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DermaVir for initial treatment of HIV-infected subjects demonstrates preliminary safety, immunogenicity and HIV-RNA reduction versus placebo immunization

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Abstract

Background: It is a concern that vaccinations paradoxically increase viral load. Therefore, GIEU006 (NCT00711230) was designed to evaluate the safety of repeated DermaVir immunizations in antiretroviral-naïve subjects and to test immunogenicity and antiviral efficacy to guide later development. DermaVir consists of a pDNA expressing an HIV (Clade B) virus-like particle formulated into a topically administered synthetic nanomedicine.

Methods: Thirty-six HIV-infected adults (HIV-RNA: 5,000 to 150,000 copies/mL and $CD4^+$: ≥400 cells/mm^3) were randomized to receive one of three DermaVir doses (0.2, 0.4 or 0.8 mg of pDNA) or placebo at weeks 0, 6, 12 and 18. Standard parameters and HIV(gag)-specific precursor T cells were quantified through week 24. Intent-to-treat (ITT) analyses were performed with non-parametric statistical tests and the treatment effect was analyzed using the Hodges-Lehmann estimator.

Results: Baseline characteristics were comparable across all groups (median age: 38 years; $CD4^+$: 506 cells/mm^3; HIV-RNA: 20,250 [4.31 $\log_{10}$] copies/mL; 83% Caucasian; 97% male). No subject stopped vaccinations due to an Adverse Event and only one subject initiated ARV. No AE ≥ Grade 2 occurred, grade 1 and 2 incidences were similar across groups, and only one Grade 2 AE was possibly-related to the vaccine. Anti-dsDNA decreased, ANA and $CD4^+$ counts did not change, and HIV-RNA did not increase. Based on secondary analyses, the DermaVir 0.4 mg group was superior to the others. In this group, the HIV gag-specific precursor T cells increased from 5,055 to 9,978 cells/million PBMC (P=0.07). The median $\log_{10}$ HIV-RNA decreased from 4.5 to 4.0, significantly different from the placebo (P=0.045). The treatment effect compared to placebo at 95% confidence interval was -0.23 (-0.70 to 0.09) for $\log_{10}$ HIV-RNA.

Conclusions: DermaVir did not increase viral load nor reduce $CD4^+$ counts and was as safe as placebo. The antiviral and immune-boosting effects of DermaVir support further development in the challenging antiretroviral-naïve setting. The DermaVir 0.4mg dose emerged as the vaccine candidate for the early treatment of HIV infection.

Key words: Therapeutic vaccine; First-line therapy, Nanomedicine, DermaPrep medical device, virus-like particles

Background

DermaVir Therapeutic Vaccine

Inspired by an idea:

- Based on a rare clinical observation: “The Berlin Patient”
- Demonstrated control of HIV replication through “auto-immunization”

Built on a sound foundation:

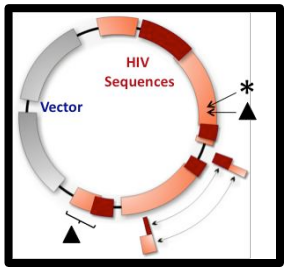
- Prophylactic vaccine technology (antibody immunity) is not appropriate for therapeutic vaccines that require new technologies to induce cellular immunity
- A comprehensive technology platform was designed to translate the idea into a commercially viable therapeutic vaccine

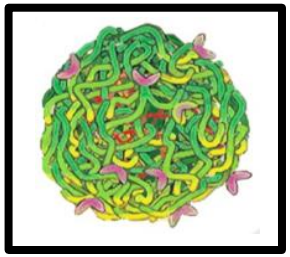
Addresses the challenges of:

- Appropriate antigen composition
- Delivery, targeting and expression in dendritic cells
- Clinical development and commercialization

DermaVir Therapeutic Vaccine

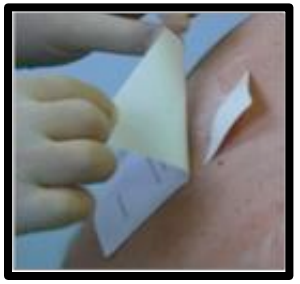
API: A single pDNA expressing 15 HIV proteins to form complex HIV virus-like particles

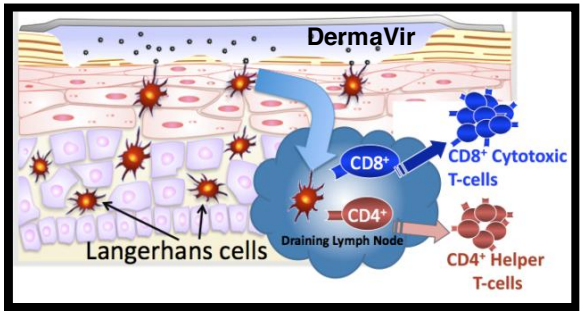




Nanomedicine: The pDNA is formulated into pathogen-like nanoparticles for effective gene expression in dendritic cells (Tőke et al. AIDS2010 Abstract # MOPE0052)

Administration: The nanomedicine is applied topically by a proprietary medical device (DermaPrep). It targets the lymph nodes via epidermal Langerhans cells.

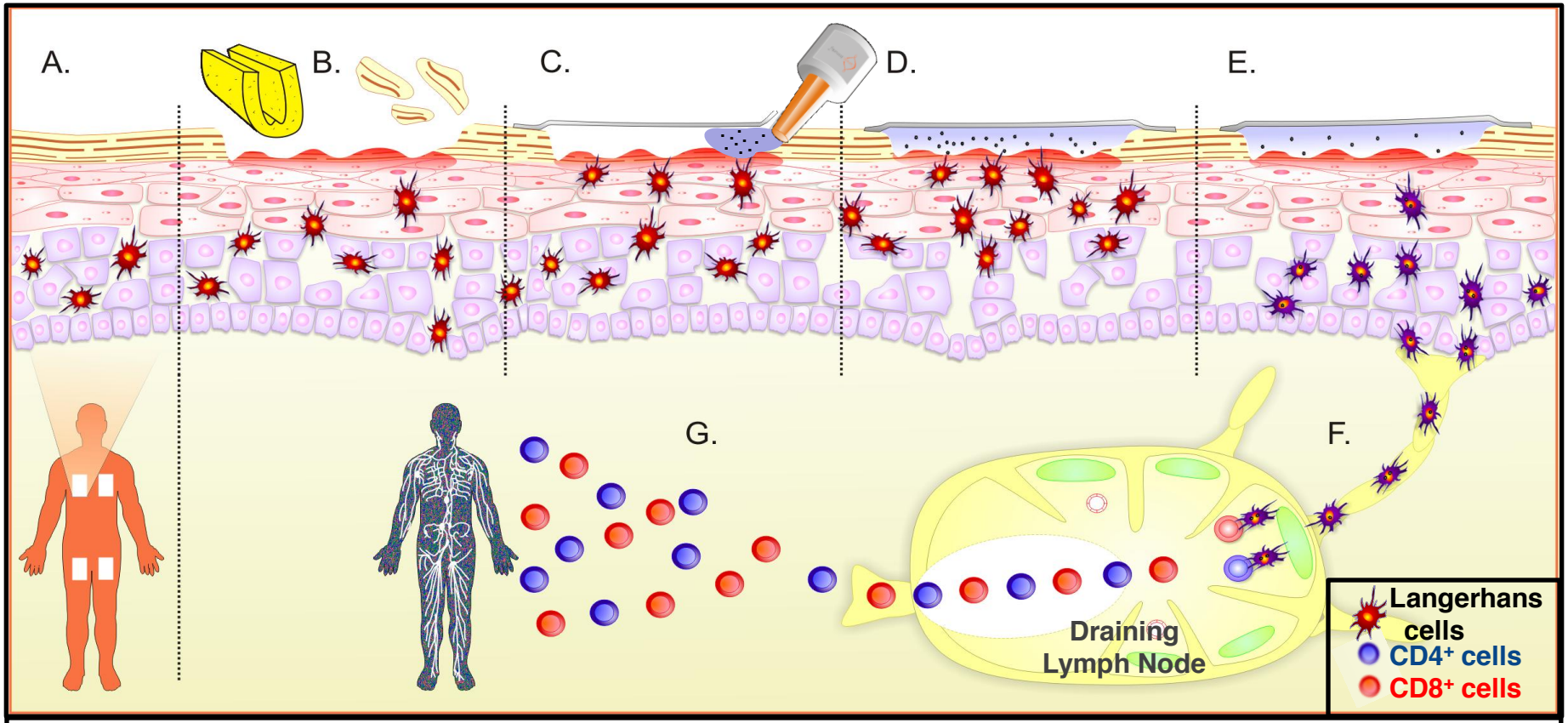




Therapeutic effect: Dendritic cells prime HIV-specific $CD4^+$ and $CD8^+$ T-cell precursors that proliferate in the body and eliminate HIV-infected cells

DermaVir Therapeutic Vaccine

A Topically Administered pDNA Nanomedicine



A. Skin sites selected
B. Skin preparation using DermaPrep
C. Patch applied and DermaVir administered for three hours
D. Activated Langerhans cells (LC) capture DermaVir nanoparticle
E. LCs migrate to lymph node, mature into dendritic cells (DC)
F. DCs present DermaVir-encoded epitopes to naïve T cells
G. HIV-specific $CD4^+$ and $CD8^+$ precursor T cells proliferate to search for and destroy HIV-infected cells throughout the body

Why Administer DermaVir Topically?

May 14, 1796

Edward Jenner demonstrated that inoculating healthy people with cowpox across *superficially injured skin* prevented smallpox resulting in the first vaccine.

February 2010

LETTERS

nature medicine

Epidermal injury and infection during poxvirus immunization is crucial for the generation of highly protective T cell–mediated immunity

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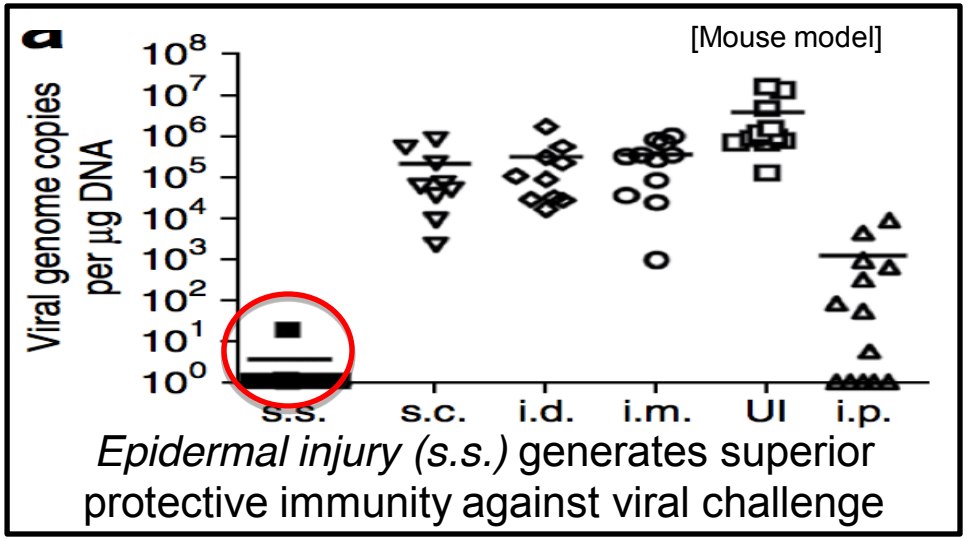


Epidermal injury (s.s.) generates superior protective immunity against viral challenge

Vaccination is ineffective if delivered by hypodermic injection.

Methods

GIEU006 Phase II Study
Study Design

36 Antiretroviral-naïve subjects: Nine subjects per cohort

- Multicenter study conducted in Germany
- Doses: 0.2, 0.4 or 0.8 mg DermaVir$_{(B\ Clade)}$ and placebo
- Schedule: Applications at Weeks 0, 6, 12, and 18

Entry Criteria:

- HIV viral load: 5,000 to 150,000 HIV RNA copies/mL
- $CD4^+$: ≥400 cells/mm^3
- No exclusion for non-Clade B HIV

Primary endpoint:

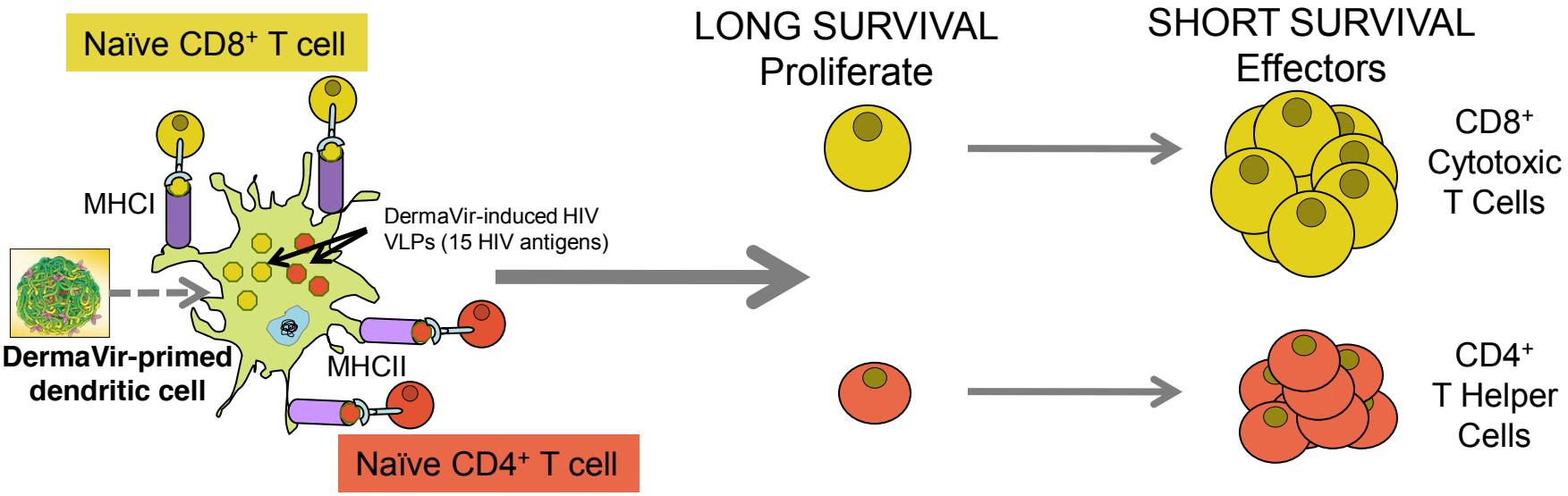
- Safety at Week 24

Secondary endpoints:

- Changes in HIV RNA, $CD4^+$ cell counts and HIV-specific T cells

Immunogenicity of DermaVir
Induction of HIV-specific Memory/Precursor T-cells

DermaVir-induced dendritic cell-mediated priming of naïve T cells	Antigen-specific memory/ precursor T cells	Antigen-specific cells: T_{helper} and $T_{cytotoxic}$



- DermaVir-primed dendritic cells activate naïve $CD4^+$ and $CD8^+$ T cells (Lisziewicz et al. J Virol 2001)
- $CD4^+$ T cell help during $CD8^+$ T cell priming is essential for the establishment of memory (Janssen Nature 2003)

- DermaVir immunization induces antigen-specific memory/precursor T cells

(Lisziewicz et al. J Virol 2001; Lisziewicz et al. JID 2004; Calarota et al. Vaccine 2008; Cristillo at al. Virology 2007)

DermaVir
Immunodiagnostic Basis for Patient Monitoring

Therapeutic vaccines should induce HIV-specific memory T cells

Accurate monitoring of memory phenotype Cytotoxic T Lymphocytes (CTLs) is required for therapeutic vaccine strategies (Janssen Nature 2003)

- Assays monitoring the physical or functional presence of CTLs in short-term assays detect effectors incapable of further expansion
- Antigen-specific effector cells measured by ELISPOT do not correlate with control of viremia (eg, Addo et al. J Virol 2003; Calarota et al. J Immunol 2008)

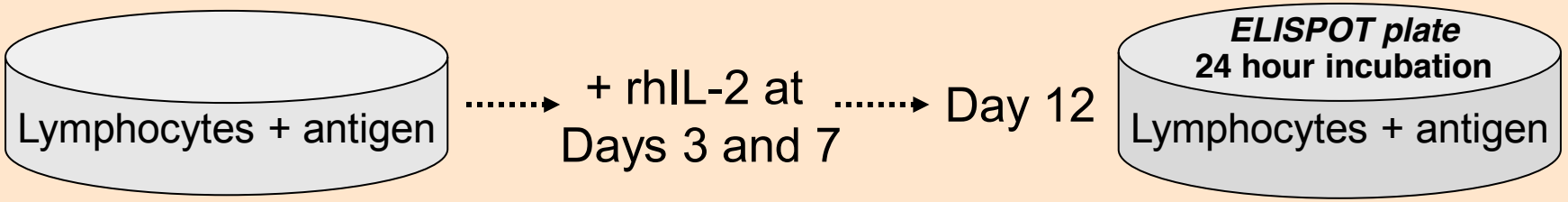
We have developed a proprietary PHPC* assay that is appropriate for the monitoring of therapeutically effective CTLs

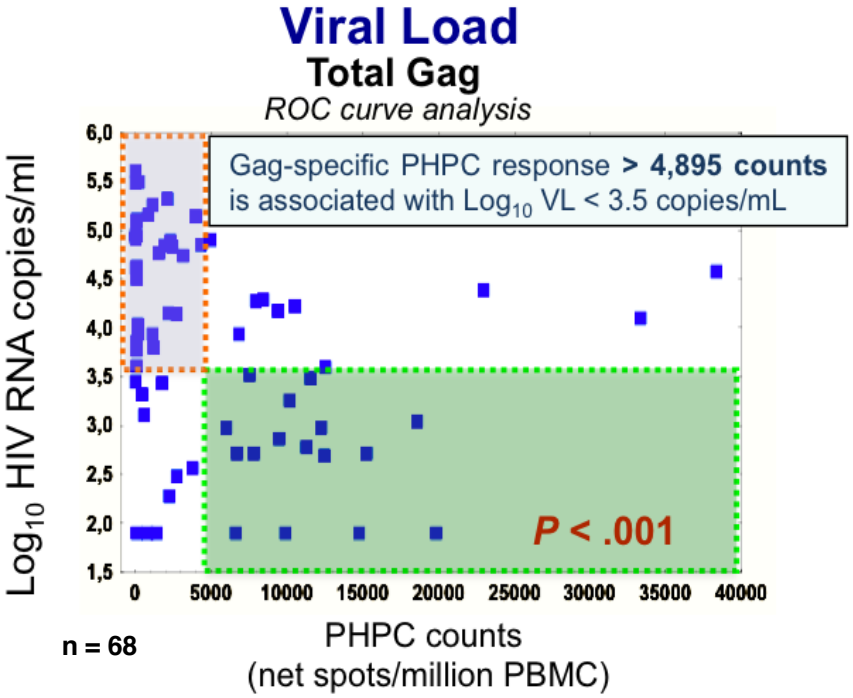
- The PHPC assay measures CTL effector function following antigen-specific expansion
- Higher PHPC counts correlate with lower HIV viral loads in untreated individuals (Calarota et al. J Immunol 2008)

* Precursors with High Proliferative Capacity

PHPC Analysis
Precursors with High Proliferative Capacity (PHPC)

Quantification of HIV-specific T cell precursors





High PHPC counts correlate with low viral load in HIV$^+$ subjects not yet receiving antiretrovirals

(Calarota et al. J Immunol 2008)

Results

GIEU006
Baseline Characteristics

Characteristic	Statistical parameter	DermaVir 0.2 mg (n=9)	DermaVir 0.4 mg (n=9)	DermaVir 0.8 mg (n=9)	Placebo (n=9)	Total (n=36)	*P* value
Age - years	Median	37	40	38	37	38	*P* = .52
Gender	Male	8	9	9	9	35	*P* > .99
	Female	1	0	0	0	1	
Ethnic origin Number	Caucasian	7	9	5	9	30	*P* = .18
	Latino/Hispanic	1	-	2	-	3	
	Black	1	-	1	-	2	
	Asian	-	-	1	-	1	
HIV RNA Copies/mL (log_{10})	Median	35,000 (4.54)	29,500 (4.47)	19,500 (4.29)	16,000 (4.20)	20,250 (4.31)	*P* = .36
$CD4^+$ Cells/mm^3	Median	497	547	523	454	506	*P* = .54
Gag-specific T cell memory/precursors PHPCspots/10^6 PBMC	Subjects	**(n=8)**	**(n=7)**	**(n=8)**	**(n=4)**	**(n=27)**	*P* =. 81
	Median	1950	5055	2262	1896	2034	

Safety
Reported Adverse Events

Adverse Events	Grade 1								Grade 2							
DermaVir Dose	Placebo		0.2 mg		0.4 mg		0.8 mg		Placebo		0.2 mg		0.4 mg		0.8 mg	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Chemistries	10	5.7	9	5.1	6	3.4	4	2.3	4	2.3	-	-	-	-	3	1.7
Hematology	1	0.6	2	1.1	-	0.0	1	0.6	-	-	-	-	-	-	-	-
Cardiovascular	4	2.3	-	0.0	3	1.7	1	0.6	-	-	-	-	-	-	2	1.1
Gastrointestinal	2	1.1	-	0.0	1	0.6	2	1.1	-	-	-	-	-	-	2	1.1
Genitourinary	2	1.1	2	1.1	-	0.0	1	0.6	-	-	-	-	-	-	-	-
Infection	2	1.1	9	5.1	10	5.7	7	4.0	-	-	-	-	-	-	-	-
Musculoskeletal	1	0.6	-	0.0	2	1.1	1	0.6	-	-	2	1.1	1	0.6	-	-
Neurologic	4	2.3	2	1.1	1	0.6	-	-	-	-	-	-	1	0.6	-	-
Ocular/Visual	-	-	1	0.6	1	0.6	-	-	-	-	-	-	-	-	-	-
Respiratory	-	-	1	0.6	3	1.7	-	-	-	-	-	-	1	0.6	-	-
Dermatological	13	7.4	5	2.9	4	2.3	7	4.0	-	-	-	-	-	-	1	0.6
Systemic	9	5.1	5	2.9	4	2.3	11	6.3	-	-	2	1.1	2	1.1	-	-
Total	**48**		**36**		**35**		**35**		**4**		**4**		**5**		**8**	

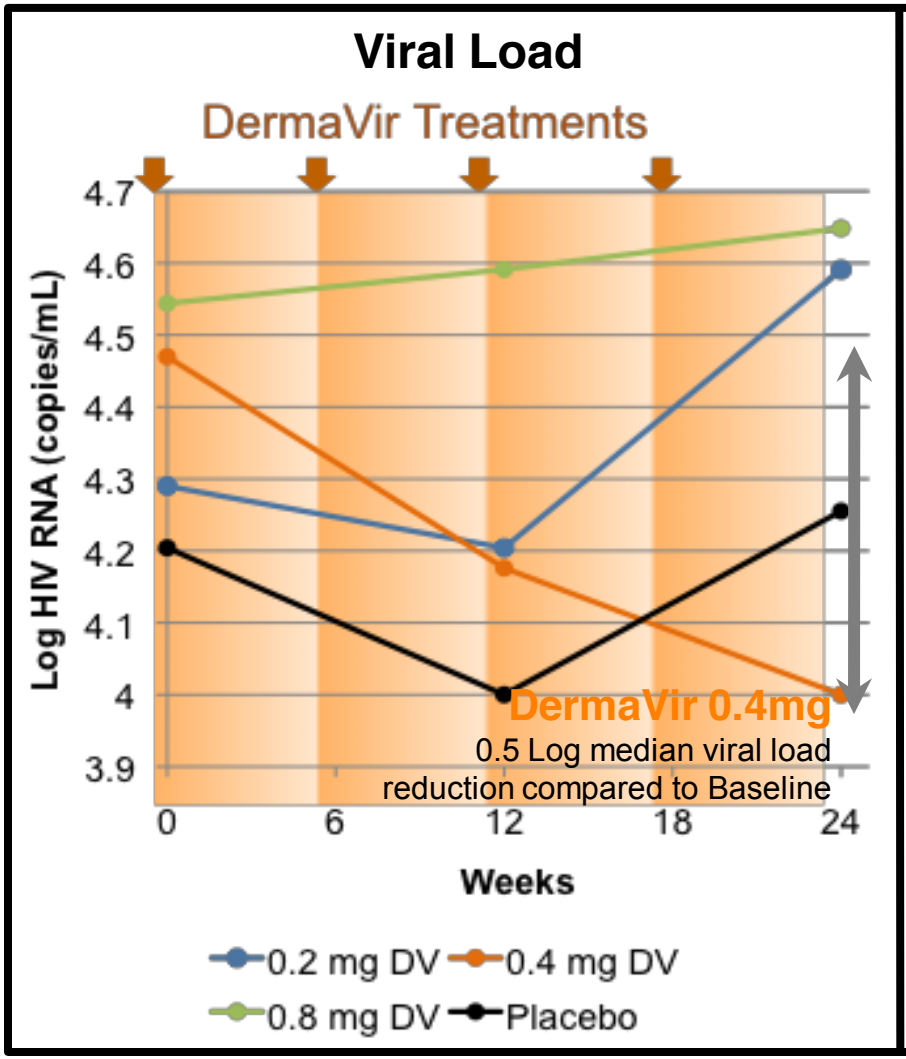
- No Adverse Event above Grade 2
- Only one Grade 2 AE judged possibly related to treatment:

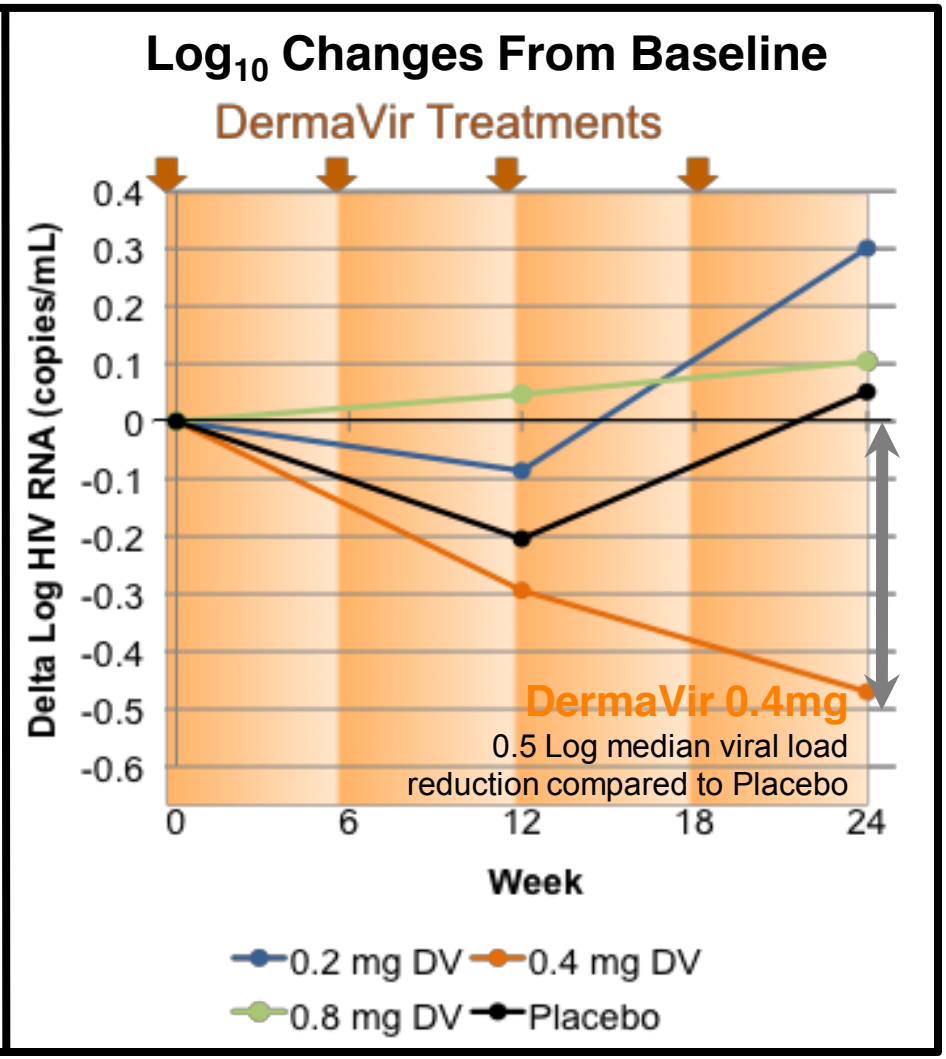
Positive Gaenslen's Test* (DermaVir 0.2 mg: resolved)

* Limb pain under stress

Antiviral Effect

HIV RNA Levels (Viral Load)





HIV RNA Levels

Viral Load Decrease Compared to Placebo (Week 0 to 24)

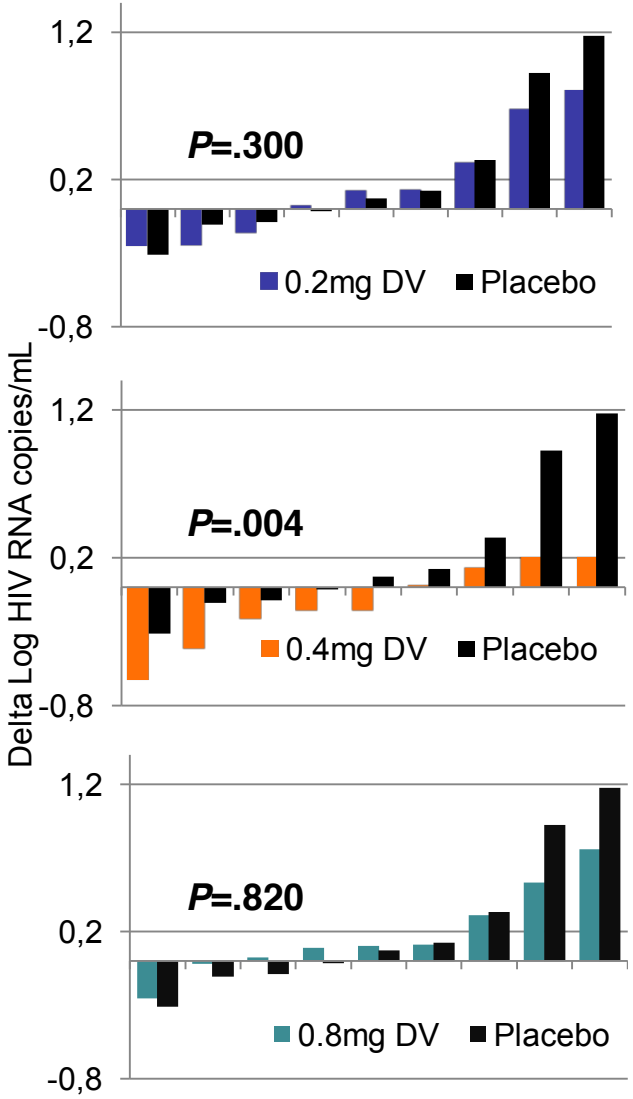
Statistical analysis:

1-sided Wilcoxon Matched-Paired Signed-Rank Test (individual subjects were ranked by degree of viral load change)

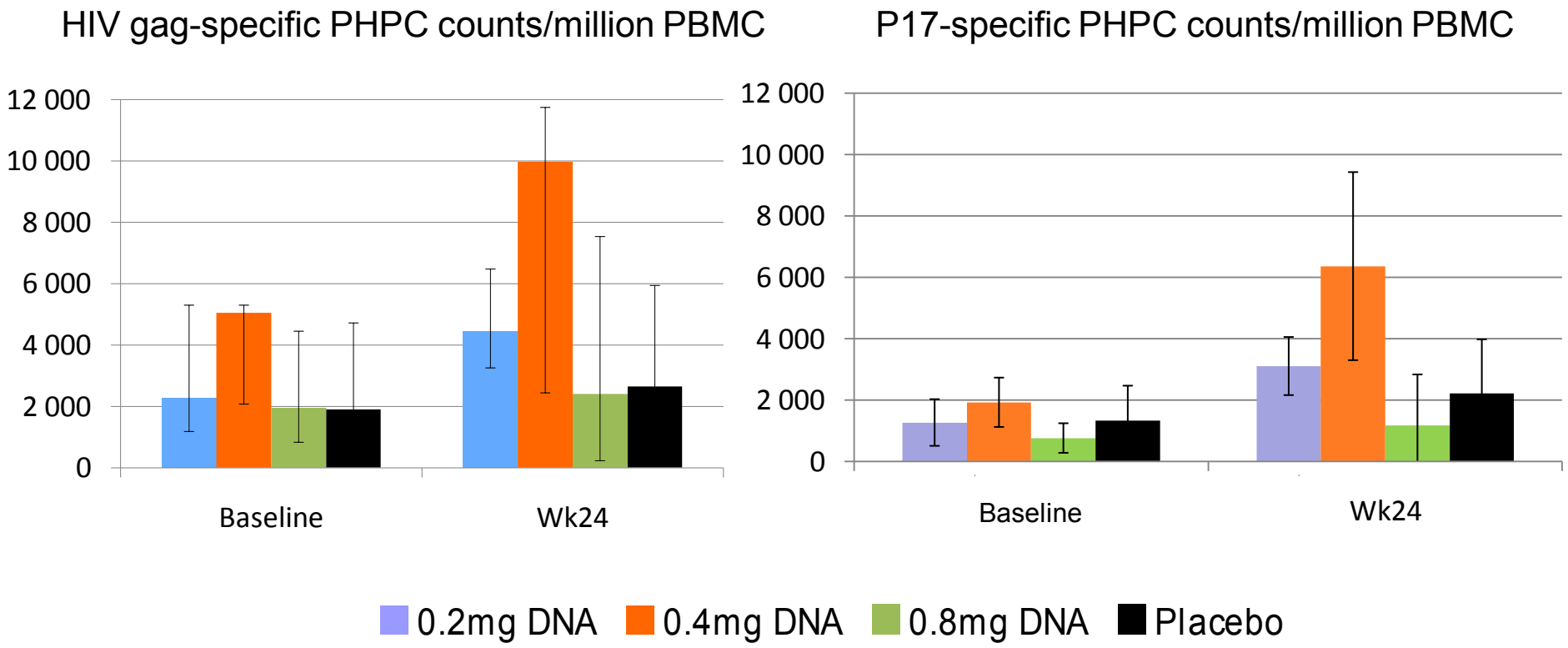
Results

Significant differences in the 0.4 mg DermaVir cohort compared to Placebo (*P*=.004)

No statistically significant differences in the 0.2 and 0.8 mg DermaVir cohorts compared to Placebo



Preliminary Immunogenicity
Priming of HIV-specific Precursor T cells



Further analyses ongoing

Objective Treatment Effect
Viral Load Reduction After Repeated Treatments

Statistical analysis of treatment effects:

Hodges Lehman Estimator at 95% Confidence Interval

(A robust statistic for the median of the differences)

Results

During the initial phase of treatment (Weeks 0 to 12)

- No detectable treatment effect in any DermaVir cohorts compared to Placebo

Treatment effect becomes apparent after the third DermaVir treatment (Weeks 12 to 24)

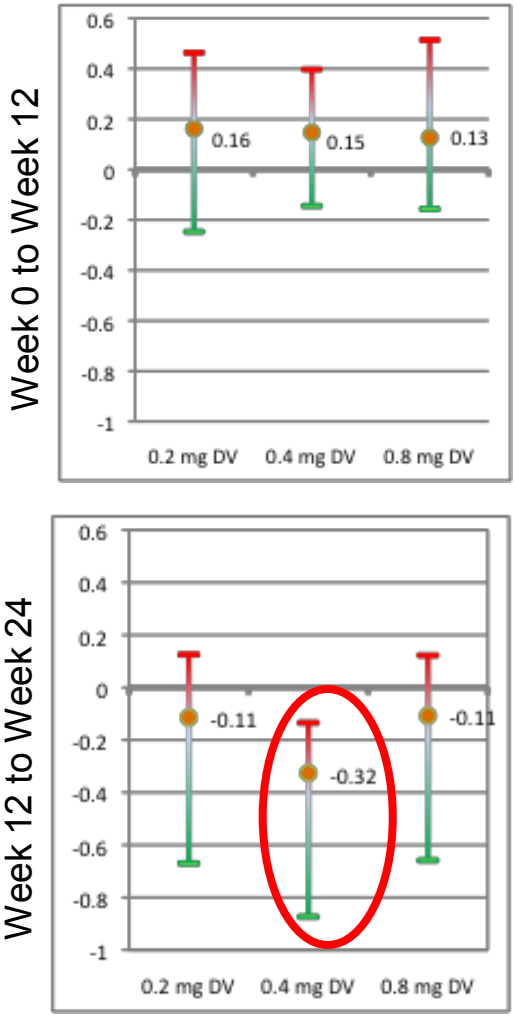
- Treatment effect detectable in all DermaVir cohorts
- Effect most prominent for DermaVir 0.4 mg

0.2 mg: -0.11 (95% CI, -0.67 to +0.12)

0.4 mg: -0.32 (95% CI, -0.87 to -0.13)

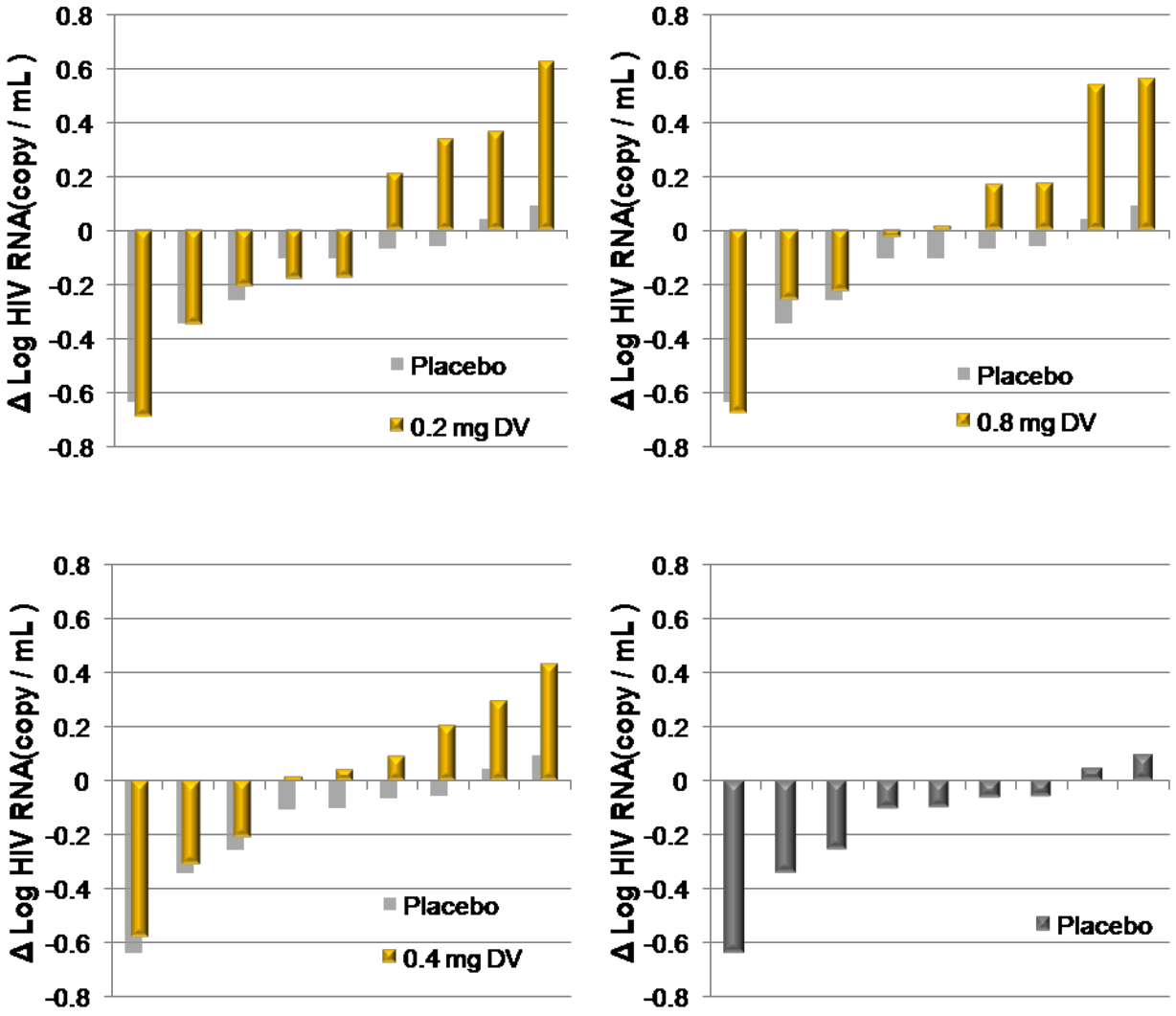
0.8 mg: -0.11 (95% CI, -0.66 to +0.12)

HIV RNA change compared to Placebo



Viral Load Changes

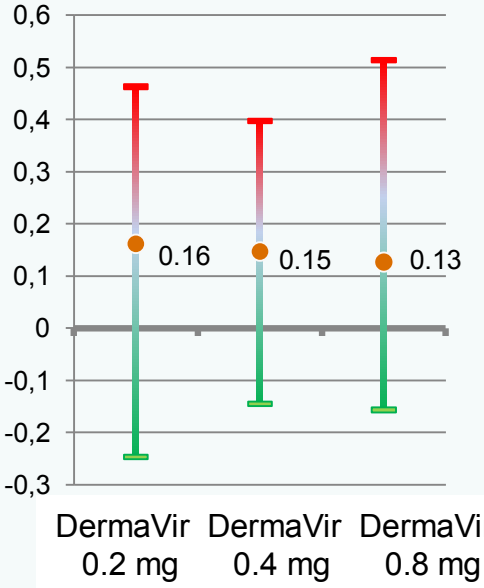
Between Week 0 and Week 12



Visual pair-wise comparisons of subject responses to therapy

Treatment Effect

Between Week 0 and Week 12
at 95% Confidence Interval

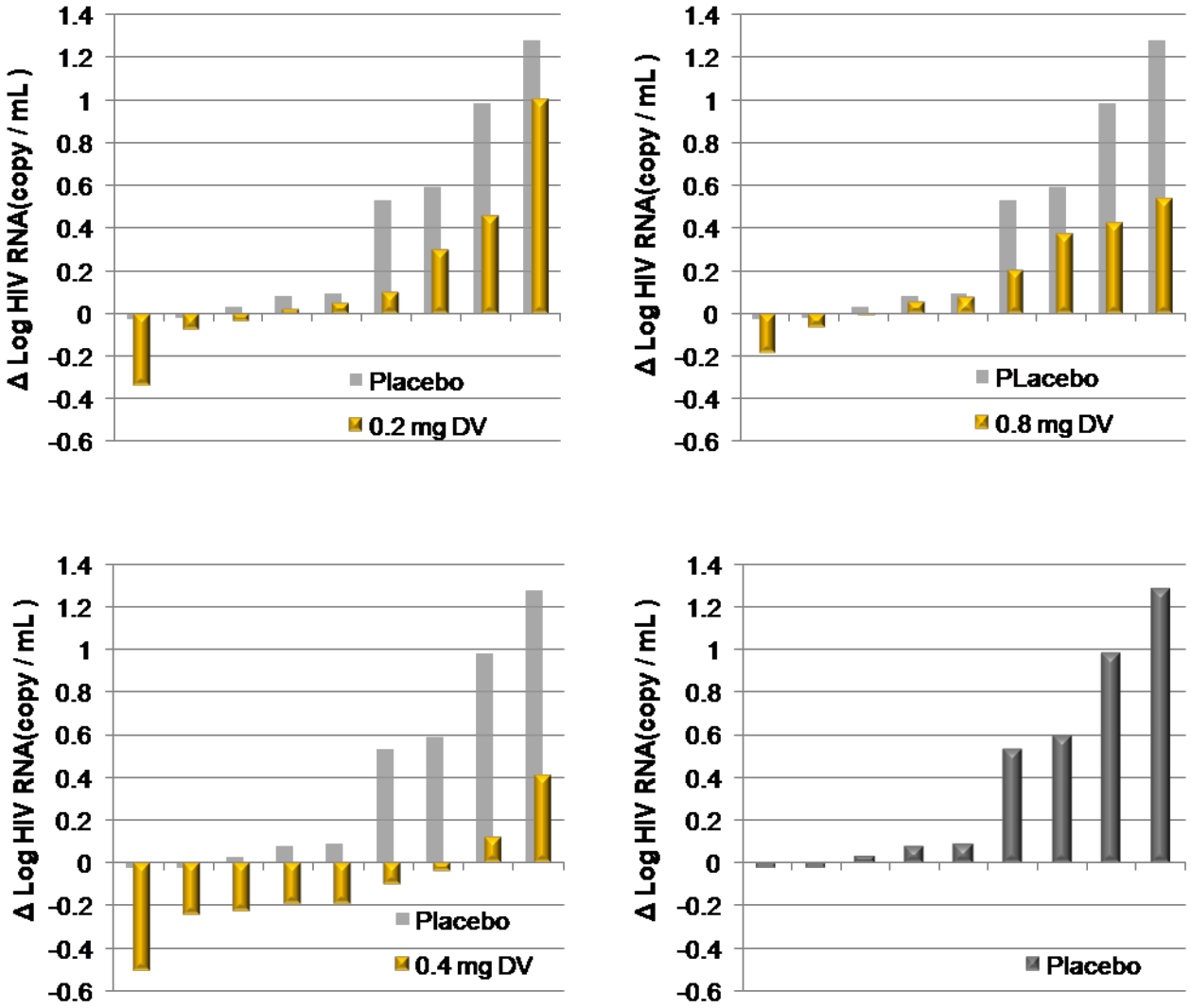


Changes of Log Viral Load
DermaVir versus Placebo

Hodges Lehmann Estimator

Viral Load Changes

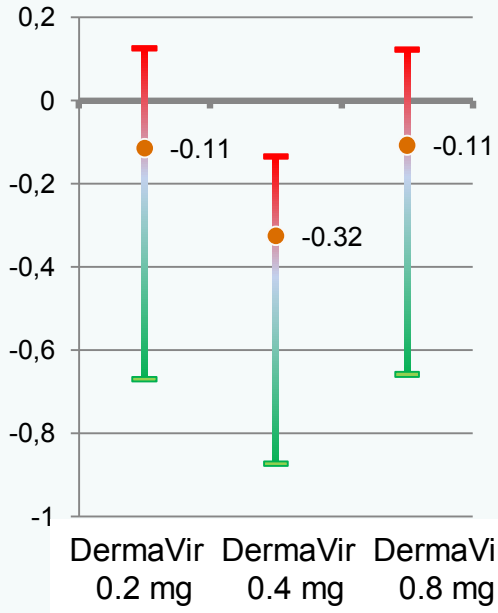
Between Week 12 and Week 24



Treatment Effect

Between Week 12 and Week 24

at 95% Confidence Interval



Changes of Log Viral Load

DermaVir versus Placebo

Hodges Lehmann Estimator

Visual pair-wise comparisons of subject responses to therapy

Conclusions

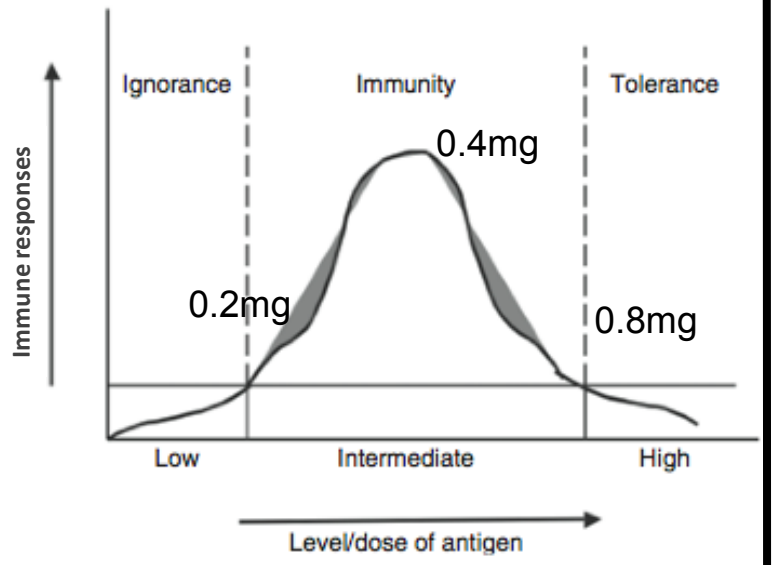
GIEU006 Phase II Study
Selection of the Optimal DermaVir Dose (0.4mg)

Therapeutic vaccines differ from prophylactic vaccines:

- Induce cellular responses rather than antibody responses
- Administered repeatedly for sustained boosting of immunity

Therapeutic Vaccines differ from drugs:

- DermaVir displays a bell-shaped dose-response curve
  - **0.4 mg DermaVir dose** had higher immunogenicity than 0.2 and 0.8 mg doses
  - **0.4 mg DermaVir dose** had the optimal treatment effect (viral load reduction)



This effect is well-known in immunology:

- Low-dose antigen is optimal for T cell responses in Chiron's HIV vaccine nanoparticle formulation (Borkowsky et al. JID 2000)
- Medium-dose antigen is optimal for both T cell responses and survival in a therapeutic vaccine against pancreatic cancer (Bernhardt et al. Br J Cancer 2006)
- Sustained high-dose antigen expression induces immune tolerance (Kelly et al. Molecular Therapy 2009)

GIEU006: Summary of Results
24 Weeks of DermaVir Treatment (Primary Endpoint)

Safety*

- DermaVir was well-tolerated
- There were no significant Adverse Events

Preliminary Immunogenicity

- Priming of HIV-specific memory/precursor T cells was observed

Preliminary Efficacy

- Viral load suppression by DermaVir vaccinations occurs slowly as predicted by its mechanism of action

The 0.4 mg DermaVir dose emerged as the optimal dose

- Highest boosting of HIV-specific immunity compared to other cohorts
- Median 0.5 Log_{10} HIV RNA decrease compared to Placebo
- Selected as candidate for early treatment of HIV infection

* See also: Rodriguez et al. AIDS2010 Abstract # A-240-0111-10145

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