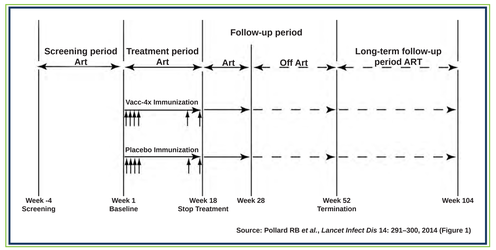
Use of preART-Adjusted Endpoints in the Analysis of an HIV Therapeutic Vaccine Trial

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Introduction

- Vacc-4x is a peptide-based therapeutic vaccine targeting conserved domains on the HIV protein p24^{Gag}.
- In a recent randomized, double-blind, placebo-controlled phase 2 clinical trial of Vacc-4x.
  - 136 HIV-infected participants virologically suppressed on combination antiretroviral therapy (cART) were randomized in a 2:1 ratio to receive six Vacc-4x or placebo immunizations at weeks 1, 2, 3, 4, 16 and 18.
  - 126 participants (Vacc-4x:Placebo = 88:38) received all six immunizations and underwent an analytical treatment interruption (ATI) 10 weeks after the last immunization (per-protocol cohort).
  - 103 participants (Vacc-4x:Placebo= 71:32) at week 40, 83 participants (Vacc-4x:Placebo = 58: 25) at week 48, and 80 participants (Vacc-4x:Placebo = 56:24) at week 52 stayed in the study and remained off-cART with available data.



Source: Pollard RB *et al.*, *Lancet Infect Dis* 14: 291–300, 2014 (Figure 1)

- All observed participant baseline characteristics appeared to be balanced between Vacc-4x and placebo groups, except that available preART viral load (VL) values were higher among Vacc-4x recipients (median = 80,400 copies/mL) vs. placebo recipients (median = 42, 636 copies/mL). preART VL corresponded to a maximum of two values taken within 6 months before ART initiation.
- The pre-specified primary analysis did not account for the pre-baseline differences between treatment. The study did not meet the primary efficacy endpoints of extending time to cART resumption and in maintaining CD4 count during ATI compared to placebo.

- We conducted additional exploratory analyses of the effect of Vacc-4x (vs. placebo) on VL and CD4 count during cART interruption by accounting for:
  - Missing cART-free data due to early withdrawal or cART resumption
  - Baseline prognostic factors

Objectives and Endpoints

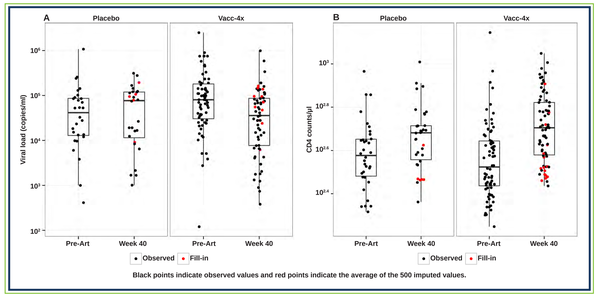
- **Objective:** To evaluate the effect of Vacc-4x on cART-free VL and CD4 count as compared to placebo.
  - cART-free VL and CD4 count are measured or estimated while off-cART
- **Endpoints:**
  - Week 40 VL and CD4 count
  - "Set-point" viral load and CD4 count: geometric mean of Weeks 48 and 52 values
  - Longitudinal VL and CD4 count between weeks 32 – 52
- **Analysis cohort:** Participants with available preART VL and preART CD4 count values in the per-protocol cohort.

Methods

- Multiple imputation models were used to fill in missing VL or CD4 count data during ATI.
  - 500 sets of plausible values from model-based predictive distribution
  - Baseline imputation predictors: treatment assignment, gender, age, country, time on cART, time since HIV diagnosis, reasons for resuming cART, CD4 count nadir, and preART VL or preART CD4 count
- Two types of univariate and multivariate linear regression models were performed and compared to account for preART values in the evaluation of vaccine effect.
  - Covariate-adjusted models: included baseline preART VL or preART CD4 count as a covariate in the regression models
  - Fold-change models: evaluated the fold-change of cART-free VL or CD4 count over participants' baseline preART values
- The Rubin's rule was used to calculate the final estimates and standard errors of vaccine effect based on regression model estimates from each imputed dataset (Little *et al*, Wiley, 2002).
- Simulation studies were also performed to compare the statistical power of assessing vaccine effect based on the two models.

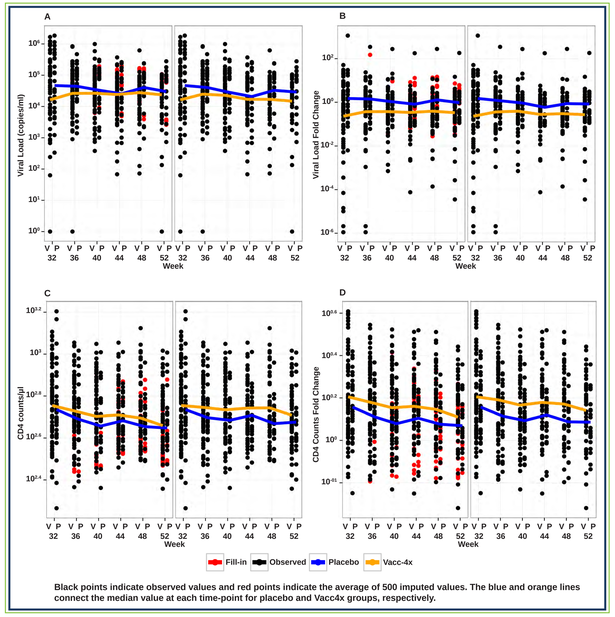
Results

Distribution of preART VL and week 40 VL (Panel A) and preART CD4 Count (Panel B)



Black points indicate observed values and red points indicate the average of the 500 imputed values.

Distribution of VL and CD4 Count Over Time Between Weeks 32 and 52 (Panels A-D)



Black points indicate observed values and red points indicate the average of 500 imputed values. The blue and orange lines connect the median value at each time-point for placebo and Vacc4x groups, respectively.

Estimates of Vaccine Effect per $\log_{10}$ Increase of Endpoint

Endpoint	Covariate Adjusted Models[1]			Fold-change Models[2]		
	Estimate (vaccine vs. placebo)	95% CI	p-value	Estimate (vaccine vs. placebo)	95% CI	p-value
Univariate Analysis[3]						
Week 40 VL	-0.23	(-0.57, 0.12)	0.20	-0.45	(-0.84, -0.06)	0.02
VL set-point	-0.26	(-0.62, 0.09)	0.15	-0.49	(-0.89, -0.09)	0.02
Longitudinal VL (wk 32-52)	-0.27	(-0.59, 0.05)	0.10	-0.53	(-0.92, -0.15)	0.01
Multivariate Analysis[4]						
Week 40 VL	-0.21	(-0.57, 0.15)	0.25	-0.47	(-0.88, -0.06)	0.02
VL set-point	-0.24	(-0.61, 0.14)	0.22	-0.50	(-0.93, -0.07)	0.02
Longitudinal VL (wk 32-52)	-0.21	(-0.53, 0.12)	0.22	-0.51	(-0.91, -0.12)	0.01
Univariate Analysis[3]						
Week 40 CD4 Count	0.06	(0.00, 0.12)	0.03	0.07	(0.01, 0.14)	0.02
CD4 count set-point	0.04	(-0.01, 0.09)	0.12	0.06	(-0.01, 0.12)	0.07
Longitudinal CD4 count (wk 32-52)	0.04	(-0.00, 0.09)	0.07	0.06	(0.00, 0.12)	0.05
Multivariate Analysis[4]						
Week 40 CD4 Count	0.07	(0.01, 0.12)	0.02	0.08	(0.02, 0.15)	0.02
CD4 count set-point	0.04	(-0.00, 0.09)	0.07	0.06	(-0.00, 0.12)	0.05
Longitudinal CD4 count (wk 32-52)	0.05	(0.00, 0.09)	0.04	0.06	(0.00, 0.12)	0.04

1 Covariate-adjusted models indicate that all models adjusted for preART VL or CD4 count

2 Fold-change models indicate that the fold-change endpoint was used; preART values were not adjusted in the models.

3 Univariate Analysis indicates that only treatment and preART values were included in the covariate adjusted models, and only treatment was included in the fold-change models as predictors.

4 Multivariate Analysis indicates that in addition to the covariates in the univariate models, the following covariates were also adjusted for in the regression models: baseline gender, age, country, time on cART and time since HIV diagnosis.

Conclusions

- After accounting for missing data and differences in participants' baseline values between treatment groups, the Vacc-4x group was confirmed to have achieved a better VL control. Furthermore, an improved maintenance of CD4 count during ATI.
- Based on the Vacc-4x trial data, the fold-change model more effectively accounted for the imbalance in baseline preART VL values between treatment groups, as compared to the covariate-adjusted model.
- Additional simulation studies confirmed that the fold-change model can render a significantly greater power when baseline values differ between treatment groups.
- Future HIV therapeutic vaccine studies may adopt similar fold-change endpoints to account for important prognostic factors of trial outcomes, especially in subgroup (including PP cohort) analysis.

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