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Genetic diversity from proviral DNA as a proxy for time since HIV-1 infection

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BACKGROUND

- Time since infection is important for clinical care and research
  - often unknown
- HIV-1 RNA genetic diversity predicts time since infection
  - RNA under suppressive ART not available, but proviral DNA
- **Can proviral HIV DNA sampled post ART initiation predict the time since infection?**

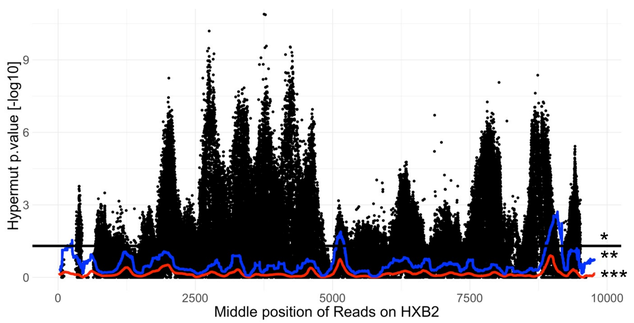
METHODS

Population: 221 people with HIV-1 (PWH)
- Known infection time
- Swiss HIV Cohort Study (SHCS)
- Zurich Primary HIV Infection Cohort Study (ZPHI)

Outcome:
- Time since infection until ART initiation ($t_{InfectionToART}$)
- Infection recency ($t_{InfectionToART}$ <1y)

Predictor: genetic diversity as Average Pairwise Diversity (APD)
- Derived from proviral NGS sequences
- Stratified by *gag*, *pol*, *env*
- Bulk sequencing
- Stratified by sequence length (partial vs full)
- Filtering of APOBEC3G/F hypermutated NGS reads

NGS hypermutation filters:
- Uniform p<0.05*, liberal dynamic**, conservative dynamic***



Statistical models:
- Time since infection
  - R^2, explained variance of APD for time since infection
- Infection recency
  - Receiver Operator Curve, Area Under the Curve (ROCAUC)

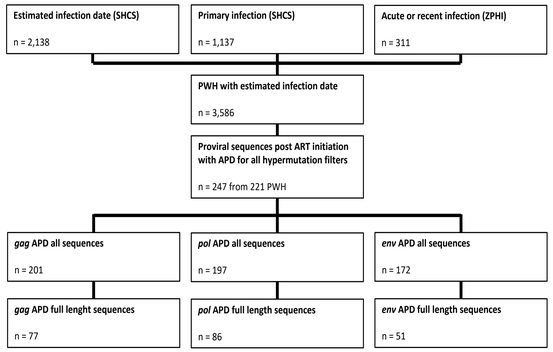
Genetic diversity derived from **proviral HIV DNA** under suppressive ART predicts **time since infection** until ART initiation and HIV **infection recency**

RESULTS

Time since infection prediction
- R^2 maximum 0.25 with *pol*

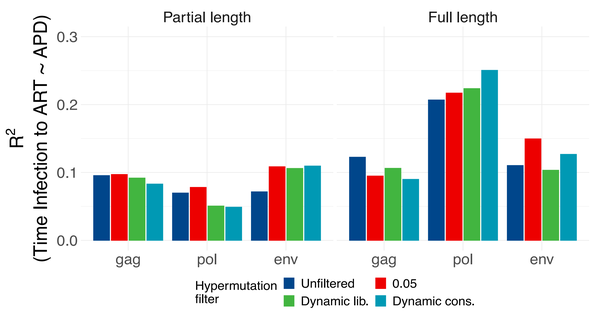
Infection recency prediction
- ROC-AUC maximum 0.85 with env

Hypermutation filtering improves predictions

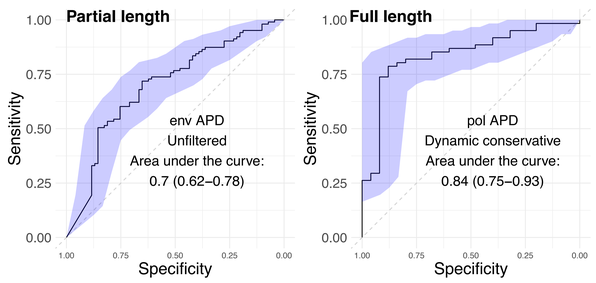


Flowchart of study population with know infection date and sequence availability.

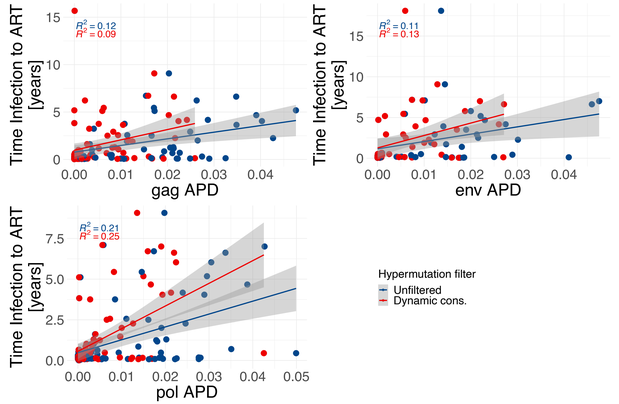
Explained variance (R^2) of APD for $t_{InfectionToART}$



ROC AUC curve predicting $t_{InfectionToART}$ <1y with APD



Correlation of APD with $t_{InfectionToART}$



ROC AUC values predicting $t_{InfectionToART}$ <1y with APD

AUC recent infection prediction	*gag*	*pol*	*env*	*gag*	*pol*	*env*
Hypermutation filter	Partial length			Full length		
Unfiltered	0.73	0.74	0.70	0.81	0.79	0.81
0.05	0.73	0.76	0.74	0.82	0.82	0.85
Dynamic liberal	0.71	0.75	0.76	0.82	0.84	0.83
Dynamic conservative	0.70	0.73	0.76	0.79	0.84	0.85

CONCLUSION

Proviral DNA can be used to infer…
- HIV time since infection
- HIV infection recency

Plasma RNA performs better
- but often difficult to acquire

Method will be useful for…
- Research:
  - e.g., time since infection affects viral reservoir
- Clinical applications for virally suppressed PWH
  - e.g., optimal treatment choice

ADDITIONAL INFORMATION

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