

Synopsis PHPC-02

ANTIRETROVIRAL-SPARING CONCEPT: AN EXPLORATORY PHASE II, RANDOMIZED, SINGLE BLIND PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFECT OF THERAPEUTIC IMMUNIZATION ON THE QUANTITY OF HIV-SPECIFIC T CELL PRECURSORS DURING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY FOLLOWED BY ANALYTICAL TREATMENT INTERRUPTION

DESIGN: PHPC-02 is a phase II, randomized, placebo-controlled trial designed to investigate whether therapeutic immunization during highly active antiretroviral therapy (HAART) induces elevations of HIV-specific T cell precursors with high proliferative capacity (PHPC) in HIV-1-infected individuals, and whether the quantity of PHPC correlate with the viral load set point following analytical treatment interruption (ATI). Subjects will be randomized to receive either DermaVir Patch (8 subjects per cohort) or DermaVir Patch Placebo (8 subjects per cohort) every four weeks for three applications while receiving maximally suppressive HAART. HAART will be discontinued at Week 9 for an ATI period of 20 weeks.

SAMPLE SIZE:

A total of 16 subjects will be enrolled and randomized to receive DermaVir Patch (8 subjects) or DermaVir Patch Placebo (8 subjects).

POPULATION:

- HIV-1-infected adults; Age: ≥ 18 years and < 50 years
- On a non-hydroxyurea based HAART for at least one year
- Pre-HAART CD4 nadir > 250 cells/mm³
- Pre-HAART viral load $> 5,000$ copies/mL
- At least two viral load and two CD4 measurements for determination of viral set point and nadir, respectively, prior to HAART initiation
- Undetectable viral load (*i.e.*, three or more determinations of < 50 copies/mL with no values of > 50 copies/mL) for the six month period preceding the study
- CD4 T-cell count > 500 cells/mm³ for the six month period preceding the study

REGIMEN:

Subjects will receive three DermaVir/Placebo Patches over eight weeks (Weeks 0, 4 and 8) while receiving HAART. HAART will be discontinued for a 20 week ATI.

HAART stands for an antiretroviral therapy completely suppressive, that is able to maintain plasma viral load below 50 copies/mL.

The standard DermaVir dose unit per patch is 0.1 mg DNA (0.8 mL). Patch dimensions are 12 cm x 14 cm. Interior “pouch” area containing DermaVir or Placebo is 80 cm² or 3.15 x 3.94 inches (smaller than a 4 x 4 inch gauze pad). One DermaVir treatment dose is four patches (0.4 mg DNA).

Placebo treatment dose is four patches. Placebo contains glucose/dextrose solution.

Patients will be randomized to receive:

DermaVir Patch: Eight subjects will receive three separate DermaVir Patch treatments on study Days 0, 28, and 56, (Weeks 0, 4, and 8). Antiretroviral therapy will be stopped on Day 63 for a 20-week ATI.

or

Placebo Patch: Eight subjects will receive three separate Placebo Patch treatments on study Days 0, 28, and 56 (Weeks 0, 4, and 8). Antiretroviral therapy will be stopped on Day 63 for a 20-week ATI.

NOTE: Non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as Rescriptor® (delavirdine), Sustiva® (efavirenz), and Viramune® (nevirapine) remain in cells longer than other drugs, which could increase the risk of inducing drug resistance when all drugs are discontinued simultaneously. Subjects will be given the option of discontinuing NNRTI drugs up to 48 hours before stopping their other antiretrovirals when they begin their analytical treatment interruption (this will be noted in the medication records).

SCHEMA

Table 1: Dosing Table of Subjects

Group	Active DermaVir	DermaVir Placebo
Total Number per group:	8	8
Number of patches per immunization day (active patch area = 80 cm ²)	4 patches (0.4 mg DNA)	4 patches (no DNA)
Application Schedule	Day 0, 28, 56	Day 0, 28, 56
Total patches	12 / Subject	12 / Subject
Total DNA	1.2 mg / Subject	0 mg/ Subject

DermaVir Standard Unit per patch: 0.1 mg DNA = 0.8 mL of DermaVir. The Placebo patch contains 0.8 mL of Dextrose/D-Glucose solution; DermaPrep topical administration procedures will be used for DermaVir and Placebo Patches.

DURATION: Subjects will be on study for a total of 29 weeks (8 weeks of therapy, 1 week to discontinue HAART, followed by 20 weeks of ATI). Each subject’s DermaVir/Placebo application schedule will be administered

over an 8-week period (Day 0, 28, and 56). HAART will be discontinued on Day 63 and will be resumed on Day 203. Subsequently, individuals who do not meet HAART restarting criteria can elect not to restart therapy. For them, and for all other participants, there will be a safety and immunogenicity follow up evaluation every 3 months for one additional year after week 29.

Criteria for HAART Resumption During ATI:

Resumption of HAART is recommended if, during ATI, subjects experience:

- A confirmed (defined as two consecutive values two weeks apart) CD4+ cell decrease by > 50% from the level when treatment is discontinued
- A confirmed (defined as two consecutive values two weeks apart) CD4+ cell decrease to less than 350
- A confirmed (defined as two consecutive values one week apart) VL increase > 300,000 copies
- Emergence of CDC AIDS related event(s)
- Signs or symptoms of clinically significant immunosuppression
- The subject or the subject's clinician wishes to restart HAART
- The subject becomes pregnant

Primary Hypothesis

HIV+ adult subjects on fully-suppressive HAART who receive DermaVir Patches will have higher proliferative capacity (PHPC) at study week 9 than will subjects who received Placebo Patches

Primary Objective

To investigate whether HIV PHPC counts measured at week 9 during maximally suppressive HAART in HIV+ adults is higher in subjects receiving DermaVir Patches treatment than in Placebo subjects

Secondary Objectives

- To determine whether subjects on fully-suppressive HAART who develop increases in HIV-specific PHPC have lower HIV-1 RNA during ATI (defined as the geometric mean of HIV-1 RNA obtained at Week 16 and Week 20) than subjects who do not increase PHPC
- To investigate whether HIV-specific PHPC counts measured during maximally suppressive HAART correlate with a lower Viral Load Time Averaged Area Under the Curve (TA-AUC) during ATI

- To determine if subjects who experience an increase in PHPC Gag p17 counts $\geq 2,000$ and/or PHPC total Gag counts $\geq 5,000$ prior to ATI are more likely to maintain HIV-1 RNA levels
 - a.) below 400 copies/mL
 - b.) below 5,000 copies/mL
 - c.) lower than prior to HAART treatment

at 16 and 20 weeks of an ATI than subjects who have PHPC Gag p17 counts $< 2,000$ and/or PHPC total Gag counts $< 5,000$ prior to ATI

- To investigate whether increases in PHPC Gag p17 counts $\geq 2,000$ and/or PHPC total Gag counts $\geq 5,000$ obtained prior to ATI delay Viral Load rebound (HIV-1 RNA above 400 or 5,000 copies/mL) during ATI
- To investigate whether increases in PHPC Gag p17 counts $\geq 2,000$ and/or PHPC total Gag counts $\geq 5,000$ prior to ATI maintain CD4+ and CD8+ T-cell counts in adults infected with HIV-1 undergoing ATI
- To determine whether DermaVir Patch treatment as a strategy to increase in HIV-specific PHPC counts is safe and well tolerated.