



Safety and viral load changes in HIV-1 infected subjects treated with autologous dendritic cell immune therapy following ART discontinuation (CTN #239)

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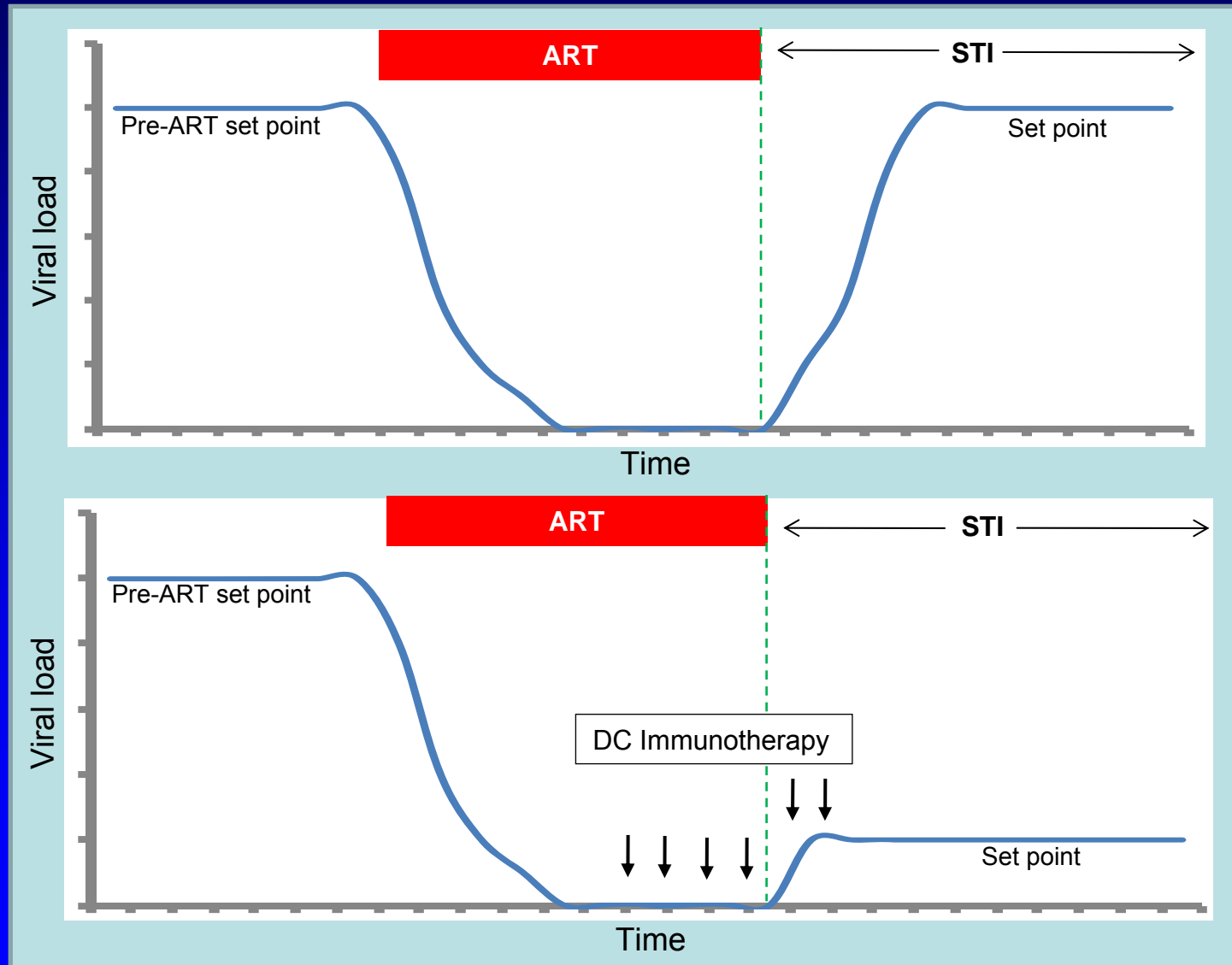
McGill University

Paris

21 octobre, 2009



Treatment strategy with DC therapy



Results of DC immunotherapy trials in HIV infection

Maturat.	HIV Ag	Route	patients	Imm.resp	Vir resp	Authors
None	Gp 160, Gag, pol	IV	6	3	0	Kundu 1999
IL-1, IL-6, TNF α	Auto HIV	SC	18	18	8 (80%)	Lu 2004
Monocyt. condition	Auto HIV	SC	12	0	0	Garcia 2005
TNF α	Gag, Env, Nef	SC	7	2	0	Ide 2006
IL-1, IL-6, TNF α	Gag, Env, Nef	IV, SC	18	18	No STI	Connolly 2008

Improving HIV DC immunotherapy

- Limited activity in DC immunotherapy may be explained by:
 - HIV diversity
 - Insufficient co-stimulation and immune potency
- To overcome these issues:
 - Use autologous vs. consensus antigens
 - CD40L mRNA transfection into DC to enhance CD8 response without CD4 help
 - DC administration while patients on ART
 - DC short-lived: Repeat dosing to maintain response

Results from Phase 1 DC immunotherapy trial (n=10)

- Manufactured at Argos Therapeutics
Durham, NC, USA
- DC transfected with amplified autologous HIV
Gag, Nef, Rev, Vpr RNAs (Vpr modified)
- Perfectly matched to each patient's unique
viral antigens
- Safe and well tolerated
- Induce CTL response without need for CD4
help

Phase 1 immunomonitoring results

Difference in Frequency of CD8 and CD4 T Cell Proliferation Pre and Post DC Treatment

CD8

Subjects	Week	GVRN				GAG				VPR				REV				NEF			
		0	4	8	12	0	4	8	12	0	4	8	12	0	4	8	12	0	4	8	12
Subjects	002	0.00	0.00	0.00	0.00	0.92	0.00	0.00	0.00	0.00	1.58	0.00	0.00	0.39	3.48	0.00	0.00	0.09	0.00	0.00	0.00
	003	11.75	20.18	21.16	10.32	11.86	25.16	17.88	13.87		24.92				9.30		2.64				
	004	6.43	8.15	9.11	6.15	3.52	1.04	0.00	1.37	0.85	0.22	0.00	0.58	0.00	0.00	0.00	0.00	3.38	11.40	0.00	2.36
	005	12.96	10.23	23.35	26.86	22.80	22.84	25.70	30.86	0.00	0.00	0.00	0.00	11.66	11.40	14.03	20.80	7.86	5.30	4.86	10.10
	007	0.00	0.11	0.00	0.00	1.42	0.92	1.09	0.80	0.31	0.31	0.18	0.23	0.12	0.32	0.08	0.05	0.10	0.16	0.34	0.27
	008	0.00	0.00	0.10	0.00					0.00	0.62	0.22	0.00								
	010	0.00	0.00	0.00	0.00		0.60	0.00	0.00		0.11	0.00	0.00		0.00	0.00	0.00		1.73	0.17	1.35
	011	2.31	2.87	2.37		0.74	1.66	1.24		3.97	1.91	3.63		0.64	1.06	1.00		0.33	0.23	0.00	
	013	1.01	1.56	2.06	1.33	0.46	0.00	0.13	0.08	0.69		0.00	0.00	0.95		0.00	0.00	5.84	3.98	14.43	4.07

CD4

Subjects	Week	GVRN				GAG				VPR				REV				NEF			
		0	4	8	12	0	4	8	12	0	4	8	12	0	4	8	12	0	4	8	12
Subjects	002	0.00	0.00	0.87	0.00	0.00	0.00	0.00	0.00	0.00	0.61	0.00	0.00	0.00	2.38	0.00	0.00	0.00	0.00	0.00	0.00
	003	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		0.00			8.59			3.16				
	004	0.00	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0.00
	005	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	007	0.00	0.00	0.00	0.00	0.53	0.00	0.00	0.00	1.26	0.00	0.00	0.00	0.74	0.32	0.00	0.26	0.26	0.00	2.17	4.27
	008	0.00	0.00	0.00	0.00					0.00	0.00	0.00	0.00								
	010	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.63	0.00	0.00
	011	0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00	
	013	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Study objectives

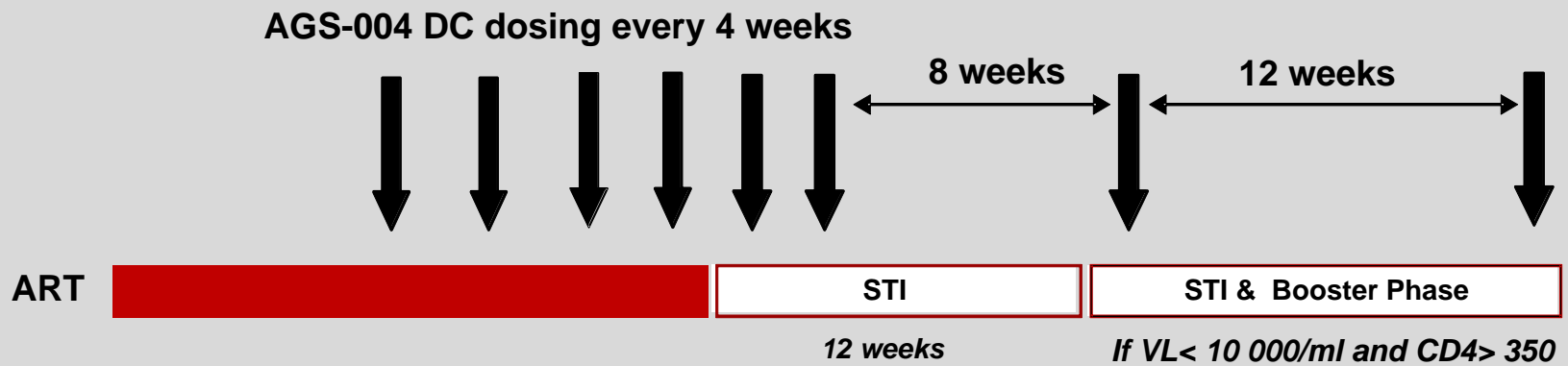
- Safety and tolerability
- Mean time to VL rebound and peak after STI
- Mean time to best VL response after STI
- Change in VL after a 12-week STI:
 - Proportion of subjects with CD4 > 350 and:
 - VL < 1 000 at 3 time points
 - VL < 10 000 at 3 time points
 - Change in VL compared to pre-ART

Eligibility criteria

- At screening visit:
 - First ART regimen for > 12 weeks
 - VL < 50 copies/ml for 12 weeks
 - Pre-ART plasma:
 - Availability of 1.2 ml
 - VL > 15 000 copies/ml
 - CD4 > 450 cell/ μ l
 - CD4 nadir > 200 cell/ μ l
 - No co-infection or autoimmunity

Study Design HIV DC immunotherapy Phase 2a

- N=24
- 10 clinical centers



Patient characteristics (n=24)

	Total (N = 24)
N	24
Mean Age	40.5
Male	24 (100%)
White	23 (95.8%)
First nation Canadian	1 (4.2%)

Treatment emergent AEs

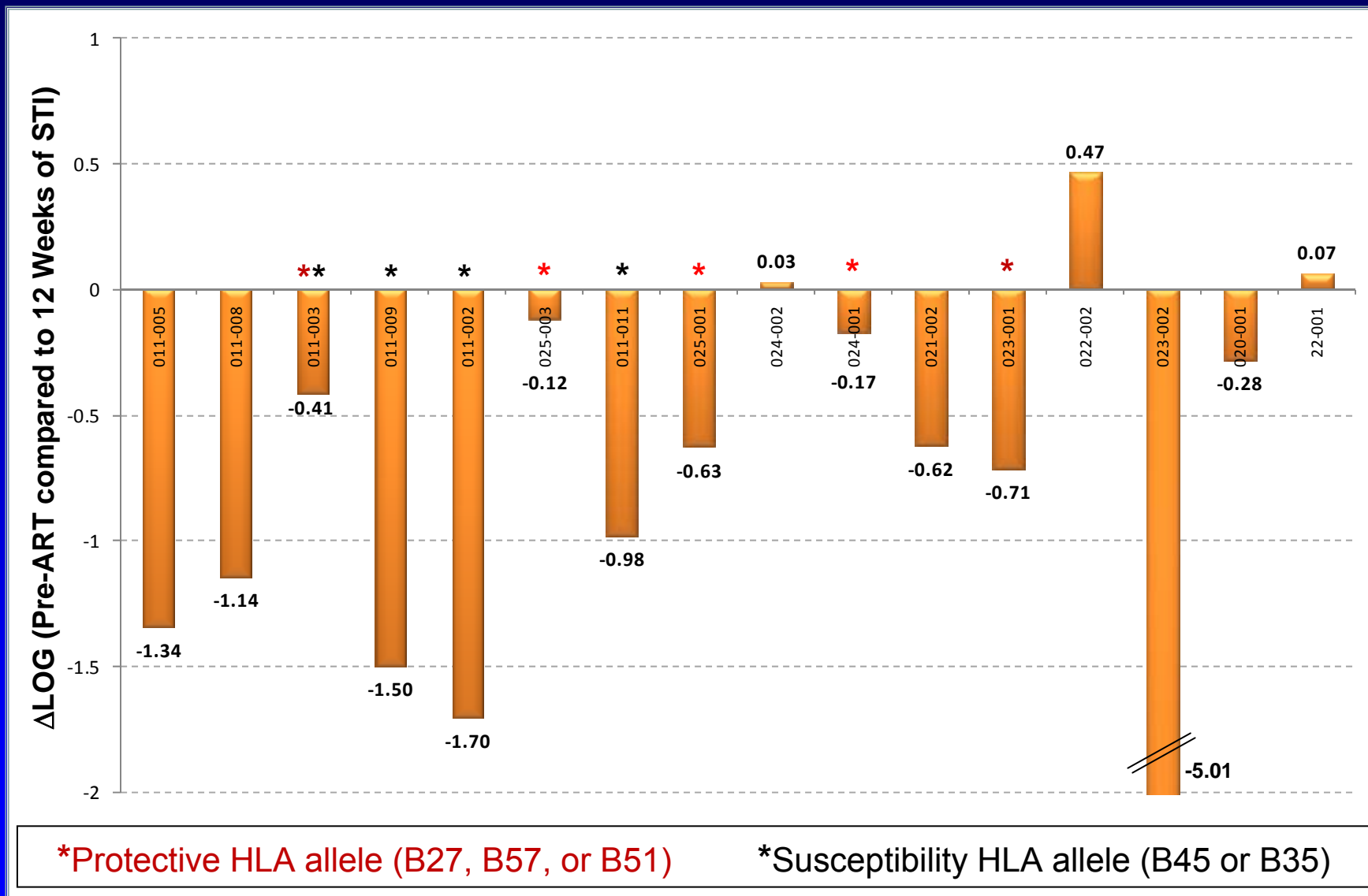
Treatment Emergent Adverse Event	Total (N = 24)
Subjects with Treatment Emergent AE grade ≥ 3	0
Subjects with Treatment Emergent AE grade < 3	24
Gastrointestinal symptoms	14
Diarrhea	7
Other	7
Constitutional and administrative site symptoms	23
Fatigue	9
Influenza like illness	7
Injection site erythema	18
Injection site induration	15
Injection site pain	7
Clinical laboratory changes	1
Rheumatoid factor > 20	1
Neurological symptoms	9
Headache	4
Other	5
No HIV-related events observed	

Viral load dynamics at 12 weeks post STI (n=16)

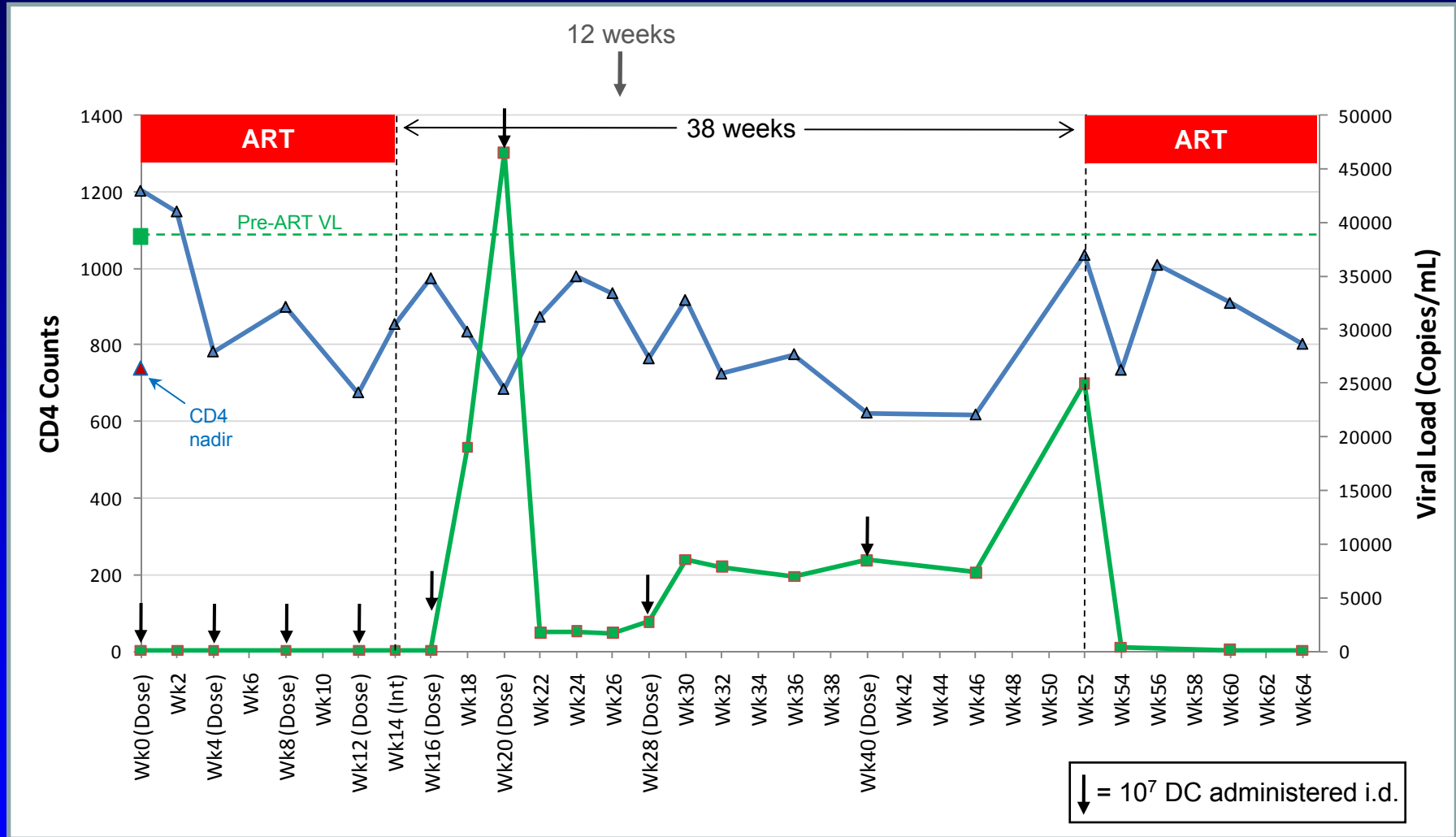
Mean time to:	Weeks	VL and CD4 Changes	
Viral rebound (>50)	4.5	Mean Change of VL from pre-ART (N=13 responders)	-1.13Log (-80%)
Peak VL	7.9	Mean CD4 at screening	663 (366-1203)
Best VL response (13/16 with reduced VL)	10.1*	Mean CD4 at STI start	644 (383-995)
		CD4 at 12 weeks of STI	521 (243-935)

*4 weeks after last dose; Consistent with requirement for continued monthly dosing in the presence of viremia

Changes in VL after 12 weeks of STI

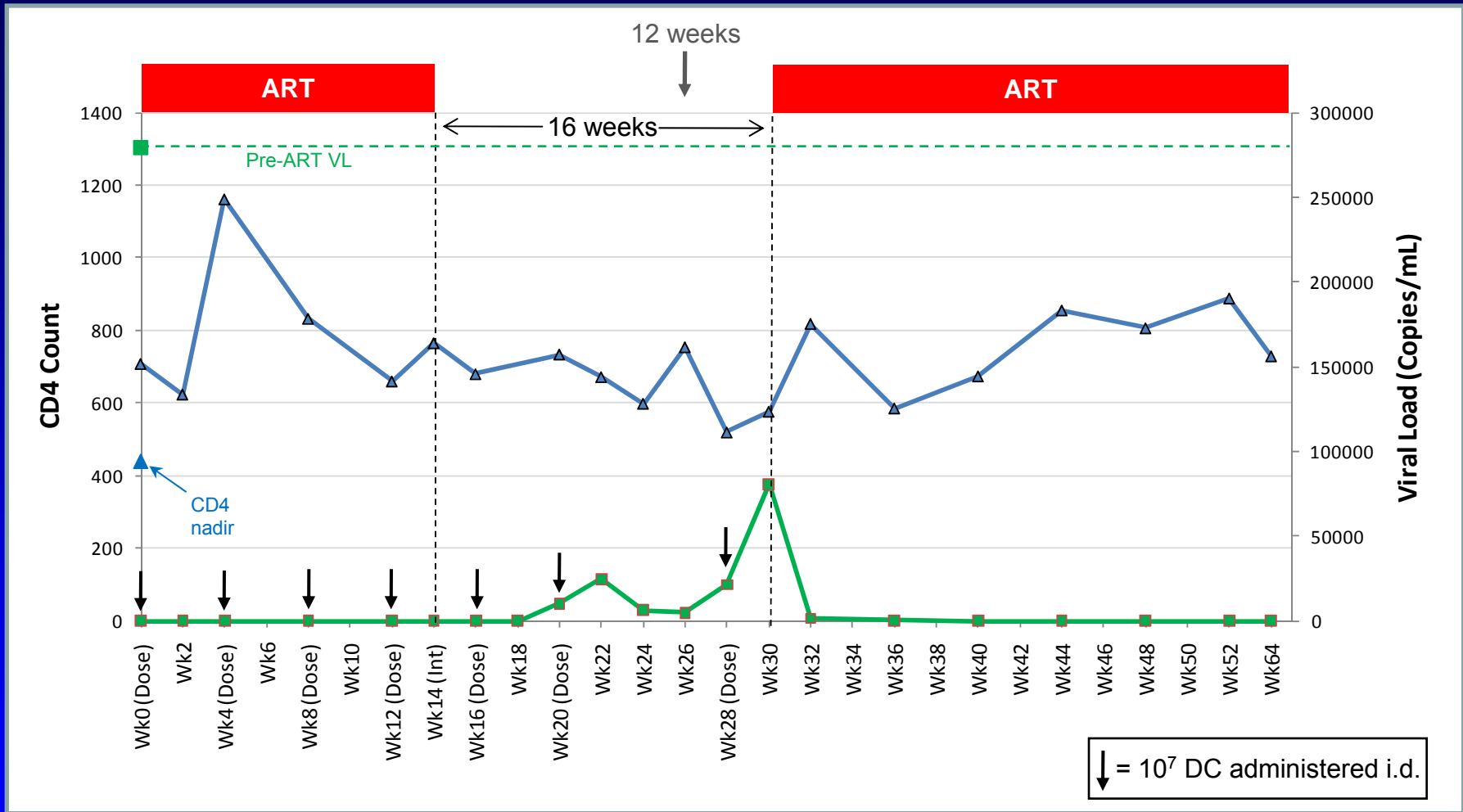


Patient 11-005: boosting strategy



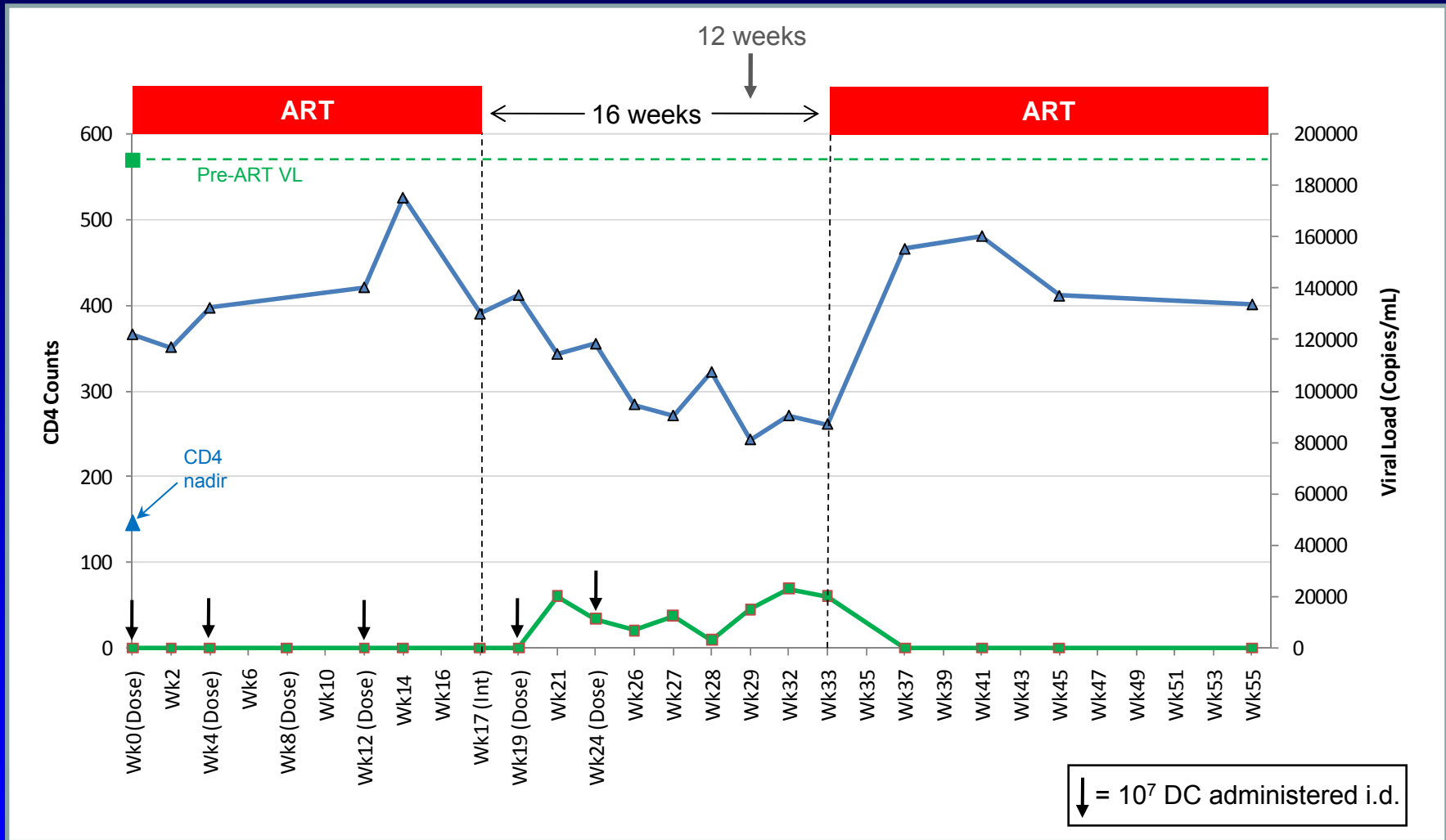
Patient ID	HLA-A	HLA-B	HLA-Bw	HLA-Cw	DQB1	DRB1
AGS-004-001-011-005	0101	0801	6, 6	0701	0201, 0302	0301, 0404

Patient 11-002: VL rebound



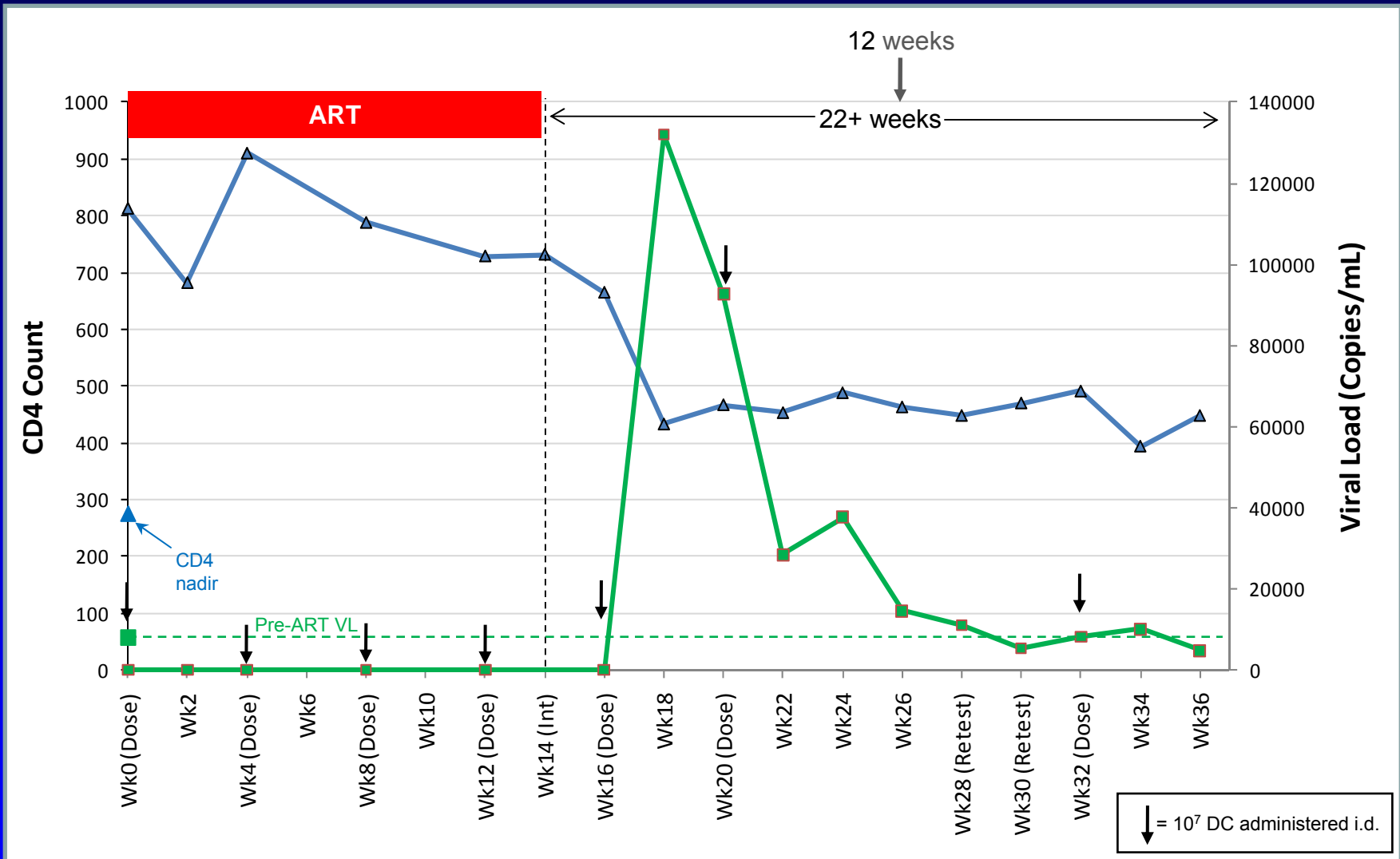
Patient ID	HLA-A	HLA-B	HLA-Bw	HLA-Cw	DQB1	DRB1
AGS-004-001-011-002	O10101, 1101	O801,350101	6,6	O4010701	O503,0603	1301,14BCAD

Patient 11-008: CD4 T cells decrease



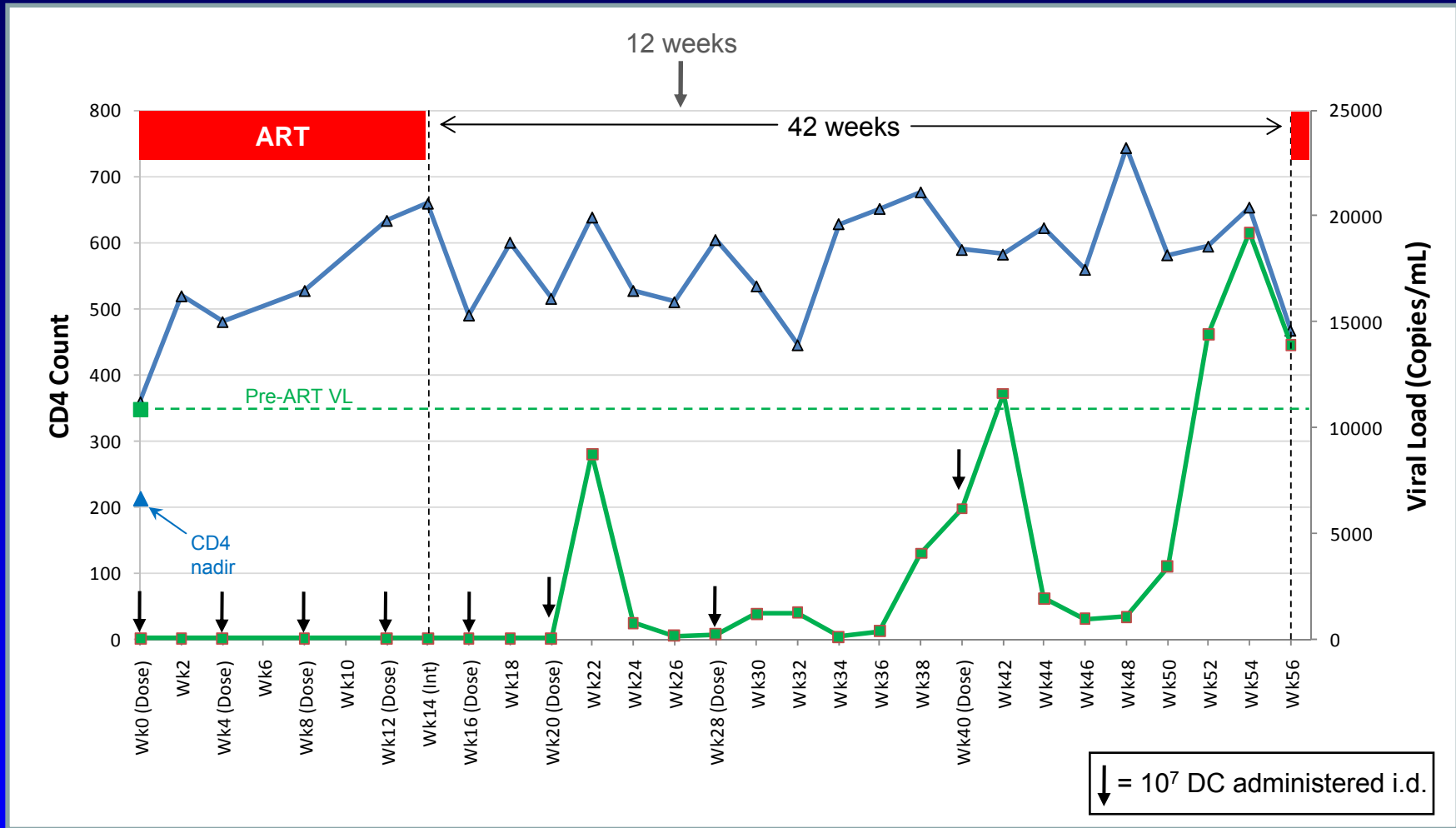
Patient ID	HLA-A	HLA-B	HLA-Bw	HLA-Cw	DQB1	DRB1
AGS-004-001-011-008	0101, 0201	080101, 580101	4, 6	0302, 0701	0201	0301

Patient 22-002:



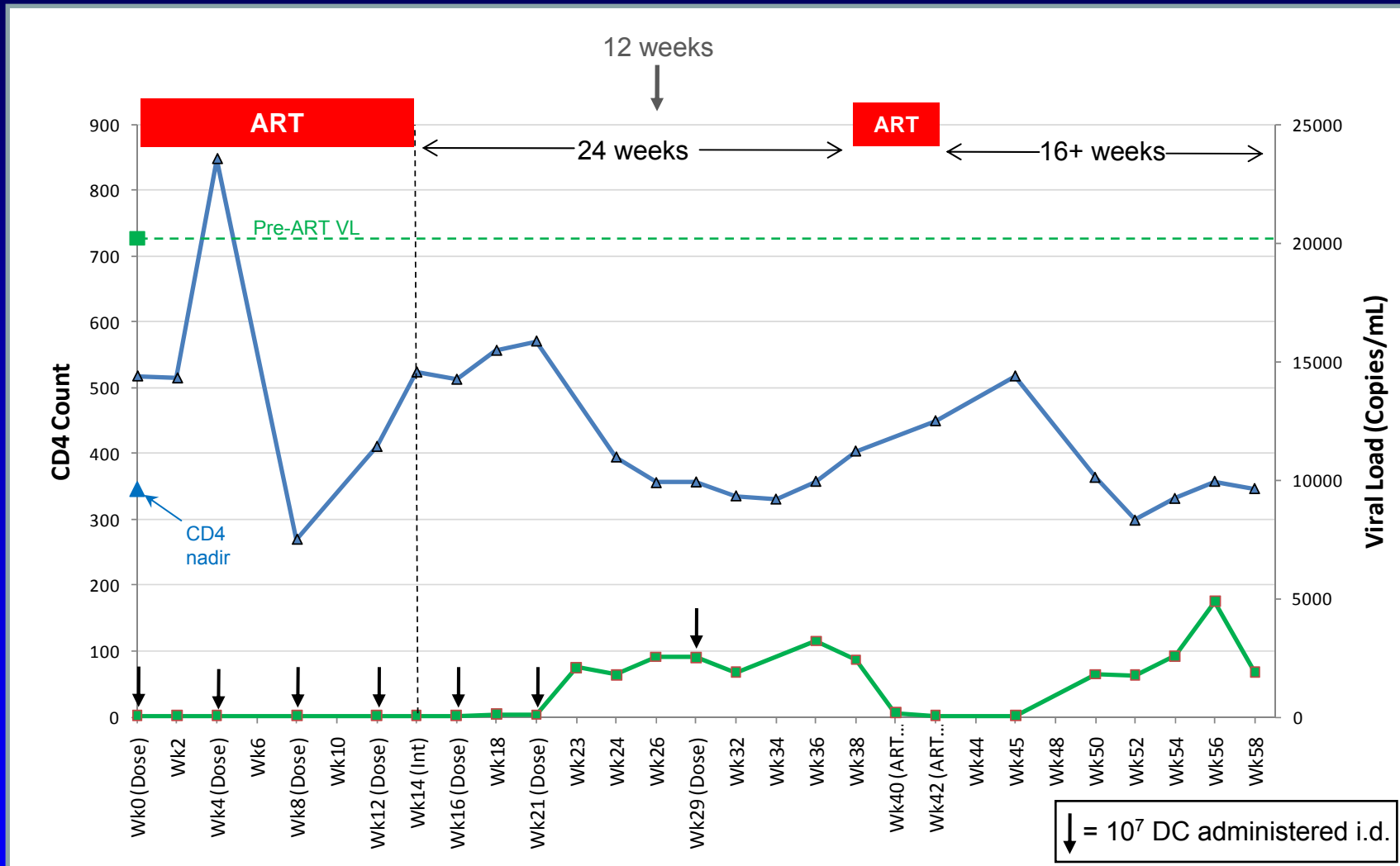
Patient ID	HLA-A	HLA-B	HLA-Bw	HLA-Cw	DQB1	DRB1
AGS-004-001-22-002	0601, 3001	080101, 4001	6,6	0304, 0702	0302	0401, 0404

Patient 11-009:



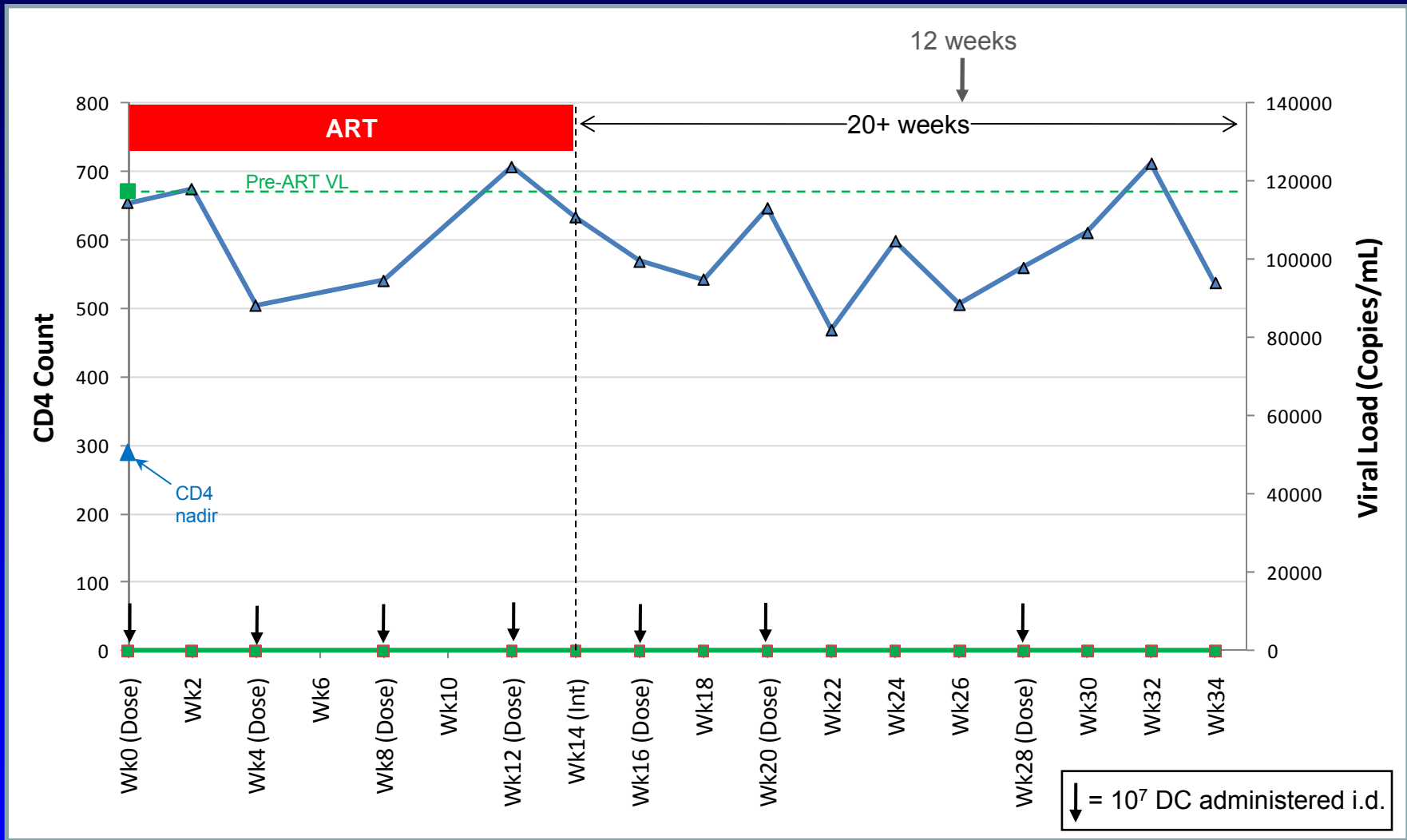
Patient ID	HLA-A	HLA-B	HLA-Bw	HLA-Cw	DQB1	DRB1
AGS-004-001-011-009	2601, 330301	4501, 580101	4, 6	0302, 060201	0202, 0301	0701, 1101

Patient 11-011:



Patient ID	HLA-A	HLA-B	HLA-Bw	HLA-Cw	DQB1	DRB1
AGS-004-001-011-011	0101, 0201	0801, 3503	6, 6	0401, 0701	0201, 0301	0301, 1104

Patient 23-002:



Patient ID	HLA-A	HLA-B	HLA-Bw	HLA-Cw	DQB1	DRB1
AGS-004-001-023-002	0301, 3002	108101, 4403	4, 6	0501, 1601	0201, 0202	0301, 0701

Conclusions

- DC immunotherapy is safe and well tolerated during both ART and STI
- Demonstrated feasibility in multicenter setting
- During 12-week STI:
 - 5/16 subjects had VL < 1 000 at 3 time points
 - 9/16 subjects had VL <10 000 at 3 time points
- Need to optimize DC dosing frequency
- Based on these interim data we are planning a phase 2b randomized placebo-controlled multicenter clinical trial

Acknowledgements

- Université de Montréal
 - Yassine-Diab B
 - Yegorov O
 - Sekaly RP
- McGill University
 - Boulassel MR
 - Clinical investigators:
 - Jacobson J
 - Angel J
 - Baril JG
 - Gill J
 - Loutfy M
 - Raclis A
 - Smail F
 - Tremblay C
 - Vezina S
 - Walmsley S
- National Immune Monitoring Laboratory (NIML), Montréal:
 - Landry C
 - Coutsinos Z
 - Gagnon D
 - Caroline Benoît-Hébert
- Argos Therapeutics, Durham, NC
 - Healey D
 - Tcherepanova I
 - Chew T
 - Jain R
 - Nicolette C



**This study has been funded by NIAID, NIH, (No NO1-A1-60019),
CANVAC-001C and CTN-CIHR #239 and Argos Therapeutics**