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Effect of Universal Testing and Treatment on HIV Incidence — HPTN 071 (PopART)

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ABSTRACT

BACKGROUND

A universal testing and treatment strategy is a potential approach to reduce the incidence of human immunodeficiency virus (HIV) infection, yet previous trial results are inconsistent.

METHODS

In the HPTN 071 (PopART) community-randomized trial conducted from 2013 through 2018, we randomly assigned 21 communities in Zambia and South Africa (total population, approximately 1 million) to group A (combination prevention intervention with universal antiretroviral therapy [ART]), group B (the prevention intervention with ART provided according to local guidelines [universal since 2016]), or group C (standard care). The prevention intervention included home-based HIV testing delivered by community workers, who also supported linkage to HIV care and ART adherence. The primary outcome, HIV incidence between months 12 and 36, was measured in a population cohort of approximately 2000 randomly sampled adults (18 to 44 years of age) per community. Viral suppression (<400 copies of HIV RNA per milliliter) was assessed in all HIV-positive participants at 24 months.

RESULTS

The population cohort included 48,301 participants. Baseline HIV prevalence was 21% or 22% in each group. Between months 12 and 36, a total of 553 new HIV infections were observed during 39,702 person-years (1.4 per 100 person-years; women, 1.7; men, 0.8). The adjusted rate ratio for group A as compared with group C was 0.93 (95% confidence interval [CI], 0.74 to 1.18; P=0.51) and for group B as compared with group C was 0.70 (95% CI, 0.55 to 0.88; P=0.006). The percentage of HIV-positive participants with viral suppression at 24 months was 71.9% in group A, 67.5% in group B, and 60.2% in group C. The estimated percentage of HIV-positive adults in the community who were receiving ART at 36 months was 81% in group A and 80% in group B.

CONCLUSIONS

A combination prevention intervention with ART provided according to local guidelines resulted in a 30% lower incidence of HIV infection than standard care. The lack of effect with universal ART was unanticipated and not consistent with the data on viral suppression. In this trial setting, universal testing and treatment reduced the population-level incidence of HIV infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; HPTN 071 [PopArt] ClinicalTrials.gov number, NCT01900977.)

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In 2017, approximately 37 million people were living with human immunodeficiency virus (HIV) infection worldwide, with 1.8 million new infections that year.[1] HIV incidence is declining worldwide but is unlikely to reach the Joint United Nations Program on HIV/AIDS (UNAIDS) target of less than 500,000 new infections per year by 2020.[2] Steep reductions in incidence are needed to curb the HIV–acquired immunodeficiency syndrome (AIDS) epidemic.

A universal testing and treatment strategy has been proposed as an important component of HIV combination prevention programs.[3,4] The HIV Prevention Trials Network (HPTN) 052 trial showed that early initiation of antiretroviral therapy (ART) dramatically reduced HIV transmission among couples,[5,6] and the Partners of People on ART — A New Evaluation of the Risks (PARTNER) study showed that viral suppression (<200 copies per milliliter) prevented sexual transmission of HIV.[7,8] Mathematical modeling predicted that HIV incidence would fall steeply if HIV testing were provided throughout a population and ART initiated immediately after diagnosis.[9-11] Early ART also confers individual health benefits.[12,13] In 2014, UNAIDS proposed that by 2020, 90% of HIV-positive persons should know their status, 90% of those persons (i.e., 81% of HIV-positive persons) should be receiving ART, and 90% of those receiving ART (i.e., 73% of HIV-positive persons) should have viral suppression; these are the UNAIDS 90-90-90 targets.[14] In 2015, the World Health Organization updated its guidelines to recommend immediate ART for all HIV-positive persons.[15]

Although there is compelling evidence supporting the concept of universal testing and treatment for HIV prevention, it was not clear whether this could be implemented effectively at a population level and could affect HIV incidence. Four community-randomized trials in sub-Saharan Africa addressed these questions: two (Treatment as Prevention [TasP] and Sustainable East Africa Research in Community Health [SEARCH]) showed no effect on HIV incidence; a third (Ya Tsie) showed a 30% lower incidence of HIV infection in the intervention group than in the standard-care group, but the difference was not significant.[16-18] Here we report the primary results of the fourth trial, HPTN 071 (PopART). We also describe the uptake of the combination prevention intervention used in the trial and its effect on viral suppression.

Methods

Trial Design

The trial was designed by members of the HPTN 071 (PopART) Study Team with input from the sponsor (the National Institute of Allergy and Infectious Diseases), other funders, and government and nongovernmental partners in Zambia and South Africa, listed in the acknowledgments at the end of the article. The data were collected by staff of Zambart and the Desmond Tutu Tuberculosis Center in collaboration with the London School of Hygiene and Tropical Medicine (LSHTM) and the HPTN Statistical and Data Management Center. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The trial design has been described previously[19] and is summarized below.

Trial Population

The trial was conducted from 2013 through 2018, in 21 urban or periurban communities in Zambia and Western Cape Province, South Africa (total population, approximately 1 million; mean, approximately 50,000 per community). Each community was the catchment population of a government clinic. Communities were grouped in seven triplets matched on the basis of geographic location and estimated HIV prevalence. Communities in each triplet were randomly assigned to three trial groups in simultaneous public ceremonies. Restricted randomization was used to ensure balance across the trial groups with respect to population size, baseline ART coverage (the percentage of HIV-positive persons who were receiving ART), and HIV prevalence.[19]

Randomization and locations of the trial communities are shown in Figure S1 in the Supplementary Appendix, available at NEJM.org. Group A communities received a combination prevention intervention (described below) with universal ART. Group B communities received a combination prevention intervention with ART provided according to local guidelines. Group C communities did not receive a combination prevention intervention but received standard care

at government clinics, including HIV testing and ART offered according to local guidelines.

INTERVENTION

The combination prevention intervention (Fig. S2 in the Supplementary Appendix) was delivered to group A and B communities. Specially trained community health workers (community HIV-care providers) delivered services at annual household visits (see the Supplementary Appendix). The community health workers worked in pairs, with each pair responsible for approximately 500 households. Data that were collected by the community health workers were used primarily to support service delivery but also to evaluate intervention coverage.

At each visit, the community health workers offered HIV counseling and rapid testing, and they provided support for linkage to care and ART adherence for HIV-positive clients. They referred uncircumcised HIV-negative men for voluntary medical male circumcision and referred HIV-positive pregnant women for antenatal care, including prevention of mother-to-child HIV transmission. The community health workers also screened clients for symptoms of tuberculosis and sexually transmitted infections, with referral for diagnosis and treatment, and promoted and provided condoms.

In all 21 communities, HIV care and ART were provided at local government clinics. In group A, these clinics offered ART irrespective of CD4 cell count throughout the trial, with written consent for patients initiating ART outside local guidelines until universal ART became standard. In groups B and C, the clinics provided ART initially at a CD4 threshold of 350 cells per microliter, which increased to 500 cells per microliter in 2014. Universal ART was offered from April 2016 onward (in Zambia) and October 2016 onward (in South Africa) (Fig. S3 in the Supplementary Appendix).

OUTCOME EVALUATION

The effect of the intervention on population-level HIV incidence was measured in a population cohort (enrolled from December 2013 to March 2015) that included one randomly selected adult 18 to 44 years of age from a random sample of households in each community (Fig. S4 in the Supplementary Appendix). Participants were surveyed at baseline and after 12, 24, and 36 months. Because the original enrollment target (2500 adults per community) was not reached at baseline, additional participants were enrolled at 12 months and in groups A and C only at 24 months, excluding households sampled previously.

At each visit, participants were interviewed by a field research assistant (separate from the community health workers) using a structured questionnaire that included the collection of demographic, socioeconomic, and behavioral data as well as data related to HIV prevention, diagnosis, and treatment. After the interview, blood was collected by a research nurse, who also offered HIV rapid testing to all participants.

The predefined primary outcome was HIV incidence between 12 and 36 months, comparing group A with group C and comparing group B with group C. This approach provided 1 year to fully establish the trial intervention before measurement of trial outcomes. Because the group A and group B interventions were equivalent during most of the primary analysis period, we also report a post hoc analysis of groups A and B combined as compared with group C. Other outcomes that are reported here include viral suppression (<400 copies of HIV RNA per milliliter) and the estimated coverage of HIV testing and ART on the basis of data from groups A and B that were collected by the community health workers.

LABORATORY METHODS

Laboratory-based HIV testing was performed for all participants at all visits. Central laboratories in South Africa and Zambia performed a single fourth-generation HIV test. The HPTN Laboratory Center (Baltimore) performed additional testing to determine HIV status (see the Supplementary Appendix). If seroconversion was confirmed, testing was performed to determine whether the participant had acute infection at the previous visit. HIV viral-load testing was performed at the HPTN Laboratory Center for selected samples: all HIV-positive participants at 24 months and a random subgroup of approximately 75 HIV-positive participants per community at 0, 12, and 36 months. HIV viral-load testing was performed with the RealTime HIV-1 assay (Abbott Molecular), with a level of less than 400 copies of HIV RNA per milliliter as the threshold of quantification.

ETHICAL CONSIDERATIONS

All participants in the population cohort provided written informed consent before enrollment. Community members who were visited by the community health workers provided verbal consent for participation in the intervention and data collection. In group A, clinic patients provided written informed consent when ART was initiated outside of prevailing local guidelines (from 2013 to 2016). Ethical approval for the trial was granted by ethics committees at the LSHTM, University of Zambia, and Stellenbosch University.

STATISTICAL ANALYSIS

Sample-size calculations were informed by initial projections of intervention effect based on mathematical modeling,[19,20] which suggested that HIV incidence might be lower by up to 60% in group A and up to 25% in group B than in group C. Under the assumption of an HIV incidence in group C of 1.0 to 1.5 per 100 person-years, a between-community coefficient of variation within matched triplets of 0.15 to 0.20, a total of 2500 participants per community with 85% HIV-negative status at baseline, and 25% loss to follow-up over a period of 3 years, the power of the trial would exceed 75% or 85% for effects of 35% or 40%, respectively.

Analysis methods are described in detail in the statistical analysis plan (available with the protocol), which was completed before data unblinding,[21] and in the Supplementary Appendix. In brief, HIV incidence was measured among participants who were HIV-negative at enrollment; HIV infection was assumed to occur at the midpoint between the last HIV-negative sample and the first HIV-positive sample, or at a visit in which acute infection was identified. When the time of infection was unclear because of missed visits, it was estimated by means of imputation (see the Supplementary Appendix, including Table S2). For the primary outcome, statistical inference used a two-stage approach recommended for cluster-randomized trials with fewer than 15 clusters per group.[22,23] In groups A and B, data that were collected by the community health workers were used to estimate the percentage of HIV-positive community members who knew their HIV status and were receiving ART, according to methods and assumptions described in the Supplementary Appendix.

RESULTS

ENROLLMENT AND FOLLOW-UP

The enrollment and follow-up of the population cohort are shown in Figure 1. A total of 38,474 adults were enrolled at baseline, with 5014 additional enrollments at 12 months and 4813 at 24 months (total enrolled, 48,301).

At 12 months and again at 24 months, 13% of the participants discontinued the trial, most because of confirmed permanent relocation out of the trial community (Table S3 in the Supplementary Appendix), and their data were censored from further observation; approximately 75% of the remaining participants completed each visit. The final survey at 36 months reached 72% of eligible participants, with similar retention across the trial groups (73%, 73%, and 71% in groups A, B, and C, respectively).

BASELINE COMPARISONS

More women (71%) than men (29%) were enrolled, with 40% of the participants younger than 25 years of age (Table 1). Sociodemographic and behavioral characteristics were similar across the trial groups (Table 1, and Table S1 in the

Figure 1 (facing page). Enrollment and Follow-up of the Population Cohort.

The trial included 21 communities that were matched in seven sets of 3 communities each; the 3 communities in each triplet were randomly assigned to group A (combination prevention intervention with universal antiretroviral therapy [ART]), group B (combination prevention intervention with ART provided according to local guidelines), or group C (standard care). The purpose of the population cohort was to enroll and follow a representative sample of residents to assess the effect of the combination prevention intervention on the incidence of human immunodeficiency virus (HIV) infection and on viral suppression. Participants in the population cohort were enrolled from randomly selected households in the community, with one member 18 to 44 years of age selected at random for eligibility assessment. A total of 38,474 participants were enrolled at the start of the trial. Additional participants were enrolled at 12 months in communities with fewer than 2000 participants at the start of the trial; additional participants were enrolled in groups A and C at 24 months to preserve power for this comparison. (Values for participant enrollment in each triplet are for the entire trial.) The status of participants at each survey year (12, 24, and 36 months) is reported. Participants who missed yearly follow-up visits were eligible to complete subsequent annual surveys, whereas participants who discontinued the trial were not.

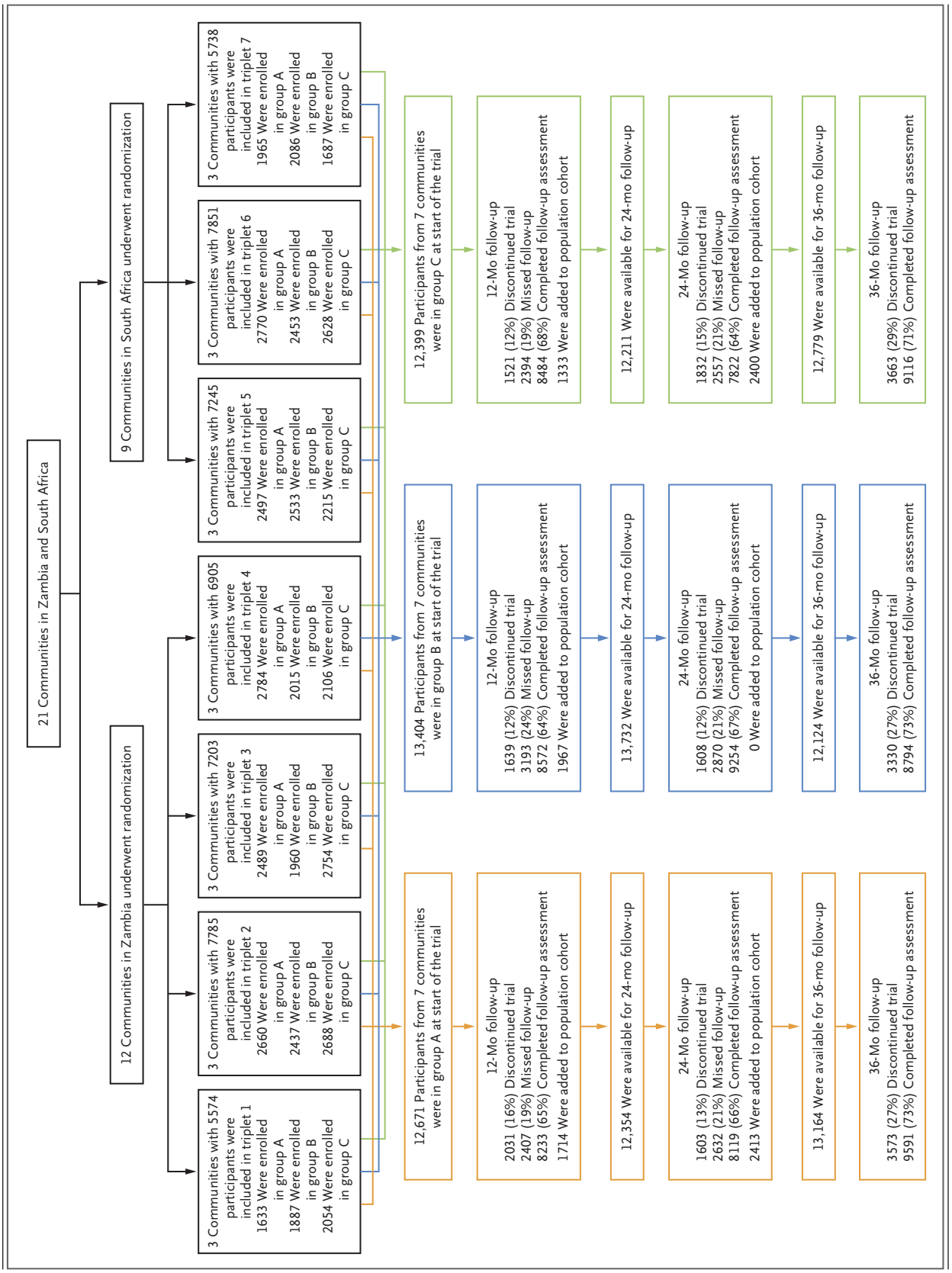

Table 1. Characteristics of the Population Cohort at Baseline.*

Characteristic	Group A (N = 12,671)	Group B (N = 13,404)	Group C (N = 12,399)
	number/total number (percent)		
Sex			
Male	3595/12,637 (28)	3906/13,364 (29)	3701/12,340 (30)
Female	9042/12,637 (72)	9458/13,364 (71)	8639/12,340 (70)
Age			
18–24 yr	5065/12,636 (40)	5179/13,364 (39)	4981/12,336 (40)
25–34 yr	4928/12,636 (39)	5170/13,364 (39)	4688/12,336 (38)
35–44 yr	2643/12,636 (21)	3015/13,364 (23)	2667/12,336 (22)
Marital status			
Married or living as married	5363/12,560 (43)	5210/13,233 (39)	4693/12,199 (38)
Never married	6292/12,560 (50)	6923/13,233 (52)	6644/12,199 (54)
Divorced, separated, or widowed	905/12,560 (7)	1100/13,233 (8)	862/12,199 (7)
Male circumcision status†			
Not circumcised	1725/3405 (51)	1974/3758 (53)	1904/3445 (55)
Medical circumcision	567/3405 (17)	613/3758 (16)	646/3445 (19)
Traditional circumcision	1113/3405 (33)	1171/3758 (31)	895/3445 (26)
Current use of ART by HIV-positive participants†			
Yes	788/2375 (33)	1048/2582 (41)	878/2526 (35)
No	1587/2375 (67)	1534/2582 (59)	1648/2526 (65)
HIV status‡			
Negative	9594/12,177 (79)	10,235/12,969 (79)	9301/11,988 (78)
Positive	2583/12,177 (21)	2734/12,969 (21)	2687/11,988 (22)
HSV-2 status§			
Negative	6506/12,237 (53)	7005/13,019 (54)	6585/12,016 (55)
Positive	5667/12,237 (46)	5959/13,019 (46)	5357/12,016 (45)
Indeterminate	64/12,237 (1)	55/13,019 (<1)	74/12,016 (1)
HIV viral suppression¶			
Yes	295/523 (56)	300/525 (57)	267/494 (54)
No	228/523 (44)	225/525 (43)	227/494 (46)

* The table is restricted to participants who were enrolled in the population cohort at baseline (month 0). Data are pooled across all seven communities in each trial group. Group A communities received a combination prevention intervention with universal antiretroviral therapy (ART). Group B communities received a combination prevention intervention with ART provided according to local guidelines. Group C communities received standard care. Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, and HSV-2 herpes simplex virus type 2.

† Status regarding male circumcision was reported by the participants, as was use or nonuse of ART by HIV-positive participants.

‡ HIV status was not determined when a participant did not consent to specimen collection, when no sample was available, or when laboratory testing did not result in a determination of infection status.

§ HSV-2 status was not determined when a participant did not consent to specimen collection or when no sample was available.

¶ Viral suppression was assessed in a random sample of approximately 75 HIV-positive participants per community at baseline.

Supplementary Appendix). Approximately 17% of the men reported having undergone medical circumcision.

The baseline HIV prevalence was 22% (women, 26%; men, 12%), and the baseline herpes simplex virus type 2 (HSV-2) prevalence was 46% (women, 54%; men, 24%). The prevalence of both infections was similar across the trial groups (HIV, 21% in group A, 21% in group B, and 22% in group C; HSV-2, 46% in group A, 46% in group B, and 45% in group C). Reported ART coverage was highest in group B (33% in group A, 41% in group B, and 35% in group C), but the percentage of HIV-positive participants who had viral suppression at baseline was similar across the trial groups (56% in group A, 57% in group B, and 54% in group C).

EFFECT OF THE INTERVENTION ON HIV INCIDENCE

Estimated effects of the intervention on HIV incidence are shown in Table 2 and Figure 2. Between 12 and 36 months (primary outcome), 553 incident HIV infections were observed during 39,702 person-years (overall incidence, 1.4 per 100 person-years; women, 1.7 per 100 person-years; men, 0.8 per 100 person-years). The incidence in group C (geometric mean across communities) was 1.6 per 100 person-years (Table 2). The incidence in group A was 1.5 per 100 person-years; the adjusted rate ratio as compared with group C was 0.93 (95% confidence interval [CI], 0.74 to 1.18; P=0.51). The incidence in group B was 1.1 per 100 person-years; the adjusted rate ratio as compared with group C was 0.70 (95% CI, 0.55 to 0.88; P=0.006). HIV incidence was lower in group B than in group C in all seven matched triplets, whereas the incidence was lower in group A than in group C in four triplets (Fig. 2). A permutation test based on the restricted randomization scheme showed even stronger evidence of an effect in group B as compared with group C (P=0.001), but not in group A as compared with group C (P=0.48). The findings were similar when the analysis was restricted to participants enrolled at baseline (Table S7 in the Supplementary Appendix).

In group B as compared with group C, subgroup analyses according to sex (Table 2) and age and sex (Table S4 in the Supplementary Appendix) showed a greater effect on HIV incidence in men (adjusted rate ratio, 0.52; 95% CI, 0.24 to 1.12) than in women (adjusted rate ratio, 0.73; 95% CI, 0.55 to 0.97), although this difference in effect could have occurred by chance (P=0.40 for interaction). There was also evidence of a greater effect in older participants (adjusted rate ratio in participants ≥25 years of age, 0.58; 95% CI, 0.43 to 0.76) than in younger participants (adjusted rate ratio in participants 18 to 24 years of age, 0.92; 95% CI, 0.70 to 1.20; P=0.04 for interaction). HIV incidence and estimated effects for individual years of follow-up and for the entire trial period (0 to 36 months) are shown in Tables S4 and S5 in the Supplementary Appendix. HIV incidence decreased in group C by 12% (95% CI, 0 to 23) per year (Fig. S5 in the Supplementary Appendix). HIV incidence was approximately 20% lower in groups A and B combined than in group C (adjusted rate ratio, 0.81; 95% CI, 0.66 to 0.99).

EFFECT OF THE INTERVENTION ON VIRAL SUPPRESSION

The percentage of HIV-positive participants at 24 months who met our case definition of viral suppression was 71.9% in group A, 67.5% in group B, and 60.2% in group C (Table 2). The adjusted prevalence ratio for viral suppression in group A as compared with group C was 1.16 (95% CI, 0.99 to 1.36; P=0.07), and the ratio in group B as compared with group C was 1.08 (95% CI, 0.92 to 1.27; P=0.30). In groups A and B, the prevalence of viral suppression at 24 months was higher among women than among men and higher among participants 25 years of age or older than among those 18 to 24 years of age (Table 2, and Table S8 in the Supplementary Appendix). The prevalence of viral suppression in groups A and B increased from approximately 55% at baseline to approximately 75% at 36 months and was 86 to 91% among participants in groups A and B who reported ART use (Tables S9 and S10 in the Supplementary Appendix).

COVERAGE OF THE INTERVENTION

On the basis of data collected by the community health workers, the estimated percentage of all HIV-positive adults in the community who were receiving ART at the end of the trial was 81% in group A and 80% in group B (Table S11 in the

Table 2. Effect of the Combination Prevention Intervention on HIV Incidence and HIV Viral Suppression.*

Variable	Group A	Group B	Group C	Group A vs. Group C		Group B vs. Group C	
				Adjusted Rate Ratio (95% CI)†	P Value	Adjusted Rate Ratio (95% CI)†	P Value
	no./total person-yr (rate per 100 person-yr)						
Participants with new HIV infection, 12–36 mo‡							
Triplet 1	28/1687 (1.64)	19/1979 (0.94)	24/2054 (1.17)				
Triplet 2	33/2086 (1.57)	29/2408 (1.20)	33/2262 (1.48)				
Triplet 3	23/1695 (1.36)	22/1687 (1.30)	29/1811 (1.63)				
Triplet 4	41/2013 (2.04)	19/1698 (1.13)	37/1561 (2.39)				
Triplet 5	36/1507 (2.35)	33/1811 (1.80)	28/1304 (2.15)				
Triplet 6	26/1808 (1.43)	26/2078 (1.24)	32/1375 (2.31)				
Triplet 7	13/2195 (0.57)	10/2488 (0.40)	14/2195 (0.59)				
Overall§	198/12,990 (1.45)	157/14,149 (1.06)	198/12,563 (1.55)	0.93 (0.74–1.18)¶	0.51¶	0.70 (0.55–0.88)¶	0.006¶
Men	36/3766 (0.77)	23/4301 (0.45)	39/4115 (0.92)	0.88 (0.41–1.88)‖		0.52 (0.24–1.12)‖	
Women	162/9225 (1.71)	134/9848 (1.26)	159/8448 (1.79)	0.96 (0.72–1.28)‖		0.73 (0.55–0.97)‖	
	no./total HIV-positive participants (%)						
Participants with viral suppression at 24 mo**							
Triplet 1	140/175 (80.0)	183/244 (75.0)	212/290 (73.1)				
Triplet 2	204/311 (65.6)	276/371 (74.4)	179/271 (66.1)				
Triplet 3	225/295 (76.3)	177/255 (69.4)	174/284 (61.3)				
Triplet 4	356/518 (68.7)	219/324 (67.6)	354/476 (74.4)				
Triplet 5	270/389 (69.4)	275/381 (72.2)	211/315 (67.0)				
Triplet 6	250/355 (70.4)	126/202 (62.4)	338/506 (66.8)				
Triplet 7	86/116 (74.1)	62/114 (54.4)	12/41 (29.3)				
Overall§	1531/2159 (71.9)	1318/1891 (67.5)	1480/2183 (60.2)	1.16 (0.99–1.36)††	0.07††	1.08 (0.92–1.27)††	0.30††
Men‡‡	183/294 (63.0)	153/244 (60.8)	179/330 (40.0)	1.46 (0.86–2.48)§§		1.41 (0.83–2.41)§§	
Women‡‡	1348/1865 (73.3)	1165/1647 (68.4)	1301/1853 (65.8)	1.10 (1.00–1.22)§§		1.03 (0.93–1.13)§§	

* CI denotes confidence interval.
† The adjusted prevalence ratio is shown for viral suppression. For HIV infection, the rate ratio was adjusted for age, sex, and baseline HIV prevalence. For viral suppression, the prevalence ratio was adjusted for age and sex.
‡ Imputation was used to estimate the timing of HIV infection in participants with seroconversion who missed the follow-up assessment at 12 months or 24 months (see the Supplementary Appendix). The estimated overall number of infections in each group may not match the total of the estimated numbers in the seven triplets because of rounding.
§ The overall rate of incident HIV infection is the geometric mean of the rates in individual communities. The overall percentage of participants with viral suppression is the geometric mean of the percentages in individual communities.
¶ The unadjusted rate ratio for group A as compared with group C was 0.94 (95% CI, 0.77 to 1.15; P=0.505) and for group B as compared with group C was 0.68 (95% CI, 0.56 to 0.84; P=0.002).
‖ For group A as compared with group C, the P value for interaction according to sex was 0.79. For group B as compared with group C, the P value for interaction according to sex was 0.40.
** Viral suppression was defined as an HIV viral load of less than 400 copies per milliliter.
†† The unadjusted prevalence ratio for group A as compared with group C was 1.19 (95% CI, 0.97 to 1.47; P=0.09) and for group B as compared with group C was 1.12 (95% CI, 0.91 to 1.38; P=0.26).
‡‡ The sex-specific percentages are geometric means of the percentages for each sex across the trial communities.
§§ For group A as compared with group C, the P value for interaction according to sex was 0.22. For group B as compared with group C, the P value for interaction according to sex was 0.16.

Supplementary Appendix). Figure 3 shows estimated ART coverage according to age and sex, with the results indicating similar coverage in groups A and B, lower coverage among men than among women, and lower coverage among younger participants than among older participants. ART coverage was also similar in groups A and B in most triplets (Fig. S6 in the Supplementary Appendix).

DISCUSSION

This trial provides evidence that a combination prevention intervention including universal testing and treatment can reduce HIV incidence at a population level. HIV incidence was lower by 30% in group B than in the standard-care control group; surprisingly, there was no evidence of such an effect in group A.

A universal testing and treatment strategy is hypothesized to reduce HIV transmission by increasing the percentage of HIV-positive community members who know their HIV status, the percentage of those persons who are receiving ART, and the percentage of those receiving ART who have viral suppression. Data from this trial indicate that the UNAIDS 90-90-90 targets (with testing and treatment leading to 73% viral suppression) were achieved by the end of the 3-year intervention in both group A and B communities (approximately 75% viral suppression). Higher levels of viral suppression were observed among HIV-positive population-cohort participants in group A and B communities at 24 months than at baseline (approximately 70% vs. approximately 55%).

There are several possible explanations for the lack of an effect on HIV incidence when the combination prevention intervention was added to universal ART (group A). First, written informed consent, required for initiation of ART outside local guidelines from the start of the trial until 2016, may have inadvertently discouraged ART initiation, although this is not supported by data showing similar ART coverage and viral suppression in groups A and B. Second, wide-scale ART delivery in group A may have led to sexual disinhibition or de-emphasis of primary prevention, offsetting the observed increase in viral suppression. Data on participant-reported risk behaviors do not support this hypothesis; further analyses are planned once data on HSV-2 seroconversion (a proxy for sexual risk behavior) become available. Third, although the three trial groups appeared well matched at baseline, there may have been unrecognized differences across communities in sociodemographic or other factors, such as mobility and migration resulting in exposure to HIV-positive partners from other

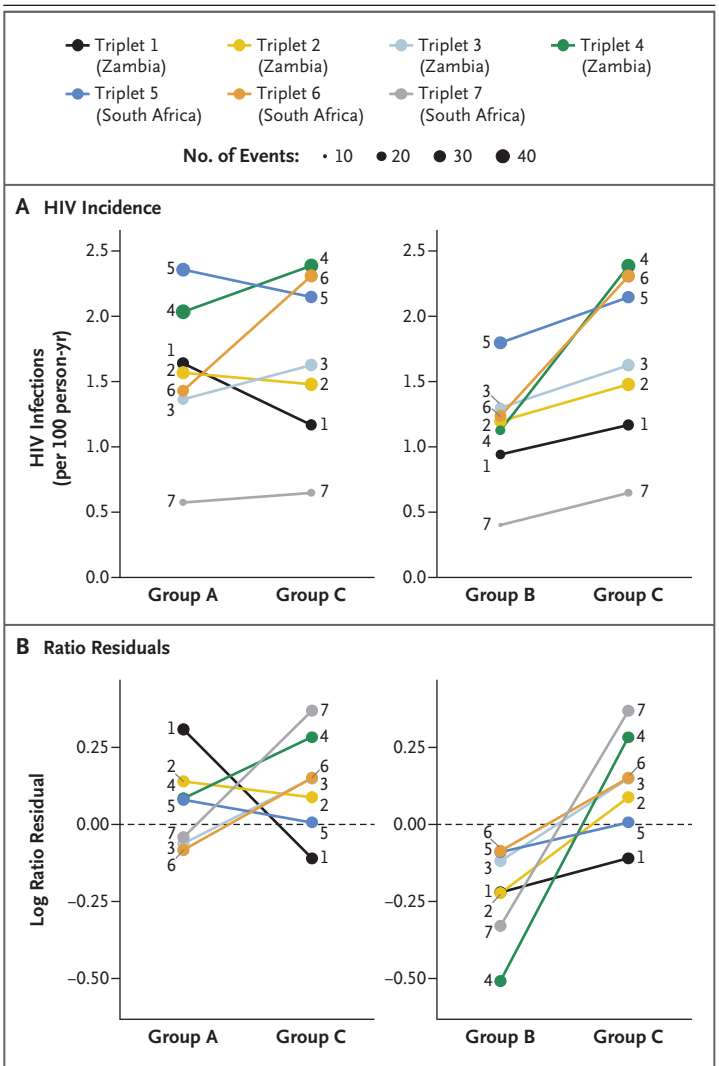

Figure 2. Estimates of HIV Incidence and Log Ratio Residuals for the Seven Triplets (Three Communities Each).

The plots show estimates of HIV incidence (plotted per 100 person-years) (Panel A) and log ratio residuals (ratio of observed to expected HIV infections, with adjustment for age, sex, and baseline HIV prevalence) (Panel B) for group A as compared with group C and for group B as compared with group C. Data are shown for the trial period included in the primary outcome analysis (between months 12 and 36). Colored lines represent each of the seven triplets (numbered 1 to 7). For HIV incidence, the size of the colored dot at the end of each line represents the number of events contributing to the incidence estimate for each community.

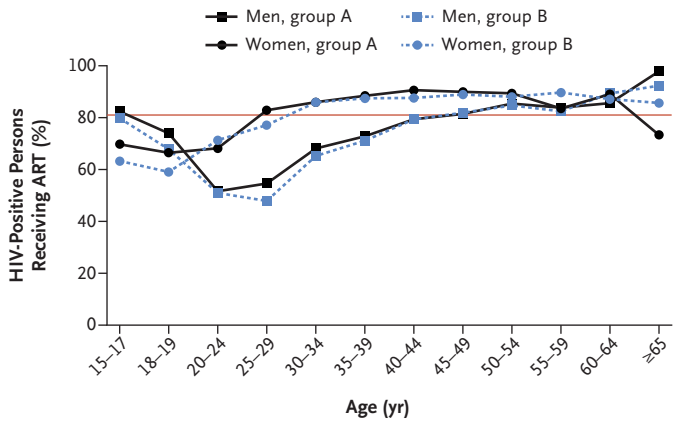

Figure 3. Estimated ART Coverage at the End of the Trial, According to Age, Sex, and Trial Group.

The plot shows estimated ART coverage among the total population 15 years of age or older in group A and B communities at the end of the trial, according to sex, age group, and trial group. (Estimates are based on data collected by community health workers.) The Joint United Nations Program on HIV/AIDS 90-90-90 target for ART coverage (81%) is shown in red. The estimated number of HIV-positive men who were resident in the community at the time that community health workers first visited their household during the third (and last) annual round of the intervention, and remained resident in the trial community at the end of the trial, was 8388 in group A and 8948 in group B, and the estimated number of women in this category was 15,936 in group A and 17,586 in group B. The estimated number of HIV-positive men receiving ART was 6286 in group A and 6378 in group B, and the estimated number of HIV-positive women receiving ART was 13,600 in group A and 14,481 in group B.

communities. Although these urban communities had high mobility, analysis of available data does not suggest any appreciable differences in migration across the trial groups. Further analyses of qualitative and quantitative data from the trial communities, and data from an ongoing phylogenetic study, may shed light on the unexpected result in group A.

In the absence of alternative explanations and given that the interventions in groups A and B were identical for most of the primary analysis period, it is possible that the difference in observed effects was due to chance. This possibility underlay our decision to carry out a post hoc analysis combining groups A and B, which showed a 20% lower HIV incidence than in group C.

Strengths of the trial included the large sample size, enrollment of a randomly sampled cohort to measure HIV incidence and viral suppression at the community level, delivery of ART through routine services at government clinics, extensive process data used to refine delivery of the intervention, and strong community engagement. Although our trial communities were not chosen to be representative of Zambia or South Africa as a whole, conduct of the trial in large urban communities with high mobility should increase the generalizability of the findings to other urban areas of southern Africa with widespread HIV epidemics.

One limitation is that data on uptake of interventions among HIV-positive participants in the population cohort may be subject to a Hawthorne effect, because participants had regular contact with research staff offering HIV testing and providing referral to care. This Hawthorne effect would probably be greatest in group C, in which participants did not have access to the services provided by the community health workers for testing and referral. Thus, for uptake estimates, we relied mainly on intervention data, which were available only for group A and B communities. In addition, men were underrepresented in the population cohort, and a substantial number of participants moved out of the community during follow-up, so their data were censored from further observation. Thus, we cannot rule out selection bias, although there was no evidence that these factors differed between trial groups.

The results of the HPTN 071 (PopART) trial are consistent with programmatic and survey data[24-27] and should be considered alongside those of the other three trials that measured the effect of universal testing and treatment on HIV incidence in Africa, all of which were smaller and undertaken in largely rural communities. The TasP trial[16] showed no effect on HIV incidence, which may have reflected the similar HIV testing services provided in the intervention and control groups, with low levels of ART coverage in both groups. The SEARCH trial[17] also showed no effect on HIV incidence, which may have reflected intensive baseline community-based HIV testing in both the intervention and control groups. The Ya Tsie trial[18] showed a 30% lower incidence in the intervention group than in the control group, but the difference was not significant.

Our finding of a 20 to 30% reduction in HIV incidence at a population level was measured against a background of decreasing incidence in

communities providing standard care, possibly attributable to gradually increasing coverage of ART in the general population. This indicates that combination prevention including universal testing and treatment can make a substantial contribution to HIV epidemic control. It is notable that the effects seen in our trial, the Ya Tsie trial, and others[28] were achieved by delivering intensive household-based HIV-testing services; this may have played a more important role than changes in ART guidelines. The universal "test" component of a "test and treat" strategy is vital, as is continued attention to primary HIV prevention interventions.[29,30] Results from planned cost-effectiveness and modeling studies will provide information on the cost-effectiveness (value for money) and longer-term effect of such strategies, which will help to inform policy and practice. Data on ART coverage from the HPTN 071 (PopART) trial, like data from other studies, draw special attention to the challenges in achieving ART coverage targets in young people, men, and communities with high mobility.[31-33] If HIV transmission is concentrated in these subgroups, the effect of universal testing and treatment on HIV transmission may be compromised. Special efforts will be needed to address these coverage gaps to realize the full potential of universal testing and treatment for HIV epidemic control.

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APPENDIX

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