Cytoreductive Therapy for Autologous Cell Therapy in HIV

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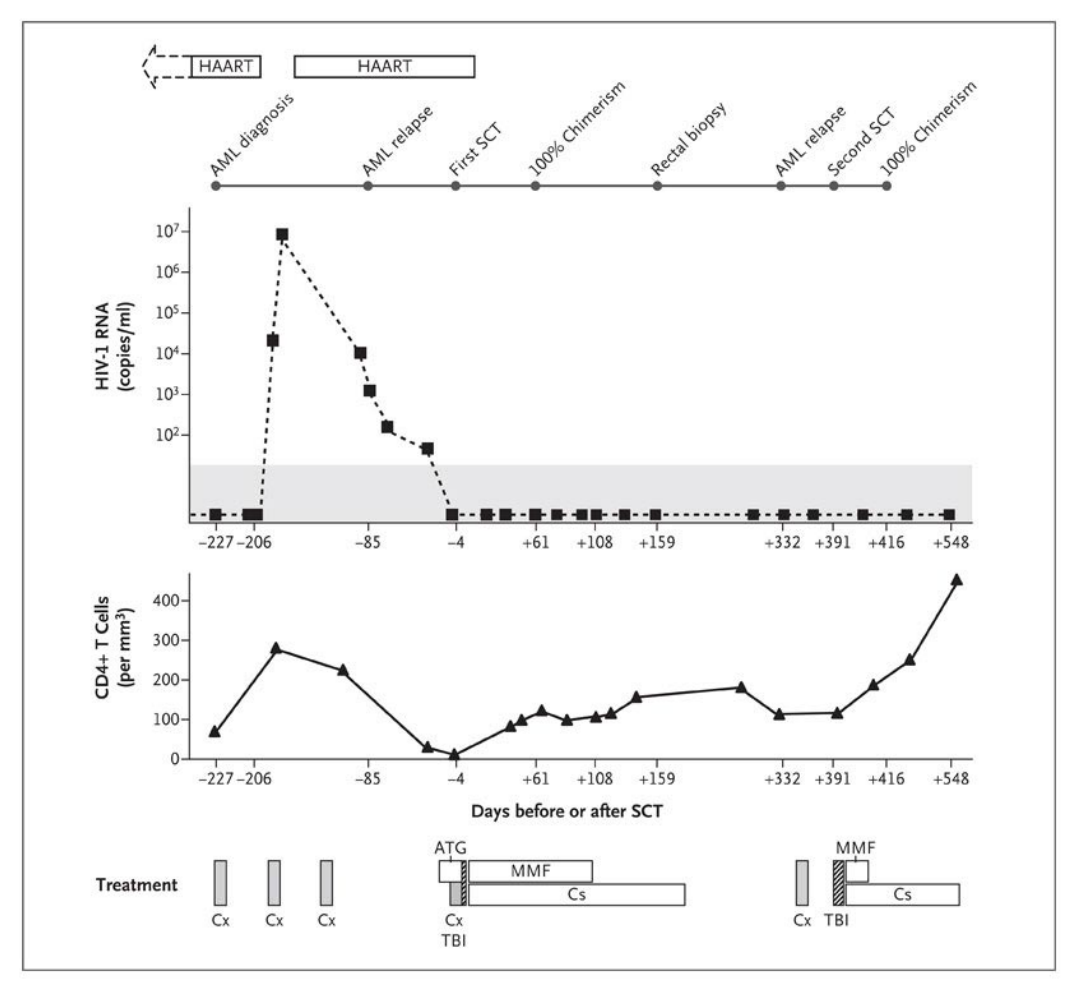
HSC Transfer from CCR5-delta 32 Donor Eliminates HIV in Recipient



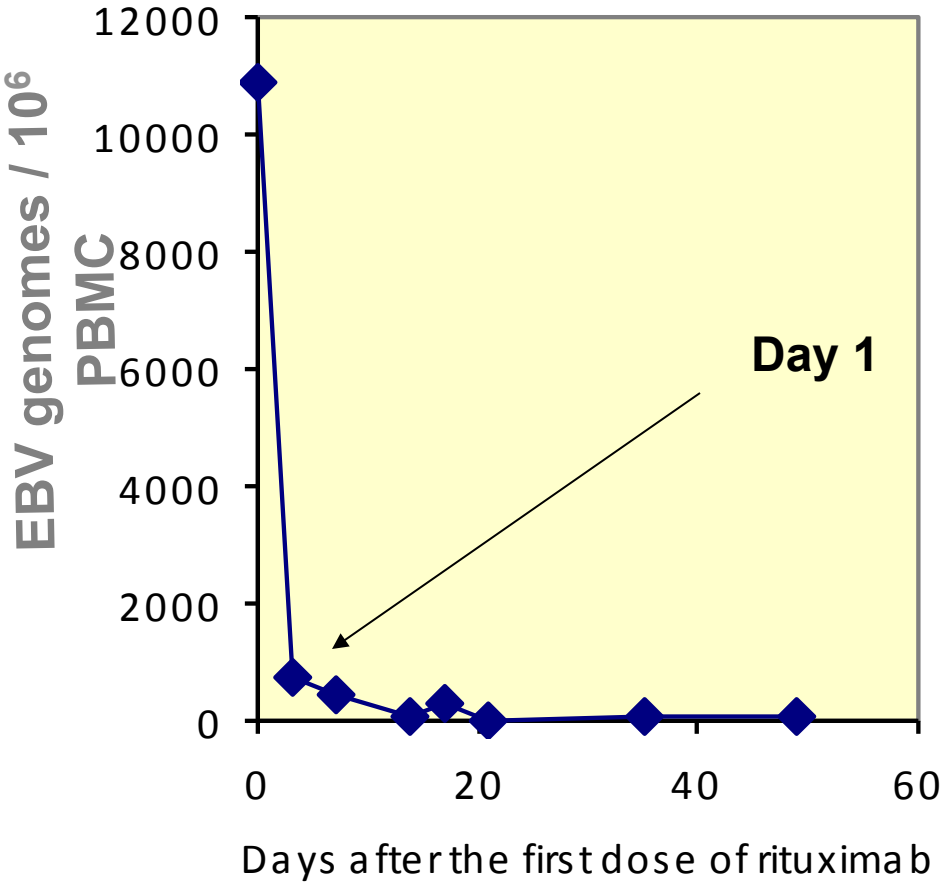
Hutter G, et al NEJM 2009,360:692-698.
Hutter G and Thiel. AIDS 2011,25:273-4.

Possible Reasons for Non-detectable HIV in the "Berlin Patient"

- Long term ART had reduced HIV burden to minimum
- Ablative chemotherapy removed infected cells in patient on long-term ARV suppression
- Transplanted cells protected from HIV infection due to CCR5 delta 32 mutation
- Allogeneic cells contributed to a GVH-like reaction further clearance of latently infected cells
- Generation of host protective immune effect
- Combination of above

What Effect Does Chemotherapy Have on HIV?

The effect of rituximab alone in post-transplant lymphoma on cell associated virus is very rapid



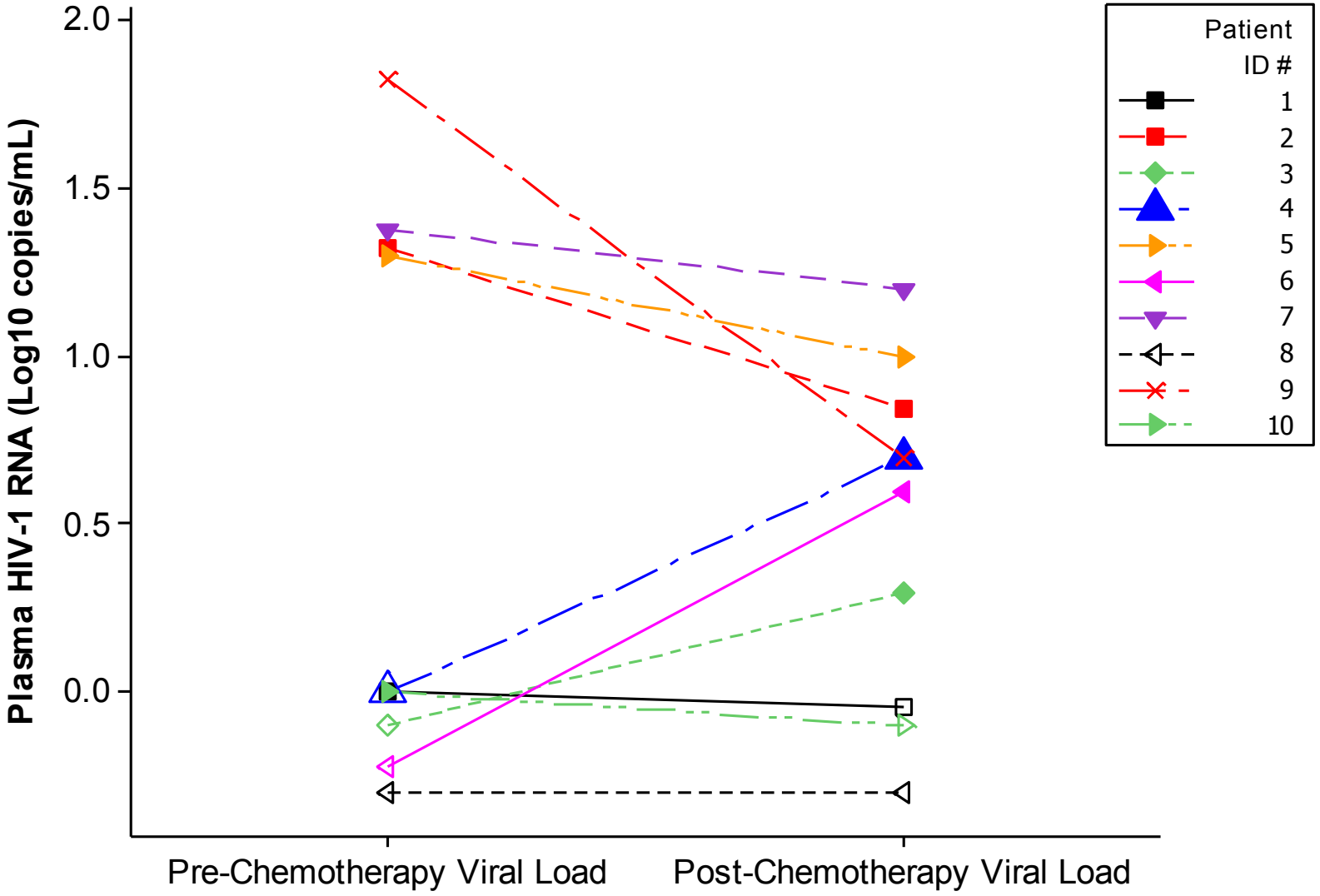
Yang J et al. Blood, 2000; 96:4055-4063

AIDS Lymphoma Treated Patients
ACTG ALLRT cohort

Patient ID Number	Gender	Race/Ethnicity	Age at Lymphoma Diagnosis	Lymphoma Diagnosis	Chemotherapy Administered
1	Male	White	69	NHL	R-CHOP
2	Male	Black	69	HL	ABVD
3	Male	White	45	NHL	CHOP
4	Male	White	46	NHL	R-CHOP
5	Male	Hispanic	61	HL	ABVD
6	Male	Black	35	NHL	ABVD
7	Male	White	54	NHL	CHOP
8	Male	Hispanic	35	HL	ABVD
9	Male	White	37	NHL	Rituximab
10	Male	Hispanic	48	NHL	CHOP

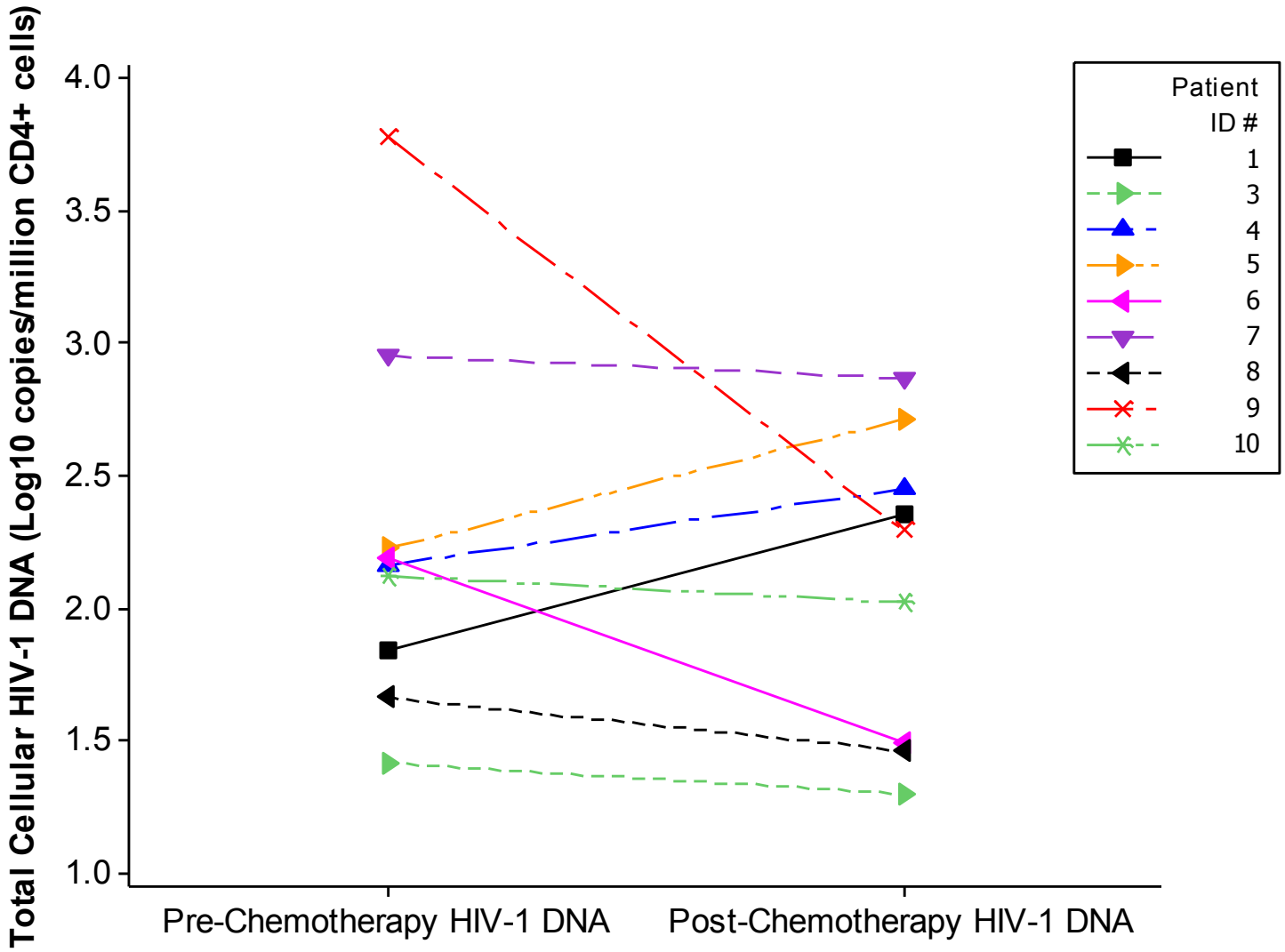
Cillo, A et al. CROI 2012, abs 353

Pre- and Post Chemotherapy Plasma HIV RNA



Cillo A et al, CROI 2012, abst 353.

Pre- and Post-chemotherapy Total Cellular HIV DNA



Cillo A et al, CROI 2012, abs 353

HIV RNA and DNA by HS assay post Autlogous SCT

Age	Days Post-ASCT	Lymphoma Diagnosis	ART Regimen	CD4+ Post-ASCT (cells/uL)	SCA HIV-1 RNA (cps/mL)	Total HIV-1 DNA (cps/10^6 PBMC)	2-LTR Circles (cps/10^6 PBMC)
48	+ 967	Burkitt	EFV/TNV/FTC	1015	2	52	<3
49	+ 1057	Non-Hodgkin	EFV/TNV/FTC	355	1	75	<1.5
39	+ 2194	Burkitt	FPV/r TNV/FTC	480	26	562	1
52	+ 155	Burkitt	DRV/r TNV/FTC	194	1	1070	<2.5
51	+ 210	Hodgkin	EFV/TNV/FTC	398	25	546	<1.5
55	+ 1288	Hodgkin	LPV/r TNV/FTC	422	2	640	<1.5
53	+ 4192	Non-Hodgkin	ABC/3TC/NVP	697	<0.2	2179	7
24	+ 100	Hodgkin	TNV/FTC/NVP	210	8	1318	<3.5
60	+180	Non-Hodgkin	EFV/TNV/FTC	808	1	<0.5	<0.5
50	+ 4077	Non-Hodgkin	ABC/AZT/3TC/ NVP	920	1	186	<1

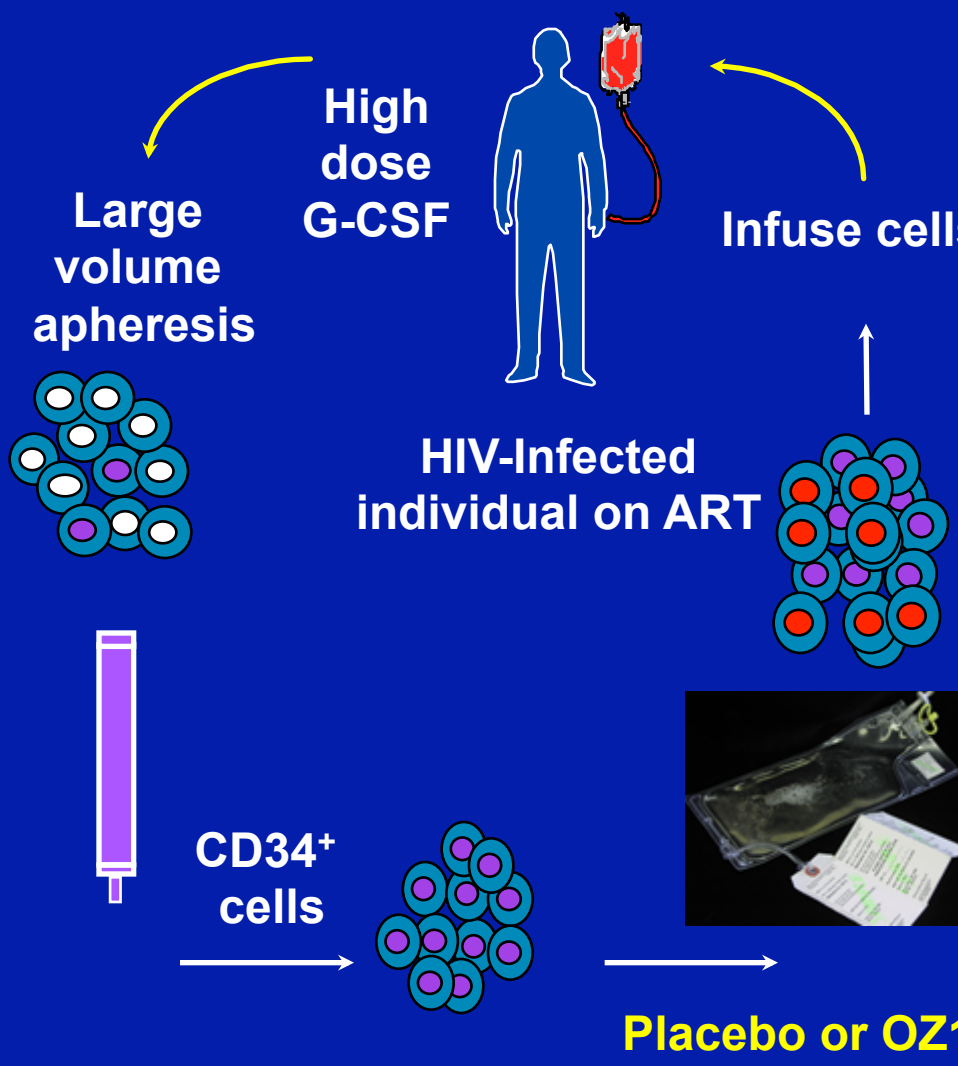
Cillo A et al. CROI 2012, Seattle, abs 154

Assessing effects of standard chemotherapy on HIV

- **NWCS 334 - Using single copy assay on stored specimens from ALLRT pt with HL or NHL undergoing chemotherapy**
- **AMC 075 – R-CHOP or R-EPOCH ± Vorinostat as first line therapy for AIDS-NHL**
- **AMC 079 - Prospective use of single copy HIV assay in pts on AMC 073-SWOG 0816: ABVD ± BEACOPP for HIV-HD**
- **AMC 071 and 080 (BMT CTN 0803 and 0903) – Effects of high dose chemotherapy with auto or allo SC transplant in HIV lymphoma/leukemia**

Gene Modified Stem Cells

Phase IIA Trial



Assessed for eligibility (n=107)

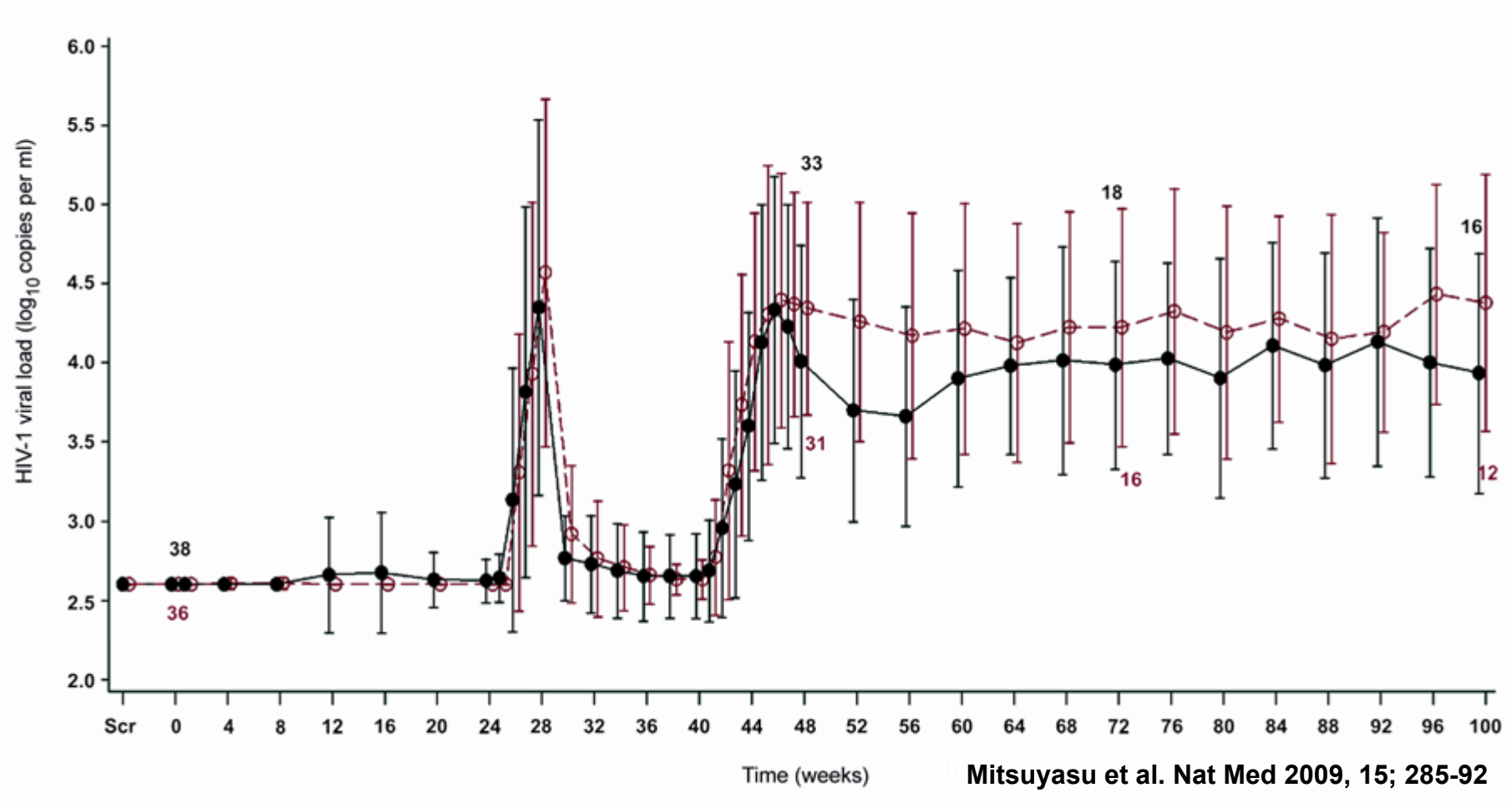
Randomised (n=76)
Infused = ITT (n=74

Data analysis at weeks 47/48 & 100

OZ1	Placebo
ITT n=38	ITT n=36
PP n=32	PP n=33

Mitsuyasu et al. Nat Med 2009, 15; 285-92

HIV-1 Viral Load ITT population



Mitsuyasu et al. Nat Med 2009, 15; 285-92

OZ1 Phase II: Conclusions

- Validation of the safety of cell/gene transfer approach for treatment of HIV
- Biologically active with multiple indicators of positive impact on viral load and CD4 count
- Demonstrates the feasibility of gene and cellular therapy for HIV
- Low level of persistence of gene modified cells suggests need for better engraftment and maintenance of these cells

Mitsuyasu et al. Nat Med 2009, 15; 285-92

Rationale for cytoreductive therapy in autologous cell therapy

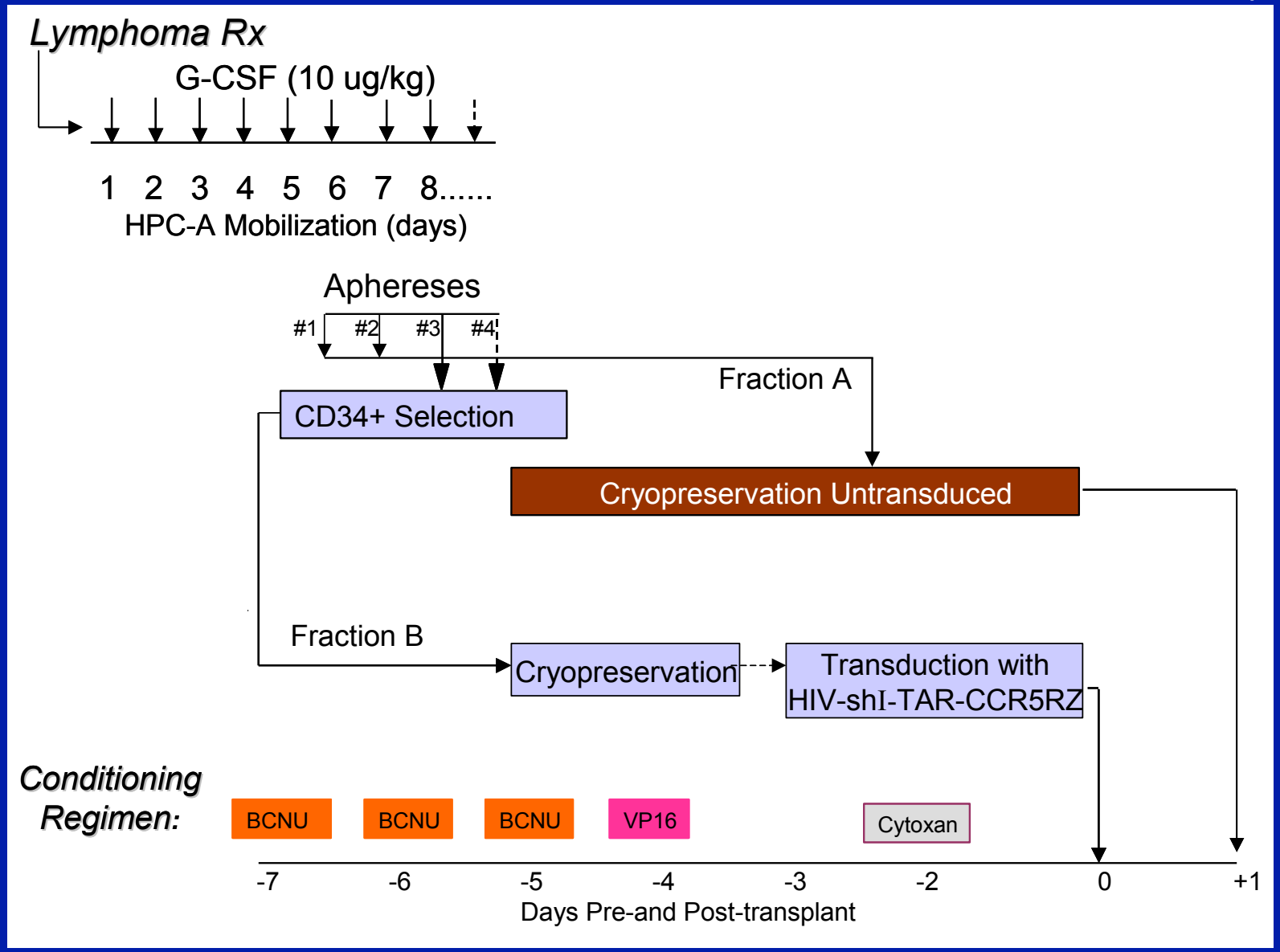
- To reduce number of unmarked cells to “make space” for new, gene-modified effector cells and improve engraftment of T cells or stem cells
- New cells will have a proliferative advantage in presence of selective pressure from HIV
- Low dose, non-ablative therapy used safely and effectively in other diseases to effect improved engraftment and induce beneficial biologic effect
- Fully ablative therapy considered standard of care for high grade lymphoma in relapse or second remission with autologous stem cell transplant

Examples of Effective and Safe Use of non-ablative Chemotherapy prior to T cell or stem cell gene therapy

- Pentostatin 4mg/m^2 + cyclosphosphamide 600mg/ m^2 given 4 days prior to Zn-finger modified anti-CD19 T cells for CLL (Porter DL et al, NEJM 2011, 365:725-33.)
- Busulfan 4mg/kg/d X2 or 5mg/kg/d X2 for CGD (Ott et al, Nat Med 2006, 12;401-9. Kang et al, Blood, 2010;783-91.)
- Busulfan 4mg/kg/d X2 for WAS (Boztug et al, NEJM 2010, 363; 1918-27.)
- Busulfan 3.2 mg/kg/d X4 for Thalassemia (Cavazanna- Calvo et al. Nature 2010, 467:318-22.)
- Busulfan 2 mg/kg/d X2 for SCID-ADA (Aiuti et al. Science 2002, 296;2410-3 and Auiti et al NEJM 2009, 360;447-58.)

Selected cohort: AIDS Lymphoma Gene Rx

Di Gusto et al. Sci Transl Med 2010 Jun 16;2(36):36ra43



Results in first 4 subjects

- Evidence of engraftment at 11 days in all 4 subjects
- Low level vector expression seen in subjects for 6-24 months and in some, gene (shRNA) and ribozyme expression at low levels
- No untoward side effects or complications attributed to stem cell manipulation and transplant
- All 4 patients remain in remission from lymphoma
- No changes were noted in HIV viral loads, but some increase in gene marking immediately after HIV viremia upon holding of ART, but did not persist
- Suggest approach is feasible and that no acute hematologic or other toxicities arise from transplantation of gene modified CD34 autologous stem cells after ablative chemotherapy

Di Gusto et al. Sci Transl Med 2010 Jun 16;2(36):36ra43

Questions to Address

- What degree of engraftment is required to see an active biologic effect?
- Is fully ablative therapy required for sufficient engraftment to show effective HIV control (functional cure)? What about for HIV eradication (sterilizing cure)?
- If less than complete ablation needed to effect HIV control, what level of chimerism and what degree of myeloablation is required?
- What are the trade offs between functional control of HIV and short and long term side effects of therapy?

Thank You

Questions and Comments