PrEPVacc Analysis Plan

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(On behalf of the PrEPVacc study team 11th Jan 2024)

This project is part of the EDCTP2 Programme supported by the European Union

PrEPVacc Study objectives

- To assess the safety and efficacy of two HIV-1 prophylactic vaccine regimens, each compared to placebo in reducing HIV incidence.

- To compare the safety and effectiveness of Descovy relative to Truvada in reducing HIV incidence, in the context of background incidence.

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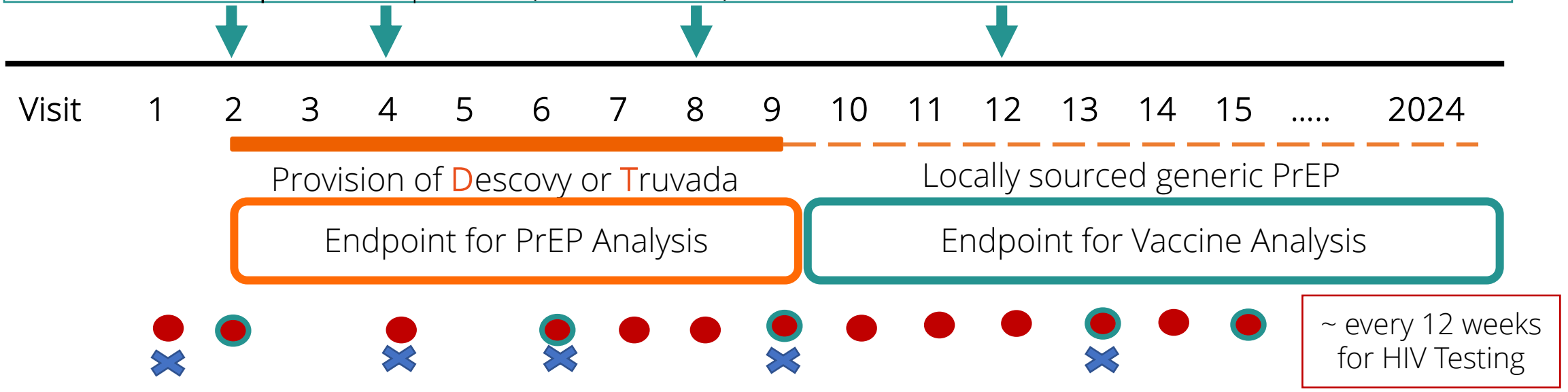
Study Schema

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

Analysis of the primary vaccine efficacy outcome

- Primary outcome (vaccine study)
  - HIV acquisition by a participant who completed their first 3 immunisations and was HIV negative two weeks after 3rd .
  - At least one follow-up assessment thereafter
  - Participants are followed up until censored or infection
- Main analysis
  - HRs will be estimated in a time-to-event analysis using Cox PH regression adjusted for site and sex
  - Vaccine efficacy defined as 1 minus the hazard ratio for each active arm against placebo
  - P-values and 95% CIs for the VE estimates will be presented
- Supplementary analyses
  - Truncated at visit 15 (target week 74) & expanded follow up (From week 0)

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Independent Data Monitoring Committee

- Biannual IDMC reviews of the accruing safety and incidence data by treatment arm (both vaccine and PrEP) were conducted.
- Additionally: 1 planned formal interim analysis to assess vaccine efficacy after approximately seven HIV infections (in participants who complete 3 immunisations) observed in the placebo arm.
- if # participants with infections in one or both of the active arms equal or exceed # infections in the placebo arm the IDMC could recommend stopping further enrolments & vaccinations in the relevant arms(s) after reviewing additional analyses (e.g conditional power)

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Analysis of safety and secondary vaccine outcomes

- Primary safety outcome
  - A clinical decision to discontinue the vaccine regimen for an AE related to product

- Secondary outcomes
  - Grade 3 and above solicited AE lasting more than 72 hours
  - Grade 3 and above laboratory AE
  - AE leading to discontinuation/interruption of vaccine schedule regardless of relationship
  - Serious adverse events
  - Other clinical and lab AEs

(All above outcomes will be compared across arms using descriptive analyses showing number and proportion/rate as appropriate, with 95% CIs.)

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Analysis of the primary PrEP effectiveness outcome

- Primary outcome (PrEP comparison)
  - HIV acquisition by a participant before visit 9
  - HIV negative at enrolment
  - Randomised (to either Truvada or Descovy) and dispensed drug

- Analysis
  - The # and rate of infections will be presented for each PrEP arm
  - The rate difference and rate ratio will be presented with 95% CIs
  - The Averted Infections Ratio (AIR; Dunn et al., 2018) will be calculated.
  - + Supplementary analyses

$$\left(AIR = \frac{\text{rate in placebo arm}* - \text{rate in } \textit{Descovy} \text{ arm}}{\text{rate in placebo arm}* - \text{rate in } \textit{Truvada} \text{ arm}} \right) \quad \Rightarrow \quad AIR = \frac{0.040 - 0.020}{0.040 - 0.015} = \frac{0.020}{0.025} = \frac{20}{25} = 0.80$$

*Hypothetical/ counterfactual

Analysis of safety and secondary PrEP outcomes

- Primary safety outcome
  - A clinical decision to discontinue the PrEP regimen for an AE related to product
- Secondary outcomes
  - AE leading to discontinuation/interruption of vaccine schedule regardless of relationship
  - Serious adverse events
  - Genotypic resistance at HIV seroconversion
  - Adherence to PrEP

(All above outcomes will be compared across arms using descriptive analyses showing number and proportion/rate as appropriate, with 95% CIs.)

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Estimating the placebo incidence for the PrEP analysis

PrEPVacc Statistical Analysis Plan

The Averted Infections Ratio will be calculated based on:

a) An estimate of hypothetical placebo incidence from the registration cohort, utilising statistical modelling to adjust for any calendar time trends and differences between the registration cohort and the trial population in terms of important predictors of HIV incidence

b) An estimate of the hypothetical placebo incidence based on follow-up of trial participants during the vaccine study follow-up phase (after Visit 9), likely excluding participants who regularly take non-trial PrEP

If the trial provides evidence that vaccine efficacy is null, then all vaccine arms will be combined for the estimate

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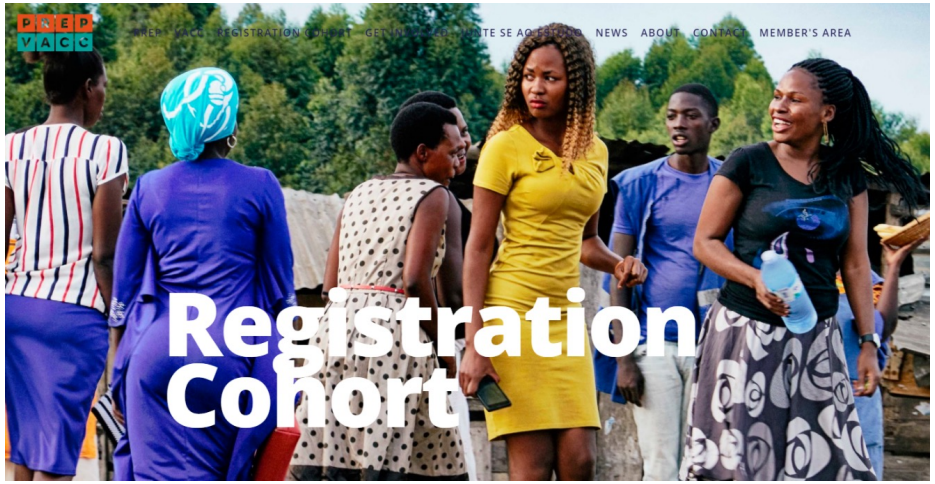
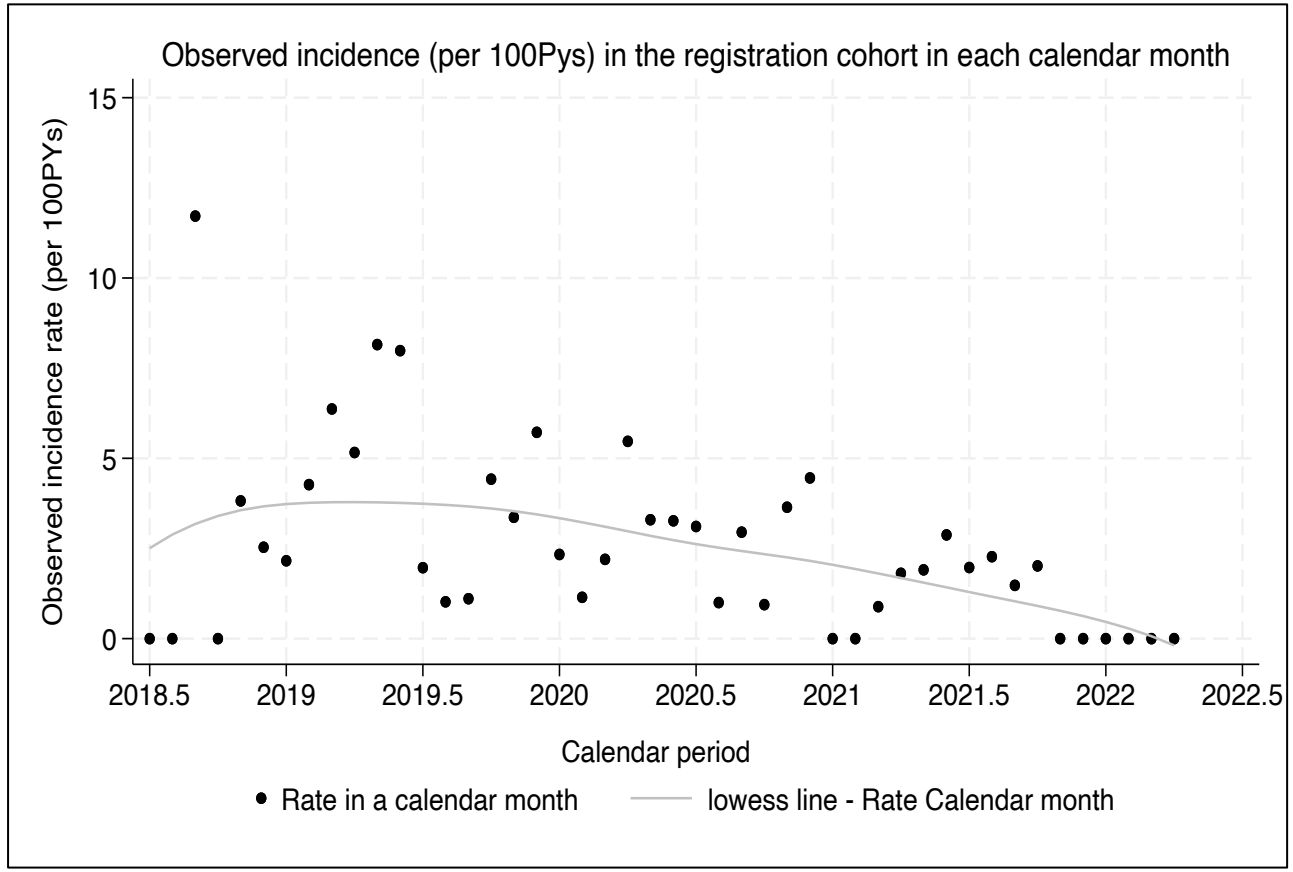
Rationale for Registration Cohort

- Could recruit in the 18 months it would take to prepare the study products, trial protocol and obtain approvals
- HIV-negative adults (18-45 yrs) at risk of HIV infection seen quarterly
- Assess access to PrEP as it evolved
- Would provide measure of HIV incidence
- And prepare communities for the Trial – envisaged to facilitate speedy enrolment



HIV incidence in the registration cohort



- Overall: 2.9 per 100Py (95% CI, 2.4-3.5)
- Decline over calendar period
- 2019: cluster of seroconversions
- 2020/2021: COVID-19 lockdowns
- Dec 2020: Start of PrEP trial – shorter follow-up in cohort

Cohort start date: July 2018, few person-years in 2018
Data cut-off date: March 2022, few person-years in 2022/2023

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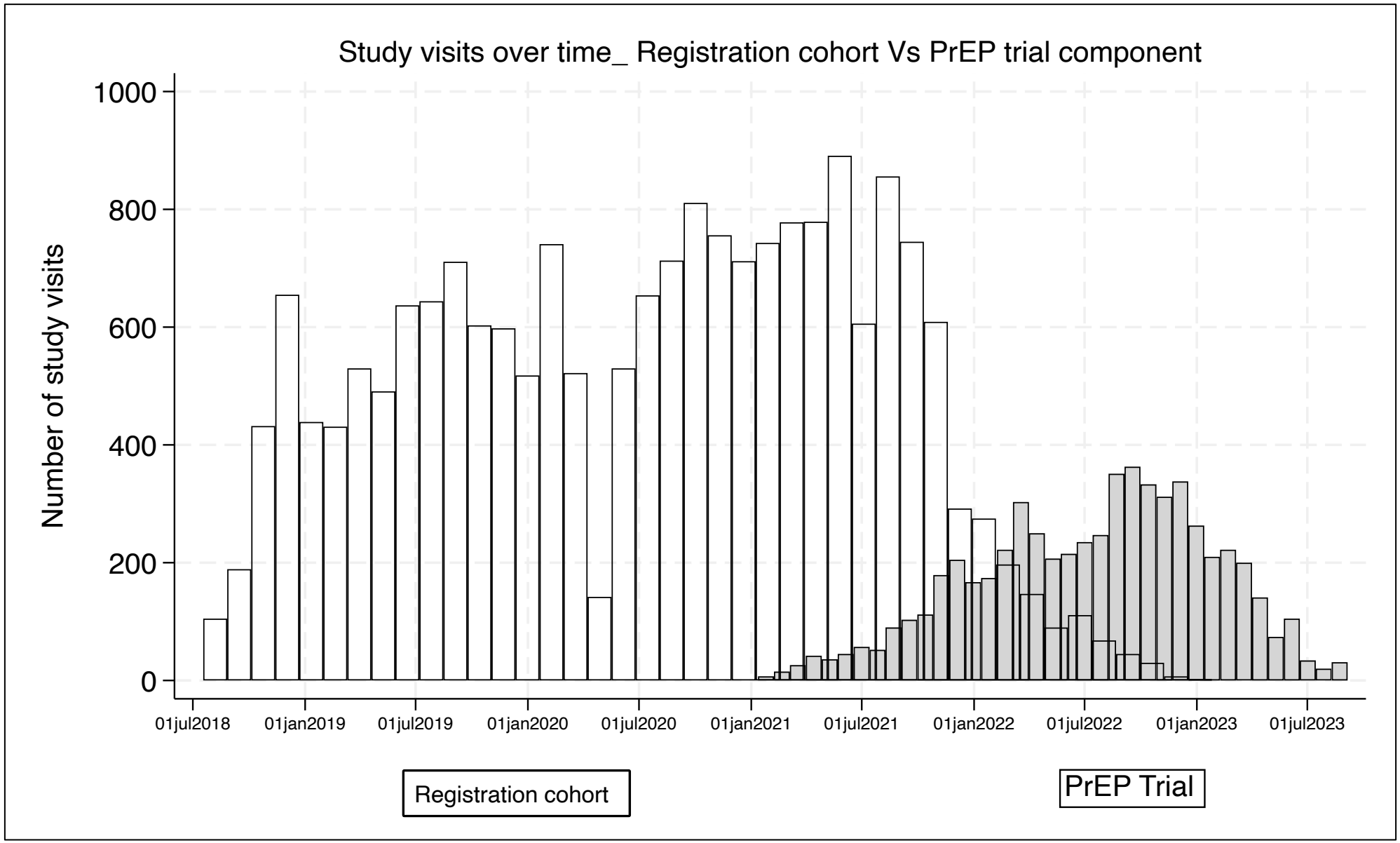
Study visits over time_ Registration cohort Vs PrEP trial component
Number of study visits
1000
800
600
400
200
0
01jul2018
01jan2019
01jul2019
01jan2020
01jul2020
01jan2021
01jul2021
01jan2022
01jul2022
01jan2023
01jul2023
Registration cohort
PrEP Trial

Approach – adherence data

We will also explore the possibility of deriving the AIR based on adherence data (which can be used to infer the effectiveness of Truvada)

- Self report on adherence around sex acts

DBS tests

- Current funding supports 600 tests at visit 6.
- Approximately 42% of the trial population
- 100 tests at visit 9 – To determine how well the visit 6 result predicts overall adherence in the study PrEP period.

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PrEP analyses - Conclusion

- Sensitivity analyses making different assumptions on the calendar period effect predicted varying counterfactual placebo HIV incidence rates.
- Ranging from 1.2 per 100PYs (95% CI: 0.4 -2.8), to 5.1 per 100PYs (95% CI: 2.9 – 8.4).
- Data post PrEP trial component - Available.
- Adherence data – (Self-report on adherence around unprotected sex; DBS data).
- Discussions on synthesising data from various counterfactual estimation approaches are ongoing.

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