The quest for a prophylactic HIV vaccine continues: results from a phase I trial using novel routes of DNA vaccination in HIV uninfected volunteers

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Background

- As the HIV epidemic continues to expand, it is widely accepted a preventative HIV vaccine is a vital public health priority
- DNA vaccines are being increasingly utilized based on several advantages over other vaccines including rapid manufacture, cost effectiveness and lack of concerns associated with the administration of infectious agents[1]
- Limitations to DNA vaccination are related to inefficient uptake of DNA into cells and rapid degradation, thus ineffective antigen presentation
- Ongoing efforts investigating DNA vaccine delivery are therefore of great interest in an effort to improve immunogenicity and these include cutaneous routes
- Previous studies have shown a dose sparing effect of intradermal (ID) vaccination, where only 10-20% of a conventional intramuscular dose (IM) is needed to be adequately immunogenic[2]
- Transcutaneous (TC) vaccine delivery, is 'needle-free' and in a recent Phase I clinical trial using an influenza/tetanus vaccine[3], this method favoured the development of CD8+ T cell responses, a potentially crucial killing mechanism in HIV. This method has never been utilised in a DNA preventative HIV vaccine trial
- Physical methods of delivering DNA such as in vivo electroporation (EP) have been shown to enhance DNA immunogenicity in early clinical trials[4]
- In this Phase I RCT we report on the safety and immunogenicity of a GTU® MultiHIV B clade DNA vaccine in HIV uninfected participants administered via the 3 different routes described above

Methods

- 30 HIV uninfected participants deemed eligible according to strict criteria, were randomised to received GTU® MultiHIV Clade B DNA vaccine at weeks 0/4/12 by 1 of 3 routes: IM+ID, IM+TC and IM+EP
- Participants were assessed for local and systemic reactogenicity and adverse events
- T cell responses to vaccine encoded peptides (*rev, tat, nef, gag, CTL* coded for by *pol* and *env* genes) made were measured by IFN-ɣ ELISpot and intracellular cytokine staining (ICS)
- An exploratory end point to assess CD8+ T cell function was conducted using a viral inhibition assay (VIA)

References:

1. Martinon et al. Persistent immune responses induced by a human immunodeficiency virus DAN vaccine delivered in association with electroporation in the skin of non human primates. *Hum Gen Ther* 2009,**20**:1291-1307
2. Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. *N Engl J Med* 2004,**351**:2295-2301.
3. Combadiere B, Vogt A, Mahe B, Costagliola D, Hadam S, Bonduelle O*, et al.* Preferential amplification of CD8 effector-T cells after transcutaneous application of an inactivated influenza vaccine: a randomized phase I trial. *PLoS One* 2010,**5**:e10818.
4. Vasan S, Hurley A, Schlesinger SJ, Hannaman D, Gardiner DF, Dugin DP*, et al.* In vivo electroporation enhances the immunogenicity of an HIV-1 DNA vaccine candidate in healthy volunteers. *PLoS One* 2011,**6**:e19252.
5. Spentzou A, Bergin P, Gill D, Cheeseman H, Ashraf A, Kaltsidis H*, et al.* Viral inhibition assay: a CD8 T cell neutralization assay for use in clinical trials of HIV-1 vaccine candidates. *J Infect Dis* 2010,**201**:720-729.

Results

Recruitment and participant flow

•59 participants were screened with 30 deemed eligible according to inclusion/exclusion criteria. The table below shows the demographics of enrolled participants (Table 1)

Table 1

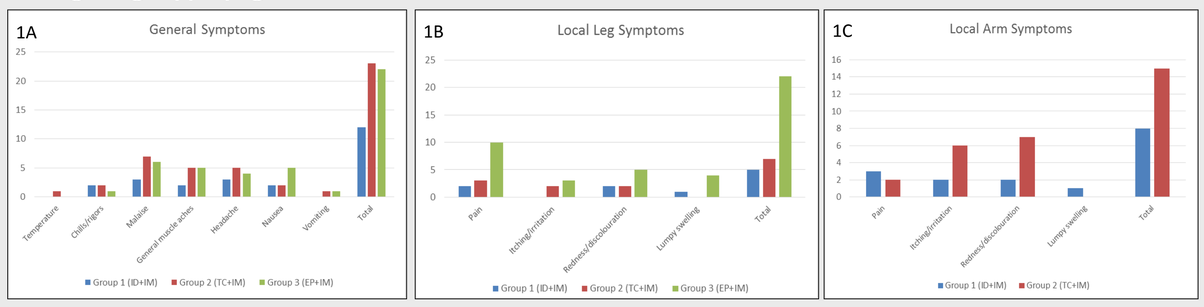
		Group 1 ID+IM	Group 2 TC+IM	Group 3 EP+IM	Total (%)
Demographics					
Gender	Male	5	6	6	**17 (56)**
	Female	4	5	4	**13 (43)**
Ethnicity	White	8	7	8	**23 (77)**
	Black	0	2	2	**4 (13)**
	Asian	0	2	0	**2 (7)**
	Other Ethnic Group	1	0	0	**1 (3)**
Age (years)	Mean (range)	27.4 (22-34)	31.5 (21-42)	31.7 (23-39)	**30.4 (21-42yrs)**

3 participants did not complete all vaccine visits, but remained in follow up: In the ID+IM group the participant moved away before trial completion. In the TC+IM group the participant chose to not have the final vaccine due to ongoing hypopigmentation over the vaccine site, and in the EP+IM group the participant chose not to continue with vaccinations due to pain linked to the EP procedure

Reactogenicity and safety

•Overall there were no safety concerns with no significant differences between groups with respect to local and systemic reactogenicity (Fig 1A). In the EP+IM group there were a greater number of participants documenting pain in the leg on their diary cards following EP (Fig 1B), although over 90% participants in this group thought it to be an acceptable route of vaccine delivery.

•In the TC+IM group, a greater number of participants documented redness and discolouration secondary to the procedure compared to the ID+IM group (7 responses compared to 2 respectively Fig 1C). 5/11 participants in the TC group had either hypo or hyperpigmentation related to post-inflammatory changes as a direct result of the TC procedure (example shown in Fig 2). All these changes resolved over time, although notably 1 person in the TC+IM group declined the final vaccination as a result of ongoing hypopigmentation over the vaccine site



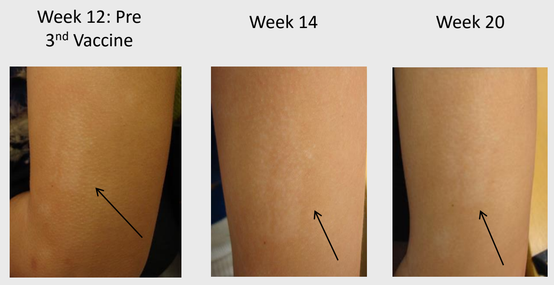


Figure 2: Example of post inflammatory hypopigmentation as a result of TC procedure. This participant was Caucasian and declined the final vaccine due to persisting changes.

Immunogenicity

1.T Cell ELISpots (primary end point = 2 weeks post final vaccine)

•At the primary end point, EP+IM performed better than both ID+IM and TC+IM groups with 9/10 responders to any peptide in the EP+IM group compared to 1/9 in the ID+IM group and 0/11 in the TC+IM group (Fig 3A). Pooled peptide responses were also greater in the EP +IM group (Fig 3B)

•Within the EP+IM group, the greatest magnitude of IFN-ɣ response was to Nef and Gag peptide pools with 8/10 (80%) and 9/10 (90%) participants responding to these antigens respectively (Figure 3C). The weakest responses were to Tat and this was consistent across all 3 vaccination groups. The EP+IM group also showed duration of response across time (Figure 3D).

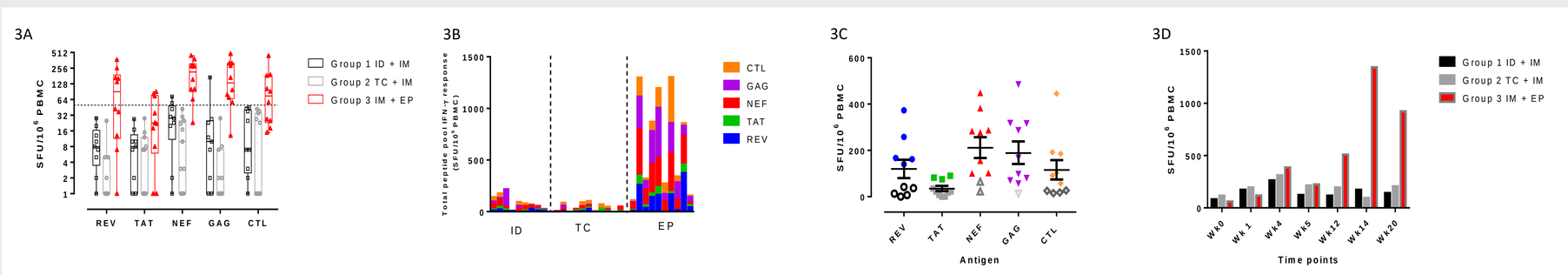
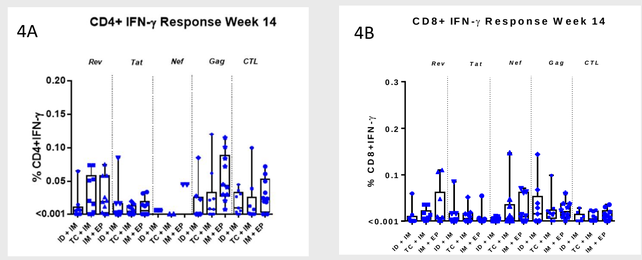


Figure legend: **3A**-Primary end point data comparing IFN-ɣ response to all peptide pools. Dotted line denotes cut off for positive response (>55 SFU/M PBMC). **3B**-pooled peptide response by group at the primary end point. **3C**- EP+IM group only showing IFN-ɣ response to the peptides. **3D**- IFN-ɣ response in different groups across time.

2. Intracellular cytokine staining (ICS)

•ICS analysis showed a significant increase in CD4+ gag specific IFN-ɣ responses in the IM+EP group, with few CD8+ specific responses (Fig 4)



3. Viral inhibition assay (VIA)

•A viral inhibition assay was used to measure the in vitro ability of CD8+ cells to inhibit HIV replication based on a previously published assay[5] and using a panel of 6 viruses (Table 2)

•All groups showed viral inhibitory activity to at least one virus at the primary end point, in 2/9, 4/9 and 5/7 participants across groups ID+IM, TC+IM, EP+IM respectively.

•The greatest number of participants with detectable HIV-specific CD8+ cells capable of inhibiting any virus was in the EP+IM group (71% participants) and to the greatest number of viruses in the panel (4/6), with the greatest cross clade inhibition (Figs 5A and 5B).

Table 2: Panel of 6 viruses using in VIA

VIRUS	CLADE	TYPE	CXCR4/CCR5
IIIB	B	Lab	X4
CH077	B	IMC	R5
CH106	B	IMC	R5
ELI	AD	Lab	X4
U455	A	Lab	X4
CBL4	D	Lab	X4

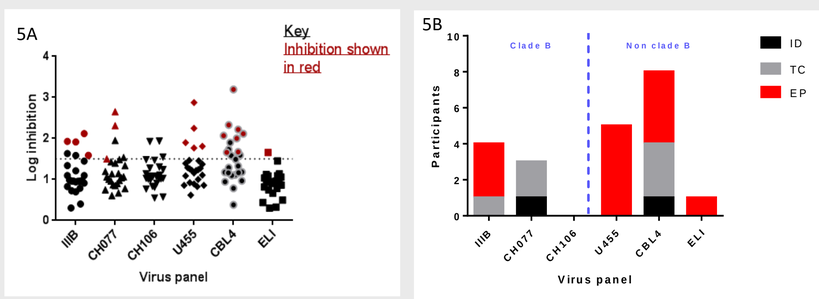


Figure legend: **4A**- ICS data showing CD4+ IFN-ɣ response at primary end point **4B**- ICS data showing CD8+ IFN-ɣ response at primary end point. **5A**- Viral inhibition assay showing inhibition in red according to IAVI criteria (>1.5 log and >0.6 baseline inhibition). **5B**- No. participants inhibiting virus by group showing clade B and non clade B viruses

Conclusions

- The GTU® MultiHIV B clade DNA vaccine was safe and well tolerated across all routes of vaccine administration and showed the greatest cellular immunogenicity when administered IM with EP
- The use of EP induced the greatest and broadest CD8+ viral inhibitory activity, although all groups also showed inhibition
- Importantly and in line with other clinical trials using EP, participants found the procedure to be tolerable and acceptable
- It is important to place this predominantly T cell based DNA vaccine in the context of wider clinical trials assessing combined T can B cells responses, in the ultimate goal of developing a robust HIV preventative vaccine