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Can combination prevention strategies reduce HIV transmission in generalized epidemic settings in Africa? The HPTN 071 (PopART) study plan in South Africa and Zambia

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Abstract

The HIV Prevention Trials Network (HPTN) is conducting the HPTN 071(PopART) study in 21 communities in Zambia and South Africa with support from a consortium of funders. HPTN 071(PopART) is a community-randomized trial of a combination prevention strategy to reduce HIV incidence in the context of the generalized epidemic of southern Africa. The full PopART intervention strategy is anchored in home-based HIV testing and facilitated linkage of HIV-infected persons to care through community health workers, and universal antiretroviral therapy for seropositive persons regardless of CD4+ cell count or HIV viral load. In order to further reduce risk of HIV acquisition among uninfected individuals, the study aims to expand voluntary medical male circumcision, diagnosis and treatment of sexually transmitted infections, behavioral counseling, and condom distribution. The full PopART intervention strategy also incorporates promotion of other interventions designed to reduce HIV and tuberculosis transmission, including optimization of the prevention of mother to child HIV transmission and enhanced individual and

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public health tuberculosis services. Success for the PopART strategy depends upon the ability to increase coverage for the study interventions whose uptake is a necessary antecedent to a prevention effect. Processes will be measured to assess the degree of penetration of the interventions into the communities. A randomly sampled population cohort from each community will be used to measure the impact of the PopART strategy on HIV incidence over three years. We describe the strategy being tested and progress to date in the HPTN 071(PopART) study.

Keywords

HIV; prevention; combination prevention; cluster randomized trial; treatment for prevention; antiretroviral therapy; HIV testing; circumcision; South Africa; Zambia

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Combining prevention interventions is a familiar approach for public health interventions in low and middle income countries (LMIC). Control of tuberculosis (TB), for example, is recommended through the combination of case finding, contact tracing, isoniazid preventive therapy, optimized therapy, often directly observed, and environmental risk reduction to improve fresh air exchange in airplanes, housing, prisons or health care settings.[1-6] The public health challenge is how to implement what we know works to reduce TB transmission. Another example is malaria control that relies on the use of insecticide-treated bednets, environmental control of mosquito breeding sites, indoor residual spraying, seasonal malaria chemoprophylaxis, improved diagnosis and therapy (e.g., artemisinin combination therapy) in the context of expanded primary care access, community education and engagement, and use of mosquito repellents.[7,8] A malaria vaccine may join this list of intervention tools within a decade.[9] Similar to tuberculosis and malaria, HIV now has a sound public health evidence base from both clinical trials[10] and from observational studies to suggest appropriate elements of a strong combination prevention package suitable to target the generalized epidemic of sub-Saharan Africa (Table 1).

There is mixed evidence supporting the benefits of other biomedical interventions (i.e., those not listed in Table 1). A tenofovir-containing vaginal microbicide worked to reduce short-term risk in the CAPRISA 004 trial, as did tenofovir-emtricitabine oral pre-exposure prophylaxis (PrEP) for men who have sex with men (MSM in the iPrEx trial) and discordant couples in Africa (Partners PrEP and TDF-2 trials), while other clinical trials have been disappointing.[49-54] Adherence levels have not yet been high enough to take full advantage of the biological potential of the topical or oral PrEP concept. Similarly, tools like the control of sexually transmitted infections (STI)[15,55-58] and diagnosis/treatment of co-infections[59-66] have demonstrated inconsistent evidence for their utility in HIV control, though they are valuable contributions to the health of individuals and the well-being of the community and may be justified as components of combination prevention in certain epidemic settings. Hence both STI and TB programmatic improvements are being included in the PopART intervention, but oral/topical PrEP are not.

As evidence accumulates in the future, other prevention approaches may be considered in combination prevention. HIV vaccines are an obvious choice if products prove efficacious, safe, and are licensed and produced for use.[67,68] Future trials may prove both topical and oral PrEP to be more consistently efficacious if adherence can be improved. For example two dapivirine vaginal ring microbicide efficacy trials are underway, one called The Ring Study, sponsored by the International Partnership for Microbicides[69] and a sister trial sponsored by the Microbicides Trials Network, called ASPIRE (MTN-020).[70,71] The dapivirine microbicide ring delivers drug with only a monthly ring change needed, to potentially mitigate the adherence barrier of event-driven or daily use of oral or topical products.[72-74]

Rationale for the HPTN trial

In the context of growing evidence of the efficacy of multiple modalities for HIV prevention, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) leadership determined the need to conduct research to determine the effectiveness of a combination of prevention interventions on HIV incidence at a population level. With support from PEPFAR, the National Institute of Allergy and Infectious Disease (NIAID), the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), as well as the Bill and Melinda Gates Foundation (BMGF), the HPTN 071 (PopART) study, (Population Effects of Antiretroviral Therapy [**ART**] to Reduce HIV Transmission) was designed to answer this important question. The implementation of the study interventions in South Africa and Zambia is supported through PEPFAR supplements to implementing partners through the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Agency for International Development (USAID).

Covering greater numbers of persons with such interventions as testing and enhanced linkage to expanded care and VMMC would both help reduce morbidity and mortality among HIV-infected persons receiving combination antiretroviral therapy (cART) and also reduce transmission risk to others. While there are encouraging data from ecological and observational studies supporting the potential for HIV treatment to help with HIV prevention,[29-31] none to date have tested the acceptability and operational challenges of delivering a combination universal test and treat and prevention intervention package in SSA.

Testing expansion as an intervention in and of itself was assessed in the NIMH Project Accept (HPTN 043) study which found that although expanded HIV testing was well accepted,[20] it did not confer a significant reduction in population level HIV incidence.[19] One might speculate that the lack of a substantial impact on HIV transmission from expanded testing alone was the consequence of limited post-testing behavioral change and suboptimal linkage to ART-based care for those found to be HIV-infected. In addition, the balance of benefits versus risks associated with very early and longer-term therapy (currently under trial in the START study),[75] and particularly in LMIC settings, is unknown. LMIC with limited health care resources and minimal access to viral load testing might experience a high risk of the emergence of viral resistance from suboptimal adherence in asymptomatic persons, for example.[76-79] At a population level, the need for controlled clinical trials in real world field settings is underscored by the challenges of behavioral disinhibition (also termed risk compensation) for persons on cART who may sometimes perceive themselves healthier and/or less infectious to others.[80-85] Finally, we do not know the logistical feasibility and cost effectiveness of implementing expanded HIV detection and cART coverage within health care systems struggling to manage high overall disease burdens.[86,87]

HPTN 071(PopART) Study Design

Of the 21 communities participating in HPTN 071(PopART) study, 14 previously participated in the Zambia-South Africa TB and AIDS Reduction (ZAMSTAR) study, conducted by some of the investigators involved in this study.[88-93] Thus, HPTN 071(PopART) study builds on strong relationships established between the investigators and the communities including the presence of active community advisory groups. Continuous consultative feedback from both communities and from government health officials has been essential in forged the details of the trial. The Ministries of Health of South Africa and Zambia and the relevant state, provincial and district health authorities have been fully engaged in ethical vetting, implementation, and planning for dissemination of study results.

The 21 communities of HPTN 071(PopART) include nine in the Western Cape Province of South Africa and 12 communities in Zambia, and arranged in seven matched triplets, with four triplets in Zambia and three in South Africa. Within each country, communities were matched based on the best available estimates of HIV prevalence and on geographical location and implementing partner for HIV services, with the aim of minimizing the between-community variance in baseline HIV incidence within matched triplets. Restricted randomization was used to ensure overall balance in cluster size, ART uptake and mean HIV prevalence across the study arms.[94] In a public randomization ceremony in February 2013, one community from each triplet was randomly assigned to each of the three study arms (Figure 1):

Arm A: to receive the full PopART combination prevention program consisting of:

- Offering voluntary HIV counseling and testing annually to every household (i.e., home-based testing[18] and couples counseling) with expanded HIV testing in health facilities
- Linking those with HIV infection to care at the local health facility
- Offering immediate cART to all HIV-infected persons regardless of CD4+ cell count or viral load
- Initiating cART for those HIV-infected persons already in care
- Promoting voluntary medical male circumcision (VMMC) for men who test HIV seronegative
- Promoting prevention of mother-to-child HIV transmission (PMTCT) services to HIV-infected pregnant women
- Improving the diagnosis and treatment of STI
- Providing risk reduction education and condoms in the community and in the health facilities

Arm B: to receive all of the HIV prevention strategies in the PopART combination prevention program, except that cART will not be universal, but will be offered to those who are eligible according to prevailing national guidelines, typically at a threshold of ≤350 CD4+ cells/μL.[95]

Arm C: to receive the current standard of care. However, special attention will be paid to ensure that there are no drug and laboratory reagent shortages or stock-outs in any of the 21 communities, i.e., in all three study arms.

The full population in all 21 communities is estimated to be about 1.2 million persons. To measure the impact of the strategy, a Population Cohort will be selected from the general population consisting of a random sample of 2,500 adults (one per household) aged 18-44 years from each community. Thus, the Population Cohort will have 52,500 persons recruited from the 21 communities (all three study arms). A baseline survey of the cohort will be carried out at the time the intervention is initiated to assess the comparability of the three study arms. Follow-up surveys of the cohort will be carried out at 12, 24, and 36 months to measure HIV incidence, success in coverage of the interventions in the communities, and other outcomes.

The primary study outcome will be HIV incidence over three years in members of the *population cohort* who are HIV-negative at baseline, and will be compared in the intervention and control clusters to measure the population-level effectiveness of the PopART intervention. HPTN 071 (PopART) is very well powered to detect an effect of 35% or larger in Arm A or Arm B compared with Arm C, and is moderately well powered to

detect an effect of 30%. To compare Arms A and B, the study is well powered to detect a difference between effects of 60% and 30%, 55% and 25%, and 50% and 20%. Assumptions are that there is a baseline HIV prevalence of 15% and that there will be losses to follow-up of 25% over three years in the *population cohort*.

The secondary outcomes will be measured in the *population cohort* to assess the effect of the intervention on a number of additional factors, including: HIV incidence during each year of follow up; reported sexual risk behavior; ART adherence and toxicity; HIV-related stigma; HIV disease progression; community viral load; ART drug resistance; HSV-2 incidence; and TB case notification rates.

Process variables to be measured in the *intervention clusters* will include the following: Acceptance of HIV testing and re-testing; uptake of male circumcision among men testing HIV-negative; proportion started on cART within 3 months of HIV diagnosis; and uptake of PMTCT services. In addition, case control studies will be conducted to examine factors related to the following: Uptake of HIV testing during the first round of home-based testing in Arms A and B; uptake of immediate treatment in Arm A; and uptake of HIV testing in the second round of home-based testing in Arms A and B.

Formative research

In order to inform the intervention before it is deployed in the communities, social science research has been undertaken to better understand the communities, their prior and current HIV landscape, as well as attitudes toward different prevention approaches. In addition, further social science research will be carried out throughout the study period to examine the acceptability of the PopART intervention and to document the effects of the interventions on a number of factors, including risk behaviors, social networks, HIV identity and community-level HIV associated stigma. At the end of the testing campaign in each community, random samples of individuals who accept or decline testing will be interviewed to explore the reason for their decision. In addition, interviews will be carried out with randomly selected patients with good or poor adherence to ART.

Economic evaluations and modeling

Economic studies are planned to measure the incremental cost of the intervention packages, to estimate their cost-effectiveness and to measure the burden on local health facilities of implementing the intervention. Hence, we are recording costs of all implementation efforts for such activities as testing, linkage, care, VMMC, expanded laboratory and ART costs, and community-level educational efforts. Mathematical modeling will use these data to assess the magnitude of the expected impact, given the process inputs, as the trial progresses.

Other population-level combination prevention studies

A large population-based combination prevention study is also planned in Botswana with funding from PEPFAR and sponsorship of the CDC.[96-99] The study builds on work from an ongoing study of the Botswana-Harvard AIDS Institute Partnership in Mochudi, a community of 40,000 persons in Botswana.[100-105] PEPFAR and the BMGF have subsequently sponsored a harmonization effort between the HPTN 071(PopART) study and the Botswana Combination Prevention Project that shares similar goals as those of HPTN 071(PopART), but has a different study design. Laboratory, questionnaire, cost/economic assessments, and design/analytic issues have all been addressed to facilitate future meta-analysis opportunities. Another large combination prevention study is planned by the Agence Nationale de Recherche sur le Sida et les Hépatites Virales (ANRS in France) with the Africa Centre for Health and Population Studies in KwaZulu Natal Province, South

Africa.[30,106-108] Initial work of the Africa Centre is promising in suggesting the potential impact of increases in cART coverage in patients with advanced HIV disease on HIV incidence.[30,109] The findings from the latter study in rural South Africa is encouraging as it provides more rigorous ecological data than hitherto available.[31,32,110,111]

Conclusion

The opportunity to combine known efficacious interventions for HIV prevention into combination packages allows the examination of potential synergies that may be achieved in control of HIV transmission.[10,15,16,112-115] Challenges are daunting given the need to have a high degree of coverage and efficiency in testing coverage, linkage to care, and high adherence in the context of expanded cART coverage.[86,87,116,117] The extent to which efforts are successful in deploying needed interventions to the field at the levels needed to interrupt transmission cycles is the critical unknown at present. The engagement of national health authorities and local communities is essential for conduct of the study, dissemination of results, and future scale-up of successful approaches that are discovered. Combining known efficacious prevention approaches is complex to design and test, but their use in a synergistic strategy may open the door to substantial reductions in HIV incidence in some of the world's most afflicted nations.

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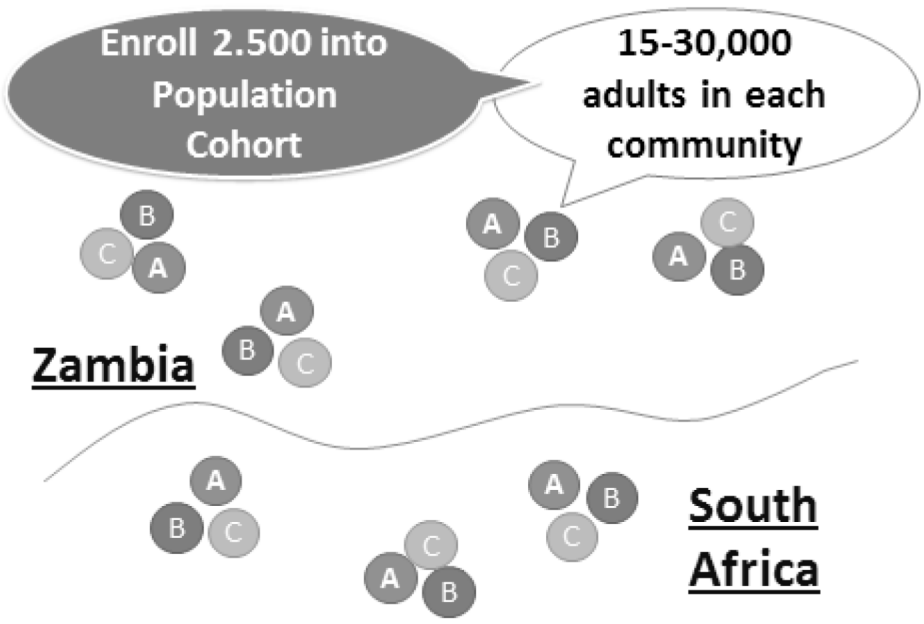

Figure 1.
HPTN 071/PopART study schema for the 21 community, 3-arm community-randomized clinical trial in Zambia and South Africa.

Table 1

Elements of combination HIV prevention that have strong evidence base for decrease risk behavior or HIV incidence from the published literature and whether they are included as a part of the HPTN 071(PopART) trial

Prevention Element to Reduce HIV Transmission	References
• Voluntary medical male circumcision (VMMC)*	11-13
• Treatment for prevention with integrated elements*	14-16
○ Expanded HIV testing as an entry point for services, both therapeutic and preventive	17-20
○ Linkage to care to ensure that all seropositive persons receive ongoing primary care	21
○ Expanded access and earlier use of combination antiretroviral therapy (cART) to benefit the HIV-infected person and reduce his/her infectiousness to others	22-32
○ Opt-out routine HIV testing for pregnant women and use of cART for prevention of mother to child transmission of HIV (PMTCT)	33,34
• Correct and consistent use of male condoms (some evidence, too, to support use of female condoms)*	35-38
• Behavior change focused on reducing the number of sexual partners, avoidance of concurrent sexual partners, and selection of lower risk partners, with couples counseling when possible*	39-41
• Clean needle use in the formal and informal health sectors and for persons self-medicating legal or illegal drugs	42,43
• Improving decisions as to when blood and blood products should be used, and universal screening of transfused products for HIV and other key infectious agents relevant for local conditions (e.g., hepatitis C virus [HCV] and hepatitis B virus [HBV], Human T-lymphotropic virus Type I [HTLV-1], malaria, and others)	44
• Post-exposure prophylaxis for occupational exposure (e.g., health care workers with a needle stick) or among recently infected infants	45-48

All the listed elements are components of our community and clinical training efforts. The * indicate those that represent a major focus of the PopART intervention package. Other elements of the PopART package are the improved control of sexually transmitted diseases and co-infections like tuberculosis (see text).