Yale SCHOOL OF PUBLIC HEALTH

*Biostatistics*

# Modeling Viral Rebound Trajectories After Analytical Antiretroviral Treatment Interruption


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## 12:00 Noon Eastern time, Tuesday, December 1, 2020

## Virtual seminar via Zoom


**ABSTRACT**

Despite the success of combined antiretroviral therapy (ART) in achieving sustained control of viral replication, the concerns about side-effects, drug-drug interactions, drug resistance and cost call for a need to identify strategies for achieving HIV eradication or an ART-free remission. Following ART withdrawal, patients' viral load levels usually increase rapidly to a peak followed by a dip, and then stabilize at a viral load set point. Characterizing features of the viral rebound trajectories (e.g., time to viral rebound and viral set points) and identifying host, virological, and immunological factors that are predictive of these features requires addressing analytical challenges such as non-linear viral rebound trajectories, coarsened data due to the assay's limit of quantification, and intermittent measurements of viral load values. We first introduce a parametric nonlinear mixed effects (NLME) model for the viral rebound trajectory and compare its performance to a mechanistic modeling approach. We then develop a smoothed simulated pseudo maximum likelihood method for fitting NLME models that permits flexible specification of random effects distributions. Finally, we investigate the association between the time to viral suppression after ART initiation and the time to viral rebound after ART interruption through a Cox proportional hazard regression model where both the outcome and the covariate are interval-censored observations.