OPEN ACCESS

High prevalence and incidence of gonorrhoea and chlamydia in young women eligible for HIV pre-exposure prophylaxis in South Africa and Zimbabwe: results from the HPTN 082 trial

Sinead Delany-Moretlwe ,[1] Nyaradzo Mgodi,[2] Linda-Gail Bekker ,[3] Jared M Baeten,[4,5] Chuwen Li,[6] Deborah Donnell ,[6] Yaw Agyei,[7] Denni Lennon,[7] Scott M Rose,[8] Marcia Mokgatle,[1] Sheetal Kassim,[3] Shorai Mukaka,[2] Adeola Adeyeye,[9] Connie Celum[4]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/sextrans-2022-055696).

For numbered affiliations see end of article.

Correspondence to
Dr Sinead Delany-Moretlwe, Wits RHI, 22 Esselen Street, Hillbrow, Johannesburg, 2001, South Africa; sdelany@wrhi.ac.za

Received 14 November 2022
Accepted 7 February 2023

To cite: Delany-Moretlwe S, Mgodi N, Bekker L-G, *et al*. *Sex Transm Infect* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/sextrans-2022-055696

ABSTRACT

Introduction We investigated the prevalence, incidence and factors associated with sexually transmitted infections (STIs) among young African women seeking HIV pre-exposure prophylaxis (PrEP).

Methods HPTN 082 was a prospective, open-label PrEP study enrolling HIV-negative sexually active women aged 16–25 years in Cape Town and Johannesburg, South Africa, and Harare, Zimbabwe. Endocervical swabs from enrolment, months 6 and 12 were tested for *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) by nucleic acid amplification, and *Trichomonas vaginalis* (TV) by a rapid test. Intracellular tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots were measured at months 6 and 12. Associations between risk characteristics and STI outcomes were assessed using Poisson regression.

Results Of 451 enrolled participants, 55% had an STI detected at least once. CT incidence was 27.8 per 100 person-years (py) (95% CI 23.1, 33.2), GC incidence was 11.4 per 100 py (95% CI 8.5, 15.0) and TV incidence was 6.7 per 100 py (95% CI 4.5, 9.5). 66% of incident infections were diagnosed in women uninfected at baseline. Baseline cervical infection (GC or CT) risk was highest in Cape Town (relative risk (RR) 2.38, 95% CI 1.35, 4.19) and in those not living with family (RR 1.87, 95% 1.13, 3.08); condom use was protective (RR 0.67, 95% CI 0.45, 0.99). Incident CT was associated with baseline CT (RR 2.01; 95% CI 1.28, 3.15) and increasing depression score (RR 1.05; 95% CI 1.01, 1.09). Incident GC was higher in Cape Town (RR 2.40; 95% CI 1.18, 4.90) and in participants with high PrEP adherence (TFV-DP concentrations ≥700 fmol/punch) (RR 2.04 95% CI 1.02, 4.08).

Conclusion Adolescent girls and young women seeking PrEP have a high prevalence and incidence of curable STIs. Alternatives to syndromic management for diagnosis and treatment are needed to reduce the burden of STIs in this population.

Trial registration number NCT02732730.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Adolescent girls and young women in sub-Saharan Africa (SSA) experience a disproportionate burden of sexually transmitted infections (STIs), including HIV. Current approaches to the diagnosis and treatment of curable STIs are limited. Expanding pre-exposure prophylaxis (PrEP) programmes in SSA provides a potential platform for integrating and strengthening novel STI prevention and control approaches. Data are needed on the prevalence and incidence of STIs in populations initiating PrEP in SSA.

WHAT THIS STUDY ADDS

⇒ The prevalence and incidence of curable STI in adolescent girls and young women are much higher than in the general population. Adolescent girls and young women with high PrEP adherence based on drug concentrations had an increased risk of incident gonorrhoea. Location appeared to be a stronger influence on risk rather than individual behavioural risk factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These data provide a strong rationale for the integration of aetiological STI testing and other novel STI prevention approaches within PrEP services in SSA.

BACKGROUND

Women in sub-Saharan Africa (SSA) bear a disproportionate burden of sexually transmitted infections (STIs), including HIV.[1] In 2019, adolescent girls and young women (AGYW) aged 15–24 years accounted for 26% of new HIV infections in eastern and southern Africa.[1] In 2016, the WHO African region had the highest prevalence and incidence of gonorrhoea and trichomoniasis in women globally.[2] Untreated gonorrhoea (*Neisseria gonorrhoeae* (GC)) and chlamydia (*Chlamydia trachomatis* (CT)) increase the risk of pelvic inflammatory disease (PID), ectopic pregnancy, chronic pelvic pain and tubal infertility significantly.[3] Up to 15%–20% of women with documented chlamydial or gonococcal PID develop infertility.[4–6] Infertility has serious social consequences for many women

including poor mental health and intimate partner violence.[7] Women with secondary infertility may increase their risk of HIV in their attempts to conceive through frequent condomless sex.[8] STIs increase the risk of HIV acquisition and transmission several-fold, even if STIs are asymptomatic.[3 9] Untreated bacterial STIs are also associated with poor pregnancy and infant outcomes, including prematurity, death and congenital infections.[10] Overall, untreated STIs and their complications result in a considerable number of disability-adjusted life years lost, particularly in women and infants in SSA.[11]

Syndromic case management (SM) is still the mainstay of STI prevention and control programmes in Africa, and is based on the recognition of signs and symptoms associated with particular pathogens, and treatment for the most frequent causes of that syndrome.[12] While SM has some advantages over other approaches in resource-constrained settings, limitations in the diagnosis and management of cervical infections in women are well established.[12] The vaginal discharge algorithm is a poor predictor of cervical infection, even after the addition of risk scores or simple laboratory evaluations.[13–1513–16] As a result, high numbers of women are either overtreated or miss treatment (due to frequent asymptomatic infections) with the potential for serious long-term consequences.

Expanding pre-exposure prophylaxis (PrEP) programmes in SSA provides an opportunity to strengthen failing STI prevention and control programmes by providing a platform to integrate aetiological STI testing for at-risk persons and to link at-risk individuals to novel STI prevention interventions. To date, few data on STIs in African women taking PrEP have been available. HPTN 082 was an open-label PrEP demonstration project that assessed oral PrEP uptake and adherence among African AGYW and included laboratory testing and treatment for prevalent and incident STIs. We assessed the prevalence and incidence of chlamydia and gonorrhoea and predictors of infection in this cohort, as well as explored the relationship between PrEP adherence based on tenofovir-diphosphate (TFV-DP) concentrations and subsequent STIs.

METHODS

Study population

Between October 2016 and October 2018, 451 HIV-negative women aged 16–25 years were recruited for HPTN 082 from Cape Town and Johannesburg, South Africa, and Harare, Zimbabwe (ClinicalTrials.gov *NCT02732730*). Women were eligible if they had vaginal or anal sex in the month prior to screening, showed interest in PrEP based on the HIV Prevention Readiness Measure (adapted from the HIV Treatment Readiness Measure),[17] had regular access to a mobile phone, were hepatitis B surface antigen negative, had creatinine clearance >60 mL/min, were not pregnant and had a score of >5 on the VOICE risk score.[18] VOICE risk scores ≥5 have been associated with HIV incidence >5 per 100 person-years (py) in previous cohorts of African women seeking HIV prevention.[19]

Study procedures

Details of the study procedures have been published elsewhere.[18] Briefly, consenting AGYW were eligible to enrol regardless of their decision to initiate PrEP, and those who did not initiate PrEP at enrolment were offered PrEP at each subsequent visit. Cervicovaginal and blood samples collected at screening, month 6 and month 12 visits. Swabs were self-collected unless a pelvic examination was indicated in which case clinician-directed samples were collected. Dried blood spots (DBS) for PrEP adherence measurements were also collected at months 6 and 12. Participants with STI symptoms and signs received immediate treatment according to national syndromic management guidelines. Asymptomatic participants with positive laboratory test results were treated with appropriate antibiotics at the earliest subsequent visit. No test of cure was performed. Participants with an STI also received risk reduction counselling and condoms, and were encouraged to have their partner treated (ie, partner notification) using direct referral.

Cervicovaginal swabs were tested for GC and CT by nucleic acid amplification test (Cepheid GeneXpert, Sunnyvale, California, USA), and *Trichomonas vaginalis* (TV) by rapid test (OSOM Trichomonas Test, Seikusui Diagnostics, Burlington, Massachusetts, USA). Syphilis was assessed by Rapid Plasma Reagin (Macro-Vue RPR Test, Becton Dickinson, Sparks, Maryland, USA) followed by a treponemal-specific confirmatory assay (Serodia-TPPA, Fujirebio, Tokyo, Japan). DBS were assessed for intracellular TFV-DP at the University of Colorado, using liquid chromatography/tandem mass spectrometry.[20] Intracellular TFV-DP concentrations in red blood cells have a 17-day half-life and 25-fold drug accumulation that provides a cumulative measure of dosing and average adherence to PrEP in the prior 6 weeks based on studies of directly observed dosing of PrEP.[20 21]

Statistical analysis

Descriptive statistics summarise sociodemographic, partner and risk characteristics and infection data. Multiple imputation methods were used to impute missing individual components of the depression score. Imputation increases statistical power and has been shown to be an appropriate approach to handling missing data for the Center for Epidemiological Studies Depression Scale used in this study and is preferred over assigning a 0 score for missing data, which would potentially underestimate levels of depression.[22] We compared participant characteristics by site to determine any significant behavioural or risk characteristics by site using linear regression for continuous variables (VOICE risk score and number of vaginal sex episodes) and X^2 tests for categorical variables.

Outcomes of interest were any cervical infection (CT/GC), as well as CT or GC alone at baseline or at either follow-up visit (months 6 and 12). STI incidence rates and 95% CIs were assessed assuming a Poisson distribution. Associations between risk characteristics at baseline and over time and outcomes of interest were assessed using Poisson regression fitted using Generalized Estimating Equations assuming an exchangeable correlation structure. We developed separate models for each outcome (ie, GC, CT or both infections) and for prevalent and incident infections. Factors considered significant at the 0.05 level in bivariate regression were included in the final multivariate model. To assess the association between PrEP use and subsequent STI outcomes, we included the categorical variables of any versus no detectable TFV-DP in DBS, as well as TFV-DP >700 fmol/punch vs <700 fmol/punch, at month 6 or 12. The threshold of 700 fmol/punch is associated with an average of four or more PrEP doses per week in directly observed dosing studies that included both men and women, and in the iPrEx Study, the 700 fmol/punch threshold was associated with 100% PrEP efficacy among men who have sex with men.[20 21 23] At the time of study design, no in vivo data were available to support specific thresholds in women.

Table 1 Baseline characteristics, by STI diagnosis (N=451)

	Neisseria gonorrhoeae (n=35)	*Chlamydia trachomatis* (n=136)	*Trichomonas vaginalis* (n=28)	Any STI at baseline (n=174)	No STI at baseline (n=277)	P value
Site						0.0001
Cape Town, South Africa	21 (60%)	56 (41%)	7 (25%)	72 (41%)	69 (25%)	
Johannesburg, South Africa	6 (17%)	50 (37%)	10 (36%)	62 (36%)	100 (36%)	
Harare, Zimbabwe	8 (23%)	30 (22%)	11 (39%)	40 (23%)	108 (39%)	
Age (years)						0.036
Median (IQR)	20 (18–21)	20 (19–22)	21 (20–24)	20 (19–22)	21 (19–23)	
Lives with						0.080
Partner	5 (14%)	24 (18%)	8 (29%)	31 (18%)	67 (24%)	
Parents and/or siblings	24 (69%)	75 (55%)	14 (50%)	98 (56%)	160 (58%)	
Others	6 (17%)	37 (27%)	6 (21%)	45 (26%)	50 (18%)	
Partner age difference						0.154
Less than 5 years	29 (83%)	97 (71%)	19 (68%)	125 (72%)	177 (64%)	
≥5 and <10 years	6 (17%)	31 (23%)	7 (25%)	40 (23%)	75 (27%)	
≥10 years	0 (0%)	8 (6%)	2 (7%)	9 (5%)	25 (9%)	
Partner has made you feel unsafe, afraid or in danger in past year	9 (26%)	20 (15%)	3 (11%)	27 (16%)	63 (23%)	0.069
CES-D score ≥10*	21 (60%)	79 (58%)	16 (57%)	102 (59%)	166 (60%)	0.765
Contraceptive method						0.045
Injectable contraceptives	23 (66%)	68 (50%)	7 (25%)	87 (50%)	104 (38%)	
Implants	5 (14%)	25 (18%)	10 (36%)	35 (20%)	69 (25%)	
IUD-copper/hormone	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1%)	
Sterilisation	0 (0%)	0 (0%)	1 (4%)	1 (1%)	0 (0%)	
Oral contraceptives	1 (3%)	18 (13%)	6 (21%)	20 (11%)	34 (12%)	
Condoms, natural methods or none	6 (17%)	25 (19%)	4 (15%)	31 (18%)	66 (24%)	
Transactional sex, past month	7 (20%)	28 (21%)	12 (43%)	42 (24%)	59 (21%)	0.489
Anal sex, past month						
Yes	7 (20%)	21 (15%)	2/28 (7%)	27 (16%)	41 (15%)	0.391
No	20 (57%)	78 (57%)	17 (61%)	101 (58%)	146 (53%)	
Prefer not to answer	8 (23%)	37 (27%)	9 (32%)	46 (26%)	90 (32%)	
No of vaginal sex episodes, past month						0.307
Median (IQR)	5 (2–10)	4 (2–6)	6 (4–12)	4 (2–8)	4 (3–8)	
Condom use at last vaginal sex†	8 (29%)	33 (31%)	7 (29%)	44 (31%)	96 (45%)	0.033
Coinfection with other STIs						
C. trachomatis	19 (54%)	136 (100%)	7 (25%)	136 (78%)	0 (0%)	
N. gonorrhoeae	35 (100%)	19 (14%)	1 (4%)	35 (20%)	0 (0%)	
T. vaginalis	1 (3%)	7 (5%)	28 (100%)	28 (16%)	0 (0%)	
High self-perceived HIV risk in next year‡	1 (3%)	10 (7%)	3 (11%)	12 (7%)	22 (8%)	0.430
Modified VOICE risk score§						0.544
Median (IQR)	7 (6–8)	7 (5–7)	6 (5–7)	7 (6–7)	7 (5–7)	
PrEP accepted at baseline	33 (94%)	120 (88%)	27 (96%)	157 (90%)	255 (92%)	0.500

*Missing values imputed, n=9 missing responses.
†Missing responses n=33 for those with STI and n=66 for those with no STI.
‡Missing responses n=2 for those with no STI.
§Modified risk score does not include score for curable STI at baseline; includes age <25 years=2, ≥25 years=0; married or living with primary partner no=2, yes =0; partner provides material support no=1, yes =0; primary partner has other partners yes=2, don't know=2, no=0.
CES-D, Center for Epidemiological Studies Depression; IUD, intrauterine device; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

RESULTS

Participant characteristics at enrolment

Of 646 women screened, 451 participants were eligible and enrolled. Participant median age was 21 years (IQR 19–22) (table 1). More than half (57%, 258 of 451) lived with parents and/or siblings, 33% (149 of 451) had a partner who was 5 or more years older than them, and 65% (299 of 451) used a long-acting reversible contraceptive (LARC). Participants reported a

median of four episodes (IQR 2–8) of vaginal sex in the prior month, with 22% (101 of 451) reporting transactional sex (ie, having sex with a partner because he provided or participant expected he would provide food, clothes, cellphone airtime, etc) and 15% (68 of 451) anal sex in the prior month, and 40% (140 of 352) used a condom at last sex. A minority (8%, 34 of 449) had a high HIV risk perception, even though the median VOICE risk score was 7 (IQR 5–7). Most (91%, 412 of 451) accepted PrEP at the enrolment visit, while an additional 15 participants initiated PrEP during follow-up. Visit completion rates in this study were high with 83%–97% of planned visits completed.

STIs at baseline

At baseline, 39% (174 of 451) of participants were diagnosed with either CT (30%, 136 of 174), GC (20%, 35 of 174) or TV (6%, 10 of 174,) for a total of 199 curable STI episodes (table 1). Mixed infections were common. Among participants with CT, 14% (19 of 136) also had GC and 5% (7 of 136) had TV. Half (19 of 35) of those with GC also had CT, and a quarter (7 of 28) with TV also had CT. Syphilis was rare with reactive syphilis serology in <1% (2 of 451) and was therefore not included in further analyses.

Participants with a curable STI at baseline were more likely to be younger (p=0.036), from Cape Town (p=0.0001) and to use LARC (p=0.022) (table 1). AGYW with a curable STI were also less likely to report condom use at last sex (p=0.033). STI status did not appear to influence the decision to initiate PrEP with >90% PrEP uptake across sites (p=0.501).

In multivariable analysis, AGYW living in Cape Town had a twofold higher risk of prevalent CT compared with their peers in Harare (relative risk (RR) 2.41, 95% CI 1.31, 4.43), while AGYW living with non-family members also had a higher risk of prevalent CT compared with those living with family members (RR 1.93, 95% 1.14, 3.27) (table 2). In contrast, the only significant predictor of baseline GC was the reported number of vaginal sex acts in the prior month. Risk increased by 3% for every unit increase in sex acts reported (RR 1.03, 95% CI 1.03, 1.06). When assessing risk for any cervical infection, that is, either CT or GC as baseline, risks were similar to those for baseline CT infection alone, although the strength of association weakened. Reported condom use at last sex however emerged as protective against any prevalent cervical infection (RR 0.67, 95% CI 0.45, 0.99).

Incident curable STIs

A total of 204 new curable STIs were detected during 448.8 py of follow-up giving an incidence of 27.8 per 100 py for CT (95% CI 23.1, 33.2), 11.4 per 100 py for GC (95% CI 8.5,

Table 2 Baseline characteristics associated with prevalent or incident GC, CT or combined CT/GC infection

	CT/GC		CT		GC	
	Univariate RR (95% CI)	Multivariable RR (95% CI)	Univariate RR (95% CI)	Multivariable RR (95% CI)	Univariate RR (95% CI)	Multivariable RR (95% CI)
Baseline infection						
Site						
Cape Town vs Harare	2.10 (1.38, 3.18)	2.38 (1.35, 4.19)**	1.96 (1.26, 3.06)	2.41 (1.31, 4.43)**	2.76 (1.22, 6.22)	2.28 (0.88, 5.89)
Johannesburg vs Harare	1.46 (0.96, 2.26)	1.13 (0.67, 1.91)	1.52 (0.96, 2.40)	1.27 (0.73, 2.22)	0.68 (0.24, 1.98)	0.52 (0.15, 1.84)
Age (years)*					0.86 (0.72, 1.02)	0.95 (0.79, 1.14)
Living arrangements						
Lives with partner vs parents and/or siblings	0.54 (0.20, 1.44)	0.85 (0.44, 1.64)	0.84 (0.54, 1.34)	1.01 (0.51, 1.98)		
Lives with other vs parents and/or siblings	0.68 (0.28, 1.66)	1.87 (1.13, 3.08)*	1.34 (0.90, 1.98)	1.93 (1.14, 3.27)*		
Modified risk score*					1.34 (0.96, 1.84)	1.25 (0.87, 1.79)
No of vaginal sex acts, past month*					1.04 (1.00, 1.06)	1.03 (1.00, 1.06)*
Condom use at last sex	0.66 (0.46, 0.98)	0.67 (0.45, 0.99)*	0.68 (0.46, 1.02)	0.69 (0.46, 1.05)		
Incident infection						
Site						
Cape Town vs Harare	1.60 (1.08, 2.36)	1.14 (0.70, 1.86)	1.50 (0.94, 2.42)	1.39 (0.78, 2.48)	2.20 (1.12, 4.34)	2.40 (1.18, 4.90)*
Johannesburg vs Harare	0.96 (0.62, 1.48)	0.56 (0.31, 1.00)*	1.22 (0.76, 1.98)	0.87 (0.48, 1.56)	0.14 (0.04, 0.64)	0.15 (0.33, 0.70)*
Age (years)*			0.94 (0.86, 1.00)	1.01 (0.91, 1.11)		
CES-D score*	1.02 (1.00, 1.06)	1.02 (0.99, 1.05)	1.04 (1.02, 1.08)	1.05 (1.01, 1.09)**	1.00 (0.94, 1.06)	1.00 (0.95, 1.06)
Age difference of primary partner	0.94 (0.88, 1.00)	0.94 (0.88, 1.01)	0.94 (0.88, 1.02)	0.95 (0.88, 1.02)		
Long-acting contraceptive use (baseline)†			1.42 (0.92, 2.18)	1.18 (0.69, 2.03)		
Anal sex, past month						
Yes vs no	1.18 (0.74, 1.90)	1.34 (0.76, 2.33)				
Prefer not to answer vs no	0.70 (0.50, 0.98)	0.75 (0.49, 1.15)				
CT/GC at baseline	1.66 (1.20, 2.32)**	1.66 (1.12, 2.45)*				
CT at baseline			1.84 (1.26, 2.66)	2.01 (1.28, 3.15)**		
Detectable TFV-DP‡	1.00 (0.73, 1.35)		0.78 (0.54, 1.13)		1.46 (0.86, 2.49)	
TFV-DP ≥700 fmol/punch‡	1.00 (0.63, 1.58)		0.76 (0.43, 1.34)		1.96 (0.98, 3.91)	2.04 (1.02, 4.08)*

*P<0.05, **p<0.005.
*Continuous variables.
†Long-acting reversible contraceptive includes injectables, implants and intrauterine devices.
‡Based on DBS collected at month 6 and/or 12.
CES-D, Center for Epidemiological Studies Depression; CT, *Chlamydia trachomatis*; DBS, dried blood spots; GC, *Neisseria gonorrhoeae*; RR, relative risk; TFV-DP, tenofovir-diphosphate.

Table 3 STI incidence over 12 months, by site

	Overall (N=451)	Cape Town (N=141)	Johannesburg (N=162)	Harare (N=148)
Neisseria gonorrhoeae				
Events	51	32	2	17
Person-years	445.58	134.13	161.23	150.23
Event rate (100 person-years)	11.4	23.9	1.2	11.3
95% exact CI for event rate	(8.5, 15.0)	(16.3, 33.7)	(0.2, 4.5)	(6.6, 18.1)
Chlamydia trachomatis				
Events	123	50	38	35
Person-years	441.7	135.1	155.2	151.4
Event rate (100 person-years)	27.8	37	24.5	23.1
95% exact CI for event rate	(23.1, 33.2)	(27.5, 48.8)	(17.3, 33.6)	(16.1, 32.1)
Trichomonas vaginalis				
Events	30	6	7	17
Person-years	448.8	138	161.2	149.6
Event rate (100 person-years)	6.7	4.3	4.3	11.4
95% exact CI for event rate	(4.5, 9.5)	(1.6, 9.5)	(1.7, 9.0)	(6.6, 18.2)

STI, sexually transmitted infection.

15.0) and 6.7 per 100 py for TV (95% CI 4.5, 9.5) (table 3). Of these 204 incident STIs, 66% (135 of 204) were in AGYW who had not had an STI at baseline: 84% (43 of 51) of incident GC cases were new GC diagnoses, while 73% (22 of 30) of incident TV cases and 57% (70 of 123) of incident CT cases were new episodes.

Incident CT infection risk was significantly higher in those with an increasing depression score—every point increase on the score was associated with a 5% increase in the risk of incident CT (RR 1.05; 95% CI 1.01, 1.09), while a baseline CT infection was associated with a twofold higher risk of incident CT infection at follow-up (RR 2.01; 95% CI 1.28, 3.15) (table 2). By comparison, incident GC risk was higher in AGYW who live in Cape Town compared with Harare (RR 2.40; 95% CI 1.18, 4.90) and lower in Johannesburg compared with those living in Harare (RR 0.15, 95% CI 0.33, 0.70). AGYW with high PrEP adherence (TFV-DP concentrations >700 fmol/punch) also had a twofold higher risk of incident GC (RR 2.04 95% CI 1.02, 4.08). This appeared to be most strongly influenced by differences in drug concentration at the week 52 visit (online supplemental table 1). This association was not observed for incident CT infections (RR 0.78, 95% CI 0.54, 1.13) or incident cervical infection (either CT or GC). Cervical infection at baseline was in fact the strongest predictor of a repeat infection at follow-up (RR 1.66, 95% CI 1.12, 2.45), while living in Johannesburg was associated with a lower cervical infection risk compared with living in Harare (RR 0.56, 95% CI 0.31, 1.00) (table 2).

Differences in characteristics of participants by site

Given the strong influence of geographical location on STI infection risk, we investigated differences in behavioural characteristics by site (online supplemental table 2). Compared with participants in Johannesburg and Harare, participants in Cape Town were significantly younger (median 19, IQR 18–21), more likely to use LARC, to have a partner who was 10 or more years older than them, and to report having anal sex. They were also less likely to live with their partner, or suspect their partner of having other partners, and to report sex under the influence of drugs.

DISCUSSION

Over two-thirds of the 451 AGYW at substantial risk of HIV infection in South Africa and Zimbabwe who enrolled in a PrEP demonstration project were diagnosed with one or more curable STIs during 1 year of follow-up. The high prevalence and incidence of infection in this population indicate that PrEP programmes can reach sexually active AGYW with ongoing risk of HIV and other STIs, and that aetiological STI testing and treatment should be integrated with PrEP services. The finding that high TFV-DP drug concentrations in the prior month were associated with incident gonorrhoea indicates both that AGYW on PrEP continue to be at risk and suggests based on drug levels associated with higher PrEP adherence that they have confidence in the HIV prevention benefits of PrEP and are motivated to use it. Strengthened STI prevention and control efforts in this population are therefore a priority. Mathematical modelling from South Africa provides supportive evidence that aetiological STI testing using a GeneXpert-like test and treatment in youth 15–24 years could lead to the greatest reductions in population-wide bacterial STI incidence and prevalence over 10 years, even with low coverage levels.[24]

Our data suggest that universal aetiological STI testing rather than targeted testing based on individual risk factors may need to be implemented in PrEP programmes for African AGYW. Few behavioural risk factors for prevalent or incident cervical infection, or CT and GC alone significantly discriminated AGYW with STIs from those without STIs, and those behaviours that did are very prevalent among African AGYW. For example, inconsistent condom use was associated with having any STI, as well as a higher risk of any prevalent cervical infection or CT alone but was reported by 60% of participants at baseline. Instead, we found that recruitment site was the most common factor associated with risk of both prevalent and incident cervical infection, as well as incident GC. Differences in risk behaviours and partner characteristics were observed in each of the sites. Location is likely a proxy for a range of unmeasured partner factors, sexual networks and social norms, in addition to individual-level differences by site. A combination of individual risk behaviours, partner risk and community infection prevalence likely influenced infection risk.[25] Where targeted STI testing approaches are preferred because of resource constraints, then targeting interventions by location may be more effective than targeting individuals with particular behaviours.

One-third of incident STIs occurred in AGYW with an STI at enrolment, and those with a prevalent CT infection were twice as likely to have a repeat infection at follow-up. Given that treatment failure for chlamydia is rare, repeat infection likely reflects a high prevalence of untreated CT infection in male partners and a failure of partner notification.[26] Partner notification by direct referral is the main approach used in SSA, but only 25% of partners seek treatment.[27] Alternative strategies like provider referral or expedited partner therapy (EPT) have been shown to have much greater reach, but concerns have been raised about using these approaches in populations such as those in HPTN 082 where rates of intimate partner violence are high.[27] Notably, 16% of participants with an STI in this study reported feeling unsafe or afraid of their partner. A small non-randomised study in women in South Africa showed that EPT following point-of-care STI testing was highly acceptable, without social impacts,

and with lower rates of STI detected at follow-up, supporting the evaluation of these approaches more widely.[28]

AGYW who did not live with family were almost twice as likely to have a cervical infection at enrolment as those who did; those with increasing depression scores were more likely to have incident CT infection. Taken together, these findings highlight the role that social support, self-esteem and mental health play in young women's abilities to negotiate risk reduction strategies like condom use and partner treatment, especially in relationships where power is unequal.[29] These data support the need for comprehensive, integrated services for adolescents who address their HIV, sexual and reproductive health, as well as mental health needs.

There were several limitations to this study. We did not systematically record STI symptoms in the database and cannot report on the performance of syndromic management in identifying prevalent or incident infections. However, we note in a similar study in several of the same locations that 7% of participants reported STI symptoms despite the prevalence of CT (29%) and GC (10%) being similar to prevalence observed in our study.[30] We may have underestimated GC prevalence and incidence by collecting only cervical samples, especially given that 16% reported anal sex in the month prior to enrolment. By enrolling participants with access to a mobile phone, we may also have excluded individuals who were more economically vulnerable; this may have led to an underestimate of the STI burden. The significant differences by site point to the influence of individual, partner and sexual network characteristics on STI transmission that we did not measure, and which may limit generalisability. Despite this, the data highlight an urgent unmet need for better STI diagnosis and prevention options for at-risk African AGYW seeking PrEP.

CONCLUSION

In summary, STI prevalence and incidence in this AGYW population seeking PrEP were high and signal the need for alternatives to syndromic management. STI testing provides an important entry point for current and future STI prevention interventions like EPT, pre-exposure or post-exposure prophylaxis for STIs, or STI vaccines that could be integrated into PrEP service delivery. Like PrEP, they could be under the control of young women. Importantly, integrated sexual and reproductive health services may also have benefits for HIV programmes given the premium that many place on sexual health, and may drive demand for PrEP in many settings. New approaches to STI diagnosis, treatment and prevention that go beyond syndromic management are urgently needed to reduce the burden of current infection and future disease in AGYW and respond to the threat of antimicrobial resistance. Given the success of PrEP as a sexual and reproductive health technology used by people at substantial risk of HIV infection, we must prioritise the development of novel interventions that allow PrEP users to stay both HIV and STI free.

Author affiliations
[1]Wits RHI, University of the Witwatersrand, Johannesburg, South Africa
[2]Clinical Trials Research Centre, University of Zimbabwe, Harare, Zimbabwe
[3]Desmond Tutu Health Centre, University of Cape Town, Cape Town, South Africa
[4]Departments of Global Health, Medicine and Epidemiology, University of Washington, Seattle, Washington, USA
[5]Gilead Sciences, Foster City, California, USA
[6]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
[7]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[8]FHI 360, Durham, North Carolina, USA
[9]Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA

Handling editor Ming Jie Lee

Twitter Linda-Gail Bekker @lind.gail.bekker

Acknowledgements The authors would like to acknowledge the participants, CABs, communities and HPTN 082 study teams for their significant contributions to this study. They would also like to thank Subash Pathak for some of the initial analyses, and Kari Chansky for her final review of these analyses.

Contributors SD-M and CC designed the study, with input from NM, L-GB, JMB, DD, SMR and AA. SD-M, NM, L-GB, MM, SK and SM implemented the study. YA and DL contributed essential reagents or tools. CL and DD analysed the data. SD-M wrote the first draft of the manuscript, accepts full responsibility for the work, had access to the data, and controlled the decision to publish. All authors provided critical review of the manuscript and approved the final version.

Funding The HIV Prevention Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068619, UM1AI068613, UM1AI1068617), with co-funding from the National Institute of Mental Health and the National Institute on Drug Abuse, all components of the US National Institutes of Health. Gilead Sciences gave donation of Truvada for the study.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was reviewed and approved by the research ethics committees at each of the study sites (University of the Witwatersrand (160304), the University of Cape Town, the University of Zimbabwe and the University of California San Francisco). All participants provided written informed consent in English or their preferred local language. Following local regulations, participants below the legal age for consent provided assent and parent/guardian informed consent was obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Sinead Delany-Moretlwe http://orcid.org/0000-0003-0376-1019
Linda-Gail Bekker http://orcid.org/0000-0002-0755-4386
Deborah Donnell http://orcid.org/0000-0002-0587-7480

REFERENCES

1 UNAIDS. *The gap report*. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS, 2014: 24–6.
2 Rowley J, Vander Hoorn S, Korenromp E, *et al*. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ* 2019;97:548–562P.
3 Unemo M, Bradshaw CS, Hocking JS, *et al*. Sexually transmitted infections: challenges ahead. *Lancet Infect Dis* 2017;17:e235–79.
4 Haggerty CL, Gottlieb SL, Taylor BD, *et al*. Risk of sequelae after Chlamydia trachomatis genital infection in women. *J Infect Dis* 2010;201 Suppl 2:S134–55.
5 Ness RB, Soper DE, Holley RL, *et al*. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the pelvic inflammatory disease evaluation and clinical health (peach) randomized trial. *Am J Obstet Gynecol* 2002;186:929–37.
6 Weström L, Joesoef R, Reynolds G, *et al*. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sex Transm Dis* 1992;19:185–92.

7 Brady M. Preventing sexually transmitted infections and unintended pregnancy, and Safeguarding fertility: triple protection needs of young women. *Reprod Health Matters* 2003;11:134–41.
8 Dhont N, Muvunyi C, Luchters S, *et al*. Hiv infection and sexual behaviour in primary and secondary infertile relationships: a case -- control study in kigali, Rwanda. *Sex Transm Infect* 2011;87:28–34.
9 Wasserheit JN. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis* 1992;19:61–77.
10 Moodley P, Sturm AW. Sexually transmitted infections, adverse pregnancy outcome and neonatal infection. *Semin Neonatol* 2000;5:255–69.
11 Murray CJL, Vos T, Lozano R, *et al*. Disability-adjusted life years (dalys) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2197–223.
12 Mayaud P, Mabey D. Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges. *Sex Transm Infect* 2004;80:174–82.
13 Pettifor A, Walsh J, Wilkins V, *et al*. How effective is syndromic management of STDs?: a review of current studies. *Sex Transm Dis* 2000;27:371–85.
14 Zemouri C, Wi TE, Kiarie J, *et al*. The performance of the vaginal discharge syndromic management in treating vaginal and cervical infection: a systematic review and meta-analysis. *PLoS One* 2016;11:e0163365.
15 van Gemert C, Hellard M, Bradshaw CS, *et al*. Syndromic management of sexually transmissible infections in resource-poor settings: a systematic review with meta-analysis of the abnormal vaginal discharge flowchart for Neisseria gonorrhoea and Chlamydia trachomatis. *Sex Health* 2018;15:1–12.
16 Wi TE, Ndowa FJ, Ferreyra C, *et al*. Diagnosing sexually transmitted infections in resource-constrained settings: challenges and ways forward. *J Int AIDS Soc* 2019;22 Suppl 6:e25343.
17 Fernández MI, Hosek S, Warren JC, *et al*. Development of an easy to use tool to assess HIV treatment readiness in adolescent clinical care settings. *AIDS Care* 2011;23:1492–9.
18 Celum C, Hosek S, Tsholwana M, *et al*. Prep uptake, persistence, adherence, and effect of retrospective drug level feedback on PreP adherence among young women in southern Africa: results from HPTN 082, a randomized controlled trial. *PLoS Med* 2021;18:e1003670.
19 Balkus JE, Brown E, Palanee T, *et al*. An empiric HIV risk scoring tool to predict HIV-1 acquisition in African women. *J Acquir Immune Defic Syndr* 2016;72:333–43.
20 Castillo-Mancilla JR, Zheng J-H, Rower JE, *et al*. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* 2013;29:384–90.
21 Anderson PL, Liu AY, Castillo-Mancilla JR, *et al*. Intracellular tenofovir-diphosphate and emtricitabine-triphosphate in dried blood spots following directly observed therapy. *Antimicrob Agents Chemother* 2018;62:e01710-17.
22 Bono C, Ried LD, Kimberlin C, *et al*. Missing data on the center for epidemiologic studies depression scale: a comparison of 4 imputation techniques. *Res Social Adm Pharm* 2007;3:1–27.
23 Grant RM, Anderson PL, McMahan V, *et al*. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014;14:820–9.
24 Esra RT, Johnson LF. Modelling the impact of screening for Chlamydia and gonorrhoea in youth and other high-prevalence groups in a resource-limited setting. *Int J Public Health* 2020;65:413–23.
25 Aral SO, Hughes JP, Stoner B, *et al*. Sexual mixing patterns in the spread of gonococcal and chlamydial infections. *Am J Public Health* 1999;89:825–33.
26 Kong FYS, Hocking JS. Treatment challenges for urogenital and anorectal chlamydia trachomatis. *BMC Infect Dis* 2015;15:293.
27 Taleghani S, Joseph-Davey D, West SB, *et al*. Acceptability and efficacy of partner notification for curable sexually transmitted infections in sub-Saharan Africa: a systematic review. *Int J STD AIDS* 2019;30:292–303.
28 Garrett NJ, Osman F, Maharaj B, *et al*. Beyond syndromic management: opportunities for diagnosis-based treatment of sexually transmitted infections in low- and middle-income countries. *PLoS One* 2018;13:e0196209.
29 Chen Y, Wu J, Yi Q, *et al*. Depression associated with sexually transmitted infection in Canada. *Sex Transm Infect* 2008;84:535–40.
30 Celum CL, Bukusi EA, Bekker LG, *et al*. Prep use and HIV seroconversion rates in adolescent girls and young women from Kenya and South Africa: the power demonstration project. *J Int AIDS Soc* 2022;25:e25962.

Supplementary table 1. STI status by tenofovir diphosphate concentrations at week 26 and week 52 among PrEP acceptors

	Overall	Low TFV-DP concentration (<700 fmol/punch)	High TFV-DP concentration (>=700fmol/punch)
Week 26			
CT/GC positive	142/363 (39.1%)	123/287 (42.9%)	19/76 (25.0%)
CT positive	114/363 (31.4%)	102/287 (35.5%)	12/76 (15.8%)
GC positive	44/363 (12.1%)	35/287 (12.2%)	9/76 (11.8%)
Week 52			
CT/GC positive	142/347 (40.9%)	123/317 (38.8%)	19/30 (63.3%)
CT positive	114/347 (32.9%)	102/317 (32.2%)	12/30 (40.0%)
GC positive	44/347 (12.7%)	35/317 (11.0%)	9/30 (30.0%)

CT: C. trachomatis; GC: N. gonorrhoeae; TVF-DP: tenofovir diphosphate

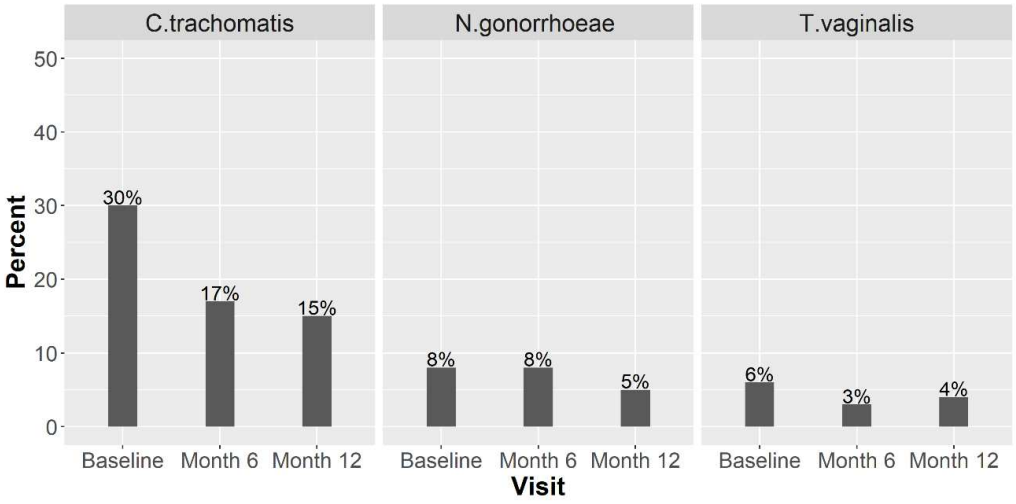
Supplementary table 2. Baseline characteristics, by site

	Overall (N=451)	Cape Town (n=141)	Johannesburg (N=162)	Harare (N=148)	p-values
Age					**<0.0001**
Median (IQR)	21 (19, 22)	19 (18, 21)	22 (20, 24)	21 (20, 23)	
Highest Level of Education					**<0.0001**
Primary school or less	9/2%)	1 (0%)	1 (0%)	7 (5%)	
Secondary school, not complete	160 (35%)	80 (57%)	27 (17%)	53 (36%)	
Secondary school, complete	228 (51%)	46 (33%)	96 (59%)	86 (58%)	
Post-secondary school	54 (12%)	14 (10%)	38 (23%)	2 (1%)	
Ever Dropped out of School	128 (28%)	45 (32%)	24 (15%)	59 (40%)	**<0.0001**
Regular place to stay	404 (90%)	129 (92%)	140 (87%)	135 (91%)	**0.038**
Live with					**<0.0001**
Living with parents or siblings	258 (57%)	129 (91%)	78 (48%)	51 (34%)	
Living with partner	98 (22%)	7 (5%)	24 (15%)	67 (45%)	
Living with someone else	95 (21%)	5 (4%)	60 (37%)	30 (20%)	
Partner age difference (n=349)					**<0.0001**
Less than 5 years	200 (57%)	44 (37%)	81 (64%)	75 (73%)	
>=5 and <10 years	115 (33%)	52 (43%)	37 (29%)	26 (25%)	
>=10 years	34 (10%)	24 (20%)	8 (6%)	2 (2%)	
Partner has other partners, past 3 mo. (n=379)					**<0.0001**
No	76 (20%)	26 (23%)	40 (28%)	10 (8%)	
Yes	121 (32%)	26 (23%)	37 (26%)	58 (47%)	
Don't know or prefer not to answer	182 (48%)	62 (55%)	64 (45%)	56 (46%)	

	Overall (N=451)	Cape Town (n=141)	Johannesburg (N=162)	Harare (N=148)	p-values
Partner has made you feel afraid, unsafe or in danger – past year	90/449 (20%)	23/140 (16%)	18/161 (11%)	49/148 (33%)	**<0.0001**
Ever pregnant (n=449)	238 (53%)	46 (33%)	76 (47%)	116 (78%)	**<0.0001**
Contraceptive method at baseline					**<0.0001**
Injectable Contraceptives	191 (42%)	88 (62%)	76 (47%)	27 (18%)	
Implants	104 (23%)	25 (18%)	11 (7%)	68 (46%)	
IUD or Sterilization	5 (1%)	2 (1%)	1 (1%)	2 (0%)	
Oral Contraceptives	54 (12%)	9 (6%)	11 (7%)	34 (23%)	
Condoms, natural methods or none	79 (22%)	17 (12%)	63 (38%)	17 (11%)	
Transactional sex Past month	101/451 (22%)	30/141 (21%)	17/162 (10%)	54/148 (36%)	**<0.0001**
No. vaginal sex episodes, past mo. (n=359)					**<0.0001**
Median (IQR)	4 (2, 8)	4 (3, 5)	3 (2, 7)	6 (3, 17)	
Condom use at last sex (n=352)	140 (40%)	46 (42%)	50 (38%)	46 (42%)	
Drug use before/during sex, past mo. (n=449)	23 (5%)	2 (1%)	7 (4%)	14 (9%)	**0.0079**
Anal Sex Past month					**0.0507**
Yes	68 (15%)	30/141 (21%)	18/162 (11%)	20/148 (14%)	
Prefer Not to Answer	136 (30%)	36/141 (26%)	47/162 (29%)	53/148 (36%)	
No	247 (55%)	75/141 (53%)	97/162 (60%)	75/148 (51%)	
High self-perceived risk of HIV (n=449)	34 (8%)	5 (4%)	1 (1%)	28 (19%)	**<0.0001**
Modified voice score					**0.0002**
Median (IQR)	7 (5, 7)	7 (6, 7)	7 (6, 7)	6 (5, 7)	

IQR: interquartile range

Supplementary figure 1. Prevalence of curable STIs, by visit



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	22
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12

		(*b*) Report category boundaries when continuous variables were categorized	21
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.