Immunogenicity of AGS-004 Dendritic Cell Therapy in Patients Treated during Acute HIV Infection

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BACKGROUND

Enhancing HIV-1 specific immunity without CD4 T cell activation may clear productively infected cells, a key aspect of eradication strategies. AGS-004 consists of matured autologous dendritic cells (DCs) co-electroporated with in vitro transcribed RNA encoding Gag, Nef, Rev, and Vpr amplified from participants' pre-ART plasma. Autologous DCs are matured by sequential exposure to IFN-g followed by an adaptive signal (synthetically derived CD40L RNA) to achieve DC functionality.

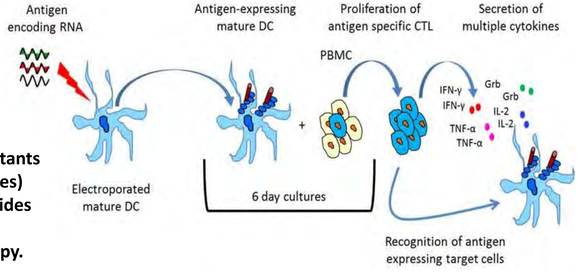

Fig 1. Using Autologous DCs and autologous HIV antigens, (including mutants or quasi species) AGS-004 provides personalized immunotherapy.

METHODS

- Open-label, single arm sub-study of AGS-004-003
- 6 male patients who **initiated ART within 45 days of acute HIV infection** (HIV RNA <50 c/ml for >6 months). AHI defined as negative/indeterminate EIA or negative HIV RNA test within 45 days of detectable plasma HIV RNA.
- Monthly doses of AGS-004 administered on ART; immune responses (IR) assessed after 3-4 doses (wk 12 or 16).
- Positive IR defined as ≥ 2-fold increase from baseline in the number of $CD28^+/CD45RA^-$ $CD8^+$ CTL **and** ≥3 SDs above a negative control.
- If IR increased after 3 doses, eligible for voluntary analytic treatment interruption (ATI) with continued monthly DC dosing.
- ART restarted if CD4 count <350 cell/mm^3, >20% decline in absolute CD4 count or percentage, or confirmed HIV RNA ≥10,000 c/ml.
- HIV RNA was measured by a single-copy assay (SCA).
- Frequency of resting CD4+ T-cell infection (RCI) was measured by quantitative viral outgrowth assay (QVOA) at baseline and after 3 doses (wk 10).

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Multi-Functional T Cell Responses

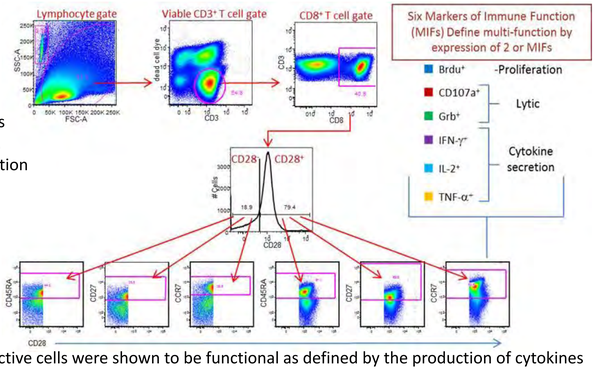

Fig 2. PBMC collected pre and post treatment were cultured *in vitro* with autologous AGS-004 DC vaccine. After *in vitro* stimulation multi-color flow cytometry identified AGS-004-induced HIV Ag-reactive CTL subsets by expression of surface markers CD28, CD45RA, CD27 and CCR7. Reactive cells were shown to be functional as defined by the production of cytokines (IFN-γ, TNF-α, IL-2), cytolytic markers (Granzyme b, CD107) and proliferation (BrdU) were identified in each CTL subset.

RESULTS

Table 1. Demographic and clinical characteristics of AHI participants who received AGS-004 dendritic cell therapy

Participant ID	Age (years)	Race/ethnicity	Baseline CD4 count (cells/mm^3)	Baseline SCA (cps/mL)	Criteria met for IR	Duration of ATI (days)	Reason for ART restart	Viral suppression after ATI	Baseline Frequency of RCI (IUPM)[a]	Post-treatment Frequency of RCI (IUPM)[a]
51-100	34	African American	662	<0.6	Yes	36	VL >10,000	Yes	0.266	0.140
51-102	31	African American	397	_	Yes	268+[b]	N/A	N/A	0.767	0.572
54-100	56	White, non-hispanic	574	<0.4	Yes	90	VL >10,000 / >20% ↓ CD4%	Yes	0.179	0.067
54-101	26	White, non-hispanic	482	<0.5	Yes	147	VL >10,000	Yes	0.043	0.049
54-102	51	African American	937	<0.5	Yes	58	>20% ↓ CD4%	Yes[c]	0.088	0.195
54-104	26	African American	714	0.8	Yes	41	>20% ↓ CD4%	Yes[c]	0.525	0.691

[a]IUMP= infectious units per million [b]Remains on ATI; [c]Viremic after initial re-suppression due to non-compliance with daily ART adherence.

- Few treatment-related AEs were all Grade 1.
- All participants met criteria for positive IR and ATI.
- Median ATI duration was 58 days (range 36-147).
- One participant remains in ATI after 268 days.
- Baseline SCA was <1c/ml in all participants .
- Only 1 participant (54-100) had a >2-fold decrease in frequency of RCI at W10 but maintained ATI for 90d.

Table 2. Antigenic response meeting positivity criteria

PID	GNVR	GAG	Nef	Vpr	Rev
51-100	+	-	-	-	-
51-102	+	+	+	+	+
54-100	+	-	-	-	+
54-101*	GNR +	-	-	NT	+
54-102	+	-	-	NT	+
54-104*	GVR +	-	NT	+	-

*Two participants received AGS-004 with 3 gene products; NT = not tested.

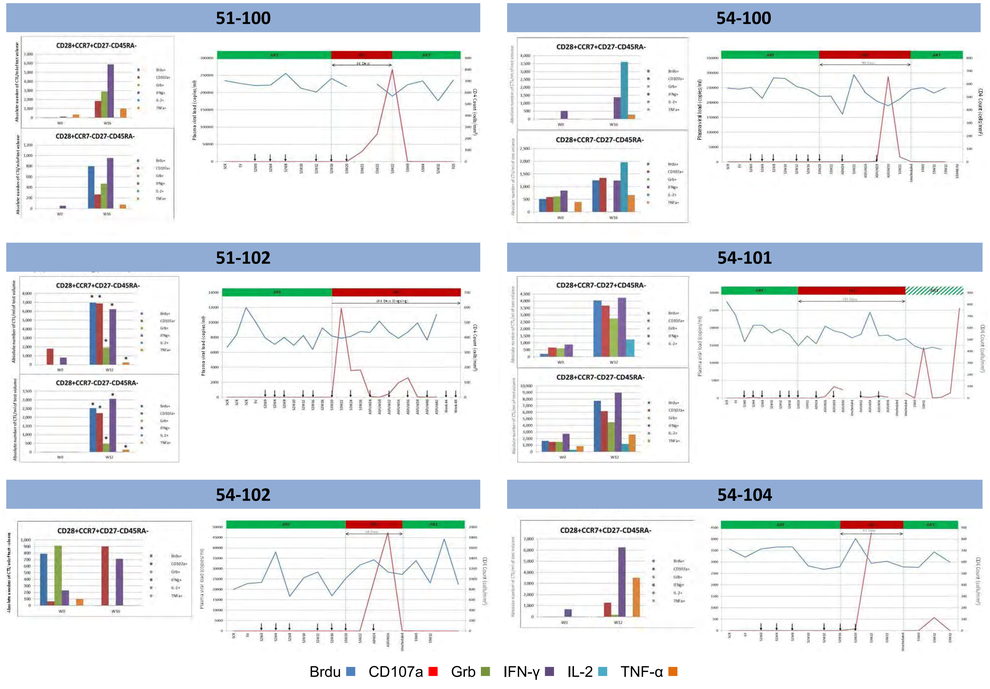

Fig 3. Multi-functional immune responses and viral load trajectories before, during and after ATI with AGS-004. Absolute numbers of $CD28^+/CD45RA^-$ CTL for each marker responding to GNVR RNA are shown (left) and paired with VL trajectories (right) for each participant. Antigen specific response for each MIF was determined by subtracting the absolute number of CTL in the control GFP response plus 3 times the SD from GNVR antigen responses at W0 and W12. Starred functional markers represent CTL responses that met criteria of positivity defined as: 2 fold increase in the absolute number of CTL for a given test antigen determined post dosing versus the absolute number of CTL for a given test antigen determined pre AGS-004 dosing (W0).

CONCLUSIONS

- **AGS-004 DC therapy was safe, well-tolerated, and led to increased HIV-specific immune responses, but did not allow sustained ART interruption.**
- **The one participant with a >2-fold decrease in the frequency of RCI at week 10 underwent ATI for 90 days.**
- **However, this DC therapy might result in depletion of persistent HIV infection in ART-suppressed patients following administration of anti-latency therapy.**
- **Next step: determine the optimal timing of administration of an anti-latency compound following 4 doses of AGS-004.**