Interim modelling analysis to validate reported increases in condom use and assess HIV infections averted among female sex workers and clients in southern India following a targeted HIV prevention programme

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ABSTRACT

Objectives This study assesses whether the observed declines in HIV prevalence since the beginning of the 'Avahan' India HIV/AIDS prevention initiative are consistent with self-reported increases in condom use by female sex workers (FSWs) in two districts of southern India, and provides estimates of the fraction of new infections averted among FSWs and clients due to increases in condom use in commercial sex after 2004.

Methods A deterministic compartmental model of HIV/sexually transmitted infection (STI) transmission incorporating heterogeneous sexual behaviour was developed, parameterised and fitted using data from two districts in Karnataka, India. Three hypotheses of condom use among FSWs were tested: (H_0), that condom use increased in line with reported FSW survey data prior to the Avahan initiative but remained constant afterwards; (H_1) that condom use increased following the Avahan initiative, in accordance with survey data; (H_2) that condom use increased according to estimates derived from condom distribution data. The proportion of fits to HIV/STI prevalence data was examined to determine which hypothesis was most consistent.

Results For Mysore 0/36/82.7 fits were identified per million parameter sets explored under hypothesis H_0/H_1/H_2, respectively, while for Belgaum 9.7/8.3/0 fits were identified. The HIV epidemics in Belgaum and Mysore are both declining. In Mysore, increases in condom use during commercial sex between 2004 and 2009 may have averted 31.2% to 47.4% of new HIV infections in FSWs, while in Belgaum it may have averted 24.8% to 43.2%, if there was an increase in condom use.

Discussion Increased condom use following the Avahan intervention is likely to have played a role in curbing the HIV epidemic in Mysore. In Belgaum, given the limitations in available data, this method cannot be used alone to decide if there has been an increase in condom use.

INTRODUCTION

Karnataka, in southern India, has one of the highest prevalences of HIV among Indian states,[1] and is among the states included in the 'Avahan' India HIV/AIDS initiative established by the Bill & Melinda Gates Foundation in 2004. Working through state-level partners and local non-governmental organisations (NGOs), the initiative is a multifaceted HIV preventive intervention promoting prevention strategies among high-risk groups, including distribution of condoms to and promotion of condom use among female sex workers (FSWs).[2–4]

Assessing the impact of the Avahan intervention is crucial, not only to ensure that Avahan achieves its goals of reducing HIV transmission in India, but also to inform future large-scale interventions.[5] However, the dynamics of an HIV epidemic are complicated: declines in HIV prevalence can occur without any intervention effects, due to natural infection dynamics and, conversely, increases can occur even in the presence of an effective intervention.[6 7] In order to separate out the impact of the Avahan initiative from natural HIV transmission dynamics, and because of the difficulty and huge expense of implementing community randomised controlled trials, a tailor-made transmission dynamics model will be used as one important component of the impact assessment, the framework for which is described in Boily *et al*.[8]

The final impact and cost effectiveness analysis, planned for 2011, will estimate the impact of the Avahan initiative on the HIV and sexually transmitted infection (STI) epidemics among high-risk groups and the broader population across more than 30 intervention sites.[5 8] This paper presents the results of an interim analysis focusing on FSWs and their clients in two districts where sufficient data are currently available, and which represent different HIV/STI epidemic trends and behavioural profiles: Belgaum Urban, a higher prevalence district in which Avahan was not the first but is now the only intervention; and Mysore Urban, a lower prevalence district in which Avahan was the first and remains the only intervention.

The objective of this analysis is to determine whether the observed changes in HIV prevalence among FSWs could be solely due to natural disease dynamics rather than to a change in condom use following the intervention. We address this question by testing whether the null hypothesis (H_0) of stable (ie, no increase in) condom use following the initiation of the Avahan intervention in 2004 is less likely than the alternative hypotheses (H_1) that condom use actually increased by as much as reported in FSW survey data, or (H_2) that there was a lower level of preintervention condom use and a sharper postintervention increase than indicated by FSW survey data, as suggested by records of condom availability.[9]

METHODS

In order to model the HIV/STI epidemics in urban Belgaum and Mysore districts, an in-depth mathematical modelling analysis was undertaken with the key elements described below.

Methodological framework of evaluation

The structure of the evaluation follows the methodological framework designed and described in Boily *et al*.[8] In short, a mathematical model was used within a Bayesian framework, where available data were first used to specify what was known about each model parameter by defining a plausible range of values (the 'prior distribution'). This distribution was then randomly sampled repeatedly, to test the model with a large number of parameter combinations and identify those parameter sets (the 'posterior distribution') that agreed with the empirical HIV/STI prevalence data shown in table 1.

One of the advantages of this approach is that the percentage of parameter sets producing a model fit to the prevalence data gives a measure of how compatible the prior parameter sets were with the observed prevalence data for the specified model. This approach was used here to test the three hypotheses described above concerning possible trends in condom use before and after the Avahan intervention. Finally, the posterior distribution was used to simulate a control group without the intervention, which was then compared to the original scenario to produce estimates of intervention impact.

Model structure and parameterisation

A purpose-built deterministic compartmental model of HIV, herpes simplex virus (HSV)-2 and syphilis transmission was constructed and parameterised to incorporate key aspects and heterogeneities of the complex FSW and client structure specific to each setting.[10] In summary, the model consisted of an open population, growing at the rate described by census data,[11] stratified into 'high-risk' (FSWs and their clients) and 'low-risk' (the remaining population) groups. Based on work by Vickerman *et al*[4] (***see page 33***), it was assumed in this model that there is no transmission between low-risk individuals. The high-risk groups (FSWs and their clients) were further stratified by variables showing strong associations with HIV prevalence and high-risk behaviour in analyses of data from serial cross-sectional surveys termed integrated behavioural and biological assessments (IBBAs).[10 12]

The model simulates the transmission of HIV/STIs between FSWs and their clients through commercial and longer-term non-commercial partnerships, and the bridging infections from clients to low-risk women through their non-commercial partnerships, as shown in figure 1. The force of infection depends on the disease-specific infectivity, type and duration of partnership, frequency of sex acts for the type of partnership, condom use and STI coinfection status of both partners. The three parameters influencing HIV prevalence the most in a sensitivity analysis of a representative sample of the unrestricted model runs were the number of sex acts per partnership between FSWs and occasional clients, the male to female HIV transmission per sex act and the RR for increased transmissibility of primary HIV. Further details of the model and equations are provided in the supplementary material.

HIV was modelled with an initial short acute phase of high infectivity, followed by a long low-infectivity phase and a pre-AIDS phase of increased infectivity.[13] It was assumed that those with AIDS are chronically ill, and cease being sexually active. HSV-2 coinfection[14] and syphilis[15] were also modelled dynamically, with cofactors representing facilitation of HIV and HSV-2 acquisition and transmission.

The setting-specific behaviour-related, demographic-related and intervention-related prior model parameter distributions were derived from detailed serial cross-sectional behavioural and biological data (from IBBAs) collected from FSWs and their clients, and general population surveys (GPS) carried out as part of the Avahan monitoring programme, as well as from complementary data from other sources. The non-setting specific biological parameter ranges were based on reviews of relevant literature (tables 2 and 3). Prior distributions were assumed to be uniform across each parameter range; this was a 'conservative' choice to reflect the lack of precise knowledge

Table 1 HIV/sexually transmitted infection (STI) prevalence data from integrated behavioural and biological assessment (IBBA) surveys in Belgaum and Mysore used to fit (FSW IBBA rounds 1 and 2, and client IBBA round 1) and validate (FSW IBBA rounds 2 and 3) the model

Survey	District and date carried out	CI for prevalence HIV	HSV-2	Syphilis
Fitting data				
FSW IBBA round 1	Mysore (August 2004)	21.9% to 30.3%	59.6% to 69.1%	21.0% to 29.0%
	Belgaum (October 2005)	27.6% to 40.2%	78.6% to 89.1%	3.0% to 13.0%
Client IBBA				
Round 1	Mysore (October 2008)	3.2% to 7.6%	8.0% to 33.0%	1.3% to 4.6%
	Belgaum (October 2007)	3.6% to 8.8%	23.3% to 32.3%	2.0% to 6.5%
Crossvalidation and fitting data				
FSW IBBA round 2	Mysore (December 2006)	19.1% to 29.5%		
	Belgaum (July 2008)	22.2% to 32.5%		
Crossvalidation data				
FSW IBBA round 3	Mysore (April 2009)	8.11% to 14.1%		

FSW, female sex worker; HSV, herpes simplex virus.

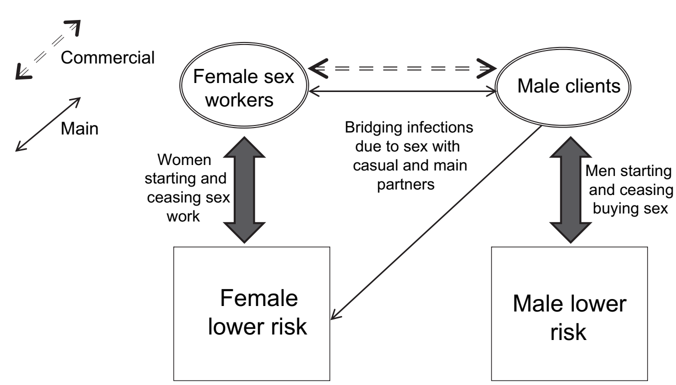

Figure 1 Outline of the main aspects of sexual behaviour structure and population movements between risk groups that are included in the model. HIV/sexually transmitted infection (STI) transmission through main (plain arrow) and casual (dotted arrow) partnerships is shown. Female sex workers and clients engage in commercial sex for a time before returning to the general population and being replaced from the general population (thick arrow).

and possibility of bias in the data used to estimate the parameters.

The parameterisation of condom use before and after the intervention was data driven and specific to each hypothesis tested, resulting in three different prior condom use distributions. The prior distribution of condom use for hypothesis H_1 was based on estimates (with CIs) of site-specific condom use from 2001 onwards given by the analysis of Lowndes *et al*.[75] That analysis used data from the IBBA round 2 surveys concerning time since starting to use condoms consistently with occasional clients to retrospectively ‘reconstruct’ the fraction of FSWs consistently using condoms each year from 2001 to the year of the survey. The null hypothesis H_0 assumed the same increase in condom use prior to 2004 as hypothesis H_1 but no further increase after the start of the Avahan intervention in 2004. A further hypothesis (H_2) was based on HIV prevention programme data and other sources regarding the availability of condoms for FSWs[9] from 2004 to 2008 across Karnataka. This study suggested that the proportion of consistent condom users among FSWs in 2004 was much lower than suggested in hypothesis H_1 due to low availability, but that it rose steeply during 2006–2008 due to the Avahan intervention. The three different condom prior distributions are shown in figure 2, with the round 1 and 2 FSW IBBA point estimates shown for comparison.

Parametric uncertainty analysis, model fitting and validation

This step involved identifying combinations of model parameters that agreed with (‘fit’) the HIV/STI prevalence data from each site for each condom use hypothesis tested. Latin hypercube sampling (LHS) was used to sample several million parameter sets from all ‘prior’ parameter ranges for each hypothesis and district, with the sampling done so that the same set of parameters, excluding the intervention parameters being tested, were used for the different hypotheses in each district. The model was run with each sampled parameter set to predict HIV/STI prevalences. A parameter set was accepted as a fit if the model predictions simultaneously lay within the 95% CIs of the HIV, HSV-2 and syphilis prevalence data of the relevant FSW and client IBBAs, as described below.

The HIV/STI prevalence data from FSWs and clients for each district were used in two stages: (1) as validation and (2) for hypothesis testing. In stage 1, the model was first fitted to just the round 1 FSW and client IBBA HIV, HSV-2 and syphilis prevalence data (see table 1), and the predictive value of these model fits was assessed against the HIV prevalence data not used directly at this stage of the fitting process, namely FSW HIV prevalence from the second round FSW IBBA in Mysore and Belgaum (table 1) and third round in Mysore (table 1), and FSW HIV prevalence by typology (street, brothel or home based) in rounds 1 and 2 (see supplementary material). In stage 2, the second round of IBBA HIV prevalence data were included in the fitting procedure along with the first round of FSW and client IBBA HIV/STI prevalence data (table 1) to produce a reduced set of model fits for hypothesis testing.

Testing hypotheses of condom use

The most likely condom use hypothesis was determined based on the relative proportions of fits to the first round FSW and client IBBA HIV/STI prevalence data and the second round FSW HIV prevalence data. For each hypothesis, the fraction of model fits from all parameter sets was compared to determine which hypothesis was more likely. This method, which is related to the version of Approximate Bayesian Computing as described by Weiss and von Haeseler,[76] is also similar to the Bayesian methods used by Vickerman *et al* for determining the likelihood of different injecting drug user risk behaviour scenarios in Pakistan,[77] and Hallett *et al* for examining behaviour change in Zimbabwe.[78]

Impact analysis

The posterior distribution of the most likely condom use hypothesis was used to simulate HIV prevalence and incidence over time following the start of the intervention, and in a matched control population. In the latter, each model fit was run again with condom use kept constant at 2004 levels (ie, at the start of the Avahan initiative). Comparing the impact and control scenarios, estimates of the impact of the increase in condom use following the start of the intervention among high-risk groups were derived for a 5-year period (2004–2009). These estimates derived from the posterior distribution include credibility intervals (CrI) generated by using all the parameter combinations that fit the prevalence data to reflect the uncertainty in parameter assumptions, since more than one set of parameters may produce an equally good fit to epidemiological trends.

RESULTS

Hypothesis testing

The proportion of fits to each hypothesis is shown in table 4. In Mysore, the hypothesis H_2, derived from analysing availability of condoms, gives the largest proportion of simulations which are consistent with prevalence data, and scenarios H_2 and H_1 of increasing condom use following the introduction of Avahan are more likely than the null hypothesis H_0 of no condom increase after the start of Avahan, for which no model fits were obtained. In Belgaum, however, the null hypothesis H_0 of no increase use in condom use following Avahan and the alternative hypothesis H_1, based on the historical condom use reconstruction, cannot be distinguished by this method, although both are much more likely than the hypothesis H_2. An alternative method to comparing the proportion of fits would be a likelihood-based approach, calculating the likelihood for each run; however this method gave comparable results (data not shown).

Crossvalidation of results

Table 4 shows that fits to only the round 1 FSW and client IBBA prevalence data (table 4) also generally fit the round 2 FSW IBBA HIV prevalence data well for all hypotheses (90% or more of posterior runs also fit FSW HIV round 2 prevalence). This then validates the model with respect to time trends in HIV (see also supplementary material). A third round of IBBA data was available for Mysore only, and the model HIV prevalence projections were slightly higher (12.1% to 20.6% for H_2; 12.4% to 19.6% for H_1) than the third round IBBA data (8.1% to 14.1%). This is consistent with the fact that any further increases subsequent to the IBBA round 2 in condom use were not incorporated in the model.

Lastly, validation of the model by comparing its projections with FSW HIV prevalence by typology generally showed good agreement, although there was some residual heterogeneity, as might be expected (see supplementary material).

Trends in HIV/STI prevalence and incidence

The predicted prevalences over time for the model fits from the favoured hypotheses (H_0 and H_1 for Belgaum and H_2 for Mysore) suggest that the HIV epidemics among FSWs and clients are declining in both districts (figure 3A–F). In Belgaum, it is likely

Table 2 Prior biological model input parameters sampled at the fitting stage to obtain the posterior parameter sets for Mysore and Belgaum for the Avahan impact model (all durations are in months)

Types of model input	Definition of model input	Model inputs	Reference for model input value
Duration of infection stages	Average duration of Ng/Ct:		Reviewed in Korenromp *et al*.[16] Also depends on level of STI treatment.
	Males	2–5	
	Females	2–12	
	Female sex workers (FSWs)	0.5–3	
	Average duration of syphilis stages:		Available data was reviewed by Boily *et al* and Garnett *et al*[8 15]
	Primary (no treatment)	1.51	
	Secondary (no treatment)	3–4.5	
	Primary and secondary stage (with treatment)	1–5	
	Latent phase (including treatment)	2–24	
	Time between potential recurrences	6	
	Immune/resistant phase	12–60	
	Average duration of HSV-2 stages:		From Cheong *et al*, Corey *et al*, Diamond *et al*, Koelle *et al*, Guinan *et al* and Benedetti *et al*.[17–24]
	Primary stage	0.36–0.66	
	Symptomatic recurrence	0.1–0.16	Using Corey *et al*, Guinan *et al* and Wald *et al*.[18 20 23 25–27]
	Rate of HSV-2 symptomatic recurrences while:		
	HIV negative	0.09–0.41	Corey *et al*, Diamond *et al*, Benedetti *et al*, Lafferty *et al* and Kim *et al*[18 20 21 24 28–30]
	HIV positive	1–2×HIV negative rate	Using Schacker *et al* and Conant *et al*[31 32]
	Average duration of HIV stages:		Based on Grover and Shivraj, and Kumarasamy *et al*[33 34]
	Initial HIV high viraemia phase	4–6	
	Between initial high viraemia and pre-AIDS	70–90.5	
	Pre-AIDS high viraemia phase	6–18	
Transmission probabilities	Probability of HIV transmission per sex act:		Reviewed in Holmes *et al*.[40 67]
	Male to female:	0.0006–0.0011	
	Female to male	0.0001–0.0014	
	Sexual transmission multiplicative cofactor:		
	Initial high viraemia phase	4.5–18.8	
	Pre-AIDS high viraemia phase	4.5–11.9	
	Probability of Ng/Ct transmission per sex act	0.05–0.2	Reviewed by Holmes *et al*, Hooper *et al*[40 67]
	Probability of syphilis transmission per sex act (male to female):	0.1–0.3	Reviewed by Garnett *et al*[15]
	Ratio of transmission probabilities female to male:male to female	0.33–1.0	
	Probability of HSV-2 transmission:		
	Latent/asymptomatic shedding stage (male to female)	0.0005–0.002	Using Wald *et al* and Corey *et al*[37 38]
	RR male to female: female to male transmission	2–5	
	Primary stage	2–6×6.7–25 times asymptomatic/latent transmission probability	From Kim *et al*, Wald *et al* and Corey *et al*[30 37 38]
	Symptomatic recurrence stage	1–3×6.7–25 times latent/asymptomatic transmission probability	Wald *et al*, Kim *et al*, and Mertz *et al*[25 30 39–41]
Cofactors for HIV	Average Ng/Ct cofactor per sex act for increasing susceptibility to HIV	1.2–2.5	Using Rottingen *et al*[13]
	Average syphilis cofactor per sex act for increasing susceptibility to HIV	2.1–3.3	
	HSV-2 cofactor per sex act for increasing HIV infectivity:		
	Primary and symptomatic recurrence phases	1.27–2.57×1–2	
	Asymptomatic/latent phase	0.27–1.57×0.04–0.15×2–3	
	HSV-2 cofactor per sex act for increasing HIV susceptibility:		Using Schacker *et al*, Nagot *et al*, Zuckerman *et al*, Baeten *et al*, Celum *et al*, Dunne *et al*, Delany *et al*, Mbopi-Keou *et al*, Augenbraun *et al*, LeGoff *et al* and Serwadda *et al*[31 42–54] and Quinn *et al*[55] to convert from differences in HIV viral load
	Asymptomatic/latent phase	1–4.75	
	Primary phase and symptomatic recurrence phase	1.5–4.0 times asymptomatic cofactor	
Cofactors for HSV-2	HIV cofactor per partnership for increasing HSV-2 infectivity:		Using Celum *et al*, Corey *et al*, Freeman *et al* and Watson-Jones *et al*[45 56–58] and converting to probability using Quinn *et al*[55]
	Primary phase	1–2.5	
	Asymptomatic/latent phase	2–4	
	Symptomatic recurrence phase	Same as primary	
Condom efficacies	Condom efficacy per sex act for HIV	80% to 95%	Pinkerton *et al*[59 60]
	Condom efficacy per sex act for HSV-2 and syphilis	40% to 70%	Based on Wald *et al*, Oberle *et al*, Dobbins *et al*, Obasi *et al* and Huerta *et al*[37 61–65]
	Condom efficacy per sex act for Ng/Ct	60% to 90%	Based on Holmes *et al*, Hooper *et al*, Austin *et al*, Barlow, Joesof *et al*, Sanchez *et al*, Gaydos *et al*, Niccolai *et al* and Zenilman *et al* [66–74]

Ct, *Chlamydia trachomatis*; HSV, herpes simplex virus; *Neisseria gonorrhoeae*; STI, sexually transmitted infection.

Table 3 Prior behavioural model input parameters sampled at the fitting stage to obtain the posterior parameter sets for Mysore and Belgaum for the Avahan impact model

Types of model input	Definition of model input	Mysore	Belgaum
Demography			
Population size and demographic inputs	Initial size of sexually active population	278000 (M) 268000 (F)	268000 (M) 257000(F)
	Fraction of female general population sexually active	75% to 95%	77% to 95%
	Fraction of male general population sexually active	Determined by available partnerships	Determined by available partnerships
	Average time spent sexually active	41.3 years (M) 42.4 years (F)	41.5 years (M) 42.2 years (F)
	Entry rate into sexually active population per year	12000 (M) 11000 (F)	12000 (M) 11000 (F)
Migration of female sex workers (FSWs)	Proportion of FSWs migrating	0.3—0.44	0.05—0.20
	Multiplicative cofactor increasing prevalence of HIV among clients in sites to which FSWs migrate	1—2	1—2
Sexual behaviour			
Long-term partnerships of FSWs and clients	Percentage of clients currently married/cohabiting by duration:		
	0—1 years and 2—4 years	68%	43% to 59%
	5—9 years and 10+ years	68%	83% to 93%
	Percentage of FSWs currently married/cohabiting by duration:		
	0—1 years	38.2% to 57.2%	9.8% to 40.3%
	2—4 years	39.9% to 54.9%	11.6% to 39.9%
	5—9 years	28.6% to 50.4%	21.5% to 48.6%
	10+ years	23.1% to 46/7%	5.3% to 20.7%
	Percentage of FSWs currently married/cohabiting by typology:		
	Home based	25.9% to 54.1%	11.4% to 29.7%
	Brothel based	8.8% to 66.9%	13.1% to 28.9%
	Street based	39.3% to 49.3%	9.0% to 43.9%
	Average frequency of sex acts with married/cohabiting partner for FSWs/ clients (per month)	5.9—8.2 (clients) 5.9—8.2 (FSWs)	9.5—11.7 (clients) 5.6—9.5 (FSWs)
	Duration of long-term partnerships (cohabiting/married) if FSW, years	8.6—13.0	16.6—21.7
	Duration of long-term partnerships between clients and low-risk females, years	20—30	20—30
FSW sexual behaviour	Average weekly frequency of clients for:		
	Home-based FSWs duration 0—1 years	2.5—5.1	5.5—26.1
	Home-based FSWs duration 2—4 years	3.8—7.9	1.8—10.3
	Home-based FSWs duration 5—9 years	2.8—8.2	5.7—10.0
	Home-based FSWs duration 10+ years	4.6—14.6	7.0—11.0
	Brothel-based FSWs duration 0—1 years	15—25	6.3—34.2
	Brothel-based FSWs duration 2—4 years	12—45	13.5—26.2
	Brothel-based FSWs duration 5—9 years	4—15	13.1—25.3
	Brothel-based FSWs duration 10+ years	5.2—16.6	8.9—17.9
	Street-based FSWs duration 0—1 years	6.5—9.2	4.8—13.6
	Street-based FSWs duration 2—4 years	7.5—9.4	1.1—13.0
	Street-based FSWs duration 5—9 years	7.2—9.8	2.4—10.2
	Street-based FSWs duration 10+ years	6.5—9.1	3.8—10.2
	Number of sex acts with each client	1—3	1—3
	Average duration of sex work in months for:		
	Home-based FSWs	35—69	160—224
	Brothel-based FSWs	49—189	94—127
	Street-based FSWs	53—66	138—251
Client sexual behaviour	Number of FSWs visited/month if:		
	Below median activity level	0.8—1.2	0.8—1.2
	Above median activity level	2.9—3.8	2.32—2.78
	Average duration of being client in months if below/above median activity level	84—240/84—240	83—119/90—143

Continued

Table 3 Continued

Types of model input	Definition of model input	Mysore	Belgaum
Proportions of FSWs/clients by each stratification	Percentage of female population who are FSWs	0.3% to 1.4%	0.2% to 1.1%
	Percentage of male population who are clients	Determined by number of FSW partnerships	Determined by number of FSW partnerships
	Proportion of FSWs that are:		
	Home based	0.08–0.15	0.23–0.50
	Brothel based	0.00–0.01	0.31–0.61
	Street based	0.85–0.91	0.11–0.24
	Proportion of male clients who visit FSWs:		
	Below median level (ie, low activity clients)	0.5	0.58–0.69
	Above median level (ie, high activity clients)	0.5	0.31–0.42
Condom use			
Condom use in main partnerships	Average consistency of condom use between married/cohabiting partners per sex act.	4.3% to 10.3%	5.2% to 12.7%
Condom use between FSWs and clients	Fraction of sex acts with occasional clients for which a condom is used, by FSWs who:		
	Report 'always' using	0.81–0.93	0.81–0.93
	Report often/sometimes using	0.54–0.67	0.54–0.67
	Report 'never' using	0.07–0.38	0.07–0.38
	Fraction of FSWs who are consistent condom users:		
	At the start of the HIV epidemic in India	0–0.1	0–0.1
	Under H_0 and H_1:		
	At first time point	0.111–0.228	0.286–0.422
	At second time point	0.233–0.395	0.759–0.855
	Under H_1, at time of IBBA R2	0.615–0.729	0.855–0.926
	Under H_2:		
	At first time point	0.1–0.220	0.1–0.220
	At second time point	0.321–0.416	0.321–0.416
	At time of IBBA R2	0.777–0.847	0.777–0.847
	Fraction of FSWs who report 'sometimes/often' using condoms with occasional clients at IBBA R2	0.245–0.367	0.074–0.145
Dates	Start of HIV epidemic in India	1976–1985	1976–1985
	Under H_0 and H_1:		
	At first time point	2002	2002
	At second time point	2004	2005
	At time of IBBA R2	2007	2008
	Under H_2:		
	At first time point	2004	2004
	At second time point	2006	2006
	At time of IBBA R2	2008	2008

FSW, female sex worker; H, hypothesis; IBBA, integrated behavioural and biological assessments; R, round.

that this decline began before Avahan started, around the year 2000, while in Mysore the decline probably started shortly after Avahan, in 2004–2005. Modelled incidence and the prevalence for hypothesis H_1 for Mysore show similar trends (see supplementary material). More details of the general characteristics of the model runs and fits are included in the supplementary material.

In Mysore, the median relative decline in HIV prevalence in 2009 compared to 2004 ('time decline') under H_2 was 36.2% (95% CI 21% to 51%) in FSWs (median 25.6%, 95% CI 7% to 42% in clients), whereas the median relative decline in 2009 prevalence compared to a simulated scenario without any increase in condom use since 2004 ('intervention decline') was 44.7% (95% CI 35% to 52%) in FSWs (37.9%, 95% CI 30% to 45% in clients). In Belgaum, under H_1, the median time decline was 47.6% (95% CI 39% to 58%) in FSWs (median 55.7%, 95% CI 48% to 66% in clients) while the median intervention decline was actually lower at 23.1% (95% CI 17% to 30%) in FSWs (28.4%, 95% CI 22% to 36% in clients). Thus, the time decline in HIV prevalence slightly underestimates the intervention decline in Mysore for hypothesis H_2 and overestimates it in Belgaum for hypothesis H_1.

Intervention impact among high-risk groups

We estimated the impact of the increase in condom use following the start of Avahan using the most likely hypothesis as the simulated intervention group/population, and using the null hypothesis H_0 as the simulated matched control group/population. In Mysore, the increase in condom use between 2004 and 2009 may have prevented 31.3% to 47.4% of new HIV infections in FSWs and 32.7% to 47.2% in clients under hypothesis H_2 (figure 4 shows this in comparison to the impact projections for hypothesis H_1). Impact increases over time, with 58.7% to 82.2% of new HIV infections prevented among FSWs in 2008 and 64.1% to 85.1% among clients under hypothesis H_2 (41.2% to 72.2% and 47.1% to 77.6% under H_1).

In Belgaum, hypothesis H_0, where condom use remains constant from 2004 onwards, suggests no impact. In

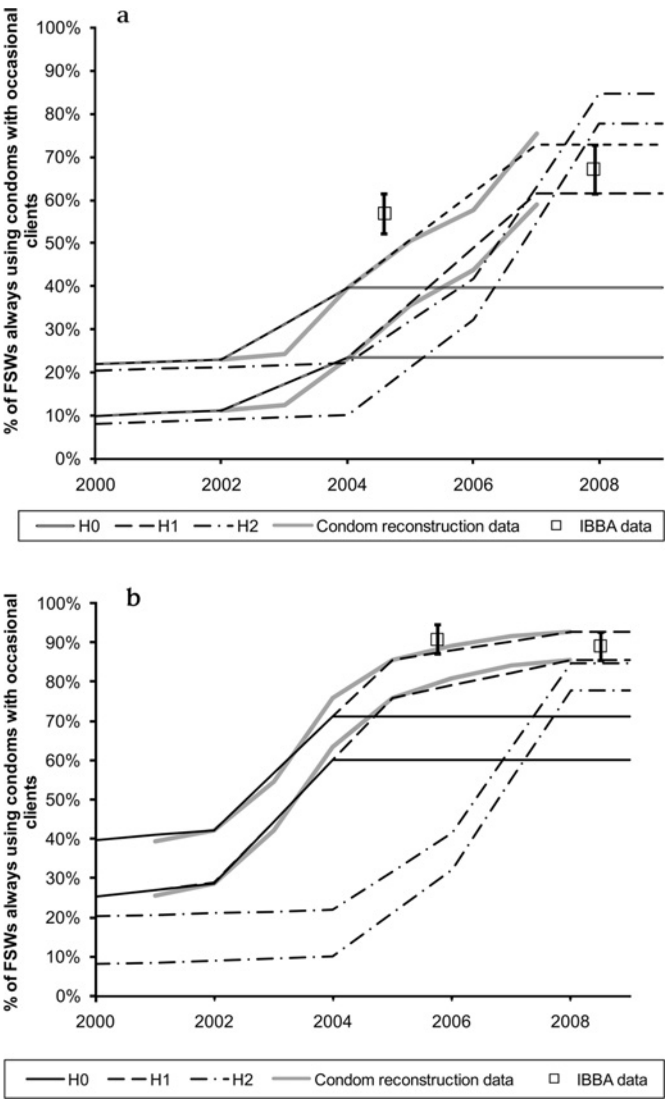

Figure 2 Prior parameter ranges for hypotheses H_0–H_2 reflecting the proportion of female sex workers (FSWs) who are consistently using condoms for (a) Mysore and (b) Belgaum. The upper and lower lines show the range of the prior. Also shown is the data from the historic condom reconstruction, and mean and 95% CIs for the FSW integrated behavioural and biological assessment (IBBA) values.

comparison, the H_1 scenario projects that 24.8% to 43.2% of new FSW HIV infections and 30.9% to 53.1% of new client infections were prevented in Belgaum by the increase in condom use between 2004 and 2009 (figure 4). As for Mysore, impact increases over time in the H_1 scenario, with 32.7% to 59.7% of new infections in FSWs and 42.0% to 72.6% in clients prevented in 2008.

DISCUSSION

With sufficient data to inform model parameters and validate model predictions, the use of mathematical models within a Bayesian framework enables the testing of hypotheses about the value or range of more uncertain parameters,[77 78] such as the evolution of condom use over time. In this analysis we have tested whether condom use is likely to have increased following the implementation of the Avahan intervention. In theory this could have been done more directly if unbiased baseline data on condom use had been collected; however, in practice it was not possible because such data could only be collected once the intervention was sufficiently well established to map and sample FSWs.

The success rates obtained in the hypothesis-testing analysis support the conclusion that in Mysore condom use during commercial sex increased substantially after the beginning of the intervention. This increase most likely occurred shortly after the beginning of the intervention, as suggested by data on availability of condoms. Although there was no significant decrease in the FSW IBBA prevalence data between rounds 1 and 2, the model suggests that, in the absence of an increase in condom use after 2004, prevalence would have increased, and so to obtain the required trend a significant increase in condom use was required. In Belgaum, the model results show that decreases in prevalence alone from the IBBA surveys are insufficient to distinguish between the hypotheses of increased condom use as reported by FSWs and constant condom use following the beginning of the intervention. Without information from other sources, it is not possible to definitely conclude that there has been an increase in condom use in commercial sex in Belgaum. The results also suggest that the level of condom use was higher in Belgaum than in Mysore prior to 2004. In Belgaum, a smaller-scale intervention was present for some years prior to 2004,[79] before it was scaled up by Avahan. Condom use by FSWs with clients may therefore have been higher at the start of the intervention than in Mysore, where there was no prior intervention.

The model results indicate that HIV incidence and prevalence have declined over time. The decline occurred earlier in Belgaum than in Mysore because condom use became widespread earlier, but perhaps also because the epidemic matured earlier. In Mysore, the decline roughly coincides with the beginning of the intervention. This pattern of decrease in prevalence agrees with that seen by Vickerman *et al*,[4] and by Boily *et al*[80] examining ANC data. While this study only considers high-risk individuals, the decline observed among FSWs and clients should translate to a slower decline in the general population in both districts, as shown in the analysis by Vickerman *et al*.[4]

The relative decline in HIV prevalence in Mysore in 2009 compared to the simulated control group ('intervention decline') is higher than the decline over time since 2004 ('time decline'). This is because the epidemic was still growing in 2004. In Belgaum, under the hypothesis of increasing condom use after

Table 4 Number of fits per million runs for each hypothesis (H) (fits to round (R)1 data only are shown for comparison to validate time trends of the model in HIV prevalence)

	Mysore			Belgaum		
	H_0: condom use fixed since 2004	H_1: condom use as reconstructed from IBBA round 2 data	H_2: condom use follows condom availability trends[9]	H_0: condom use fixed since 2004	H_1: condom use as reconstructed from IBBA round 2 data	H_2: condom use follows condom availability trends[9]
Fits to R1 FSW and client IBBAs	0	48.3	86	11.3	9.7	0
Fits to R1+R2 FSW and client IBBAs	0	36 (S)	82.7 (S)	9.7	8.3 (NS)	0 (S)

FSW, female sex worker; IBBA, integrated behavioural and biological assessments; NS, not statistically different to H_0 at the 5% level using χ^2 test; S, statistically significantly different to H_0.

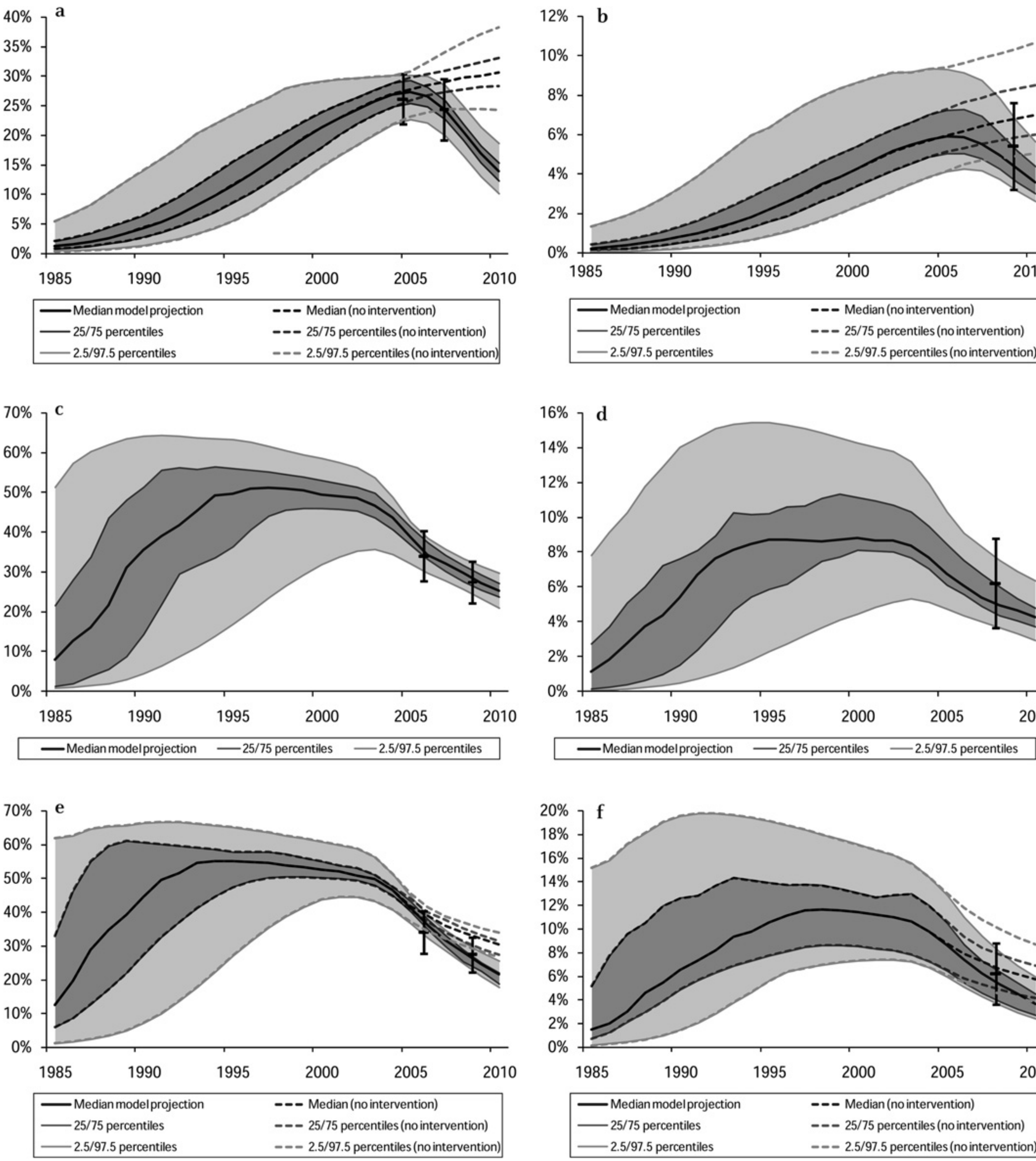

Figure 3 HIV prevalence over time for most likely hypothesis for (a) female sex workers (FSWs) and (b) clients in Mysore (H_2); (c) FSWs and (d) clients in Belgaum (H_0); and (e) FSWs and (f) clients in Belgaum (H_1). Shown on the graphs are median, 25th and 75th percentiles, and the 95% credibility interval (lighter shaded area). For H_1 Belgaum and H_2 Mysore the prevalence of the simulated control groups is also shown (median, 25th and 75th percentiles, and 95% credibility interval). Also shown is the integrated behavioural and biological assessment (IBBA) prevalence data.

Avahan, the intervention decline is smaller than the time decline, as the epidemic there was already declining prior to Avahan. This highlights that time trends alone should not be used to evaluate an intervention, and that modelling results are important to complement prevalence data in carrying out an evaluation.[6 8 80]

Strengths and limitations

The model described in this paper was specifically tailored to reflect the behavioural and biological heterogeneities present in these settings, with dynamical modelling of HSV-2 and syphilis in addition to HIV in each site. It was parameterised using data from multiple surveys among FSWs, clients and general

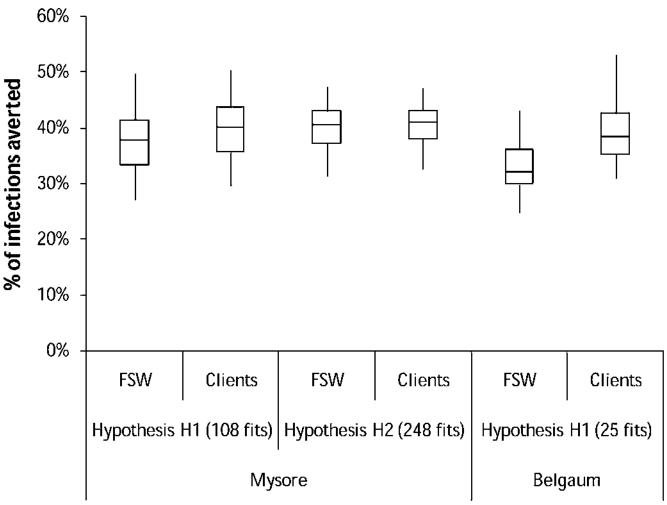

Figure 4 Fraction of new HIV infections averted over a 5-year period from 2004 in female sex workers (FSWs) and clients as a result of increases in condom use for (A) Mysore under hypotheses H_1 and H_2 and (B) Belgaum under hypotheses H_1. Shown on the graph are the median (middle line in the box), 25th and 75th percentiles (box) and the 95% credibility interval (whiskers). Belgaum hypothesis H_0 corresponds to no impact, and is not shown.

population, and captured key epidemiological trends in HIV, HSV-2 and syphilis by risk groups. This model also compared well to an independent model by Vickerman *et al*,[4] and it was also validated with respect to time trends in HIV and FSW HIV prevalences by typology.

The framework described in Boily *et al*[8] was used to produce point estimates and credibility intervals of intervention impact by the creation of control groups that assumed no increase in condom use. This control group gives the impact due to the increase in condom use since the beginning of the intervention, and, in situations where condom use would have increased naturally even without an intervention to drive it, will overestimate intervention impact. Conversely, in the absence of a likely increase in condom use following Avahan, as may have been the case in Belgaum, this choice of control group results in the model projecting no HIV infections averted, while it is possible that there would still have been a decline in condom use in this situation without an intervention to sustain it. Indeed, analysis of a slow, modest decrease in consistent condom use of 10% over 5 years suggests that even such a small decline in condom use leads to a large impact (17.3% to 29.7% additional new FSW HIV infections between 2004–2009 due to the decrease in condom use), and thus the contribution of the intervention in sustaining condom use is important, although it is difficult to attribute directly.

The precision of the estimates was limited by data availability. In both districts, the fitting success rate was modest because conservative (wide) prior ranges were used for most parameters to capture their uncertainty, and because the model had to fit seven separate prevalence outcomes. If more data were available, then it would be possible to use this additional information to reduce the width of these priors and so possibly identify a higher proportion of model fits. This would allow a stronger comparison between the condom use scenarios, and would better reflect uncertainty in the impact projections. HIV prevalence data for earlier in the epidemic would also enable us to better constrain the trajectory of the early epidemic and so rule out unlikely epidemics with high early prevalence. However, using a constraint such as FSW prevalence being <10% in 1985 did not change the impact estimates significantly (data not shown).

The picture is further complicated in Belgaum because the first IBBA survey was carried out 16 months after the start of the Avahan initiative, and so behavioural and epidemiological data reflected a situation in which Avahan was already present and where consistent condom use rates reported by FSW in the 2005 IBBA were already very high, at 91%. In contrast, the survey in Mysore is likely to be more comparable to the pre-Avahan baseline as it took place 8 months after the start of Avahan. It is difficult to quantify the impact of a change in behaviour in situations where there was a pre-existing intervention and a long delay between the start of the intervention and the first IBBA survey, such as in Belgaum. Impact estimation is more uncertain in such settings because it is hard to define and simulate a control group reflecting how condom use would have decreased without the intervention, for which no data are available. An additional round of behavioural and HIV prevalence data for FSWs in Belgaum could help to further inform impact estimates by giving extra information about how the epidemic there is changing.

In Belgaum, the low number of fits from the model to the prevalence data may be largely explained by the difficulty of fitting the relatively high HIV prevalence in clients. This analysis modelled the transmission of HIV/STIs among urban clients, since the IBBA was carried out in urban areas where the intervention started. However the size of the FSW population is higher in rural areas, and as city clients may also go to smaller towns and villages to visit FSWs, the urban client HIV prevalence may be influenced by the large rural FSW population. Future data collection strategies for programme evaluation should be adapted to reflect the reality of how the epidemic is driven and the nature of the intervention.

Conclusions

Dynamical modelling, used within a Bayesian framework, is useful for testing hypotheses and providing informative and less subjective impact estimates on which to base decisions. This method of comparing proportions of fits of different scenarios is relatively straightforward to implement, as shown here and in another recent analysis,[77] and helps to further augment survey findings of behaviours that are prone to reporting biases, such as condom use.

This analysis suggests that the HIV epidemics in Belgaum and Mysore are declining. In Belgaum, it is probable that the decline in HIV prevalence started before the beginning of the Avahan intervention, since condom use by FSWs with their clients was already high in this district due to pre-existing interventions. The model, using current prevalence data alone, is unable to distinguish between scenarios where condom use in commercial sex was sustained at existing levels and where it increased after Avahan. If there was a rise in condom use, as suggested by other data[9] and equally likely compared to the null hypothesis from this method, this increase would have averted 24.8% to 43.2% of HIV infections in FSWs and 30.9% to 53.1% of infections in clients between 2004 and 2009. If, however, Avahan only sustained the existing level of condom use attained by FSWs prior to Avahan, this is still important for controlling the epidemic, as even a small, gradual decline in condom use can greatly increase the number of new infections. This conclusion on impact, of including both scenarios, is conservative (which is deemed preferable), since the difference in proportion of fits between the hypotheses where condom use does or does not increase after 2004 is small. However, combined with the additional data

Key messages

- Transmission dynamics models used within a Bayesian framework are useful tools to help evaluate large-scale intervention in absence of a control group. Such a framework enables testing of different hypotheses and provides credibility intervals for estimates of infections averted.
- Our modelling analysis suggests there has been a decrease in HIV prevalence in high-risk groups due to an increase in condom use since the beginning of the Avahan intervention in Mysore.
- Due to data limitations, our analysis could not say conclusively whether the change in prevalence in Belgaum was due to an increase in condom use following the start of the intervention, or simply the result of the natural dynamics and increase in condom use before 2004.

presented in Bradley *et al*[9] regarding the availability of condoms in Belgaum, it can be argued that it is likely that there has been an increase in condom use since the start of Avahan.

In Mysore, the findings strongly suggest that condom use during commercial sex has increased since the introduction of the Avahan programme, and that this increase in condom use has averted 31.3% to 47.4% of HIV infections in FSWs and 32.7% to 47.2% in clients in Mysore over the first 5 years.

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REFERENCES

1. **National AIDS Control Organisation, National Institute of Medical Statistics Ministry of Health and Family Welfare, Government of India.** *Technical report: India HIV estimates 2006*. http://nacoonline.org/upload/NACO PDF/Technical Report on HIV Estimation 2006.pdf (accessed 22 May 2009).
2. **Avahan — the India AIDS initiative.** *The business of HIV prevention at scale*. New Delhi: Bill & Melinda Gates Foundation, 2008. http://www.gatesfoundation.org/avahan/Documents/Avahan_HIVPrevention.pdf.
3. **Moses S,** Ramesh BM, Nagelkerke NJ, *et al*. Impact of an intensive HIV prevention programme for female sex workers on HIV prevalence among antenatal clinic attenders in Karnataka state, south India: an ecological analysis. *AIDS* 2008;**22** (Suppl 5):S101—8.
4. **Vickerman P,** Foss AM, Pickles M, *et al*. Is the Indian HIV epidemic driven by commercial sex? A modelling analysis from south India. 18th ISSTDR: 28 June—1 July 2009, London. http://www.isstdrlondon2009.com.
5. **Chandrasekaran P,** Dallabetta G, Loo V, *et al*. Evaluation design for large-scale HIV prevention programmes: the case of Avahan, the India AIDS initiative. *AIDS* 2008;**22** (Suppl 5):S1—15.
6. **Boily MC,** Lowndes C, Alary M. The impact of HIV epidemic phases on the effectiveness of core group interventions: insights from mathematical models. *Sex Transm Infect* 2002;**78**(Suppl 1):i78—90.
7. **Garnett GP,** Gregson S, Stanecki KA. Criteria for detecting and understanding changes in the risk of HIV infection at a national level in generalised epidemics. *Sex Transm Infect* 2006;**82**(Suppl 1):i48—51.
8. **Boily MC,** Lowndes CM, Vickerman P, *et al*. Evaluating large-scale HIV prevention interventions: study design for an integrated mathematical modelling approach. *Sex Transm Infect* 2007;**83**:582—9.
9. **Bradley JE,** Moses S, Blanchard J, *et al*. Assessing reported condom use among female sex workers in southern India through examination of condom availability. *Sex Transm Infect* 2010;**86**(Suppl 1):i44—8.
10. **Ramesh BM,** Moses S, Washington R, *et al*. Determinants of HIV prevalence among female sex workers in four south Indian states: analysis of cross-sectional surveys in twenty-three districts. *AIDS* 2008;**22**(Suppl 5):S35—44.
11. Census of India. 2001. http://www.censusindia.net (accessed 19 May 2008).
12. **Deering KN,** Blanchard J, Moses S, *et al*. Characterising the factors associated with the numbers of client partners of female sex workers in south India: a geographic comparison. 18th ISSTDR; 28 June—1 July 2009, London. http://www.isstdrlondon2009.com.
13. **Rottingen JA,** Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis* 2001;**28**:579—97.
14. **Foss AM,** Vickerman PT, Chalabi Z, *et al*. Dynamic modeling of herpes simplex virus type-2 (HSV-2) transmission: issues in structural uncertainty. *Bull Math Biol* 2009;**71**:720—49.
15. **Garnett GP,** Aral SO, Hoyle DV, *et al*. The natural history of syphilis. Implications for the transmission dynamics and control of infection. *Sex Transm Dis* 1997;**24**:185—200.
16. **Korenromp EL,** Sudaryo MK, de Vlas SJ, *et al*. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS* 2002;**13**:91—101.
17. **Cheong WK,** Thirumoorthy T, Doraisingham S, *et al*. Clinical and laboratory study of first episode genital herpes in Singapore. *Int J STD AIDS* 1990;**1**:195—8.
18. **Corey L,** Adams HG, Brown ZA, *et al*. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983;**98**:958—72.
19. **Corey L,** Fife KH, Benedetti JK, *et al*. Intravenous acyclovir for the treatment of primary genital herpes. *Ann Intern Med* 1983;**98**:914—21.
20. **Corey L,** Wald A. Genital herpes. Holmes KK**,** Mardh PA, Sparling PF, *et al*, eds. *Sexually transmitted diseases*. 3rd ed. New York: McGraw-Hill, 1999: 285—312.
21. **Diamond C,** Selke S, Ashley R, *et al*. Clinical course of patients with serologic evidence of recurrent genital herpes presenting with signs and symptoms of first episode disease. *Sex Transm Dis* 1999;**26**:221—5.
22. **Koelle DM,** Benedetti J, Langenberg A, *et al*. Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* 1992;**116**:433—7.
23. **Guinan ME,** MacCalman J, Kern ER, *et al*. The course of untreated recurrent genital herpes simplex infection in 27 women. *N Engl J Med* 1981;**304**:759—63.
24. **Benedetti JK,** Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med* 1999;**131**:14—20.
25. **Wald A,** Corey L, Cone R, *et al*. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. *J Clin Invest* 1997;**99**:1092—7.
26. **Wald A,** Zeh J, Selke S, *et al*. Genital shedding of herpes simplex virus among men. *J Infect Dis* 2002;**186**(Suppl 1):S34—9.
27. **Wald A,** Zeh J, Selke S, *et al*. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 2000;**342**:844—50.
28. **Benedetti J,** Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Intern Med* 1994;**121**:847—54.
29. **Lafferty WE,** Coombs RW, Benedetti J, *et al*. Recurrences after oral and genital herpes simplex virus infection. Influence of site of infection and viral type. *N Engl J Med* 1987;**316**:1444—9.
30. **Kim HN,** Wald A, Harris J, *et al*. Does frequency of genital herpes recurrences predict risk of transmission? Further analysis of the valacyclovir transmission study. *Sex Transm Dis* 2008;**35**:124—8.
31. **Schacker T,** Zeh J, Hu HL, *et al*. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis* 1998;**178**:1616—22.
32. **Conant MA,** Schacker TW, Murphy RL, *et al*. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. *Int J STD AIDS* 2002;**13**:12—21.
33. **Grover G,** Shivraj SO. Survival pattern of reported HIV infected individuals in the city of Delhi (India). *J Commun Dis* 2004;**36**:83—92.
34. **Kumarasamy N,** Solomon S, Flanigan TP, *et al*. Natural history of human immunodeficiency virus disease in southern India. *Clin Infect Dis* 2003;**36**:79—85.
35. **Boily MC,** Baggaley RF, Wang L, *et al*. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis* 2009;**9**:118—29.
36. **Wawer MJ,** Gray RH, Sewankambo NK, *et al*. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005;**191**:1403—9.
37. **Wald A,** Langenberg AG, Link K, *et al*. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA* 2001;**285**:3100—6.
38. **Corey L,** Wald A, Patel R, *et al*. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004;**350**:11—20.
39. **Wald A,** Huang ML, Carrell D, *et al*. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. *J Infect Dis* 2003;**188**:1345—51.

40. **Holmes KK,** Johnson DW, Trostle HJ. An estimate of the risk of men acquiring gonorrhea by sexual contact with infected females. *Am J Epidemiol* 1970;**91**:170–4.
41. **Mertz GJ,** Schmidt O, Jourden JL, *et al*. Frequency of acquisition of first-episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985;**12**:33–9.
42. **Nagot N,** Ouedraogo A, Foulongne V, *et al*. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007;**356**:790–9.
43. **Zuckerman RA,** Lucchetti A, Whittington WL, *et al*. Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. *J Infect Dis* 2007;**196**:1500–8.
44. **Baeten JM,** Strick LB, Lucchetti A, *et al*. Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. *J Infect Dis* 2008;**198**:1804–8.
45. **Celum C,** Wald A, Hughes J, *et al*. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**371**:2109–19.
46. **Dunne EF,** Whitehead S, Sternberg M, *et al*. Suppressive acyclovir therapy reduces HIV cervicovaginal shedding in HIV- and HSV-2-infected women, Chiang Rai, Thailand. *J Acquir Immune Defic Syndr* 2008;**49**:77–83.
47. **Delany S,** Mlaba N, Clayton T, *et al*. Impact of aciclovir on genital and plasma HIV-1 RNA in HSV-2/HIV-1 co-infected women: a randomized placebo-controlled trial in South Africa. *AIDS* 2009;**23**:461–9.
48. **Schacker T,** Hu HL, Koelle DM, *et al*. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. *Ann Intern Med* 1998;**128**:21–8.
49. **Mbopi-Keou FX,** Gresenguet G, Mayaud P, *et al*. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. *J Infect Dis* 2000;**182**:1090–6.
50. **Augenbraun M,** Feldman J, Chirgwin K, *et al*. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. *Ann Intern Med* 1995;**123**:845–7.
51. **Nagot N,** Foulongne V, Becquart P, *et al*. Longitudinal assessment of HIV-1 and HSV-2 shedding in the genital tract of West African women. *J Acquir Immune Defic Syndr* 2005;**39**:632–4.
52. **LeGoff J,** Weiss HA, Gresenguet G, *et al*. Cervicovaginal HIV-1 and herpes simplex virus type 2 shedding during genital ulcer disease episodes. *AIDS* 2007;**21**:1569–78.
53. **Serwadda D,** Gray RH, Sewankambo NK, *et al*. Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: a nested case-control study in Rakai, Uganda. *J Infect Dis* 2003;**188**:1492–7.
54. **Nagot N,** Ouedraogo A, Konate I, *et al*. Roles of clinical and subclinical reactivated herpes simplex virus type 2 infection and human immunodeficiency virus type 1 (HIV-1)-induced immunosuppression on genital and plasma HIV-1 levels. *J Infect Dis* 2008;**198**:241–9.
55. **Quinn TC,** Wawer MJ, Sewankambo N, *et al*. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000;**342**:921–9.
56. **Corey L,** Wald A, Celum CL, *et al*. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr* 2004;**35**:435–45.
57. **Freeman EE,** Weiss HA, Glynn JR, *et al*. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS* 2006;**20**:73–83.
58. **Watson-Jones D,** Weiss HA, Rusizoka M, *et al*. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. *N Engl J Med* 2008;**358**:1560–71.
59. **Pinkerton SD,** Abramson PR, Turk ME. Updated estimates of condom effectiveness. *J Assoc Nurses AIDS Care* 1998;**9**:88–9.
60. **Pinkerton SD,** Abramson PR. Effectiveness of condoms in preventing HIV transmission. *Soc Sci Med* 1997;**44**:1303–12.
61. **Wald A,** Langenberg AG, Krantz E, *et al*. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med* 2005;**143**:707–13.
62. **Oberle MW,** Rosero-Bixby L, Lee FK, *et al*. Herpes simplex virus type 2 antibodies: high prevalence in monogamous women in Costa Rica. *Am J Trop Med Hyg* 1989;**41**:224–9.
63. **Dobbins JG,** Mastro TD, Nopkesorn T, *et al*. Herpes in the time of AIDS: a comparison of the epidemiology of HIV-1 and HSV-2 in young men in northern Thailand. *Sex Transm Dis* 1999;**26**:67–74.
64. **Obasi A,** Mosha F, Quigley M, *et al*. Antibody to herpes simplex virus type 2 as a marker of sexual risk behavior in rural Tanzania. *J Infect Dis* 1999;**179**:16–24.
65. **Huerta K,** Berkelhamer S, Klein J, *et al*. Epidemiology of herpes simplex virus type 2 infections in a high-risk adolescent population. *J Adolesc Health* 1996;**18**:384–6.
66. **Holmes KK,** Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. *Bull World Health Organ* 2004;**82**:454–61.
67. **Hooper RR,** Reynolds GH, Jones OG, *et al*. Cohort study of venereal disease. I: the risk of gonorrhea transmission from infected women to men. *Am J Epidemiol* 1978;**108**:136–44.
68. **Austin H,** Louv WC, Alexander WJ. A case-control study of spermicides and gonorrhea. *JAMA* 1984;**251**:2822–4.
69. **Barlow D.** The condom and gonorrhoea. *Lancet* 1977;**2**:811–13.
70. **Joesoef MR,** Linnan M, Barakbah Y, *et al*. Patterns of sexually transmitted diseases in female sex workers in Surabaya, Indonesia. *Int J STD AIDS* 1997;**8**:576–80.
71. **Sanchez J,** Campos PE, Courtois B, *et al*. Prevention of sexually transmitted diseases (STDs) in female sex workers: prospective evaluation of condom promotion and strengthened STD services. *Sex Transm Dis* 2003;**30**:273–9.
72. **Gaydos CA,** Howell MR, Pare B, *et al*. *Chlamydia trachomatis* infections in female military recruits. *N Engl J Med* 1998;**339**:739–44.
73. **Niccolai LM,** Rowhani-Rahbar A, Jenkins H, *et al*. Condom effectiveness for prevention of *Chlamydia trachomatis* infection. *Sex Transm Infect* 2005;**81**:323–5.
74. **Zenilman JM,** Weisman CS, Rompalo AM, *et al*. Condom use to prevent incident STDs: the validity of self-reported condom use. *Sex Transm Dis* 1995;**22**:15–21.
75. **Lowndes C,** Alary M, Verma S, *et al*. Assessment of intervention outcome in the absence of baseline data: 'reconstruction' of condom use time trends using retrospective in analysis of survey data. *Sex Transm Infect* 2010;**86**:i49–55.
76. **Weiss G,** von Haeseler A. Inference of population history using a likelihood approach. *Genetics* 1998;**149**:1539–46.
77. **Vickerman P,** Platt L, Hawkes S. Modelling the transmission of HIV and HCV among injecting drug users in Rawalpindi, a low HCV prevalence setting in Pakistan. *Sex Transm Infect* 2009;**85**(Suppl 2):ii23–30.
78. **Hallett TB,** Gregson S, Mugurungi O, *et al*. Assessing evidence for behaviour change affecting the course of HIV epidemics: a new mathematical modelling approach and application to Zimbabwe. *Epidemics* 2009;**1**:108–17.
79. **Karnataka Health Promotion Trust.** About BIRDS. http://www.khpt.org/birds.htm (accessed 15 July 2009).
80. **Boily MC,** Pickles M, Vickerman P, *et al*. Using mathematical modelling to investigate the plausibility of attributing observed antenatal clinic declines to a female sex worker intervention in Karnataka state, India. *AIDS* 2008;**22**(Suppl 5):S149–64.