HPTN
HIV Prevention Trials Network

Determinants of the Predicted Effectiveness of Universal Test and Treat in a High Prevalence Generalised HIV Epidemic: Insights from the HPTN 071 (PopART) Individual-Based Model

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PopART HPTN 071

HPTN 071 PopART TRIAL

BACKGROUND

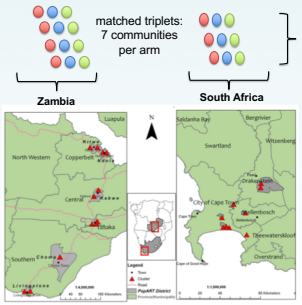
The HPTN 071(PopART) trial is a 3 arm cluster-randomized trial with 21 communities, 12 in Zambia and 9 in South Africa, measuring the impact of a combination prevention intervention including universal testing and treatment (UTT) on population-level HIV incidence.

Arm A: Full PopART intervention including immediate ART irrespective of CD4 count

Arm B: PopART intervention except ART initiation according to current national guidelines

Arm C: Standard of care at current service provision levels including ART initiation according to current national guidelines

Community HIV-care Providers (CHiPs) deliver PopART UTT intervention in Arm A and B communities in 3 rounds in 2014, 2015/16 and 2016/17

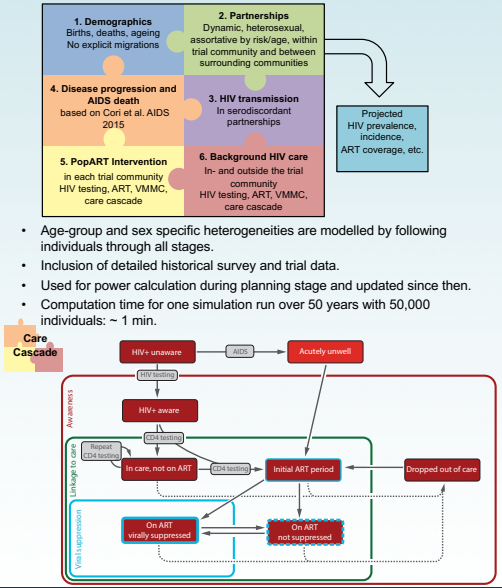


Population Cohort (PC)
N = 42,000
2000 random sample from each community at base-line and follow-up at 12, 24, 36 months

Primary endpoint:
HIV incidence based on PC-data between 12 and 36 months since baseline (PC12-PC36)

INDIVIDUAL-BASED MODEL (IBM)

FIGURE 1. IBM components and HIV-care cascade processes



- Age-group and sex specific heterogeneities are modelled by following individuals through all stages.
- Inclusion of detailed historical survey and trial data.
- Used for power calculation during planning stage and updated since then.
- Computation time for one simulation run over 50 years with 50,000 individuals: ~ 1 min.

CALIBRATION TO HISTORICAL SURVEY AND TRIAL DATA

The IBM output is calibrated to historical surveys and community-level trial data using a binomial likelihood criterion for prevalence and care-cascade with components for each 5 year age-group stratified by sex. In this way we identify the most likely combinations of IBM parameter values.

- Historical prevalence surveys:
  - Zambia DHS surveys on province level in 2002, 07, 13
  - South Africa HSRC national surveys in 2002, 05, 08, 12
- PopART trial data collected by CHiPs round 1 to 3:
  - HIV prevalence
  - proportion aware of HIV status
  - proportion on ART

For each trial community the IBM simulations are calibrated separately with 38 parameters being drawn from a prior distribution and with 353 fixed parameters informed by data or literature.
A combination of parameter uncertainty and model stochasticity is assessed by running 10 repetitions for each of the 10 best fitting parameter combinations, so 100 IBM simulations in total.

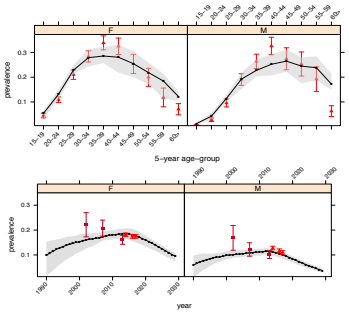


FIGURE 2. Calibrated IBM prevalence projection for an arm A community in Zambia by 5 year age-groups stratified by sex (F: female, M: male) after completion of the first CHiPs round in 2014 (top) and over time between 1990 and 2030 (bottom). The line shows the mean and the grey area the range (min. and max.) based on 10 repetitions for each of the 10 best fitting IBM parameter combinations. The observed prevalence is shown as red triangle (PopART CHiPs) or square (DHS survey) together with a 95% confidence interval.

IBM DETERMINANTS OF PROJECTED PRIMARY ENDPOINT

PROJECTED PRIMARY ENDPOINT

After community-specific calibration of the IBM the simulation is run twice:

- with trial intervention according to arm A or B
- as a counter-factual arm C, where the intervention is switched off

Table 1 shows the country-specific primary endpoint and the UTT impact for a scenario with a national roll-out of the intervention, reporting the relative reduction in incidence from 2020 to 2030 compared to a counter-factual case.

Country-specific differences in input parameters:

- Relative rate of partnerships formed with someone outside the trial community in Zambia (0.45) and South Africa (0.66).
- Proportion of Voluntary medical male circumcision (VMMC) uptake as part of the UTT intervention is in Zambia (22%) and in South Africa (10%).

FIGURE 3. projected mean and range of the primary outcome: relative change in incidence from PC12 to PC36 for arm A (left) and arm B communities (right) compared to their counter-factual arm C community.

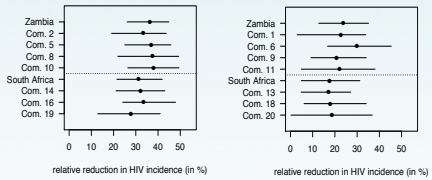


TABLE 1. Projected trial impact for arm A compared to their counter-factual arm C communities aggregated by country as mean (and range) based on 100 IBM simulations.

	Zambia (arm A)	South Africa (arm A)
Primary endpoint (relative reduction in HIV incidence PC12 to PC36)	36.3% (26.1 – 44.9)	31.3% (21.5-41.9)
UTT impact between 2020 and 2030 (national roll-out after 2020)	74% (67.4 – 77.5)	56.1% (50.6 – 60.7)

SENSITIVITY ANALYSES

The following analyses investigate how the primary outcome is affected if selected model parameters change. Other parameters remain unchanged (no re-calibration).

Country-specific differences

- Sensitivity analysis: if the two parameters are set to be equal to the ones in Zambia then the trial impact increases for South Africa by **3%**.

Infectivity during acute phase and partnerships

- Two crucial IBM input parameters are:
  - the infectivity during the acute phase of an HIV infection
  - the proportion of partnerships where one partner lives outside the trial community
- Sensitivity analysis: a reduction in relative acute phase infectivity and a decrease in the proportions of outside partnerships from 20% to 10% causes an increase in the trial impact of **4%**.

ART uptake

- An increase in the weekly number of ART initiations in CHiPs round 2 by 25% will increase the trial impact by **2%**.

Partnership formation and risk-groups

- HIV-transmission between two individuals occurs only if they are in a partnership.
- An individual's risk group determines the number of partnerships and risk groups are informed by baseline PC data. The assortativity parameter defines the probability to choose a partner from the same risk group.
- If the proportion of partnership from the same risk group (assortativity) is increased from 63% to 90% then the trial impact will be decreased by **2%**

PROJECTED TRIAL IMPACT FOR ONE COMMUNITY

FIGURE 4. left projected incidence (100 person years) between 2010 and 2018 for an arm A community (black line) and for the counter-factual arm C community (blue line) stratified by sex (F female and M male). The range for model stochasticity based on 100 IBM simulations is shown as grey and blue area. **right** corresponding projected relative change in incidence between arm A and counter-factual C community (orange).

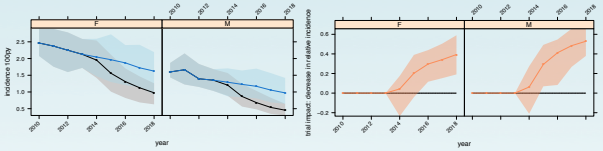


TABLE 2. Determinants of predicted trial endpoint: attributable changes in the projected relative reduction in HIV incidence between arm A and counter-factual arm C communities.

Determinant	Impact on primary endpoint (* based on sensitivity analysis)
Differences arm A vs. B communities	13%
Difference between Zambia and South Africa	5%
of which explained by VMMC, relative rate of partnerships outside trial community	3%
Low acute infectivity and low contamination	+ 4% *
Increase in weekly ART uptake in round 2 by 25%	+ 2% *
Increase in risk-group assortativity from 63% to 90%	- 2% *

CONCLUSION

- The IBM predicts a variable, but potentially substantial impact in PC12-PC36.
- The IBM addresses age-group and sex specific heterogeneities and replicates historical data accurately.
- Important determinants of the UTT impact can be identified by using sensitivity analyses.
- The efficient and fast IBM implementation allows exploration of the parameter space and uncertainty.
- The long-term IBM projections offer insight into developments far beyond the trial horizon.

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