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Persistence of Transmitted HIV-1 Drug Resistance Mutations Associated with Fitness Costs

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Introduction

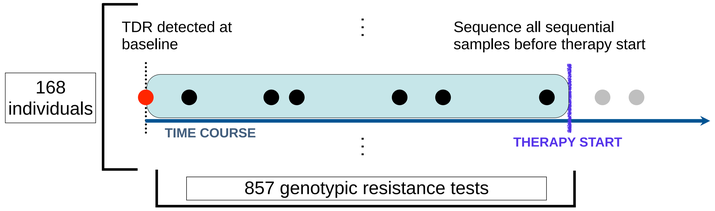
- Transmitted HIV-1 drug resistance mutations (TDR) impair antiretroviral treatment
- Persistence of many TDRs is poorly understood
- We assessed the persistence lengths of TDRs and compared them with fitness costs of TDRs

Conclusions

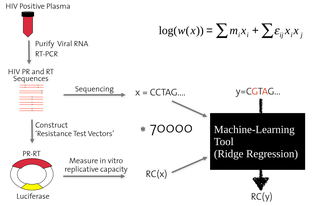
- Large variations in reversion rates across different TDRs were observed
- Reversion rates were strongly associated with fitness of individual mutations

Methods

- We retrospectively sequenced sequential plasma samples from treatment-naïve individuals carrying TDR within the protease / reverse transcriptase regions.
- Inclusion criteria: 1. individuals carried TDR at baseline & had ≥ 1 samples
  2. TDRs carried by ≥ 5 individuals



- We estimated fitness costs of TDR in the genetic background in which they occurred using a machine learning algorithm (*Hinkley et al., Nature Genetics ,2011)*

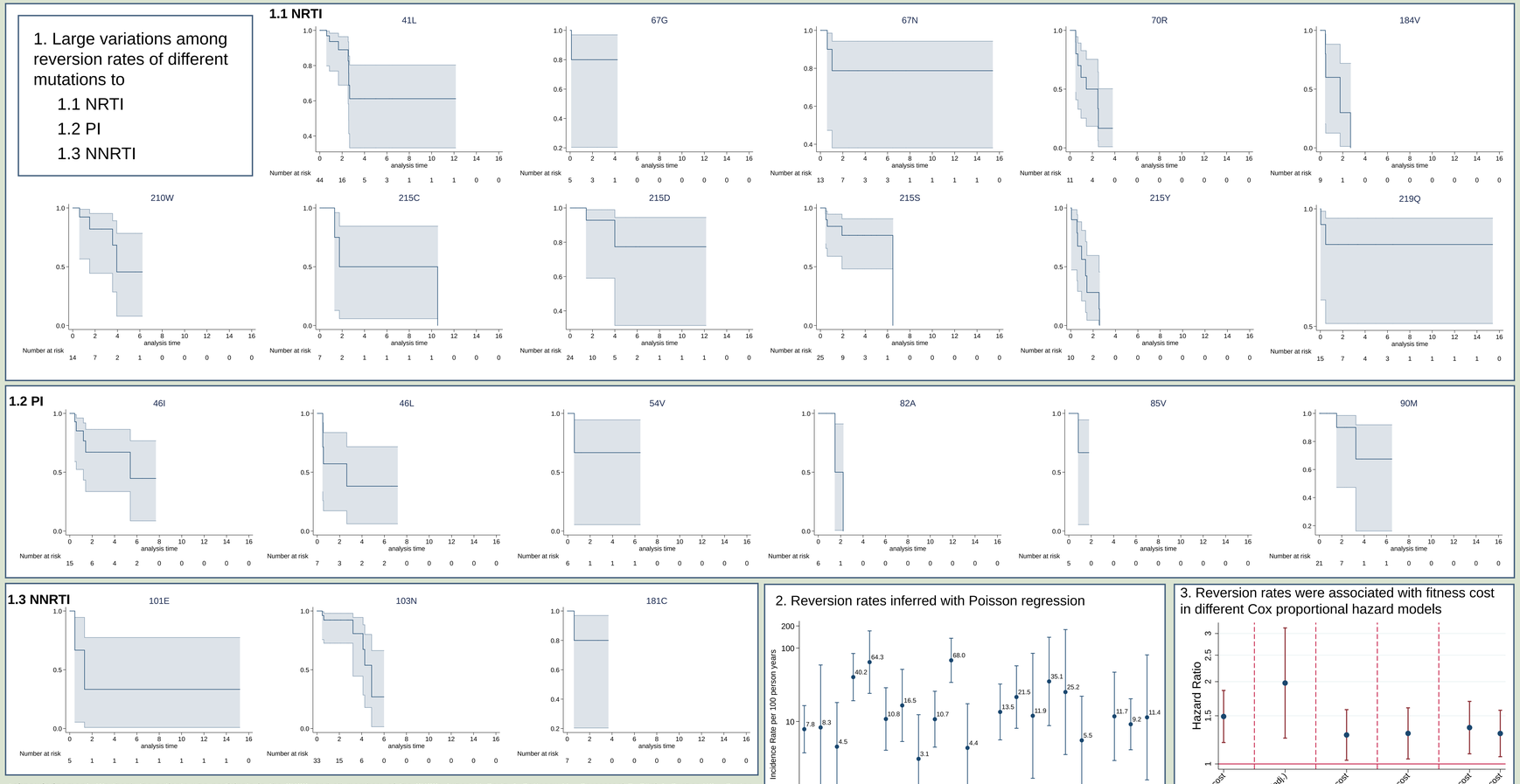


$$\log(w(x)) = \sum m_i x_i + \sum \varepsilon_{ij} x_i x_j$$

- According to the gene sequence, replicative capacity (RC) was predicted
- Fitness cost was calculated as :
  RC with TDR - RC without TDR
  (standardized as mean(0), standard deviation(1))

Results

1. Large variations among reversion rates of different mutations to
   1.1 NRTI
   1.2 PI
   1.3 NNRTI



2. Reversion rates inferred with Poisson regression

3. Reversion rates were associated with fitness cost in different Cox proportional hazard models

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