Universal Test and Treat and the HIV epidemic in rural South Africa; a community cluster randomized trial.


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Abstract

**Background:** Universal antiretroviral treatment (ART), as per World Health Organization 2015 recommendations, may reduce population HIV incidence. We investigated the impact of universal test and treat on HIV acquisition at population level in a high prevalence setting.

**Methods:** We carried out a cluster-randomized trial in 2x11 communities in rural South Africa. Randomisation was carried out with MapInfo version 11.0 within each prevalence stratum to derive an equal number of control and intervention communities per stratum.

We offered residents ≥16 years repeat rapid HIV testing during 6-monthly home-based visits and referred HIV-positive participants to trial clinics for ART regardless of CD4 cell count (intervention) or according to national guidelines (control). There was no blinding of the treatment allocation to either study participants or investigators. We used repeat dried blood spots (DBS) provided by participants at each round to estimate the primary outcome of HIV incidence using cluster-adjusted Poisson generalized estimated equations.

**Findings:** Between 9 March 2012 and 30 June 2016, we contacted 26,518 (93·3%) of 28,419 eligible individuals. Of 17,808 individuals with a first negative DBS test (67·2%), 14,223 (79·9%) had subsequent DBS tests of whom 503 seroconverted after 22,891 person-years (PY) follow-up. Estimated HIV incidence in intervention was 2·11 per 100 PY (95% CI 1·84-2·39) and 2·27 (2·00-2·54) in control arm, adjusted Hazard Ratio 1·01 (0·87-1·17), p=0·89. There was no difference in population ART coverage at conclusion of the trial, being 1,541/2,888 (53·6%) and 1,763/3,338 (52·9%) in intervention and control arms respectively.

We documented one case of suicidal attempt in a female following HIV seroconversion. 128 patients on ART experienced 189 life-threatening or Grade 4 clinical events; 69/1,652 (4·2%) in control and 59/1,367 (4·3%) in intervention arm (p=0·83)

**Interpretation:** Population ART coverage remained similar in both arms of the trial with no demonstrable impact on HIV incidence, most likely due to the poor linkage to care observed. Policy change to HIV universal test and treat without innovation to improve health access is unlikely to reduce HIV incidence.

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Research in context

Evidence before this study

The HPTN 052 trial demonstrated that antiretroviral therapy (ART) significantly reduces HIV transmission from the HIV-infected to the HIV-negative individual 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 fail to 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 1 Jan 2004 to 30 July 2017 using the following 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)). We identified two prospective cohort studies reporting an association between ART coverage and population HIV incidence from 2 378 abstracts. Tanser et al followed up a total of 16 667 adults who were HIV negative at baseline from 2004 to 2011 in the same sub-district as the ANRS 12249 TasP trial. This study showed that an HIV-uninfected individual living in a community with ART coverage of 30 to 40% was 38% less likely to acquire HIV than an individual living in a community where ART coverage was <10%. The other study by Kong et al in Rakai, Uganda from 1999 to 2013 showed that increased ART coverage in females was associated with lower community HIV incidence in males but no association between ART coverage in males and HIV incidence in females, attributable to lower ART coverage in males during this period.

Four cluster-randomised trials (including ours) are implemented in South Africa, Zambia, Botswana, Kenya and Uganda to investigate the impact 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 demonstrated no reduction in HIV incidence 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 significant improvements in linkage to care is unlikely to reduce HIV incidence.
Introduction

HIV incidence in South Africa remains high, with an estimated 380,000 adults and children newly infected in 2015\(^1\). Since HIV-1 plasma viral load (VL) is strongly associated with sexual transmission risk\(^2\), expanded use of antiretroviral treatment (ART) allowing to reach undetectable VL has been suggested key to HIV prevention while providing individual health benefits\(^3,4\). Ecological\(^5\) and cohort studies\(^6\) and a randomized trial conducted among heterosexual serodiscordant couples\(^7\) have demonstrated 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 when diagnosed HIV-positive\(^8\). However, the hypothesis that universal test and treat (UTT) will reduce HIV incidence has not been demonstrated in a trial at population level. The aim of the ANRS 12249 Treatment as Prevention (TasP) cluster-randomised trial was to investigate whether universal ART initiation offered to all HIV-positive individuals (vs. ART initiation according to national guidelines), identified through home-based HIV testing, reduces HIV incidence in a rural and hyper-endemic region of South Africa.

Methods

Study design and study population

The study design was a phased two-arm cluster-randomised trial. Trial protocol and procedures have previously been reported (https://www.ahri.org/tasp-study-protocol)\(^9,10\). We implemented the trial from 9 March 2012 to 30 June 2016 in Hlabisa sub-district, northeast KwaZulu-Natal (KZN) (Figures S1, p8 and S2, p9), where estimated HIV prevalence is 30\(^%\)\(^11\). Inclusion criteria were community residence (defined as spending ≥ 4 nights a week in the study area) and age ≥16 years. We note mobility of individuals in and out of the study area, with some community members only visiting their families at the weekend. The Biomedical Research Ethics Committee, University of KwaZulu-Natal, South Africa (BFC 104/11) and the Medicines Control Council of South Africa approved the trial. The trial was also registered on ClinicalTrials.gov: NCT01509508 and South African National Clinical Trials Register: DOH-27-0512-3974.

Sample size

We used the CEPAC mathematical model\(^12\) to simulate an intervention of bi-annual HIV screening of the adult population, comparing the impact of universal ART initiation irrespective of CD4 count (intervention) with national eligibility guidelines - CD4 cell counts of ≤350 cells/μL (control). Preliminary sample size calculations based on this model concluded that 34 clusters (2x17) of 1,000 eligible residents each followed-up for two years could detect a 30% reduction in cumulative HIV incidence\(^9\). We subsequently amended the trial design to account for a phased introduction of clusters over a three-year time period; sample size calculations explicitly accounting for this phased cluster follow-up demonstrated that 22 clusters (2x11, with an estimated 800 HIV uninfected individuals per cluster), followed 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 detailed STDSIM\(^13\) modelling approach using the following parameters: 90% of HIV test offer to those registered, 80% test uptake amongst those offered, 70% linkage-to-care upon diagnosis among those accepting the test, baseline HIV prevalence of 24% and a cross-arm contamination of
10%. The sample size calculation allowed for 20% loss to follow-up and assumed a coefficient of variation of 0.25 to account 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 (Figure S2, p9). 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 among those HIV-negative at baseline to be 15040 per arm. At an annual incidence of 2·25% per year, we estimated 338 seroconversions in the 11 control clusters by the end of the study period. The corresponding figure for the 11 intervention clusters, with an incidence of 1·485% per year, was estimated to be 223 seroconversions.

**Randomization**
The clusters were composed of aggregated local areas (neighbourhoods). To minimise the degree of between-cluster variation, we stratified the clusters on predicted antenatal HIV prevalence (six strata), extrapolated from HIV surveillance data from the neighbouring Africa Health Research Institute’s HIV surveillance site. The study statistician carried out randomisation within each stratum to derive an equal number of control and intervention communities per HIV prevalence stratum. We used MapInfo version 11.0 to generate the random numbers and perform the randomisation procedure. The nature of the trial meant it was not possible to blind participants and investigators to the intervention.

**Study procedures**

We used global positioning system coordinates to identify households in the trial area and assigned a unique identification number to each of them. At each six-monthly home-based survey round, HIV counsellors obtained verbal consent to proceed from the head of the household and enumerated all eligible adult members. These adult members constitute the population cohort. Eligible individuals providing written informed consent in isiZulu responded to a socio-demographic and sexual behaviour questionnaire and gave a finger prick sample collected as a dried blood spot (DBS) which we used to estimate population HIV prevalence and incidence through 3rd generation ELISA.

HIV counsellors offered individuals point-of-care rapid HIV counselling and testing using local Department of Health (DoH) approved test kits. 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. We informed those in the intervention arm that they would be offered ART immediately, regardless of their CD4 count to prevent transmission to their sexual partners and that it was possible that the individual health of those with high CD4 count could also be improved, while those in the control arm were informed that ART would be provided according to national guidelines.

Self-identified HIV-positive participants already on ART could opt to continue with their current DoH 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 re-contact HIV-positive participants in both trial arms who were not in care having failed to attend the trial clinic within three months of referral. They were re-contacted by either phone, home visit or both.

Trial nurses clinically evaluated consenting HIV-positive patients at their cluster trial clinic, including the performance of a point-of-care CD4 measurement (Alere Pima CD4 test, Alere, Waltham, MA, USA). The only trial-specific randomised intervention was ART eligibility: in intervention clusters HIV-positive participants were offered ART regardless of CD4 count,
whereas in control clusters, ART was provided according to national guidelines (initially CD4 count \( \leq 350/\mu L \), then <500/\mu L from January 2015\(^{15}\)). ART was to be initiated within 2 weeks of baseline visit, or sooner if severely immunocompromised. First-line ART was fixed-dose combination tenofovir/emtricitabine/efavirenz (Atripla®) as per national guidelines, other than where clinically contra-indicated. Genotypic resistance testing informed switch to second-line ART. Trial nurses saw patients receiving ART monthly for ART prescription but took blood samples for toxicity monitoring (full blood count, liver function tests, urea, electrolytes and creatinine) and HIV VL measurements at the first visit, three and six months post-ART initiation, and six-monthly thereafter. We allowed unscheduled clinic visits for patients with clinical complaints arising before their protocol visit. In control clusters, nurses invited patients not yet eligible for ART to return within 4-6 months for pre-ART care, repeat clinical assessment, and CD4 count measurement\(^{8,14}\). Investigators defined loss-to-follow up as being >3 months late for next clinic appointment. Trial clinics also provided care for common co-existing chronic medical conditions, including diabetes and hypertension.

**Study outcomes**

The primary outcome was HIV incidence, defined by seroconversion between repeat (6-monthly) DBS samples collected within the population cohort. All secondary outcomes and plan for dissemination are listed in tables S1a and S1b, p5-6. We report some of them in this manuscript including: 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 among those presenting as ART-naïve, retention in care, virological suppression estimated among the people ascertained as HIV-positive. Investigators estimated population ART coverage (proportion being on ART among all HIV-infected) and the 90-90-90 HIV care cascade for all HIV-positive participants at the population level (Table S2, p6 for detailed definitions).

**Statistical analysis**

We summarised continuous variables with median and interquartile range (IQR) and categorical variables with frequencies and percentages.

We calculated HIV incidence among participants with an initially HIV-negative sample and at least one further sample, and stratified by arm. 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 arm. We used an intention-to-treat Poisson generalized estimating equation (GEE) taking cluster effect into account with an exchangeable working correlation matrix to estimate the marginal effect of the intervention on HIV incidence\(^{16}\). To improve efficiency of the estimated effect of the intervention, we complemented this main analysis with an augmented GEE. To do so, we performed an outcome model including as cluster-level covariates: age at inclusion (proportion of participants <30 and \( \geq 60 \) years), sex (proportion of females), 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 amongst 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 known to be alive at the date of their last clinic visit date. We calculated mortality rate by dividing the number of deaths
by the person-years of follow-up, stratified by arm. All analyses were performed with SAS® version 9.4 (SAS Institute, Cary, NC, USA), R package CRTgeeDR® (The R Foundation, 1020 Vienna, Austria) was used to perform the augmented GEE.

Role of the funding source

Representatives of the sponsor were part of the study team and were involved in the design of the study, data interpretation and writing of the manuscript. Pharmaceutical companies providing study drugs had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. No listed author received any payments to write this article from a pharmaceutical company or any other agency. 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

Trial registration and enrolment of participants

28 419 individuals (13 381 intervention, 15 038 control) were eligible for inclusion in the trial (Figure 1); cluster size ranged between 324 and 2872 residents aged 16 years and above. Median age was 30.2 years (IQR 21.4-49.4), 63% were women (Table 1). Overall, 26 518 (93%) of eligible individuals were contacted at least once, of whom 23 476 participants (89%) had their HIV status ever ascertained (i.e. had a HIV rapid test or self-reported being HIV-positive) by a trial fieldworker (Figure S3, p10).

Contacted individuals were more likely to be female and older compared to non-contacted individuals, and similar between arms (Table S3, p11).

8 960 of the 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 (Table S4, p11).

Population HIV incidence

We excluded a total of 8 710 (33%) of those contacted from the incidence calculation either because their first DBS sample was positive (7 775) or because no valid result was obtained from available sample (935). Of the 17 808 (67.2%) individuals with a first sample being negative, who were thus eligible for inclusion for the incidence cohort, (Figure 1) 79.8% (n=14 223: 6 756 intervention, 7 467 control) had a second sample test and contributed data for the incidence analysis. Those available for the incidence analysis were significantly older (median 29.9 years vs. 23.5 years) and less likely to be male (35.6% vs. 52.6%) than the remaining 20.1% of HIV-negative individuals with only one sample, with no difference between trial arms (Table S5a, p12). They also differed from those HIV-positive at baseline (Table S6, p13). 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). Overall, the incidence of 2.27 per 100 person-years in the control arm (Table 2) was remarkably similar to the rate of 2.25 per 100-years assumed in our sample size calculations. The crude hazard ratio (intervention vs. control) was 0.95 (95% CI 0.75-1.20; p=0.68) and adjusted hazard ratio was 1.01 (95% CI 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 (Tables S7a, p13 and S8, p14).
Identification of HIV-positive individuals and linkage to care

The proportion of registered individuals contacted per round was slightly lower in the intervention arm than in the control arm (72.7% vs. 73.9%, p<0.0001). Amongst those contacted, HIV status ascertainment was also slightly lower in the intervention arm than in the control arm (79.5% vs. 81.1%, p<0.0001) (Table 3). One female participant who tested HIV-positive suffered an acute adjustment reaction with suicidal attempt. Cumulatively in all survey rounds, 7615 adults were ever ascertained HIV-positive and referred to trial clinics in their cluster; 1 972/3 247 (60.7%) of those already in follow-up in DoH clinics switched their care to the trial clinics, while 1 047/4 368 (24.0%) who were never previously in care linked to the trial clinics 1 072 of the 7 615 HIV positive were newly diagnosed during the trial (Figure S3, p10). We estimated entry into care within six months among individuals not previously in care to be 29.7%, similar between arms (p=0.49) and much lower than expected in our model assumptions (Table 3). Amongst those linked to trial clinics, median time between referral and first trial clinic visit was 2.7 weeks (IQR 0.9-21.7) (Table S9, p15).

**ART uptake and clinical outcomes in trial clinics**

HIV counsellors referred all 7 615 HIV-positive individuals identified to the trial clinics. Of the 3019 who ever linked to trial clinics, 1 492 (49.4%) were ART naïve at the first visit. 635/704 (90.2%) in intervention and 525/788 (66.6%) in control arms initiated ART. At ART initiation, median CD4 was 401 cells per µL (IQR 265-572) and median VL 4.4 log copies per mL (IQR 3.8-5.1) in intervention arm and 320 cells per µL (IQR 212-442) and 4.5 log copies per mL (3.7-5.1) in control arm (Table S9, p15). Of the 698 participants who had been on ART for 12 months, 628 had documented viral load, of whom 611 (97.3%) achieved viral suppression (VL <400 copies per mL), similar between arms. 1 478 ART-experienced participants had been on ART for a median of 3-80 years (IQR 1-75-5-99) at their first visit (639 in intervention and 839 in control), with no difference between arms. The ART status of the remaining 49 individuals was unknown at the first clinic visit (Table S9, p15). Retention in care 12 months after the first clinic visit was 81.6% (1 004/1 230) in intervention arm and 75.4% (1 027/1 495) in the control arm. Among all HIV-positive individuals seen in trial clinics, crude mortality rates were 1.28 per 100 PY (95% CI 0.84-1.72) in intervention arm (N=33) and 1.86 per 100 PY (95% CI 1.38-2.34) in control arm (N=58), adjusted hazard ratio intervention vs. control of 0.69 (95% CI: 0.42-1.15, p=0.15) (Table S10, p16). 128 patients experienced 189 life-threatening or Grade 4 clinical events; 69/1 652 (4.2%) in control and 59/1 367 (4.3%) in intervention arm (p=0.83) (Table S11, p16).

**ART coverage and HIV care cascade at population level**

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 intervention arm and 33.7% in control arm, below the initial ART coverage of 40% assumed in STDSIM modelling (Table 3). ART coverage rose to 53.4 (+23.8) in the intervention arm and 52.8% (+19.1) in the control arm by 1 January 2016, with the difference between arms not statistically significant (p=0.69) (Table 4). As of 1 January 2016, we estimated population 90-90-90 cascade for both arms 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; similar in intervention and control arms (Table S12, p16).

**Sexual risk activity**

In the last survey round, among 6 968 participants who reported a sexual partner in the previous six months, condom use at last sexual intercourse was 44·2%, similar between arms. The frequencies of reporting having a sexual partner outside the TasP trial area during the previous six months were 41·6% and 37·1% in the intervention and control arms, respectively (p <0·001) (Table S13, p16).

**Discussion**

This is the first of four cluster-randomised trials investigating the impact of ART on HIV incidence17-20. In our trial, HIV incidence was high and we found no significant population-level impact of universal ART (vs. national ART initiation guidelines) on HIV incidence. HIV testing uptake was high and repeat testing acceptable11. However, linkage-to-HIV care was both slow and poor, leading to a lower than anticipated increase of population ART coverage (from 31·7% to 53·2%), with no significant difference in ART coverage between arms at trial completion. In this way, the conditions required for a policy of test and treat to translate into a reduction in HIV incidence were not met. Viral suppression among participants on ART was high (>90%) with few serious adverse events. The overall HIV care cascade did not differ by trial arm and fell considerably short of the UNAIDS 90-90-90 targets for 202021, contrary to what has been recently reported in Eastern Africa22. Those in the intervention arm showed a trend towards a mortality advantage even after a relatively short period of follow-up of one year on average.

The most obvious explanation for a lack of difference in HIV incidence between the two trial arms relates to the low linkage-to-care, particularly disappointingly so in the intervention arm. The rate of linkage-to-care was similar in both arms, with only 30% of individuals registering at the trial clinic within six months of home HIV diagnosis, considerably lower than the expected 70%. This was despite HIV-positive individuals in the intervention arm being informed they would be offered ART regardless of their CD4 count and those in the control arm being informed ART will be offered only if eligible according to national guidelines. The consequence of this poor linkage was that even though 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 arms. The inability to create experimental separation between the two arms of the trial would have contributed to the null finding seen with HIV incidence.

The poor linkage-to-HIV care despite the introduction of UTT is comparable to South African national estimates23, but lower than reported in another trial in Uganda and South Africa24, 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 HIV-positive and increasing distance between home and the trial clinic25. Trial clinics only catered for HIV-positive people, who may thus have had increased concerns relating to stigma and unintended HIV status disclosure26, although we had hypothesized that mobile clinics close to participants homes would encourage attendance. Home-based ART initiation could mitigate against some of these challenges. Indeed, it was shown to triple linkage to care in Malawi, although follow-up was too short to evaluate long-term ART adherence and
retention on treatment\textsuperscript{27}. More studies on the effectiveness and safety of home ART initiation are urgently required.

Other factors may have also contributed to the null finding in secondary ways, especially population mobility, which is high in our setting\textsuperscript{28}, and could have contributed to low linkage-to-care and fuelled a contamination effect. We previously showed\textsuperscript{29} that mobility dilutes the HIV care cascade at population level due to differences between in- and out-migrations. The impact of a UTT approach could be improved if implemented over a larger geographical area and/or access to care was more actively facilitated and recorded. Mobility was also associated with sexual mixing patterns. We assumed when designing the trial\textsuperscript{30} that those in the trial area would preferentially have sexual contacts with people in the same locality. We have indeed reported previously that HIV prevalence in the local community is the strongest determinant of HIV acquisition\textsuperscript{6}. However, in this trial, some 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, this phenomenon could also have played a role in diluting the effect size between study arms. Phylogenetic work is ongoing to determine whether external sexual partnerships could have also led to a significant 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\textsuperscript{31}, there was extraordinary variation in HIV prevalence, which ranged from 17\% in deep rural areas to 39\% in communities close to the national highway (Table S6). A more focused approach of interventions targeted to areas of high transmission and people most at-risk may have a greater impact; such an approach is supported by modelling, using the Kenyan epidemic as a case study\textsuperscript{32}.

Apart from the lack of impact 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 count\textsuperscript{33} for individual benefits\textsuperscript{3, 4} and transmission reduction in serodiscordant couples\textsuperscript{7}, concerns were expressed regarding ART adherence in asymptomatic individuals. We observed high viral suppression at 12 months, also reported in the SEARCH trial conducted in Uganda and Kenya\textsuperscript{22} and a weak evidence of a 30\% reduction in mortality amongst trial clinic attendees over a relatively short period of time. We also found a higher retention rate in the intervention than control arm, with participants on ART more likely to be retained in care than those pre-ART\textsuperscript{34}. These are strong arguments to roll out UTT without any restriction.

The TasP trial has a number of limitations. Our home-based HIV testing strategy failed to 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 arm than in the intervention arm. Linkage-to-care counsellors were not present from trial start, and we only intervened after a three-month delay in linkage to care. The South African ART guidelines evolved during the study from a 350 CD4 threshold to 500 cells/µL\textsuperscript{15}, which could have diluted the anticipated effect size, thus reducing the statistical power to observe a difference between arms. Older females were more likely to have contributed to the incidence analysis, with no difference between arms. Because incidence is lower in older individuals, this may have contributed to a lower overall incidence, but would not have biased the estimate of the difference in incidence between arms. We further assessed sensitivity to violation of missing
data assumptions and robustness of the estimates by re-analysing the data under two assumptions; all missing second DBS were considered as positive or negative. We observed that neither the point estimate nor the significance changed. We conclude that although missing completely at random is a strong assumption, it is not invalidated by the sensitivity analysis, and the primary analysis can be trusted. Finally, our estimates of population ART coverage and of the HIV care cascade are lower bounds 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 arms 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 arms but not differentially by arm, 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. Whilst our study demonstrated 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 our setting. Comprehensive intervention packages that increase ART uptake and retention in care are urgently required in order to achieve the 90-90-90 targets so as to maximise the individual and societal benefits of ART.

Authors and contributions

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

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Service des Maladies Infectieuses, HIV Unit, Hôpitaux Universitaires de Genève, Geneva, Switzerland (Alexandra Calmy)
Centre Population et Développement UMR 196, Université Paris Descartes, Institut de Recherche pour le Développement, Paris, France (Joseph Larmarange, Maxime Inghels, Hassimiou Diallo)
AP-HP, Virology, Hôpital Pitié-Salpêtrière, INSERM-Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1136, Paris, France (Vincent Calvez, Anne Derache, Anne-Geneviève Marcelin)
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Department of Global Health and Infection, Brighton and Sussex Medical School, University of Sussex, Brighton, United Kingdom (Collins Iwuji)
Academic Unit of Primary Care and Population Sciences, and Department of Social Statistics and Demography (Nuala McGrath)
University of KwaZulu-Natal, Nelson R Mandela School of Medicine, College of Health Sciences, Durban, South Africa (Tulio de Oliveira)
Academic Unit of Human Development and Health, University of Southampton, UK (Colin Newell)
Department of Public Health, Erasmus MC, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands (Jan Hontelez)
Sponsor representatives (Brigitte Bazin, Claire Rekacewicz)

Declaration of interests
CI received honoraria for consulting services rendered to Gilead Sciences. All other authors declare that they have no conflicts of interest.

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References


Table 1. Characteristics* at inclusion of the population cohort (n=28,247) by trial arm. ANRS 12249 TasP trial (2012-2016).

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=13,381)</th>
<th>Control (n=15,038)</th>
<th>Total (n=28,419)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>8,446 (63.1)</td>
<td>9,399 (62.5)</td>
<td>17,845 (62.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Men</td>
<td>4,935 (36.9)</td>
<td>5,639 (37.5)</td>
<td>10,574 (37.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at inclusion in years (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-29</td>
<td>5,715 (42.7)</td>
<td>6,366 (42.3)</td>
<td>12,081 (42.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>30-59</td>
<td>4,207 (31.4)</td>
<td>4,714 (31.3)</td>
<td>8,921 (31.4)</td>
<td></td>
</tr>
<tr>
<td>60 and more</td>
<td>1,596 (11.9)</td>
<td>1,766 (11.7)</td>
<td>3,362 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Year of birth unknown</td>
<td>1,863 (13.9)</td>
<td>2,192 (14.6)</td>
<td>4,055 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Median age at inclusion (IQR)</td>
<td>30.2 (21.5-49.5)</td>
<td>30.3 (21.3-49.2)</td>
<td>30.2 (21.4-49.4)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Highest education level (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Primary or less</td>
<td>4,517 (33.8)</td>
<td>4,988 (33.2)</td>
<td>9,505 (33.4)</td>
<td></td>
</tr>
<tr>
<td>Some secondary</td>
<td>4,323 (32.3)</td>
<td>5,232 (34.8)</td>
<td>9,555 (33.6)</td>
<td></td>
</tr>
<tr>
<td>At least completed secondary</td>
<td>3,245 (24.3)</td>
<td>3,341 (22.2)</td>
<td>6,586 (23.2)</td>
<td></td>
</tr>
<tr>
<td>Never documented</td>
<td>1,296 (9.7)</td>
<td>1,477 (9.8)</td>
<td>2,773 (9.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never been married</td>
<td>8,730 (65.2)</td>
<td>9,884 (65.7)</td>
<td>18,614 (65.5)</td>
<td></td>
</tr>
<tr>
<td>Engaged</td>
<td>530 (4.0)</td>
<td>787 (5.2)</td>
<td>1,317 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>2,166 (16.2)</td>
<td>2,122 (14.1)</td>
<td>4,288 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Divorced/Separated/Windowed</td>
<td>667 (5.0)</td>
<td>772 (5.1)</td>
<td>1,439 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Never documented</td>
<td>1,288 (9.6)</td>
<td>1,473 (9.8)</td>
<td>2,761 (9.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Professional status (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Employed</td>
<td>1,192 (8.9)</td>
<td>1,364 (9.1)</td>
<td>2,556 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>2,564 (19.2)</td>
<td>2,916 (19.4)</td>
<td>5,480 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Looking for work</td>
<td>2,886 (21.6)</td>
<td>3,096 (20.6)</td>
<td>5,982 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Other inactive</td>
<td>5,413 (40.5)</td>
<td>6,146 (40.9)</td>
<td>11,559 (40.7)</td>
<td></td>
</tr>
<tr>
<td>Never documented</td>
<td>1,326 (9.9)</td>
<td>1,516 (10.1)</td>
<td>2,842 (10.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Age was computed at inclusion in the population-cohort. All other indicators were estimated from the first known information provided in an individual questionnaire.
** If day and/or month of birth were missing, the day and/or month of birth were randomly assigned.
IQR inter-quartile range
Table 2. Number of new HIV-positive tests and number of person-years among eligible participants, per trial arm at inclusion. ANRS 12249 TasP trial (2012-2016).

<table>
<thead>
<tr>
<th></th>
<th>Number of HIV-positive DBS tests</th>
<th>Person-years</th>
<th>Incidence for 100 person-years*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>274</td>
<td>12 053</td>
<td>2·27</td>
<td>2·00-2·54</td>
</tr>
<tr>
<td>Intervention</td>
<td>229</td>
<td>10 838</td>
<td>2·11</td>
<td>1·84-2·39</td>
</tr>
<tr>
<td>Clusters opened in 2012</td>
<td>106</td>
<td>5 723</td>
<td>1·85</td>
<td>1·50-2·20</td>
</tr>
<tr>
<td>Clusters opened in 2013</td>
<td>222</td>
<td>9 097</td>
<td>2·44</td>
<td>2·12-2·76</td>
</tr>
<tr>
<td>Clusters opened in 2014</td>
<td>175</td>
<td>8 071</td>
<td>2·17</td>
<td>1·85-2·49</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>503</strong></td>
<td><strong>22 891</strong></td>
<td><strong>2·20</strong></td>
<td><strong>2·01-2·39</strong></td>
</tr>
</tbody>
</table>

* not taking into account cluster effect
CI confidence interval
DBS Dried Blood Spot

Table 3. STDSIM modelling assumptions and ANRS 12249 TasP trial observations (2012-2016).

<table>
<thead>
<tr>
<th>STDSIM modelling</th>
<th>TasP trial observations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td><strong>Assumptions</strong></td>
</tr>
<tr>
<td><strong>Situation at the beginning of the trial</strong></td>
<td></td>
</tr>
<tr>
<td>Proportion of all HIV+ on ART in end 2011</td>
<td>40%</td>
</tr>
<tr>
<td>HIV prevalence in end-2011 (16 years +)</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Uptake rates</strong></td>
<td></td>
</tr>
<tr>
<td>HIV test offer among those registered</td>
<td>90%</td>
</tr>
<tr>
<td>Test acceptance among those offered</td>
<td>80%</td>
</tr>
<tr>
<td>Linkage to care upon diagnosis among those accepting the test</td>
<td>70%</td>
</tr>
</tbody>
</table>

Parameter settings and characteristics of HIV epidemic as modelled by the STDSIM model. Model was quantified to represent the HIV epidemic in rural KwaZulu-Natal, South Africa, using demographic, behavioural, and epidemiological data from the Africa Centre. Model and quantification described elsewhere.

Proportion of individuals contacted and whose HIV status was ascertained was computed per home-based survey round, i.e., 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
<table>
<thead>
<tr>
<th>01/07/2012*</th>
<th>01/01/2013†</th>
<th>01/07/2013</th>
<th>01/01/2014</th>
<th>01/07/2014‡</th>
<th>01/01/2015</th>
<th>01/07/2015</th>
<th>01/01/2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 clusters opened in 2012</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention arm</td>
<td>31.7% (126/397)§</td>
<td>43.1% (176/408)</td>
<td>43.7% (185/423)</td>
<td>45.5% (192/422)</td>
<td>47.5% (205/432)</td>
<td>48.4% (209/432)</td>
<td>54.2% (202/373)</td>
</tr>
<tr>
<td>Control arm</td>
<td>30.7% (99/323)§</td>
<td>43.4% (122/281)</td>
<td>46.5% (139/299)</td>
<td>48.1% (148/308)</td>
<td>45.6% (150/320)</td>
<td>47.0% (154/326)</td>
<td>55.4% (160/289)</td>
</tr>
<tr>
<td>Difference vs. control</td>
<td>+1.1% (p=0.8162) (p=1-00)</td>
<td>-0.3% (p=0.51)</td>
<td>-2.8% (p=0.54)</td>
<td>-2.6% (p=0.66)</td>
<td>+1.9% (p=0.75)</td>
<td>+1.4% (p=0.82)</td>
<td>-1.2% (p=0.99)</td>
</tr>
<tr>
<td><strong>6 clusters opened in 2013</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention arm</td>
<td>29.8% (230/772)§</td>
<td>40.5% (346/854)</td>
<td>46.9% (477/1,016)</td>
<td>47.1% (505/1,073)</td>
<td>49.9% (553/1,108)</td>
<td>57.0% (576/1,011)</td>
<td>59.3% (589/993)</td>
</tr>
<tr>
<td>Control arm</td>
<td>34.7% (429/1,237)§</td>
<td>37.4% (400/1,070)</td>
<td>41.3% (620/1,500)</td>
<td>42.9% (655/1,527)</td>
<td>44.1% (703/1,593)</td>
<td>51.0% (761/1,492)</td>
<td>54.3%</td>
</tr>
<tr>
<td>Difference vs. control</td>
<td>-4.9% (p=0.03)</td>
<td>+3.1% (p=0.18)</td>
<td>+5.6% (p=0.01)</td>
<td>+4.2% (p&lt;0.04)</td>
<td>+5.8% (p&lt;0.001)</td>
<td>+6.0% (p=0.01)</td>
<td>+6.0%</td>
</tr>
<tr>
<td><strong>12 clusters opened in 2014</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention arm</td>
<td>28.9% (439/1,517)§</td>
<td>37.1% (589/1,588)</td>
<td>44.7% (691/1,547)</td>
<td>48.4% (732/1,511)</td>
<td>50.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control arm</td>
<td>33.5% (528/1,576)§</td>
<td>36.2% (633/1,659)</td>
<td>45.5% (783/1,722)</td>
<td>45.5% (853/1,677)</td>
<td>45.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference vs. control</td>
<td>-4.6% (p&lt;0.01)</td>
<td>-1.1% (p=0.56)</td>
<td>-0.8% (p=0.67)</td>
<td>-0.8% (p=0.18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All clusters combined</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention arm</td>
<td>31.7% (126/397)</td>
<td>34.4% (406/1,180)</td>
<td>41.6% (531/1,277)</td>
<td>46.5% (669/1,438)</td>
<td>38.0% (1,149/3,022)</td>
<td>43.2% (1,351/3,128)</td>
<td>50.4% (1,469/2,931)</td>
</tr>
<tr>
<td>Control arm</td>
<td>30.7% (99/323)</td>
<td>36.3% (551/1,518)</td>
<td>39.4% (539/1,369)</td>
<td>42.5% (768/1,808)</td>
<td>38.8% (1,333/3,432)</td>
<td>41.6% (1,490/3,580)</td>
<td>48.6% (1,704/3,503)</td>
</tr>
<tr>
<td>Difference vs. control</td>
<td>+1.1% (p=0.81)</td>
<td>-1.9% (p=0.33)</td>
<td>+2.2% (p=0.26)</td>
<td>+4.0% (p=0.02)</td>
<td>-0.8% (p=0.52)</td>
<td>+1.6% (p=0.20)</td>
<td>+1.5% (p=0.25)</td>
</tr>
</tbody>
</table>

§: estimated at the beginning of the trial. † inclusion of 6 additional clusters in January 2013. ‡ inclusion of 12 additional clusters; survey rounds were biannual from June 2014 until trial end. Please note that, as of 1st July 2012, first round was not finished yet in the four first clusters.

* Start first 4 clusters, intervention rounds: March – October 2012; November 2012 – April 2013; May – August 2013; biannually from June 2014 onwards.
**Figure 1.** Flow diagram of individuals contacted aged 16 years or older selected for the incidence analysis, by trial arm. ANRS 12249 TasP trial (2012-2016).