Transmission dynamics in the universal test and treat era in Rakai, Uganda: A mathematical modeling study

OVERVIEW

Significant declines in HIV incidence have been observed with scale-up of antiretroviral therapy (ART) and voluntary medical male circumcision (VMMC) programs as part of the Rakai Community Cohort Study (RCCS), an open, population-based cohort of 15 to 49 year-olds in 30 communities in Rakai, Uganda. Disaggregating the relative contribution of different interventions to declines in incidence is challenging using standard statistical approaches since interventions were scaled simultaneously. Mathematical modelling provides an alternative approach. The proposed mathematical modeling project aims to assess the dynamics of HIV incidence in the era of large-scale combination HIV treatment and prevention in the Rakai Community Cohort Study (RCCS). Two individual-based mathematical models will be used to simulate the local HIV epidemic and estimate the effects of various prevention efforts, including scale-up of antiretroviral therapy (ART) and of voluntary medical male circumcision (VMMC), as observed in the RCCS between 1999 and 2019. Using calibration endpoints of HIV prevalence by age, sex, and year, models will estimate incidence trajectories to date compared to three counterfactuals: 1) no scale-up of VMMC; 2) no scale-up of ART; and 3) no scale-up of either VMMC or ART. Further modeling will aim to estimate the effects of changing sexual risk behavior on changes in incidence. Preliminary results from a joint modeling effort using data from RCCS through 2016 to calibrate our models are shown below. Our goal in the second phase of this project is to update and recalibrate our models using data through the most recent round of survey (through round 18). We will calibrate our models to HIV prevalence and ART coverage and update structural inputs related to sexual network (age-pairing probabilities by sex) and secular changes in sexual risk behavior (including changes in age of sexual debut, condom use, age-gaps in relationships, concurrency, etc.) from the most recent RCCS survey rounds.

Modeling aims:

1.Estimate the absolute and relative contribution of ART and VMMC scale-up (to date) to reductions in incidence considering secular changes in sexual risk behaviour (EMOD and IBM).

1. Estimate the sensitivity of incidence reductions by scenarios to uncertainty in key behavioural, biological, and transmission-specific parameters:
2. Estimate the cost-effectiveness of various VMMC age-targeting scenarios over time under high ART coverage.
3. Estimate the effect of improvements in cascade metrics (decreasing time-to-initiation versus increasing retention-in-care and adherence).

Hypothesis: Compared to a counterfactual without VMMC (but including ART) scenarios with the scale-up of VMMC to young men will produce the largest relative declines in incidence first in young men, then young women, followed by older men and older women. The lag in incidence declines will be governed by sexual network structure and concurrency heterogeneity, both of which will determine how quickly declines in incidence in one age-gender group is felt in others.

Table 1. Time from initial VMMC scale-up in men 15-24 until full potential of incidence reduction is felt

	Men	**Women**
15-24	0-5yrs	5-10yrs
25-49	5-10yrs	10-15yrs

2. Quantify the contribution of major sources of onward transmission by demographic and disease-specific strata (age; sex; time-since-seroconversion; cascade-of-care state, i.e., tested, treated, on ART, ART dropout, reengagement in care; HIV stage) (EMOD and IBM)

a. Estimate the sensitivity of source-contribution from uncertainty in key parameters:
    i. Rates of ART drop-out and re-initiation
    ii. ART effectiveness by adherence profile and drug resistance
    iii. acute and early HIV elevated viral load interaction with behavioural factors (concurrency and partner turnover rates).

3. Project the long-term impacts of universal test and treat (UTT) and Dolutegravir scale-up on viral load dynamics and trajectories of resistance (IBM only)

Additional questions from the PST (Maaya Sundaram and Michelle Morrison):

1. Given the evolution of HIV epidemiology and disease response in our priority countries, is continued scale up of VMMC and maintain (sustaining) coverage necessary to maintain low incidence and / or “epidemic control”?
    a. If so, under what scenarios – e.g. with current tx coverage and viral suppression? Only if we lose ground on tx coverage and viral suppression
2. Under what HIV epi and disease response scenarios does maintaining VMMC coverage remain cost effective and / or cost saving?
3. For scenarios where sustaining VMMC coverage makes sense, for how long and what age groups should we focus on for the greatest immediacy of impact, magnitude of impact, and most cost effectiveness?
4. Under future scenarios of continued tx coverage and viral suppression as well as introduction and scale of effective prevention (e.g. CAB LA, Islatravir, etc), does sustaining VMMC remain relevant and cost effective to maintain low incidence or epidemic control?
5. If we are considering sustaining VMMC as an “insurance policy”, under what do we have to believe for the investment to be cost effective or justifiable? E.g. how much ground must we lose in tx coverage or viral suppression or inability to scale CAB that high coverage of VMMC will help maintain lower incidence?

Data needs:

Data for the first iteration of this project (through 2016) were provided by Kate Grabowski in the file whopico_modeling_rakaidata.rda and a snapshot of the codebook is shown here:

Oxford (IBM) data used for fitting 2017 model:

- Age-/gender-stratified (5-year age groups) of **HIV prevalence** for each Rakai round
- Age-/gender-stratified (5-year age groups) of **ART coverage** for each Rakai round
- Demographic data (natural mortality and fertility) from Uganda (we use data from UN's Popn Division)
- Proportion of TMC in the community (we looked at table S3B of Grabowski et al., 2017).
- Start dates of VMMC and ART.
- Most sexual behaviour parameters were informed from the Zambian data from PopART.

The following additional data elements are requested for the next iteration of modeling:

Cascade metrics:

a. Number tested
b. Number initiated on ART (first-time initiators)
c. Number reinitiated on ART
d. Number with viral suppression (<400 copies/mL or other threshold) among first time initiators versus re-initiators.

Behavioural metrics

a. Age of sexual debut by sex and year
b. Reported sexual partners in the last 12 months and lifetime by age, sex, and year
c. Concurrent partnerships (?)

Partnership formation metrics:

a. Number of partnerships by age (male) - age (female) in 5-year bins and by sex

METHODS

Micro-simulation modelling will be implemented using the epidemiological modelling software EMOD-HIV (https://github.com/InstituteForDiseaseModeling/EMOD), which is described in detail at www.idmod.org/idmdoc and elsewhere [1]. EMOD incorporates data on age-specific fertility, mortality, and sexual relationship formation, and explicitly models the flow of individuals through a configurable HIV cascade of care – including testing, time-variable linkage to care, retention in care, treatment eligibility, and retention on ART [2]. EMOD uses three key structural components to simulate the age, gender, and risk-group specific sexual network and the age- and gender- specific scale-up of ART. The first is a sexual partner pair formation algorithm (PFA) described previously [3]. The PFA provides a detailed representation of the age-specific structuring of heterosexual networks – a phenomenon that contributes to the age and gender-specific patterns of HIV transmission [5,64]. ART is assumed to reduce infectiousness on average by 92% [7], an estimate that incorporates "real-world" barriers to suppression including adherence and undetected drug resistance. The transmission benefit of ART is assumed to grow linearly over the six months after ART initiation, with no impact on transmission on the day of ART initiation, and increasing impact over time until a 92% reduction in transmission is achieved and maintained after six months.

PRELIMINARY RESULTS

Table 1. Attributable risk % (AR%), indicates the percent of incidence reduced with the scale-up of ART only, VMMC only, and the two combined (ART + VMMC), relative to a counterfactual without either (no ART and no VMMC).

			All		Women		Men	
Year start	end	scenario	AR%	CI	AR%	CI	AR%	CI
2000	2016	ART + VMMC	23.1	(10.4 - 31.2)	20.2	(5.6 - 28.8)	27.0	(17.2 - 36.6)
2005	2016	ART + VMMC	28.8	(15.9 - 37.6)	25.4	(12 - 35.5)	33.9	(21.6 - 43.1)
2015	2016	ART + VMMC	49.3	(32.3 - 63.7)	44.5	(25.5 - 61.7)	54.1	(35.7 - 71.0)
2000	2016	VMMC only	9.6	(-3.9 - 20.8)	7.3	(-8.6 - 18.1)	14.3	(2.2 - 26.5)
2005	2016	VMMC only	12.7	(-5 - 22.1)	9.1	(-10.4 - 18.8)	16.8	(2.3 - 27.9)
2015	2016	VMMC only	18.4	(-5.7 - 34.1)	15.3	(-14.1 - 31.8)	23.3	(-15.5 - 47.0)
2000	2016	ART only	13.2	(6.1 - 21.0)	12.8	(4.3 - 21.6)	13.4	(4.3 - 22.0)
2005	2016	ART only	17.2	(7.7 - 26.9)	17.0	(6.7 - 26.7)	17.8	(7.8 - 28.9)
2015	2016	ART only	35.7	(16.2 - 51.5)	35.0	(9.4 - 50.3)	38.1	(7.9 - 56.5)

References:

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7. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; **375**(9731): 2092-8.