

Augmentation of HIV-1-specific Memory Subsets of T Lymphocytes and decrease of immune activation in HIV-1 + individuals treated with a therapeutic vaccine plus antiretrovirals: Impact on viral load.

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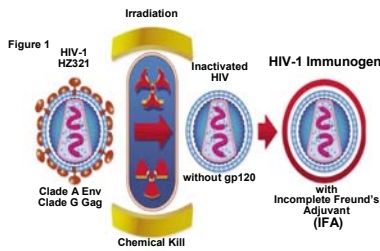
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INTRODUCTION

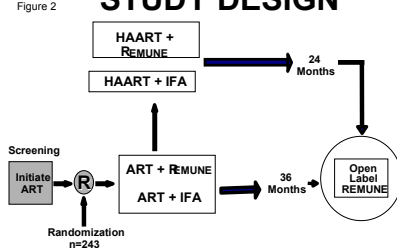
*We hypothesized that HIV-1 therapeutic immunization can induce HIV-specific immune responses that might impact on viral suppression in subjects on antiviral drug therapy.

*A protocol began in 1997 examining the effect of therapeutic immunization with REMUNE on the time to virologic failure or CD4 decline in subjects with chronic HIV-1 infection on antiretroviral drug therapy.

REMUNE



STUDY DESIGN



*243 HIV-1 ART-naïve, chronically infected subjects enrolled.

*Inclusion criteria: CD4 300-700 cells/mL and Viral suppression on ART required for randomization (AZT/DDI for 6 weeks prior to randomization)

*REMUNE or IFA (placebo) was given IM Q three months

*Patients allowed to switch to HAART (D4T/3TC/indinavir) for medical reasons

*Maximum time on ART is 36 months or HAART for 24 months

*Patients stratified by pre-drug baseline viral load/CD4

*Functional Immunologic assays on pre-determined subset.

Endpoints in the Two Drug (AZT/DDI) and in the Three Drug (D4T/ 3TC/indinavir) Phases

Time to first increase of viral load above 5,000 particles/mL (two drug phase) or above 2,000 particles/mL (three drug phase) or a decrease in CD4+ count below 250 cells/mm³ or a decrease to 50% below baseline. Endpoint had to be confirmed by a test done 4 weeks after trigger test.

STIR-2102 Study Team

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CLINICAL RESULTS

Primary Endpoints

Table 1

	IFA	REMUNE
Endpoint	50	35
No Endpoint	71	83

Fisher's Exact Test p=0.04

Figure 3

Cox analysis including covariates (controlling for possible prognostic factors)

Study drug plus Baseline Viral load < and > 10,000 copies/mL: When controlling for VL hazard ratio is 0.63 (a reduction in risk of 37%) and the differences between the study drug groups are significant (P=0.0340). VL higher than 10,000 copies/mL has a hazard ratio of 2.3 times the hazard of the group with less than 10,000 copies.

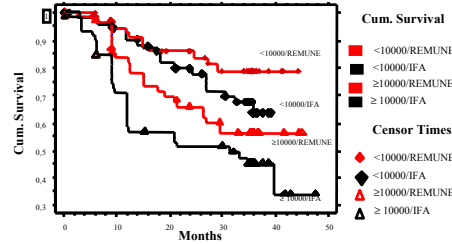


Table 2 Stratified Cox (Proportional Hazards) Models

Model	Main Effect	Strata by Baseline	REMUNE vs. IFA Hazard Ratio	95% CI	P
1	Treatment	none	0.66	(0.43-1.01)	0.054
2	Treatment	VL <10,000	0.63	(0.41-0.97)	0.034
3	Treatment	VL >10,000	0.62	(0.40-0.95)	0.029

Table 3 Cox Analysis CD4: REMUNE vs IFA

In the REMUNE-treated group: hazard ratio is very similar in all groups (varying from 1.33 in the group with less than 400 to 0.72 in the range of 350 to 450 cells/mm³). CD4 is not significant in any strata.

Table 3

DF	Coef	Std. Error	Coef/SE	Chi-Square	P-Value	Exp(Coef)	
VL<10k	1	-0.86	0.38	-2.27	5,17	0,0230	0,42
CD4Range	2	*	*	*	2,46	0,2925	*
<350	1	0,29	0,44	0,66	0,43	0,5119	1,33
≥350-450	1	-0,33	0,43	-0,76	0,57	0,4491	0,72

Table 3

In the IFA-treated group: the group of ≥ 450 CD4 cells/mm³ is significantly different from the group of < 450 where hazard ratios triple the risk of an endpoint.

DF	Coef	Std. Error	Coef/SE	Chi-Square	P-Value	Exp(Coef)	
VL<10k	1	-0,67	0,30	-2,23	4,96	0,0260	0,51
CD4Range	2	*	*	*	6,32	0,0424	*
<350	1	1,10	0,53	2,08	4,34	0,0373	3,00
≥350-450	1	1,21	0,48	2,51	6,29	0,0122	3,36

CONCLUSION: CD4 Count does not vary the prognosis in REMUNE-treated group, mean while IFA group shows a different prognosis with different ranges of CD4 count

Serious Adverse Events Profile

- *48 patients had experienced one or more SAEs in the study.
- > 24 patients belong to the IFA treatment group and 24 patients belong to the REMUNE treatment group.
- > Relationship with Study Drug was deemed "None" by investigators in all cases.

CLINICAL SUMMARY

- *REMUNE provides a better clinical outcome in terms of maintaining virologic suppression in patients on ART or HAART (P = 0.04; Table 1)
- *REMUNE improves the rate maintained virologic suppression in patients on ART or HAART. This effect is impacted by baseline viral load in patients on ART or HAART (p = 0.029; Figure 3)
- *REMUNE helped maintain virologic suppression in those patients with high baseline viral load (Figure 3)
- *REMUNE treated patients were 37% less likely to develop virological failure and improves the maintenance of virologic suppression in patients on ART or HAART (Table 2)
- *REMUNE was shown to be well tolerated and safe in this trial

IMMUNOLOGICAL RESULTS

Figure 4

Induction of memory CD8+ T-cell subsets in REMUNE +ART-treated patients vs ART alone

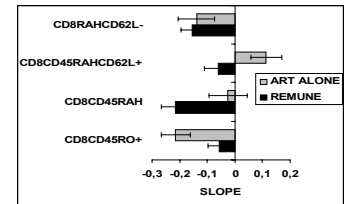


Figure 5

Increase of CTLs to HIV-1 Gag/pol proteins in REMUNE +ART-treated patients vs ART alone

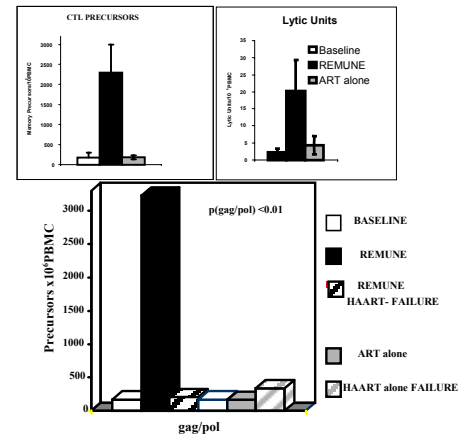
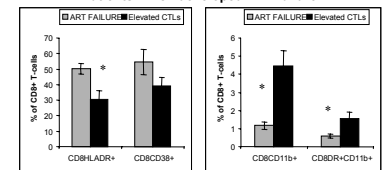


Table 3 Correlation between CTLs to HIV-1 Gag/pol proteins and Viral Load in REMUNE +ART-treated patients vs ART alone

	REMUNE	IFA
Mean Gag/pol Precursors	2294 ± 702	185 ± 53
Correlation with Viral Load at month 24	-0.582	-0.210
Correlation coefficient (P value)	(<0.05)	(0.535)

Figure 6

REMUNE +ART treated patients with high levels of CTLs had decreased activated CD8+ T-cell and elevated CD11b+ CD8+ T-cell levels compared to Patients which developed ART failure



IMMUNOLOGICAL SUMMARY

- Therapeutic vaccination with REMUNE increases Helper and CTL HIV-specific immunological memory responses
- REMUNE induces increases in memory CD8+ T-cells and memory-activated CD4+ and CD8+ T-cells as compared with placebo group. These increases are associated with immunological responses, but not with higher viral load or lower CD4 counts as in the group with ART alone
- Expansion of CD11b CD8+ T-cells and decrease of immune activation are associated with HIV-specific CTL responses and control of viral replication in the REMUNE-treated group