WEB MATERIAL

The Effect of HIV Treatment Interruption on Subsequent Immunological Response

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WEB APPENDIX

CD4 Trends Conditional on Baseline CD4 Counts

Based on model assumptions, it follows that

$$\begin{pmatrix} \boldsymbol{m_i(0)} \\ \boldsymbol{m_i(t)} \end{pmatrix} \sim \boldsymbol{N}\left\{ \begin{pmatrix} \mathbf{x_i^\top(0)\beta} \\ \mathbf{x_i^\top(t)\beta} \end{pmatrix}, \begin{pmatrix} \mathbf{z_i^\top(0)Dz_i(0)} & \mathbf{z_i^\top(t)Dz_i(0)} \\ \mathbf{z_i^\top(t)Dz_i(0)} & \mathbf{z_i^\top(t)Dz_i(t)} \end{pmatrix} \right\}$$

Our goal is to estimate CD4 trajectories conditional on CD4 count at baseline, e.g. $E\{m_i(t)|m_i(0) < \sqrt{50}\}$. To simplify the presentation of formulas and to allow for generic truncation limits, let us assume that

$$\begin{pmatrix} \boldsymbol{X_1} \\ \boldsymbol{X_2} \end{pmatrix} \sim \boldsymbol{N}\left\{ \begin{pmatrix} \boldsymbol{\mu_1} \\ \boldsymbol{\mu_2} \end{pmatrix}, \begin{pmatrix} \boldsymbol{\sigma_1^2} & \boldsymbol{\rho\sigma_1\sigma_2} \\ \boldsymbol{\rho\sigma_1\sigma_2} & \boldsymbol{\sigma_2^2} \end{pmatrix} \right\},$$

where X_1 refers to $m_i(0)$ and X_2 refers to $m_i(t)$ and the remaining quantities are defined accordingly. Then,

$$E(X_2|l < X_1 < u) = \frac{\int_l^u \int_{-\infty}^{+\infty} x_2 f(x_1, x_2) dx_2 dx_1}{\Pr\,(l < X_1 < u)}$$

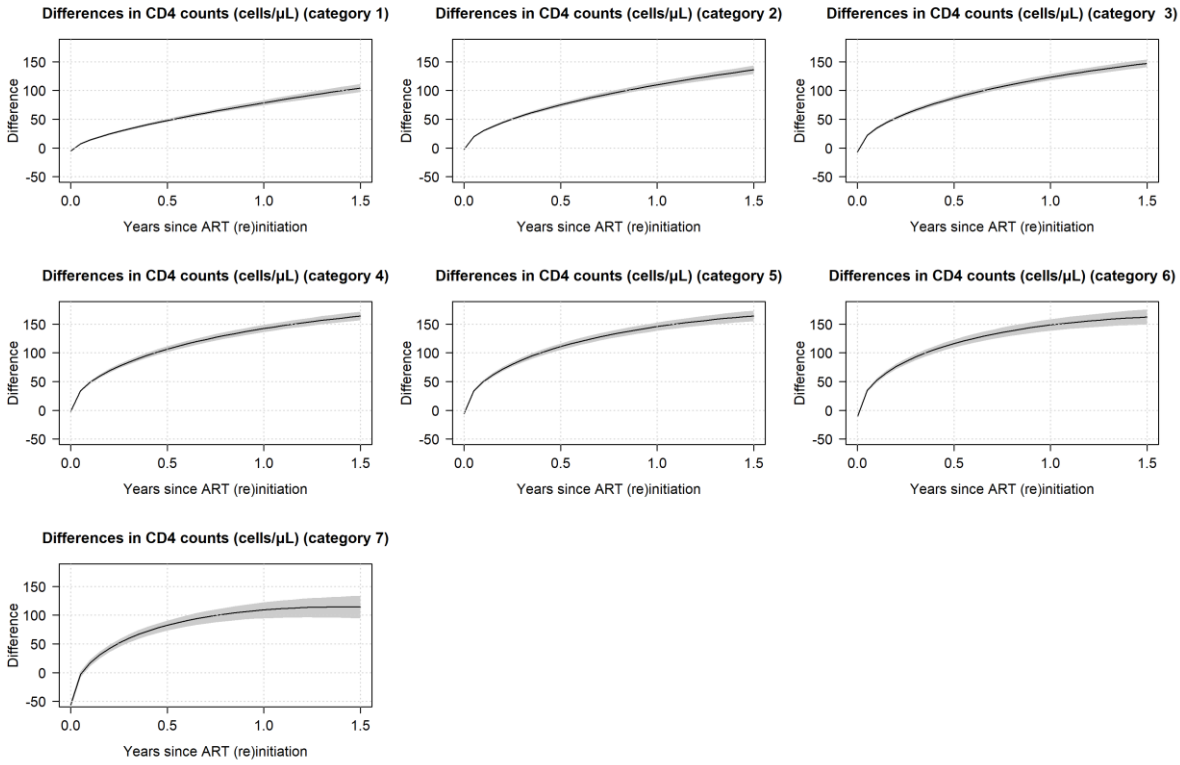
with $f(x_1, x_2)$ denoting the joint distribution of (X_1, X_2) and $-\infty \leq l < u \leq \infty$. Moreover, let $\varphi(x)$ and $\Phi(x)$ denote the probability density function and cumulative distribution function of a standard Normal distribution, i.e. $N(0,1)$, evaluated at x, and $\alpha = \frac{l-\mu_1}{\sigma_1}$ and $\beta = \frac{u-\mu_1}{\sigma_1}$. By simple calculations, it follows that,

$$E(X_2|l < X_1 < u) = \frac{\int_l^u \int_{-\infty}^{+\infty} x_2 f(x_2|x_1) dx_2 f(x_1) dx_1}{\Phi(\beta) - \Phi(\alpha)} = \frac{\int_l^u E(X_2|X_1 = x_1) f(x_1) dx_1}{\Phi(\beta) - \Phi(\alpha)}$$

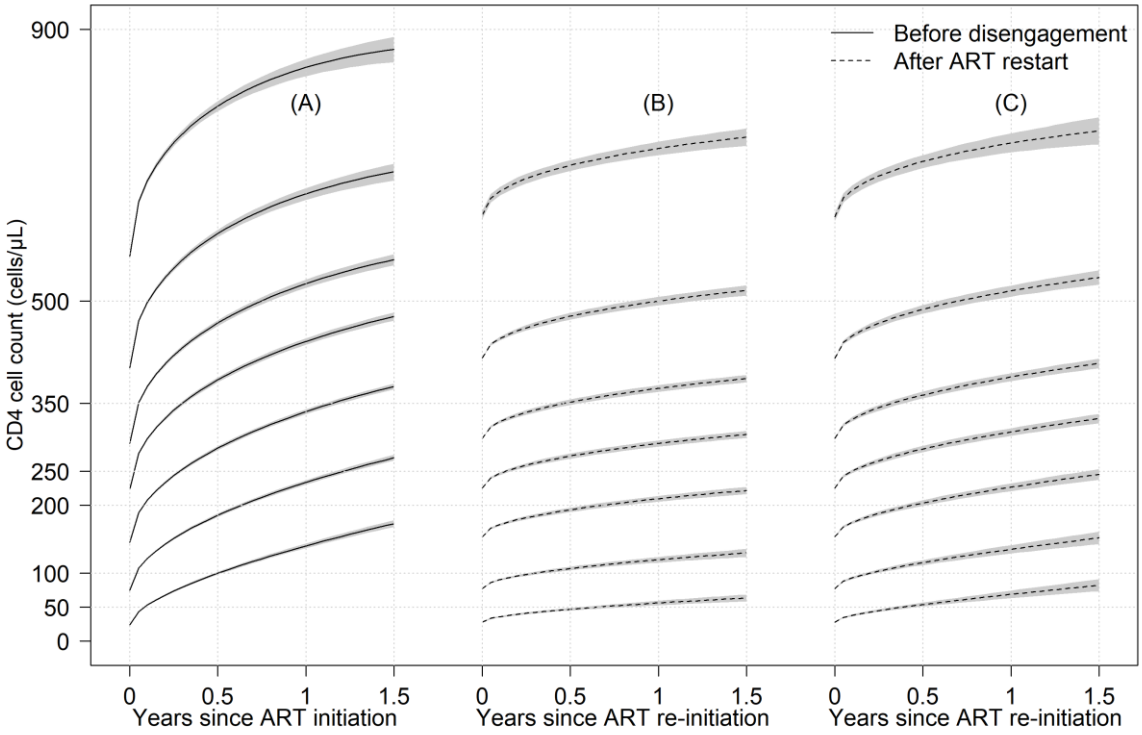
where, by standard properties of the bivariate Normal distribution, it follows that $E(X_2|X_1 = x_1) = \mu_2 + \rho\frac{\sigma_2}{\sigma_1}(x_1 - \mu_1)$. After making the change of variables $w = \frac{x_1-\mu_1}{\sigma_1}$ in the above integral, it can be easily shown that

$$E(X_2|l < X_1 < u) = \frac{\int_{\alpha}^{\beta}(\mu_2 + \rho\sigma_2 w)\varphi(w)dw}{\Phi(\beta) - \Phi(\alpha)} = \mu_2 - \rho\sigma_2 \frac{\varphi(\beta) - \varphi(\alpha)}{\Phi(\beta) - \Phi(\alpha)}, \qquad (1)$$

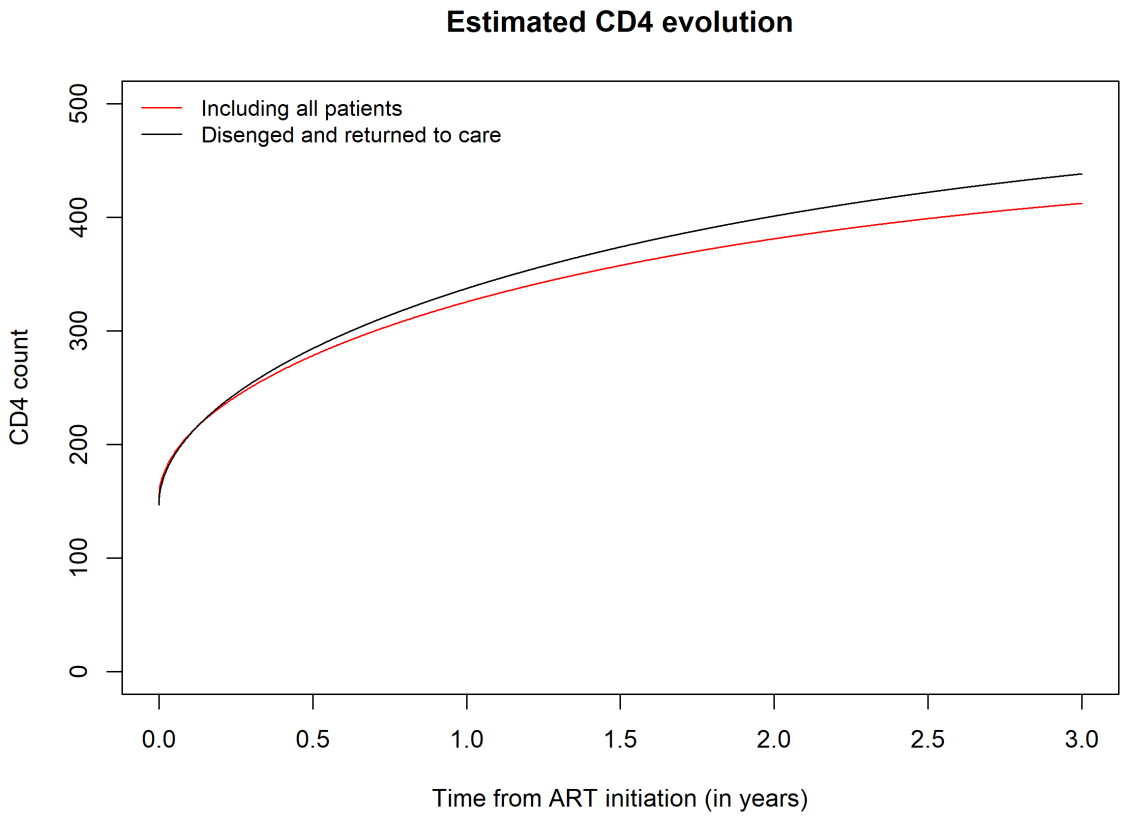
with the last equation following using integration by parts. Therefore, using Equation 1, we can very easily estimate the CD4 trends conditional on the initial levels, $E\{m_i(t)|m_i(0) < \sqrt{50}\}$. As estimation of the standard error of Equation 1 is difficult, we relied on a Monte Carlo procedure by drawing samples from the approximate posterior distribution of the parameters and repeatedly estimating Equation 1 to derive the standard error.



Web Figure 1: Differences (and 95% CIs) between estimated CD4 cell count before disengagement from care and after ART re-initiation over time since ART initiation or re-initiation, respectively. Estimates are conditional on being on the same CD4 categories at ART initiation and ART re-initiation. Categories were: 1: [0,50), 2: [50,100), 3: [100,200), 4: [200,250), 5: [250,350), 6: [350,500), 7: [500,] CD4 cells/μl.



Web Figure 2: Estimated CD4 evolution since ART initiation (A) and after ART re-initiation (B and C) for individuals who have disengaged from care and subsequently re-engaged in care, with at least one available CD4 count both at/after ART initiation and ART re-initiation, conditionally on being on the same CD4 category at ART initiation and ART re-initiation. (B): All CD4 data at/after ART restart were used (ignoring any subsequent disengagement from care), (C) CD4 data have been censored at the time of the second disengagement.



Web Figure 3: Estimated CD4 evolution since ART initiation (i) including individuals who disengaged from care and subsequently re-engaged in care (black solid line; shown is the estimated CD4 evolution before disengagement from care) and (ii) including all individuals initiating ART (red solid line; data censored at the first loss to clinic event, i.e. death or disengagement from care).