SECOND JOINT CONFERENCE
OF BHIVA AND BASHH 2010

British HIV Association
BHIVA
16th Annual Conference

BASHH
8th Annual Conference

Dr Sheena McCormack

MRC Clinical Trials Unit, London

20-23 April 2010, Manchester Central Convention Complex

MRC Clinical Trials Unit

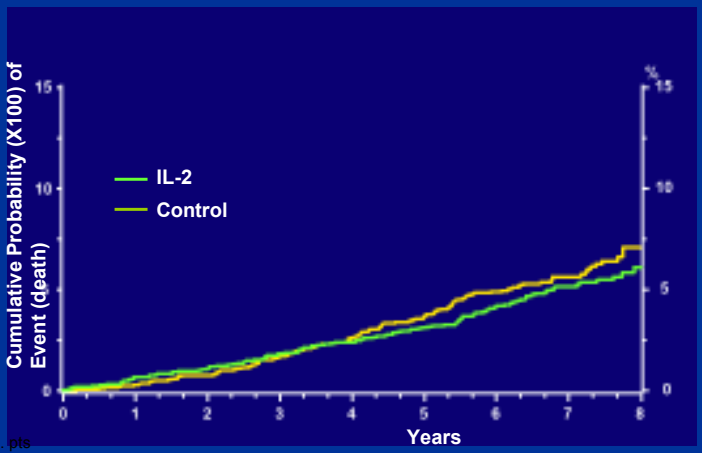
HIV treatment trials using novel strategies and drug combinations

MRC Clinical Trials Unit

The current portfolio…

- Immune based therapy - HCQ-01
- PI monotherapy - PIVOT
- Raltegravir-based 1st line - NEAT 001
- Raltegravir-based 2nd line – EARNEST
- (When to start therapy – START)

Immune based therapy: life after ESPRIT…..

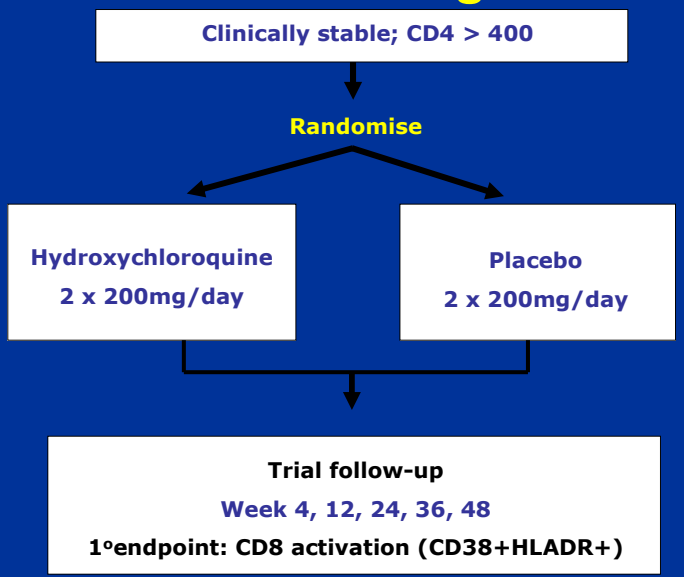


No. pts									
IL-2:	2071	2040	2016	1980	1952	1920	1595	998	336
Control:	2040	2018	1989	1956	1922	1875	1530	941	292

Immune based therapy

- Immune activation is an important therapeutic target
- Hydroxchloroquine is safe in long term use
- *In vitro* decreases immune activation

HCQ-01 design



HCQ-01 trial status

	Number screened																				Total screened per site	Total randomised per site
	2008							2009														
Sites	**M**	**J**	**J**	**A**	**S**	**O**	**N**	**D**	**J**	**F**	**M**	**A**	**M**	**J**	**J**	**A**	**S**	**O**	**N**	**D**	**J**	
Barts & The London					3	1										1	3	1	1	2		**12**	**6**
Brighton			2	3		3	2	1	3		1	1	3	2		1	1			1		**24**	**12**
Chelsea & Westminster		1	3	1	3		1	2	4	2	1		5	6	4	1	3	1	1			**39**	**22**
Royal Free																						**0**	**0**
St Georges									2													**2**	**2**
St Mary's	1	1	1		1								1	2		1			1	2		**11**	**8**
UCL-Mortimer Market Centre			1		3				2	1	4	2	2	8	1	1	1	3	4			**33**	**18**
Central Middlesex															1					1		**2**	**0**
John Radcliffe																		1				**1**	**0**
Kings																			1	1		**2**	**2**
Newham																						**0**	**0**
North Middlesex													2		1							**3**	**2**
Royal Bournemouth																	1		4	2		**7**	**4**
Southmead Bristol																			2			**2**	**0**
St Thomas'																	2	4	5	2		**13**	**7**
Total screened per month	**1**	**2**	**7**	**4**	**10**	**4**	**3**	**3**	**11**	**3**	**6**	**3**	**13**	**18**	**7**	**5**	**11**	**10**	**19**	**11**	**0**	**151**	
Total randomised per month	**0**	**1**	**1**	**0**	**3**	**1**	**3**	**1**	**2**	**5**	**5**	**4**	**1**	**4**	**12**	**5**	**5**	**5**	**8**	**7**	**10**		**83**
Protocol version						V2					V3												

Recruitment completed Jan 2010; n =83
Last week 48 visit end November 2010
Results available January 2011

PIVOT

Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in the long term management of HIV infection

Funded by HTA (NIHR), sponsored by MRC

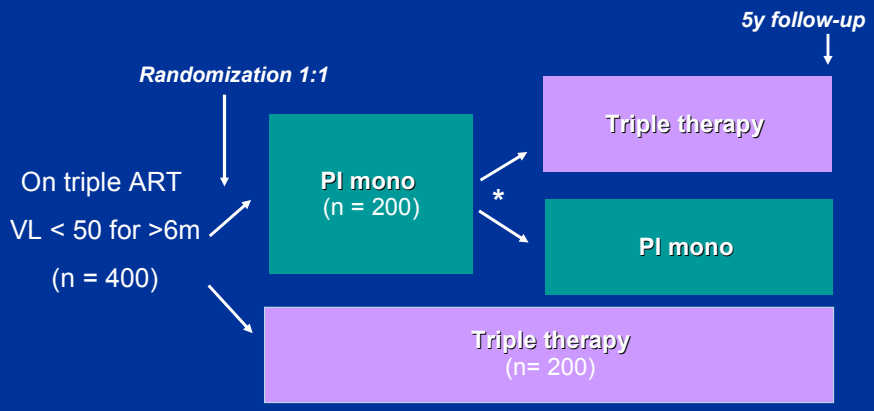
Managing HIV for the long-term

- May need 20-60 years of therapy
- Important considerations in choice of regimen:
  - Minimise long-term toxicity
  - Maximise range of sequential options for durable therapy
  - Manage costs for healthcare systems

Objectives

- To address role of PI monotherapy as alternative to 1st line therapy in NHS
- Is the strategy of switching to PI monotherapy non-inferior to continuing triple therapy at 3 years …in terms of maintaining all available drug treatment options
- To compare long-term safety and toxicity of PI monotherapy with triple therapy
- To assess the health economic benefits of PI monotherapy

Intervention Strategy



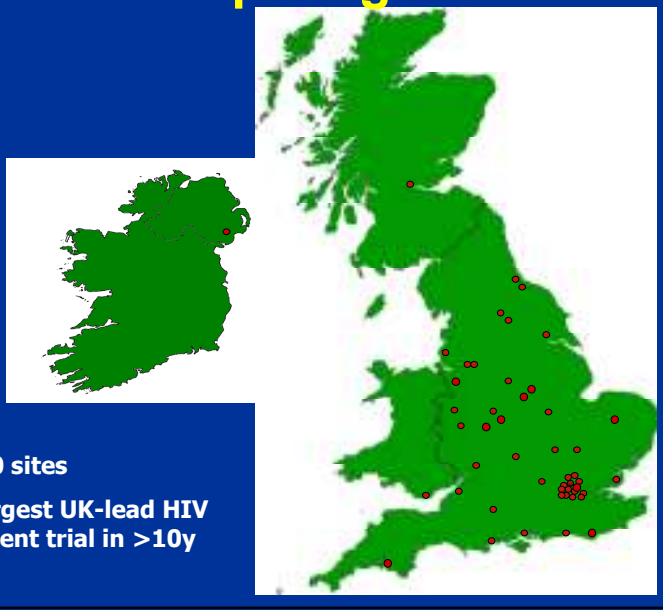
*Patients return to triple therapy if VL >50 copies X 2 tests

Primary endpoint: Preservation of future drug options (i.e. no drug resistance)

Secondary endpoints

- Serious drug or disease-related complications
- Adverse events
- Viral load rebound
- CD4 count change
- Quality of life change
- Neurocognitive function change
- Health care costs

Participating Sites



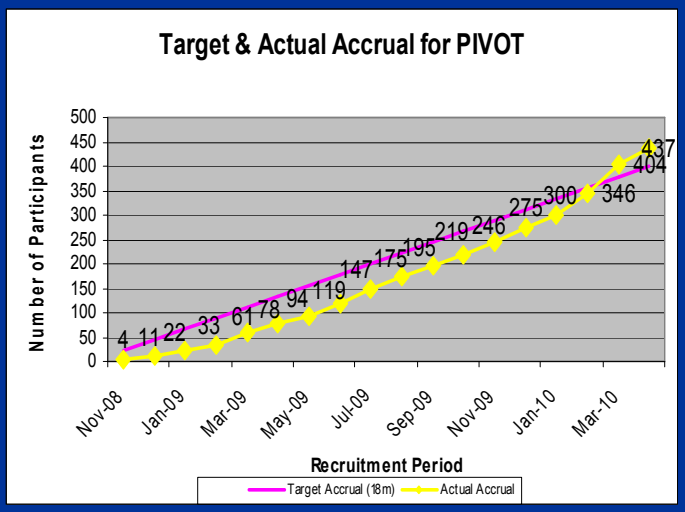
50 sites

The largest UK-lead HIV treatment trial in >10y

PIVOT Status

- 49/50 sites open
- Met initial recruitment target 400 in March
- Recruitment extended to June 2010
- Strong performance by sites outside London (>50% of total)

PIVOT recruitment



NEAT 001 – Outline

ARV Naïve HIV+ patients
ART indicated by national guidelines

RANDOMISATION
800 patients

DRV/r + TDF/FTC

DRV/r + Raltegravir

Follow-up until last patient reaches 96 weeks

PRIMARY ENDPOINT: Time to clinical or virological failure

NEAT

- 41 partner institutions
- 16 European Countries
- over 350 affiliated sites
- Funded by EU
- AIM= to strengthen European Clinical Research Capacity

★ Location of one or more NEAT partner institutions

NEAT 001 Status

- Ethics and MHRA approval obtained in UK
- In process of site R&D approval and site set-ups
- Planned first patient randomised 2nd quarter 2010

MRC Clinical Trials Unit

Europe-Africa Research Network for Evaluation of Second-line Therapy

MRC Clinical Trials Unit

EARNEST Rationale

- Failure on 2NRTI + NNRTI in Africa rollout programs often “late” i.e. with extensive resistance
- 2nd line = PI/r + 2NRTI ….but contribution of 2NRTIs uncertain
- No evidence from RCTs for 2nd line (in Africa or anywhere)

EARNEST Trial design

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1200 ELIGIBLE PATIENTS (failed 1st line NNRTI-based Rx)

RANDOMIZE

- **bPI + 2 NRTI** (NRTIs according to local standard of care)
- **bPI + RAL**
- **bPI + RAL** (12wk induction) → **bPI (Monotherapy)**

FOLLOW-UP FOR 144 WEEKS

Primary Outcome –

Good HIV disease control **– defined as:**

- No new WHO Stage 4 events by week 96 AND
- CD4 cell count > 250 cells/mm^3 at wk 96 AND
- VL < 10,000 copies/ml OR
- VL >10,000 copies/ml with no PI resistance mutations (wk 96)

EARNEST Sites

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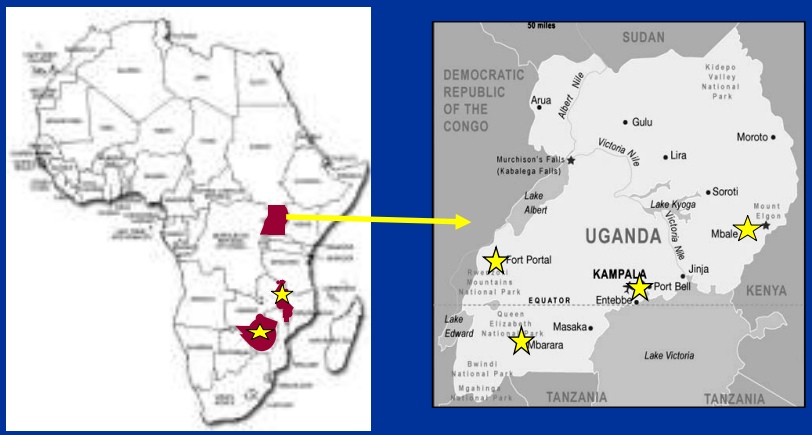
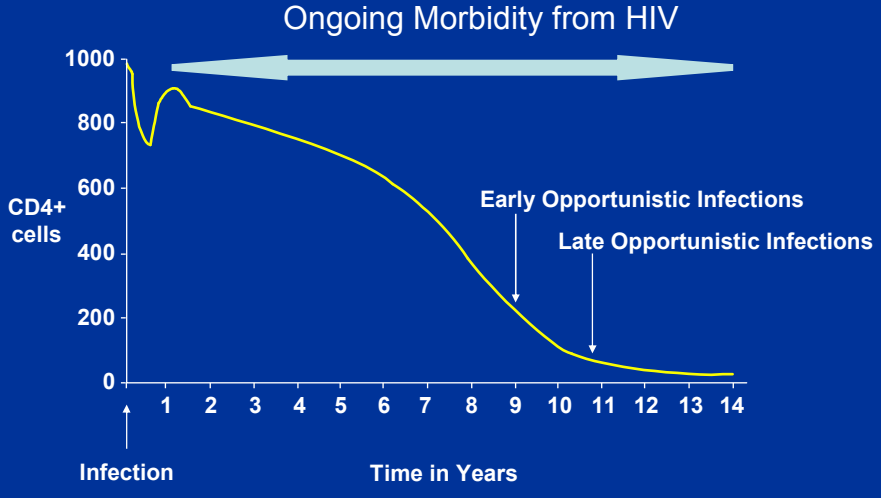


EARNEST Status

- 2 sites actively screening
- Other 6 sites will all open within next 4 weeks
- 1st patient recruited Monday 12th April 2010

START rationale

The Broader Spectrum of HIV Disease



START Design

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HIV-infected participants with CD4+ cell counts > 500 cells/mm^3

Early ART Group

Immediately initiate ART

N=450 at 70 sites for pilot phase
N=2,000 (est.) for definitive study

Deferred ART Group

Defer ART until CD4+ <350 cells/mm^3 or symptoms develop

N=450 at 70 sites for pilot phase
N=2,000 (est.) for definitive study

Primary endpoint: AIDS + serious non-AIDS + death of any cause

START status

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- Pilot phase started
- > 200 patients recruited (slow – mainly due to delayed drug repository)
- Need to increase recruitment to demonstrate success in pilot phase
- Aim to get approval for definitive (n=4000 pt) phase towards end of 2010

MRC CTU HIV Prevention Trials

Sheena McCormack

Prevention

- Key to control of infection
- Multidisiciplinary collaborations
  - Microbicides
  - Vaccines
  - Universal test and treat strategy (UTT)
- Phase I through to Phase III and networking
  - Phase I/II UK and Europe
  - Phase II/III in Africa
  - Europrise (vaccines and microbicides), MDP and EDCTP networks (epidemiological studies and capacity building for trials in Africa)

Microbicide Highlights

- HPTN 035 (CROI 2009)
  - Observed non-significant 30% reduction in HIV incidence in women allocated to 0.5% PRO2000/5 compared to placebo gel
- MDP301 completed (CROI 2010)
  - 0.5% and 2% PRO2000/5 vaginal gel each compared to placebo in 9,385 women in Africa
  - Integrated social science and preparatory studies established as gold standard by IOM review 2007
  - Last visit 18Sep09, database lock 01Nov09, report 30Nov09

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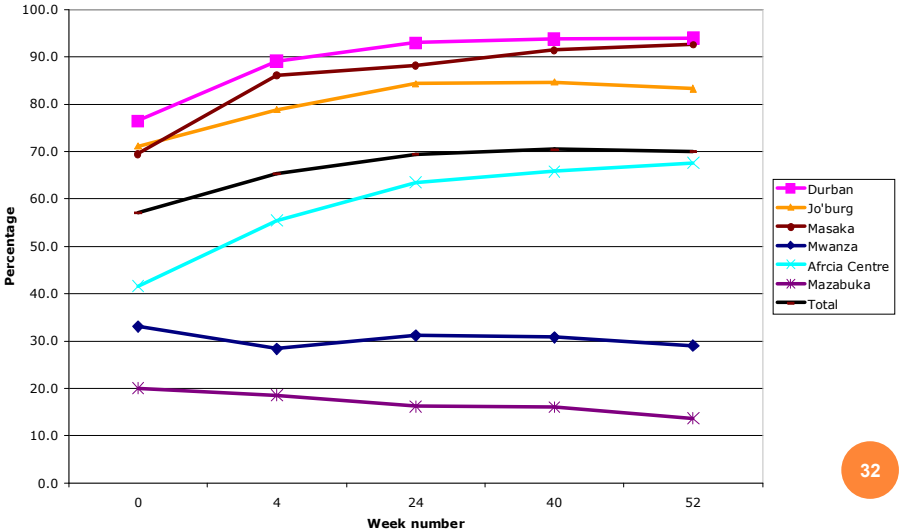
MDP 301

Efficacy and Safety of 0.5% and 2%
PRO 2000 Gel for the Prevention of Vaginally Acquired HIV Infection

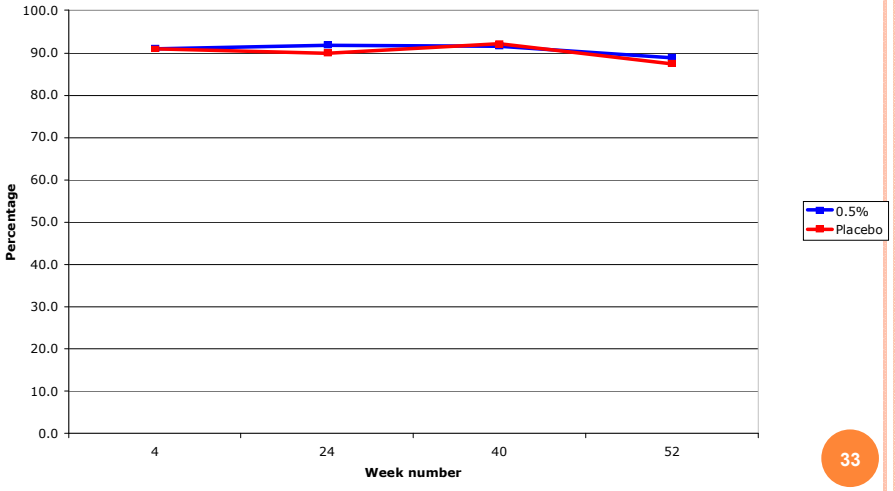
CROI 16th -19th February 2010, San Francisco

Screening and Enrolment

Condom use at last sex act with/without Gel by Centre over Time



Gel use at last sex act with/without Condom by Treatment group over Time



HIV Incidence Censored for Week 52 and at interruption for Pregnancy

	0.5%	Placebo
Number Enrolled	**3326**	**3325**
N in MITT analysis	**3156**	**3112**
Woman years Follow-up	2873	2836
Seroconversions	130	123
Incidence per 100 wy	4.5	4.3
95% Confidence Interval	(3.8, 5.4)	(3.6, 5.2)
Hazard ratio (95% CI)	**1.05 (0.82, 1.34)**	**1**

P-val=0.71

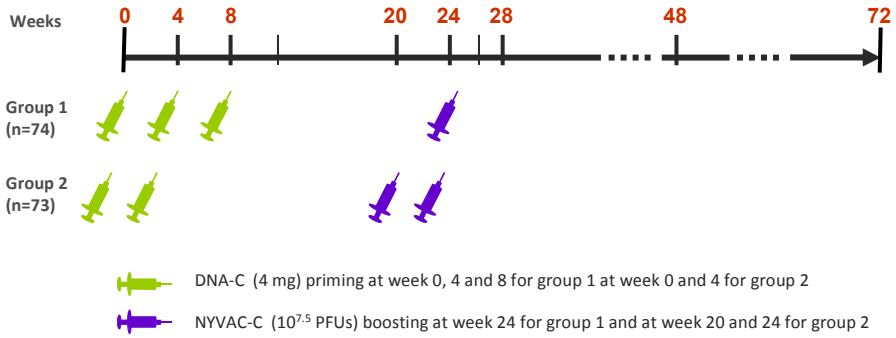
Microbicide Plans

- MDP
  - Analysis and writing
  - Fund raising for efficacy trial of tenofovir 1% gel if warranted by CAPRISA 004 result (AIDS Jul10)
  - Fund raising for clinical development of 5P12 RANTES alone and in combination
- Biomarkers
  - EDCTP cohorts in Africa matching clinical characteristics to results of 27-cytokine array and molecular typing of vaginal flora
- Europrise
  - York/Hull MAbGel (C4E10, C2G12, C2F3) Phase I

Vaccine Highlights

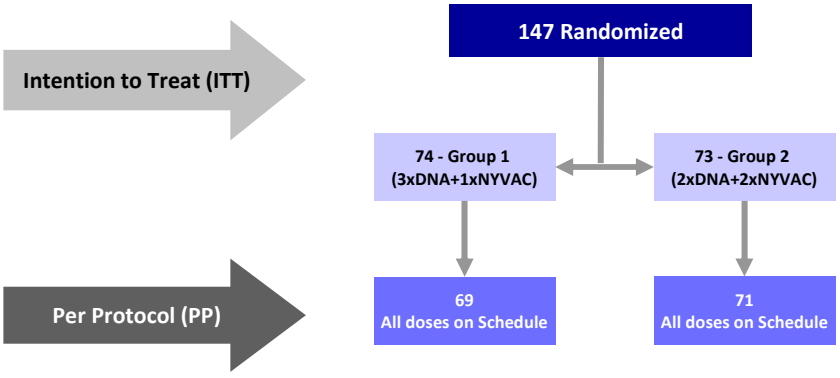
- RV144 Phase III in Thailand suggest it's possible and combination is the way forward
  - ALVAC x2 then ALVAC with B/E protein x2
  - Significant 31.2% reduction (95%CI 1.1-52.1%; p=0.0385)
- EV03-ANRS Vacc20 completed (CROI)
  - DNA x2-NYVAC x2 cf DNA x3-NYVAC x1
- TaMoVac II awarded
  - DNA by electroporation-MVA
- UK HIV Vaccine Consortium
  - Combination regimens; hub (GMP+, clinical trial management, project management) and spoke (trials)
  - Hub brings UK links to existing awards (Gates, EuroVacc, CHAAVI, Europrise, AfrEVac, TaMoVac)
  - Spoke 1 will be DNA-MVA-protein

Clinical Trial Design

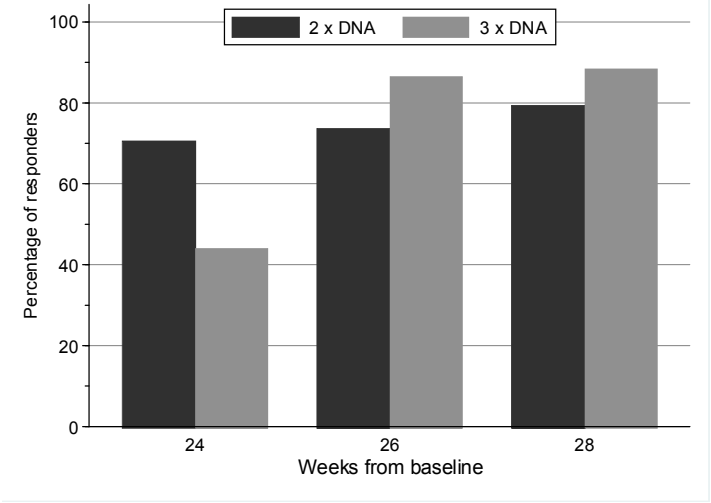


- Randomized trial with a parallel group design
- Open to the participants and investigators but blind to laboratory personnel
- 14 visits over 72 weeks
- Primary immunogenicity weeks 26 and/or 28

Definition of Analytical Methods



Proportion of Responders Overtime (Primary Endpoints: Week 26/28)



Proportion of Responders at Week 26/28 per Peptide Group

ITT Analysis	3 x DNA n = 70	2 x DNA n = 70	Total n = 140
Env	**63/70 (90%)**	**54/69 (78%)**	**117/139 (84%)**
Gag/Pol/Nef	**27/70 (39%)**	**17/70 (24%)**	**44/140 (31%)**

PP Analysis	3 x DNA n = 67	2 x DNA n = 68	Total n = 135
Env	**62/67 (93%)**	**53/67 (79%)**	**115/134 (86%)**
Gag/Pol/Nef	**26/67 (39%)**	**17/68 (25%)**	**43/135 (32%)**

Vaccine Plans

- Impact of delivery on immune responses
  - MucoVac2: exploring recombinant protein with and without adjuvant in various combinations via the intramuscular, intravaginal and intranasal routes
  - CutHIVac: exploring intradermal application of multi-clade DNA via the hair follicles
  - TaMoVac I and II: exploring intradermal application of MVA (A-E) using the Zetajet gun and electroporation
- Impact of adding protein to DNA/MVA prime
  - Europrise: Swedish volunteers that are already primed with DNA/MVA will receive 2 protein boosts
  - AfrEVac-TaMoVac: Tanzania volunteers primed with DNA/MVA will receive 2 protein boosts
  - UK HVC Spoke 1 will explore DNA-MVA-protein schedule giving MVA-protein simultaneously
- Comparison of multi-clade and single clade regimens
  - UK HVC-TaMoVac II collaboration

MDP, UK HVC, EDCTPx5

Imperial College* UK
LSHTM*
MRC CTU*
St George's University of London
York/Hull University
Oxford University
IAVI Core Lab

CPCD, Amsterdam Medical Centre*
The Netherlands

CRESIB, University of Barcelona
Spain

Institute of Tropical Medicine, Antwerp
University of Ghent
Belgium

Universities of Munich and Regensburg
Germany

Karolinska Institute
Stockholm, Sweden

CHUV and University of Geneva (Mintanka)
Lausanne, Geneva, Switzerland

Nsambya Hospital, Kampala
MRC UK, Masaka/Entebbe, Uganda

ICRH*, Mombasa
KEMRI/CDC Kisumu
Kenya

Project Ubuzima
Rwanda

AMREF/NIMR/LSHTM*
Mwanza
Mbeya MCR (NIMR)
Mbeya
Muhimbili University*
Dar es Salaam, Tanzania

UNZA, Mazabuka,
Zambia

CISM/Mavalane Hospital/FDC
Manhica/Maputo,
Beira UCM
Beira, Mozambique
INS
Maputo, Mozambique

CAPRISA
Durban, SA

CONRAD
IPM
WRAIR
USA

CLS
Johannesburg, SA

RHRU
Johannesburg, SA

The Africa Centre
Mtubatuba, SA

HPRU, MRC SA
Durban, SA

Universal test and treat

- PopART: pilot to assess feasibility of scaling up VCT and treatment in Africa
  - Critique of current mathematical models
  - Pilot in 1 country; activities in 2-4
  - Go/no go for community randomised trial
  - Economics
- And in UK
  - Need to pool knowledge, and develop interventions to scale up testing which are appropriate to the setting

Next steps

- Microbicides
  - ARVs hinges on intermittent tfv (CAPRISA 004 reports AIDS 2010) and daily (VOICE reports 2014)
  - Bench to clinic and combinations will plod on
- Vaccines
  - Iterative work for 2-3yrs to refine regimens followed by a race for efficacy trial funding
- UTT
  - Is probably the one to concentrate on and most relevant to UK