Molecular epidemiology of HIV in a declining but historically generalized African epidemic: A longitudinal, population-based study in Uganda

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BACKGROUND

- In African settings with high treatment coverage and declining incidence, it is unclear whether residual HIV infections are driven by external introductions or persistent local transmission.
- We examined HIV transmission patterns and sources of new HIV diagnoses in a multi-subtype epidemic (**Fig 1**).

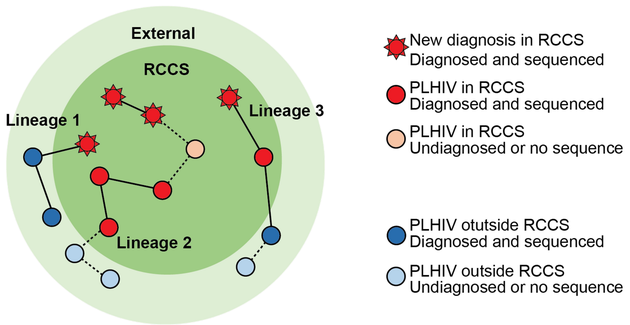


Figure 1. HIV transmission networks in the RCCS and external introductions

METHODS

- **Study population:** We analyzed HIV genome sequences and linked survey data from viremic persons with HIV collected between 2005 and 2019 from the Rakai Community Cohort Study (RCCS).
- **New HIV diagnosis:** Diagnosed with HIV in the RCCS between Dec 2016 and May 2019; **1)** Sero-incidence cases, **2)** who never received an HIV test result, or **3)** who received an HIV negative test result within the past two years.
- **Phylogenetic/phylogeographic analyses:** We reconstructed subtype-specific (A1, D, and C) p24 and gp41 ML phylogenies using sequences from the RCCS and external sources. We identified subtrees using *Cluster Picker* (GD: 5.3%) (**Fig 2A**) and long-horizon phylogeographic subtrees using *phyloscanner* (**Fig 2B**). Subtrees from *p24* and *gp41* were linked if any subtrees shared individuals, irrespective of their HIV subtypes (**Fig 2C**).
- **Statistical analyses:** A Bayesian negative binomial branching process model estimated under-sampled phylogeographic chain sizes and case reproduction numbers after ART rollout in 2005.

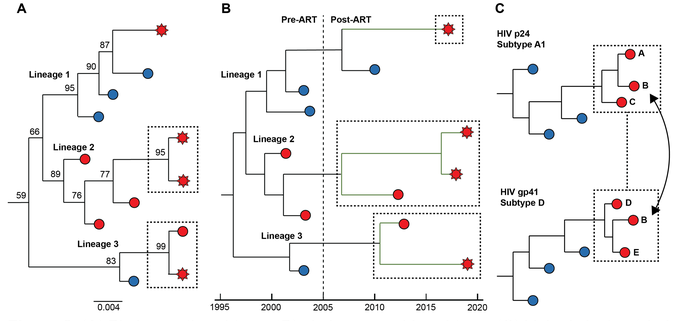


Figure 2. (A) Phylogenetic subtrees (B) phylogeographic subtrees (C) Linked clusters/chains

In settings with high ART coverage and declining incidence, HIV transmission is diffuse and diverse, with residual spread shaped by long-standing local lineages, sporadic transmission events, occasional external introductions, and viral recombination.

RESULTS

- Among 4,215 participants living with HIV between Dec 2016 and May 2019, 435 were newly diagnosed, of whom 252 had at least one pure-subtype sequence available for phylogenetic analyses.
- New diagnoses were more likely to be adolescent and young adults (p <0.0001), to report extra-community sexual partners (p <0.0001), and to have recently migrated into RCCS communities (p <0.0001).
- We identified 663 phylogenetic clusters and 673 phylogeographic chains including ≥2 individuals (**Fig 3A** and **Fig 4**); 599 (90·3%) clusters and 546 (81·1%) chains contained five or fewer individuals, with new diagnoses broadly dispersed across them and rarely clustering together (**Fig 3B, 3C** and **Fig 4**).
- Phylogeographic analyses revealed that **only 15·1% of new diagnoses had external origins**, while the remaining 84·9% were partially or fully linked to local lineages (**Data not shown**).

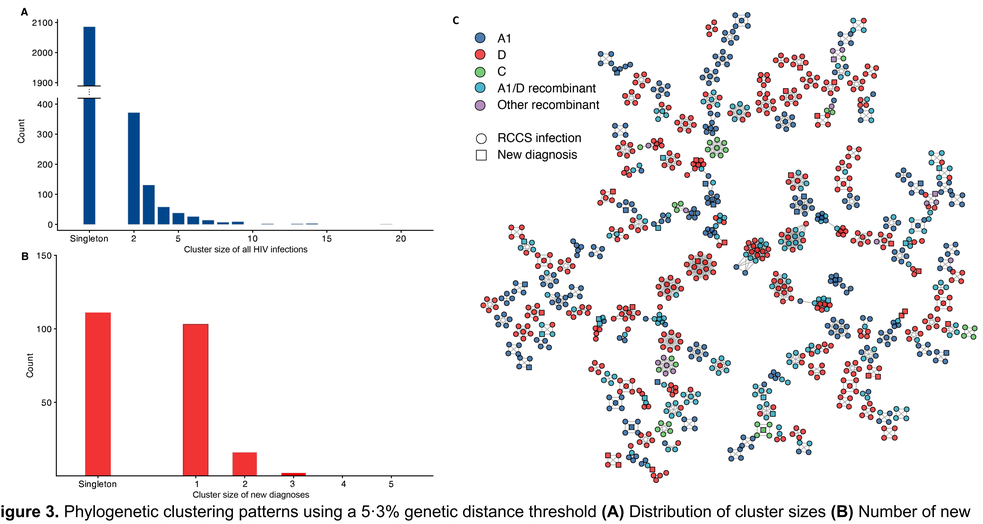


Figure 3. Phylogenetic clustering patterns using a 5·3% genetic distance threshold **(A)** Distribution of cluster sizes **(B)** Number of new HIV diagnoses in RCCS clusters **(C)** Network representation of phylogenetic clusters

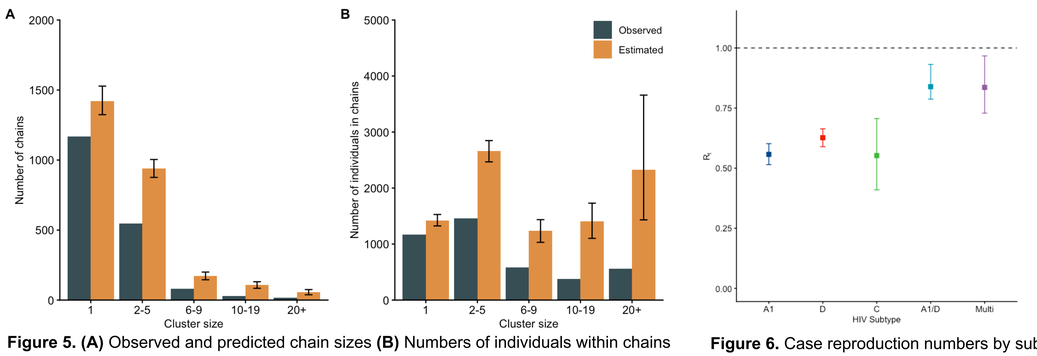


Figure 5. (A) Observed and predicted chain sizes **(B)** Numbers of individuals within chains

Figure 6. Case reproduction numbers by subtype

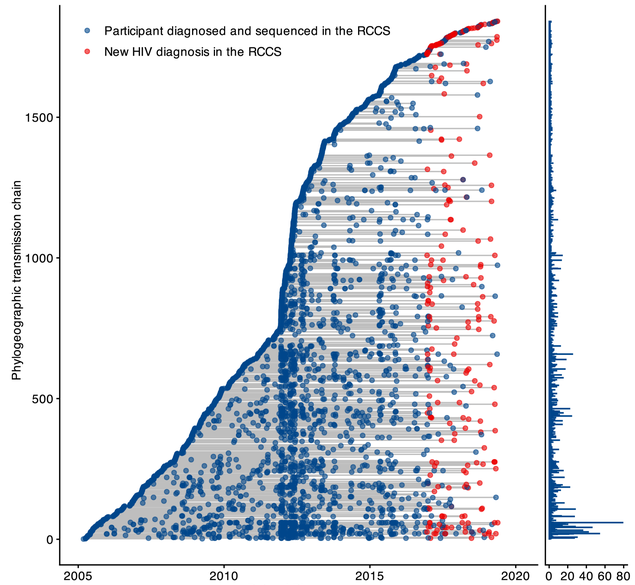


Figure 4. Phylogeographic transmission chains following ART roll-out

- The model predicted slightly more singletons than observed (1,421 vs 1,168), but roughly twice as many chains of 2–5 (940; 95% CrI: 876–1004) and 6–9 individuals (173; 145–200), and more than three times as many chains with 10 or more members (162; 132–195) (**Fig 5**).
- Mixed-subtypes/recombinant chains were larger and had higher case reproduction numbers than single-subtype chains, yet all estimates were less than one (**Fig 6**).

CONCLUSIONS

- HIV transmission was fragmented across numerous, slowly propagating lineages, maintained by persistent local clusters and recurrent introductions.
- **Because transmission is diffuse, prevention may need to be delivered widely, beyond a small set of locations or groups.**

ADDITIONAL KEY INFORMATION

Funding

The National Institute of Allergy and Infectious Diseases (R01AI155080 R01AI143333) and the Gates Foundation.

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PLAIN LANGUAGE SUMMARY

Even with widespread HIV treatment and declining incidence in Uganda, HIV transmission persists mainly through many small, slow-moving local transmission networks rather than a few large outbreaks—suggesting prevention should address diffuse, residual spread.