Potential vs Realized Immune Reconstitution and Nonresponse

Senay Topal[a,b], Benjamin Ridenhour[c], Brian K. Agan[a,b]

[a] Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
[b] The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA
[c] Department of Mathematics and Statistical Science, University of Idaho, Moscow, ID, USA

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Background

Context
- Immune nonresponse is inadequate immune system recovery after antiretroviral therapy initiation in spite of viral suppression
- 10 to 40% of people with HIV are classified as immune nonresponders

Problem
- The range is too wide to be informative
- No consistently applied single definition of nonresponse
- Existing definitions do not capture current immune nonresponse
- Existing definitions do not predict future immune reconstitution

Solution
- Define immune nonresponse based on predicted immune reconstitution
- Provide formula to predict immune reconstitution
- Uncover the causes of immune nonresponse

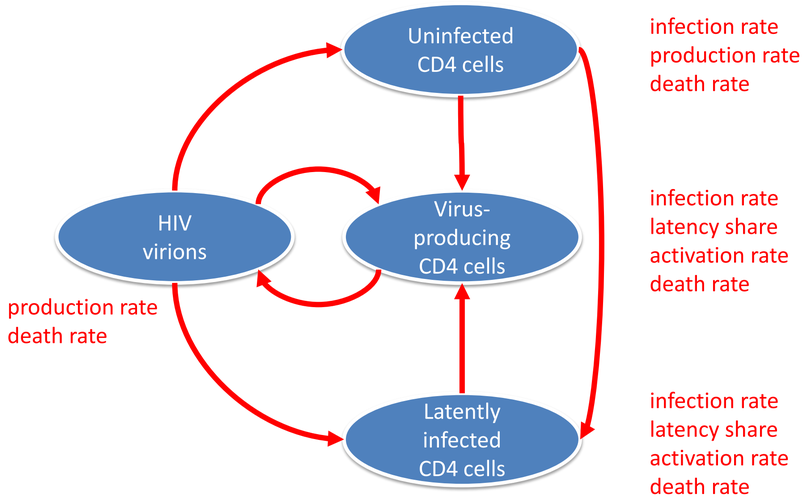
Methods

Simulation of immune reconstitution and nonresponse
- Mechanistic model of HIV infection
  - system of differential equations
- In-silico trials of
  - lymphocyte regeneration
  - apoptosis due to immunosenescence
  - ART effectiveness
  - immune activation
  - residual virus replication
- Simulate paths of
  - uninfected CD4 cells
  - virus-producing CD4 cells
  - latently infected CD4 cells
  - HIV virions

Mathematical formula of immune reconstitution
- derived from mechanistic model of HIV infection
- predicts the level of CD4 count a patient will reconstitute to

Data testing the accuracy of the formula of immune reconstitution
- Retrospective cohort study
- U.S. Military Health System Data Repository
- Universal access to care, minimizes system-level confounding
- 2,996 people with HIV, 87% Male
- Years 2008 – 2018

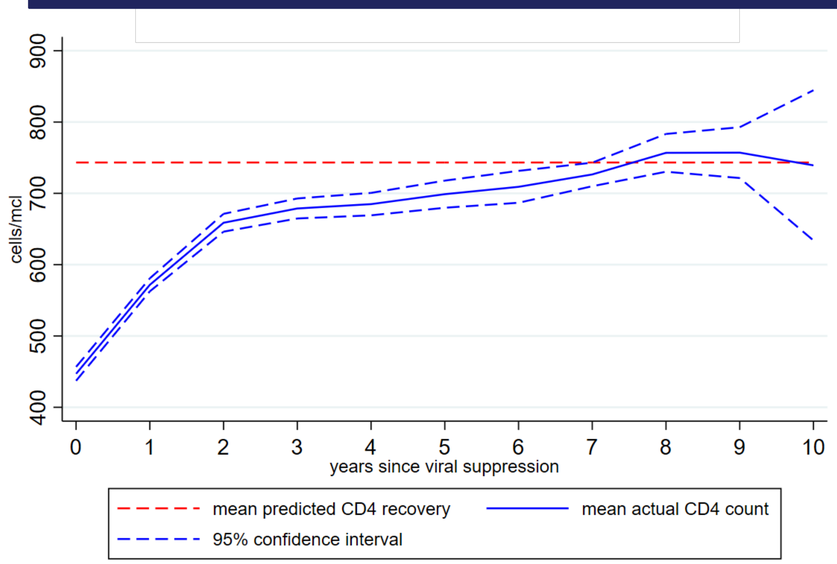
Results



Mechanistic model of HIV infection
- Potential immune reconstitution (maximum attainable CD4 count under perfect antiretroviral therapy) was determined by
  - CD4 cell production rates
  - CD4 cell death rates
- Realized immune reconstitution (maximum attained CD4 count) was determined by
  - antiretroviral therapy effectiveness
  - CD4 cell infection rates
  - virus replication rates
  - virus clearance rates

Plain Language Summary

Inadequate immune system recovery after HIV treatment initiation should be defined in terms of ability to realize potential recovery. Recovery can be predicted early using 3 lab tests after treatment initiation. Intervention should target the causes of potential recovery first and the causes of realized recovery second.



Mathematical formula of immune reconstitution
- $CD4^* = \frac{CD4_1 CD4_3 - CD4_2^2}{CD4_1 + CD4_3 - 2CD4_2}$
- Predicts the maximum CD4* count that will be realized
- Based on 3 CD4 measurements over time that are
  - taken before immune reconstitution
  - equally spaced over time
  - increasing over time

Conclusions

Previous definitions of immune nonresponse
- No single consistently applied definition
- Definitions based on CD4 count change do not capture current nonresponse
- Definitions based on 2 CD4 count measurements do not capture the nonlinear path of future reconstitution

Proposed definition of immune nonresponse
- Ability to realize potential reconstitution
- Based on predicted realized immune reconstitution
- Predicts the patient's maximum attained CD4 count
- The CD4 measurement conditions necessary for the predictive formula's accuracy are largely met due to existing clinical practice:
  - taken before immune reconstitution – met due to interest in early detection of nonresponders and hence use of early measurements
  - equally spaced over time – met due to provider scheduling practices
  - increasing over time – met due to focus on predicting recovery
- Targets for nonresponse intervention
  - potential reconstitution limits realized reconstitution
  - target causes of potential reconstitution first
  - target causes of realized reconstitution second

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Correspondence

STOPAL@IDCRP.ORG
SENAY.TOPAL.CTR@USUHS.EDU