Clinical trials design and methodology

OC - (8491) - PREPvacc: A PHASE III, MAMS ADAPTIVE PROPHYLACTIC HIV VACCINE TRIAL WITH A SECOND RANDOMISATION TO COMPARE F/TAF WITH TDF/FTC PREP

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Background: There remains an urgent need for a prophylactic HIV vaccine to control generalised epidemics. PrEP has demonstrated effectiveness of 86% and is recommended by WHO; uptake is generally high, but retention is disappointing in some settings. PrEPVacc (EDCTP:RIA2016V-1644) will assess the efficacy of two combination prophylactic vaccine regimens (DNA, MVA and Env protein/adjuvant) each compared to placebo and also the proportion of infections averted by F/TAF in comparison to TDF/FTC. A Registration Cohort, recruiting HIV negative volunteers at risk of HIV will precede the trial.

Methods: The PrEPVacc partnership agreed that 70% vaccine efficacy had public health relevance. The trial uses nstagesoftware for multi-arm, multi-stage designs (MAMS) and the averted infections ratio (AIR) methodology with participants randomised (i) 1:1:1:1 to active product or placebo (ii) 1:1 to TDF/FTC:F/TAF until week 26 (presumed peak immunogenicity). Access to PrEP in the Registration Cohort and after week 26 will be standard of care. HIV seroconversions occurring between weeks 0-26 will inform the PrEP analysis, incorporating HIV incidence amongst those who do not take up PrEP locally in the Registration Cohort. Seroconversions after week 26 will inform vaccine analyses.

Results. Up to 556 participants per group affords 92% power to detect vaccine efficacy of 70% at the final analysis, assuming incidence of 4/100 person years and 10% loss with 81% and 97% power to conclude that F/TAF can avert half or more of the infections prevented by TDF/FTC if effectiveness of TDF/FTC is 70% and 80% respectively.

Conclusion: PrEPvacc adopts a pragmatic approach to uncertainties around HIV incidence in settings where PrEP is increasingly available. This innovative adaptive trial
design uses validated software to determine vaccine efficacy and novel methodology to evaluate a new PrEP agent, overcoming the challenge of demonstrating non-inferiority when adherence to TDF/FTC is high and the number of outcome events very low.