

A summary of the evidence, questions and the trials addressing TasP?

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Treatment as Prevention and Pre-Exposure Prophylaxis

Overview

- What is the evidence
- Is a trial needed
- What are the current trials
- PopART HPTN071



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ART for prevention: background

- HIV incidence continues to be unacceptably high especially in many countries in Africa
- Unless incidence can be reduced dramatically it will become increasingly difficult over time to sustain effective ART services
- Lack of proven effective HIV prevention strategies
- Risk of HIV transmission closely correlated with HIV viral load and ART can be used to reduce HIV viral load and hence infectivity
- Current guidelines limit ART to those with late-stage HIV infection ($CD4 < 350$) but **most transmissions occur before ART initiation**



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Goals of ART as prevention

To significantly reduce/eliminate onward HIV transmission at a population level- whilst ensuring universal access to lifelong treatment for all living with HIV

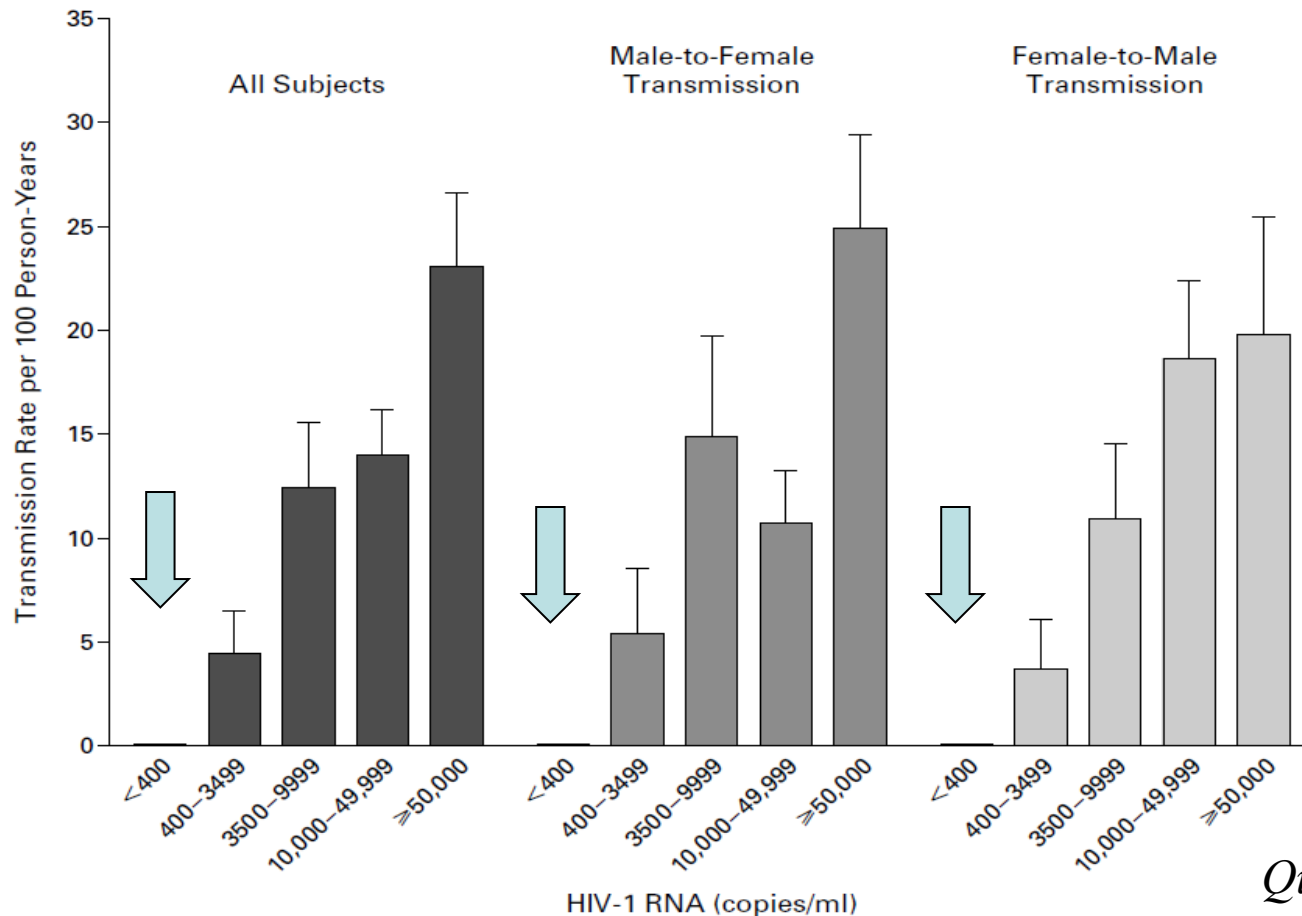
Additional individual benefits of TasP

- Reduction of morbidity and mortality in those receiving ART by earlier onset of treatment
- Reduction of TB and other HIV-related illnesses
- (Potential) elimination of mother to child HIV transmission
- (Eventual) cost savings
- Normalisation of HIV and reduction in HIV-related stigma



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Rakai Study of viral load and HIV transmission



Quinn et al, NEJM
2000



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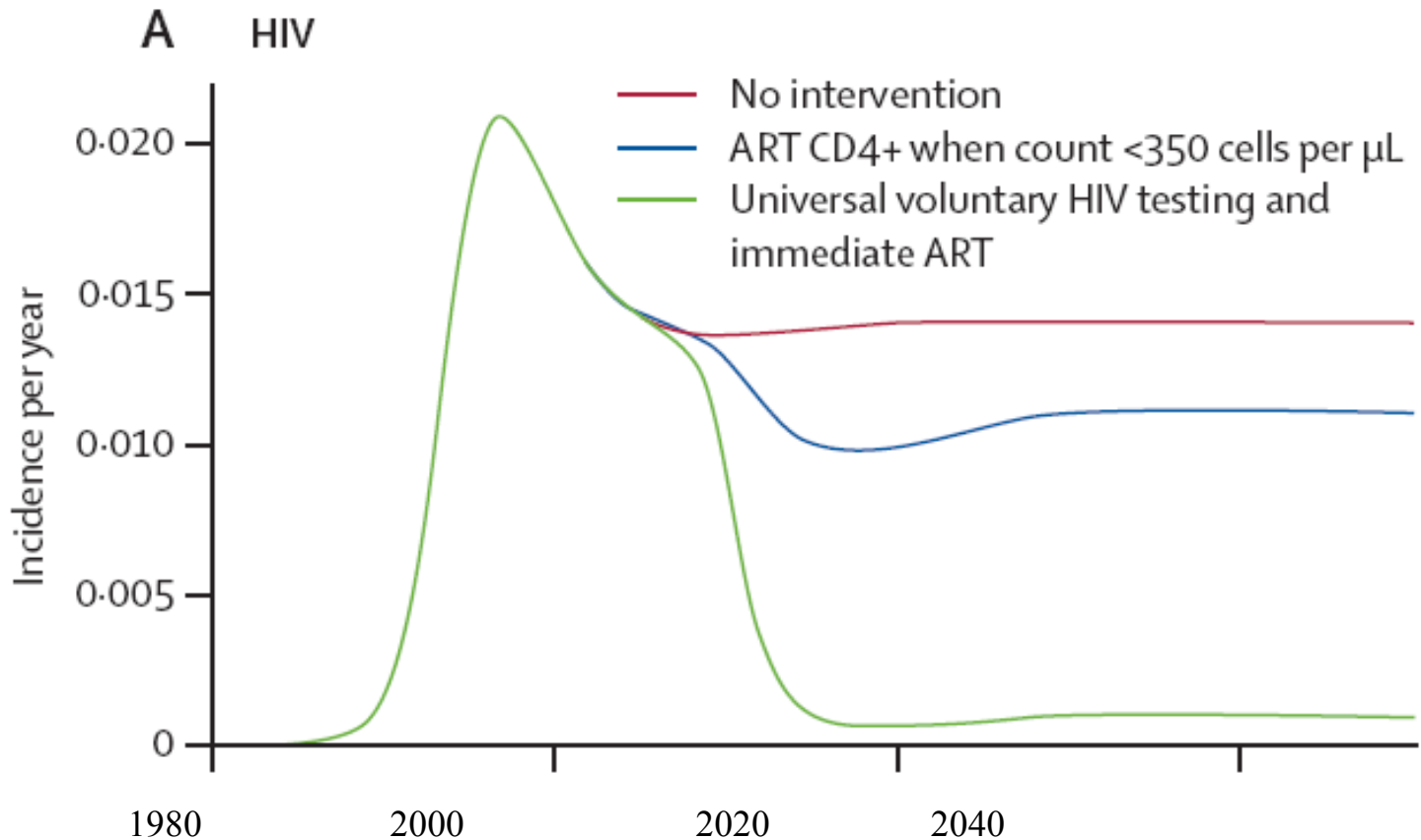
HPTN 052

- 1763 HIV-discordant couples in 9 countries, CD4=250-550
- Stopped for efficacy
- 39 HIV-ve partners were infected of which 29 were linked virologically to the HIV+ study partner
- Of these 29 only 1 was in the immediate treatment group
- HR = 0.04 (95% CI: 0.01–0.27)
- 96% reduction in HIV transmission ($p=0.001$)



Models of HIV Universal test and Treat

Granich et al 2008 Lancet



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Is this enough evidence to roll out? the strategy of ART for all HIV+

- Efficacy vs effectiveness?
- How would we deliver this strategy at a population level?
- Is this feasible?
- Is this acceptable ?
- What are the potential problems/challenges?



‘Ecological studies’

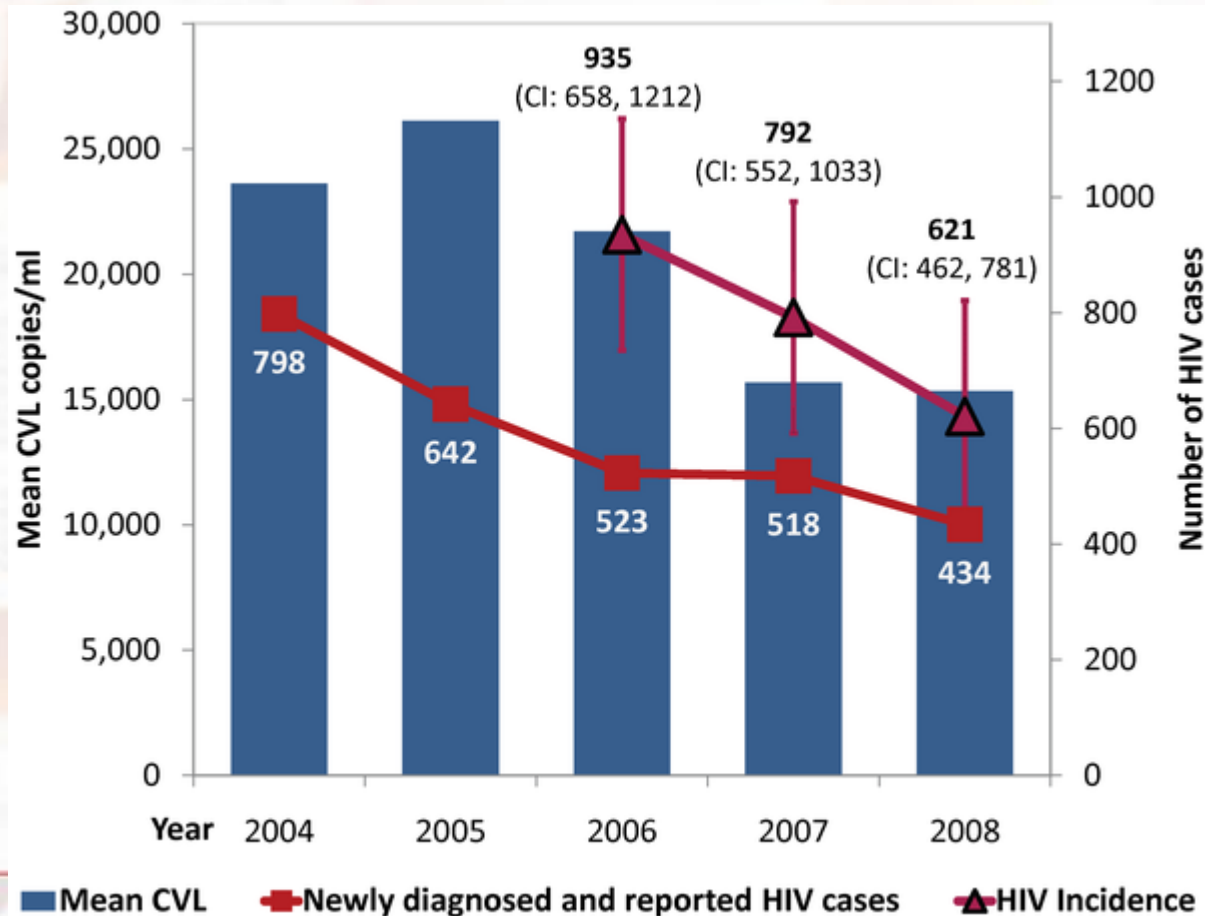
- There is no need to wait for data from more trials there is sufficient evidence that this should be directly implemented
- Immediate UTT approach- San Francisco, and Canada



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Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco.

Das et al PlosOne 2010

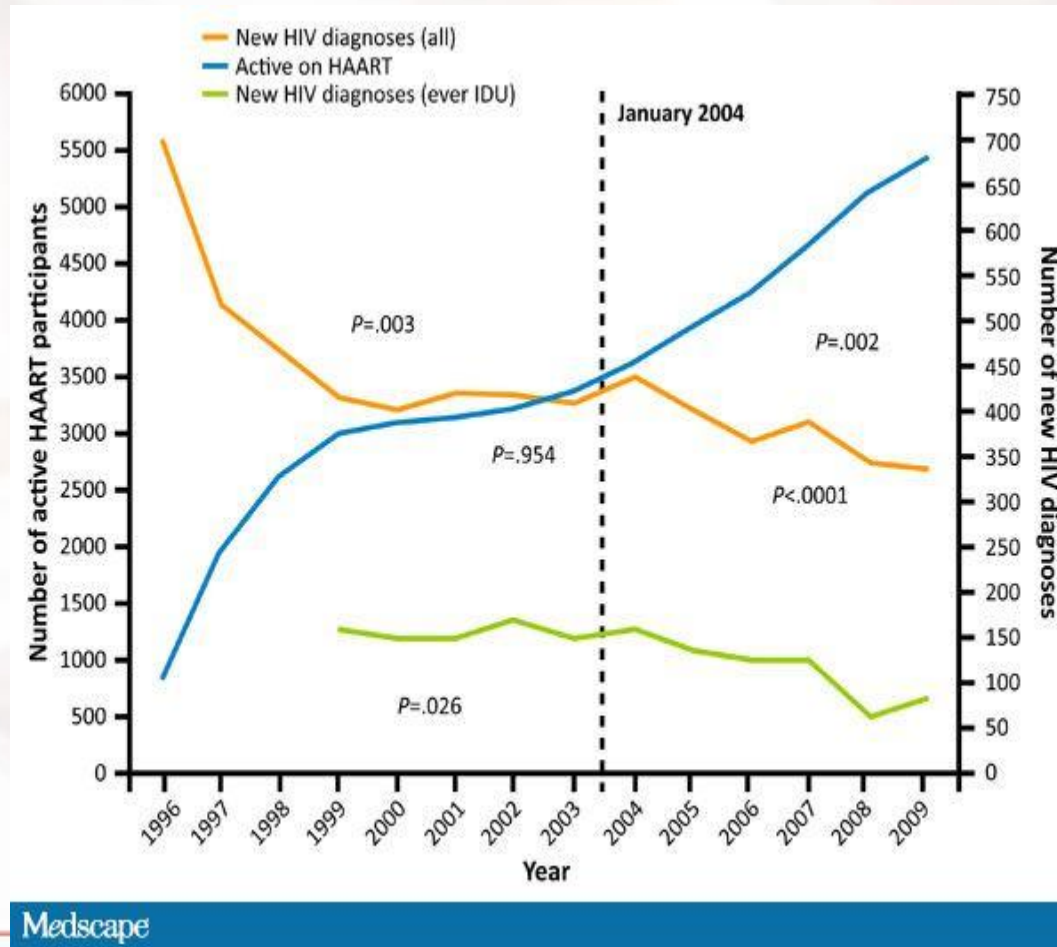


Mean CVL was calculated as the mean of the most recent viral load of all reported HIV-positive individuals in a particular community
HIV VCT 72%
ART uptake 90%



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Vancouver ecological study



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Are there any safety concerns?

- How safe is ART? If we use ART as prevention in healthy individuals will we end up with increased toxicity, drug resistance
- The START study will not report until 2015



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Laboratory Abnormalities from 052

IAS July 2011

- 403 participants had a severe or life-threatening laboratory abnormality
 - 27% immediate arm
 - 18% delayed arm

	Immediate		Delayed	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutrophils	8%	2%	4%	1%
Phosphate	6%	<1%	6%	<1
Total Bilirubin	5%	1%	<1%	<1%
ALT	1%	<1%	1%	<1%
AST	1%	1%	1%	<1%
Hemoglobin	1%	1%	<1%	1%

Adverse Events 052

IAS July 2011 Rome

- Events coded using the MedDRA System
- 246 participants had one or more severe or life-threatening adverse events
 - 14% immediate arm 14% delayed arm
 - **41% reduction in clinical events**

	Immediate	Delayed
Infections	5%	6%
Psychiatric disorders	3%	<1%
Nervous system disorders	2%	1%
Metabolism and nutrition disorders	2%	2%
Gastrointestinal disorders	1%	2%

Only events reported for >1% of participants are shown

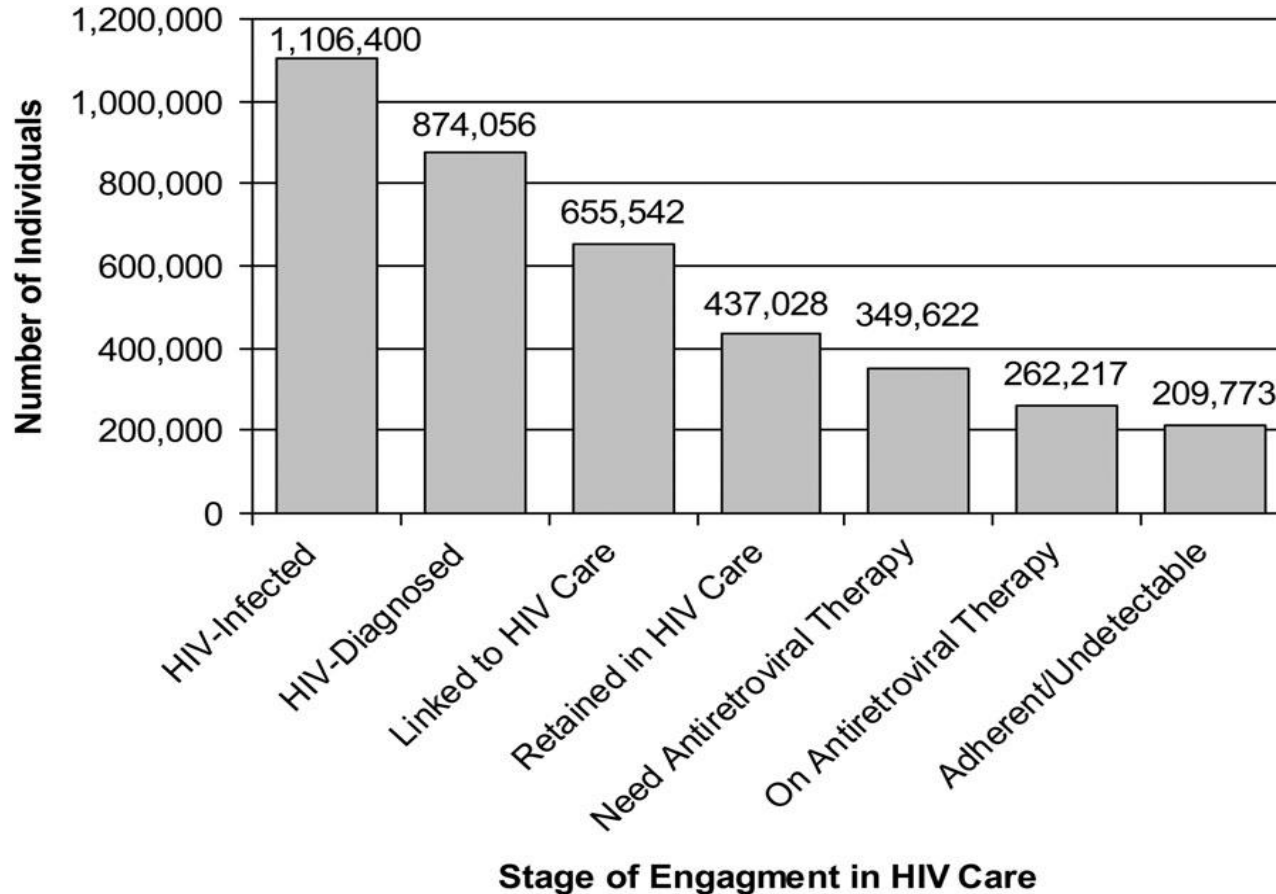
What are the challenges to delivering TasP?

- **Uptake of HIV testing** : (models recommend > 90%)especially in high risk and high prevalence settings so people (both HIV+/- are unaware of their status)
- **Keeping the HIV- Negative**
- **Cost:** (HIV incidence although falling is still too high to sustain ART costs- health, societal and economic)
- **Accessing and sustaining universal ART** for HIV+ in the context of challenges delivering ART to all those in need
- **Human Rights** Coercion, marginalisation of vulnerable groups, stigmatisation of those not choosing to test or start ART



Test, Link and Treat: The Reality

Gardner et al CID, 2011



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Figure 2. The cascade of engagement in HIV care in the United States and the gap in HIV acquisition to full engagement in care. In 2008, only 19% of HIV-infected individuals in the United States have an undetectable HIV load.

So- Do we need a trial?

- Not known whether a UTT intervention **can be delivered** with high enough uptake and acceptability that can confer population level changes in HIV incidence
- Many **uncertainties in model** parameters
- **Population-level impact of (feasible)** intervention package is not known
- Many potential concerns; sexual risk disinhibition, HIV-related stigma, coercion **overload of health services**
- A rigorously designed trial can measure the costs and benefits of this strategy and provide reliable evidence on **cost-effectiveness** for health policy makers



What trials are there?

- Sub Saharan Africa
- 3 OGAC funded studies:
 - **HPTN 071- PopART** (OGAC,NIH,NIAID,Gates) Zambia, S Africa
 - **Iringa** JHU
 - **Botswana** Havard
- **TasP** (ANRS) S Africa
- **HPTN 065 TLC-Plus**: A Study to Evaluate the Feasibility of an Enhanced Test, Link to Care, Plus Treat Approach for HIV Prevention in the United States



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HPTN 071 = PopART

Population effect of universal testing and
immediate ART therapy to Reduce HIV
Transmission



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3-arm community randomised trial

Primary end point HIV incidence

Arm A	Arm B	Arm C
Universal HIV testing Immediate ART for all	Universal HIV testing ART for CD4<350	Standard of Care

- *21 clusters: 12 in Zambia, 9 in South Africa*
- *Cluster = catchment area of a health centre*
- *30k-60000 in each cluster, of which 50% adults (1.2m total)*



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Primary & secondary outcome

Population cohort n=52,500 (2500/community, 10%)

- HIV incidence over 2 years
- Will also look at impact during first year and second year of follow-up
- **Secondary outcome**
- HSV-2 sero-incidence
- Sexual risk behaviour and HIV-related stigma
- Community HIV viral load, CD4 count, drug resistance
- HIV-free infant survival
- TB prevalence
- Uptake of services, cost effectiveness



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The PopART intervention package

CHiPs

- Universal voluntary HIV testing delivered through a house-to-house campaign
- **CHiPs team (Community HIV Providers)** to deliver testing, counselling, linkage to care and treatment support
- Male circumcision offered to men who test HIV-negative
- Immediate ART offered to all who test HIV-positive
- Counselling and condom provision
- Strengthening of PMTCT services
- Syndromic STI treatment at clinic



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Is ART for prevention a ‘game changer’

We need **clear answers**

- The humanitarian dilemma; Clean water, education, malaria, TB, infant mortality, death in childbirth.....
- Only with unlimited resources not only funding but trained personnel, laboratory trained staff and equipment can ART on a population level be **sustainable**
- Sustainability is the critical challenge ART is for life and because it works it must be for the next 60 years



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