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Clinical Infectious Diseases

MAJOR ARTICLE

Modeling Combination Interventions to Prevent Human Immunodeficiency Virus in Adolescent Girls and Young Women in South Africa (HIV Prevention Trials Network 068)

Marie C. D. Stoner,[1,2] Daniel Westreich,[3] Jennifer Ahern,[4] Jessie Edwards,[3] F. Xavier Gómez-Olivé,[5] Stephen M. Tollman,[5,6] Sheri Lippman,[5,7] Kathleen Kahn,[5,6,8] and Audrey Pettifor[1,3,5]

[1]Carolina Population Center, University of North Carolina, Chapel Hill, North Carolina, USA, [2]Women's Global Health Imperative, RTI International, San Francisco, California, USA, [3]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, [4]School of Public Health, Division of Epidemiology and Biostatistics, University of California, Berkeley, Berkeley, California, USA, [5]Medical Research Council/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [6]INDEPTH Network, Accra, Ghana, [7]Department of Medicine, University of California, San Francisco, San Francisco, California, USA, and [8]Epidemiology and Global Health Unit, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

Background. Combination interventions may be an effective way to prevent human immunodeficiency virus (HIV) in adolescent girls and young women. However, current studies are not designed to understand which specific interventions and combinations will be most effective. We estimate the possible impacts of interventions on a combination of factors associated with HIV.

Methods. We used the g-formula to model interventions on combinations of HIV risk factors to identify those that would prevent the most incident HIV infections, including low school attendance, intimate partner violence, depression, transactional sex, and age-disparate partnerships. We used data from the HIV Prevention Trials Network (HPTN) 068 study in rural South Africa from 2011 to 2017. We estimated HIV incidence under a potential intervention that reduced each risk factor and compared this to HIV incidence under the current distribution of these risk factors.

Results. Although many factors had strong associations with HIV, potential intervention estimates did not always suggest large reductions in HIV incidence because the prevalence of risk factors was low. When modeling combination effects, an intervention to increase schooling, decrease depression, and decease transactional sex showed the largest reduction in incident infection (risk difference, –1.4%; 95% confidence interval [CI], –2.7% to –.2%), but an intervention on only transactional sex and depression still reduced HIV incidence by –1.3% (95% CI, –2.6% to –.2%).

Conclusions. To achieve the largest reductions in HIV, both prevalence of the risk factor and strength of association with HIV must be considered. Additionally, intervening on more risk factors may not necessarily result in larger reductions in HIV incidence.

Keywords. adolescent girls and young women; combination HIV prevention; South Africa; HIV; causal inference.

Adolescent girls and young women (AGYW) in rural South Africa have a high 16% prevalence of human immunodeficiency virus (HIV) infection, a burden much larger than their male counterparts [1]. HIV risk among AGYW is associated with factors at multiple levels including interpersonal relationships with peers and partners, parental support, and community norms [2–5]. Thus, researchers and policy makers have increasingly called for the use of strategies to prevent HIV that combine interventions on multiple factors [2, 3, 6].

There are several current studies evaluating the effect of combination prevention packages, and these will provide information in the coming years about whether combination prevention can successfully prevent new infections [7, 8]. For example, the DREAMS initiative is implementing combination programs to prevent HIV in AGYW in 10 countries worldwide [9]. However, most of these studies are not designed to make comparisons between multiple combinations to clarify which specific interventions and combinations would have the strongest effects on HIV incidence. Thus, modeling is 1 way to understand individual and combination effects that large-scale implementation studies like Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) or trials of combinations interventions may not be able to answer. In the absence of trial data, we used observational data to investigate the population-level impacts of potential interventions on HIV risk and explored interventions on combinations of HIV risk factors.

Specifically, we analyzed observational data to inform the development of combination prevention packages in 2 critical

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Correspondence: M. Stoner, Women's Global Health Imperative, RTI International, 2150 Shattuck Ave, Suite 1200, Berkeley, CA 94704 (mcstoner@rti.org).

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ways. First, we estimate effects that contrast incidence had all participants been exposed to each risk factor to incidence had none been exposed, which is analogous to what is done in most standard analyses (Figure 1) [10, 11]. We then use the parametric g-formula to estimate HIV incidence under a potential intervention that reduced each HIV risk factor and compared this to HIV incidence under the current distribution of the risk factor [10–12]. We consider interventions on factors associated with HIV in prior analyses of these data including low school attendance [13], intimate partner violence (IPV) [14], depression [15], age-disparate partnerships [16], and transactional sex [17] and estimate the effects of reducing the prevalence of various risk factors by 100% (eliminated), 50%, and 25% on HIV incidence compared to the current incidence of HIV in the population. In a second analysis, we estimate the effect of reducing the prevalence of these risk factors independently and jointly by amounts that prior real-world interventions deem feasible, again compared to current HIV incidence [10–12].

METHODS

Data

We analyzed data collected during the main trial period (2011–2015) and postintervention visit (2016–2017) of the HPTN 068 study. HPTN 068 was a randomized trial of a conditional cash transfer intervention to prevent HIV acquisition in AGYW in rural South Africa [18, 19]. The study enrolled 2533 AGYW aged 13–20 years who were not pregnant or married, had a parent/guardian in the household, and were attending school in the Bushbuckridge subdistrict of Mpumalanga province, South Africa [20].

During the study period, young women were followed for up to 3 years until study completion or graduation from high school. The girls were then visited again 1 to 2 years after the study ended in the postintervention visit (6 years possible follow-up time). Each annual visit included an audio computer-assisted self-interview survey and a test for HIV and herpes simplex virus type 2 for those who tested negative at the last visit. To identify incident HIV infections, our study includes only AGYW who had at least 1 follow-up visit and were HIV negative at enrollment. Prior analyses have examined baseline HIV infections [19].

Definitions

The outcome of incident HIV infection was defined as new cases of HIV identified over the 6-year study period. The exposures of interest were depression, physical IPV, low attendance in school, any transactional sex, and having an age-disparate partnership. We selected these exposures because they have all been associated with incident HIV infection in previous HPTN 068 analyses, and are plausible to change through intervening [14–17, 21]. Depression was a binary variable defined as having a children's depression inventory score of ≥7 at baseline [22]. School attendance or dropout was a time-varying variable defined as low attendance in school (<80% school days) vs high attendance (≥80% school days) or dropout without completing grade 12 [18, 23]. Ever experiencing physical IPV is a binary variable defined as experience of any IPV by a partner at baseline [18, 24]. Age difference with a partner was a dichotomous, time-varying variable defined as having at least 1 partner 5 or more years older [16]. Transactional sex was a dichotomous, time-varying variable defined as whether a young woman said that she felt that she had to have sex with a male partner because he gave her money or gifts [17]. Additional details of variables and data collection procedures have been previously published [18, 19].

Statistical Analysis

We modeled the impact of potential interventions on each risk factor using the g-formula. The g-formula is a generalization

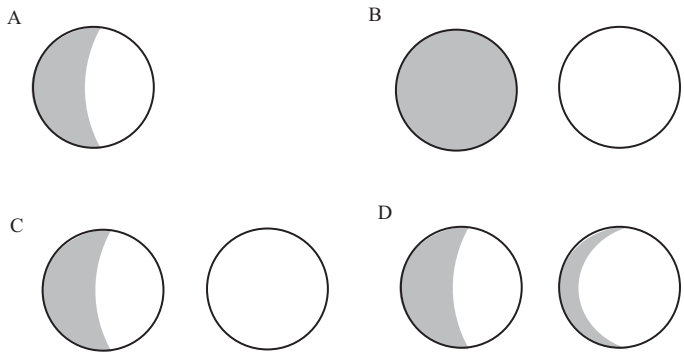


Figure 1. Contrasts estimated in this analysis. *A*, The observed exposure distribution, showing 2 levels of an exposure as shaded/unshaded. *B*, Population "traditional" exposure effect, comparing "entirely exposed" and "entirely unexposed." *C*, Population attributable effect, comparing the observed distribution to a population in which no one was exposed. *D*, Generalized intervention effect, comparing the observed exposure distribution to a population in which fewer individuals were exposed (adapted from Westreich [10]).

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of standardization that accounts for time-varying confounders affected by prior exposure and can be used to predict the effects of interventions [25]. First, we estimated the average effect (exposure effect) of each exposure on HIV incidence comparing all-exposed vs none-exposed (Figure 1). This is analogous to the comparison that is made in standard analyses that compare exposed and unexposed persons. Second, we compared the observed (real) distribution of each risk factor to a population in which the risk factor was eliminated (reduced 100% or unexposed). Third, we estimated population intervention effects for each exposure, comparing outcomes under the observed distribution of each risk factor to outcomes in a population in which fewer individuals were exposed (50% fewer or 25% fewer). Last, we modeled the effects of reducing exposures by a plausible amount based on known interventions and combinations of these interventions. We assumed a reduction in these risk factors distributed across the population at random (ie, this reduction was not based on other participant characteristics).

For example, considering the exposure of low school attendance, which was prevalent in 20.6% of participants over the study period, we first estimated the difference in HIV incidence if all participants were exposed to low school attendance at all visits vs if none were exposed (the traditional comparison). Next, we compared HIV incidence under the observed prevalence of low school attendance (20.6%) to HIV incidence had no one had low school attendance (all unexposed). Then, we compared the observed prevalence of the same exposure (again, 20.6%) to a 25% and a 50% reduction on the relative scale (15.4%, and 10.3%, respectively). Last, we compared the observed prevalence of low attendance to a 3.9% absolute reduction based on a prior intervention.

A relative reduction of 25% or 50% in some of these risk factors may be unattainable with current interventions. To estimate the expected effects under realistic reductions in these risk factors, we used the absolute percentage reduction from real interventions that were reported in the literature. We used the absolute scale because absolute reductions are more often used as targets for prevention interventions. We selected illustrative examples of interventions that have impacted these exposures. For transactional sex, a study of the South African Child Support Grant found that 5.5% of girls had transactional sex in the past year in households that had not received a grant, compared with 2.5% in recipient households. Accordingly, we estimated the effect of a 3% absolute-scale reduction in transactional sex [26]. For depression, we used 36.2% absolute-scale reduction in depression from a psychological intervention in adults in Zimbabwe [27]. For school attendance, we used a 3.9% absolute-scale reduction in low school attendance from a conditional cash transfer intervention in Malawi [28]. For age-disparate partnerships, we used a 1.5% absolute-scale reduction in prevalence of pregnancy from a randomized experiment to test the effect of providing information on the risk of HIV infection by partner's age [29]. We could not find many examples of illustrative interventions to reduce age-disparate partnerships and therefore used pregnancy as a proxy because this intervention was focused on age as a risk factor. For IPV, we used a 10% absolute-scale reduction: the reduction in IPV in the last 12 months observed with the HPTN 068 conditional cash transfer intervention [18].

To implement the parametric g-formula, we followed several predefined steps [30, 31]. We (*i*) parametrically modeled probabilities of the exposures, and time-varying confounders and the outcome at each time point until infection conditional on covariates in the observed data. Logistic regression was used for all binary variables and linear regression was used for continuous variables. We then (*ii*) drew a Monte Carlo sample of 10 000 young women with replacement from the observed data. In the Monte Carlo sample, we (*iii*) used the conditional probabilities estimated in (*i*) to predict risk of HIV by time *t*. We then (*iv*) compared our predicted risk under no intervention on the exposure (ie, under the "natural course" [25]) with the observed data to assess the fit of the parametric models [25, 30]. Finally, we (*v*) estimated risk under each "intervention" scenario by setting the values of these variables in the Monte Carlo simulation. Two-way interaction terms were included between all exposures in the outcome model. We also modeled school attendance to affect age-disparate partnerships based on prior findings [32].

Confounders that were included were time (a binary indicator for each time interval), age at baseline, time-varying socioeconomic status (quartiles based on assets), time-varying orphan status (1 or both parents died when the young woman was <18 years of age), time-varying alcohol use (ever use), and time-varying pregnancy or having a child in the last 12 months. Confounders were selected for all parametric models based on prior literature indicating the importance of these variables and by drawing a diagram of the relationships for the exposures, time-varying confounders, and outcome.

Risk of HIV under each intervention was estimated using the complement of the extended Kaplan-Meier estimator [30]. We compared risk of HIV at the end of the study period (6 years) under each intervention using risk differences and risk ratios. We computed 95% confidence intervals (CIs) using the standard errors from 500 nonparametric bootstrap resamples.

RESULTS

We included 2362 young women who were HIV negative at enrollment and had at least 1 follow-up visit. Our simulated cohort closely matched the observed data on all characteristics (Table 1). At baseline, 5.6% of the observed cohort had a partner 5 or more years older, 3.7% had transactional sex in the last 12 months, 18.4% were depressed, 17.3% ever experienced IPV, and 6.0% had low attendance in school or had dropped out. The simulated cumulative incidence of HIV (12.1%) was similar

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Table 1. Characteristics of Young Women Aged 13–20 Years Without Prevalent Human Immunodeficiency Virus in Agincourt, South Africa, Enrolled in the HIV Prevention Trials Network 068 Study

Characteristic	Baseline Observed (n = 2362)[a]	All Visits (n = 11 016 Visits)	Baseline Simulated (n = 10 000)	All Visits Simulated (n = 48 337 Visits)
Participant age at baseline, y				
13–14	739 (31.29)	3831 (34.78)	3129 (31.29)	15 305 (31.66)
15–16	1009 (42.72)	4771 (43.31)	4214 (42.14)	20 435 (42.28)
17–18	505 (21.38)	2010 (18.25)	2178 (21.78)	10 403 (21.52)
18–20	109 (4.61)	404 (3.67)	479 (4.79)	2194 (4.54)
Household wealth				
Low	599 (25.40)	1749 (16.04)	2401 (24.04)	8682 (17.97)
Middle to low	627 (26.59)	2810 (25.77)	2709 (27.12)	12 626 (26.11)
Middle	575 (24.39)	3207 (29.41)	2454 (24.57)	13 757 (28.5)
High	557 (23.62)	3140 (28.79)	2424 (24.27)	13 267 (27.45)
CCT randomization arm	1215 (51.44)	5770 (52.39)	5122 (51.22)	24 744 (51.19)
Partner ≥5 y older	129 (5.55)	1144 (10.46)	550 (5.59)	4316 (8.96)
Transactional sex in last 12 mo	82 (3.71)	1089 (10.60)	344 (3.67)	5132 (10.76)
Ever pregnant or had a child	192 (8.22)	2115 (19.71)	835 (8.43)	9335 (19.35)
Alcohol use once a month or more	51 (2.16)	265 (2.41)	224 (2.24)	990 (2.05)
Double or single orphan	102 (4.37)	628 (5.74)	400 (4.04)	1947 (4.07)
Children's Depression Inventory score ≥7	415 (18.45)	1924 (18.35)	1770 (18.55)	8403 (18.25)
Ever experienced any physical IPV at baseline	400 (17.3)	1763 (16.33)	1730 (17.61)	8174 (17.22)
Low attendance in school (<80% of school days) or did not complete school	142 (6.01)	2435 (22.11)	627 (6.27)	9969 (20.62)

Data are presented as No. (%).

Abbreviations: CCT, (conditional cash transfer) intervention; IPV, intimate partner violence.

[a]Missing data in observed at baseline: exchange sex, 152; partner age, 38; depression, 113; IPV, 47; attendance, 51; alcohol, 1; wealth, 4; orphan, 27; pregnant, 26. Missing data in observed overall visits; transactional sex, 745; older partner, 74; depression, 529; IPV, 223; low attendance, 4; alcohol, 18; pregnant, 288; orphan, 73; assets, 110.

to the cumulative incidence in the observed data (Appendix Figure 1), providing a check on the modeling procedures.

When examining traditional effects comparing all exposed vs none exposed, all individual exposures reduced HIV incidence, although low school attendance and age-disparate partnerships had the largest reductions (Figure 1; Table 2). Reductions in HIV incidence were much smaller when estimating effects that compared the observed HIV risk in the population (12.1%) with HIV risk if all were unexposed to each HIV risk factor (100% reduction) (Table 2). Compared to the observed risk HIV at 6 years, reductions in each exposure were each were associated with <1% reduction in HIV incidence at 6 years.

Table 3 shows intervention effects that compare the observed incidence of HIV in the population with an intervention to reduce each individual exposure by 50% and 25% (relative reductions; ie, 20% reduced by 50% = 10%) and by an absolute percentage from a prior intervention (ie, 20% reduced by 3% = 17%). Only reducing low school attendance or dropout

Table 2. Standard Exposure Effect of Each Individual Exposure on Cumulative Incidence of Human Immunodeficiency Virus (HIV) Infection Versus the Effect Comparing Unexposed Versus the Observed Distribution of HIV at Year 6 at the End of the 6-Year Study Period

Effect	School Attendance or Dropout	Depression	IPV	Age-Disparate Partnership	Transactional Sex
Exposure effect (standard exposed vs unexposed comparison)					
Risk all exposed, %	18.1	15.0	14.7	18.6	17.0
Risk all unexposed, %	11.1	11.4	11.1	11.7	11.9
Risk difference, % (95% CI)	–6.94 (–12.16 to –1.71)	–3.62 (–8.11 to .86)	–3.78 (–8.99 to 1.43)	–6.94 (–14.48 to .6)	–5.04 (–11.6 to 1.52)
Risk ratio (95% CI)	0.62 (.44–.86)	0.76 (.55–1.04)	0.76 (.52–1.1)	0.63 (.4–.99)	0.70 (.47–1.06)
Eliminating each exposure (100% reduction)					
Risk under observed, %	12.1	12.1	12.1	12.1	12.1
Risk under removed, %	11.1	11.4	12.0	11.7	11.9
Risk difference, % (95% CI)	–1.0 (–2.4 to .4)	–0.7 (–2.0 to .5)	–0.4 (–1.7 to .9)	–0.4 (–1.5 to .6)	–0.2 (–1.4 to 1.0)
Risk ratio (95% CI)	0.92 (.81–1.05)	0.76 (.55–1.04)	0.97 (.86–1.09)	0.97 (.88–1.06)	0.99 (.89–1.09)

Abbreviations: CI, confidence interval; IPV, intimate partner violence.

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Table 3. Intervention Effects for Reducing Each Individual Exposure on Cumulative Incidence of Human Immunodeficiency Virus Infection at Year 6 at the End of the 6-Year Study Period

Effect	Low School Attendance or Dropout	Depression	IPV	Age-Disparate Partnership	Transactional Sex
Reduced 25% (relative reduction)					
Risk under observed, %	12.1	12.1	12.1	12.1	12.1
Risk under removed, %	11.3	11.7	12.1	11.9	11.5
Risk difference, % (95% CI)	–0.8 (–1.7 to 0.1)	–0.4 (–1.2 to .3)	0.0 (–.8 to .7)	–0.2 (–.8 to .5)	–0.6 (–1.3 to .2)
Risk ratio (95% CI)	0.93 (.87–1.0)	0.96 (.91–1.02)	1.0 (.94–1.06)	0.99 (.93–1.04)	0.95 (.9–1.01)
Reduced 50% (relative reduction)[a]					
Risk under observed, %	12.1	12.1	12.1	12.1	12.1
Risk under removed, %	11.1	11.4	11.6	11.3	11.7
Risk difference, % (95% CI)	–1.0 (–2.0 to .0)	–0.7 (–1.6 to .2)	–0.5 (–1.4 to .4)	–0.8 (–1.6 to .0)	–0.4 (–1.3 to .5)
Risk ratio (95% CI)	0.92 (.84–1.0)	0.94 (.87–1.02)	0.96 (.89–1.03)	0.94 (.88–1.0)	0.97 (.9–1.04)
Reduced by percentage from prior intervention (absolute reduction)[a]					
Absolute percentage reduction	3.9%	36.2%	10%	1.5%	3.0%
Risk under observed, %	12.1	12.1	12.1	12.1	12.1
Risk under removed, %	11.8	11.3	11.5	12.1	12.1
Risk difference, % (95% CI)	–0.3 (–1.1 to .5)	–0.8 (–2.0 to .5)	–0.6 (–1.5 to .4)	0.0 (–.5 to .5)	–0.1 (–.8 to .7)
Risk ratio (95% CI)	0.98 (.92–1.04)	0.94 (.84–1.04)	0.95 (.88–1.03)	1.0 (.96–1.04)	1.0 (.93–1.06)

Abbreviations: CI, confidence interval; IPV, intimate partner violence.

[a]Similarities between reduced 50% and reduced 100% are due to random chance in the simulation.

reduced incident HIV infection by >1% at 6 years when reduced by 50% (risk difference [RD], –1.0% [95% CI, –2.0% to 0.0%]). Based on estimates from prior studies, intervening on schooling alone (3.9% reduction), depression alone (36.2% reduction), age-disparate partnerships alone (1.5% reduction), IPV alone (10% reduction), and transactional sex alone (3.0% reduction) did not generate a statistically significant reduction in incident HIV infection.

Figure 2 shows the reduction in HIV risk when intervening to reduce combinations of exposures. The amount that each exposure is reduced is based on an illustrative prior intervention. Interventions 1, 4, and 6 resulted in similar reductions in HIV incidence; intervention 1 to reduce low school attendance, depression, and transactional sex was associated with a reduction in HIV incidence of 1.4% (95% CI, –2.7% to –.2%), intervention 4 reduced HIV risk by 1.3% (95% CI, –2.5% to –.1%) and included transactional sex and depression, and intervention 6 reduced HIV incidence by –1.4% (95% CI, –2.6% to –.2%) and included schooling, depression, age-disparate partnerships, and transactional sex.

DISCUSSION

In this study using empirical data from a large, longitudinal cohort of AGYW in South Africa, we found that schooling and age-disparate partnerships had the largest exposure effects on incident HIV infection when using the traditional analytic approach of comparing all exposed vs all unexposed. When considering the effect of removing each exposure compared to the observed prevalence of that exposure in the population, reductions in HIV incidence were much smaller and were between 0% and 1%. A number of hypothetical combination interventions reduced incidence by at most 1.4% in this population. An intervention to reduce depression and transactional sex had the largest reduction in incidence (–1.3%) and required intervening on a smaller number of exposures compared to an intervention with a similar effect size that included intervening on depression, transactional sex, and school attendance. Other combinations of interventions, including those that intervened on all 5 exposures, did not produce larger reductions in HIV incidence.

Intervening on factors with strong associations with HIV did not always translate into big reductions in HIV incidence because the prevalence of most risk factors was relatively low in our population. For example, the most prevalent risk factor was depression in 18% of girls at baseline. Most analyses compare all exposed vs all unexposed and have much larger effects. When we make comparisons such as 18% exposed (real prevalence) vs 0% exposed, the contrast and reductions in HIV risk are smaller. Furthermore, when using this method, the population-level impact of interventions on HIV incidence will depend on the distribution of characteristics in the population. For example, we found that a 50% reduction in low school attendance did not have a large effect on HIV incidence (RD, –1.0 [95% CI, –12.0 to .0]) because low school attendance or dropout was low (20.6%) in our study population. In a hypothetical population with a higher prevalence of low school attendance and all else being equal, we would expect elimination of low school attendance to have a bigger impact. Both the prevalence of a risk factor and the strength of its association with HIV should

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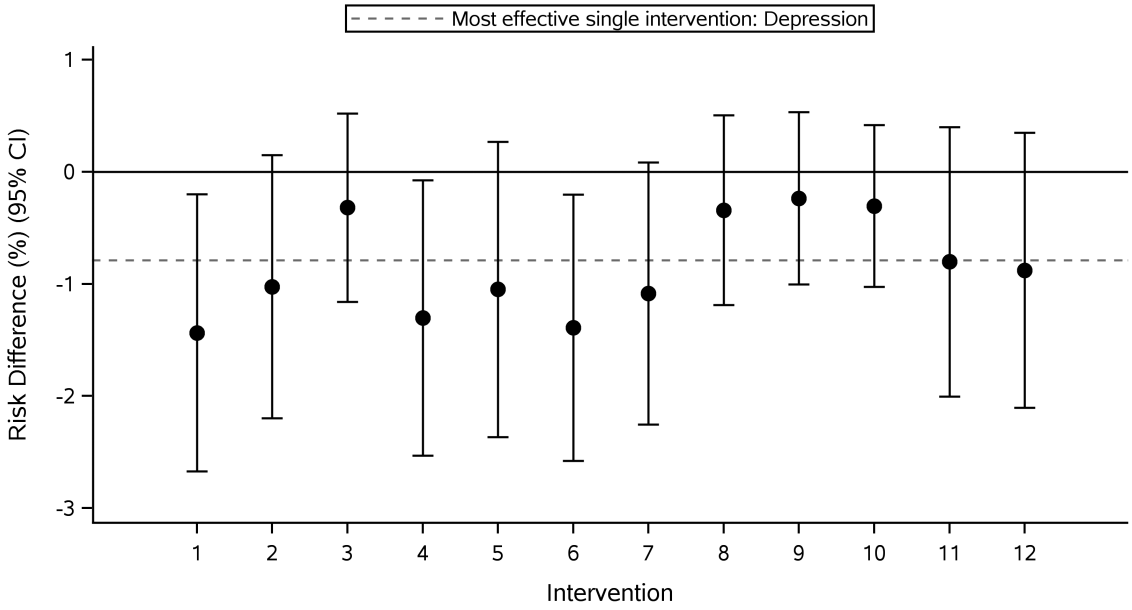


Figure 2. Risk differences (%) and 95% confidence intervals (CIs) for the effect of various interventions on schooling (3.9% reduction), depression (36.2% reduction), intimate partner violence (IPV) (10% reduction), age-disparate partnerships (1.5% reduction), and transactional sex (3% reduction) on cumulative incidence of human immunodeficiency virus infection at 6 years of follow-up. Intervention 1: Intervention on schooling, depression, and transactional sex. Intervention 2: Intervention on schooling and depression. Intervention 3: Intervention on schooling and transactional sex. Intervention 4: Intervention on transactional sex and depression. Intervention 5: Intervention on schooling, depression, age-disparate partnerships, IPV, and transactional sex. Intervention 6: Intervention on schooling, age-disparate partnerships, depression, and transactional sex. Intervention 7: Intervention on schooling, age-disparate partnerships, and depression. Intervention 8: Intervention on schooling, age-disparate partnerships, and transactional sex. Intervention 9: Intervention on schooling and age-disparate partnerships. Intervention 10: Intervention on age-disparate partnerships and transactional sex. Intervention 11: Intervention on age-disparate partnerships and depression. Intervention 12: Intervention on age-disparate partnerships, depression, and transactional sex.

be considered when deciding which risk factors will have the potential to impact HIV. Therefore, modeling approaches such as the g-formula are important for intervention design because they take into consideration the intervention context and demonstrate the potential for intervention impact in that context. Although associations were small, the findings indicate that the following approaches might be effective to achieve stronger relationships with HIV: (*i*) targeting populations with a high incidence of HIV where risk factors are also more prevalent; (*ii*) combination prevention; and (*iii*) continuing to improve the effectiveness of individual interventions to have larger effects on the prevalence of these exposures, not just do they have an effect (eg, depression had a 36% reduction and therefore made a larger impact).

Packages that combine interventions on multiple factors known to be associated with HIV may be more effective at reducing HIV incidence in AGYW than single interventions alone [6]. Currently, several large-scale combination intervention packages are being implemented worldwide [7]. Although informative, the majority of these studies are not designed to determine which combinations are most effective. We found that simply intervening on the largest number of risk factors did not always have the largest reductions in HIV risk. In this population, a more parsimonious intervention addressing 2 risk factors had equally large reductions in HIV incidence as a more complex intervention addressing 3 risk factors and larger reductions than interventions addressing up to 5 risk factors.

The interpretation of these results as estimates of causal effect assumes no measurement error, no unmeasured confounding and that the parametric models used to predict the outcome, exposures, and time-varying confounders are correctly specified. Although it is impossible to assess these assumptions in the data, we did control for all relevant variables included in our diagram. Additionally, the predicted natural course of HIV in the final specification of the model closely replicated the observed data, suggesting that the models were adequately specified [30]. These methods also assume consistency (that changes in each exposure would be assigned the same way for all individuals), positivity (we have individuals exposed and unexposed in all covariate strata), and that the interventions that we modeled from prior studies could be reasonably transported to have similar effects in this population. It is also important to note that while this paper focused on HIV incidence, combination interventions can have broader effects on health and well-being beyond reducing HIV incidence. Last, prior analyses of this data have shown that girls in the study were more likely to be enrolled in school and stay in school than the underlying population [33]. If the prevalence of school dropout were higher, as we would expect in the larger underlying population, then changes in school attendance and other related characteristics may have

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had more of an effect on HIV incidence because reductions in prevalence would be larger.

Our study is the first to model combination HIV prevention interventions in AGYW using observational data and epidemiologic methods that account for the distribution of characteristics in the population and observed HIV incidence. We found that intervening on factors with strong associations with HIV from epidemiologic analyses may not translate into big reductions on HIV incidence if the prevalence of those risk factors are low in the population. Given this, intervening on risk factors with the highest prevalence and strong associations with HIV may result in greater reductions in HIV incidence. Additionally, we find that intervening on more risk factors may not necessarily result in larger reductions in HIV incidence. In this population, a more parsimonious intervention addressing 2 risk factors (depression and transactional sex) had equally large reductions in HIV incidence compared to a more complex intervention addressing more risk factors. Similar modeling approaches should be applied in other populations to estimate the expected effectiveness of combination HIV prevention packages and identify the optimal combination of interventions to reduce HIV incidence.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. C. D. S., D. W., and A. P. contributed to the conception, design of the analysis, and writing of the paper. D. W., J. E., and J. A. provided statistical support on the analysis. The remaining authors were involved in data acquisition, data collection, study management, and design of the original parent study. All authors reviewed the manuscript, provided comments and edits to the manuscript, and read and approved the final manuscript.

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