Are high prevalence fishing communities on Lake Victoria the predominant source of new infections in Rakai, Uganda?

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PANGEA HIV

Rakai Health Sciences Program
Improved Health Through Research

Oliver Ratmann

- 2009: PhD in Bayesian Statistics and Network Science, Imperial College London
- since 2013: research focus on viral phylogenetics and HIV (Dutch observational HIV cohort, PANGEA, HTEAM, HIV in cities: Seattle)
- since 2017: Lecturer in Statistics at Imperial; PhD students Xiaoyue Xi, Devrat Kaushal; post-doc Paul-Marie Grollemund
- two kids (Jonas and Timos)

Spatial heterogeneity in African HIV epidemic

- HIV epidemic markedly heterogeneous
- Foci of high HIV incidence and prevalence communities ("HOTSPOTS")
- Hypothesis: GEOGRAPHIC TARGETING of combination HIV prevention (CHP) to hotspots is ESSENTIAL
    - ➢ substantially ameliorate broader epidemic
    - ➢ cost-efficient use of resources

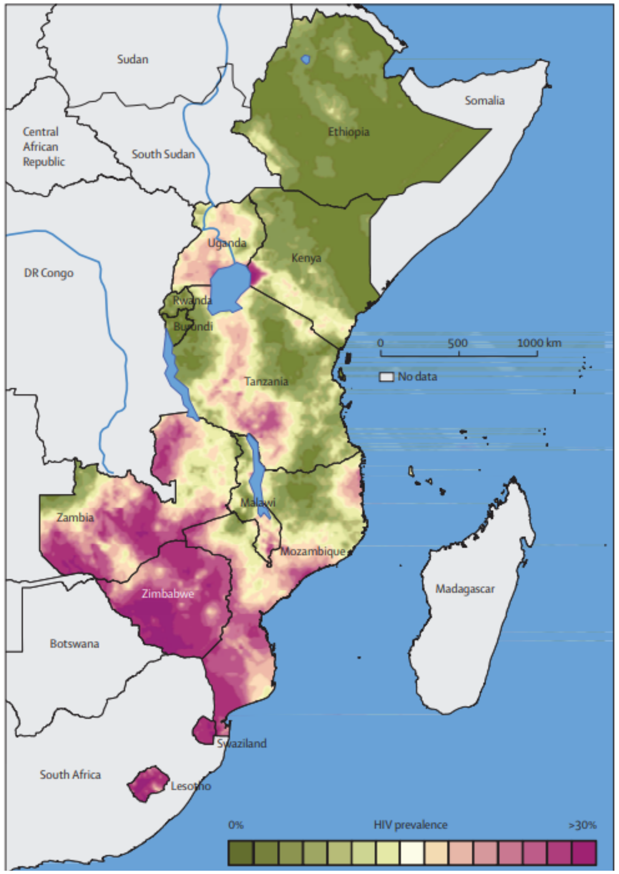
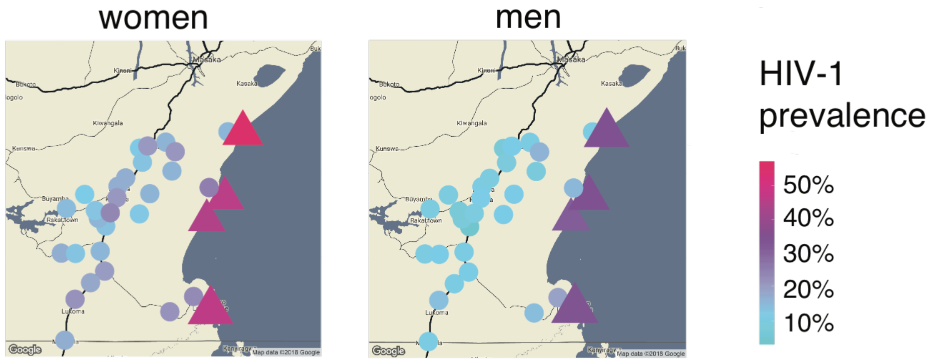


figure from Anderson et al., Lancet (2014)

Example: Lake Victoria Fishing Communities



- Lake Victoria fishing sites are hotspots

- Since 2014, targeting of CHP to fishing communities recommended

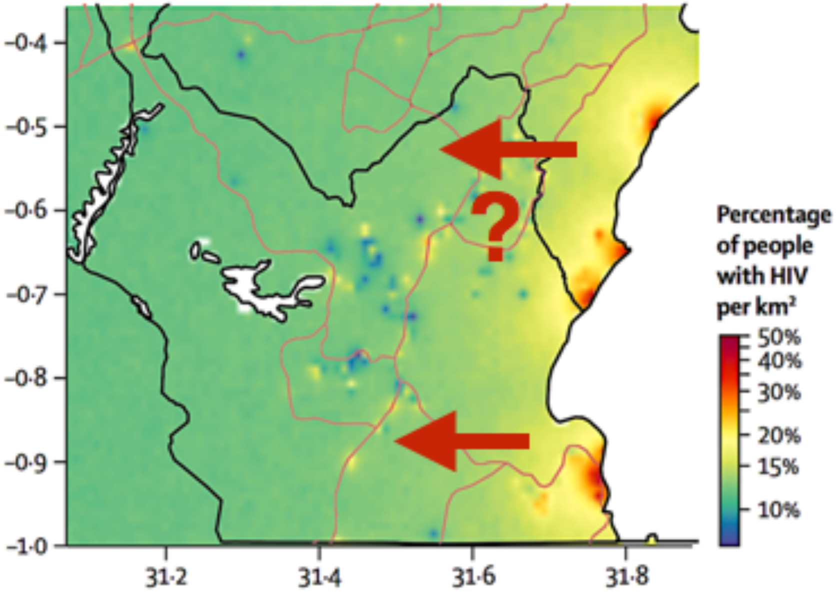
- Recommendation based on:

  - ➢ high incidence

  - ➢ assumption that fishing sites are major source of new infections among inland communities

Study objective

- Confirm the assumption that fishing communities are a major source of new infections among inland communities



Methods overview

- Two ways in which fishing sites can seed new infections in inland communities:
    - ➢ transmission from individuals who reside in fishing sites
    - ➢ migration to inland communities and subsequent spread of HIV
- Used a combination of techniques and data sources.

Acknowledgements

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Deenan Pillay
Andrew Rambaut

Rakai Health Science Program Staff and Study participants

Methods overview

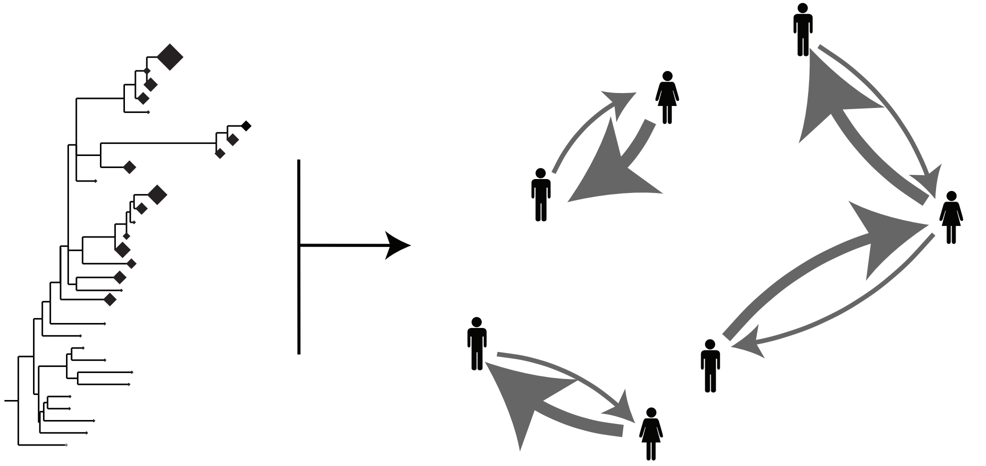
- First, surveillance was extended to include 4 largest fishing sites in the area

	🟩 36 inland communities	🟥 4 fishing sites
Eligible	29,115	8,529
Present	20,089	6,152
Participated	19,799 (99%)	6,083 (99%)
Infected	2,703 (14%)	2,439 (40%)
ART-naive	1,819 (67%)	2,059 (84%)

Methods overview

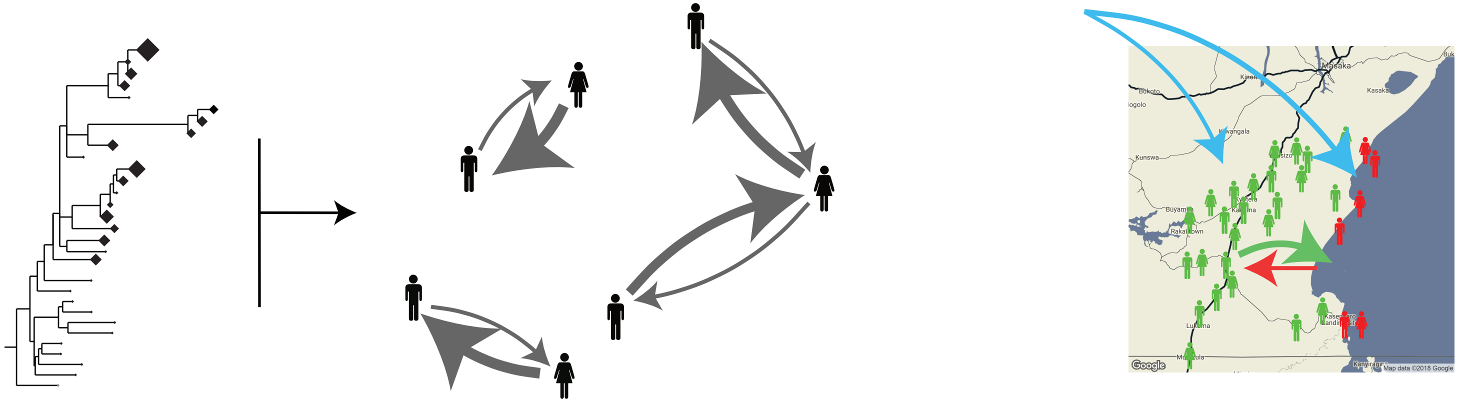
- Second, reconstructed likely HIV-1 transmission networks with viral phylogenetic analysis

	🟩 36 inland communities	🟥 4 fishing sites
Infected	2,703 (14%)	2,439 (40%)
ART-naive	1,819 (67%)	2,059 (84%)
Sequenced	1,138 (63%)	1,514 (74%)



Methods overview

- Third, households and migration events were geo-coded.



location of individuals after adjusting for recent migration

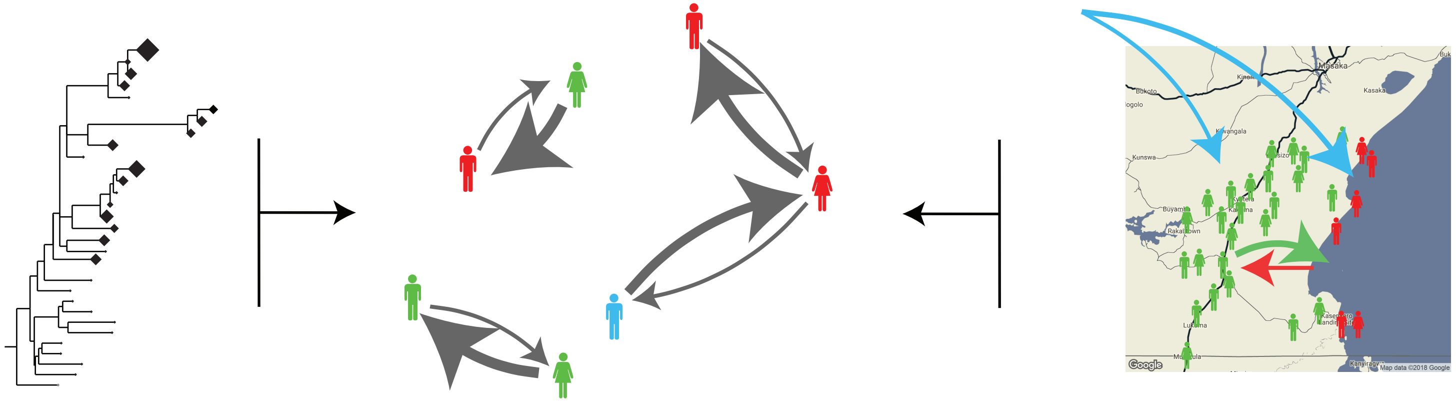
🟩 inland communities

🟥 fishing sites

🟦 external

Methods overview

- Third, households and migration events were geo-coded.
- This allowed us to interpret phylogenetic transmission networks at a resolution below 50km and while accounting for population movement



location of individuals after adjusting for recent migration

🟩 inland communities

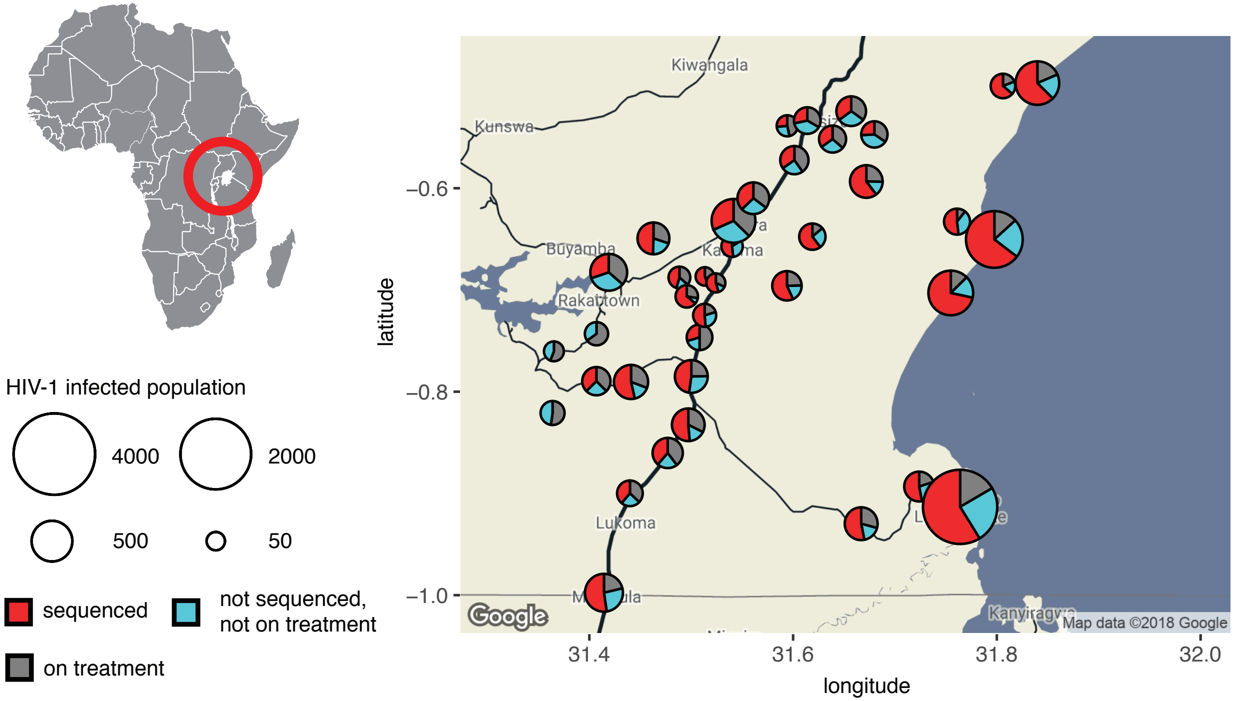
🟥 fishing sites

🟦 external

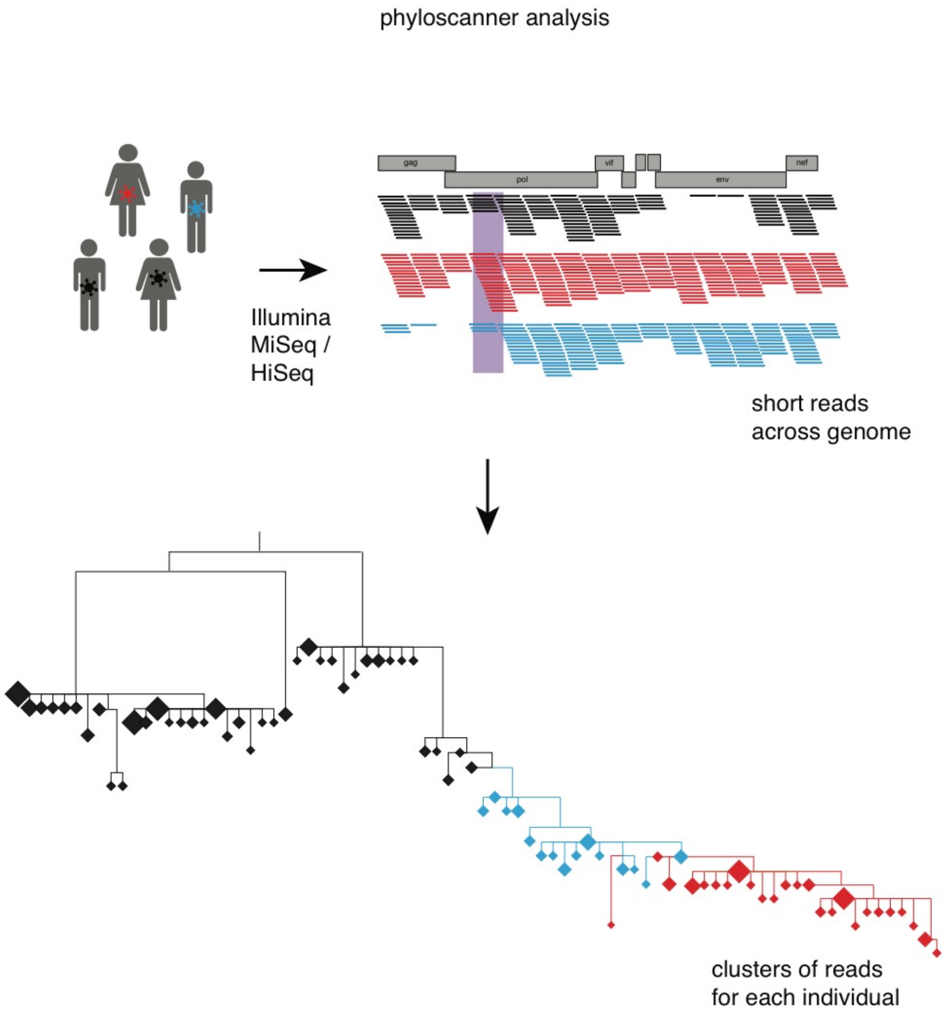
Obtaining population-based samples of NGS data is feasible

- 5,142 HIV positive
- 3,878 ART naïve
- 3,758 deep sequenced
- 2,652 with sufficient sequence depth (30X)

- Overall sequence coverage 48.1% assuming individuals who did not participate were infected in proportion to surveyed population



Deep sequence phylogenetics enables to infer the direction of transmission



phyloscanner analysis

Illumina MiSeq / HiSeq

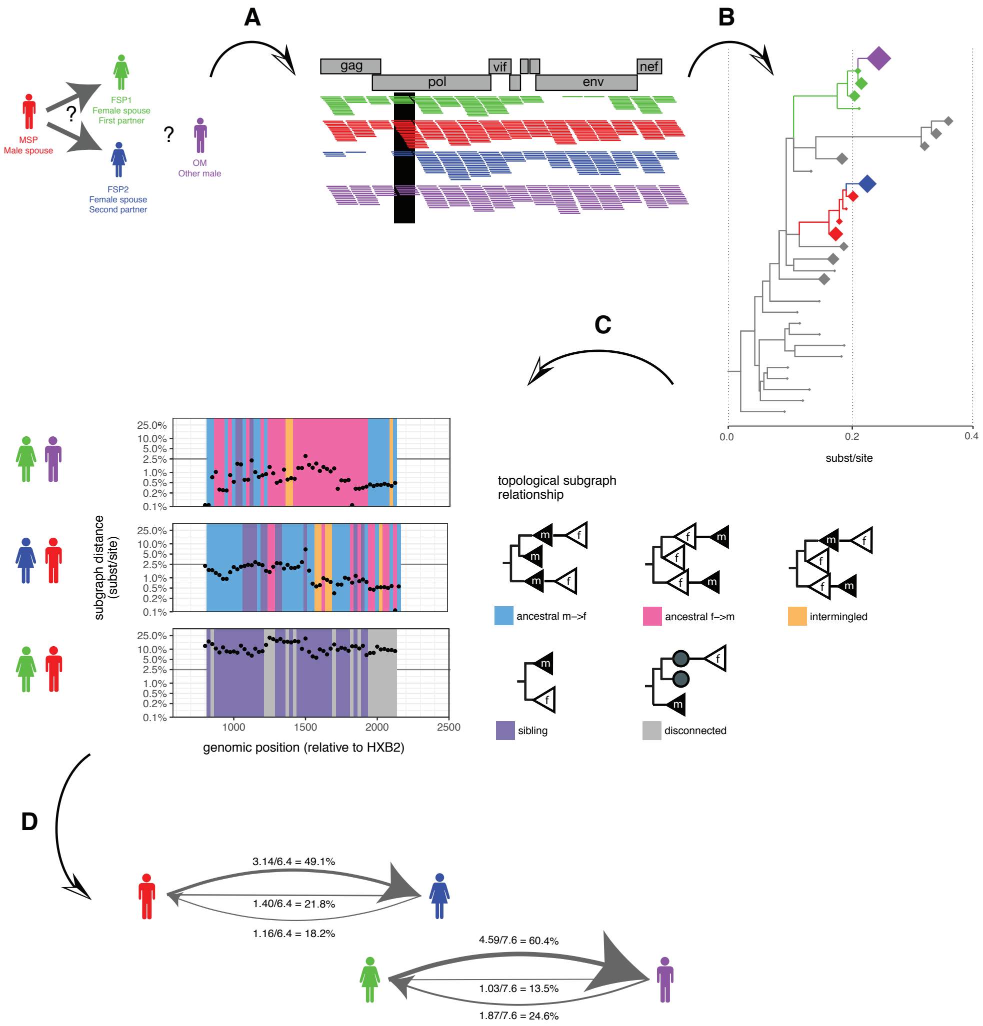
short reads across genome

clusters of reads for each individual

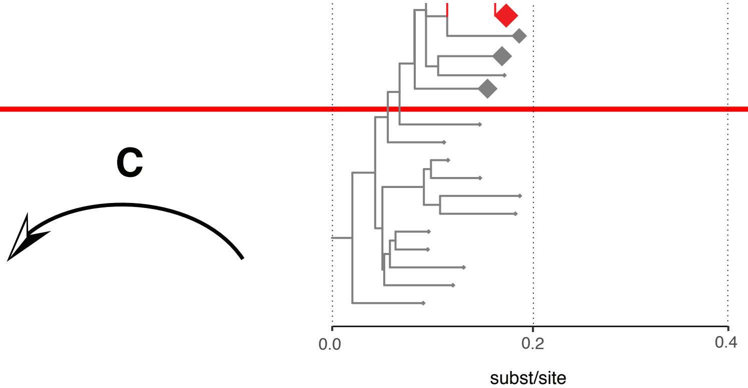
- Gives estimates on who might be the source case
- Validated against epidemiological data, found accuracy 83.7%

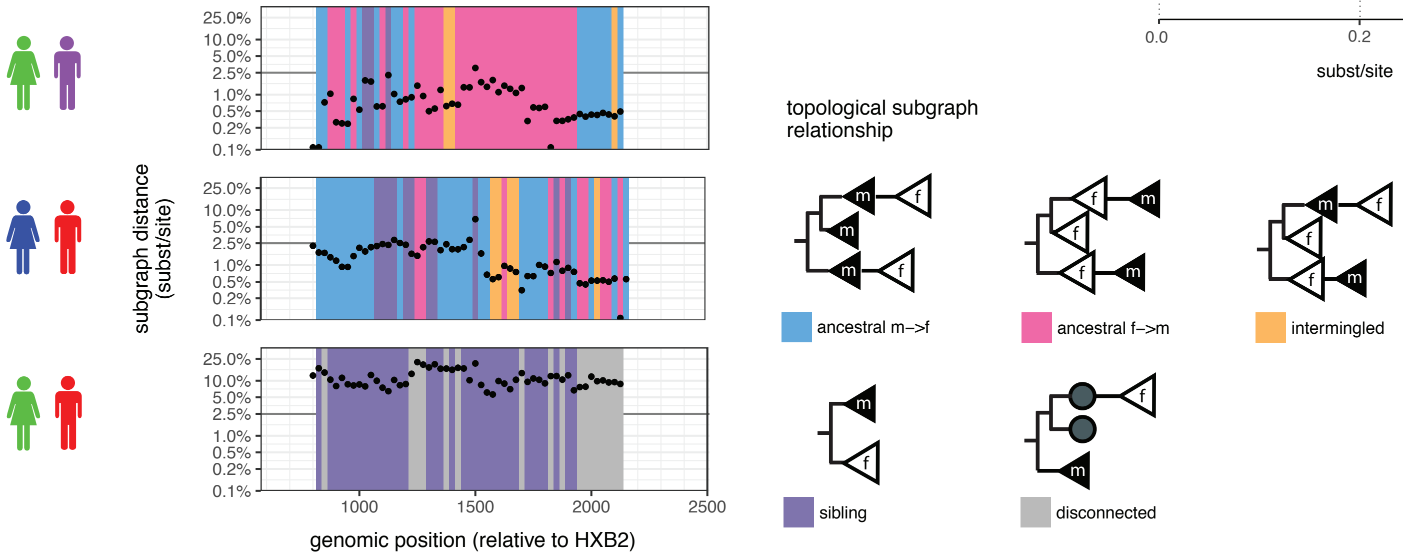
- Wymant et al. Virus Evolution 2018;
- Wymant et al. MBE 2017;
- Ratmann et al. (in prep);
- Rose et al. on behalf of HPTN052 #TUPEA001

Phyloscans across the genome

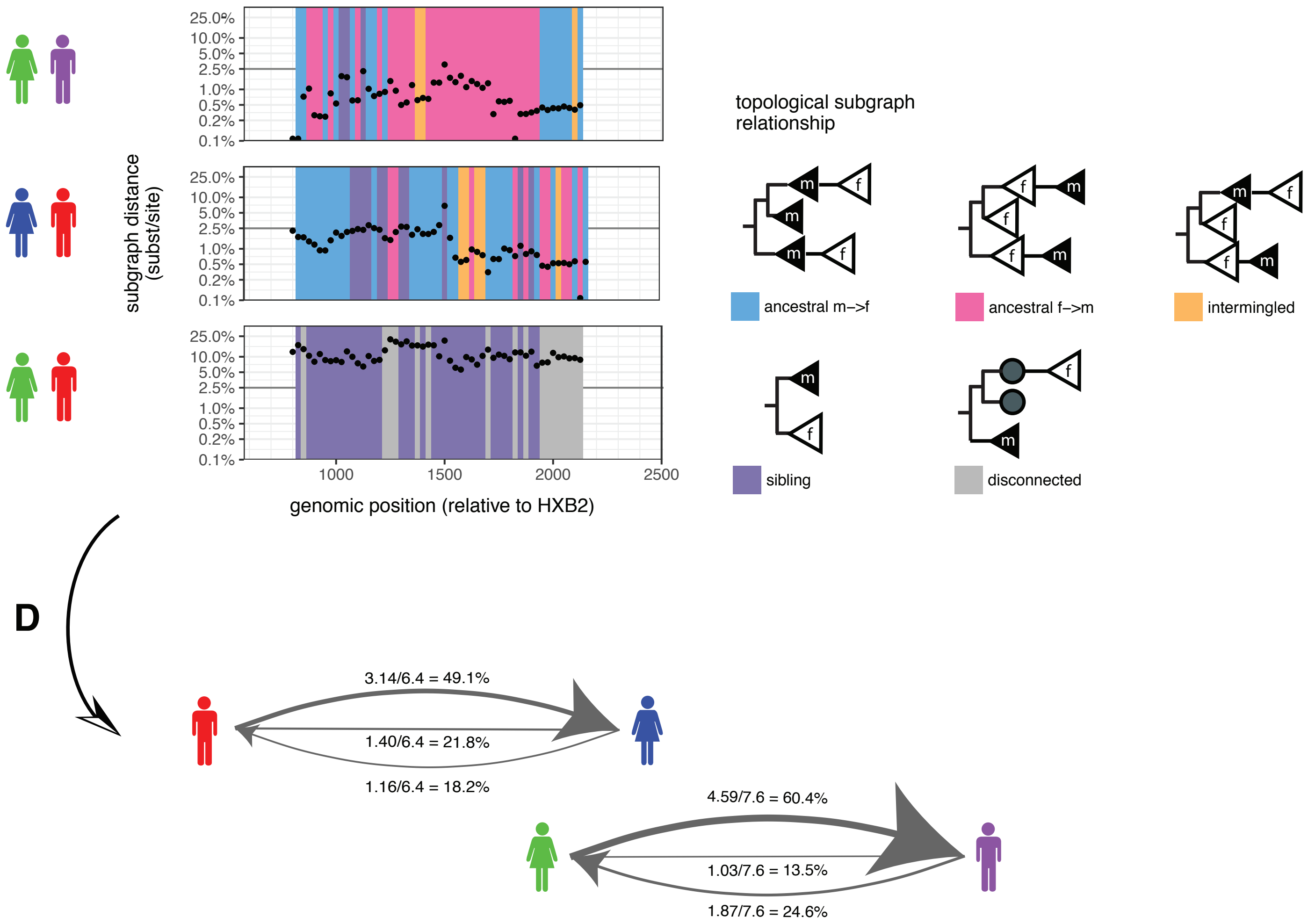


Phyloscans across the genome

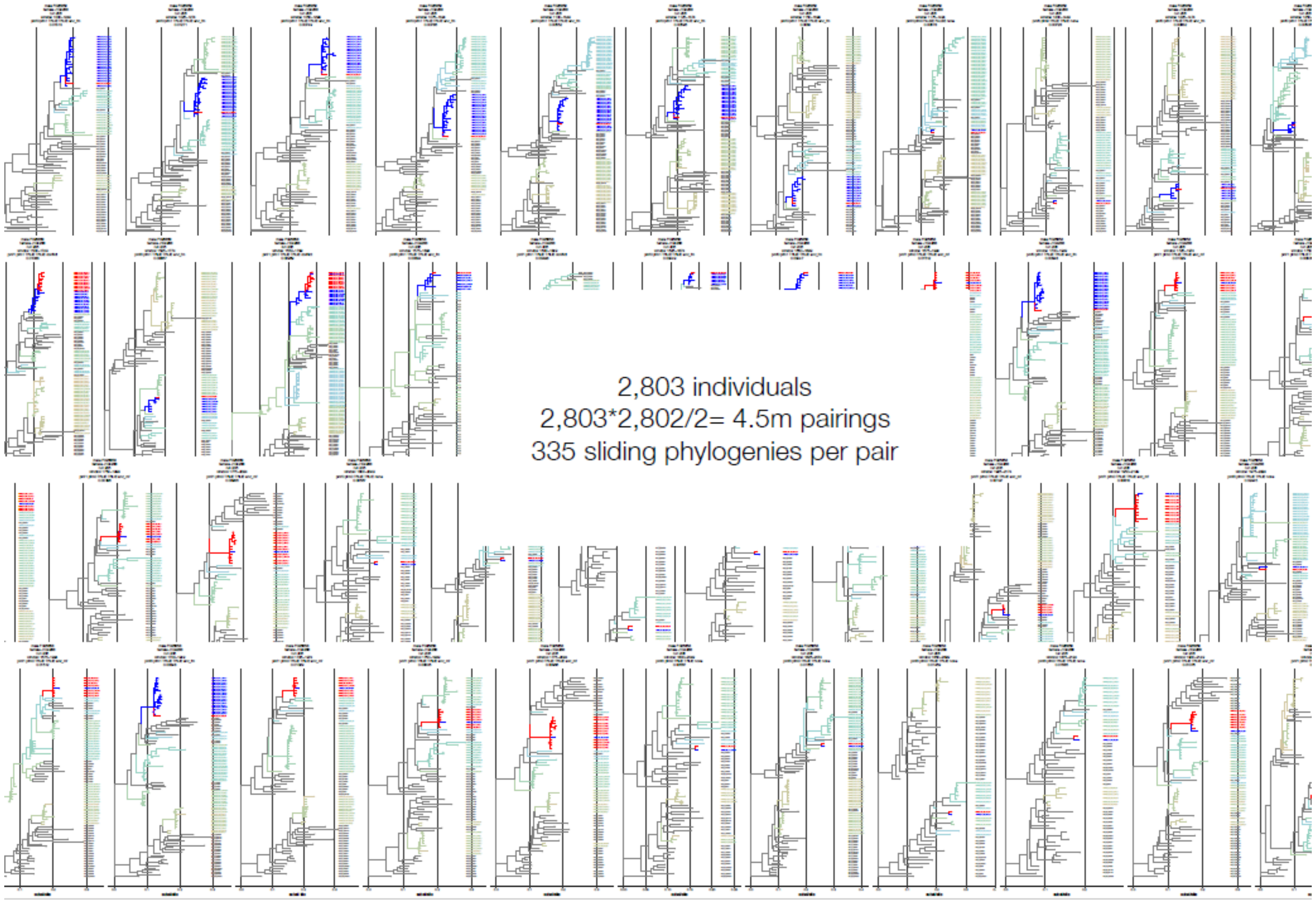




Phyloscans across the genome

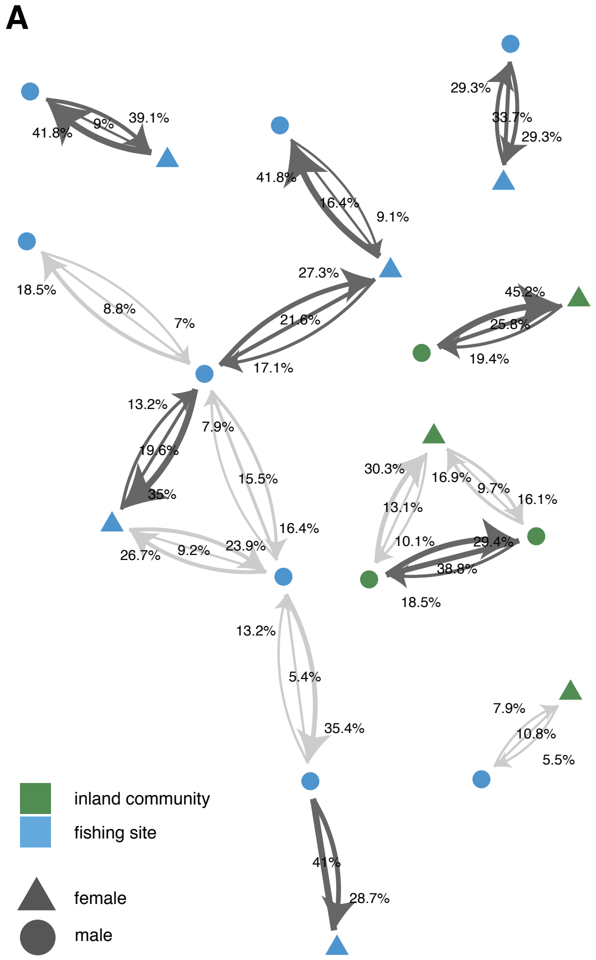


Highly parallelized phylogenetic inference based on NGS data



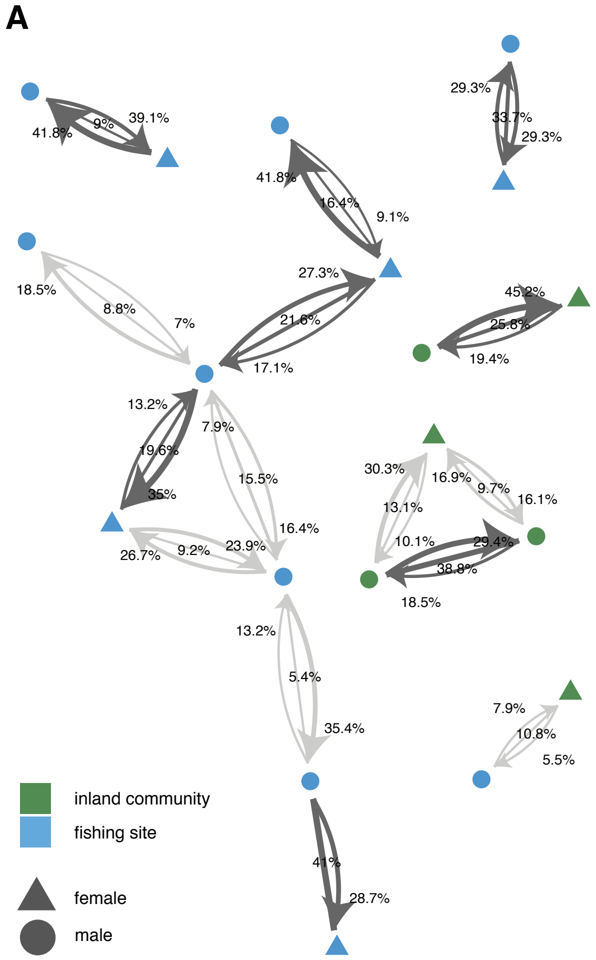
2,803 individuals
2,803*2,802/2= 4.5m pairings
335 sliding phylogenies per pair

Phylogenetically reconstructed transmission networks



- 446 reconstructed transmission networks, containing 888 phylogenetic linkages

Phylogenetically reconstructed transmission networks

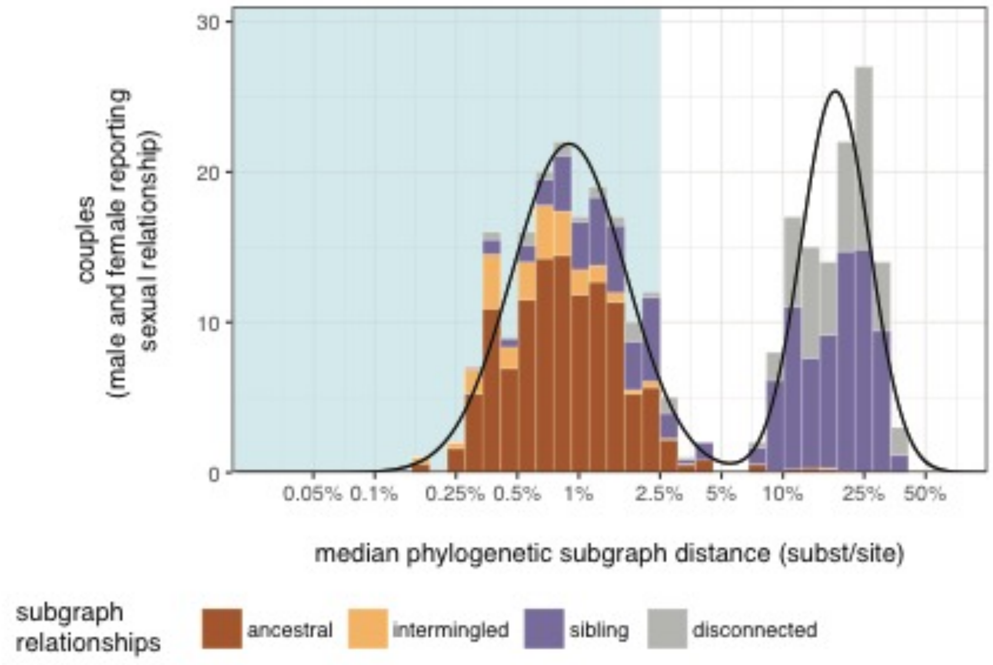


- 446 reconstructed transmission networks, containing 888 phylogenetic linkages
    - 351 linkages had low statistical support
    - 80 further FF
    - 81 further MM

- 376 highly supported male-female linkages

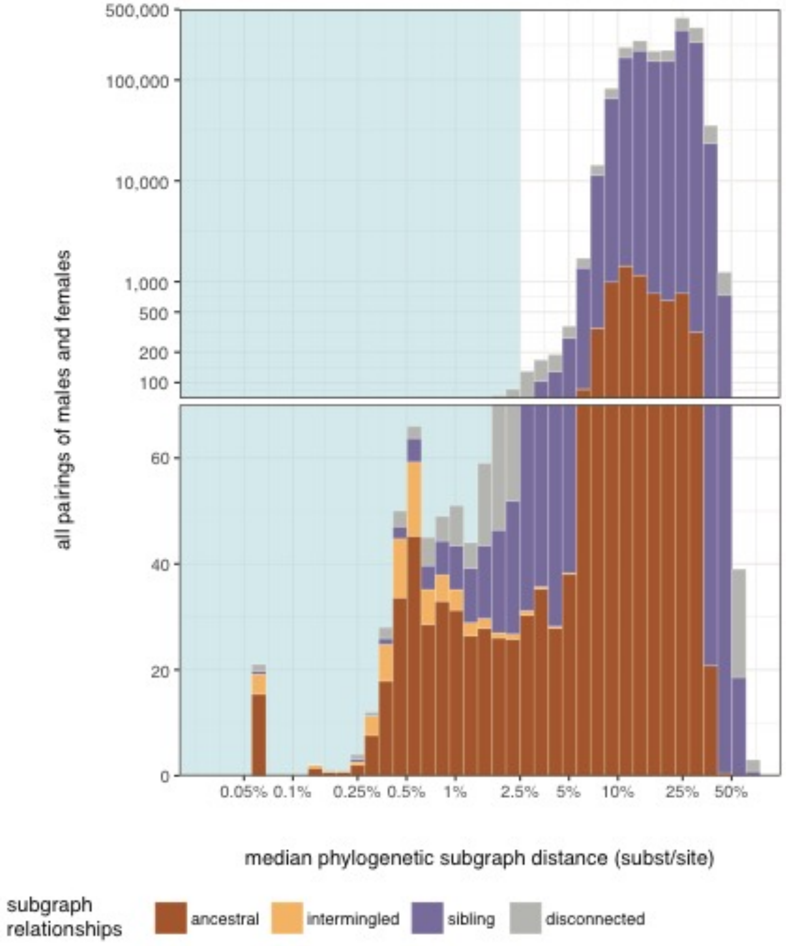
- 293 (78%) linkages had one direction of transmission highly supported

Direct transmission cannot be proven in population-based sample



- Phyloscanner inference among couples
- Couples were either phylogenetically close or distant
- 76% of close couples had strong evidence that transmission occurred in one direction

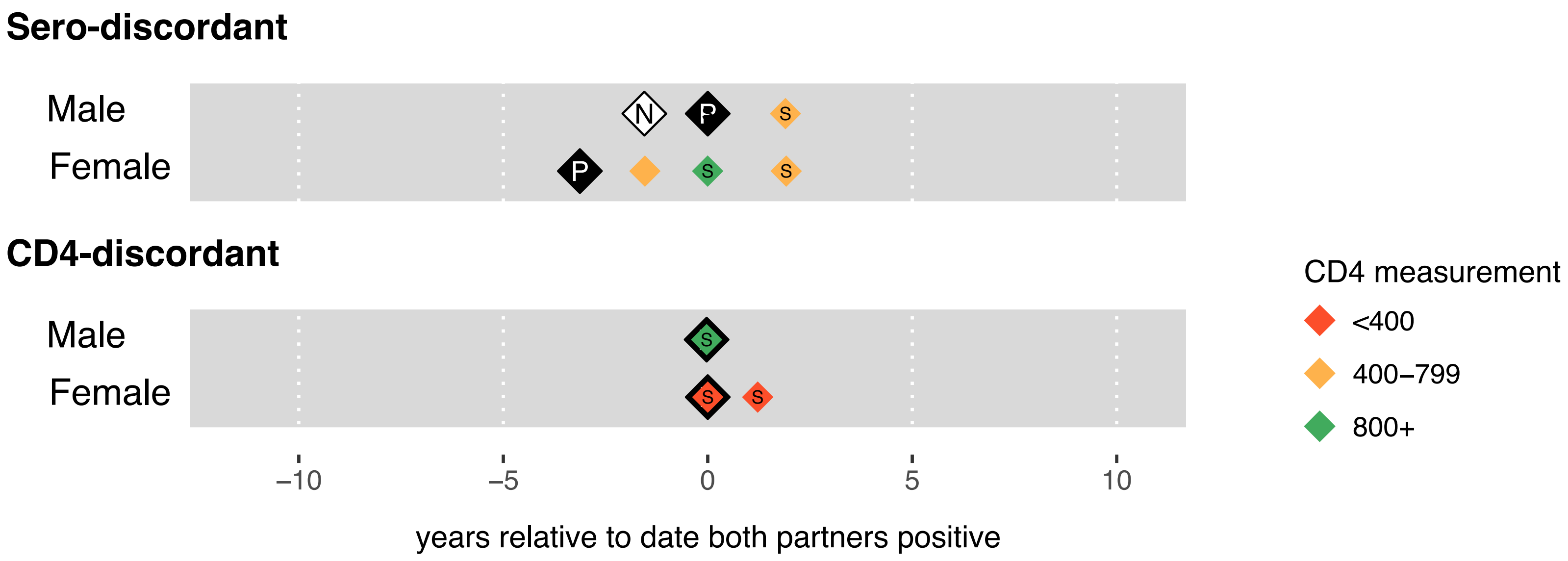
Direct transmission cannot be proven in population-based sample



- Phyloscanner inference on the population-based sample
- Phylogenetic linkage not clear-cut
- Up to 35% of phylogenetically linked pairs in transmission network may not represent direct transmission events
- 78% of phylogenetically close pairs had strong evidence that transmission occurred in one direction

Inferred direction of transmission has low false-discovery rate

- We cross-validated our results against clinical data from which the direction of transmission could be inferred.



Inferred direction of transmission has low false-discovery rate

Pairs in population-based sample with clinical evidence for transmission in one direction	
classified as phylogenetically linked	71
direction consistent with clinical evidence	46
direction ambiguous	16
direction inconsistent with clinical evidence	9
false discovery rate	16.3%

Conclusions Part 1

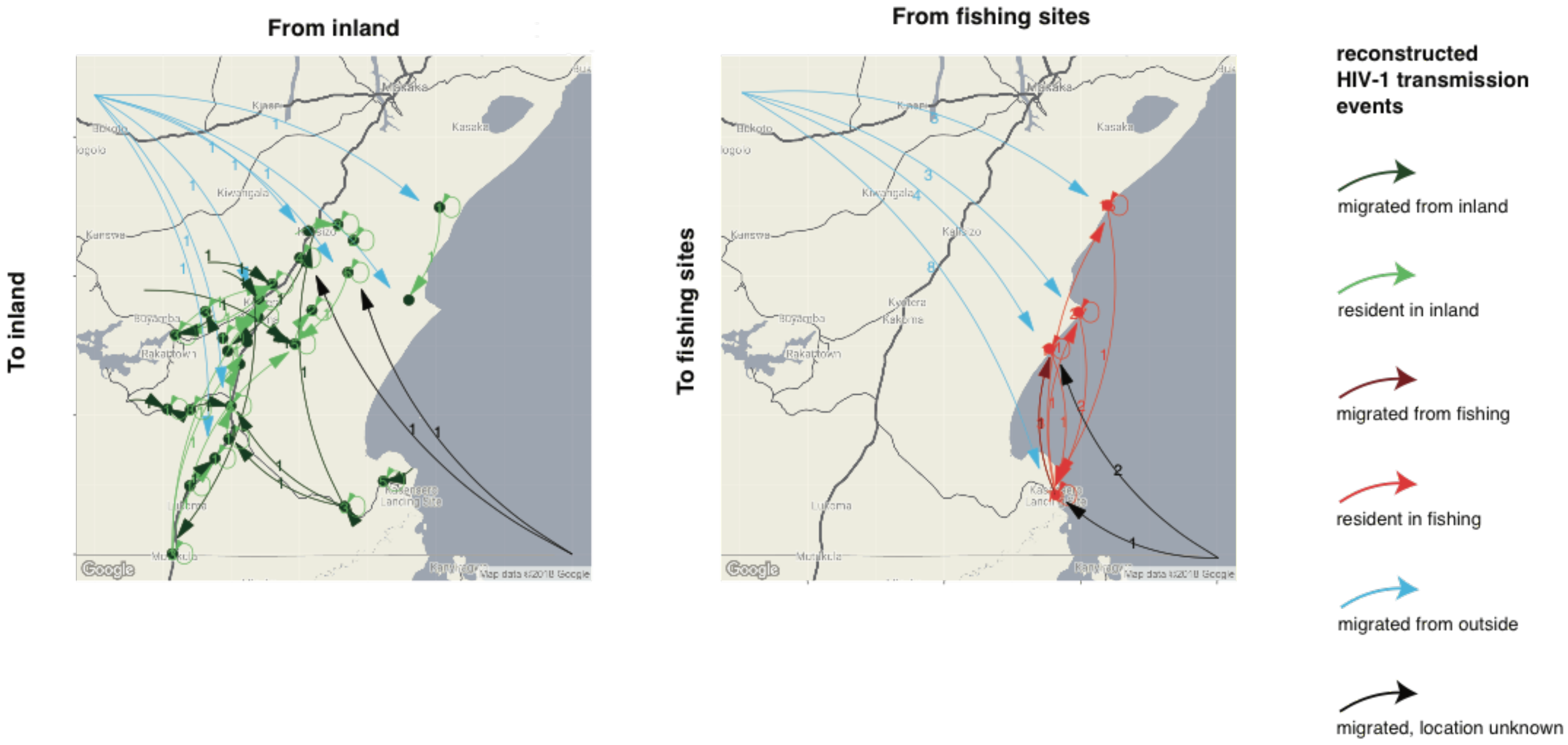
- Deep sequence phylogenetic analyses can be conducted at the scale of population-based surveys with the phyloscanner method.
- Linkage analyses using deep sequence reads have similar limitations compared to using consensus sequences.
- Phyloscanner analysis cannot prove transmission of HIV between two individuals.
- The direction of transmission could be inferred in the large majority of closely related pairs, and with small error.

Results

Reconstructed transmission flows

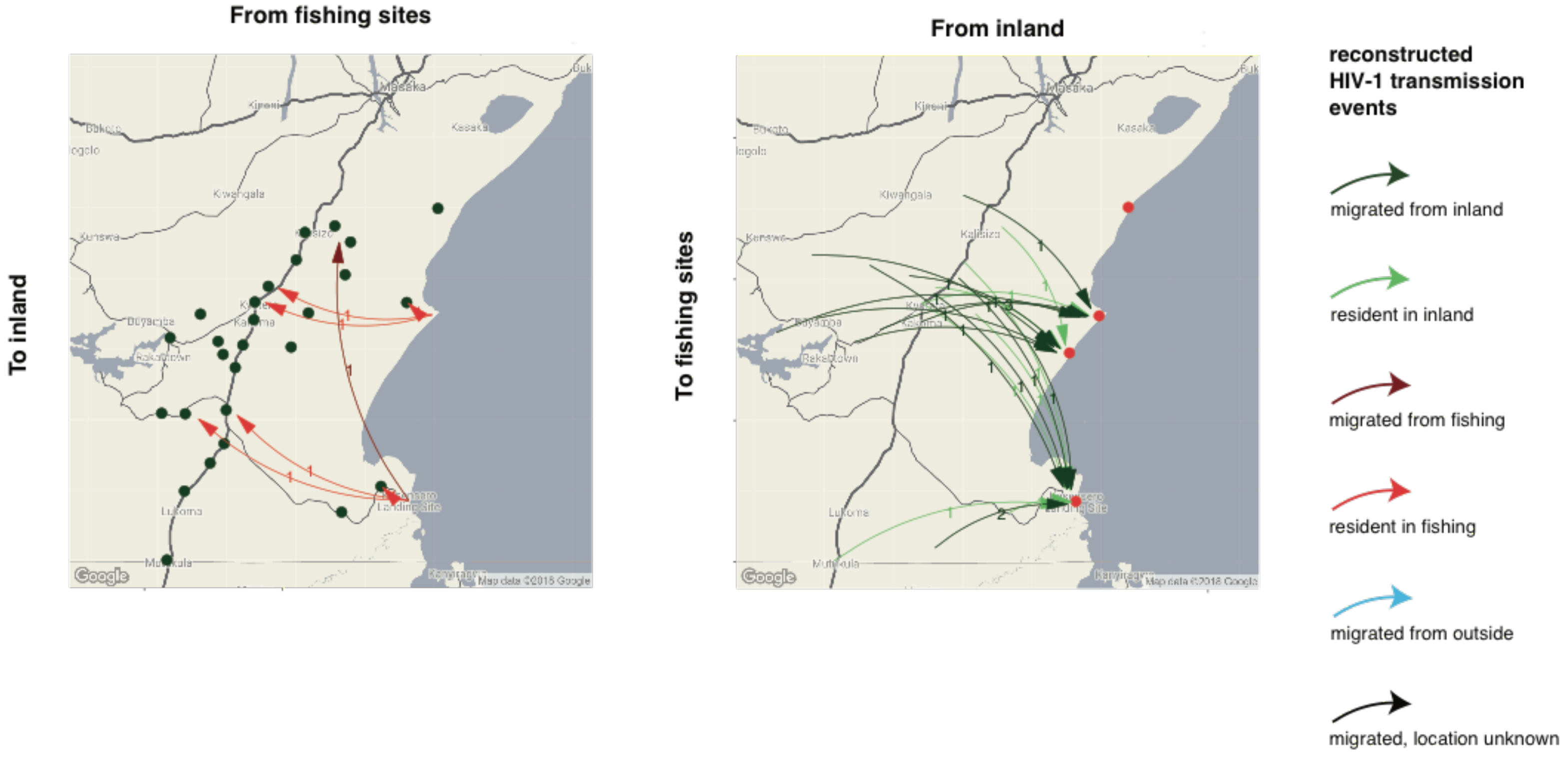
- 293 source-recipient pairs reconstructed

Reconstructed transmission flows



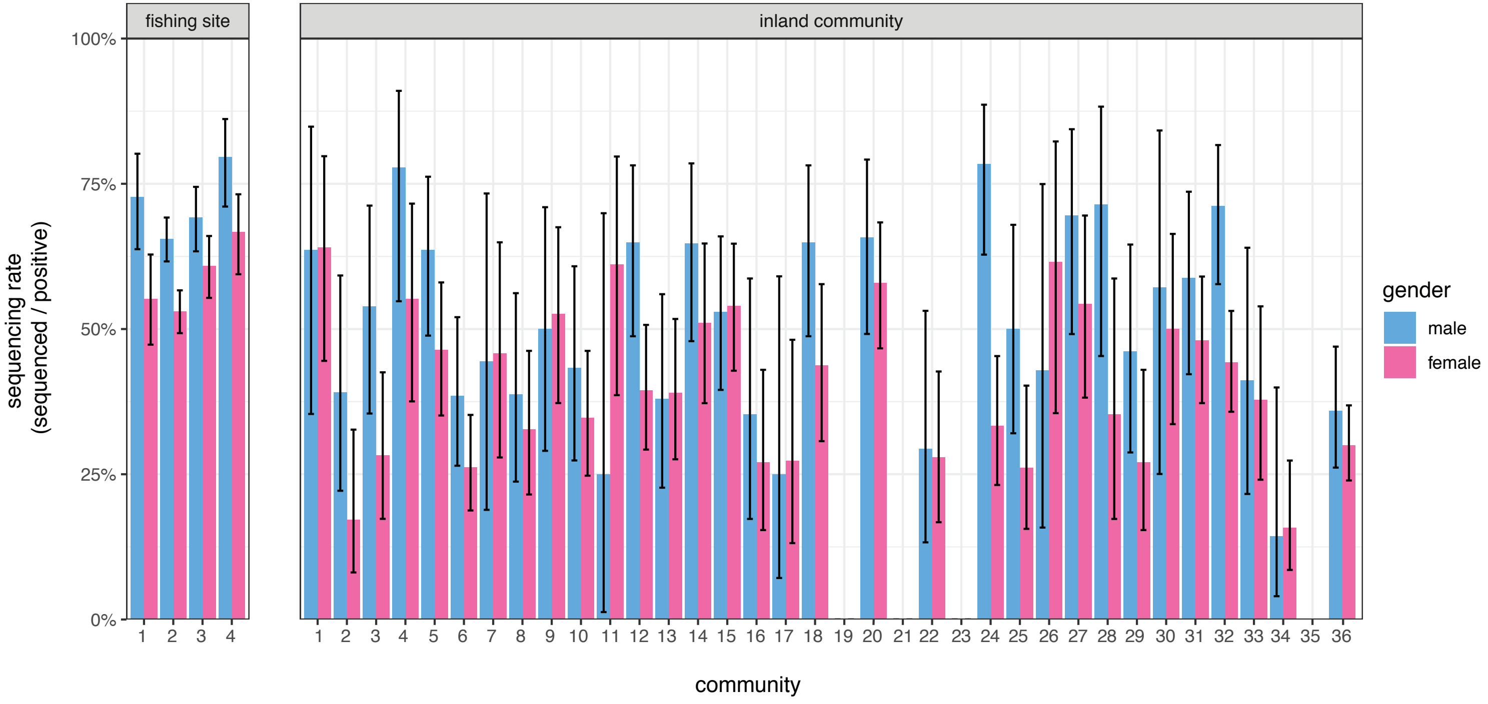
- 265/293 (91%) were not between inland and fishing
- Suggesting largely distinct transmission networks.

Reconstructed transmission flows



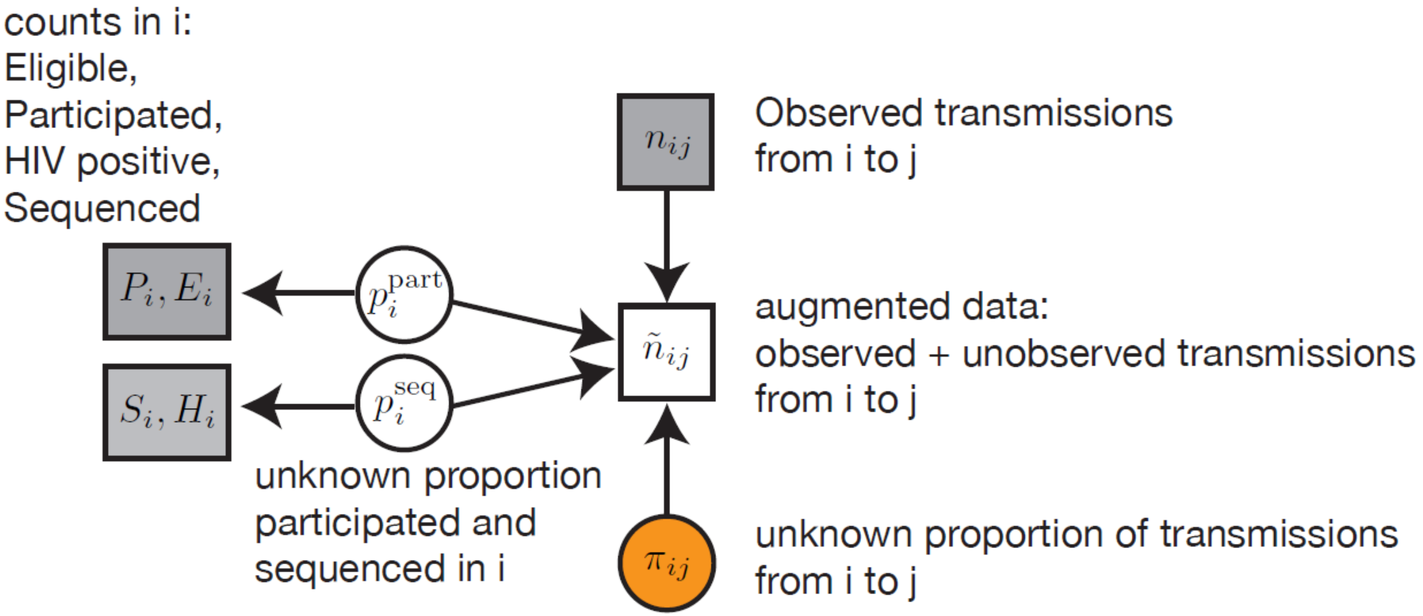
- 7/293 (2.3%) from fishing to inland.
- 21/293 (7.2%) from inland to fishing.

One more complication



- Substantial differences in participation and sequencing rates

Adjusting for participation and sequencing biases



counts in i:
Eligible,
Participated,
HIV positive,
Sequenced

unknown proportion participated and sequenced in i

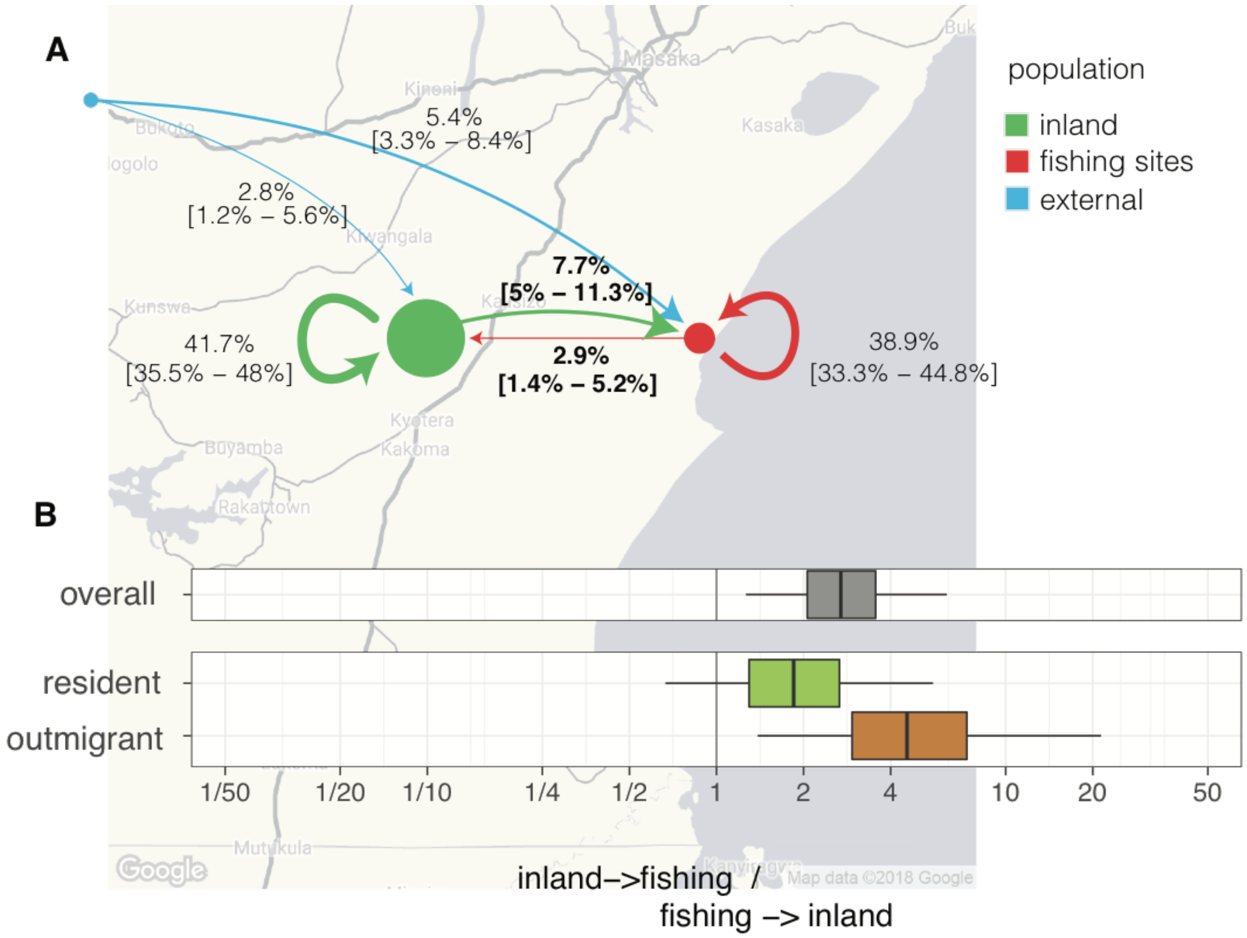
Observed transmissions from i to j

augmented data:
observed + unobserved transmissions from i to j

unknown proportion of transmissions from i to j

- Adjusted analysis for known biases with Bayesian data augmentation (Givens et al. 1997, Stat Sci)

Fishing sites are net sinks despite being hotspots



Implications for geographic targeting

- Cautious case study:
- Hotspots are not necessarily the main sources of new infections in neighboring low risk areas.
- Populations in hotspots will directly benefit from geographic targeting of CHP.
- Indirect benefits of geographic targeting to neighboring low risk areas may be limited.

Going forward

- Mapping may not be enough.
- Comparative assessment of hotspots on their contribution to the broader spread of HIV should be a priority.
- Similar analyses could help allocation of limited resources, by prioritizing those hotspots for geographic targeting that have a large impact on the epidemic.

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