UMC Utrecht

Potential for HIV Cure by stem cell transplantation

IciStem

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Stem cell transplantation in HIV patients

- HIV-infected patients have a higher risk for hematological malignancies, such as AML, MDS and lymphoma‘s
- There is a lower overall survival rate after allogeneic stem cell transplantation (SCT) for these conditions as compared to a matched control group of HIV negative patients

→ Timothy Brown, the so called “Berlin patient” was cured from both AML and HIV-infection after SCT with CCR5Δ32 donor cells

Sutton et al, Br J Hematol 2001; Hutter et al, aids Res Ther 2016; Kaner et al, Blood 2016; Aboulafia et al, AIDS 2002; Ryu Intern Med 2001

Treatment interruption in HIV patients transplanted with CCR5Δ32stem cells (peri-SCT)

- Berlin Patient: diagnosed with AML and transplanted **twice** with CCR5Δ32 donor cells[1]
  - Transplanted in 2007 and off combination ART ever since
  - Prior to SCT a minority population predicted to use the CXCR4 coreceptor
  - Phenotypic analyses demonstrated that these variants were still dependent on CCR5 for viral replication[2]

- One other case reported of a patient transplanted with CCR5Δ32 donor cells stopping ART

- Essen patient: diagnosed with anaplastic large-cell lymphoma and transplanted with CCR5Δ32 donor cells[3]
  - 27 year old HIV-1 infected patient transplanted in 2012
  - Successful engraftment
  - Treatment interruption 7 days before transplantation
  - Viral rebound of **pre-existing CXCR4-tropic virus (PBMCs)** three weeks after SCT[4]

[1]Hutter et al, NEJM, 2008; [2]Symons et al, CID, 2014 ; [3]Kordelas et al, NEJM, 2014; [4]Verheijen et al, CID, 2018

Treatment interruption in HIV patients transplanted with CCR5WT stem cells (post-SCT)

- Boston Patients: transplanted with CCR5WT donor cells[1]
  - No HIV DNA and infectious virus detected in blood and rectal mucosa
  - 2.6-4.3 years: ATI and viral rebound was observed after 12, 32 weeks
  - Rebound virus is monophyletic and **related to viral PBMC DNA** sequences observed peri-SCT

- Minnesota Case: transplanted with CCR5WT donor cells[2]
  - HIV DNA +/- detectable in PBMCs, no infectious virus detected in PBMCs
  - In situ hybridization was negative in colon
  - 2.1 years: ATI and viral rebound was observed after 41 weeks
  - Rebound virus is phylogenetic **distinct from circulating PBMCs** prior to SCT

- Determinants of HIV Cure after SCT?
  - CCR5Δ32 donor cells; two transplants; GvhD; TBI, conditioning?
- Where is the virus hiding that can fuel the rebound?

[1]Henrich et al, Ann. Intern. Med., 2014; [2]Cummins et al, PLoS Medicine, 2017;

IciStem Consortium

International collaboration to guide and investigate the potential for HIV cure in HIV-infected patients requiring allogeneic stem cell transplantation for hematological disorders

AIM 1

To guide clinicians involved in allogeneic SCT procedures in HIV infected individuals

AIM 2

To better understand the underlying biological processes leading to viral reservoir reduction and potential cases of HIV-1 eradication/remission.

Principal Investigators:

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www.icistem.org

amfAR
MAKING AIDS HISTORY

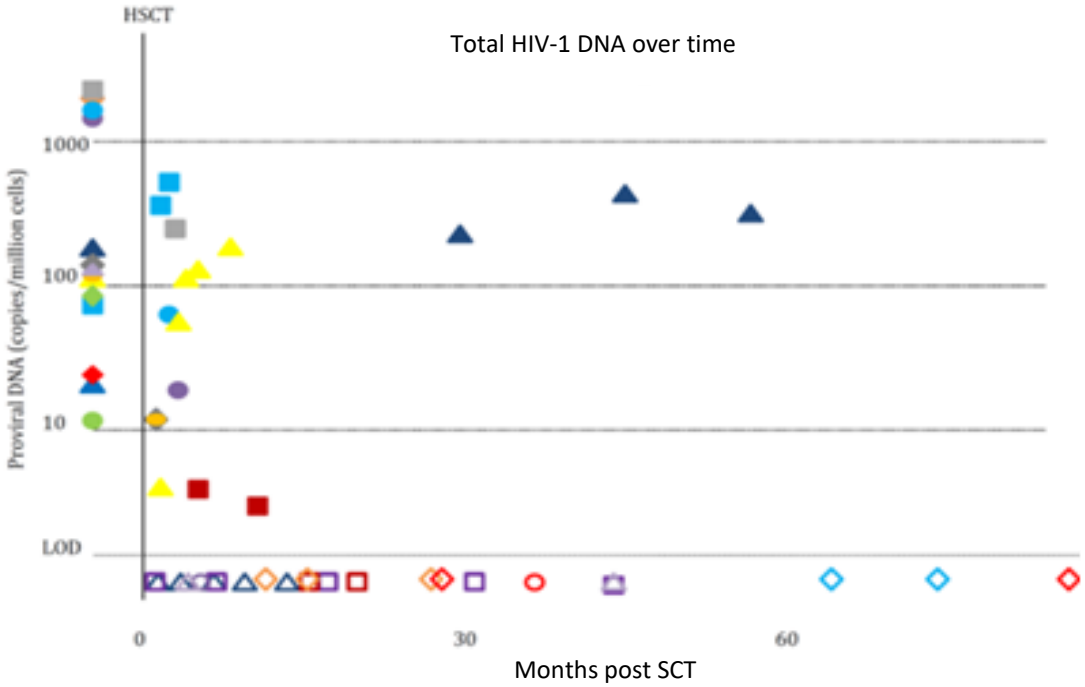
Overview of registration

- 37 patients registered from 9 different countries
- 30 patients transplanted

- Mean follow-up: 887 days
  12 patients beyond 2nd year post-SCT

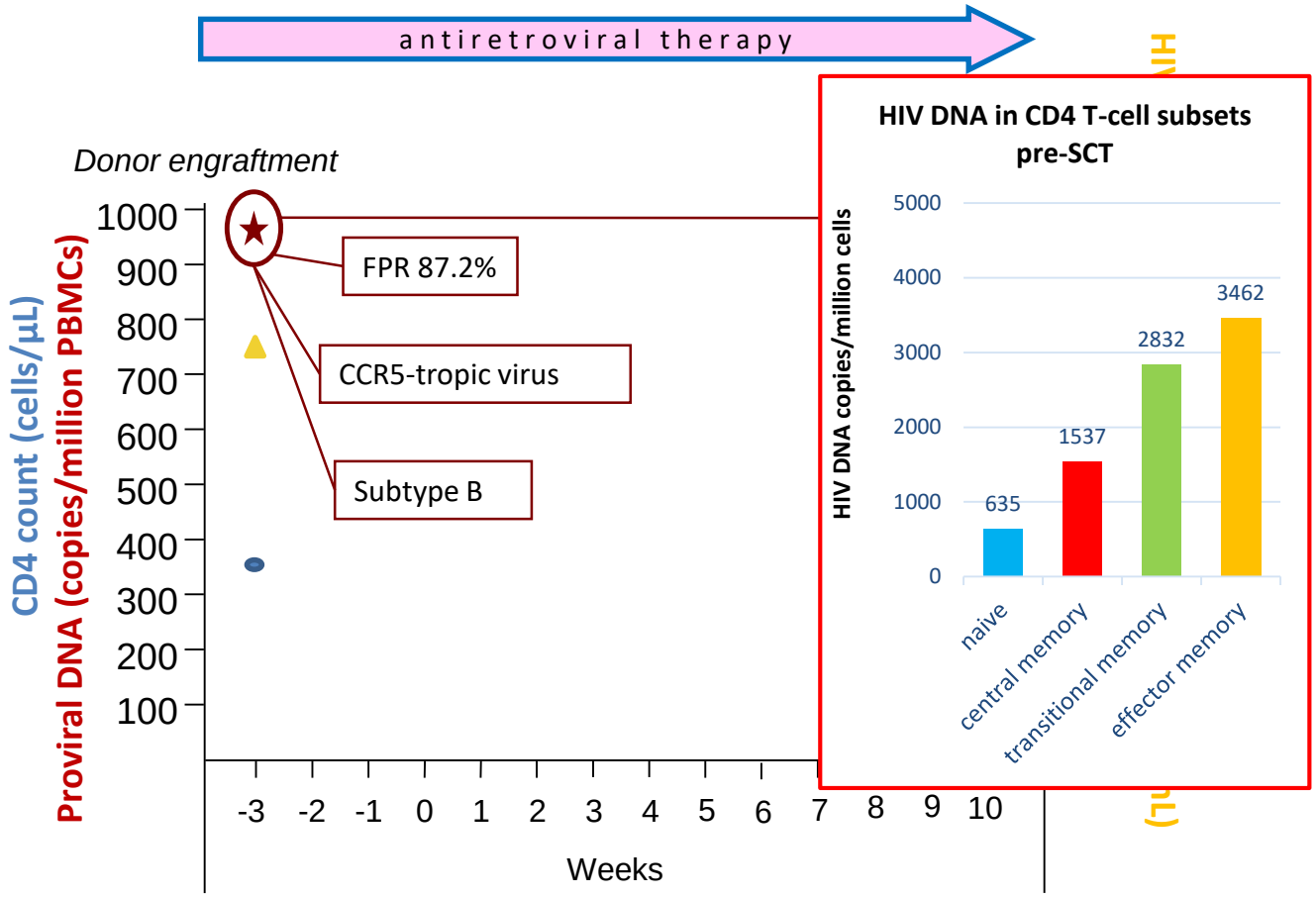
	CCR5WT/WT	CCR5Δ32/Δ32			alive
Adult Donor	20*	7	27	→	17
Umbilical Cord	1	2	3	→	1
	21	9			
	↓	↓	*3 CCR5 Δ32/WT		
alive	13	5			

The viral reservoir (total HIV DNA in PBMCs)

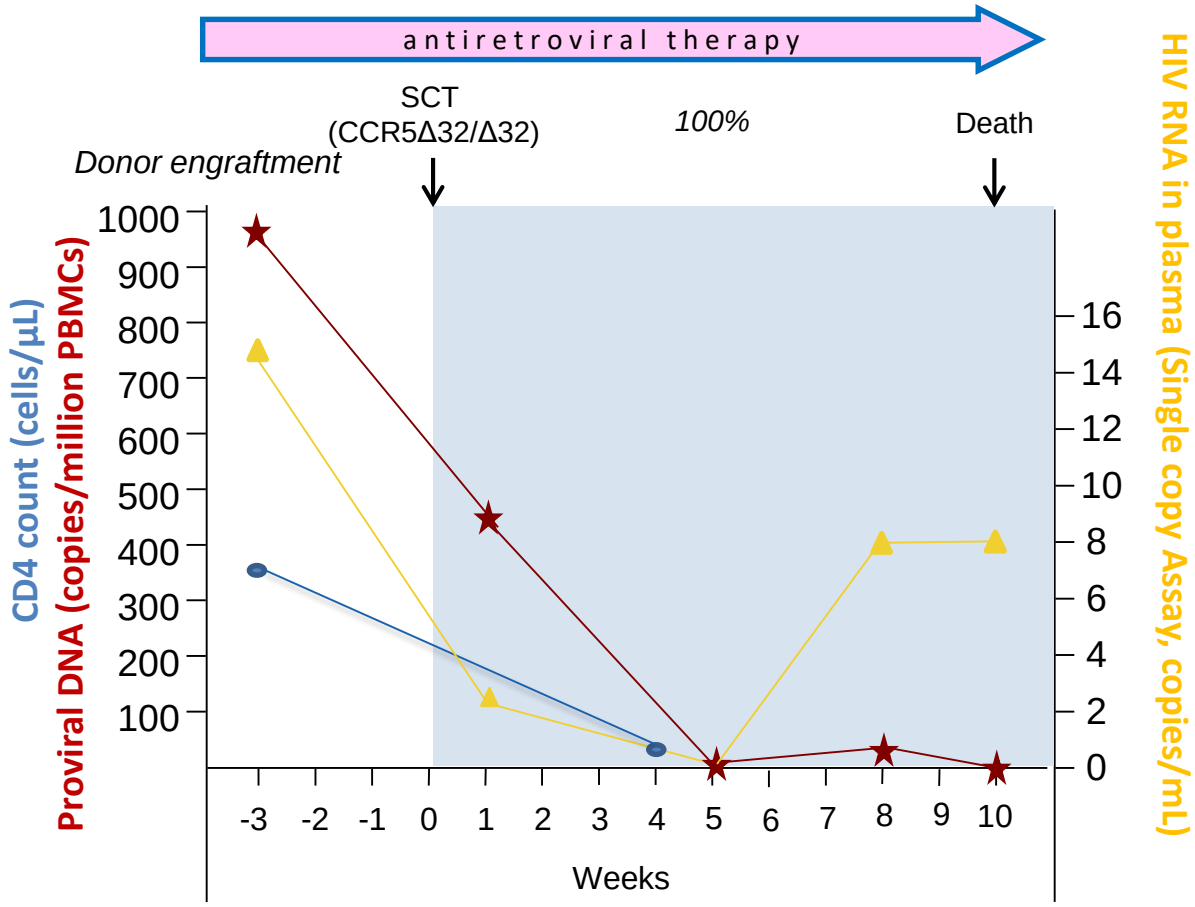


No difference in HIV DNA decay in patients transplanted with CCR5WT or mutant stem cells

Patient IciS-05 (MDS, CCR5Δ32 cord)



Patient IciS-05 (MDS, CCR5Δ32 cord)

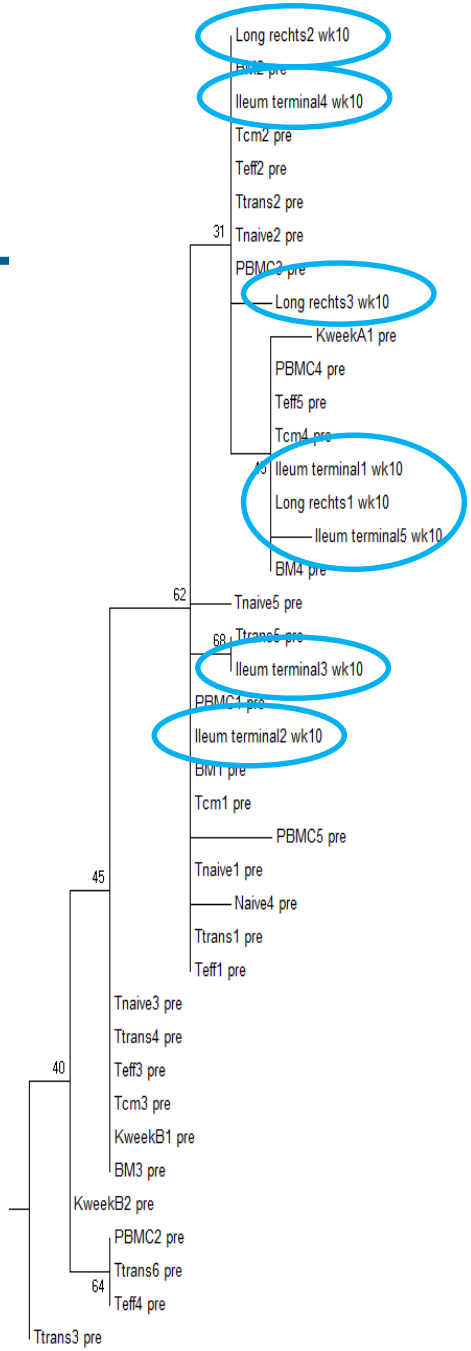


Autopsy

		Biopsy 1	Biopsy 2		
Autopsy		**ddPCR LTR**	**ddPCR LTR**	**ddPCR Integrase**	**Envelope gp120 sequencing**
		Total HIV-1 DNA (c/million cells)	**Total HIV-1 DNA (c/million cells)**		
Patient IciS-05	Liver	54	<24	<24	No amplification
	Lung (left)	36	49	trace*	Amplification
	Lung (right)	90	32	trace*	Amplification
	Spleen	43	67	34	No amplification
	Terminal Ileum	549	81	89	Amplficaton

Autopsy

		Biopsy 1	Biopsy 2		
Autopsy		**ddPCR LTR**	**ddPCR LTR**	**ddPCR Integrase**	**Envelope gp120 sequencing**
		Total HIV-1 DNA (c/million cells)	**Total HIV-1 DNA (c/million cells)**		
Patient IciS-05	Liver	54	trace	<8	No amplification
	Lung (left)	36	49	trace*	Amplification
	Lung (right)	90	32	trace*	Amplification
	Spleen	43	67	34	No amplification
	Terminal Ileum	549	81	89	Amplification



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Patient IciS-05	Liver	54	trace	<8	No amplification
	Lung (left)	36	49	trace*	Amplification
	Lung (right)	90	32	trace*	Amplification
	Spleen	43	67	34	No amplification
	Terminal Ileum (CD4)	549	81	89	Amplficaton

		Biopsy 1	Biopsy 2		
Autopsy		**ddPCR LTR**	**ddPCR LTR**	**ddPCR Integrase**	**Envelope gp120 sequencing**
		Total HIV-1 DNA (c/million cells)	**Total HIV-1 DNA (c/million cells)**		
Patient IciS-11	Liver	60	<7	trace	No amplification
	Lung (left)	28	<4	<4	No amplification
	Lung (right)	trace	<3	<3	No amplification
	Spleen	60	<6	<6	No amplification
	LN CD4 (donor 38%)	10	ND	ND	No amplification

IciS-11: transplanted twice, donor engraftment PBMCs 100%: no HIV DNA could be detected

Title: Mechanisms that Contribute to a Profound Reduction of the HIV-1 Reservoir after Allogeneic Stem Cell Transplantation

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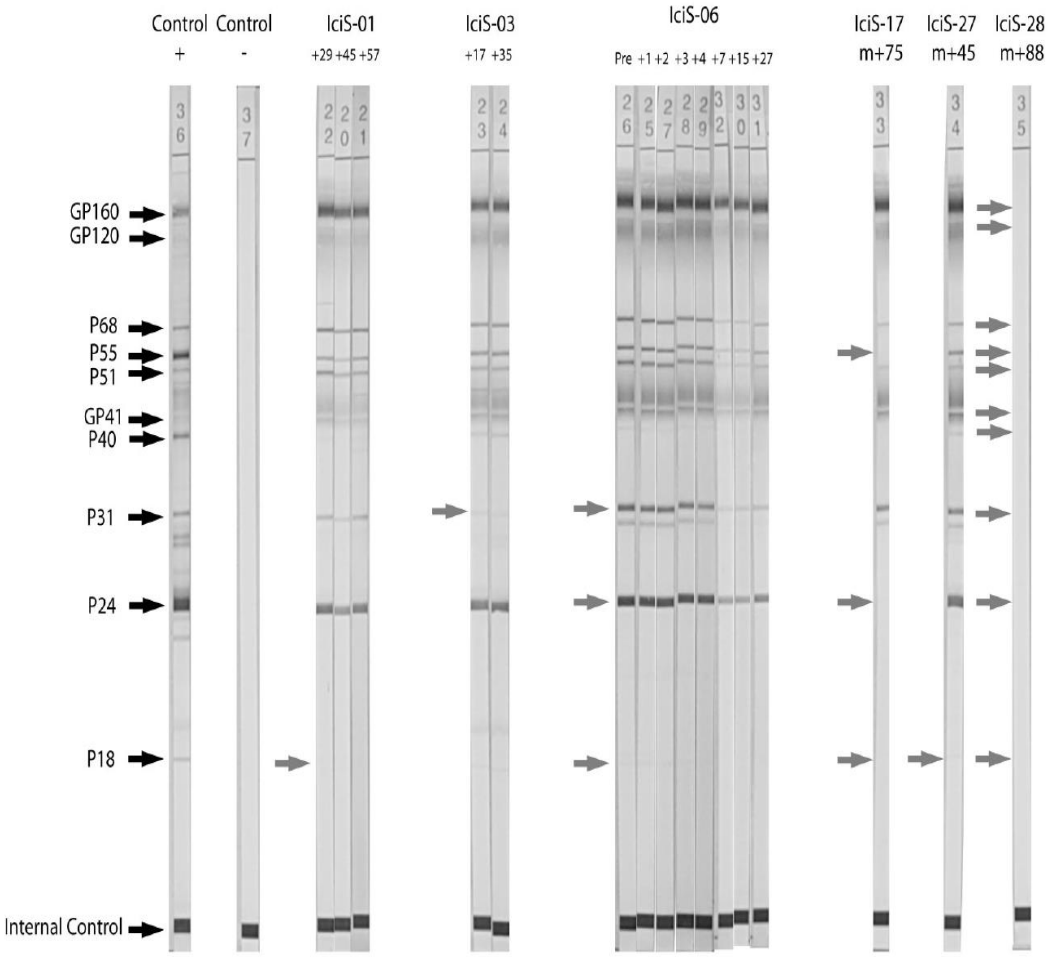
Table 1. Clinical, hematological and virological data from 6 participants.

	IciS-01	IciS-03	IciS-06	IciS-17	IciS-27	IciS-28
Hematological data						
Gender, age	♂ 34	♂ 51	♂ 40	♂ 46	♂ 47	♂ 44
Origin	Spain	Spain	Spain	Italy	Spain	Spain
Hematological Diagnosis	Burkitt NHL stage IV	NK-NHL stage IV	HL stage IV	NHL (DLBCL)	NHL stage III	HL stage III
Year of HSCT	2012	2013	2014	2010	2013	2009
Status at transplant	CR2	CR1	CR1	CR2	CR1	CR3
Donor type / graft source	Cord blood 7/8 (mismatch in DRB1)+ mismatched related PBPC*	HLA-identical sibling/PBPC	HLA-Haploidentical sibling/PBPC	HLA-identical sibling/PBPC	HLA-identical sibling/PBPC	HLA-identical unrelated/PBPC
Donor CCR5 type	CCR5 wt/wt	CCR5 wt/wt	CCR5 wt/wt	CCR5 wt/wt	CCR5 wt/wt	CCR5 wt/wt
Recipient HLA	A*02/02 B*44/51 Cw02/05 DRB1*04/07 DQB1*03/03	A*25/01 B*18/15 Cw12/03 DRB1*13/03 DBQ1*06/02	A*02/03 B*44/51 Cw05/07 DRB1*07/04 DQB1*02/03	A*03/24 B*18/51 Cw12/14 DRB1*07/11 DQB1*02/03	A*01/34 B*08/18 C*07/12 DRB1*01/11 DQB1*03/05	A*26/29 B*44/49 C*07/16 DRB1*01/07 DQB1*02/05
Donor-recipient HLA match	5/6 (DRB1) (3/10 with third party donor)	10/10	6/8 (B*44/57 and DRB1-07/07)	10/10	10/10	10/10
Conditioning	MAC: FLU, CY, Busulfan, ATG	RIC: FLU, Melphalan	RIC: FLU, CY, Busulfan	RIC: Thiotepa, FLU, CY	RIC: FLU, CY	RIC: FLU, Melphalan
SCT-associated infections	1) E.coli, 2) BK virus hemorrhagic cystitis	None	1) Clostridium Difficile 2) CMV Reactivation	EBV-reactivation (treated with Rituximab)	None	CMV Reactivation
GvHD prophylaxis	CsA + steroids	CsA + Mtx	PT-CY + CsA + MMF	CsA + Mtx	CsA-Mtx	Tacrolimus and Sirolimus
GvHD	No	Chronic: Mild (month +8), Skin	Acute: Severe (month +3) Skin and intestinal	No	Chronic: Mild (month +4)	Acute (grade II) (day +12) skin and intestinal, + Chronic, moderated
Neutrophil engraftment, day	15	18	22	15	11	11
Platelet engraftment, day	31	9	25	16	11	21
Time to complete chimerism, PB (months)#	2	1	3	1	No data	No data
Time to complete chimerism, TL (months)#	18	1	3	No data	5.5	1
Time to complete chimerism, BM (months)#	12	6.5	6	No data	No data	No data
Immunosuppression at last follow up	No	No	No	No	No	No
Status at last follow up	Alive, CR	Alive, CR	Alive, CR	Alive, CR	Alive, CR	Alive, CR
Virological data						
Time from HIV diagnosis to HSCT (years)	1	27	2	16	8	11
Time from ART start to HSCT (years)	1	19	2	13	8	11
HIV tropism	R5	Dual R5/X4	Dual R5/X4	ND	ND	ND
Post-transplant HIV ART	ABC+3TC+RAL, maraviroc	TDF, FTC, RAL	TDF, FTC, RAL	TDF/FTC+DRV/r+RAL	1) FTC+TDF+EFV 2) ABC+3TC+EFV 3) ABC+3TC+Rilpivirine	1) FTC+TDF+RAL 2) ABC+3TC+RAL 3) ABC+3TC+DTV
Pre-HSCT pVL (HIV-1 RNA copies/ml)	65	<50	<50	<40	<1	<1
Pre-HSCT CD4 T cell count (10^9 cells/L)	0.720	0.800	0.151	0.155	0.747	0.891
CD4 count 3 months after HSCT (10^9 cells/L)	0.410	0.558	0.324	0.320	0.160	0.390
Maximum CD4 T cell count after HSCT (10^9 cells/L)	0.891	0.660	0.759	0.773	0.815	2.550
Detectable Plasma VL after HSCT	Yes (usVL)	No	No	No	No	No

Salgado et al, Annals of Internal Med., 2018

IciStem Patient	HSCT	Year of transplant	Single copy assay (HIV-RNA cp/ml)	Total DNA (cp/10^6 CD4)	qVOA in CD4 (IUPM)	Ileum, CSF, LN
1						
3						
6						
17						
27						
28						

IciS-28 sero-reversion



Salgado et al, Annals of Internal Med., 2018

Future directions: 12 patients > 2year SCT

IciStem Patient	HSCT	Year of transplant	Single copy assay (HIV-RNA cp/ml)	Total DNA (cp/10^6 CD4)	qVOA in CD4 (IUPM)	Ileum, CSF, LN
1	CCR5WT	2012	5	25	0.034	-
3	CCR5WT	2013	undetectable	undetectable	undetectable	undetectable
6	CCR5WT	2014	undetectable	undetectable	undetectable	undetectable
17	CCR5WT	2010	undetectable	undetectable	undetectable	undetectable
19	CCR5Δ32	2013	-	undetectable	undetectable	Trace/undetectable
27	CCR5WT	2009	undetectable	undetectable	undetectable	undetectable
28	CCR5WT	2013	undetectable	undetectable	undetectable	undetectable

Summary

After SCT, a sharp decline in HIV DNA in PBMCs is observed to below level of detection in most patients and ATI with intervention is planned

Patient IciS-05:
-No viral DNA in PBMCs, but detectable in all tissue biopsies
-Tissue viral sequences indicate no compartmentalisation or viral evolution

Patient IciS-11 (Two transplantations):
-No viral DNA in PBMCs (100% donor engraftment)
- Viral DNA in tissue around level of detection
- Lymph node CD4 cells HIV DNA is detectable (engraftment 38%)

After SCT, HIV-DNA populations persisted in tissues indicating that tissues may play an important role as long-standing viral reservoirs.

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