

Mixed Effects Modelling in HIV and Hepatitis C co-infected European Children

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Introduction

Hepatitis C co-infection is a leading cause of morbidity in HIV-infected patients. Worldwide, 190million individuals are estimated to be infected with chronic hepatitis C virus (HCV) and 7 million are thought to be co-infected with HIV [3]. Adult HCV-co-infected patients have been reported to have increased incidence of liver fibrosis and end-stage liver disease. However, very little is known in children who are also at increased risk of developing these long term complications. Anti-HCV therapy remains underused in the co-infected population. As a result, there is presently no consensus amongst clinicians regarding management of HCV co-infection in children.

Aim

The overall objective of this project is to investigate the impact of HCV infection on long term immune reconstitution of $CD4^+$ T cells in HIV-infected European children receiving anti-retroviral therapy (ART).

Methods

A total of 78 age-matched European children (Figure 1) selected from an observational study conducted by the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) were included for analysis. The children were aged between 1month and 25 yrs and had all received antiretroviral therapy. There were a total of 39 HCV co-infected and 39 HIV mono-infected children who had CD4 counts measured over a 5 yr period. The CD4 counts were normalised into z scores to accommodate for age-related fluctuations [1]. Using the frame work of non-linear mixed effects modelling, we fitted a recently developed semi-mechanistic model to our dataset [2]. In this model, it was shown that immune reconstitution in children commenced on antiretroviral therapy followed an asymptotic recovery in the first 5 yrs from a pre-ART value (int) at a rate c to a steady state value (asy).

$$z_{ij} = asy_i - (asy_i - int_i)e^{-ct_{ij}} + \epsilon_{ij} \quad [2] \quad (1)$$

Estimates were obtained for pre-ART z scores (int), long term antiretroviral therapy z scores (asy) and rate of increase in CD4 z scores (c). Covariates investigated include age at start of therapy, gender, aids status, hepatitis C status and country of origin. Stepwise covariate model selection was done in PsN using a forward and backward elimination process with exit p values of 0.05 and 0.01 respectively. Model fitting was done using the first order conditional estimation method in NONMEM (version 7.3.0).

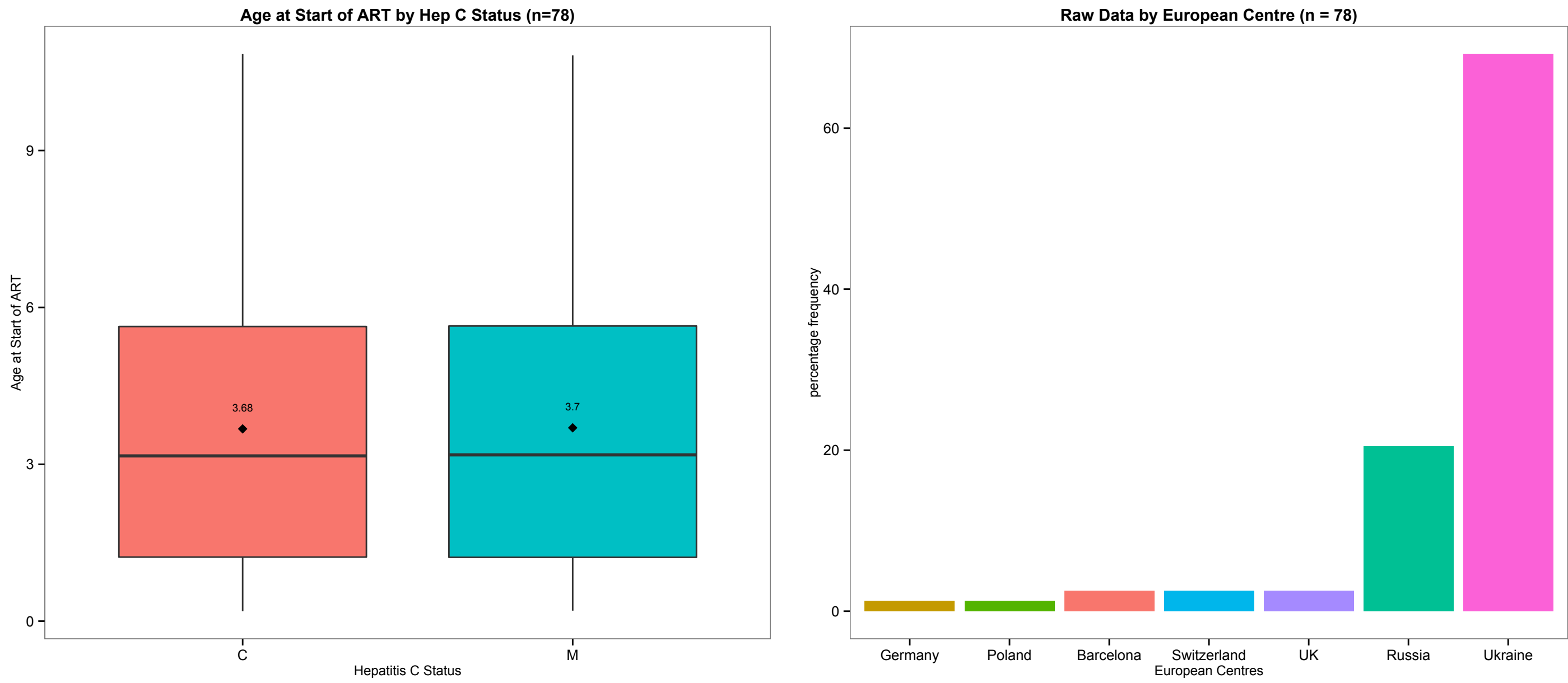


Figure 1: Left: age at start of therapy for the two cohorts (C:coi-infected, M:mono-infected). Right: percentage of children by country.

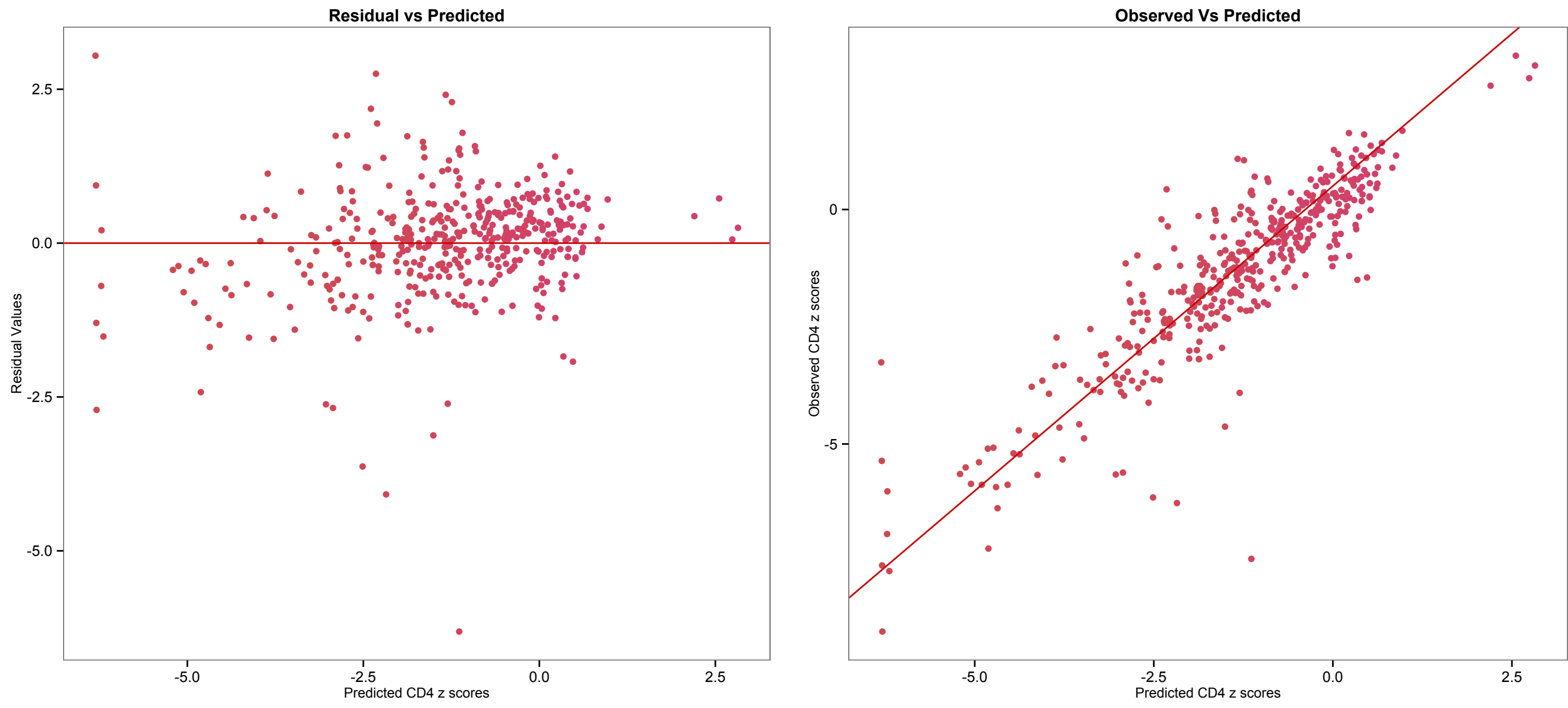


Figure 2: Left-Residual plot of the final covariate model. Right-Plot of observed values against fitted values.

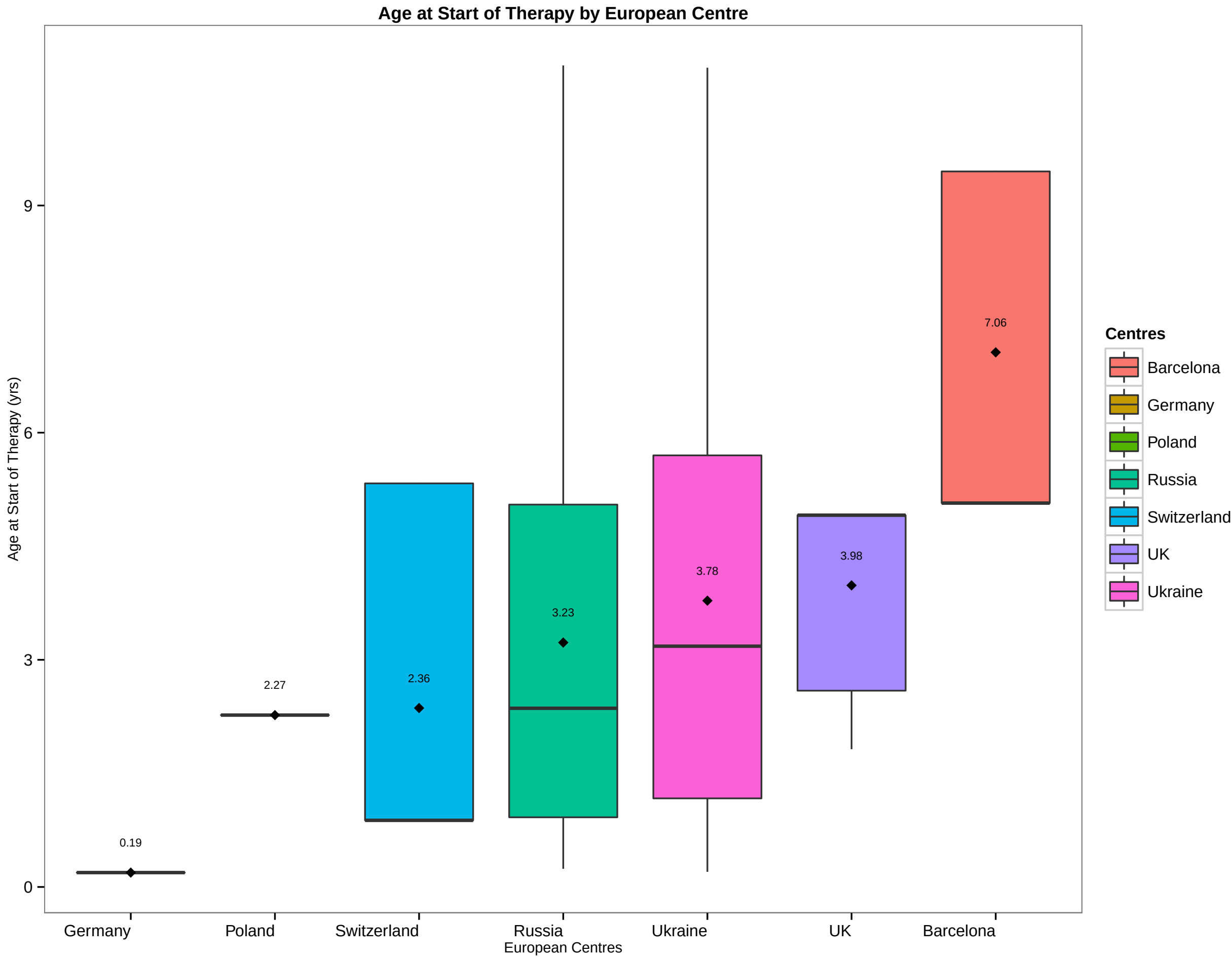


Figure 3: Age at start of antiretroviral therapy by European Centre. The black diamond dots represent mean age at start of therapy

Results

Hepatitis C does not have a significant impact on $CD4^+$ T cell reconstitution in HIV-infected European children receiving antiretroviral therapy

The analysis revealed that hepatitis C did not have a significant covariate interaction with any of the three parameters. As expected, younger children had a higher pre-ART age-adjusted CD4 counts ($p < 0.001$) compared to older children. The diagnostic plots in figure 2 illustrate that the final covariate model was an overall good fit for the data. Of the five covariates investigated, the effect of age on pre-ART was the only statistically significant interaction.

Parameter estimates obtained for int , asy and c are -1.95 ± 0.347 , -1.02 ± 0.208 and 1.19 ± 0.799 respectively. ETA Shrinkage on asy and c was quite high (82% and 64%) whilst the shrinkage on int was minimal (36%). Results of individual predictions for six selected children is illustrated in figure 4.

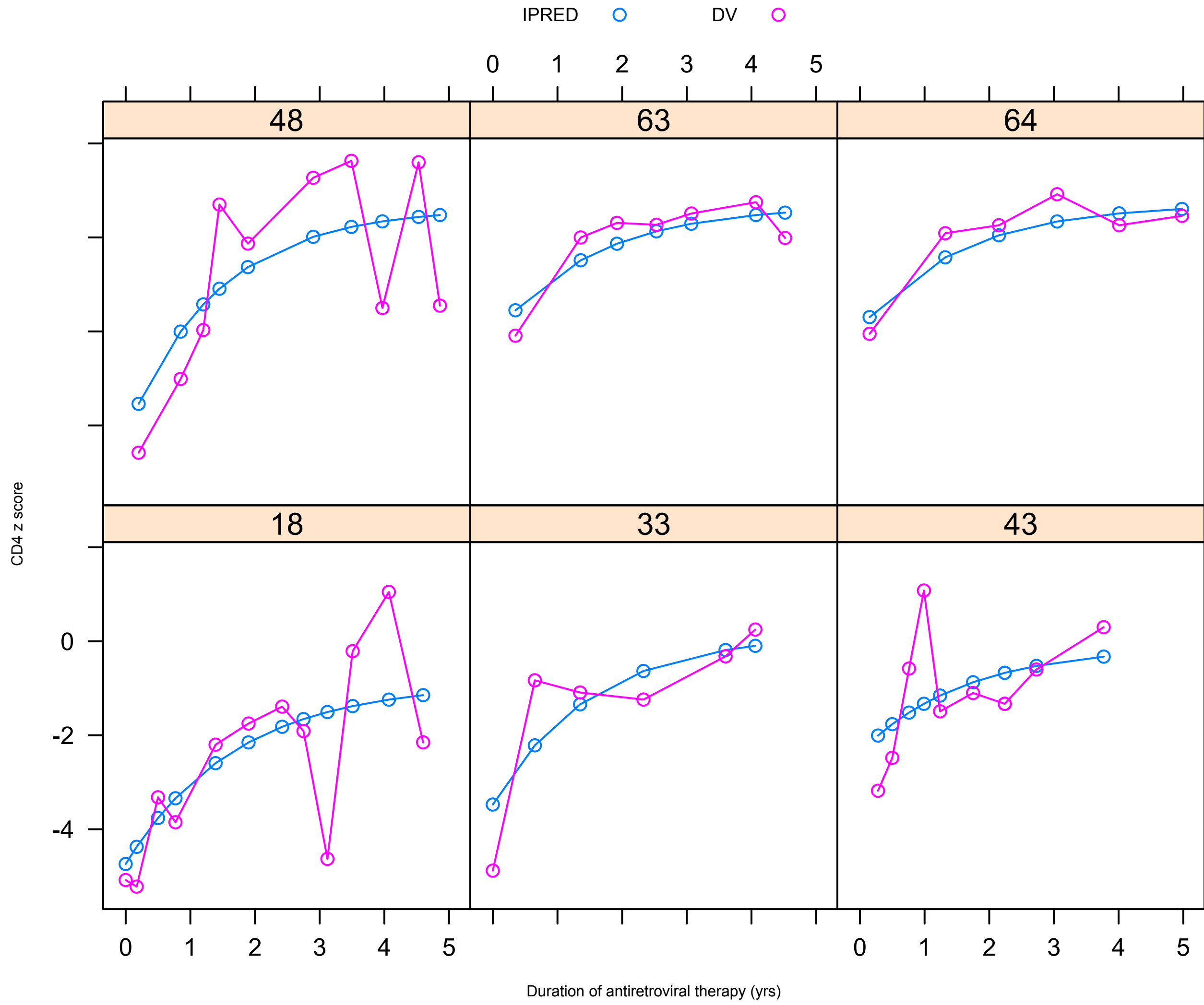


Figure 4: Model predictions(IPRED) for a selection of 6 patients alongside their raw CD4 z score profiles (DV)

Discussion

In this study, we have investigated the impact of Hepatitis C co-infection on $CD4^+$ T cell recovery in 78 HIV-infected children receiving anti-retroviral therapy. We have achieved this by fitting a non-linear mixed effects model to longitudinal data consisting of equal numbers of co-infected and mono-infected children. Our analysis shows that Hepatitis C does not have a statistically significant effect on $CD4^+$ T cell reconstitution. Our result is in agreement with a paediatric study published in 2007 by Micheloud et al which investigated the impact of HCV on immune reconstitution in 44 Spanish children [4]. Although this Spanish study did not use a modelling based approach, they established that hepatitis C did not have a statistically significant impact on $CD4^+$ T cell recovery in HIV-infected children receiving treatment. In this study, we have demonstrated using a modelling approach that there is no evidence that HCV impacts on long term $CD4^+$ T cell reconstitution in HIV-infected European children. From a clinical perspective, hepatitis C infection remains a therapeutic challenge amongst HIV co-infected individuals and new pharmacologic agents are required in the paediatric population.

Conclusions

To our knowledge, Hepatitis C co-infection does not affect $CD4^+$ T cell recovery in these 78 HIV-infected children undergoing antiretroviral therapy.

Future Work

Future studies will look into applying this model to a larger cohort of co-infected and mono-infected children to validate the findings in this study. Full covariate analysis will be carried out with visual predictive checks on model outcomes using simulated datasets.

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