SAFETY OF THERAPEUTIC HIV-1 VACCINE FOR EARLY TREATED PERINATALLY INFECTED, HIV+ ADOLESCENTS

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BACKGROUND

HVRRICANE is a phase I, proof of concept, open-label, randomized trial to evaluate safety, immunogenicity and efficacy in HIV reservoir reduction of a prime-boost strategy with a multigene, multi-subtype A, B, C HIV-DNA vaccine (HIVIS DNA) and modified vaccinia Ankara Chiang Mai Double Recombinant (MVA) vaccine ± co-administration of Toll-like Receptor 4 (TLR4) agonist (within a Human Papillomavirus Vaccine) in adolescents and youth living with perinatally acquired HIV-1.

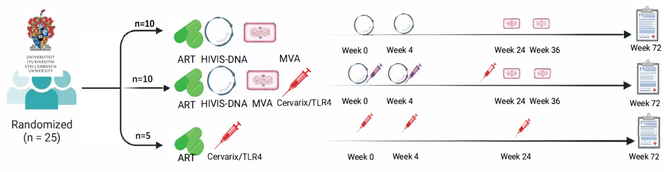
METHODS

25 South African adolescents living with perinatal HIV, 14 to 16 years of age, are enrolled. All participants initiated antiretroviral therapy < 6 months of age, were virally suppressed at enrolment and randomized into 3 arms (figure 1).

HIVIS DNA vaccines were administered through a novel needlefree device. Local and systemic reactions were captured 30 minutes after vaccination and on diary cards for seven days. Pregnancy was screened for at each visit.

The **Primary Objective** is to evaluate safety and the effect on the HIV reservoir (total HIV DNA and Inducible HIV RNA - TILDA). The **Secondary Objective** is to evaluate the dynamic of vaccine induced immune responses with and without the TLR4 agonist.

STUDY DESIGN



Enrollment Criteria
1. HIV perinatally infected
2. Know their HIV+ status
3. Initiated ART prior to 6 months of age
4. Male and female ≥ 9 years old
5. In generally good health
6. Plasma viral load < 200 copies/ml on ART at screening
7. CD4 count above 400 cells/mm^3 at screening
8. Participants of childbearing potential who are sexually active must be willing to practice effective contraception during the study
9. Negative urine β-HCG (human chorionic gonadotropin) pregnancy test for any female of childbearing age (post-menarche)
10. Availability for follow-up for planned duration of the study
11. Passing a test of understanding is required for participants ≥ 18 years old or the parent(s)/legal representative of participants < 18 years old before consent.
12. Written informed consent from participants ≥ 18 years old or parent(s)/legal representative of participants < 18 years old. Assent by participants aged 9-17 years old will also be required.
13. Laboratory criteria within 8 weeks prior to enrollment

Figure 1. HVRRICANE Study Design

This is the 1st combination therapeutic HIV vaccine study in pediatrics. All participants reported injection site reactions. There were no major safety signals & no dose limiting adverse events.

RESULTS

Demographic and clinical baseline characteristics

The mean age at enrolment was 15.3 years, 52% were male (Table 1). The median CD4+ T cell count is 768/μL. All the participants had undetectable HIV viral loads at screening (Table 2).

Table 1. Demographics

Randomized Arm	Characteristic	Male	Female	All
Arm 1 (n=10)	n (%)	5 (50%)	5 (50%)	10 (100%)
	Age - Median (Min – Max)	16.0 (15-16)	15.0 (15-15)	15.0 (15-16)
Arm 2 (n=10)	n (%)	4 (40%)	6 (60%)	10 (100%)
	Age - Median (Min – Max)	15.0 (14-16)	15.0 (15-16)	15.0 (14-16)
Arm 3 (n=5)	n (%)	4 (80%)	1 (20%)	5 (100%)
	Age - Median (Min – Max)	15.5 (15-16)	16.0 (16-16)	16.0 (15-16)
Total (n=25)	n (%)	13 (52%)	12 (48%)	25 (100%)
	Age - Median (Min – Max)	15.0 (14-16)	15.0 (15-16)	15.0 (14-16)

Table 2. Baseline CD4/8 and HIV viral loads

Lab Test	Characteristics	Results
CD4+ T cell count	n (%)	25 (100%)
	Median (Q1-Q3)	768 (654 – 895)
CD8+ T cell count	n (%)	25 (100%)
	Median (Q1-Q3)	746 (605 – 972)
HIV viral load	Not detected – N (%)	23 (92%)
	<40 copies/mL – N (%)	2 (8%)

Table 3. Study Product Administration

	Week 0		Week 4		Week 24		Week 36	
Arm (n=planned for each arm)	Visit n	Vaccinated n (%)	Visit n	Vaccinated n (%)	Visit n	Vaccinated n (%)	Visit n	Vaccinated n (%)
Arm 1 (n=10)	10	10 (100%)	10	10 (100%)	9	9 (90.0%)	9	9 (90.0%)
Arm 2 (n=10)	10	10 (100%)	10	10 (100%)	9	9 (90.0%)	9	9 (90.0%)
Arm 3 (n= 5)	5	5 (100%)	5	5 (100%)	5	5 (100%)	NA	NA
Total (n=25)	25	25 (100%)	25	25 (100%)	23	23 (92.0%)	18	18 (90.0%)

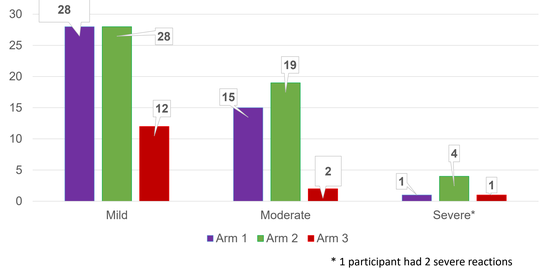


Figure 2. Adverse Events (AE)

Study product administration

4 participants missed vaccinations. 2 in **Arm 1**: 1 at week 24 (dose #1 MVA) due to school examination attendance and 1 at week 36 (dose #2 of MVA) due to pulmonary TB and 2 in **Arm 2**: 1 at week 24 (dose #1 MVA) as was pregnant and 1 at week 36 (dose #2 of MVA) due to Grade 3 reduction of estimated Glomerular Filtration Rate rate (Table 3).

Reactogenicity

All 25 participants reported **injection reactions**:

- 24 (96%) participants reported local reactions (pain, itching, swelling, redness, bruising)
- 21 (84%) participants reported systemic reactions (fever, fatigue, headache, muscle ache, joint pain, rash, chills, nausea, generally not feeling well)

5 participants reported 6 **severe** adverse events. All of which resolved (Figure 2)

- *After week 4 vaccination:*
  1 participant in **Arm 1** reported severe headache (resolved on day 1 after vaccination) and 1 participant in **Arm 2** reported severe headache (severity reduced rapidly but only resolved on day 10).
- *After week 24 vaccination:*
  1 participant in **Arm 2** reported severe injection site pain (resolved on day 3). 1 participant in **Arm 2** reported severe headache (resolved on day 2). 1 participant in **Arm 3** reported severe fatigue (resolved on day 2).
- *After week 36 vaccination:*
  1 participant in **Arm 2** reported severe fatigue, headache & chills (resolved by day 3).

CONCLUSIONS

In this 1st combined therapeutic HIV vaccine study in pediatrics, all participants reported local and/or systemic reactions to vaccination. Events were self-limiting & without dose limiting AEs. The immunogenicity and reservoir data will follow.

ADDITIONAL KEY INFORMATION

HIVIS DNA vaccine plasmids were designed and produced at Karolinska Institutet and Vecura, HIV-MVA vaccine was produced at Henry M. Jackson Foundation. Details of sequences in Heliyon 2017 Jun 29;3(6):e00339. This study was performed by the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. MD, USA and Stellenbosch University, Cape Town, South Africa. The study was sponsored by the Henry M. Jackson Foundation. Funding: Division of AIDS, National Institute of Allergy & Infectious Disease, NIH (Grant U01AI135941) and Fondazione PENTA for the treatment and care of children with HIV (and related diseases). DISCLAIMER: The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, National Institutes of Health, the Department of Health and Human Services, or the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. The investigators adhered to the policies for protection of human subjects prescribed in AR-70-25.