PrEPVacc design

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on behalf of PrEPVacc Investigators
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Background to PrEPVacc Partnership

- PrEPVacc is led by African researchers based in Entebbe, Uganda at the MRC/UVRI and LSHTM Uganda Research Unit.
- They are supported by 15 partners from Africa, Europe and the US
- PrEPVacc builds on longstanding HIV prevention partnerships developed with European funding, with a key focus on capacity building and transfer
  - EuroVacc
  - TaMoVac and AfrEVac
  - Microbicides Development Programme
- The partnership brought vaccine candidates, key populations and know-how in the fields of immunology, social science and data science
- In 2017 the vaccine candidates were ready for the next step - clinical efficacy testing

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Three trials in one

- two vaccine trials

The vaccine trials

Objectives

To assess safety and efficacy of two HIV-1 prophylactic vaccine regimens, each compared to placebo in preventing acquisition of HIV

Design

- Vaccine A: DNA-HIV-PT123 and AIDSVAX in alum wks 0, 4, 24, 48
- Vaccine B: DNA-HIV-PT123 and CN54gp140 in MPLA-L wks 0, 4 MVA_CMDR and CN54gp140 in MPLA-L wks 24, 48
- Placebo: Saline wks 0, 4, 24, 26

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Selection of Vaccines

DNA-HIV-PT123 (clade C) and AIDSVAX® B/E

- Evaluated in four Phase I/II trials in US, Europe and Uganda
- Safe and immunogenic

DNA-HIV-PT123, MVA_CMDR, CN54gp140 in MPLA-L

- MVA and CN54gp140 in GLA-AF evaluated in Tanzania and Mozambique in populations primed with multi-clade HIVIS DNA
- HIVIS DNA not available, so DNA-HIV-PT123 used as prime

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Primary Vaccine Analysis

EFFICACY

- HIV acquisition by an individual who completed the first three injections AND was HIV negative at wk 26 [Timeframe: wk 26 to wk 74 or beyond]

SAFETY

- A clinical decision to discontinue injections for an adverse event that is considered related to product

Rationale for design in 2017

- Designed to detect vaccine efficacy of *public health relevance*.
- PrEP had been shown to be highly effective (up to 86% reduction in HIV incidence) and near perfect protection when taken consistently around condomless sex acts.
- To justify implementing a multi-dose HIV vaccine regimen, it would need to be nearly as good – decision to set *target efficacy of 70% reduction in HIV incidence*
- The reduction in HIV incidence seen in RV144 in the first 12 months of follow-up was 60%, so could be achievable
- Importantly informing a decision to proceed to licensing trial for the vaccines
- Logical to incorporate PrEP as a study drug in the vaccine regimen for the time to peak responses in sexually active adults; reverting to locally sourced PrEP thereafter

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Sample size calculation

- Used nstage software for multi-arm, multi-stage design
- Assumed incidence of *4 per 100pyrs for HIV infections*
- Assumed *10% loss to follow-up*
- 556 participants per group would generate sufficient endpoints to detect a *70% reduction relative to placebo at the final analysis*
- Should incidence be lower, a longer period of follow-up would be required
- One formal interim analysis when there are approximately 7 infections in the placebo group that meet the endpoint criteria

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Sample size calculation

Efficacy	Incidence n/100py	N events in control at interim	N participants per group	Assuming 10% LTFU
70%	3	7	561	623
	4	7	500	556
	5	7	434	482
50%	3	18	919	1021
	4	18	805	894
	5	18	713	792

- If incidence is lower the sample increases *from 556 to 623* when the target efficacy is 70%
- If target efficacy is lower eg 50% the sample increases *from 556 to 894* when incidence is 4/100py

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PrEPVacc partners

Coordinating partners

Pontiano Kaleebu, Eugene Ruzagira (MRC/UVRI & LSHTM, Uganda**)**
Jonathan Weber/Julie Fox/Cherry Kingsley (Imperial College, UK)
Sheena McCormack (UCL, UK)
Kundai Chinyenze (IAVI-Kenya)
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Arianna Marini (IAVI/Imperial College)
Charlotta Nilsson (Karolinska, Sweden)
Chriss Geldmacher (LMU, Germany)
Gustavo Doncel (CONRAD/EVMS, US)

https://www.prepvacc.org/

Partners with a centre

Pontiano Kaleebu (MRC/UVRI&LSHTM, **Masaka, Uganda**)
Lucas Maganga (MMRC, **Mbeya, Tanzania**)
Said Aboud (MUHAS, **Dar es Salaam, Tanzania**)
Ilesh Jani (CISPOC, **Maputo, Mozambique**)
Glenda Gray (HPRU, **Durban, South Africa**)

Partners with a product

Song Ding (EVF, Switzerland)
Carter Lee (GSID, US)
Merlin Robb (MHRP, US)
Cherry Kingsley (Imperial, UK)
Jim Rooney (Gilead, US)

People around the centres

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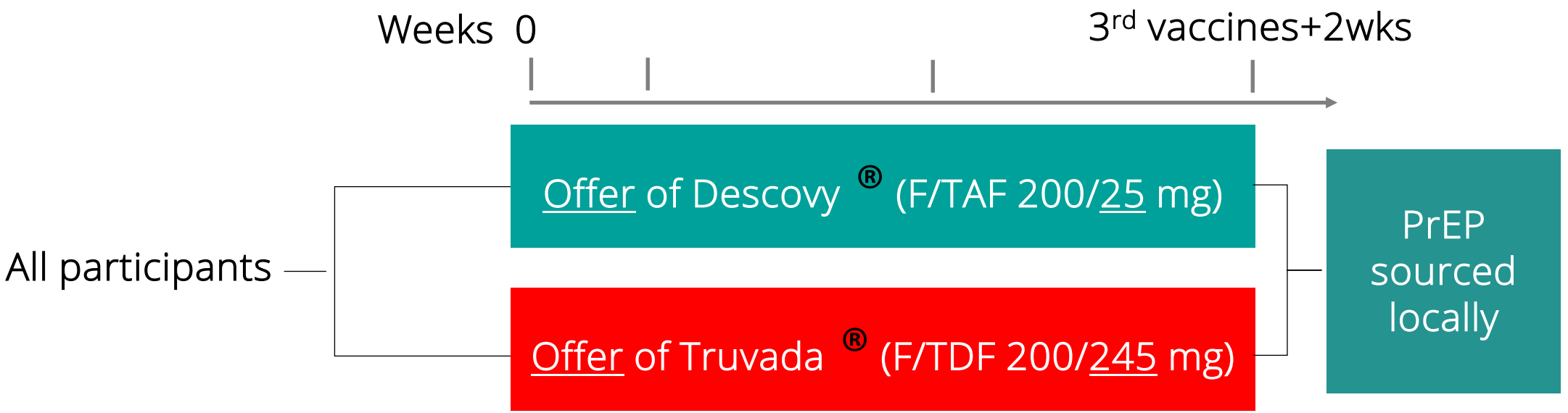
The third trial

- a PrEP trial

PrEP trial design and PrEP provision



The local source has evolved with time and is currently:

- Available in clinic in SAMRC Durban South Africa and MUHAS, Dar es Salaam Tanzania
- Available from several providers in Masaka region, Uganda; some providers but not all provide treatment
- Available through donor programmes close to the clinic in MMR Mbeya, Tanzania

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Rationale and PrEP question

- Considered how PrEP would be integrated in a national HIV vaccine programme – *to cover time to peak responses 2 weeks after third vaccines*
- Initially planned to offer Truvada to all ie not a trial
- DISCOVER reported effectiveness in men; the regulators *licensed Descovy for use by men*
- We took the *opportunity to evaluate Descovy in a predominantly female population*
- The PrEP trial was incorporated in PrEPVacc as a second randomisation – *hence the 'offer'*

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PrEP objective

- Aim to show that the *effectiveness of Descovy is not unacceptably lower than the effectiveness of Truvada*
- Effectiveness of Truvada is a challenge for new PrEP drugs – requires *innovative analysis methods*
- Effectiveness of Truvada is *broadly aligned to adherence*

Self-report Adherence data collected

On 5 occasions during the study PrEP period participants were asked

- Days since last sex act without a condom
- PrEP taken in 2 days before last sex act without a condom
- If sex was 2 or more days ago, PrEP taken in the 2 days after last sex act without a condom

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Drug Adherence data collected

Dry blood spot (DBS) samples were collected to measure drug

- on 2 occasions during the study PrEP period
- Every 6 months in the non-study PrEP period

Urine was tested in real-time when kits were available, and retrospectively when they were not

- On 3 occasions during the study PrEP period
- Every 6 months in the non-study PrEP period

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Adherence when it matters

- We know from previous trials and programmes that it's challenging to take PrEP every day
- But people don't have sex every day
- Aimed to ensure PrEPVacc participants knew the important time to take PrEP was around sex acts without a condom
- Social science key to understanding participant behaviours

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Assumptions underlying sample size

Variable	Protocol	Reality
Number of participants	1668	1512 Remove the 93 participants never dispensed PrEP
Follow-up per participants	26 weeks – 834py	Longer for participants whose 3rd vaccines were delayed up to 40 weeks
Counterfactual incidence	3-5%	Probable over-estimate Explore values between 2% and 3%.
Effectiveness of TDF/FTC	50-80%	Probable underestimate Explore values between 70% and 90%.

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Adherence assumptions

Non-inferiority margin (%)	Effectiveness (%) of TDF/FTC	Placebo incidence (per 100 PY)		
		2.0	2.5	3.0
50	70	49	57	64
50	75	61	69	76
50	80	74	82	87
50	85	88	93	96
50	90	98	99	99

- Acceptable power at higher levels of ‘adherence’

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Efficiencies and Challenges in design

- Three trials in one study population – two vaccine trials and one PrEP trial
- Only counting new infections from the time of peak responses was intended to give the *vaccines the best chance of demonstrating biological success, with few endpoints*
- *Adaptive trial, allowing change in randomisation ratio* from 1:1:1 to 1:1 for futility in regimen A or B, and potential to add a new vaccine combination in
- We knew including PrEP as a study drug *could increase non-study PrEP* uptake and persistence – this would reduce power for the vaccine trial, but be a good result for communities
- The *assumption of 4 per 100 person years HIV incidence was very uncertain* as test, treat and PrEP were increasing, and 2 study populations were new to the centres
- The *assumption of 70% adherence to Truvada was uncertain* as locally sourced PrEP was only available in one location when we started in 2018

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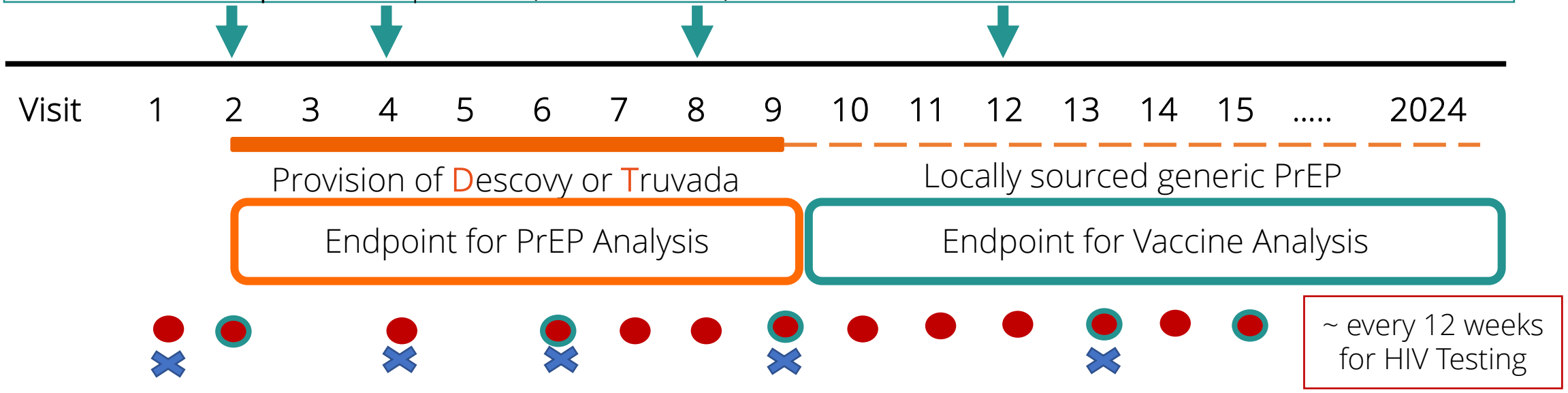
Study Schema

Injections
- Vaccine Group A: DNA-HIV-PT123 and AIDSVAX® B/E (wks 0,4,24,48)
- Vaccine Group B: DNA-HIV-PT123 and CN54gp140+MPLA-L (wks 0,4), then MVA-CMDR and CN54gp140+MPLA-L (wks 24,48)
- Vaccine Group C: Saline placebo (wks 0,4,24,48)



Blood for haematology/biochemistry at visits 1, 4, 6, 9, 13; dry blood spots for drug levels visits 2, 6, 9, 12, 15 then every 24 weeks

Blood for HIV testing/store at visits 1, 2, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, every 12 week during long-term FU

Larger blood draw for immune responses and store at visits 2, 6, 9, 13, 15 and at a new HIV infection visit