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, community 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 statistics 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 26518 (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.

Funding ANRS, GiZ, and Jie.
subdistrict, KwaZulu-Natal, South Africa, where the estimated HIV prevalence is 30%.

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.8,11

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,2 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 fulfill 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.11 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 incidence.
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 guidelines\(^*\) (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 naïve, 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 model\(^15\) 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 (two × 17) of 1000 eligible residents each followed up for 2 years could detect a 30% reduction in cumulative HIV incidence.\(^15\)

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 (two × 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 44% 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).\(^15\) 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 for
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 15 040 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. 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, 28 419 individuals (13 381 in the intervention group and 15 038 in the control group) were eligible for inclusion in the trial (figure). Median age was 30·2 years (IQR 21·4–49·4), and
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 [79.3%] 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, 7 615 adults were ever ascertained as HIV positive and referred to trial clinics, whereas 10 67 418 (24%) of 43 68 who were never previously in care linked to the trial clinics. 10 72 (14%) of the 7 615 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.
Estimated antiretroviral therapy coverage of the population in the ANRS 12 TasP trial

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

| 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%) | 1056/3126 (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%) | 3136/10,228 (30.7%) | 0.04 |

Uptake rates

| HIV test offered to those registered in this trial | 90% | Contact rate per survey round | 37,368/51,444 (72.7%) | 42,033/56,891 (73.9%) | <0.0001 |
| Test acceptance among those offered HIV test | 80% | HIV ascertainment rate per survey round | 29,690/37,368 (79.5%) | 34,097/42,033 (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 4: Estimated antiretroviral therapy coverage of the population in the ANRS 12 249 TasP trial

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Intervention group (n/N; %)</th>
<th>Control group (n/N; %)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four clusters opened in 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of all HIV-positive patients on ART at the end of 2011</td>
<td>40.0%</td>
<td>40.2%</td>
<td>0.75</td>
</tr>
<tr>
<td>HIV prevalence at the end of 2011 (≥16 years)</td>
<td>24.3%</td>
<td>24.5%</td>
<td>0.32</td>
</tr>
</tbody>
</table>

| Six clusters opened in 2013 | | | |
| Proportion of all HIV-positive patients on ART at the end of 2011 | 40.1% | 40.2% | 0.67 |
| HIV prevalence at the end of 2011 (≥16 years) | 24.4% | 24.6% | 0.20 |

| 12 clusters opened in 2014 | | | |
| Proportion of all HIV-positive patients on ART at the end of 2011 | 40.3% | 40.4% | 0.25 |
| HIV prevalence at the end of 2011 (≥16 years) | 24.7% | 24.9% | 0.18 |

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.
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 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 and 1127 (75%) of 1495 in the control group (appendix p 16). 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 clinic visit was 1004 (82%) of 1230 patients in the intervention group and 1127 (75%) of 1495 in the control group (p=0·0001).

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The poor linkage to HIV care despite the introduction of universal 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, but lower than reported in another trial in Uganda and South Africa, 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. Trial clinics catered only for HIV-positive people, who might therefore have had...
increased concerns relating to stigma and unintended HIV status disclosure, 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. 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. We previously showed 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 trial 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. 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, 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.

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 count for individual benefits and transmission reduction in serodiscordant couples, 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, 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. 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, 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, 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 PT did the statistical analysis. RT and PT 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.

**ANRS 12249 TasP Study Group**

**Scientific advisory board**

**Data safety monitoring board**

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

**Acknowledgments**
This trial was sponsored by the French National Agency for AIDS and Viral Hepatitis Research (ANRS; grant number, 2011-375), and funded by the ANRS, the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ; grant number, 81151938), and the Bill & Melinda Gates Foundation through the 3ie Initiative. This trial was done with the support of Merck and Gilead Sciences, which provided the Atripla drug supply. The Africa Health Research Institute, (previously Africa Centre for Population Health, University of KwaZulu-Natal, South Africa) receives core funding from the Wellcome Trust, which provides the platform for the population-based and clinical-based research at the centre. We thank Alpha Diallo and Severine Gibowski at the ANRS for pharmacovigilance support, and Jean-François Delfraissy (director of ANRS). We thank the study volunteers for allowing us into their homes and participating in this trial, and the KwaZulu-Natal Provincial and the National Department of Health of South Africa for their support of this study. We thank staff of the Africa Health Research Institute for the trial implementation and analysis of data, including those who did the fieldwork, provided clinical care, developed and maintained the database, entered the data, and verified data quality.

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