HAART
HAART
AML diagnosis
AML relapse
First SCT
100% Chimerism
Rectal biopsy
AML relapse
Second SCT
100% Chimerism
HIV-1 RNA (copies/ml)
10^7
10^6
10^5
10^4
10^3
10^2
−227 −206
−85
−4
+61
+108
+159
+332
+391
+416
+548
CD4+ T Cells (per mm³)
400
300
200
100
0
−227 −206
−85
−4
+61
+108
+159
+332
+391
+416
+548
Days before or after SCT
Treatment
Cx
Cx
Cx
ATG
MMF
Cs
Cx
TBI
MMF
Cs
Cx
TBI

Conclusions from Hütter et al.

- Allogeneic transplant was tolerated in the setting of HIV (twice with the Berlin pt)
- Long term (5+ years) HIV control was seen without HAART
- CCR5Δ32 homozygosity appears to effectively convey HIV resistance via HCT
- Very few patients with hematologic malignancies will have a similar donor available but the proof-of-concept is extremely valuable

BMT CTN

- The BMT CTN, created in 2001, is supported by NHLBI, NIH, and NCI funds
- BMT CTN is a group of 20 core clinical centers, some single centers, some consortia, with projects managed by a data coordinating center
- Collaboration with CIBMTR, EMMES, NMDP

BMT CTN 0903: Background

- Allogeneic HCT is
  - known to be the best or **only** curative therapy for a number of hematologic malignancies
  - inherently dangerous
  - complex, requiring multiple drugs for prevention of life-threatening complications
- Co-existent HIV infection
  - impacts the likelihood of treatment-related mortality in unknown ways
    - increased risk/severity of infections, other complications?
    - decreased efficacy of GVL effect against malignancies?
  - with HAART presents severe challenges with drug-drug interaction issues

BMT CTN 0903: Study Objectives

- Primary Objective
  - 100 day non-relapse mortality
- Secondary Objectives
  - Disease status at day 100
  - Engraftment
  - Rates of complications (GVHD, infections)
  - Immune reconstitution as measured by quantification of immune components
  - HIV reservoir estimation
- N=15 patients over 2 years

BMT CTN 0903: Eligibility

- Patients ≥ 15 y/o with HIV infection and one of the following:
  - AML: CR1 or CR2
  - ALL: CR1 or CR2
  - MDS: intermediate or high-risk disease
  - Lymphoma (Hodgkin or non-Hodgkin): >CR1
- Good organ function
- An matched related or unrelated donor

Identifying a CCR5Δ32 donor

- Complex logistics with the pressure of trying to identify an unrelated donor in a timely way
- Of the 15 pts, 1-2 will have sufficient donors to identify a CCR5Δ32 homozygous donor
- If we can replicate the Hütter case, then this will provide strong proof-of-principle that CCR5Δ32 is an excellent target

Where We Are Now

- Enrollment to date: 11 patients
  - 8 have been transplanted, 1 pending
  - 2 did not go forward to transplant
- No CCR5Δ32 donors identified to date