



Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial

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Summary

Background Universal antiretroviral therapy (ART), as per the 2015 WHO recommendations, might reduce population HIV incidence. We investigated the effect of universal test and treat on HIV acquisition at population level in a high prevalence rural region of South Africa.

Methods We did a phase 4, open-label, cluster randomised trial of 22 communities in rural KwaZulu-Natal, South Africa. We included individuals residing in the communities who were aged 16 years or older. The clusters were composed of aggregated local areas (neighbourhoods) that had been identified in a previous study in the Hlabisa subdistrict. The study statisticians randomly assigned clusters (1:1) with MapInfo Pro (version 11.0) to either the control or intervention communities, stratified on the basis of antenatal HIV prevalence. We offered residents repeated rapid HIV testing during home-based visits every 6 months for about 4 years in four clusters, 3 years in six clusters, and 2 years in 12 clusters (58 cluster-years) and referred HIV-positive participants to trial clinics for ART (fixed-dose combination of tenofovir, emtricitabine, and efavirenz) regardless of CD4 cell count (intervention) or according to national guidelines (initially ≤ 350 cells per μL and < 500 cells per μL from January, 2015; control). Participants and investigators were not masked to treatment allocation. We used dried blood spots once every 6 months provided by participants who were HIV negative at baseline to estimate the primary outcome of HIV incidence with cluster-adjusted Poisson generalised estimated equations in the intention-to-treat population after 58 cluster-years of follow-up. This study is registered with ClinicalTrials.gov, number NCT01509508, and the South African National Clinical Trials Register, number DOH-27-0512-3974.

Findings Between March 9, 2012, and June 30, 2016, we contacted 26 518 (93%) of 28 419 eligible individuals. Of 17 808 (67%) individuals with a first negative dried blood spot test, 14 223 (80%) had subsequent dried blood spot tests, of whom 503 seroconverted after follow-up of 22 891 person-years. Estimated HIV incidence was 2.11 per 100 person-years (95% CI 1.84–2.39) in the intervention group and 2.27 per 100 person-years (2.00–2.54) in the control group (adjusted hazard ratio 1.01, 95% CI 0.87–1.17; $p=0.89$). We documented one case of suicidal attempt in a woman following HIV seroconversion. 128 patients on ART had 189 life-threatening or grade 4 clinical events: 69 (4%) of 1652 in the control group and 59 (4%) of 1367 in the intervention group ($p=0.83$).

Interpretation The absence of a lowering of HIV incidence in universal test and treat clusters most likely resulted from poor linkage to care. Policy change to HIV universal test and treat without innovation to improve health access is unlikely to reduce HIV incidence.

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Introduction

HIV incidence in South Africa remains high, with an estimated 380 000 adults and children newly infected in 2015.¹ Because HIV-1 plasma viral load is strongly associated with sexual transmission risk,² expanded use of antiretroviral therapy (ART) could be key to reducing the rate of new HIV infections at the population level as well as providing individual health benefits.^{3,4} An ecological study⁵ and a population-based cohort study⁶ as well as a randomised trial⁷ done among heterosexual serodiscordant couples have shown substantial reduction in new HIV infections with increased ART coverage. Mathematical models suggest important reductions in HIV transmission are achievable with high uptake of

regular HIV testing and universal ART initiation at diagnosis.⁸ However, the hypothesis that universal test and treat will reduce HIV incidence has not been tested in a population-level trial.

In the ANRS 12249 Treatment as Prevention trial, we aimed to investigate whether universal ART initiation offered to all HIV-positive individuals reduces HIV incidence in a rural and hyperendemic region of South Africa.

Methods

Study design and population

We did a phase 4, open-label, community cluster, randomised trial of 22 communities in the Hlabisa

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Research in context

Evidence before this study

The HPTN 052 trial showed that antiretroviral therapy (ART) significantly reduces HIV transmission in serodiscordant individuals within stable partnerships. However, the applicability of these findings when applied at a population level within high prevalence settings remains unclear, particularly where many HIV-infected individuals are either unaware of their diagnosis or do not disclose their status to their sexual partners. We searched PubMed for studies in the African setting reporting on HIV transmission at the population level from Jan 1, 2004, to July 30, 2017, with the search terms “(“HIV”) AND “(antiretroviral”) OR “(anti-retroviral”) OR “(ART”) OR “(ARV”) OR “(HAART”) AND “(Incidence”) OR “(Transmission”) OR “(diagno*)” AND “(population”) OR “(community”) AND “(Africa)”” in English. We identified two prospective cohort studies reporting an association between ART coverage and population HIV incidence from 2378 abstracts. Tanser and colleagues followed up a total of 16 667 adults who were HIV negative at baseline from 2004 to 2011 in the same subdistrict as the ANRS 12249 TasP trial. This study showed that an HIV-uninfected individual living in a community with ART coverage of 30–40% was 38% less likely to acquire HIV infection than an individual living in a community where ART coverage was less than 10%. The other

study by Kong and colleagues in Rakai, Uganda, from 1999 to 2013, showed that increased ART coverage in women was associated with lower community HIV incidence in men compared with no association between ART coverage in men and HIV incidence in women, attributable to lower ART coverage in men during this period. Four cluster-randomised trials (including this study) are implemented in Botswana, Kenya, South Africa, Uganda, and Zambia to investigate the effect of population ART on HIV incidence.

Added value of this study

The ANRS 12249 trial is the first of the four trials to report its findings. We showed that HIV incidence did not decrease following the implementation of the universal test and treat strategy at community level within a very high HIV prevalence setting. Despite a higher proportion of HIV-positive individuals becoming aware of their HIV status as a result of the trial, very few of them linked to HIV care. A high proportion of those that sought care and were on ART achieved virological suppression.

Implications of all the available evidence

It is possible to achieve high levels of HIV status awareness, but policy change to universal ART without substantial improvements in linkage to care is unlikely to reduce HIV incidence.

subdistrict, KwaZulu-Natal, South Africa, where the estimated HIV prevalence is 30%.⁹ The Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BFC 104/11) and the Medicines Control Council of South Africa approved this trial. The trial protocol and procedures have previously been reported.^{10,11}

We included individuals aged 16 years or older with community residence (defined as spending ≥ 4 nights a week in the study area) in the designated cluster. The clusters were aggregated local areas (neighbourhoods) designed to encompass social and sexual networks on the basis of earlier studies in the subdistrict,¹² with the aim of keeping the potential for cross-arm contamination to a minimum. We observed mobility of individuals in and out of the study area, with some community members only visiting their families at the weekend. We excluded individuals if they did not fulfil the criteria for residency or did not have the mental capacity to give informed consent. We took oral informed consent from the head of each household and enumerated all eligible adult members, and written informed consent from individual eligible participants.

Randomisation and masking

To minimise baseline differences in cluster characteristics across treatment groups, we stratified the clusters by HIV prevalence estimated from women attending antenatal clinics in the trial area.¹³ The study statisticians randomly assigned clusters (1:1) to either the control

group or the intervention group per HIV prevalence stratum. The statisticians did not enrol participants into the study, but they contributed to data analysis. We used MapInfo Pro (version 11.0) to generate random numbers and to do the randomisation procedure. The nature of the trial meant it was not possible to mask participants and investigators to the intervention.

Procedures

We used global positioning system coordinates to identify households in the trial area and assigned a unique identification number to each. At each home-based survey round done at intervals of 6 months, HIV counsellors obtained oral consent to proceed from the head of the household and enumerated all eligible adult members. Eligible individuals providing written informed consent in the isiZulu language responded to a sociodemographic and sexual behaviour questionnaire and gave a finger prick sample, collected as a dried blood spot, which we used to estimate population HIV prevalence and incidence through third-generation ELISA (SD Bioline HIV 1/2 ELISA 3.0, Standard Diagnostics, Yongin-si, South Korea). These assessments were done at the survey rounds, which took place in the households. Because the trial was implemented in phases, follow-up was about 4 years in four clusters (enrolled March, 2012), 3 years in six clusters (enrolled January, 2013), and 2 years in 12 clusters (enrolled June, 2014). In total, there were 58 cluster-years. HIV

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For the online protocol see <https://www.ahri.org/tasp-study-protocol>

counsellors offered individuals point-of-care, rapid HIV counselling and testing with local Department of Health-approved test kits at each survey round.^{9,10} We also introduced mobile HIV testing in all clusters in the final survey round only. HIV counsellors offered rapid HIV testing again in subsequent survey rounds to participants who tested HIV-negative or refused testing in a previous round. We referred participants who tested HIV positive to their cluster trial clinic.

The only trial-specific randomly assigned intervention was ART eligibility. We informed those in the intervention group that they would be offered ART immediately, regardless of their CD4 cell count to prevent transmission to their sexual partners and that it was possible that the individual health of those with high CD4 cell count could also be improved, whereas those in the control group were informed that ART would be provided according to national guidelines¹⁴ (initially starting at CD4 counts ≤ 350 cells per μL and then < 500 cells per μL from January, 2015). ART was to be initiated within 2 weeks of the baseline visit, or sooner if patients were severely immunocompromised. First-line ART was fixed-dose combination of tenofovir, emtricitabine, and efavirenz as per national guidelines, except when these drugs were clinically contraindicated. In patients for whom first-line ART has failed, genotypic resistance testing (Sanger sequencing reaction done on an ABI 3130xl Genetic Analyser [Life Technologies, Carlsbad, CA, USA]) informed switch to second-line ART.

Self-identified HIV-positive participants already on ART could opt to continue with their current Department of Health provider or transfer to a trial clinic. From May, 2013, following a protocol amendment to improve linkage to care, study investigators set up a linkage to care team to contact HIV-positive participants in both groups who were not in care and did not attend the trial clinic within 3 months of referral. They were contacted by phone, home visit, or both.

Trial nurses clinically assessed consenting HIV-positive patients at their cluster trial clinic, including the performance of a point-of-care CD4 cell measurement (Alere Pima CD4 test, Alere, Waltham, MA, USA). Additionally, trial nurses saw patients receiving ART monthly for their prescription but took blood samples for toxicity monitoring (full blood count, liver function tests, and concentrations of urea, electrolytes, and creatinine) and HIV viral load measurements at their first visit and at visits 3 months and 6 months after ART initiation, and thereafter every 6 months for the duration of follow-up, which was dependent on when the clusters were implemented. We allowed unscheduled clinic visits for patients with clinical complaints arising before their protocol visit—eg, visits due to adverse events. These unscheduled visits were documented as part of the study. In control clusters, nurses invited patients not yet eligible for ART to return within 4–6 months for pre-ART care, clinical assessment, and CD4 cell count measurement.^{9,10} Investigators defined

loss to follow-up as being more than 3 months late for next clinic appointment. Trial clinics also provided care for common coexisting chronic medical conditions, including diabetes and hypertension.

Outcomes

The primary outcome was HIV incidence, defined by seroconversion between repeated dried blood spot samples collected within the population cohort every 6 months until after 58 cluster-years of follow-up. All secondary outcomes and plan for dissemination are listed in the appendix (pp 5, 6). Secondary outcomes included in this manuscript are HIV status ascertainment (HIV rapid test or HIV-positive self-report), linkage to care and sexual behaviours documented within the full trial population cohort, ART initiation in those presenting as ART naive, retention in care, and virological suppression estimated in the people ascertained as HIV positive. Investigators estimated population ART coverage (proportion of participants being on ART in all HIV-infected participants) and the 90-90-90 HIV care cascade for all HIV-positive participants at the population level (appendix pp 6, 7). Additionally, we reported life-threatening and grade 4 clinical adverse events observed during the study period.

Statistical analysis

We used the Cost-Effectiveness of Preventing AIDS Complications mathematical model¹⁵ to simulate an intervention of biannual HIV screening of the adult population, comparing the effect of universal ART initiation irrespective of CD4 cell count with national eligibility guidelines. We concluded on the basis of this model that the preliminary sample size of 34 clusters (2×17) of 1000 eligible residents each followed up for 2 years could detect a 30% reduction in cumulative HIV incidence.¹⁰

We subsequently amended the trial design to account for a phased introduction of clusters over 3 years; sample size calculations explicitly accounting for this phased cluster follow-up showed that 22 clusters (2×11 , with an estimated 800 individuals without HIV infection per cluster) followed up for a total of 58 cluster-years would yield 80% power to detect an overall 34% reduction in cumulative HIV incidence, with an incidence of 2.25% per year in the control clusters over the trial period. The effect size was informed by a modelling approach using the network-based simulation model STDSIM (sexually transmitted disease simulation).¹⁶ The model used the following parameters: 90% of HIV tests offered to those registered, 80% test uptake among those offered, 70% linkage to care upon diagnosis in those accepting the test, baseline HIV prevalence of 24%, and a cross-arm contamination of 10% (ie, contamination between the intervention group vs the control group rather than within clusters of the same group). The sample size calculation allowed for 20% loss to follow-up and assumed a coefficient of variation of 0.25 to account

See Online for appendix

for variation between clusters. Following this approach, the trial began in the first ten clusters between 2012 and 2013; from 2014, the trial was expanded to the full 22 clusters (appendix pp 8, 9). Taking into account the different lengths of follow-up time in the clusters, loss to follow-up, and frequency of testing patterns, we estimated the total person-years of follow-up in those who are HIV negative at baseline to be 15040 per group. At an annual incidence of 2.25% per year, we estimated 338 seroconversions in 11 control clusters; and in 11 intervention clusters, with an incidence of 1.485% per year, we estimated 223 seroconversions by the end of the study period.

We summarised continuous variables with median and IQR, and categorical variables with frequencies and percentages. We calculated HIV incidence in participants with an initially HIV-negative sample and at least one further sample, and stratified by group. To estimate person-years of follow-up, we right-censored participants who did not seroconvert to HIV at the date of the last HIV-negative sample. For those who seroconverted, the date of seroconversion was a random-point date between the last negative and the first positive sample. We calculated HIV incidence by dividing the number of seroconversions by the total person-years of follow-up, stratified by group.

We used an intention-to-treat Poisson generalised estimating equation taking cluster effect into account with an exchangeable working correlation matrix to estimate the marginal effect of the intervention on HIV incidence.¹⁷ To improve efficiency of the estimated effect of the intervention, we supplemented this main analysis with an augmented generalised estimating equation. To do so, we did an outcome model of cluster-level covariates: age at inclusion (proportion of participants <30 years and ≥60 years), sex (proportion of women), estimated population ART coverage at the beginning of the trial, estimated HIV prevalence at the beginning of the trial, and modification of WHO guidelines (time varying).

For the estimation of mortality rate among HIV-positive patients in trial clinics, patients contributed person-years of follow-up in the analysis if they had at least one follow-up visit following the baseline clinic visit date, and we censored patients who were known to be alive at the date of their last clinic visit. We calculated mortality rate by dividing the number of deaths by the person-years of follow-up, stratified by group.

We did all analyses with SAS (version 9.4) and the augmented generalised estimating equation using R with the package CRTgeeDR.

This study is registered with ClinicalTrials.gov, number NCT01509508, and the South African National Clinical Trials Register, number DOH-27-0512-3974.

Role of the funding source

Representatives of the ANRS were part of the study team and were involved in study design, data interpretation, and writing of the manuscript. The pharmaceutical

companies providing study drugs had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 9, 2012, and June 30, 2016, 28419 individuals (13381 in the intervention group and 15038 in the control group) were eligible for inclusion in the trial (figure). Median age was 30.2 years (IQR 21.4–49.4), and

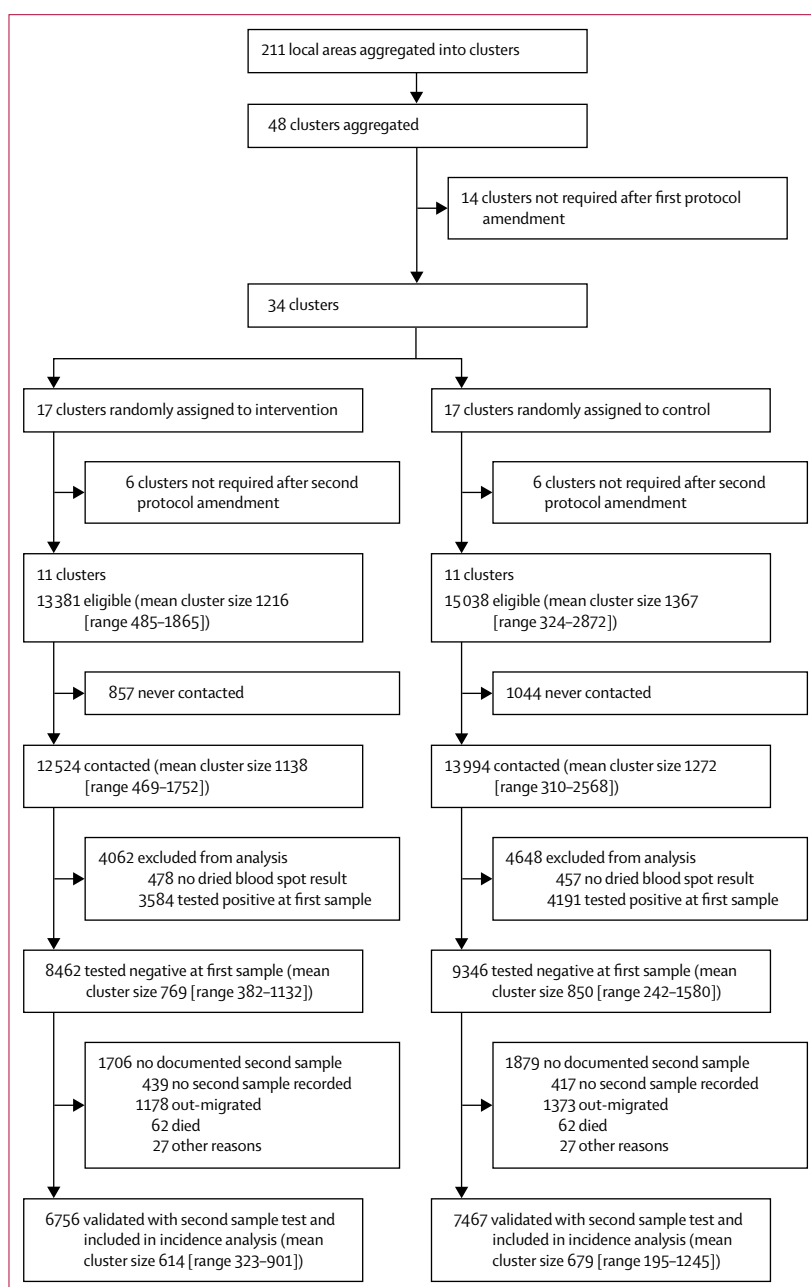


Figure: Flow diagram of individuals contacted for the incidence analysis

	Intervention group (n=13 381)	Control group (n=15 038)	Total (n=28 419)
Sex			
Women	8446 (63.1%)	9399 (62.5%)	17845 (62.8%)
Men	4935 (36.9%)	5639 (37.5%)	10574 (37.2%)
Age (years) at inclusion			
16–29	5715 (42.7%)	6366 (42.3%)	12 081 (42.5%)
30–59	4207 (31.4%)	4714 (31.3%)	8921 (31.4%)
≥60	1596 (11.9%)	1766 (11.7%)	3362 (11.8%)
Year of birth unknown	1863 (13.9%)	2192 (14.6%)	4055 (14.3%)
Median (IQR)	30.2 (21.5–49.5)	30.3 (21.3–49.2)	30.2 (21.4–49.4)
Highest education level			
Primary or less	4517 (33.8%)	4988 (33.2%)	9505 (33.4%)
Some secondary	4323 (32.3%)	5232 (34.8%)	9555 (33.6%)
At least completed secondary	3245 (24.3%)	3341 (22.2%)	6586 (23.2%)
Never documented	1296 (9.7%)	1477 (9.8%)	2773 (9.8%)
Marital status			
Never been married	8730 (65.2%)	9884 (65.7%)	18 614 (65.5%)
Engaged	530 (4.0%)	787 (5.2%)	1317 (4.6%)
Married	2166 (16.2%)	2122 (14.1%)	4288 (15.1%)
Divorced, separated, or widowed	667 (5.0%)	772 (5.1%)	1439 (5.1%)
Never documented	1288 (9.6%)	1473 (9.8%)	2761 (9.7%)
Professional status			
Employed	1192 (8.9%)	1364 (9.1%)	2556 (9.0%)
Student	2564 (19.2%)	2916 (19.4%)	5480 (19.3%)
Looking for work	2886 (21.6%)	3096 (20.6%)	5982 (21.0%)
Other or inactive	5413 (40.5%)	6146 (40.9%)	11 559 (40.7%)
Never documented	1326 (9.9%)	1516 (10.1%)	2842 (10.0%)

Data are n (%), unless otherwise specified. Age was computed at study inclusion in the population cohort. All other characteristics were estimated from the first known information provided in an individual questionnaire. When the exact day or month of birth was missing (but year of birth properly documented), day or month of birth was randomly imputed (uniform distribution).

Table 1: Baseline characteristics at inclusion

	Number of HIV-positive dried blood spot tests	Person-years	Incidence for 100 person-years* (95% CI)
Assignment groups			
Control	274	12 053	2.27 (2.00–2.54)
Intervention	229	10 838	2.11 (1.84–2.39)
Year clusters opened			
2012	106	5723	1.85 (1.50–2.20)
2013	222	9097	2.44 (2.12–2.76)
2014	175	8071	2.17 (1.85–2.49)
Total	503	22 891	2.20 (2.01–2.39)

*Not taking into account cluster effect.

Table 2: Number of new HIV-positive tests and number of person-years in eligible participants

63% were women and 37% were men (table 1). Overall, 26 518 (93%) eligible individuals were contacted at least once, of whom 23 476 (88%) had their HIV status ever ascertained (ie, had a HIV rapid test or self-reported being

HIV positive) by an HIV counsellor (appendix p 10). Contacted individuals were more likely to be women and older than non-contacted individuals, and similar between groups (appendix p 11). 8960 (34%) of 26 518 individuals contacted out-migrated from the study area at some point during the trial. Those who out-migrated were more likely to be men, younger, of better educational attainment, never married, and actively seeking employment than were those who did not (appendix p 11).

We excluded a total of 8710 (33%) of 26 518 individuals contacted from the incidence calculation either because their first dried blood spot sample was positive or because no valid result was obtained from the available sample. Of the 17 808 (67%) individuals with a first sample being negative, and thus eligible for inclusion for the incidence cohort, 14 223 (80%) had a second sample test and contributed data for the incidence analysis. Those available for the incidence analysis were significantly older (median age of 29.9 years vs 23.5 years; $p=0.036$) and were less likely to be men (36% vs 53%; $p<0.0001$) than the remaining 3585 (20%) HIV-negative individuals with only one sample, with no difference between trial groups (appendix p 12). They also differed from those who were HIV positive at baseline (appendix p 13). 503 new HIV infections were identified after 22 891 person-years, for an overall HIV incidence rate of 2.20 (95% CI 2.01–2.39) per 100 person-years (table 2). The incidence in the control group was similar to that used in our sample size calculations. The crude hazard ratio (HR; intervention vs control) was 0.95 (95% CI 0.75–1.20; $p=0.68$) and adjusted HR was 1.01 (0.87–1.17; $p=0.89$), allowing for temporal changes in national ART guidelines and cluster-level measure of sex, age, estimated HIV prevalence, and estimated population ART coverage at the beginning of the trial (appendix pp 13, 14).

The proportion of registered individuals contacted by the HIV counsellors per survey round was slightly lower in the intervention group than in the control group (37 368 [72.7%] vs 42 033 [73.9%]; $p<0.0001$; table 3). Among those contacted, HIV status ascertainment was also slightly lower in the intervention group than in the control group (29 690 [79.5%] vs 34 097 [81.1%]; $p<0.0001$). One female participant who tested HIV positive had an acute adjustment reaction with suicidal attempt.

Cumulatively in all survey rounds, 7615 adults were ever ascertained as HIV positive and referred to trial clinics in their cluster; 1972 (61%) of 3247 patients already in follow-up in the Department of Health clinics switched their care to the trial clinics, whereas 1047 (24%) of 4368 who were never previously in care linked to the trial clinics. 1072 (14%) of the 7615 HIV-positive individuals were newly diagnosed during the trial (appendix p 10).

We estimated entry into care within 6 months in individuals not previously in care to be 29.7% overall, with no differences between groups ($p=0.49$), which is much lower than expected in our model assumptions

	STDSIM modelling assumptions	TasP trial observations			
		Indicator	Intervention group (n/N; %)	Control group (n/N; %)	p value
Situation at the beginning of the trial					
Proportion of all HIV-positive patients on ART at the end of 2011	40%	Estimated population ART coverage at the beginning of the trial	795/2686 (29.6%)	1056/3136 (33.7%)	0.001
HIV prevalence at the end of 2011 (≥ 16 years)	24%	Estimated HIV prevalence at the beginning of the trial	2686/9163 (29.3%)	3136/10228 (30.7%)	0.04
Uptake rates					
HIV test offered to those registered in this trial	90%	Contact rate per survey round	37368/51414 (72.7%)	42033/56891 (73.9%)	<0.0001
Test acceptance among those offered HIV test	80%	HIV ascertainment rate per survey round	29690/37368 (79.5%)	34097/42033 (81.1%)	<0.0001
Linkage to care upon diagnosis among those accepting the test	70%	Entry into care within 6 months among individuals not in care	489/1688 (29.0%)	594/1954 (30.4%)	0.49

The STDSIM model was quantified to represent the HIV epidemic in rural KwaZulu-Natal, South Africa, with demographic, behavioural, and epidemiological data from the Africa Centre. Proportion of individuals contacted and whose HIV status was ascertained was computed per home-based survey round (ie, an individual eligible in three survey rounds, fully contacted in two rounds, but accepting a HIV rapid test only in one round will contribute three episodes in the denominator and two episodes in the numerator for estimation of contact, and two episodes in the denominator and one in the numerator for HIV ascertainment). STDSIM=sexually transmitted disease simulation. TasP=treatment as prevention. ART=antiretroviral therapy.

Table 3: STDSIM modelling assumptions and ANRS 12249 TasP trial observations

	July 1, 2012*	Jan 1, 2013†	July 1, 2013	Jan 1, 2014	July 1, 2014‡	Jan 1, 2015	July 1, 2015	Jan 1, 2016
Four clusters opened in 2012								
Intervention group	126/397 (31.7%)§	176/408 (43.1%)	185/423 (43.7%)	192/422 (45.5%)	205/432 (47.5%)	209/432 (48.4%)	202/373 (54.2%)	220/384 (57.3%)
Control group	99/323 (30.7%)§	122/281 (43.4%)	139/299 (46.5%)	148/308 (48.1%)	150/329 (45.6%)	154/328 (47.0%)	160/289 (55.4%)	147/255 (57.6%)
Difference	+1.1% (p=0.82)	-0.3% (p=1.00)	-2.8% (p=0.51)	-2.6% (p=0.54)	+1.9% (p=0.66)	+1.4% (p=0.75)	-1.2% (p=0.82)	-0.4% (p=0.99)
Six clusters opened in 2013								
Intervention group	..	230/772 (29.8%)§	346/854 (40.5%)	477/1016 (46.9%)	505/1073 (47.1%)	553/1108 (49.9%)	576/1011 (57.0%)	589/993 (59.3%)
Control group	..	429/1237 (34.7%)§	400/1070 (37.4%)	620/1500 (41.3%)	655/1527 (42.9%)	703/1593 (44.1%)	761/1492 (51.0%)	763/1406 (54.3%)
Difference	..	-4.9% (p=0.03)	+3.1% (p=0.18)	+5.6% (p=0.006)	+4.2% (p=0.04)	+5.8% (p=0.004)	+6.0% (p=0.004)	+5.0% (p=0.02)
12 clusters opened in 2014								
Intervention group	439/1517 (28.9%)§	589/1588 (37.1%)	691/1547 (44.7%)	732/1511 (48.4%)
Control group	528/1576 (33.5%)§	633/1659 (38.2%)	783/1722 (45.5%)	853/1677 (50.9%)
Difference	-4.6% (p=0.007)	-1.1% (p=0.56)	-0.8% (p=0.67)	-2.4% (p=0.18)
All clusters combined								
Intervention group	126/397 (31.7%)	406/1180 (34.4%)	531/1277 (41.6%)	669/1438 (46.5%)	1149/3022 (38.0%)	1351/3128 (43.2%)	1469/2931 (50.1%)	1541/2888 (53.4%)
Control group	99/323 (30.7%)	551/1518 (36.3%)	539/1369 (39.4%)	768/1808 (42.5%)	1333/3432 (38.8%)	1490/3580 (41.6%)	1704/3503 (48.6%)	1763/3338 (52.8%)
Difference	+1.1% (p=0.82)	-1.9% (p=0.33)	+2.2% (p=0.26)	+4.0% (p=0.02)	-0.8% (p=0.52)	+1.6% (p=0.20)	+1.5% (p=0.25)	+0.5% (p=0.69)

Data are n/N (%), unless otherwise specified. Note that as of July 1, 2012, the first survey round was not finished yet in the first four clusters. TasP=treatment as prevention. *Survey rounds started in the first four clusters: March to October, 2012; November, 2012, to April, 2013; May to August, 2013; and biannually from June, 2014, onwards. †Inclusion of six additional clusters in January, 2013. ‡Inclusion of 12 additional clusters; survey rounds were biannual from June, 2014, until the trial ended in June 30, 2016. §Estimated at the beginning of the trial.

Table 4: Estimated antiretroviral therapy coverage of the population in the ANRS 12249 TasP trial

(table 3). Among those linked to trial clinics, median time between referral and first trial clinic visit was 2.7 weeks (IQR 0.9–21.7; appendix p 15).

HIV counsellors referred all 7615 HIV-positive individuals identified to the trial clinics. Of the 3019 who ever linked to trial clinics, 1492 (49%) were ART naive at the first visit. 635 (90%) of 704 in the intervention group and 525 (67%) of 788 in the control group initiated ART. At ART initiation, median CD4 count was 401 cells per μL (IQR 265–572) and median viral load was 4.4 log copies per mL (3.8–5.1) in the intervention group, and 320 cells per μL (212–442) and 4.5 log copies per mL (3.7–5.1) in the control group (appendix p 15). Of the 698 participants who had been on ART for 12 months, 628 had documented viral load, of whom 611 (97%) achieved viral suppression (viral load <400 copies per mL), which was similar between both groups. 1478 ART-experienced participants had been on ART for a median duration of 3.80 years (IQR 1.75–5.99) at their first visit (639 in the intervention group and 839 in the control group) with no difference between groups. The ART status of the remaining 49 individuals was unknown at the first clinic visit (appendix p 15). Retention in care 12 months after the first trial clinic visit was 1004 (82%) of 1230 patients in the intervention group and 1127 (75%) of 1495 in the control group ($p=0.0001$).

In all HIV-positive individuals seen in trial clinics, the number of deaths reported was 33 in the intervention group with a crude mortality rate of 1.28 per 100 person-years (95% CI 0.84–1.72), and 58 deaths in the control group with a crude mortality rate of 1.86 per 100 person-years (1.38–2.34); adjusted HR 0.69 (95% CI 0.42–1.15; $p=0.15$; appendix p 16). 128 patients had 189 life-threatening or grade 4 clinical events: 69 (4%) of 1652 in the control group versus 59 (4%) of 1367 in the intervention group ($p=0.83$; appendix p 16).

At the beginning of the trial, population ART coverage among all HIV-positive adults living in the study area was estimated at 29.6% in the intervention group and 33.7% in the control group, below the initial ART coverage of 40% assumed in the STDSIM modelling (table 3). ART coverage increased to 53.4% in the intervention group and 52.8% in the control group by Jan 1, 2016, with no significant differences between groups ($p=0.69$; table 4).

As of Jan 1, 2016, we estimated population 90-90-90 cascade for both groups combined as follows: 91.5% of HIV-positive participants knew their HIV status, of whom 58.0% were on ART, with 85.3% of these virally suppressed, amounting to 49.4% of all HIV-positive participants virally suppressed. Estimated proportions were similar between the intervention and control groups (appendix p 16).

In the last survey round, among 6968 participants who reported a sexual partner in the previous 6 months, total condom use at last sexual intercourse was 44% and was similar between the groups. The frequencies of reporting having a sexual partner outside the trial area during the

previous 6 months were 42% in the intervention group and 37% in the control group ($p<0.0001$; appendix p 16).

Discussion

This is the first of four cluster-randomised trials investigating the effect of ART on HIV incidence.^{18–20} In our trial, HIV incidence was high and we found no significant population-level effect of universal ART compared with national ART initiation guidelines on HIV incidence. HIV testing uptake was high and repeat testing acceptable.⁹ However, linkage to HIV care was both slow and poor, leading to a lower than anticipated increase of population ART coverage, with no significant difference in ART coverage between both groups at trial completion. These findings suggest that the conditions required for a policy of test and treat to translate into a reduction in HIV incidence were not met. Viral suppression in participants on ART was high with few serious adverse events. The overall HIV care cascade did not differ between groups and fell far short of the UNAIDS 90-90-90 targets for 2020,²¹ contrary to what has been recently reported in east Africa.¹⁹ Participants in the intervention group showed a lower incidence of mortality than those in the control group even after a relatively short period of follow-up of 1 year on average, although this finding was not significant.

The most obvious explanation for this absence of difference in HIV incidence between the two trial groups relates to the low linkage to care, particularly in the intervention group. The rate of linkage to care was similar in both groups, with only about 30% of individuals registering at the trial clinic within 6 months of home HIV diagnosis, much lower than the expected 70%. This finding occurred despite HIV-positive individuals in the intervention group being informed they would be offered ART regardless of their CD4 cell count and those in the control group being informed ART will be offered only if eligible according to national guidelines. The consequence of this poor linkage was that although ART coverage increased during the trial, the increase was not as high as expected with no significant difference in population ART coverage between the study groups. The inability to create experimental separation between the two groups of the trial would have contributed to the null finding seen with HIV incidence.

The poor linkage to HIV care despite the introduction of universal test and treat is comparable to South African national estimates,²² but lower than reported in another trial in Uganda and South Africa,²³ although definitions of linkage to care differed. Delayed linkage to care could have resulted in continued HIV transmission from viraemic individuals. Factors we have previously described associated with poor linkage include being young, more educated, newly diagnosed, not knowing anyone who is HIV positive, and increased distance between their home and the trial clinic.²⁴ Trial clinics catered only for HIV-positive people, who might therefore have had

increased concerns relating to stigma and unintended HIV status disclosure,²⁵ although we had hypothesised that mobile clinics close to participants homes would encourage attendance. Home-based ART initiation might mitigate some of these factors; indeed, it tripled linkage to care in a study in Malawi, although follow-up was too short to evaluate long-term ART adherence and retention on treatment.²⁶ More studies on the effectiveness and safety of home ART initiation are urgently required.

Other factors might have also contributed to the null finding, such as population mobility, which is high in this rural setting of South Africa.²⁷ We previously showed²⁸ that mobility weakens the HIV care cascade at population level because of differences between in-migration and out-migration. The effect of a universal test and treat approach could be improved if implemented over a larger geographical area or access to care was more actively facilitated and recorded. Mobility was also associated with sexual mixing patterns. On the basis of previously published work, we assumed when designing the trial²⁹ that those in the trial area would preferentially have sexual contacts with people in the same locality. We have indeed previously empirically demonstrated that HIV prevalence in the local community is one of the strongest determinants of HIV acquisition risk, providing support for this assumption.⁶ In this trial, 40% of participants reported having a sexual partner outside of the trial area, some as far as major cities outside of KwaZulu-Natal. We expect that frequency of sexual contacts would be low for much of this group, given the large distances between partners. Nevertheless, if these self-reported sexual behaviour data are reflective of the true underlying geography of sexual partnerships, this factor could also have played a part in reducing any difference in incidence between the study groups. Phylogenetic work is ongoing to determine whether external sexual partnerships could have contributed to a greater than expected contamination effect.

Finally, we implemented the intervention uniformly across the 22 clusters in the six HIV prevalence strata used in the randomisation. However, as anticipated from our previous work in the neighbouring community,³⁰ there was substantial variation in HIV prevalence, which ranged from 17% in deep rural areas to 39% in communities close to the national highway (appendix p 13). A more focused approach of interventions targeted to areas of high transmission and people most at risk might have a greater impact on incidence than what was observed in our trial; such an approach is supported by modelling, using the Kenyan epidemic as a case study.³¹

Apart from the absence of effect on transmission, the TasP trial provides further evidence regarding the individual benefits of universal ART. Following the 2015 WHO ART guidelines recommending ART initiation regardless of CD4 cell count³² for individual benefits³⁴ and transmission reduction in serodiscordant couples,⁷ concerns were expressed regarding ART adherence in asymptomatic individuals. We observed high

viral suppression at 12 months, also reported in the SEARCH trial done in Uganda and Kenya,¹⁹ and a weak evidence of a 30% reduction in mortality among trial clinic attendees over a relatively short period. We also found a higher retention rate in the intervention group than in the control group, with participants on ART more likely to be retained in care than those not yet on ART.³³ These findings are strong arguments to roll out universal test and treat without any restriction.

The TasP trial has some limitations. Our home-based HIV testing strategy did not reach 10·8% of eligible men and 4·2% of eligible women. Non-resident household members were not included, although some visited the trial area regularly and were sexual partners of resident members. ART coverage at trial start was by chance higher in the control group than in the intervention group. Counsellors of linkage to care were not present from trial start, and we only intervened after a 3 month delay in linkage to care. The South African ART guidelines evolved during the study from a CD4 count threshold of 350 cells per μL or less to less than 500 cells per μL ,¹⁴ which could have weakened the anticipated effect size, therefore reducing the statistical power to observe a difference between groups. Older women were more likely to have contributed to the incidence analysis, with no difference between groups. Because incidence is lower in older individuals, this finding might have contributed to a lower overall incidence but would not have biased the estimate of the difference in incidence between groups. We further assessed sensitivity to violation of missing data assumptions and robustness of the estimates by reanalysing the data under two assumptions; all missing second dried blood spots were considered as positive or negative. We observed that neither the point estimate nor the significance changed. We conclude that although data missing completely at random is a strong assumption, it is not invalidated by the sensitivity analysis (appendix p 13), and the primary analysis can be trusted. Finally, our estimates of population ART coverage and of the HIV care cascade are likely to be underestimated because the status of participants receiving care outside of trial clinics or government clinics is unknown; such individuals could have been wrongly classified as not being on ART or in care. The size of this specific group is also unknown.

In this pivotal cluster-randomised trial, universal testing was implemented in both groups and we tested the hypothesis that provision of universal treatment reduces HIV transmission at population level. The implementation of universal HIV testing and enhanced linkage to care improved population ART coverage in both groups although this improvement was not significantly different between groups, despite provision of universal ART in the intervention trial clinics. Subsequently, we found no difference in HIV incidence at the conclusion of the study. An important finding, however, was the reduction by 30% in the mortality rate among all HIV-positive participants in the intervention communities receiving care in

trial facilities. Although our study showed overall good viral suppression rates and retention in those entering care, poor linkage to care, possibly associated with HIV-related stigma, remains an important obstacle in this rural setting of South Africa. In conclusion, comprehensive intervention packages that increase ART uptake and retention in care are urgently required to achieve the 90-90-90 targets, so as to maximise the individual and societal benefits of ART.

Contributors

CCI, JO-G, FT, M-LN, DP, and FD designed and implemented the study. NO, TM, JD, and KH implemented the study. CCI and JO-G searched the literature and co-wrote the first draft of the manuscript. JL, EB, RT, and FT did the statistical analysis. RT and FT did the sample size calculations. All authors contributed to the interpretation and presentation of the findings, and approved the final version of the manuscript for submission.

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Declaration of interests

CCI has received honoraria for consulting services from Gilead Sciences. All other authors declare no competing interests.

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References

- UNAIDS. Country: South Africa. Geneva: UNAIDS, 2015.
- Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000; **342**: 921–29.
- Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373**: 808–22.
- Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795–807.
- Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010; **376**: 532–39.
- Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science* 2013; **339**: 966–71.
- Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med* 2016; **375**: 830–39.
- Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373**: 48–57.
- Iwuji CC, Orne-Gliemann J, Larmarange J, et al. Uptake of home-based HIV testing, linkage to care, and community attitudes about art in Rural KwaZulu-Natal, South Africa: descriptive results from the first phase of the ANRS 12249 TasP cluster-randomised trial. *PLoS Med* 2016; **13**: e1002107.
- Iwuji CC, Orne-Gliemann J, Tanser F, et al. Evaluation of the impact of immediate versus WHO recommendations-guided antiretroviral therapy initiation on HIV incidence: the ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, KwaZulu-Natal, South Africa: study protocol for a cluster randomised controlled trial. *Trials* 2013; **14**: 230.

- 11 Orne-Gliemann J, Larmarange J, Boyer S, et al. Addressing social issues in a universal HIV test and treat intervention trial (ANRS 12249 TasP) in South Africa: methods for appraisal. *BMC Public Health* 2015; **15**: 209.
- 12 Tanser F, Hosegood V, Benzler J, Sollarsh G. New approaches to spatially analyse primary health care usage patterns in rural South Africa. *Trop Med Int Health* 2001; **6**: 826–38.
- 13 Rice BD, Bätzing-Feigenbaum J, Hosegood V, et al. Population and antenatal-based HIV prevalence estimates in a high contraceptive female population in rural South Africa. *BMC Public Health* 2007; **7**: 160.
- 14 National Department of Health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. Department of Health, Republic of South Africa, 2015.
- 15 Walensky RP, Wood R, Ciaranello AL, et al. Scaling up the 2010 World Health Organization HIV treatment guidelines in resource-limited settings: a model-based analysis. *PLoS Med* 2010; **7**: e1000382.
- 16 Hontelez JA, de Vlas SJ, Tanser F, et al. The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa. *PLoS One* 2011; **6**: e21919.
- 17 Stephens AJ, Tchetgen Tchetgen EJ, De Gruttola V. Augmented GEE for improving efficiency and validity of estimation in cluster randomized trials by leveraging cluster- and individual-level covariates. *Stat Med* 2012; **31**: 915–30.
- 18 Hayes R, Ayles H, Beyers N, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment—a study protocol for a cluster randomised trial. *Trials* 2014; **15**: 57.
- 19 Petersen M, Balzer L, Kwarsiima D, et al. Association of implementation of a universal testing and treatment intervention with HIV diagnosis, receipt of antiretroviral therapy, and viral suppression in East Africa. *JAMA* 2017; **317**: 2196–206.
- 20 Gaolathe T, Wirth KE, Holme MP, et al. Botswana's progress toward achieving the 2020 UNAIDS 90-90-90 antiretroviral therapy and virological suppression goals: a population-based survey. *Lancet HIV* 2016; **3**: e221–30.
- 21 UNAIDS. 90-90-90. An ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS, 2014.
- 22 Takuva S, Brown AE, Pillay Y, Delpech V, Puren AJ. The continuum of HIV care in South Africa: implications for achieving the second and third UNAIDS 90-90-90 targets. *AIDS* 2017; **31**: 545–52.
- 23 Barnabas RV, van Rooyen H, Tumwesigye E, et al. Uptake of antiretroviral therapy and male circumcision after community-based HIV testing and strategies for linkage to care versus standard clinic referral: a multisite, open-label, randomised controlled trial in South Africa and Uganda. *Lancet HIV* 2016; **3**: e212–20.
- 24 Plazy M, Farouki KE, Iwuji C, et al. Access to HIV care in the context of universal test and treat: challenges within the ANRS 12249 TasP cluster-randomized trial in rural South Africa. *J Int AIDS Soc* 2016; **19**: 20913.
- 25 Moshabela M, Zuma T, Orne-Gliemann J, et al. "It is better to die": experiences of traditional health practitioners within the HIV treatment as prevention trial communities in rural South Africa (ANRS 12249 TasP trial). *AIDS Care* 2016; **28** (suppl 3): 24–32.
- 26 MacPherson P, Lalloo DG, Webb EL, et al. Effect of optional home initiation of HIV care following HIV self-testing on antiretroviral therapy initiation among adults in Malawi: a randomized clinical trial. *JAMA* 2014; **312**: 372–79.
- 27 Dobra A, Barnighausen T, Vandormael A, Tanser F. Space-time migration patterns and risk of HIV acquisition in rural South Africa. *AIDS* 2017; **31**: 137–45.
- 28 Larmarange J, Iwuji C, Orne-Gliemann J, et al. Measuring the impact of test & treat on the HIV Cascade: the challenge of mobility. 2016 Conference on Retroviruses and Opportunistic Infections (CROI); Boston, MA, USA; Feb 22–25, 2016. 169LB.
- 29 Tanser F, Barnighausen T, Hund L, Garnett GP, McGrath N, Newell ML. Effect of concurrent sexual partnerships on rate of new HIV infections in a high-prevalence, rural South African population: a cohort study. *Lancet* 2011; **378**: 247–55.
- 30 Tanser F, Barnighausen T, Cooke GS, Newell ML. Localized spatial clustering of HIV infections in a widely disseminated rural South African epidemic. *Int J Epidemiol* 2009; **38**: 1008–16.
- 31 Anderson SJ, Cherutich P, Kilonzo N, et al. Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study. *Lancet* 2014; **384**: 249–56.
- 32 WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization, 2015.
- 33 Lessells RJ, Mutevedzi PC, Cooke GS, Newell ML. Retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa. *J Acquir Immune Defic Syndr* 2011; **56**: e79–86.