Use of antiretroviral therapy in households and risk of HIV acquisition in rural KwaZulu-Natal, South Africa, 2004–12: a prospective cohort study

Alain Vandormael, Marie-Louise Newell, Till Bärnighausen, Frank Tanser

Summary

Background Studies of HIV-serodiscordant couples in stable sexual relationships have provided convincing evidence that antiretroviral therapy can prevent the transmission of HIV. We aimed to quantify the preventive effect of a public-sector HIV treatment and care programme based in a community with poor knowledge and disclosure of HIV status, frequent migration, late marriage, and multiple partnerships. Specifically, we assessed whether an individual's hazard of HIV acquisition was associated with antiretroviral therapy coverage among household members of the opposite sex.

Methods In this prospective cohort study, we linked patients' records from a public-sector HIV treatment programme in rural KwaZulu-Natal, South Africa, with population-based HIV surveillance data collected between 2004 and 2012. We used information about coresidence to construct estimates of HIV prevalence and antiretroviral therapy coverage for each household. We then regressed the time to HIV seroconversion for 14 505 individuals, who were HIV-uninfected at baseline and individually followed up over time regarding their HIV status, on opposite-sex household antiretroviral therapy coverage, controlling for household HIV prevalence and a range of other potential confounders.

Findings 2037 individual HIV seroconversions were recorded during 54 845 person-years of follow-up. For each increase of ten percentage points in opposite-sex household antiretroviral therapy coverage, the HIV acquisition hazard was reduced by 6% (95% CI 2–9), after controlling for other factors. This effect size translates into large reductions in HIV acquisition hazards when household antiretroviral therapy coverage is substantially increased. For example, an increase of 50 percentage points in household antiretroviral therapy coverage (eg, from 20% to 70%) reduced the hazard of HIV acquisition by 26% (95% CI 9–39).

Interpretation Our findings provide further evidence that antiretroviral therapy significantly reduces the risk of onward transmission of HIV in a real-world setting in sub-Saharan Africa. Awareness that antiretroviral therapy can prevent transmission to coresident sexual partners could be a powerful motivator for HIV testing and antiretroviral treatment uptake, retention, and adherence.

Funding Wellcome Trust and National Institute of Child Health and Human Development (US National Institutes of Health).

Lancet Glob Health 2014; 2: e209–215

Department of Sociology, University of Minnesota, Minneapolis, MN, USA (A Vandormael MS); **Faculties of Medicine and Social and Human Sciences, University of Southampton, Southampton, UK** (Prof M-L Newell PhD); **Africa Centre for Health and Population Studies, University of KwaZulu-Natal, KwaZulu-Natal, South Africa** (M-L Newell, T Bärnighausen MD, Prof F Tanser PhD); **and Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA** (T Bärnighausen)

Correspondence to: Alain Vandormael, Department of Sociology, University of Minnesota, Minneapolis, MN 55455, USA
vando026@umn.edu

Introduction

Early initiation of antiretroviral therapy can substantially improve the health and survival outcomes of HIV-infected patients.[1] Over the past decade, several studies have shown that antiretroviral therapy can reduce the transmission of HIV from an infected to an uninfected sexual partner.[2–4] The strongest evidence for the preventive effect of antiretroviral therapy has come from studies of HIV-serodiscordant couples in stable sexual relationships.[3] In 2011, investigators of the HPTN 052 trial,[5] now regarded as the landmark HIV treatment-as-prevention study, reported that early antiretroviral therapy reduced HIV transmission by 96% in HIV-serodiscordant couples who had disclosed their HIV status to each other. This result confirmed the findings of two earlier observational studies (reported in 2006[6] and 2010[7]), which showed that antiretroviral therapy was associated with a 98%[6] and a 92%[7] reduction in HIV incidence in serodiscordant heterosexual couples.

More recently, investigators of a prospective cohort study[8] reported a 66% fall in the rate of new HIV infections among married serodiscordant couples receiving antiretroviral therapy. These impressive results have established treatment as prevention as an effective strategy to reduce the spread of HIV.[9–11] Attention is now being focused on whether findings based on the study of serodiscordant couples can be generalised to the wider population.[12]

A few ecological studies have shown increased uptake of antiretroviral therapy to be associated with a reduction in the number of new HIV diagnoses for a particular group, community, or administrative region over time.[13–15] However, such studies typically make use of aggregated outcomes and are therefore unable to assess the preventive effect of antiretroviral therapy for individuals.[16] In a previous study,[17] we reported the time to seroconversion for 16 667 HIV-uninfected individuals on the basis of antiretroviral therapy coverage in the local community.

We defined antiretroviral therapy coverage as the proportion of all HIV-infected people on antiretroviral therapy irrespective of CD4 count or disease stage. After controlling for a wide range of potential confounders, we showed that an individual living in a community with 30% antiretroviral therapy coverage was 38% less likely to acquire HIV than an individual living in a community with less than 10% coverage. This result provided powerful evidence for the community-level effectiveness of treatment as prevention. However, no previous study has assessed the preventive effect of antiretroviral therapy at the household level.

Here, we aimed to quantify the household-level preventive effect of a public-sector HIV treatment and care programme based in a rural South African community with poor knowledge and disclosure of HIV status, frequent migration, late marriage, and multiple partnerships. Specifically, we used information about the HIV serostatus and antiretroviral therapy status of household residents to assess whether antiretroviral therapy is associated with a reduction in HIV acquisition risk.

Methods

Study population

In this prospective cohort study, we linked patient records from a public-sector HIV treatment programme with population-based HIV surveillance data collected between 2004 and 2012 by the Africa Centre for Health and Population Studies. The population-based surveillance system at the Africa Centre was designed to capture the complex and dynamic demographic reality of the uMkanyakude district in the KwaZulu-Natal province of South Africa. The study area is roughly 440 km² in size with a resident population of 75 000 people and a total (resident and non-resident) population of 87 000 people. The area is generally poor and typical of a rural South African population, with scattered, informal, periurban settlements and a principal urban township.[18]

Historically, partnership stability in the study area has been profoundly affected by frequent and long-term migration—the result of apartheid-era policies that sought to regulate the rural supply of African labourers into urban centres and prevent their spouses or families from joining them.[19,20] Furthermore, marital rates (an important indicator of partnership stability) are low in the study area; in 2006, less than 20% of women and 10% of men aged 35 years or younger had ever been married.[21] Polygamous marriages constituted 12% of all marriages in women and 14% in men.[21] Men marry fairly late in life (median age 34 years),[22] because they typically need to save substantial proportions of their incomes for several years to be able to afford the Zulu bridewealth payment. Before marriage, many men will have had several casual sexual relationships, thereby increasing the risk of HIV infection.[21,23] Among sexually active men in our study area, 29% reported having had two or more concurrent partners between 2004 and 2009. The mean number of reported lifetime sexual partners in the community was six.[17,24]

The overall HIV incidence in the study area between 2004 and 2010 was 2·6 new infections per 100 person-years (95% CI 2·5–2·8).[25] Incidence peaked at 6·6 per 100 person-years in women aged 24 years, and at 4·1 per 100 person-years in men aged 29 years.[25] HIV prevalence for people aged 15–49 years has increased steadily from 22% in 2004 to 29% in 2011.[26] Antiretroviral therapy was made available to patients with CD4 counts less than 200 cells per µL through public-sector primary health-care clinics in September, 2004. Treatment eligibility was extended to patients with CD4 counts of less than 350 cells per µL for pregnant women and patients with active tuberculosis in April, 2010, and then for all adult patients in August, 2011.[27] Antiretroviral therapy coverage of all HIV-infected people in the study area rose from 0% in 2004 to 31% in 2011.[26]

The Africa Centre collects data for individuals who are members of family units or households in the study area. A household is defined as a building or group of buildings belonging to a single owner and used by residents for the purposes of living.[28] The average size of a household is seven resident members.[29] Roughly 21 500 households have been included in the Africa Centre's household surveillance since 2000. Household response rates are typically greater than 95%, and information is collected for both resident and non-resident members. Individual HIV testing has taken place within the household surveillance annually since 2003. Eligible participants aged 15 years and older are interviewed in private by trained fieldworkers, who also extract blood by finger prick for HIV testing. Overall, about 80% of all individuals in the study area consent to provide a blood sample for anonymous HIV testing.[18] Antiretroviral therapy is distributed through the HIV treatment and care programme by nurses and treatment counsellors, and records of patients' antiretroviral therapy status are updated and maintained in the antiretroviral therapy evaluation and monitoring system (ARTemis) database. The Africa Centre surveillance and HIV treatment programme are described in greater detail elsewhere.[18,29,30]

Procedures

The outcome measure for our study is the time to seroconversion for a repeat-tester. We define a repeat-tester as an individual aged 15–50 years who has had more than one HIV test, was HIV-uninfected at the first test, and was a resident member of at least one household in the surveillance area between Jan 1, 2004, and Dec 31, 2012. The repeat-testers, who are at risk of HIV infection, are a subset of the total resident population under surveillance. To obtain the date of seroconversion, we randomly selected a timepoint between a repeat-tester's latest HIV-uninfected and earliest HIV-infected test date. We right-censored repeat-testers who were HIV-uninfected at their most recent test.

The household surveillance captures the complexity of a repeat-tester's living arrangements through exposure episodes. A single exposure episode begins on the first day of the calendar year, or with the start of a new household residency, and ends on the last day of the calendar year, or with the migration of the repeat-tester to a different household within or outside the surveillance area. We used exposure episodes to measure the number of days spent by a repeat-tester in a single, distinct household within a calendar year, and to determine the coresident characteristics of the household for the corresponding exposure episode. Changes in household residencies within the surveillance area were captured with each new exposure episode. Thus, by definition, a repeat-tester cannot be a resident of two different households at the same point in time.

To investigate the time to HIV seroconversion for varying household levels of antiretroviral therapy coverage and HIV prevalence, we linked the data from 7657 adults living in the study area and enrolled in the local HIV treatment and care programme—who successfully started antiretroviral therapy and had an active follow-up status—with the data for the same individuals in the surveillance database. We used the linked records to determine whether a coresident was HIV-infected and not on antiretroviral therapy, HIV-infected and on antiretroviral therapy, or HIV-uninfected at any specific timepoint. We then used this information to construct measures of HIV prevalence and antiretroviral therapy coverage for the corresponding household. We defined HIV prevalence as the proportion of coresidents who are HIV-infected, and antiretroviral therapy coverage as the proportion of HIV-infected coresidents who are on antiretroviral therapy. HIV prevalence and antiretroviral therapy coverage were coded in units of ten percentage points on a scale of 0–100%. Because of the predominantly heterosexual transmission of HIV in our study area,[17] we stratified household HIV prevalence and antiretroviral therapy coverage by sex, and used the opposite-sex antiretroviral therapy coverage as our main exposure variable.

We used the household as a proxy for coresident partners of the repeat-tester—ie, we did not specifically identify whether the repeat-tester is in a sexual relationship with one or more opposite-sex coresidents for an exposure episode. We excluded coresident members younger than 15 years and those with an age difference of 15 years or more from the repeat-tester to exclude specific types of family members—grandparents, parents, children, and grandchildren—from being counted as possible sexual partners in the household.

To ensure sufficient exposure to HIV-infected coresidents (who are either on antiretroviral therapy or not), we excluded from our analysis repeat-testers who spend more than 50% of exposure time outside the surveillance area. We also excluded repeat-testers who lived alone, because these individuals were not eligible for the main exposure of interest (antiretroviral therapy coverage among opposite-sex household coresidents). We used detailed surveillance information about coresident deaths, migrations out of the surveillance area, and loss to follow-up to update the respective numerator or denominator of the household antiretroviral therapy coverage and HIV prevalence measures for each exposure episode for each repeat-tester.

Ethics approval for data collection, linkage, and use was obtained from the biomedical and ethics committee of the University of KwaZulu-Natal (Durban, South Africa).

Statistical analysis

We used a Cox proportional-hazards model to obtain an estimate for a repeat-tester's hazard of HIV seroconversion conditional on household opposite-sex antiretroviral therapy coverage, controlling for household opposite-sex HIV prevalence, sex and age (in 5-year sex-age strata), knowledge of own HIV status (yes, no, or refused), having heard about antiretroviral therapy (yes, no, or refused), area of residence (rural, peri-urban, or urban), household wealth (by quintile, based on an assets index generated in principal component analysis), number of opposite-sex household residents, and number of household residency changes by the repeat-tester (none, one, or two or more). All variables apart from the repeat-tester's sex were time-varying. We report 95% CIs based on SEs that have been adjusted for clustering at the household level. The main results are reported for a regression model based on data for opposite-sex coresidents only (opposite-sex model).

Even after controlling for the independent variables in the opposite-sex regression model, the relation between HIV seroconversion hazard and household opposite-sex antiretroviral therapy coverage could be confounded by a range of unobserved factors, such as conscientiousness of individual household members, attitudes towards risk, and attitudes towards health. Although we cannot include these factors in the regression because we do not have data for them, we can control for their confounding effects by adding same-sex antiretroviral therapy coverage and same-sex HIV prevalence. A household's same-sex antiretroviral therapy coverage will depend on many of the same unobserved factors, such as household members' conscientiousness and attitudes, that are also likely to affect a household's opposite-sex antiretroviral therapy coverage. Thus we also report the results after adding household same-sex antiretroviral therapy coverage and same-sex HIV prevalence to the regression (full model).

We also did an alternative analysis in which household antiretroviral therapy coverage and HIV prevalence were treated as binary variables (none *vs* one or more HIV-infected coresidents on antiretroviral therapy, and none *vs* one or more HIV-infected coresidents) rather than in units of ten percentage points.

All statistical analyses were done with Stata (version 12.1).

	Person-years	Number of HIV seroconversions	HIV incidence* (95% CI)
Calendar year			
2004	5552	208	3·75 (3·27–4·29)
2005	7060	269	3·81 (3·38–4·29)
2006	7575	321	4·24 (3·80–4·73)
2007	7347	268	3·65 (3·24–4·11)
2008	7102	275	3·87 (3·44–4·36)
2009	6389	237	3·71 (3·27–4·21)
2010	5724	203	3·55 (3·09–4·07)
2011	4858	164	3·38 (2·90–3·93)
2012	3239	92	2·84 (2·32–3·48)
Age-sex stratum			
Women aged 15–19 years	9179	451	4·91 (4·48–5·39)
Women aged 20–24 years	7478	583	7·80 (7·19–8·46)
Women aged 25–29 years	3140	204	6·50 (5·66–7·45)
Women aged 30–34 years	2271	96	4·23 (3·46–5·16)
Women aged 35–39 years	2795	70	2·50 (1·98–3·17)
Women aged 40–44 years	3513	77	2·19 (1·75–2·74)
Women aged ≥45 years	5349	73	1·36 (1·09–1·72)
Men aged 15–19 years	8373	75	0·90 (0·71–1·12)
Men aged 20–24 years	5848	192	3·28 (2·85–3·78)
Men aged 25–29 years	2082	97	4·66 (3·82–5·68)
Men aged 30–34 years	1171	38	3·25 (2·36–4·46)
Men aged 35–39 years	1039	31	2·98 (2·10–4·24)
Men aged 40–44 years	1076	24	2·23 (1·50–3·33)
Men aged ≥45 years	1531	26	1·70 (1·16–2·49)
Knows HIV status			
Yes	36 596	1372	3·75 (3·56–3·95)
No	4331	131	3·02 (2·55–3·59)
Refused	13 918	534	3·84 (3·52–4·18)
Has heard about antiretroviral therapy			
Yes	23 614	880	3·73 (3·49–3·98)
No	4452	134	3·01 (2·54–3·56)
Refused	26 778	1023	3·82 (3·59–4·06)
Area of residence			
Peri-urban	16 597	724	4·36 (4·06–4·69)
Rural	36 613	1248	3·41 (3·22–3·60)
Urban	1634	65	3·98 (3·12–5·07)
Household wealth quintile			
Poorest	11 117	368	3·31 (2·99–3·67)
Second poorest	12 251	437	3·57 (3·25–3·92)
Third poorest	11 916	467	3·92 (3·58–4·29)
Fourth poorest	10 981	464	4·23 (3·86–4·63)
Wealthiest	8580	301	3·51 (3·13–3·93)
Changes of household residencies			
None	50 481	1828	3·62 (3·46–3·79)
One	3642	169	4·64 (3·99–5·39)
Two or more	722	40	5·54 (4·06–7·55)

*New infections per 100 person-years.

Table 1: **Incidence of HIV-1 seroconversion by sociodemographic variables, 2004–12**

See Online for appendix

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

14 505 repeat-testers met our inclusion and exclusion criteria of whom 8546 (59%) were women. 2037 HIV seroconversions were recorded over 54 845 person-years of follow-up time during the 2004–12 period. The median follow-up time per repeat-tester was 3·2 years (IQR 1·8–5·5), with a maximum of 10·2 years. The unadjusted HIV incidence over the study period was 3·7 new infections per 100 person-years (95% CI 3·6–3·9). Incidence was highest in the 20–24 years age group for women and in the 25–29 years age group for men (table 1). Unadjusted HIV incidence remained stable from 2004 to 2008 and then fell from 3·9 per 100 person-years in 2008 to 2·8 per 100 person-years in 2012 (table 1).

An average of 4102 (range 1131–5119) households per year were included in the analysis during the study period. About 10% of the repeat-testers changed household residencies one or more times during the study period. Repeat-testers were exposed to a mean of 1·2 (SD 0·5) different antiretroviral therapy coverage levels (coded in units of ten percentage points).

For every increase of ten percentage points in opposite-sex household antiretroviral therapy coverage the hazard of HIV acquisition was reduced by 6% (95% CI 2–9), after controlling for household HIV prevalence and the other independent variables (table 2). Table 3 shows the adjusted HIV acquisition hazards for different percentage point increases in household antiretroviral therapy coverage. For example, an increase of 50 percentage points in opposite-sex household antiretroviral therapy coverage (eg, an increase from 0% to 50%, from 10% to 60%, or from 20% to 70%), was associated with a 26% (95% CI 9–39) reduction in the hazard of HIV acquisition.

The full model included measures of same-sex antiretroviral therapy coverage and same-sex HIV prevalence. The point estimate for the change in hazard of HIV acquisition for an increase of ten percentage points in household antiretroviral therapy coverage was the same as the one in the opposite-sex model (table 2). The adjusted hazard ratio (HR) for household same-sex HIV prevalence was not significant (table 2). Results for univariate analyses are shown in the appendix.

In the alternative analysis (in which we coded household antiretroviral therapy coverage and HIV prevalence as binary variables), the hazard of HIV acquisition for an individual living in a household with at least one HIV-infected coresident on antiretroviral therapy was 24% less than for an individual living in a household in which none of the HIV-infected coresidents were on antiretroviral therapy (adjusted HR 0·76, 95% CI 0·60–0·95, p=0·017).

	Opposite-sex model		Full model	
	Adjusted hazard ratio (95% CI)	p value	Adjusted hazard ratio (95% CI)	p value
Opposite-sex antiretroviral therapy coverage*	0·94 (0·91–0·98)	0·0036	0·94 (0·91–0·98)	0·0034
Opposite-sex HIV prevalence†	1·05 (1·03–1·07)	<0·0001	1·05 (1·03–1·07)	<0·0001
Number of opposite-sex coresidents‡	0·98 (0·96–1·02)	0·4072	0·98 (0·95–1·02)	0·3292
Knows HIV status				
Yes (reference)	1·00	..	1·00	..
No	1·11 (0·99–1·25)	0·0705	1·11 (0·99–1·25)	0·0695
Refused	1·30 (0·60–2·80)	0·5004	1·30 (0·60–2·79)	0·5027
Has heard about antiretroviral therapy				
Yes (reference)	1·00	..	1·00	..
No	0·98 (0·88–1·10)	0·7476	0·98 (0·88–1·10)	0·7846
Refused	0·70 (0·33–1·49)	0·3592	0·70 (0·33–1·50)	0·3616
Age-sex stratum				
Men aged 15–19 years (reference)	1·00	..	1·00	..
Men aged 20–24 years	3·76 (2·87–4·93)	<0·0001	3·77 (2·87–4·94)	<0·0001
Men aged 25–29 years	5·36 (3·95–7·26)	<0·0001	5·36 (3·95–7·27)	<0·0001
Men aged 30–34 years	3·72 (2·47–5·59)	<0·0001	3·70 (2·46–5·56)	<0·0001
Men aged 35–39 years	3·38 (2·23–5·13)	<0·0001	3·37 (2·22–5·11)	<0·0001
Men aged 40–44 years	2·56 (1·62–4·06)	<0·0001	2·55 (1·61–4·05)	<0·0001
Men aged ≥45 years	2·01 (1·28–3·15)	0·0023	2·00 (1·28–3·14)	0·0024
Women aged 15–19 years	5·75 (4·52–7·32)	<0·0001	5·75 (4·51–7·32)	<0·0001
Women aged 20–24 years	9·59 (7·52–12·23)	<0·0001	9·58 (7·50–12·23)	<0·0001
Women aged 25–29 years	8·04 (6·14–10·52)	<0·0001	8·03 (6·13–10·52)	<0·0001
Women aged 30–34 years	5·11 (3·78–6·90)	<0·0001	5·10 (3·77–6·90)	<0·0001
Women aged 35–39 years	3·03 (2·18–4·22)	<0·0001	3·03 (2·17–4·22)	<0·0001
Women aged 40–44 years	2·63 (1·90–3·65)	<0·0001	2·63 (1·90–3·65)	<0·0001
Women aged ≥45 years	1·68 (1·21–2·33)	0·0018	1·68 (1·21–2·33)	0·0018
Area of residence				
Rural (reference)	1·00	..	1·00	..
Peri-urban	1·29 (1·16–1·44)	<0·0001	1·29 (1·16–1·43)	<0·0001
Urban	1·27 (0·97–1·67)	0·0861	1·27 (0·97–1·67)	0·0866
Household wealth quintile				
Poorest (reference)	1·00	..	1·00	..
Second poorest	1·04 (0·90–1·20)	0·6883	1·04 (0·90–1·20)	0·5874
Third poorest	1·06 (0·92–1·23)	0·4065	1·06 (0·92–1·23)	0·4148
Fourth poorest	1·14 (0·98–1·32)	0·0848	1·14 (0·98–1·32)	0·0857
Wealthiest	0·91 (0·77–1·08)	0·2856	0·91 (0·77–1·08)	0·2843
Changes of household residencies				
None (reference)	1·00	..	1·00	..
One	1·15 (0·97–1·35)	0·1075	1·14 (0·97–1·35)	0·1067
Two or more	1·26 (0·92–1·73)	0·1437	1·26 (0·92–1·73)	0·1442
Same-sex antiretroviral therapy coverage*	..	..	1·03 (0·98–1·08)	0·2974
Same-sex HIV prevalence†	..	..	1·00 (0·96–1·05)	0·8380
Number of seroconversions	2037	..	2037	..
Number of at-risk individuals	14 505	..	14 505	..

95% CIs are based on SEs that have been adjusted for clustering at the household level. *Adjusted hazard ratio represents the change in HIV seroconversion hazard for any increase of ten percentage points in household antiretroviral therapy coverage, controlling for the other independent variables in the regression model. †Adjusted hazard ratio represents the change in HIV seroconversion hazard for any increase of ten percentage points in household HIV prevalence, controlling for the other independent variables in the regression model. ‡Adjusted hazard ratio represents the change in HIV seroconversion hazard for an increase in household size by one opposite-sex member, controlling for the other independent variables in the regression model.

***Table 2*: Results of multivariable analysis for the effect of an increase in opposite-sex household antiretroviral therapy coverage on HIV seroconversion hazard**

Discussion

Our study has shown that for each increase of ten percentage points in opposite-sex household antiretroviral therapy coverage, the HIV acquisition hazard was reduced by 6% (95% CI 2–9), after controlling for other factors. This effect size translates into large reductions in HIV acquisition hazards when household antiretroviral therapy coverage is substantially increased—eg, an increase of 50 percentage points in household antiretroviral therapy coverage (eg, from 20% to 70%) reduced the hazard of HIV acquisition by 26% (95% CI 9–39). Importantly, our results show that the preventive effectiveness of antiretroviral therapy can persist in social contexts in which stable sexual partnerships are difficult to identify, occur late in life, or are not the norm. Our study provides the first real-world evidence for the preventive effectiveness of antiretroviral therapy within the household setting (panel).

	Adjusted hazard ratio (95% CI)*
10 percentage points	0·94 (0·91–0·98)
20 percentage points	0·89 (0·82–0·96)
30 percentage points	0·84 (0·74–0·94)
40 percentage points	0·79 (0·67–0·92)
50 percentage points	0·74 (0·61–0·91)
60 percentage points	0·70 (0·55–0·89)
70 percentage points	0·66 (0·50–0·87)
80 percentage points	0·62 (0·45–0·85)
90 percentage points	0·58 (0·41–0·84)
100 percentage points	0·55 (0·37–0·82)

*Data are adjusted for opposite-sex household HIV prevalence and the other independent variables included in the opposite-sex model; the effect size for each percentage-point increase will be the same irrespective of the baseline coverage.

Table 3: **Effect of percentage-point increases in opposite-sex household antiretroviral therapy coverage on HIV acquisition hazard**

Panel: Research in context

Systematic review

We did not do a systematic review of the scientific literature, but referred to three previously published systematic reviews[2–4] (synthesising evidence from a total of one randomised controlled trial and nine observational studies), which showed that antiretroviral therapy substantially reduced or prevented HIV transmission among serodiscordant couples. The authors of two reviews[12,16] concluded that ecological studies have methodological limitations, and that the population-level preventive benefit of antiretroviral therapy has yet to be proven. Results of one study[25] showed that high antiretroviral therapy coverage was associated with a reduction in individual risk of HIV acquisition at the community level. We searched PubMed for reports published in English between Jan 1, 2004, and Dec 1, 2013, using the search terms "antiretroviral therapy", "prevention", and "household". We did not identify any studies that assessed the association between risk of HIV acquisition at the individual level and household antiretroviral therapy coverage.

Interpretation

Our study provides further evidence that treatment with antiretroviral therapy significantly reduces the risk of onward transmission of HIV in a real-world setting in sub-Saharan Africa. Public promotion of the preventive benefits of antiretroviral therapy could help to motivate individuals to learn their HIV status and seek treatment. Adherence to antiretroviral therapy is more likely to be sustained if HIV-infected individuals are aware that the therapy will protect their sexual partners from acquiring the infection. Similarly, the knowledge that antiretroviral therapy can provide protection from HIV acquisition could motivate HIV-uninfected individuals to persuade their infected coresident partners to initiate antiretroviral therapy, improving the long-term use of life-saving drugs within the household.

Our study had several limitations. Although we used linked clinical and population-based cohort data, we cannot completely rule out the effect of unobserved confounding on our results. A better approach to address confounding would be a randomised control trial, but this strategy would not be possible at the household level for ethical and methodological reasons. However, by controlling for same-sex antiretroviral therapy coverage in the household, we do account for unobserved factors at the household level that affect both opposite-sex and same-sex coverage and could confound the observed relation between opposite-sex coverage and HIV acquisition. Such factors include the conscientiousness of household members, attitudes towards risk, and attitudes towards health, which are highly plausible confounders in this study, but difficult to measure directly.

Our inability to individually link HIV-uninfected individuals to sexual partners outside the household, along with the possible migration of sexual partners outside of the study area, makes accurate measurement of the preventive effectiveness of antiretroviral therapy difficult. Since a subset of HIV-infected individuals (who might or might not be on antiretroviral therapy) in our cohort did not reside in the same household as their uninfected sexual partner and were therefore excluded from the analysis, our finding should be regarded as a minimum estimate of the preventive effectiveness of antiretroviral therapy.

In our study, we included a coresident member in the measure of household antiretroviral therapy coverage if his or her date of antiretroviral therapy initiation was before a residency in a household and if his or her clinic follow-up status was still active during the residency period. We therefore could have further underestimated the preventive benefit of antiretroviral therapy since we did not account for patients failing antiretroviral therapy.

Important strengths of our study include the use of one of the world's largest HIV incidence cohorts and the ability of our data and study design to capture the changing demographic conditions of an HIV-uninfected individual's living arrangements over time. In this respect, our study is unique because it uses information about HIV serostatus and antiretroviral therapy status among coresident household members to test the treatment-as-prevention hypothesis in a real-world setting in sub-Saharan Africa. Awareness that antiretroviral

therapy can prevent transmission to coresident sexual partners could motivate individuals to disclose their HIV status and to seek and adhere to treatment, improving the long-term use of live-saving antiretroviral therapy.

Contributors

AV did the data preparation, statistical analysis, and writing of the report, under the supervision of FT and TB. TB, FT, and M-LN suggested improvements to the statistical analysis and revisions to the report. All authors approved the final submitted version of the report.

Declaration of interests

We declare that we have no competing interests.

Acknowledgments

We thank the anonymous reviewers of this report, and Ann Meier for reviewing an earlier draft at a Population Association of America meeting in New Orleans (LA, USA) in April, 2013. Colin Newell from the Africa Centre for Health and Population Studies provided valuable data support and assistance. The Africa Centre for Health and Population Studies receives core funding, including for population-based surveillance, from the Wellcome Trust (grant number 082384/Z/07/Z). AV was partly supported by a Department of Sociology Professional Development award and a Minnesota Population Center travel grant from the University of Minnesota (Minneapolis, MN, USA). FT and TB were supported by a grant from the US National Institute of Child Health and Human Development (grant number 1R01-HD058482-01). The HIV treatment and care programme in KwaZulu-Natal was made possible by the support of the US Agency for International Development and the US President's Emergency Plan for AIDS Relief.

References

1 Nakagawa F, Lodwick RK, Smith CJ, et al. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS* 2012; **26:** 335–43.

2 Loutfy MR, Wu W, Letchumanan M, et al. Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy. *PloS One* 2013; **8:** e55747.

3 Baggaley RF, White RG, Hollingsworth TD, Boily MC. Heterosexual HIV-1 infectiousness and antiretroviral use: systematic review of prospective studies of discordant couples. *Epidemiology* 2013; **24:** 110–21.

4 Anglemyer A, Rutherford GW, Horvath T, Baggaley RC, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Database Syst Rev* 2013; **4:** CD009153.

5 Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.

6 Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS* 2006; **20:** 85–92.

7 Donnell D, Baeten JM, Kiarie J, et al, for the Partners in Prevention HSV/HIV Transmission Study Team. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; **375:** 2092–98.

8 He N, Duan S, Ding Y, et al. Antiretroviral therapy reduces HIV transmission in discordant couples in rural Yunnan, China. *PloS One* 2013; **8:** e77981.

9 Montaner JSG. Treatment as prevention—a double hat-trick. *Lancet* 2011; **378:** 208–09.

10 Hayden E. 'Seek, test and treat' slows HIV. *Nature* 2010; **463:** 1006.

11 Cambiano V, Rodger AJ, Phillips AN. 'Test-and-treat': the end of the HIV epidemic? *Curr Opin Infect Dis* 2011; **24:** 19–27.

12 Cohen MS, Smith MK, Muessig KE, Hallett TB, Powers KA, Kashuba AD. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? *Lancet* 2013; **382:** 1515–24.

13 Das M, Chu PL, Santos GM, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PloS One* 2010; **5:** e11068.

14 Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010; **376:** 532–39.

15 Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ* 2009; **338:** b1649.

16 Smith MK, Powers KA, Muessig KE, Miller WC, Cohen MS. HIV treatment as prevention: the utility and limitations of ecological observation. *PLoS Med* 2012; **9:** e1001260.

17 Tanser F, Bärnighausen T, Hund L, Garnett GP, McGrath N, Newell ML. Effect of concurrent sexual partnerships on rate of new HIV infections in a high-prevalence, rural South African population: a cohort study. *Lancet* 2011; **378:** 247–55.

18 Tanser F, Hosegood V, Bärnighausen T, et al. Cohort profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. *Int J Epidemiol* 2008; **37:** 956–62.

19 Posel D. Influx control and urban labour markets in the 1950s. In: Bonner PL, Delius P, Posel D (eds.) Apartheid's genesis, 1935–1962. Johannesburg: Ravan Press, 1993.

20 Murray C. Families divided: the impact of migrant labour in Lesotho (African Studies Series 29). Cambridge: Cambridge University Press, 1981.

21 Hosegood V, McGrath N, Moultrie TA. Dispensing with marriage: marital trends in rural KwaZulu-Natal, South Africa 2000–2006. *Demogr Res* 2009; **20:** 279–312.

22 Statistics South Africa. Marriages and divorces 2011 (statistical release P0307). Pretoria: Statistics South Africa, 2012.

23 Ott MQ, Bärnighausen T, Tanser F, Lurie MN, Newell ML. Age-gaps in sexual partnerships: seeing beyond 'sugar daddies'. *AIDS* 2011; **25:** 861–63.

24 Todd J, Cremin I, McGrath N, et al. Reported number of sexual partners: comparison of data from four African longitudinal studies. *Sex Transm Infect* 2009; **85** (suppl 1)**:** i72–80.

25 Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science* 2013; **339:** 966–71.

26 Zaidi J, Grapsa E, Tanser F, Newell ML, Bärnighausen T. Dramatic increases in HIV prevalence after scale-up of antiretroviral treatment: a longitudinal population-based HIV surveillance study in rural KwaZulu-Natal. *AIDS* 2013; **27:** 2301–05.

27 Lessells RJ, Mutevedzi PC, Iwuji CC, Newell ML. Reduction in early mortality on antiretroviral therapy for adults in rural South Africa since change in CD4+ cell count eligibility criteria. *J Acquir Immune Defic Syndr* 2014; **65:** e17–24.

28 Africa Centre for Health and Population Studies. Africa Centre Demographic Information System (ACDIS) fieldwork training manual. Somkhele: Africa Centre for Health and Population Studies, 2008.

29 Bor J, Bärnighausen T, Newell C, Tanser F, Newell ML. Social exposure to an antiretroviral treatment programme in rural Kwazulu-Natal. *Trop Med Int Health* 2011; **16:** 988–94.

30 Houlihan CF, Bland RM, Mutevedzi PC, et al. Cohort profile: Hlabisa HIV treatment and care programme. *Int J Epidemiol* 2011; **40:** 318–26.