

Use of genotypic and maraviroc (MVC) clinical trial data to develop statistical models for predicting response to a MVC-containing regimen in a treatment-experienced (TE) population

Poster TUPE0133

XVIII International AIDS Conference
July 18 - 23, 2010
Vienna, Austria

Pinaki Biswas¹, Doug Chapman¹, Xiaoyin Zhong², Guinevere Q. Lee², P. Richard Harrigan², Jayvant Heera³, Hernan Valdez¹

¹Pfizer Inc, New York, NY, USA; ²BC Centre for Excellence in HIV/AIDS, Vancouver, Canada, ³Pfizer Global Research and Development, New London, CT, USA

Introduction

- Genotypic methods for determining HIV tropism are gaining increasing acceptance for use in the selection of patients for CCR5 antagonist therapy
- Our objective was to predict clinical response at week 8 in 3 MVC trials in TE patients – MOTIVATE 1 and 2, and A4001029 – from population-based sequencing of the V3 loop at screening and from baseline clinical parameters
- This analysis set included patients with both CCR5-using and CXCR4-using virus

Methods

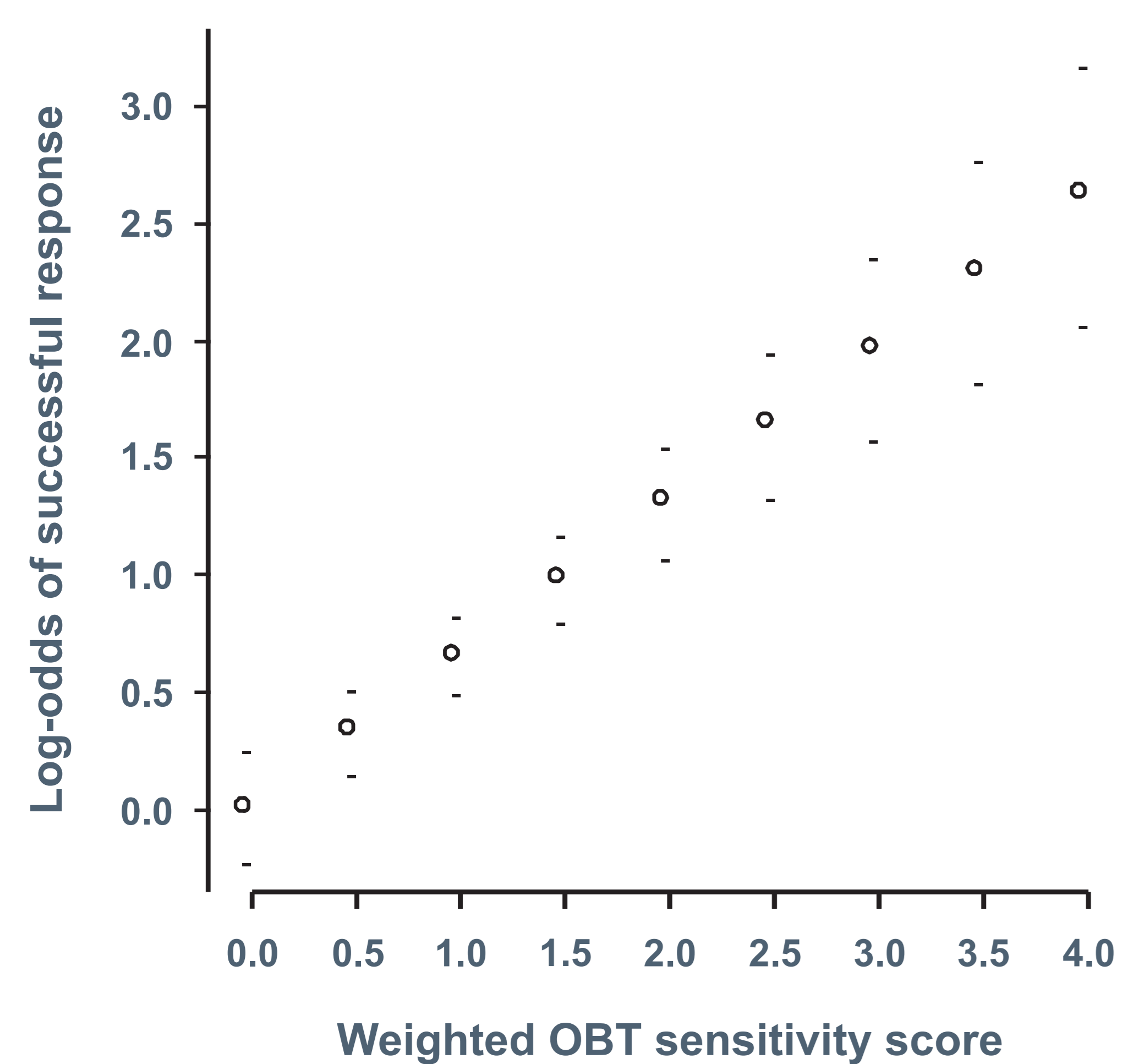
- Successful clinical response (binary) at week 8 on MVC BID and QD was defined as either a decrease of $> 2 \log_{10}$ in plasma viral load (pVL), or pVL < 50 copies/mL
 - Missing responses were imputed as failures
- A logistic regression model was fit to predict success with covariates for baseline* pVL, baseline* CD4⁺ count, weighted optimized background therapy susceptibility score (wOBTss), and screening V3 genotype score (geno2pheno [g2p] false-positive rate [FPR])
 - Fully active protease inhibitors, non-nucleosides, and enfuvirtide (determined by phenotypic or genotypic resistance testing) contributed a value of 1.0 to the wOBTss; active nucleosides contributed 0.5
- A linear regression model was also fit to predict the magnitude change in viral load at week 8 using the same covariates as in the logistic regressions
- Various g2p thresholds were explored in both models. Thresholds within a certain range were selected based on minimum Akaike's information criterion (AIC)
 - Each threshold dichotomizes g2p and yields a different model with a corresponding AIC value. Low AICs are indicative of a better model fit
- A nonparametric method – classification and regression trees (CART) – was also employed using the same covariates and the binary response at week 8
 - This method splits the data (binary) recursively based on the covariate values. Optimal splits are calculated based on ANOVA methods
- Thresholds obtained via these methods were also assessed alongside an existing threshold of 5.75 (McGovern et al)^{1,2} and baseline tropism results obtained with the original Trofile™ assay (Monogram Biosciences) by examining viral loads over time

* Baseline data were collected at the baseline visit and do not include screening data.

Results

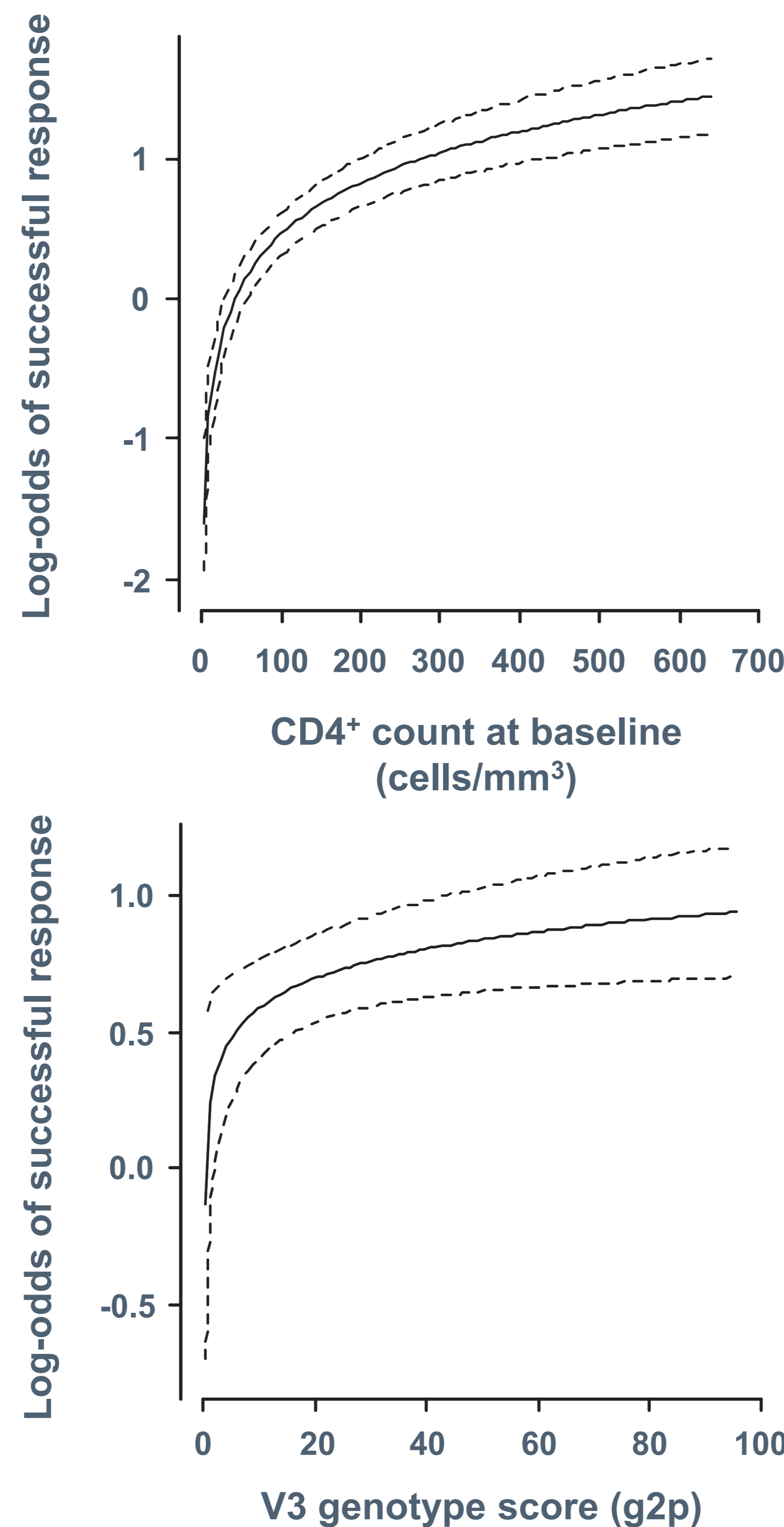
- A total of 906 patients receiving MVC were included
- All baseline variables (CD4⁺ count, wOBTss, and V3 genotype score) except baseline pVL were highly predictive of virologic success at week 8, as per the logistic regression

Figure 1. Proportion of patients responding showed linear relationship with regimen activity score



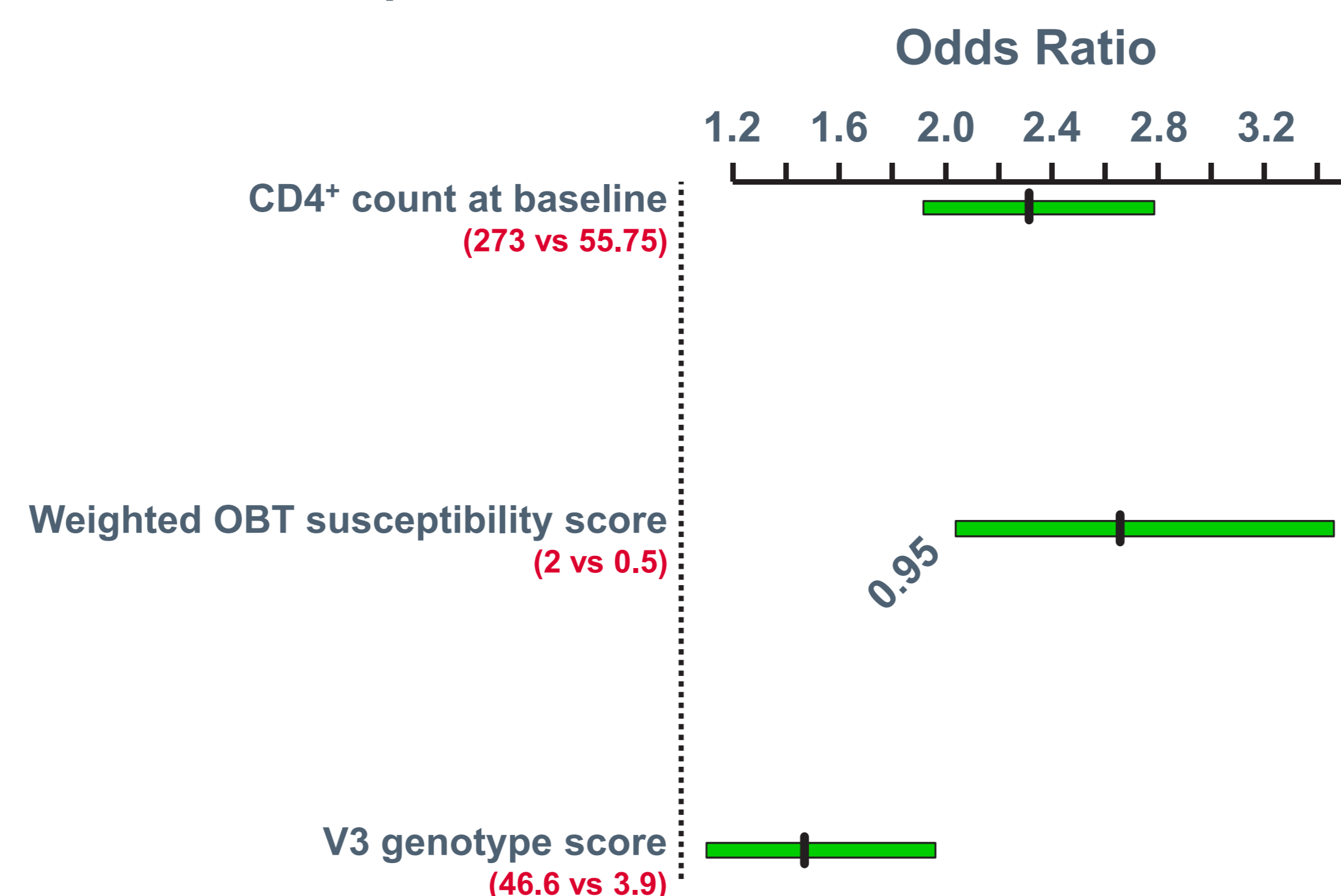
Successful response was defined as either a decrease of $> 2 \log_{10}$ in pVL, or pVL < 50 copies/mL at week 8. Bars indicate 95% confidence intervals.

Figure 2. Proportion of patients responding showed log-linear relationships with baseline CD4⁺ count and V3 genotype



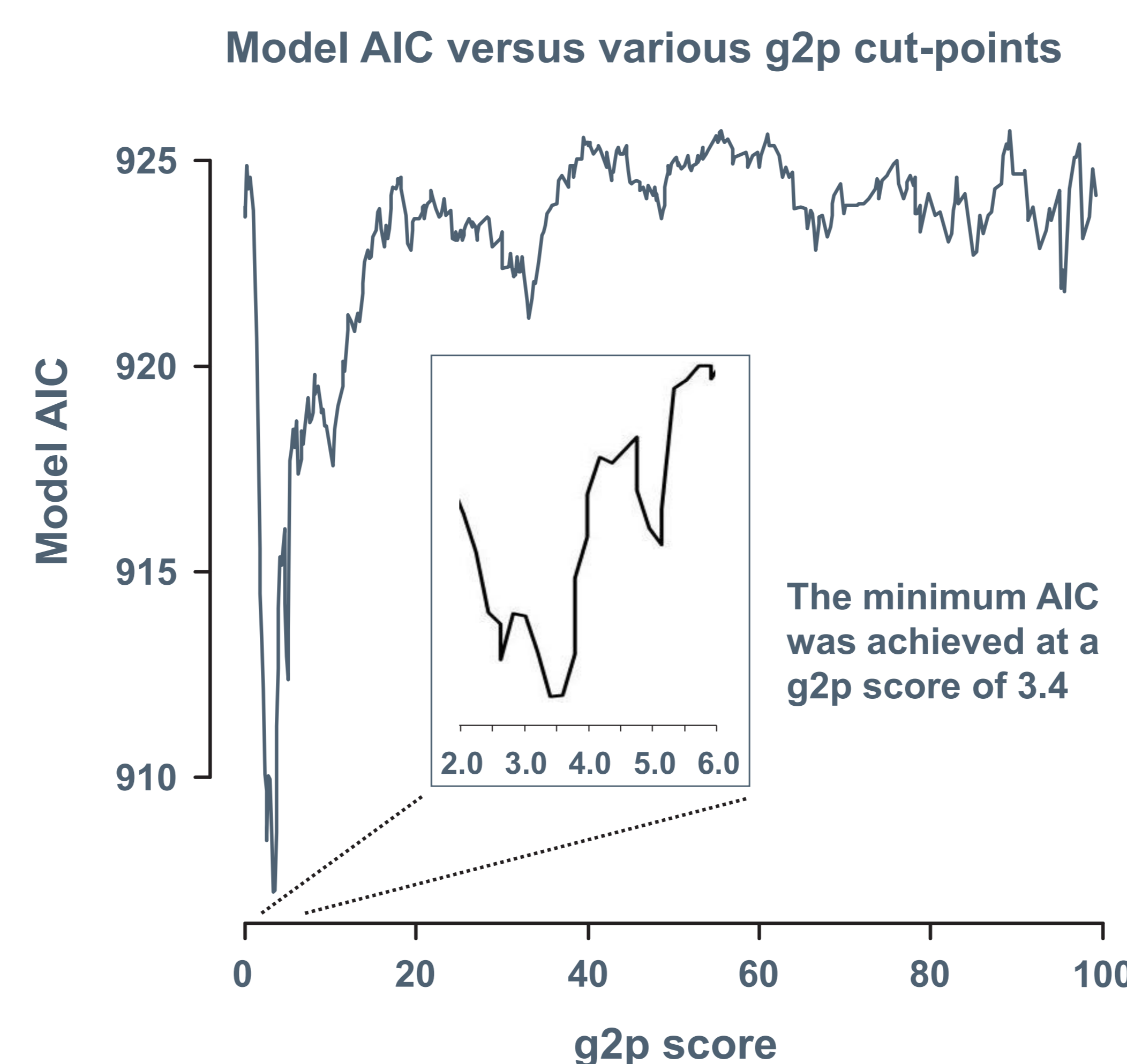
Successful response was defined as either a decrease of $> 2 \log_{10}$ in pVL, or pVL < 50 copies/mL at week 8. Dotted lines indicate 95% confidence intervals.

Figure 3. Baseline CD4⁺ count and regimen susceptibility score were significant predictors of HIV-1 RNA response



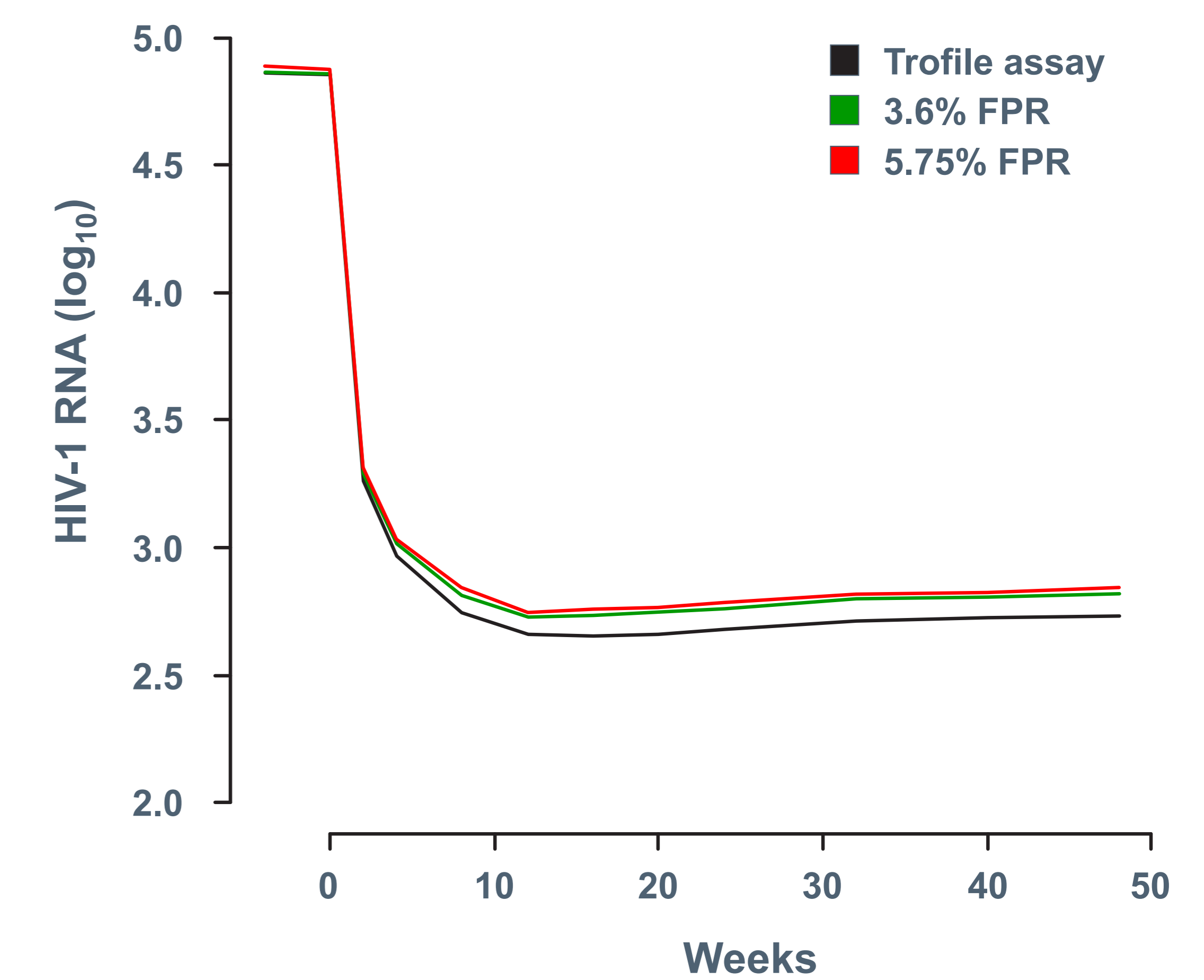
Odds ratios and 95% CIs estimated from logistic regression are displayed. Odds of a successful response are calculated based on the values indicated in red below the variable names.

Figure 4. In logistic regression models, g2p thresholds ranging from 3 to 6 yielded the best model fits based on AIC*



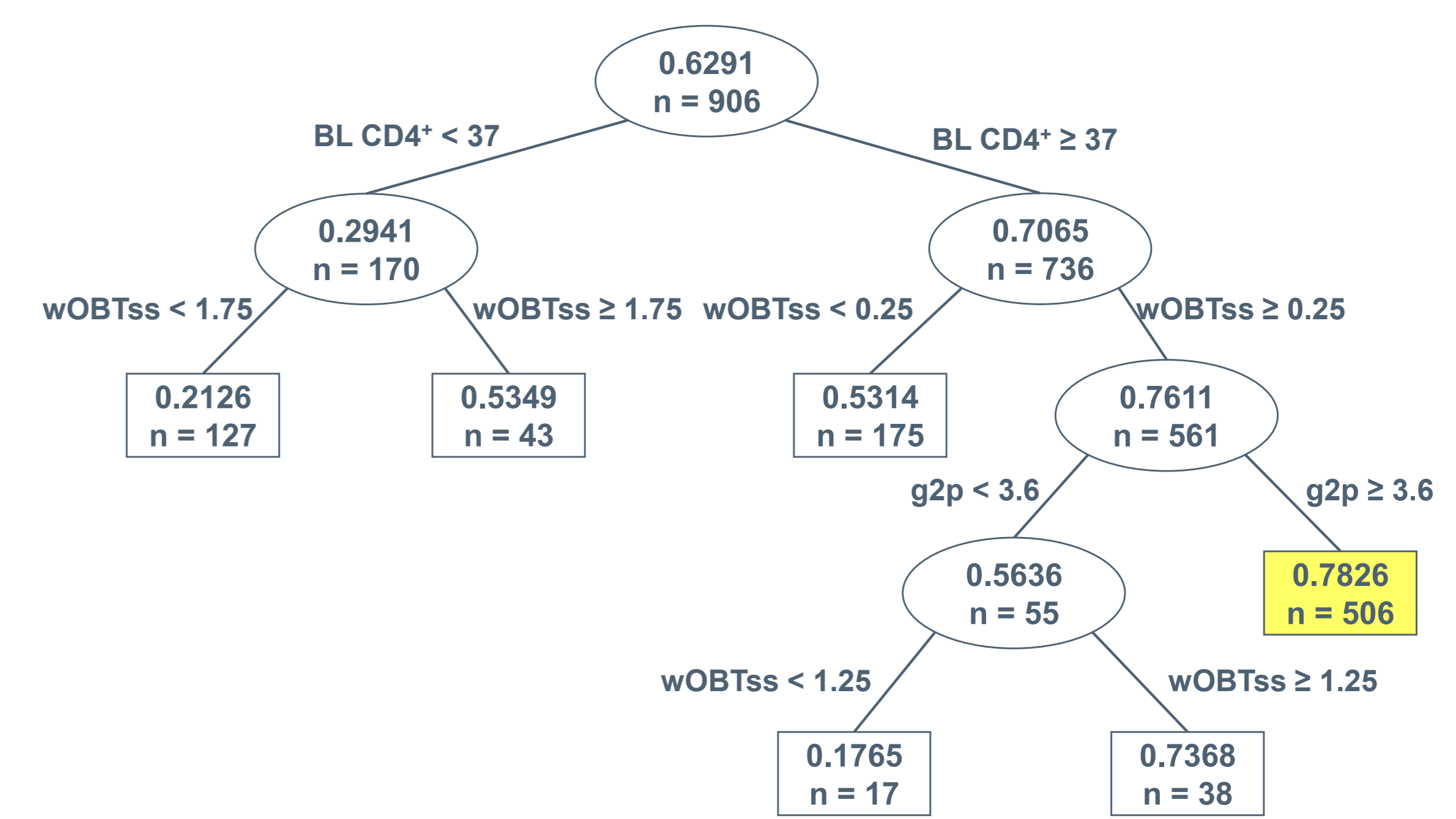
* Lower AIC indicates a better model fit. The minimum AIC was achieved at a g2p score of 3.4, which is close to the value predicted by a nonparametric CART model.

Figure 5. Similar virologic responses over time were observed using various thresholds for g2p FPR for predicting CCR5 tropism



Mean HIV-1 RNA was determined for patients classified as CCR5 tropic using various thresholds

Figure 6. CART analysis at week 8 indicated that 78% of patients with a g2p score > 3.6 responded if baseline CD4⁺ count was > 37 and wOBTss was > 0.25



The numbers in the nodes (circles and boxes) represent the fraction of patients responding, followed by the number of patients in that category.

- In CART analysis, all baseline variables included were highly predictive of week 8 change (from baseline) in viral load, also found in the linear regression
- Both linear and logistic models yielded similar ranges (3%–5% FPR) for the g2p threshold in terms of obtaining best-fit models
 - FPRs $> \approx 10$ have substantially reduced predictive value
- Virologic responses were very similar when virus was called CCR5 tropic using a threshold obtained with these methods, compared with results obtained with a 5.75% FPR, as reported by McGovern et al.^{1,2}
 - Of the 588 subjects with CD4⁺ count > 50 and g2p FPR $> 5.75\%$, 71% responded
- The CART model predicted a g2p threshold of 3.6, quite close to results from the linear and logistic models
- Responses to MVC-containing regimens were higher in patients with baseline CD4⁺ counts ≥ 100 , confirming that earlier initiation of therapy is associated with better outcomes
 - However, the relationship between baseline CD4⁺ count and virologic response is not linear

Conclusions

- Linear and logistic regression models, as well as CART methods, found that key baseline parameters (CD4⁺ count, wOBTss, and V3 genotype g2p score) were all independently predictive of virologic success or failure at week 8, with multivariate models yielding greater predictive power
 - These results confirm the importance of having adequate background drugs
- Baseline pVL was predictive of magnitude change in pVL at week 8, as from the linear regression
- These modeling approaches provide a clinically useful and mathematically validated method for selecting patients who could most benefit from a CCR5 antagonist
 - Our models have looked at week 8 response; it may also be useful to develop models incorporating responses after longer-term treatment, eg 24 and 48 weeks

References

1. McGovern RA et al. 12th European AIDS Conference. Poster PE3.4/8. 2009.
2. McGovern RA et al. 7th Conference on Retroviruses and Opportunistic Infections. Poster 92. 2010.