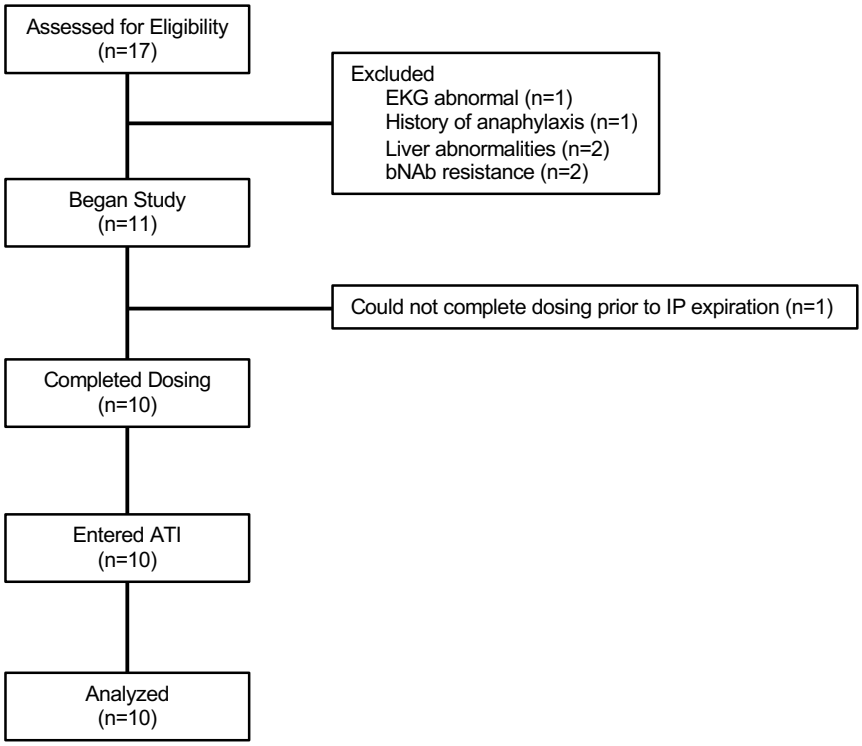
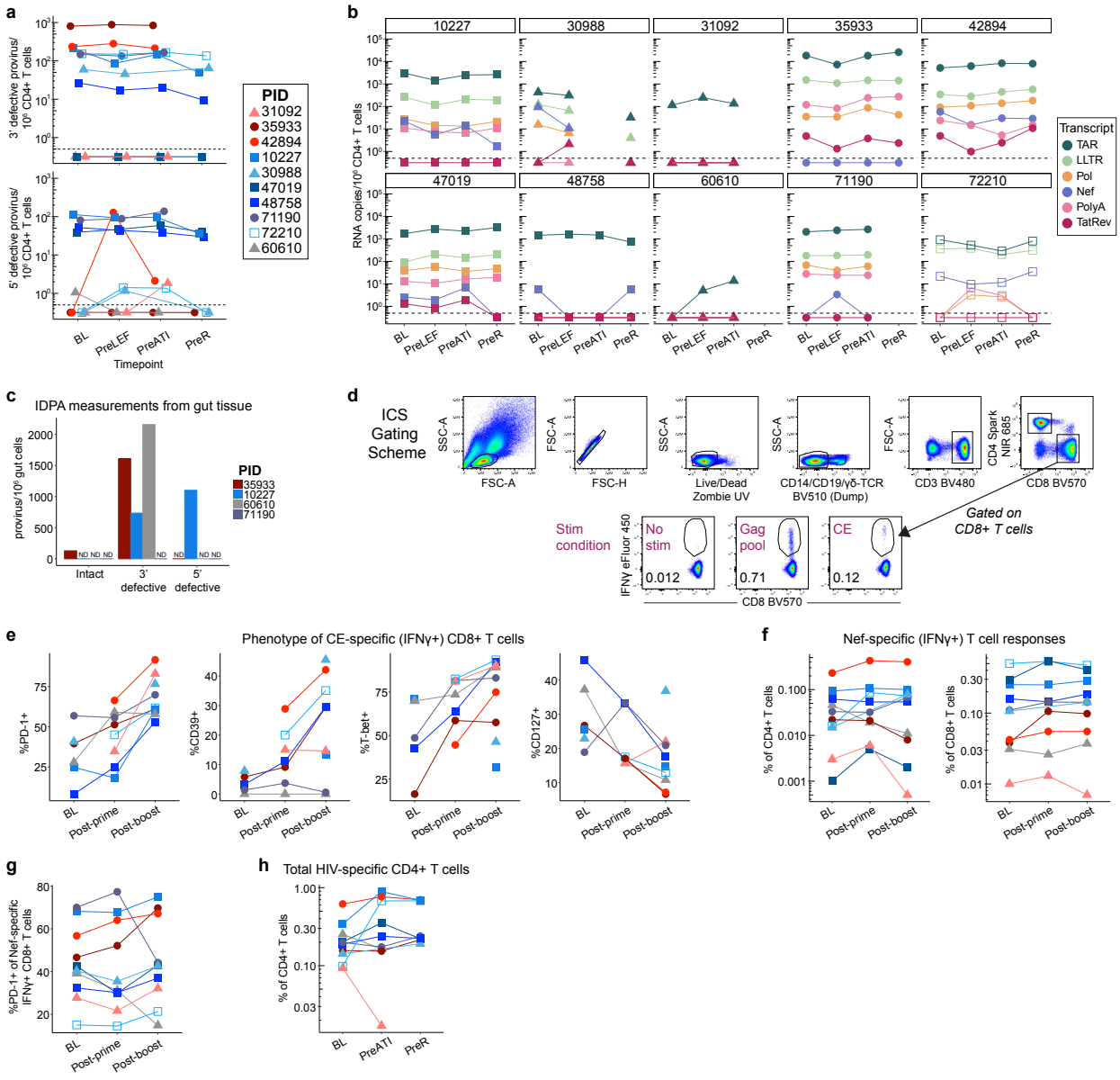


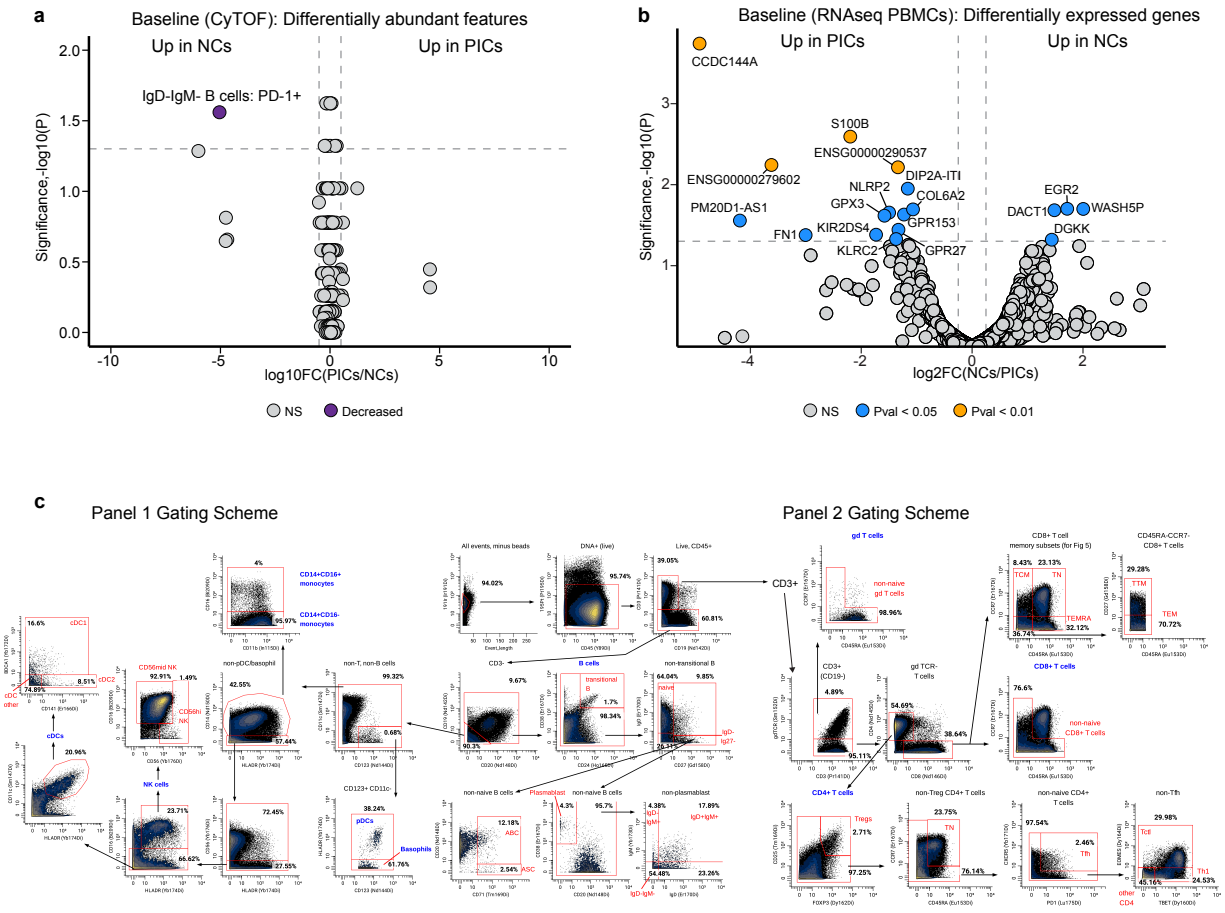
Extended Data Fig. 1. CONSORT diagram.



Extended Data Fig. 2. Longitudinal HIV reservoir measurements and HIV-specific T cell responses.

a) Cell-associated 3' and 5' defective HIV DNA in peripheral blood CD4+ T cells by IPDA.
b) Longitudinal cell-associated HIV RNA transcript measurements.
c) IPDA measurements from gut tissue in select participants (ND, not detected). All sampled post-ATI. All aviremic at the time of sampling. On ART: 35933, 10227, 71190. Off ART: 60610.
d) Intracellular cytokine staining (ICS) gating scheme.
e) Longitudinal phenotypes of HIV Gag/CE-specific (IFNγ+) CD8+ T cells. Missing points reflect timepoints with no or too few (<50) CE-specific CD8+ T cells to phenotype.
f) Frequency of Nef-specific (IFNγ+) CD4+ and CD8+ T cells.
g) PD-1 expression on Nef-specific CD8+ T cells.
h) Frequency of total (IFNγ+) HIV-specific CD4+ T cells by ICS (sum: Gag+Pol+Nef+Env).

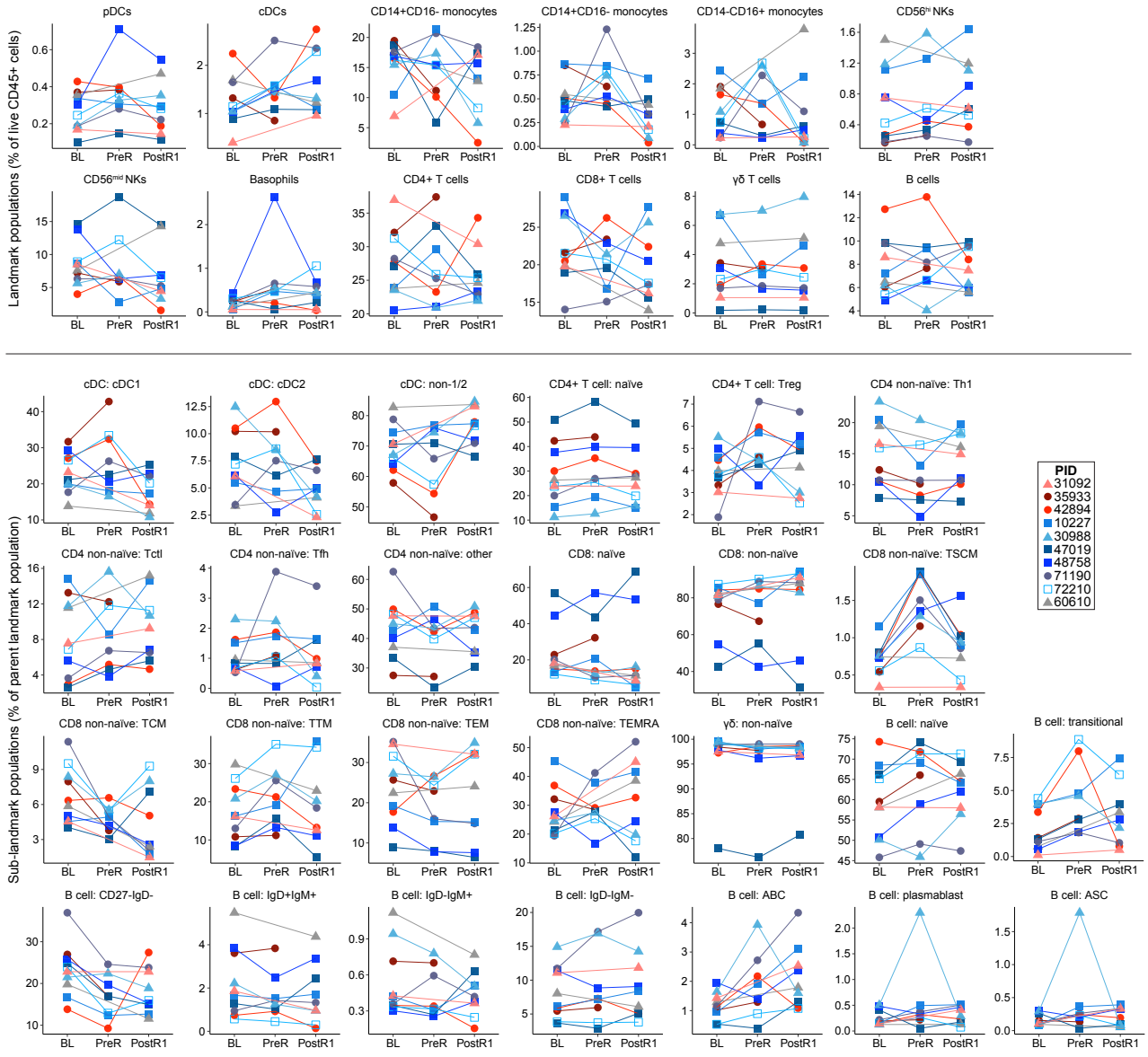
IPDA, intact proviral DNA assay. Timepoints: BL, baseline prior to interventions (i.e., on ART); Post-prime, day of MVA vaccination (>6 weeks after last DNA vaccination); Post-boost, 2 weeks after MVA vaccination; PreLEF, prior to lefitolimod dosing; PreATI, prior to ATI; PreR, last PBMC sampling timepoint available prior to rebound (sampled within 1-4 weeks prior to HIV rebound); PostR1, first PBMC sampling timepoint after rebound (for participants with sample available ≤28 days after rebound, at a low viral load [all <2,600 copies/mL]). IFNγ, interferon gamma. ICS, intracellular cytokine staining.



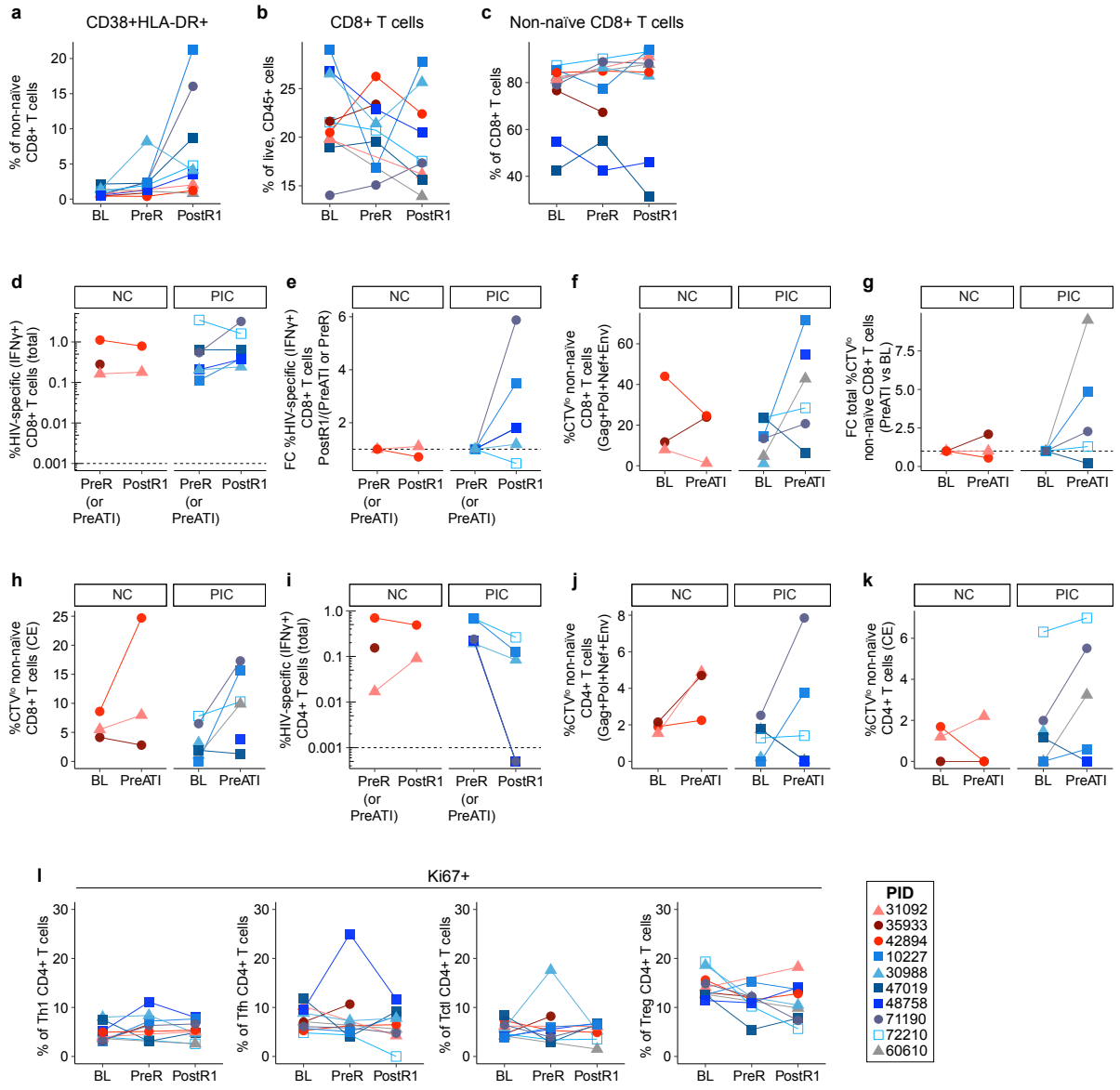
Extended Data Fig. 3. Minimal differences in baseline immune features between post-intervention controllers and non-controllers.

a) Differentially abundant CyTOF features in the peripheral blood, and
b) Differentially expressed genes in total peripheral blood mononuclear cells (PBMCs) between the viremic post-intervention controllers (n=6) and non-controllers (n=3) at baseline (on ART, prior to interventions).
c) CyTOF landmark and sub-landmark gating scheme. Populations labeled in blue represent landmark populations and populations labeled in red represent sub-landmark populations.

CyTOF, cytometry time of flight. PICs, post-intervention controllers. NCs, non-controllers.

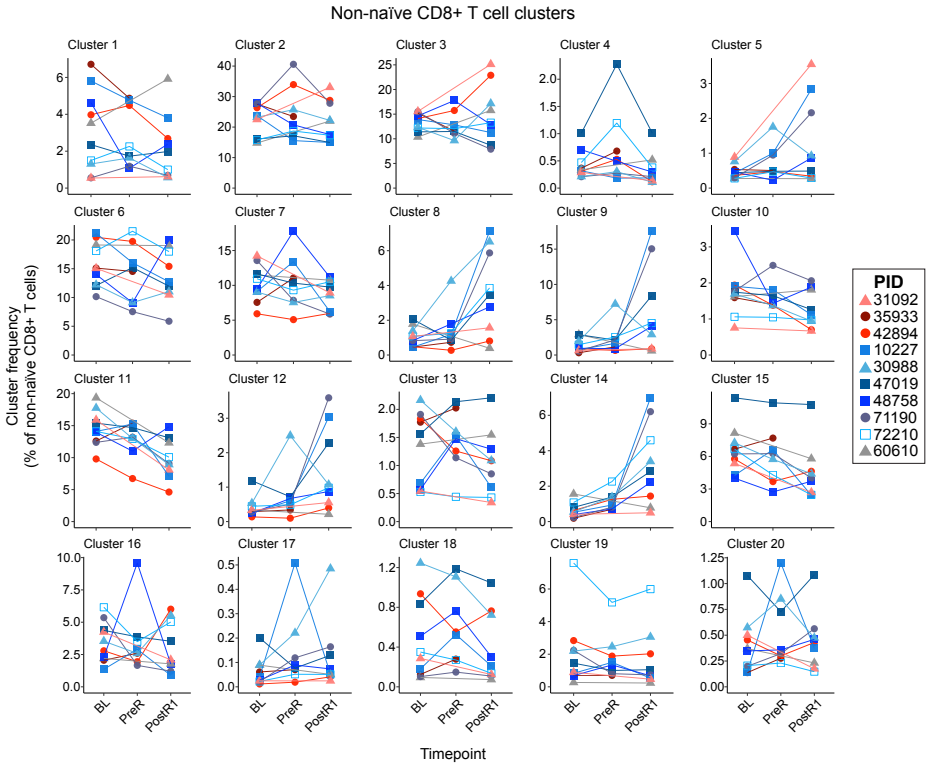


Extended Data Fig. 4. CyTOF landmark and sub-landmark populations.
Frequency of major peripheral blood landmark immune cell populations over time (as a % of total live CD45+ cells) and sub-landmark populations over time (as a % of parent landmark populations).



Extended Data Fig. 5. Additional T cell characterization.

Longitudinal frequency at baseline (BL), before rebound, (PreR) and/or after (PostR1) rebound of: a) Activated (CD38+HLA-DR+) non-naïve CD8+ T cells, b) total CD8+ T cells, c) non-naïve CD8+ T cells, d) total HIV-specific CD8+ T cells (as measured by IFNγ expression after 6-hour *in vitro* stimulation with HIV Gag, Pol, Nef, and Env peptide pools [responses summed]). e) Fold change (FC) between PreR and PostR1 in HIV-specific CD8+ T cell magnitude. f) Total HIV-specific CD8+ T cell proliferative response (as measured by the dilution of the dye, cell trace violet [CTV], after 6-day *in vitro* stimulation with HIV peptide pools). g) FC between BL and PreATI in CD8+ T cell proliferation in response to Gag+Pol+Nef+Env peptide pool stimulation. h) CE-specific CD8+ T cell proliferative response. Magnitude (i) or proliferative response (j-k) of HIV-specific CD4+ T cell responses to Gag+Pol+Nef+Env peptide pools (i-j) or CE peptide pool (k). l) Frequency of Ki67+ cells within different CD4+ T cell subsets.



Extended Data Fig. 6. Longitudinal non-naïve CD8+ T cell cluster abundances by CyTOF.

Variable	Overall N = 10[1]	---- ART start ---- Acute/Early N = 7[1]	Late N = 3[1]
Age at enrollment, years	36 (32, 55)	34 (32, 55)	36 (36, 51)
Gender			
Cisgender man	9 (90%)	7 (100%)	2 (67%)
Transgender woman	1 (10%)	0 (0%)	1 (33%)
Ethnicity			
Hispanic/Latino	4 (40%)	3 (43%)	1 (33%)
Mixed Ethnicity/Multiracial	1 (10%)	1 (14%)	0 (0%)
White/European American	5 (50%)	3 (43%)	2 (67%)
CD4+ T cell nadir	459 (357, 823)	476 (367, 823)	366 (357, 550)
Duration of HIV infection, years	6.7 (1.5, 18.2)	6.5 (1.5, 16.6)	12.4 (5.9, 18.2)
Time on ART, months	79.3 (18.5, 195.0)	75.2 (18.5, 195.0)	103.0 (65.9, 138.0)
CD4+ T cell count at enrollment	736 (392, 1,225)	639 (392, 1,225)	742 (729, 815)
Viral load at enrollment			
<40 copies/mL	10 (100%)	7 (100%)	3 (100%)
Maximum viral load prior to enrollment (copies/mL)[2]	22,508 (821, 1,597,179)	16,400 (821, 1,597,179)	61,549 (15,340, 100,000)

[1]Median (Range); n (%); all p-values > 0.2 (continuous variables: Wilcoxon Rank Sum test; categorical variables: Fisher's exact test).

[2]Some participants began antiretroviral therapy during the acute phase of infection prior to peak viremia

Extended Data Table 1. Participant characteristics.

Adverse Event (AE)	Severity Grade: Mild (no. AEs)	Moderate (no. AEs)	Severe (no. AEs)	Very severe (no. AEs)	Participants (n = 10)	%
Related to p24CE/IL-12, p24CE&p55/IL-12 or MVA[1]						
Injection site pain	80	8	0	0	10	100
Malaise	10	6	0	0	8	80
Chills	3	3	0	0	6	60
Myalgia	4	2	0	0	6	60
Headache	7	3	0	0	5	50
Nausea	4	0	0	0	2	20
Diarrhea	1	0	0	0	1	10
Elevated ALT	1	0	0	0	1	10
Fatigue	1	0	0	0	1	10
Fever	1	0	0	0	1	10
Leg cramps	1	0	0	0	1	10
Arthralgia	0	1	0	0	1	10
Night sweats	0	1	0	0	1	10
Vertigo	0	1	0	0	1	10
Total	113	25	0	0		

[1] Definitely, probably or possibly related

Extended Data Table 2. Adverse events determined to be definitely, probably, or possibly related to any of the components of the vaccine regimen.

	Severity Grade					
Adverse Event (AE)	**Mild** (no. AEs)	**Moderate** (no. AEs)	**Severe** (no. AEs)	**Very severe** (no. AEs)	**Participants** (n = 10)	**%**
Related to Lefitolimod, VRC07-523LS or 10-1074[1]						
Injection site pain	64	26	0	0	8	80
Malaise	9	8	0	0	4	40
Nausea	8	0	0	0	4	40
Myalgia	4	4	0	0	4	40
Elevated ALT	2	0	1	1	4	40
Headache	9	4	0	0	3	30
Elevated AST	1	1	1	0	3	30
Arthralgia	3	0	0	0	2	20
Fatigue	2	0	0	0	2	20
Night sweats	1	1	0	0	2	20
Vertigo	4	1	0	0	1	10
Chills	1	0	0	0	1	10
Diarrhea	1	0	0	0	1	10
Distorted vision	0	1	0	0	1	10
Hypothyroidism	0	1	0	0	1	10
Total	109	47	2	1		

[1] Definitely, probably or possibly related

Extended Data Table 3. Adverse events determined to be definitely, probably, or possibly related to lefitolimod, 10-1074, or VRC07-523LS.
All adverse events resolved within 2 months. The episode of distorted vision occurred several weeks after the first administration of the two bNAbs; it was assessed by an ophthalmologist and determined to be consistent with a previously recorded history of ocular migraines; there were no new ophthalmic abnormalities on exam. The episode of mild hypothyroidism was diagnosed during the study and associated with anti-thyroid peroxidase antibodies; this resolved with appropriate thyroid replacement therapy.

Adverse Event (AE)	Severity Grade: Mild (no. AEs)	Moderate (no. AEs)	Severe (no. AEs)	Very severe (no. AEs)	Participants (n = 10)	%
Not related to p24CE/IL-12, p24CE&p55/IL-12, MVA, Lefitolimod, VRC07-523LS or 10-1074[1]						
Cardiopulmonary						
Cough	3	2	0	0	4	40
Vasovagal syncope	0	2	0	0	1	10
Dermatologic						
Rash	3	0	0	0	1	10
Dry skin	1	0	0	0	1	10
Itching	1	1	0	0	1	10
Skin lesion on left knee	1	0	0	0	1	10
Acne	0	1	0	0	1	10
Basal cell carcinoma	0	1	0	0	1	10
Poison oak	0	1	0	0	1	10
ENT						
Sore throat	8	1	0	0	5	50
Cervical lymphadenopathy	3	0	0	0	2	20
Congestion	1	0	0	0	1	10
Loss of smell	1	0	0	0	1	10
Runny nose	1	0	0	0	1	10
Sneezing	1	0	0	0	1	10
Swollen tastebud	1	0	0	0	1	10
Swollen tongue	1	0	0	0	1	10
Ear infection	0	1	0	0	1	10
Hearing loss	0	0	1	0	1	10
Gastrointestinal						
Diarrhea	5	1	0	0	5	50
Nausea	3	1	0	0	4	40
Indigestion	2	0	0	0	2	20
Abdominal pain	1	1	0	0	2	20
Non-specific gastroenteritis	0	2	0	0	2	20
Vomiting	2	0	0	0	1	10
Acid reflux	1	0	0	0	1	10
Right upper quadrant pain	1	0	0	0	1	10
Stomach pains	1	0	0	0	1	10
General/systemic						
Elevated blood pressure	19	0	0	0	6	60
Fatigue	7	0	0	0	4	40
Malaise	3	1	0	0	4	40
Fever	3	2	0	0	3	30
Night sweats	3	2	0	0	3	30
Seasonal/Environmental allergies	3	1	0	0	3	30
Chills	6	0	0	0	2	20
Body swelling	0	1	0	0	1	10
Genitourinary						
Perianal tenderness	2	0	0	0	1	10
Foul smelling urine	1	0	0	0	1	10
Anal warts	0	1	0	0	1	10
Bladder infection	0	1	0	0	1	10
Dysuria	0	1	0	0	1	10
Kidney stones	0	1	0	0	1	10
Infectious						
Non-specific viral infection	4	5	0	0	5	50
Acute COVID-19	3	4	0	0	5	50
Herpes simplex 1 lesion	1	2	0	0	2	20
Gonorrhea	0	2	0	0	2	20
Syphilis	0	2	0	0	2	20
Tinea	0	4	0	0	2	20
Cellulitis	0	1	0	0	1	10
Chlamydia	0	2	0	0	1	10
Herpes simplex 2 lesion	0	1	0	0	1	10
Impetigo	0	1	0	0	1	10
Influenza A	0	1	0	0	1	10
Shingles	0	1	0	0	1	10
Laboratory abnormality						
Elevated ALT	10	1	0	0	5	50
Elevated AST	4	1	0	0	5	50

[†] Not related or probably not related

Extended Data Table 4. Adverse events during the ATI. These events are defined as having been reported >=4 weeks following the final dose of study products, while participants were off ART.