Quantifying the Contribution of Different Aged Men and Women to Onwards Transmission of HIV-1 in Generalised Epidemics In Sub-Saharan Africa: A Modelling and Phylogenetics Approach from the HPTN 071 (PopART) trial

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BACKGROUND

THE HIV EPIDEMIC IN SUB-SAHARAN AFRICA IS KNOWN TO BE HETEROGENEOUS [2-4], and interaction with the HIV care cascade is known to vary by age and sex [1,5]. Young people may be less likely to be aware of their HIV status and less likely to be on antiretroviral therapy (ART) (figure 1) [1,6]. Heterogeneity in the epidemic highlights the importance of investigating targeted interventions informed by those most at risk of transmitting HIV, not just those at risk of acquiring the virus. Despite targeted programming based upon age and sex throughout SSA, there is limited information on the attributable fraction of transmissions arising from particular age groups of men and women. Mathematical modelling and phylogenetics provide a means for quantifying the contribution of different age groups of men and women to transmission of HIV.

HPTN 071 (POPART) is a 3-arm cluster-randomised trial in 21 communities in Zambia and South Africa that has been testing the impact of a combination prevention package including universal testing-and-treatment [7]. The PopART individual-based model (IBM) is a computer simulation model of the HIV epidemic in the communities of the trial developed to help interpret trial findings and investigate the PopART intervention in other settings. HPTN 071-2 is an ancillary study to HPTN 071 looking at phylogenetics in HPTN 071.

OBJECTIVES

OBJECTIVE 1

Quantify the proportion of new HIV infections from men and women of different age groups **using an individual-based model** calibrated to data from an intervention community in the HPTN 071 trial in Zambia.

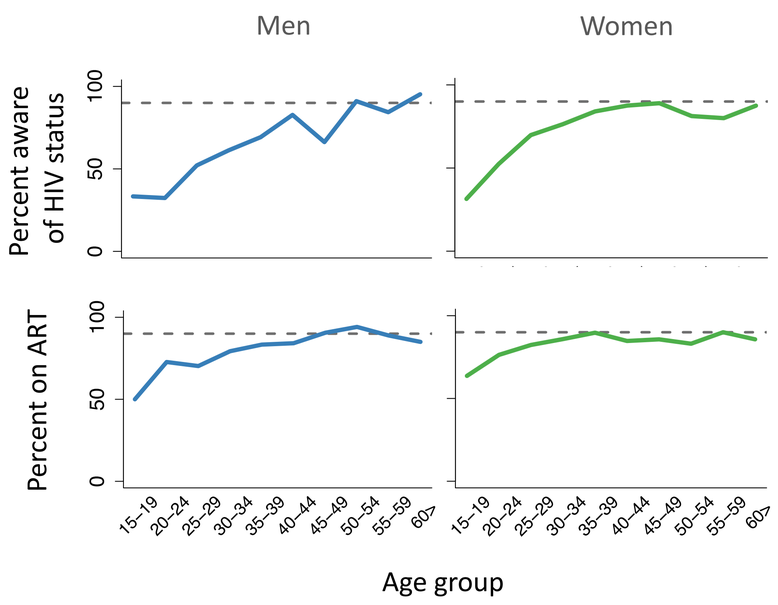
OBJECTIVE 2

Quantify the proportion of new HIV infections from men and women of different age groups **using phylogenetic estimates** obtained from viral short-read next-generation sequencing (NGS) data from three communities in the HPTN 071 trial in Zambia.

OBJECTIVE 3

Quantify the potential **impact of targeted interventions** by suppressing transmissions from each of the groups identified in objectives 1 and 2 in a simulated HIV epidemic of an intervention community in the HPTN 071 trial.

FIGURE 1. Percent aware of HIV status and percent on ART, stratified by age and sex, after two rounds of delivery of a combination HIV prevention package as part of the HPTN 071 (PopART) trial [1,6].



METHODS

MODELLING OF THE HIV EPIDEMIC

A simulated population, approximately the same size as the PopART communities is modelled. Several components model demography, the introduction of HIV, heterosexual partnership formation and dissolution, HIV progression, and both the PopART intervention and a background care cascade. Only heterosexual transmission is modelled, and age mixing is parameterised using data from the trial on up to the last 3 last partners in the last year. The model can generate complete transmission networks. We calculate the proportion of transmissions from each age and sex group that occurred over the period of the trial, mid-2014 to 2018, for 1000 simulated epidemics fitted to trial data in an intervention community in Zambia. We also model the effect of suppressing all infections from a group of men or women in a 5-year age group and summarise the difference in the number of infections with and without this group across the duration of the trial.

PHYLOGENETIC ANALYSIS

Model predictions were tested against probable transmission pairs obtained with *phyloscanner* [8] from viral short-read next-generation sequencing (NGS) data from trial communities in Zambia. Phylogenetics estimates were adjusted for sampling bias. The age discrepancy between the male and female partners in each pair was calculated by taking the difference in their recorded dates of birth.

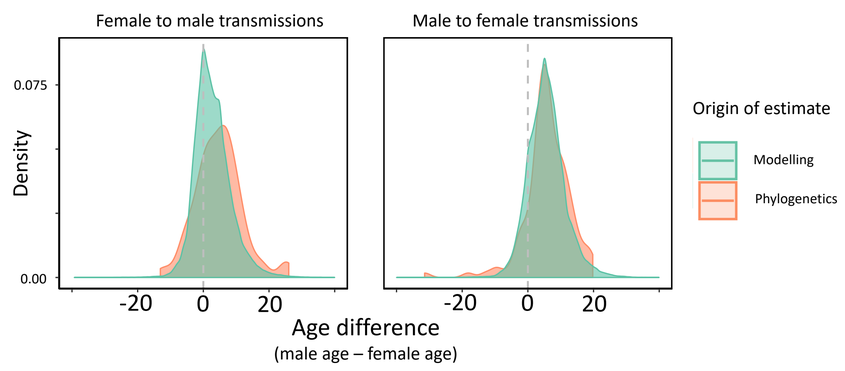
RESULTS

AGE DIFFERENCE BETWEEN PARTNERS

Phylogenetics identified 224 probable transmission pairs and the direction of transmission between them. 60% of these transmissions were from men to women, 62% was predicted by the model.

Phylogenetics predicted men to be 5.4 years older than women in male-to-female transmission (model predicted 5.5 years). Phylogenetics predicted men to be 4.1 years older in female-to-male transmissions (model predicted 2.9 years) (figure 2).

FIGURE 2. Distribution of age differences (male age – female age) as estimated using modelling and phylogenetics.

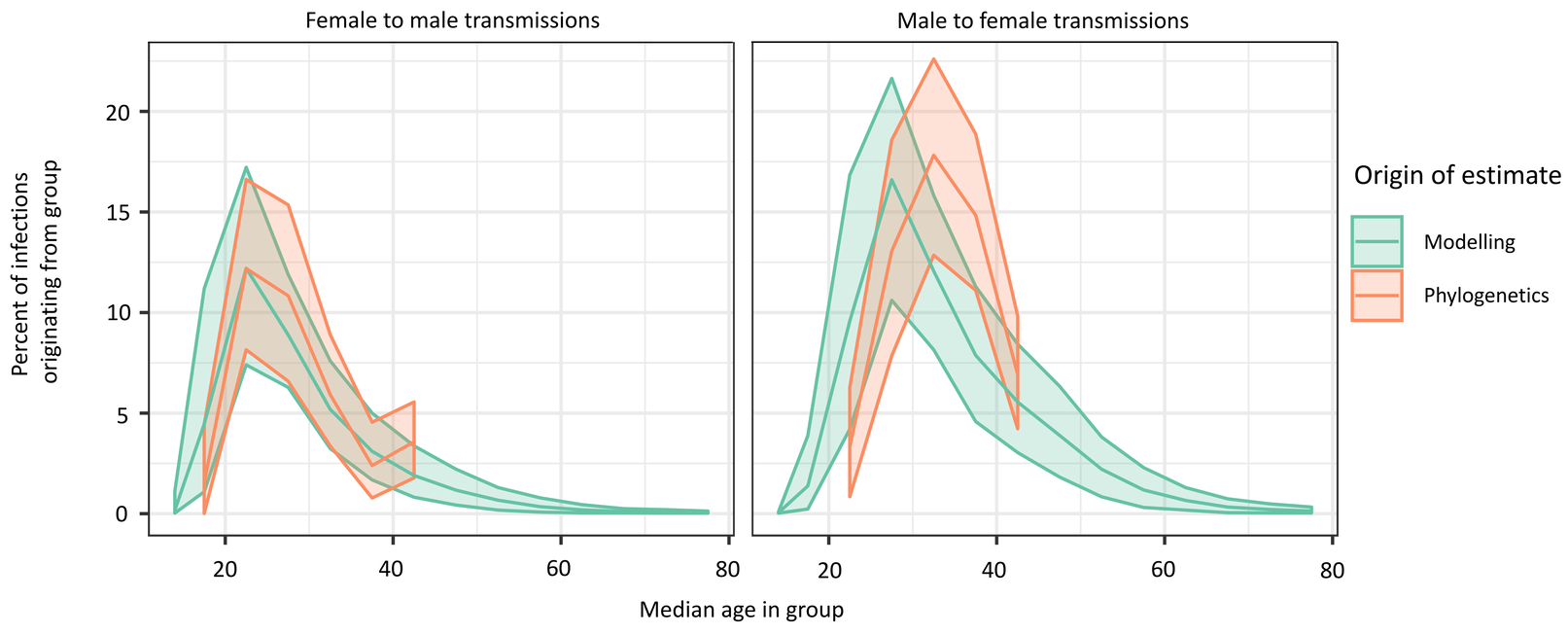


OBJECTIVES 1 & 2: QUANTIFYING ONWARDS TRANSMISSION

According to phylogenetics, onwards transmissions peaked in 30-34 year old (y.o.) men. The model predicted onwards transmissions to peak in 25-29 y.o. men (figure 3)

Both modelling and phylogenetics predicted onwards transmission to peak in 20-24 y.o. women.

FIGURE 3. Percentage of infections originating from men and women of different ages, modelling and phylogenetics estimates, mid-2014 to 2018.

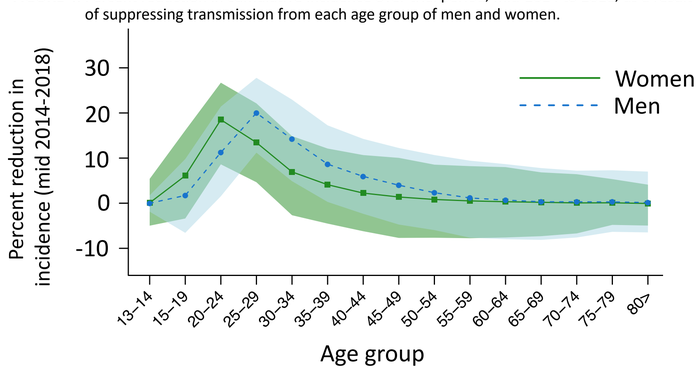


OBJECTIVE 3: TARGETED INTERVENTIONS

The impact of suppressing transmissions from each age group of men and women was carried out using the computer simulation model.

Modelling the prevention of all transmissions from 25-29 y.o. men and 20-24 y.o. women, those age groups identified as having the peak in onwards transmission, reduced cumulative incidence over the trial period (mid-2014 to 2018) by 20% and 19% respectively.

FIGURE 4. Percent reduction in cumulative incidence over trial period, mid-2014 to 2018, as a result of suppressing transmission from each age group of men and women.



LIMITATIONS

MODELLING

- We are not able to fully disentangle the effect of structural assumptions that were made during the design of the model, particularly those regarding age-assortative mixing.
- The simulated intervention (figure 4) assumes all individuals in an age group are able to be reached, and that a preventive intervention in these individuals would be 100% effective, which are logistically infeasible in practice.
- Migration is not explicitly modelled even though transmissions from outside the community are taken into account.

PHYLOGENETICS

- Phylogenetics alone cannot perfectly identify transmission pairs.
- Transmission pairs cannot rule out unsampled intermediaries.
- Sampling bias in phylogenetics may not be (fully) accounted for.

CONCLUSIONS

- Our results validate predictions of a mathematical model using phylogenetic data, with no sharing of parameter estimates across the two methods.
- Our results support observations that there is a significant contribution of young people to HIV transmission in sub-Saharan Africa, especially 25 to 34 y.o. men, and that these groups should be prioritised for targeted interventions.
- These results agree with studies that use survey data of the reported age of an individual's most recent sexual contact [9].
- Age groups of men and women that report lower awareness of status and ART coverage overlap substantially with those groups from which a large proportion of transmission events are predicted.
- Our work highlights that if universal testing-and-treatment (UTT) does not reach young people, and 25 to 34 y.o. men, then the effect of UTT on reducing incidence may be limited.

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