

Randomised, placebo-controlled, phase I/IIa evaluation of the safety, immunogenicity and antiretrovirological properties of an avipox virus vaccine expressing HIV *gag-pol* and interferon- γ in HIV-1 infected subjects

David A Cooper^{1,2}, Workman C³, Puls R¹, Bloch M⁴, Baker D⁵, Bodsworth N⁶, Anderson J⁷, Crowe S⁸, French M⁹, Hoy J¹⁰, Kelleher A¹, Aichelburg A¹, Ward L¹¹, Law MG¹ and Emery S¹

1. National Centre in HIV Epidemiology and Clinical Research, UNSW, Sydney, Australia
2. St Vincent's Hospital, Sydney, Australia
3. Ground Zero Medical Centre, Sydney, Australia
4. Holdsworth House General Practice, Sydney, Australia
5. 407 Doctors, Sydney, Australia
6. Taylor Square Clinic, Sydney, Australia
7. Carlton Clinic, Melbourne, Australia
8. Macfarlane Burnet Centre, Melbourne, Australia
9. Royal Perth Hospital, Perth, Australia
10. The Alfred Hospital, Melbourne, Australia
11. Virax Immunotherapeutics, Melbourne, Australia



Avipox vaccine

Background

- recombinant fowlpox virus vaccines available for clinical evaluation
- vaccines constructed to express HIV *gag-pol* sequences with and without co-expression of human interferon- γ
- previously shown to be immunogenic in mouse and non-human primate models
- acceptable pre-clinical safety profile



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Recombinant fowlpox virus vaccines

- similar to canary pox
- can code multiple foreign sequences in multiple locations
- foreign sequences can be derived from multiple sources

Study vaccines

Placebo – diluent alone

rFPV expressing HIV *gag/pol* – partial construct (PC)

rFPV expressing HIV *gag/pol* and human interferon- γ – full construct (FC)



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Study objectives – Initial phase

Primary objective

Safety

Additional objectives

Anti-HIV immune responses assessed using the following laboratory assays at day 0, weeks 6, 14 and 26;

CTL effector function by Cr-release

PBMC interferon- γ production by ELIspot

Lymphoproliferative responses



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Key eligibility criteria

Inclusion

- HIV positive (serologic or virologic diagnosis)
- commenced combination antiretroviral therapy during primary HIV infection and maintained ever since
- plasma HIV RNA <400 copies/mL since commencement of ART
- CD4+ cell count > 400/ μ L after commencement of ART
- safety labs within acceptable ranges
- provision of informed consent

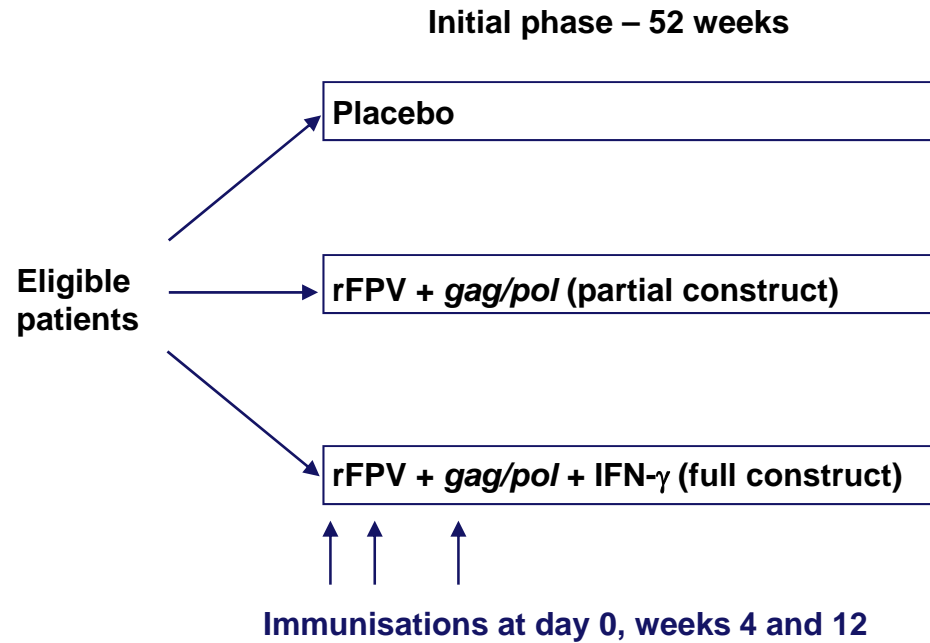
Exclusion

- prior allergic reaction to vaccination
- known allergy to egg products



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Study design – initial phase



Vaccine dose = 1mL of 5×10^7 pfu/mL

Plasma HIV RNA determination, CD4+ cell count enumeration and clinical assessments performed frequently
T cell immune responses assessed at day 0 and weeks 6, 14 and 26

Double-blind maintained throughout



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Selected demographic and clinical features – initial phase

	Placebo	Partial construct	Full construct
n	12	11	12
% male	100	100	100
% caucasian	83.3	81.8	100
Age – mean \pm SD (years)	38.1 \pm 5.0	37.5 \pm 7.5	40.9 \pm 4.2
CD4+ cell count mean \pm SD (cells/ μ L)	929 \pm 299	966 \pm 333	970 \pm 281
Percentage undetectable (<50 copies/mL) plasma HIV RNA	100	100	100
ART duration mean \pm SD (months)	41.2 \pm 22.4	40.7 \pm 20.4	48.2 \pm 20.7



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Results – safety (initial phase)

Events occurring in $\geq 10\%$ patients on $>$ one occasion attributable to immunisation

Injection site reactions

Placebo	Partial construct	Full construct
2	3	5

Serious adverse events

Placebo	Partial construct	Full construct
1 event. Cardiovascular disease 10 months after last immunisation – required ongoing management (not related)	1 event. Elevated serum transaminases with lethargy and fatigue 6 months after last immunisation – diagnosis acute hepatitis A infection (possibly related)	1 event. Elevated serum transaminases prior to first immunisation – resolved spontaneously (not related)



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RESULTS – pVL/CD4+ cell count responses (initial phase)

Eight episodes of transient detectable plasma HIV-RNA (blips) occurred in five patients throughout the study

- **three full construct recipients had four episodes**
- **two control recipients had four episodes**

No significant differences between vaccine arms in absolute CD4+ cell count nor change from baseline CD4+ cell count



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ELISPOT (anti HIV-gag) immune responses – initial phase

	Placebo	Partial construct	Full construct
sfu/10 ⁶ PBMC – mean baseline \pm SD	15 \pm 47	21 \pm 42	11 \pm 21
sfu/10 ⁶ PBMC - time weighted mean \pm SD change	64 \pm 137	-5 \pm 16	19 \pm 30
Percentage of patients with positive response after baseline	33.3	0	50

Mean change comparisons

Combined full and partial vs placebo; p=0.062

Full versus partial; p=0.026

Binary endpoint comparisons

Combined full and partial vs placebo; p=0.955

Full vs partial; p=0.024



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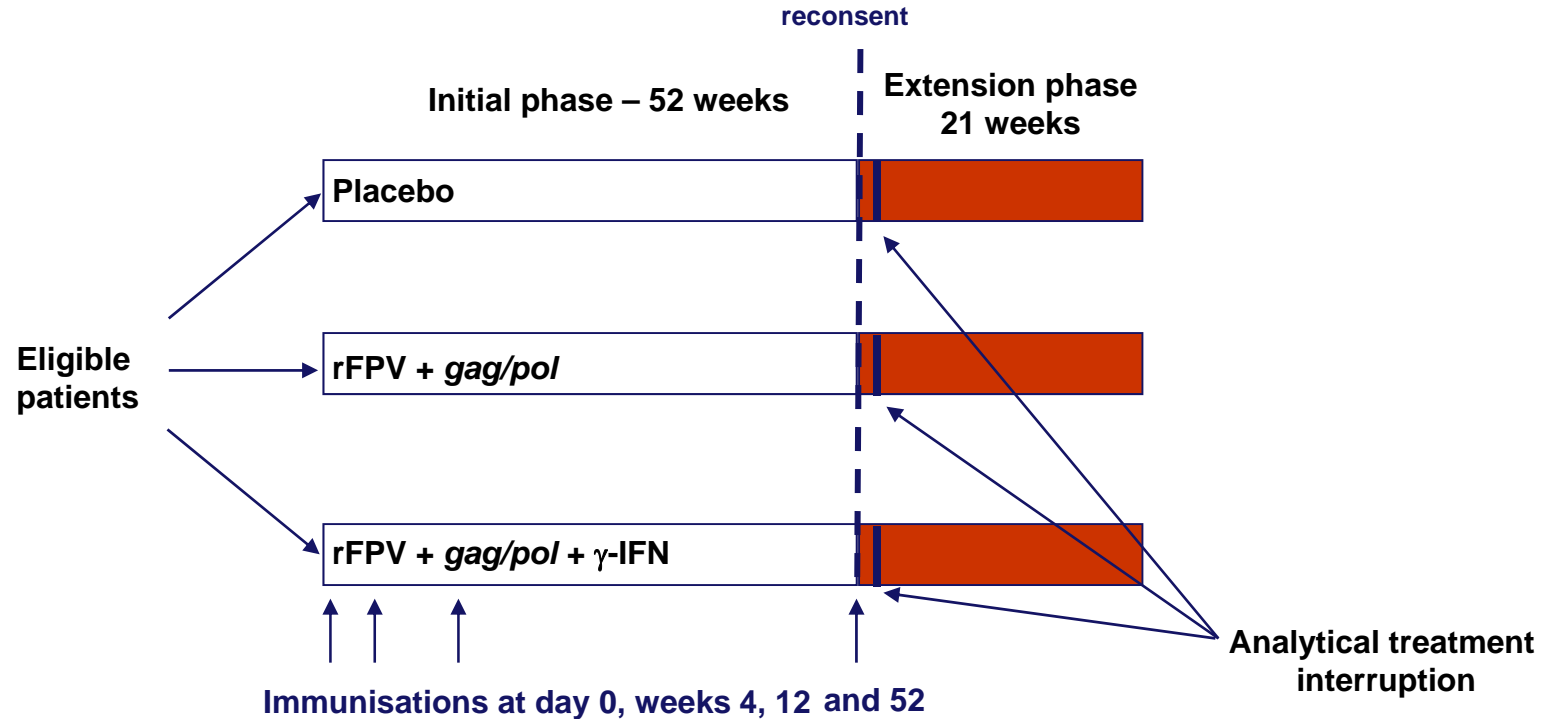
SUMMARY – INITIAL PHASE

- vaccines are safe and well tolerated
- vaccines are not associated with T-cell immune responses using a standard battery of laboratory assays



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Study design



Patients required to have undetectable pVL in order to participate in extension study

Vaccine dose = 1mL of 5×10^7 pfu/mL

Plasma HIV RNA determination, CD4+ cell count enumeration and clinical assessments performed frequently

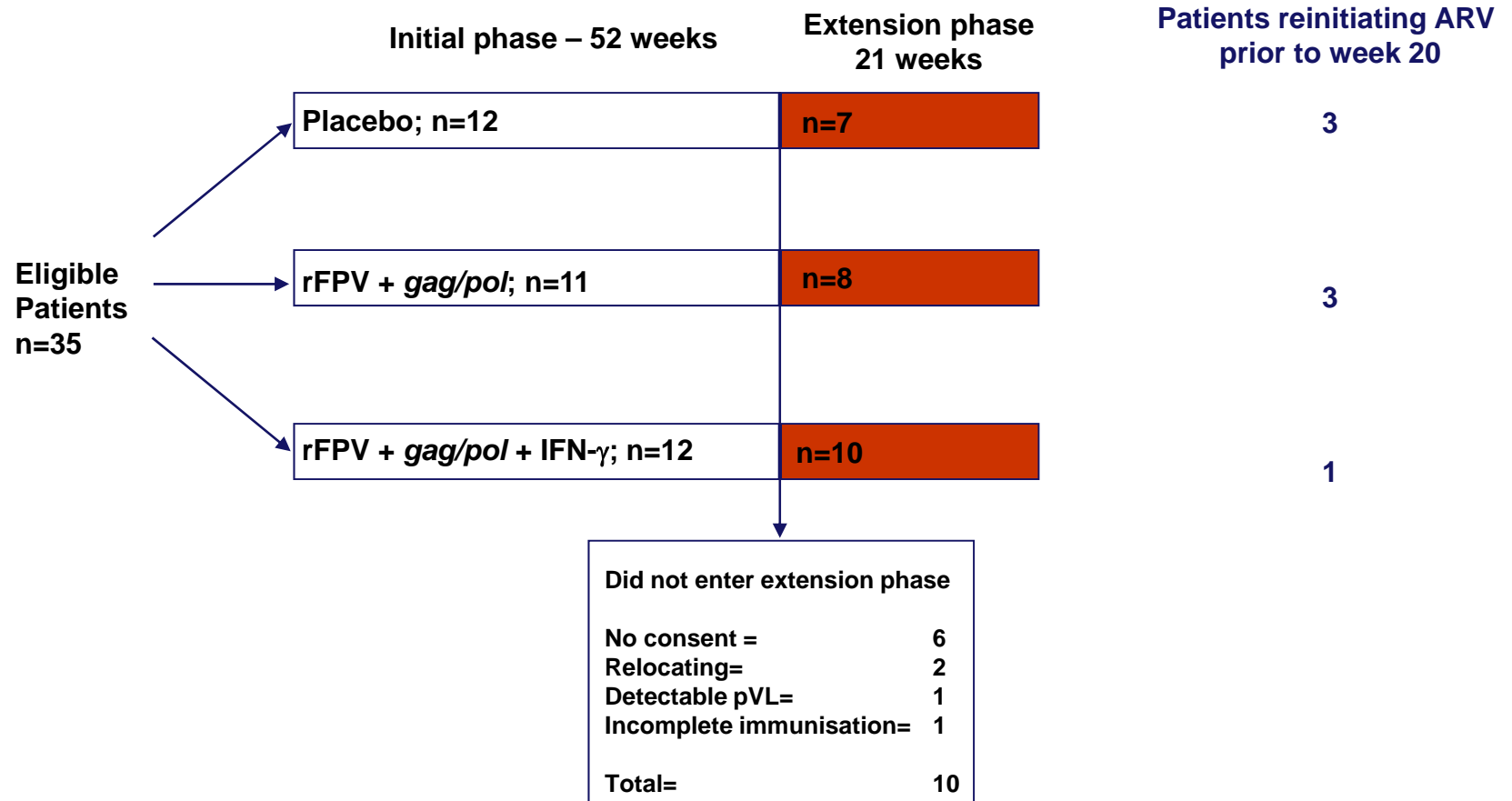
Pragmatic criteria for reinitiation of ARV

Double-blind maintained throughout both phases of investigation



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Patient disposition





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Analysis – extension phase

Primary endpoint

Time weighted area under the curve change from plasma HIV-RNA VL at baseline (day 0) until reintroduction of antiretroviral therapy

Secondary endpoints

Kinetics and rate of pVL recrudescence

Time to re-initiation of ART

Time to detectable pVL

CD4+ cell count changes

Post-hoc analyses

Time to pVL >10,000 copies/mL

Treatment group comparisons

Primary comparisons between full construct+partial construct versus placebo and FC vs PC

Post-hoc comparisons between FC and placebo



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Selected demographic and clinical features – extension study

	Placebo	Partial construct	Full construct
n	7	8	10
% male	100	100	100
% caucasian	100	100	100
age (years) mean \pm SD	43.3 \pm 3.4	38.0 \pm 7.8	39.2 \pm 4.6
CD4+ cell count (cells/ μ L) mean \pm SD	699 \pm 241	814 \pm 217	827 \pm 139
percentage of patients with undetectable (<50 copies/mL) plasma HIV RNA	100	100	100
time from HIV exposure to commencement of antiretroviral treatment mean \pm SD (months)	2.9 \pm 3.6	2.8 \pm 3.5	1.1 \pm 1.5



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Primary endpoint – extension phase

	Placebo (n=7)	Partial construct (n=8)	Full construct (n=10)
Time weighted mean change \pm SD baseline pVL (copies/mL)	1.80 \pm 0.72	1.78 \pm 0.91	0.96 \pm 0.91

Mean change comparisons

Combined full and partial vs placebo; p=0.253

Full versus partial; p=0.077

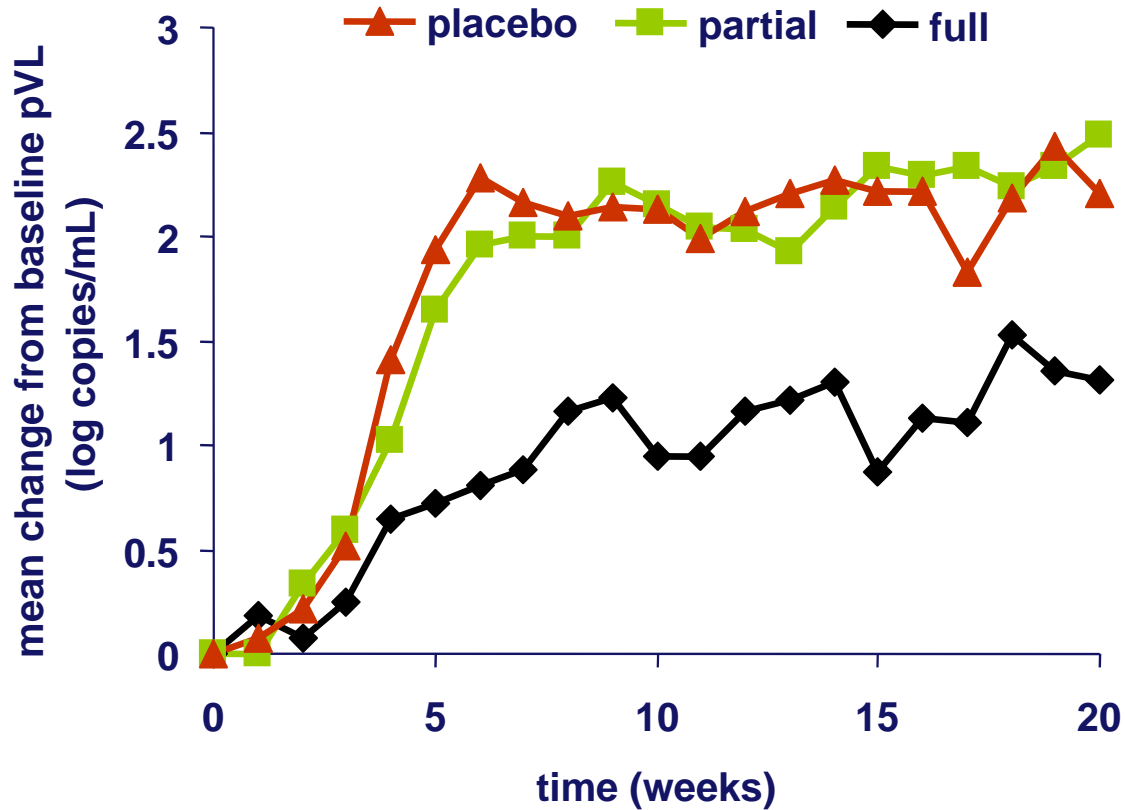
Full versus placebo; p=0.060



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Plasma virus load changes

Last value carried forward for patients reinitiating ART

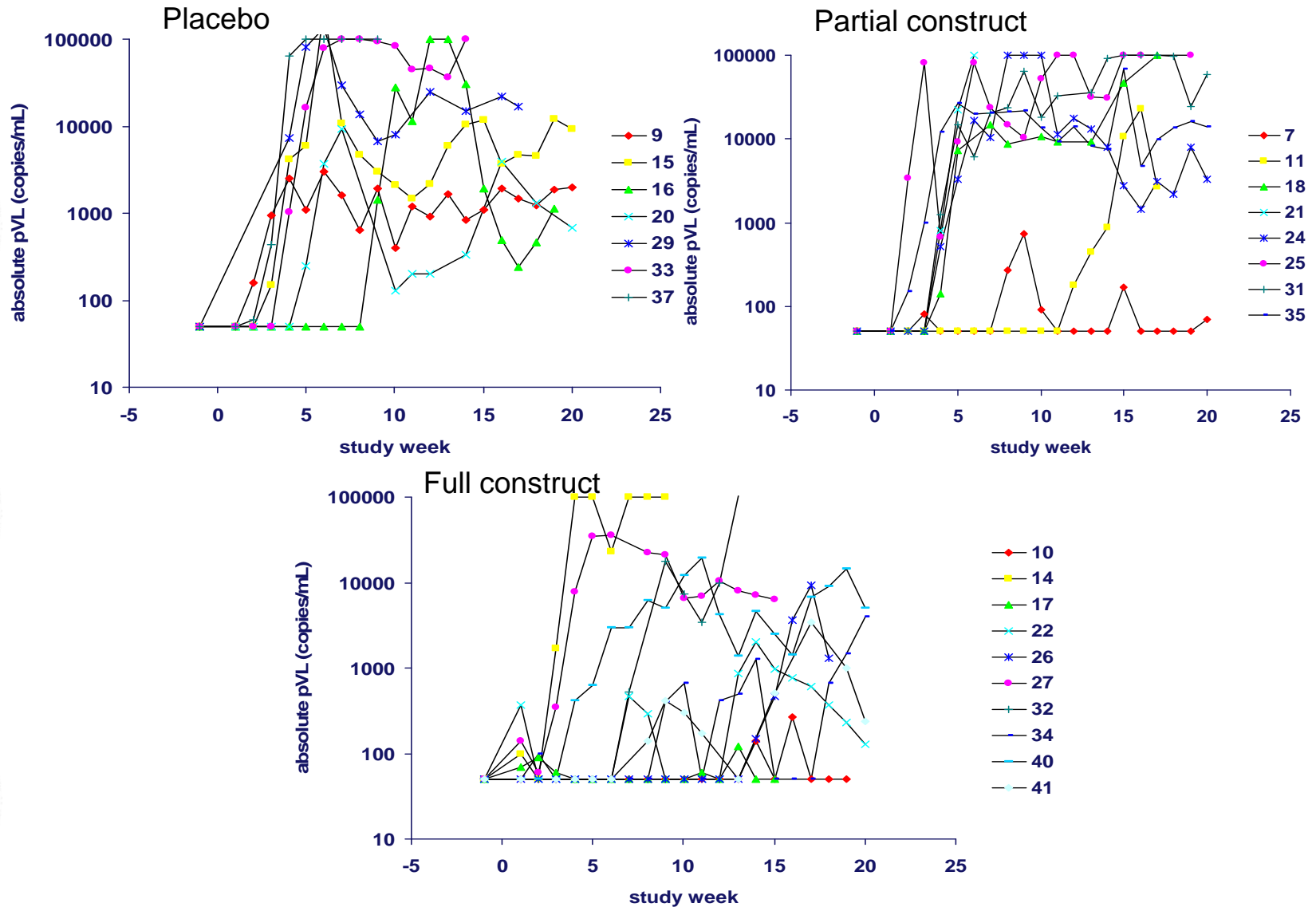


Placebo	7	7	6	6	7	5
Partial	8	7	7	6	7	7
Full	10	10	8	9	7	9



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Plasma virus load changes

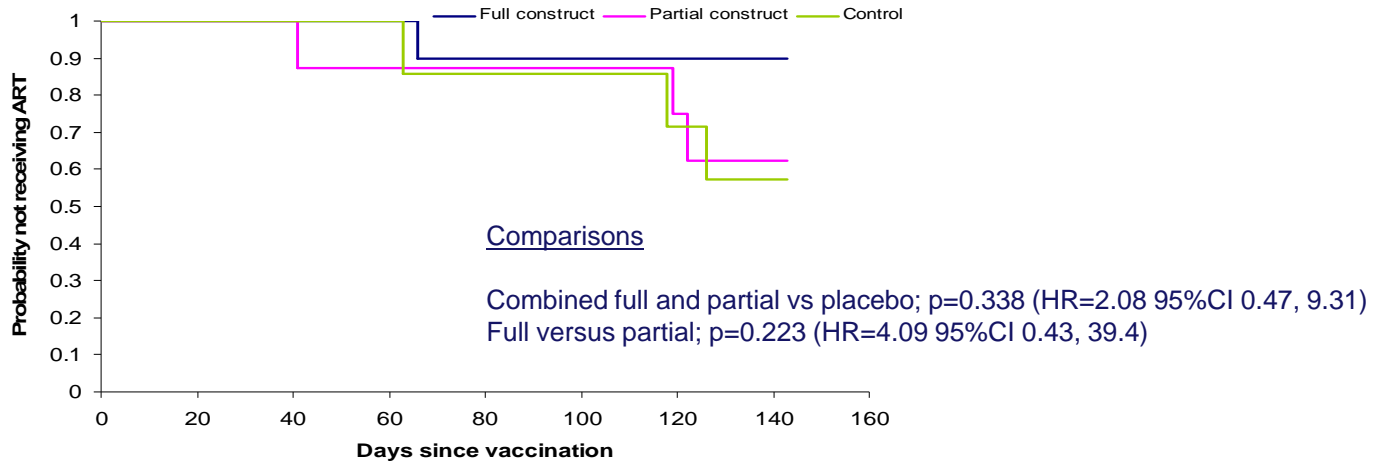




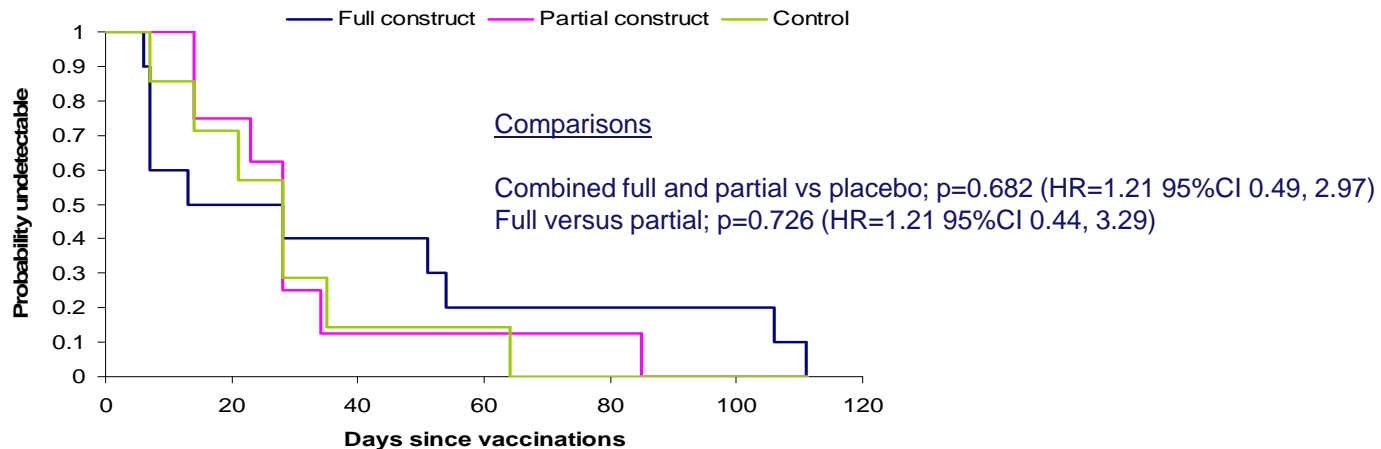
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Virological measures

Time to reinitiation of ART



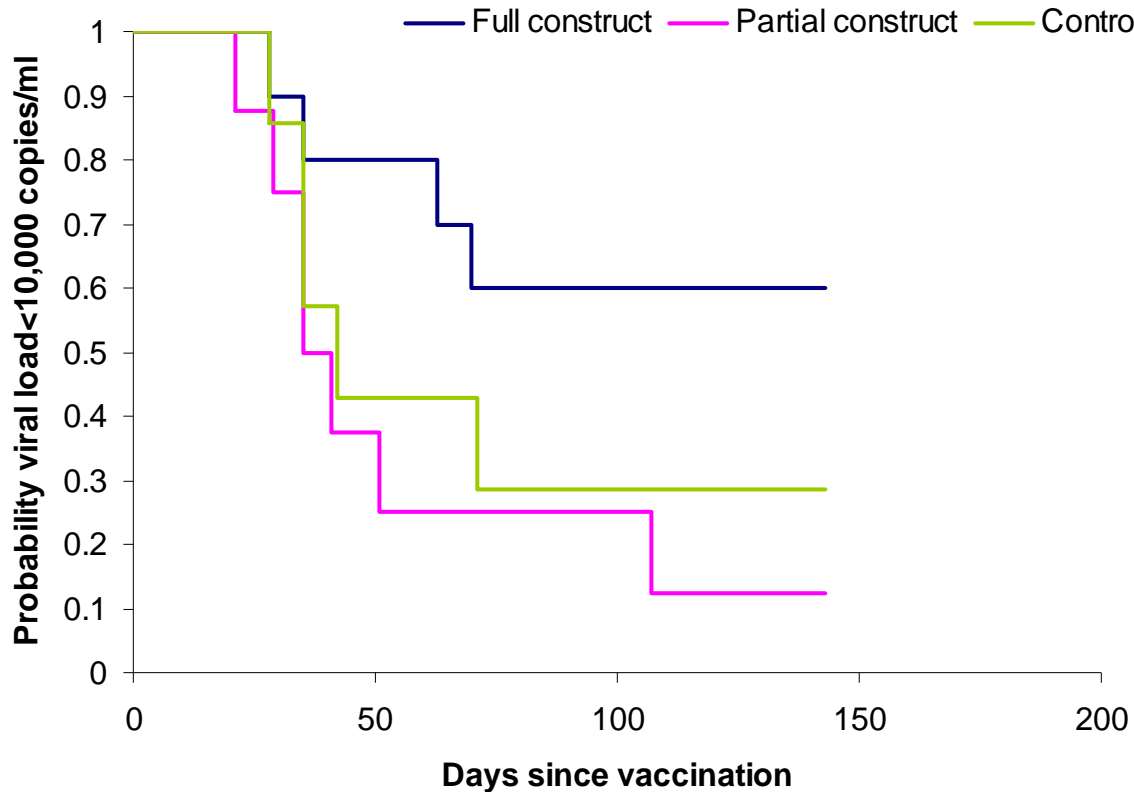
Time to detectable pVL





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Time to pVL > 10,000 copies/mL



Comparisons

Combined full and partial vs placebo; $p=0.671$ (HR=1.26 95%CI 0.44, 3.63)

Full versus partial; $p=0.049$ (HR=3.52 95%CI 1.01, 12.32)

Full versus placebo; $p=0.238$ (HR=2.22 95%CI 0.59, 8.33)



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Summary – extension phase

- **indication of biological effect of immunisation with full construct (inconsistent statistical significance)**
- **manifest as a blunted recrudescence of pVL following analytical treatment interruption**
- **effects were internally consistent in a number of analytical approaches (including covariate analyses)**
- **at present these are not relatable to any immunologic correlate (additional laboratory investigations planned)**
- **small patient numbers**
- **require further study of these constructs in HIV disease**



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Acknowledgements

All study participants

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External advisory panel

Andrew Lloyd, Stephen Kent, Roger Garsia, Sarah Pett, Kirsty Machon, John Sullivan, Graeme Stewart, Sharon Lewin, Paul McQueen – Immune Based Therapies Working Group, NCHECR

Consultants

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