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Supplementary appendix

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The International AIDS Society – *Lancet* Commission on

the Future of Global Health and the HIV Response

Supplemental Materials

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APPENDIX 1

Modelling screening for HIV, diabetes and hypertension in South Africa

Thembisa is an integrated demographic and HIV model, developed for South Africa. The South African population is stratified by age, sex, marital status, sexual experience and risk group (high risk or low risk). In addition, the male population is stratified by circumcision status and by sexual preference (bisexual or exclusively heterosexual). High risk women are further subdivided into commercial sex workers and other high risk women. HIV transmission is simulated based on assumed rates of partnership formation, frequencies of sex, probabilities of condom use and probabilities of HIV transmission per sex act. These parameters are assumed to differ depending on the relationship type (marital, short-term non-marital or sex worker-client). After individuals acquire HIV, they are initially classified as acutely infected and then progress through four stages of advancing immune suppression in the absence of ART (CD4 count ≥500, 350-499, 299-349 and <200 cells/μl). HIV-positive individuals are further stratified according to their level of engagement in HIV care (never tested, previously tested but undiagnosed, diagnosed but ART-naïve, and ART-experienced). This analysis is based on Thembisa version 3.2. An Excel version of the model is available for download at www.thembisa.org, and a comprehensive model description is available on the website.[1]

The process of calibrating the model to HIV prevalence data, HIV diagnosis data and mortality data has previously been described.[2, 3] Briefly, the model is calibrated to age-specific HIV prevalence data from antenatal surveys conducted over the 1997-2015 period,[4] to age- and sex-specific HIV prevalence data from national household surveys conducted in 2005, 2008 and 2012,[5-7] and to age- and sex-specific recorded death statistics over the 1997-2014 period.[8] The model is also calibrated to self-reported data on past HIV testing in the national household surveys, allowing for potential misreporting, and to total estimated numbers of HIV tests performed in South Africa and estimated numbers of HIV-positive test results.[3] This triangulation of HIV prevalence data from surveys, mortality data and routine HIV testing data ensures that the model captures accurately the profile of the HIV-positive South African population.

In the period up to 2017, the model simulates four types of HIV testing: testing in the general population, testing in antenatal clinics, testing in HIV-positive individuals who experience opportunistic infections, and testing in individuals who receive pre-exposure prophylaxis. The modelling of these modes of testing has been described previously.[3] In the period from 2018 to 2028, we consider a fifth type of testing: testing through mobile clinics. Although this could be considered a variation of testing in the general population, it is likely that the age- and sex profile of patients reached through a multi-disease screening intervention would be different from that achieved in HIV screening programmes.[9] The average annual fraction of the population reached by mobile testing is multiplied by age- and sex-specific adjustment factors, shown in Table S1. These assumptions are derived using data from a multi-disease screening programme in Uganda, which found relatively high rates of screening uptake in women and older adults.[10]

Table S1: Relative rates of screening uptake by age and sex

Age group	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55+

Males	0.872	0.895	0.919	0.929	0.963	1.041	1.090	1.113	1.108
Females	0.872	0.918	1.022	1.126	1.193	1.232	1.232	1.197	1.175

The average annual proportion of the adult population (aged 15 and older) screened was set to 10%. Estimates of uptake of mobile testing services from population-based studies are very inconsistent. Labhardt *et al* found that in Lesotho, 1392 individuals participated in a mobile multi-disease screening programme in 6 communities, over 1 month.[11] The median community size was 4909, and these data therefore suggest an uptake rate of 4.7% (1392/(6 × 4909)). However, Chamie *et al* found a substantially higher rate of uptake when a similar mobile multi-disease screening programme was introduced in Uganda, with 63% uptake over a 5-day period.[10] It is possible that this high rate of uptake was achieved as a result of significant prior community mobilization. Other studies have investigated the uptake of HIV testing when offered through mobile services on a continuous basis, rather than as part of a once-off campaign. Kranzer *et al* found that in a Cape Town community of approximately 12 520 adults, 922 received mobile HIV testing over a 16-month period,[12] suggesting an annual screening rate of 0.055 ((12/16) × 922/1250). Higher rates of HIV testing were found in the Accept trial, which involved mobile testing services in conjunction with community mobilization, in Tanzania and Zimbabwe.[13] In Tanzania, 2810 individuals were tested in a population of 6250 individuals over 37 months, while in Zimbabwe, 5911 individuals were tested in a population of 10700 individuals over 42 months. These data suggest annual testing rates of 0.15 and 0.16 respectively.

Estimates of numbers of individuals screened through the intervention are obtained by multiplying the population size in each population age and sex category by the corresponding mobile testing rate, and summing across the period from 1 July 2018 to 30 June 2028. Uptake of screening is assumed to be independent of HIV status, as HIV-positive individuals would benefit from diabetes and hypertension screening even if they already knew their HIV status. If diagnosed through the mobile testing programme, individuals are assumed to have a 40% probability of starting ART, the average probability of linkage to care estimated in a recent systematic review and meta-analysis of mobile HIV testing interventions.[14] HIV-diagnosed individuals are also assumed to be 58% less likely to engage in unprotected sex (compared to undiagnosed HIV-positive individuals), and unprotected sex is assumed to reduce by a further 32% once on ART.[15] Reductions in infectiousness after ART initiation are assumed to depend on levels of viral suppression, as described elsewhere.[1] HIV diagnosis and ART initiation are thus assumed to be associated with substantial reductions in HIV transmission potential.

Although the Thembisa model does not directly simulate the incidence or prevalence of diabetes and hypertension, the outputs of the model (numbers of individuals screened) can be combined with survey data to estimate the numbers of new diagnoses that are likely to occur. In this analysis, the prevalence of diabetes (defined as HbA1c ≥6.5%) and hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or current use of blood pressure medication) were estimated from the age- and sex-specific prevalence levels measured in the 2012 South African National Health and Nutrition Examination Survey (SANHANES).[16] Age- and sex-specific rates of diagnosis for diabetes and hypertension were estimated from the same survey, which asked individuals if they had a history of high blood sugar/diabetes and if they had a history of high blood pressure. Table S2 summarizes the results of the survey.

Table S2: Prevalence of diabetes and hypertension in South African adults (ages 15+)

	Diabetes prevalence (%)	% diagnosed with high blood sugar/diabetes	Hypertension prevalence (%)	% diagnosed with high blood pressure
Total	9.5%	5.0%	31.8%	16.5%
Males	7.9%	4.0%	29.8%	12.0%
Females	11.0%	6.0%	33.1%	20.6%
Age group				
15-24	0.3%	0.6%	6.7%	3.5%
25-34	2.5%	1.1%	15.0%	7.5%
35-44	4.3%	2.9%	28.5%	14.4%
45-54	16.7%	11.0%	52.0%	29.2%
55-64	24.4%	16.1%	65.6%	39.5%
65+	19.0%	16.6%	77.9%	50.8%

Source: South African National Health and Nutrition Examination Survey (SANHANES)[16]

The proportion of newly-diagnosed individuals who linked to care and started treatment soon after diagnosis was set to 45% in the case of diabetes and 33% in the case of hypertension, based on the results of a multi-disease screening programme in South Africa.[17] In sensitivity analyses, we consider more optimistic assumptions about rates of linkage to treatment services.

Sensitivity analysis

A sensitivity analysis was conducted to assess the potential effect of increasing the assumed rates of linkage to treatment services following diagnosis to 81% (for all three diseases). Although studies in sub-Saharan Africa have generally found low rates of linkage to care following diagnosis in mobile screening programmes,[14, 17-19] one South African study found that 86% of ART-eligible individuals diagnosed through a home-based screening programme started ART within 3 months of diagnosis if the newly-diagnosed individuals were followed up regularly and provided with counselling on HIV care.[20] High rates of treatment uptake are therefore possible with good follow-up and counselling.

Table S3 summarizes the results of the sensitivity analysis, and Figure S1 shows the expected yields on the multi-disease screening programme in the sensitivity analysis. The higher assumed rates of linkage are associated with substantially increased numbers of newly-treated individuals, relative to those predicted in the main analysis. For example, there are twice as many newly-treated HIV-positive adults as a result of the multi-disease screening programme than predicted in the main analysis. However, the number of infections averted is less than double in the sensitivity analysis because high levels of HIV diagnosis have already been achieved in South Africa, and thus the marginal gains from further increases in HIV testing and linkage to care in newly-diagnosed individuals are modest. The model conservatively assumes that individuals who have previously been diagnosed HIV-positive do not initiate ART at a higher rate if they test positive again. A limitation of the model is that it does not consider the possibility that individuals who were previously diagnosed (whether for HIV, diabetes or hypertension) and did not initiate treatment at diagnosis may be more likely to initiate treatment if they test positive again.

Table S3: Comparison of multi-disease screening programme impact (2018-2028) in main analysis and sensitivity analyses

	Main analysis	Sensitivity analysis (81% linkage)	Sensitivity analysis (5% coverage)
Number of newly treated HIV cases*	197 000	396 000	106 000
Number of newly treated diabetes cases*	543 000	976 000	271 000
Number of newly treated hypertension cases*	2 096 000	5 146 000	1 048 000
% reduction in HIV incidence*	3.5%	4.6%	2.5%
Number of HIV infections averted*	69 000	90 000	48 000

* Relative to baseline (no multi-disease screening intervention)

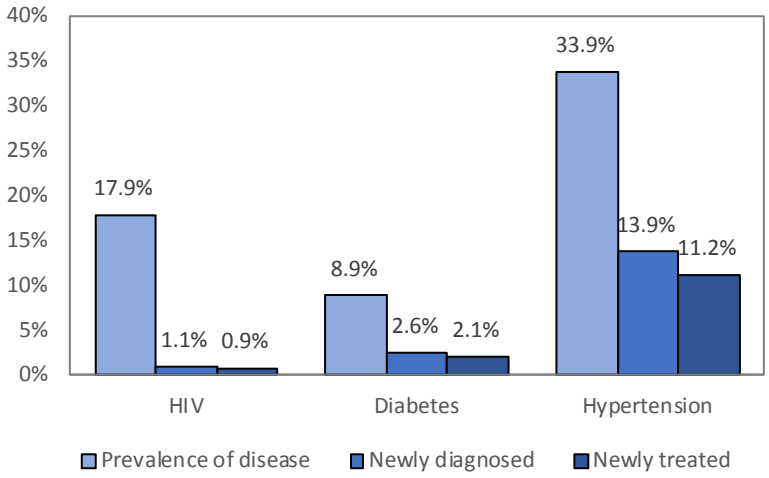

Figure S1: Yields from multi-disease screening, with enhanced linkage

A further sensitivity analysis was conducted to assess the effect of a 5% annual screening coverage (in place of the 10% coverage assumed previously). In this scenario, the numbers of diabetes and hypertension cases treated are approximately half of the numbers in the main analysis (Table S3). However, the number of newly treated HIV cases and the number of HIV infections averted is more than half that in the main analysis, which is a reflection of the saturation effects that may be expected when levels of HIV diagnosis are already high (i.e. the marginal returns to increased frequency of testing diminish as the background rates of HIV diagnosis increase). Figure S2 shows the expected yields from multi-disease screening in this scenario; results are similar to those in the main text.

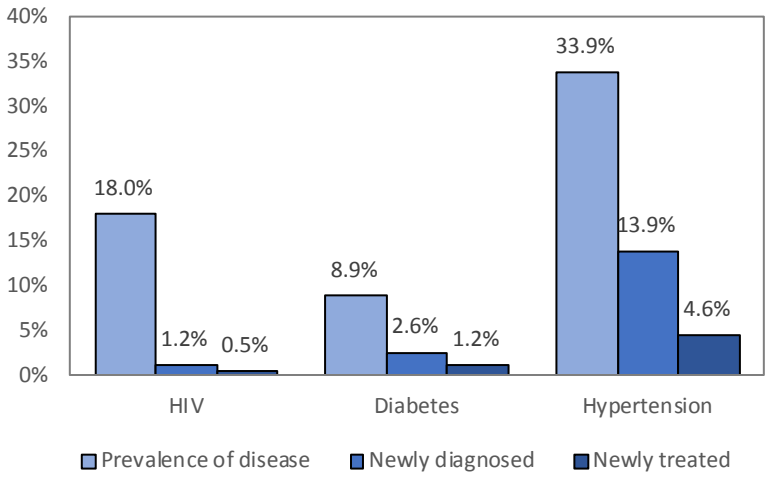

Figure S2: Yields from multi-disease screening, with reduced annual screening coverage

An additional complication to consider is that screening assays may have poor sensitivity and/or specificity. In the case of HIV, which is conventionally diagnosed using two rapid tests, specificity is generally close to 100% and false positives are consequently uncommon.[21] However, in the case of hypertension and diabetes, the tests that are commonly used in community-based testing campaigns typically have poor specificity and sensitivity.[22, 23] The use of more accurate testing is not feasible in the context of a mobile testing campaign: in the case of diabetes, the gold standard diagnosis requires an 8-hour fast prior to receiving a 75g sugar dose, followed 2 hours later by a blood measurement;[22] in the case of hypertension, the gold standard diagnosis requires several measurements at different times, ideally outside of a clinic setting.[23] Because the diagnostic criteria we have assumed (HbA1c≥6.5% in the case of diabetes and a single systolic blood pressure measurement ≥140 mmHg or diastolic blood pressure measurement ≥90 mmHg in the case of hypertension) may have poor sensitivity,[22, 23] the campaigns we have modelled are likely to miss many cases of undiagnosed disease. In addition, the poor specificity of these screening methods may lead to substantial over-diagnosis, i.e. the yields from multi-disease screening (% prevalence of disease and % newly diagnosed in Figure 14b of the main text) may be exaggerated. However, it is important to note that the South African study on which we base our assumptions about treatment initiation after diagnosis considers individuals treated only if they have received repeat testing at a health facility (to confirm the initial diagnosis),[17] and thus the fraction newly treated in Figure 14b of the main text is unlikely to be overstated (unless there remains substantial over-diagnosis even after the confirmatory testing). In this study, the positive predictive value of the initial diagnosis can be conservatively estimated as the fraction of those receiving a repeat test who subsequently started treatment: 67% in the case of diabetes and 69% in the case of hypertension (the estimates are conservative because many of those who fail to initiate treatment do so for reasons other than a negative repeat test). This implies that the true fraction newly diagnosed could be as low as 1.7% in the case of diabetes (2.6% × 0.67) and 9.6% in the case of hypertension (13.9% × 0.69).

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APPENDIX 2

Modeling the integration of health services for HIV and other health conditions in Kenya, Nigeria, and India

1 SPECTRUM MODEL: INPUT PARAMETERS AND CALIBRATION TARGETS

1.1 Parameter values

The models were set up using default values for input parameters in the demProj, AIM and Goals modules, including demographic data (e.g., population sizes by age and sex, fertility rates, life expectancy, etc), epidemiological data (e.g., STI prevalence by risk-group), and behavioral parameters (e.g., frequency of partnerships for each risk-group, proportion of sex acts protected by condom use, etc). The parameter values for respective years and their sources are provided in previous publications,[1] and are available via the help menu in the Spectrum package.

1.2 Additional epidemiological data

In addition to existing epidemiological data on national-level HIV prevalence among male and female populations in each country, which is used as a calibration target for the baseline models, we used available reports of HIV prevalence among key risk-groups including men who have sex with men (MSM), people who inject drugs (PWID) and female sex workers to better characterize the heterogeneous nature of HIV epidemic in each country. Table 1 provides a list of data points used for calibrating the sub-group specific HIV prevalence in each country.

Table 1: List of epidemiological targets and values for Nigeria, Kenya and India

Country	Risk-group	Value	Year	Reference
Nigeria				
	Injecting drug users	5.6	2007	Federal Republic of Nigeria National Agency for the Control of AIDS. Global AIDS Response Country Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/NGA_narrative_report_2014.pdf
	Injecting drug users	4.2	2010	Federal Republic of Nigeria National Agency for the Control of AIDS. Global AIDS Response Country Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/NGA_narrative_report_2014.pdf
	Injecting drug users	3.4	2014	Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2017. 2017. Available from: http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
	Men who have sex with men	13.5	2007	Federal Republic of Nigeria National Agency for the Control of AIDS. Global AIDS Response Country Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/NGA_narrative_report_2014.pdf
	Men who have sex with men	17.2	2010	Federal Republic of Nigeria National Agency for the Control of AIDS. Global AIDS Response Country Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/NGA_narrative_report_2014.pdf
	Men who have sex with men	22.9	2014	Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2017. 2017. Available from: http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
	High risk heterosexuals	32.7	2007	Federal Republic of Nigeria National Agency for the Control of AIDS. Global AIDS Response Country Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/NGA_narrative_report_2014.pdf
	High risk heterosexuals	25.2	2010	Federal Republic of Nigeria National Agency for the Control of AIDS. Global AIDS Response Country Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/NGA_narrative_report_2014.pdf
	High risk heterosexuals	14.4	2014	Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2017. 2017. Available from: http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
Kenya				
	Injecting drug users- male	49.50	2004	Ndetei DM. United Nations Office on Drugs and Crime Study on the Assessment of the Linkages between Drug Abuse and HIV/AIDS in Kenya. United Nations Office on Drugs and Crime; 2004. Available from: http://erepository.uonbi.ac.ke:8080/xmlui/bitstream/handle/11295/65170/Ndetei_A%20Study%20on%20the%20Linkages%20Between%20Drug%20Abuse%2C%20Injecting%20Drug%20Use%20and%20HIV.pdf?sequence=2&isAllowed=y
	Injecting drug users	17.1 (male), 37.3 (female)	2011	Oguya FO. Assessment of risk behaviour and HIV prevalence among people who inject drugs in Nairobi county, Kenya. Kenyatta University; 2011. Available from: http://ir-

				library.ku.ac.ke/bitstream/handle/123456789/10943/Assessment%20of%20risk%20behaviour%20and%20HIV%20prevalence%20among%20people%20who%20inject%20drugs%20in%20Nairobi%20county%2C%20Kenya.pdf?sequence=1&isAllowed=y
	Injecting drug users	14.7 (male), 43.5 (female)	2014	Syvertsen JL, Agot K, Ohaga S, Strathdee SA, Camlin CS, Omanga E, et al. Evidence of injection drug use in Kisumu, Kenya: Implications for HIV prevention. Drug Alcohol Depend. 2015 Jun 1;151:262–6.
	Men who have sex with men	43	2006	Sanders EJ, Graham SM, Okuku HS, van der Elst EM, Muhaari A, Davies A, et al. HIV-1 infection in high risk men who have sex with men in Mombasa, Kenya. AIDS. 2007 Nov 30;21(18):2513–20.
	Men who have sex with men	18.2	2010	National AIDS Control Council of Kenya. Kenya AIDS Response Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/KEN_narrative_report_2014.pdf
	High risk heterosexuals	30.6	2000	Hawken M, Melis R, Ngombo D, Mandaliya K, Ng'ang'a L, Price J, et al. Part time female sex workers in a suburban community in Kenya: a vulnerable hidden population. Sex Transm Infect. 2002 Aug;78(4):271–3.
	High risk heterosexuals	33.3	2005	Luchters S, Chersich MF, Rinyiru A, Barasa M-S, King'ola N, Mandaliya K, et al. Impact of five years of peer-mediated interventions on sexual behavior and sexually transmitted infections among female sex workers in Mombasa, Kenya. BMC Public Health. 2008 Apr 29;8:143.
	High risk heterosexuals	29.5	2010	Musyoki H, Kellogg TA, Geibel S, Muraguri N, Okal J, Tun W, et al. Prevalence of HIV, Sexually Transmitted Infections, and Risk Behaviours Among Female Sex Workers in Nairobi, Kenya: Results of a Respondent Driven Sampling Study. AIDS Behav. 2015 Feb 1;19(1):46–58.
	High risk heterosexuals	29.3	2011	National AIDS Control Council of Kenya. Kenya AIDS Response Progress Report. 2014. Available from: http://www.unaids.org/sites/default/files/country/documents/KEN_narrative_report_2014.pdf
India				
	Injecting drug users- male	13.15	2003	National AIDS Control Organization. HIV India Sentinel Surveillance National Report 2012-13. India Ministry of Health and Family Welfare; 2013. Available from: http://naco.gov.in/sites/default/files/HIV%20India%20Sentinel%20Surveillance%202012-13_Final.pdf
		11.16	2004	
		10.2	2005	
		6.92	2006	
		7.23	2007	
		9.19	2008	
		7.14	2010	
		9.9	2015	National AIDS Control Organization. National Integrated Biological and Behavioural Surveillance (IBBS) 2014-15: High Risk Groups. India Ministry of Health and Family Welfare; 2015. Available from: http://naco.gov.in/sites/default/files/IBBS%20Report%202014-15.pdf
		6.3	2016	National AIDS Control Organization. Status of National AIDS Response. India Ministry of Health and Family Welfare; 2017. Available from: http://naco.gov.in/sites/default/files/Sankalak-Final_12_12_2017_0.pdf
	Men who have sex with men	8.47	2003	National AIDS Control Organization. HIV India Sentinel Surveillance National Report 2012-13. India Ministry of Health and Family Welfare; 2013. Available from: http://naco.gov.in/sites/default/files/HIV%20India%20Sentinel%20Surveillance%202012-13_Final.pdf
		7.47	2004	

	8.74	2005	
	6.41	2006	
	7.41	2007	
	7.3	2008	
	4.43	2010	
Men who have sex with men	4.3	2015	National AIDS Control Organization. National Integrated Biological and Behavioural Surveillance (IBBS) 2014-15: High Risk Groups. India Ministry of Health and Family Welfare; 2015. Available from: http://naco.gov.in/sites/default/files/IBBS%20Report%202014-15.pdf
Men who have sex with men	2.7	2016	National AIDS Control Organization. Status of National AIDS Response. India Ministry of Health and Family Welfare; 2017. Available from: http://naco.gov.in/sites/default/files/Sankalak-Final_12_12_2017_0.pdf
High risk heterosexuals	10.3	2003	National AIDS Control Organization. HIV India Sentinel Surveillance National Report 2012-13. India Ministry of Health and Family Welfare; 2013. Available from: http://naco.gov.in/sites/default/files/HIV%20India%20Sentinel%20Surveillance%202012-13_Final.pdf
	9.43	2004	
	8.44	2005	
	4.9	2006	
	5.06	2007	
	4.94	2008	
	2.67	2010	
High risk heterosexuals	2.2	2015	National AIDS Control Organization. National Integrated Biological and Behavioural Surveillance (IBBS) 2014-15: High Risk Groups. India Ministry of Health and Family Welfare; 2015. Available from: http://naco.gov.in/sites/default/files/IBBS%20Report%202014-15.pdf
High risk heterosexuals	1.6	2016	National AIDS Control Organization. Status of National AIDS Response. India Ministry of Health and Family Welfare; 2017. Available from: http://naco.gov.in/sites/default/files/Sankalak-Final_12_12_2017_0.pdf

2 NIGERIA: INTEGRATION OF HIV WITH REPRODUCTIVE HEALTH SERVICES

2.1 Background

The weak infrastructure of reproductive health services for women in Nigeria is evident through high rate of women (over third) not attending antenatal care services through pregnancy, low rates of contraceptive use and other family planning services, as well as, low coverage of PMTCT services for HIV+ pregnant women.

Family planning is a key factor in achieving the Sustainable Development Goals, and contraceptives are the center of proper family planning. Nigeria has made no progress in improving the use of contraceptives over the last decade, and the coverage remains incredibly low. Only 15% of Nigerian women aged 15-49 use contraception for limiting and spacing of birth. A Nigerian woman gives birth to an average of 6.5 children in her lifetime. Overall, 16 percent of currently married women have an unmet need for family planning services. Thus, if all currently married women who wish to space or limit their children were to have access to contraceptives, the prevalence of contraceptive use would increase to 31 percent.[2]

From an HIV-related perspective, Nigeria has the largest number of children acquiring HIV infections through mother to child transmission (MTCT). Despite effort to improve the rate of prevention of mother to child transmission (PMTCT) among in Nigeria over the last decade, a large gap remains in coverage and uptake of services among HIV+ pregnant women, leading to an estimated 75,000 new infant HIV infections per year.[3] In line with UNAIDS's Global Plan to eliminate new HIV infections among children by 2015, Nigeria aims to scale up access to PMTCT services. To do this, the government of Nigeria (GON) has adopted the new PMTCT guidelines released by the World Health Organization (WHO) in 2013. These guidelines recommend that all pregnant women receive Option B+, a regimen that provides them with ART for life regardless of CD4 count or clinical stage. The current Nigerian PMTCT program includes a combination of option B and option B+ programs – with 11% of HIV+ pregnant women covered under Option B (ART during pregnancy through childbirth if not breastfeeding or until 1 week after cessation of breastfeeding; or ART for life if CD4 count < 350/mm^3), 12% covered under Option B+ (ART started before current pregnancy), and 4% covered under Option B+ (starting ART during current pregnancy > 4 weeks before delivery). However, plans are in motion to eliminate the option B by year 2020.

2.2 Simulation model and intervention scenarios

We applied the Spectrum package to construct a baseline representation of HIV epidemic in Nigeria and calibrated this model to available epidemiological data on prevalence of HIV at the national level and among key risk groups as listed in Table 1. We further applied the FamPlan module to create three scenarios describing integration of HIV and reproductive health services in Nigeria, including a baseline model of reproductive health among Nigerian women in absence of interventions and two additional interventions for expansion of PMTCT coverage among HIV+ pregnant women and family planning services (contraceptive use) among all women.

Baseline scenario: The 2016 PMTCT coverage (~26% of HIV+ pregnant women) and contraceptive use prevalence (~15%) were maintained at fixed levels from 2018 through 2028. Given the national plans to eliminate Option B by 2020, we developed a baseline scenario to reduce the coverage through Option B from 2018 to 2020 (a linear reduction) while maintaining the overall level of coverage at 26% over the next decade (Figure 1).

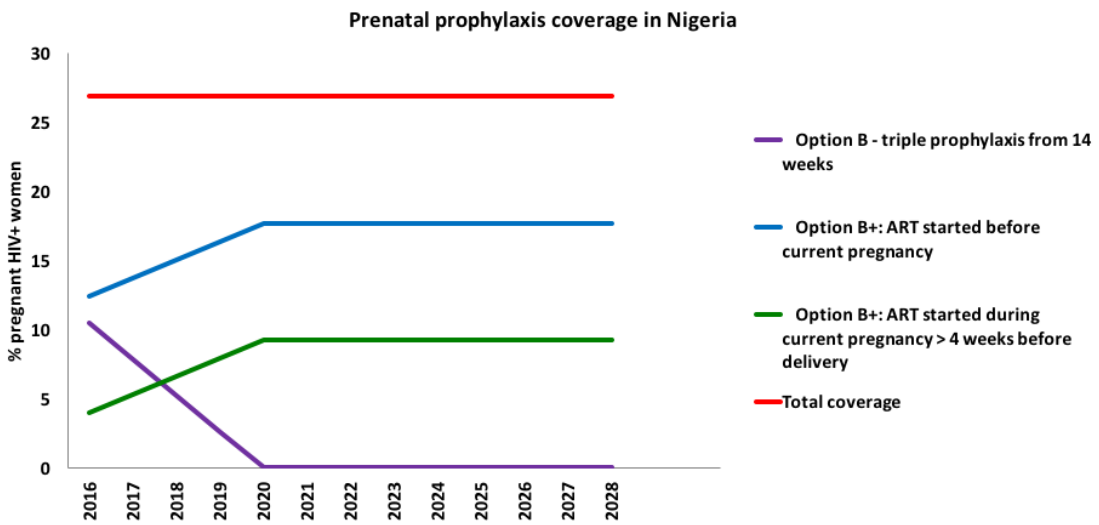

Figure 1: Nigeria's PMTCT coverage at baseline scenario.

Family planning expansion: Starting in 2018, the rate of contraceptive use was increased linearly to reach 31% prevalence in year 2023 (corresponding to meeting the unmet need for contraceptives among married Nigerian women), and was maintained at a fix level by year 2028 (Figure 2).

PMTCT expansion: Starting in 2018, the proportion of HIV-positive pregnant women receiving ARVs through Option B+ (ART started before current pregnancy) was increased linearly to reach a 90% target in year 2023 and was maintained at a fix level by year 2028. Additionally, the alternative Option B+ program (starting ART during current pregnancy > 4 weeks before delivery) was eliminated by year 2023 (Figure 2) in favor of option B+ (ART started before current pregnancy) with higher coverage.

PMTCT + Family planning: starting in year 2018, both PMTCT coverage and contraceptive use were scaled up linearly as described for each individual scenario above. See Figure 1 for a summary of PMTCT and contraceptive use in each scenario.

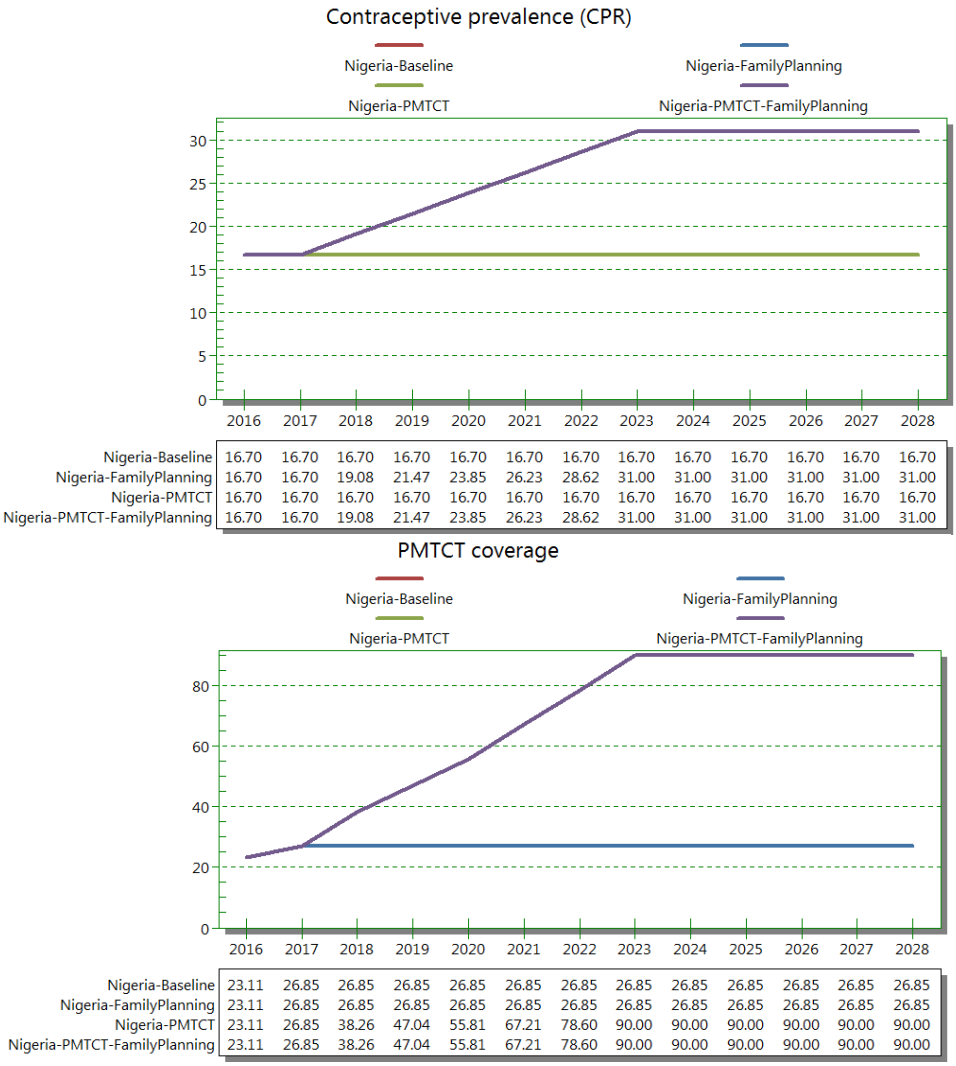

Figure 2: Assumed coverage of contraceptive prevalence and PMTCT coverage in each modeling scenario. The x-axis represents years, and the y-axis marks percent coverage for each program. The plotted values are further summarized within tables below each panel.

3 KENYA: INTEGRATION OF HIV WITH SERVICES FOR NON-COMMUNICABLE DISEASES

3.1 Simulation model and intervention scenarios

We applied the Spectrum package to construct a national model of HIV epidemic in Kenya, using epidemiological targets described in Table 1. We used this model to estimate the HIV-related impact of interventions for screening and treatment of HIV and NCDs in Kenya from 2018 to 2028.

Status quo: the status quo model was characterized by maintaining the coverage of ART in ear 2016 at fixed levels through the next decade (2018 to 2028).

HIV-related scenario: Following the framework of project SEARCH,[4] we modeled a joint community-outreach campaign for HIV and NCDs screening over the next decade. For simplicity, we assumed that this program could reach 10% of the population on an annual basis, successfully screening 90% of eligible adults ≥ 15 for HIV, diabetes and hypertension. To model potential impact on HIV-related outcomes, we assumed an 81% uptake of ART among newly diagnosed HIV individuals (i.e., assuming a target level of 90% linkage and 90% engagement in HIV care after diagnosis). This corresponds to a 73% (90% * 81%*) reduction in unmet need for ART among the HIV+ population over the next decade, modeled as a linear increase in rate of ART coverage among each sub-group from 2018 to 2028. For sensitivity analysis, we further projected the impact of program under a moderate ART uptake at 40% in accordance with the South Africa analysis (see the main report)

NCD scenario: Due to limitations of the Spectrum package for concurrent simulation of HIV and other NCDs, we adopted a simplified approach for modeling the impact of integrated NCD programs in terms of number of new diagnosis and treatment. Using a representative national survey,[5] we estimated the proportion of adults with, aware of, and receiving medication for hypertension and diabetes. Based on the number of adults screened and the expected uptake of treatment, we estimated the impact of the integrated intervention on awareness of and treatment for hypertension and diabetes (Figure 3).

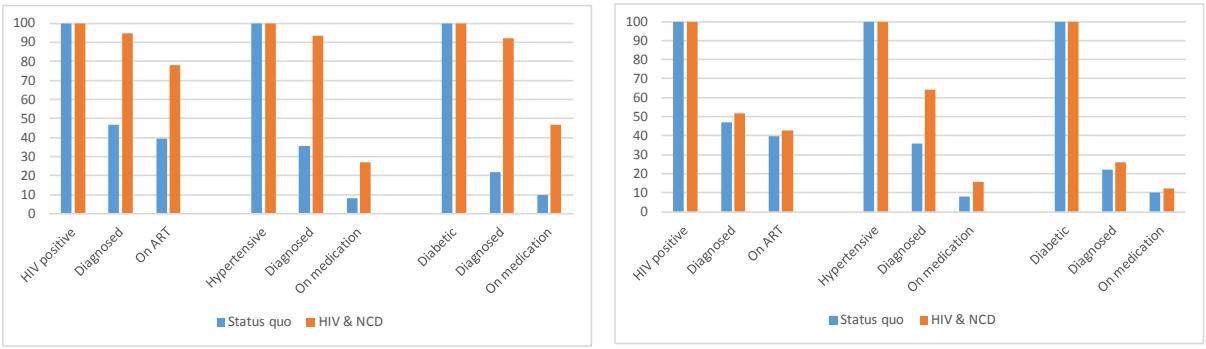

Figure 3: Care cascades for HIV, hypertension, and diabetes among adults before and after first year (2018) of implementation in intervention communities (left panel) and in Kenya (right panel). Intervention communities constitute representative 10% of adult population (≥ 15 years of age). Assumes screening uptake of 90% and treatment uptake following diagnosis of for 81% for HIV, 23% for hypertension, and 45% diabetes.

3.2 Sensitivity analyses

In sensitivity analyses we evaluated how the modeling outcomes are affected by particular parameters. These include lower ART uptake following diagnosis of HIV, reduced intervention reach, and lower sensitivity and specificity of screening tests for hypertension and diabetes. Where appropriate we also report impacts on intervention costs and cost-effectiveness. Estimates based on the sensitivity analyses are presented in Figure 4.

Sensitivity analyses with lower ART uptake following diagnosis: With the ART uptake described in the main commission report (81% among those newly diagnosed), the number of new HIV infections is projected to fall by 44% by 2028, corresponding to 217,000 new infections averted from 2018 to 2028 compared to the status quo scenario. Sensitivity analyses around antiretroviral treatment uptake suggested that even with only 40% treatment initiation among those newly diagnosed, the integration scenario would result in a 23% reduction in HIV incidence in 2028 relative to the status quo scenario. This corresponds to 113,000 infections averted from 2018 to 2028. Whereas 81% uptake among newly diagnosed would result in an estimated 6.5 million discounted DALYs averted relative to the status quo, 40% uptake would result in an estimated 2.2 million discounted DALYs averted relative to the status quo. Under the decreased ART uptake scenario, the HIV component of the intervention would remain highly cost effective relative to 2016 GDP per capita of $3,155, with an estimated cost $455 per DALY averted versus the status quo scenario.

Sensitivity analyses with reduced intervention communities: We considered a less ambitious intervention scenario where communities consisting of 5% vs. 10% of the population ≥ 15 years of age was targeted each year. Under this scenario, an estimated 2.25 million individuals 15 years of age or older would be screened in 2018, and the total costs for community mobilization and HIV testing would be $28.4 million and the cost of NCD testing $1.6 million. Compared to the incremental cost per HIV-related DALY averted in the base case of $227, the cost per DALY averted in this reduced intervention scenario would be somewhat higher at $292 but still an order of magnitude lower than the per capita GDP.

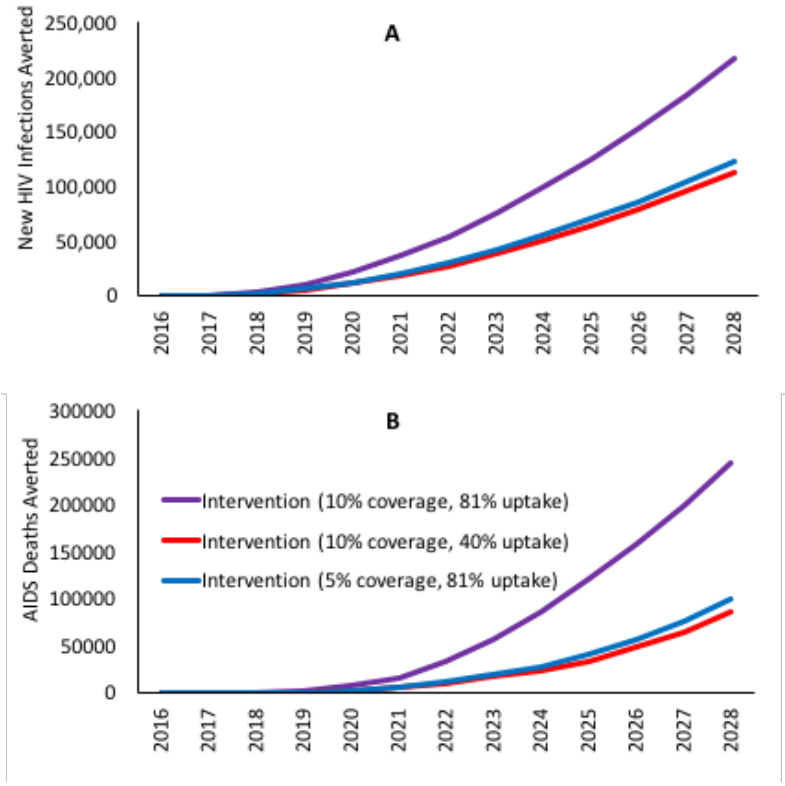

Figure 4: Sensitivity analysis of the impact of HIV-integration scenarios at varying levels of ART uptake and program coverage on new HIV infections (A) and AIDS deaths (B). Due to mathematical structure of Spectrum model and aggregate definition simulation parameters pertaining to ART uptake and program coverage (both translating into final number of people receiving ART in the model), the sensitivity analysis to variation in program coverage and ART uptake at similar levels results in very similar results in terms of changes in number of new infections and AIDS deaths averted.

Sensitivity analyses of with lower sensitivity and specificity of hypertension and diabetes screening: In modeling of NCDs for Kenya, we assumed the same criteria as used in the SEARCH study. Hypertension was defined as systolic BP≥140 or diastolic BP≥90 mm Hg on three consecutive measurements or self-reported current use of anti-hypertensives. Pre-diabetes was defined as random blood glucose 7-11 mmol/L (126-196 mg/DL) and diabetes was defined as random blood glucose >11 mmol/L (196 mg/DL).[6] In sensitivity analyses we examined the diagnostic sensitivity and specificity of these tests. Compared hypertension based on ambulatory blood pressure of 135/85 mm Hg (i.e., repeated measures over the course of a day), clinical measurement with a threshold of 140/90 mm Hg had mean sensitivity of 75% and mean specificity of 75% in meta-analyses.[7] For diagnosis of diabetes and dysglycemia, a threshold of 7.2 mmol/L for random blood glucose (slightly higher than we assumed) has sensitivity of 63% and specificity of 87% compared to oral glucose tolerance test.[8]

These estimates indicate that 25% of participants with hypertension would not be identified and 37% of participants with diabetes or dysglycemia would not be identified. In sensitivity analyses accounting for these missed diagnoses we adjusted the NCD care cascade estimates (Figure 5). In the 2018 intervention communities following screening, we estimate 443,000 individuals with

hypertension not on treatment would be identified, with the percent of hypertensive individuals with a diagnosis increasing to 79% and with 22% receiving medication (versus 94% and 27% without false-negatives). In the intervention communities 40,000 individuals with diabetes would be newly diagnosed, with the percent of individuals with diabetes or dysglycemia increasing to 66% with 33% receiving medication (versus 92% and 47% without false-negatives). We expect that individuals with false-negative screening results may be identified as having hypertension or diabetes if and when they initiated clinical care or in subsequent rounds of community-based testing or during other health care encounters. In regards to community-based screening costs, the 25% reduction in the number of individuals with hypertension or diabetes would correspond to a 33% increase in the cost per true positive diagnosed. We estimate the marginal cost per case identified would be $57 for that blood glucose screening if provided in conjunction with the HIV community health campaign, and this cost is jointly shared by hypertension screening.

With 75% specificity of clinic blood pressure screening and 24% prevalence of hypertension, approximately 51% of those with a positive screening will be false-positives. Given the 63% specificity of random blood glucose and the 2.2% prevalence of diabetes, the numbers of false-positives will be substantial, and may account for 90% of positive test results. Although there will be substantial false-positive test results for both hypertension and diabetes, many of these individuals may be at increased risk of these chronic conditions and may benefit from clinical encounters and education about lifestyle impacts. For positive screening results for both of these conditions, fuller workups may be warranted, and repeated screening with the same or different tests may be appropriate, including ambulatory blood pressure and HbA1c screening or oral glucose tolerance. We expect that many individuals with false-positive test results (i.e., misdiagnosed with hypertension or diabetes) would be identified as such if and when they initiated clinical care, albeit at some health care cost. The proportion of incorrect test results may be reduced through two-stage screening or the use of screening tests with higher sensitivity and specificity, as they become more affordable and more widely available. If all individuals screened positive based on random blood glucose were to receive HbA1c screening at $10 per test,[9] we estimate that the cost per case identified would increase to approximately $158.

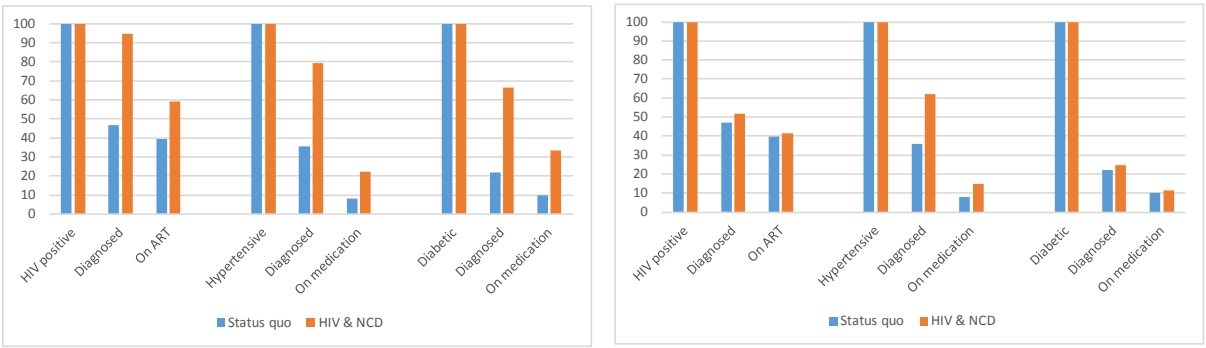

Figure 5: Sensitivity analyses care cascades for HIV, hypertension, and diabetes among adults before and after first year (2018) of implementation in intervention communities (left panel) and in Kenya (right panel). HIV & NCD scenarios assume 40% uptake of ART following diagnosis, 75% sensitivity for hypertension screening, and 63% sensitivity for diabetes screening.

4 INDIA: INTEGRATED HIV/STI MANAGEMENT FOR KEY POPULATIONS

4.1 Simulation model and intervention scenarios

We applied the Spectrum package to construct a baseline representation of HIV epidemic in India at a national-level and calibrated this model to available epidemiological data on prevalence of HIV at the national level and among key risk groups as listed in Table 1. We used this model to create alternative scenarios for integration of HIV and STI services among MSM and FSW in India. Due to limitations in software design for modeling concurrent HIV and STI programs, we only applied the Spectrum model to study the impact of integration on HIV related outcomes and used a simplified approach for estimating the potential outcomes on levels of syphilis infection (as a representative STI).

Baseline: Assuming no PrEP coverage at baseline, ART coverage was maintained at the estimated levels in 2016 (see Table 2) over the next decade (2018 to 2028).

Table 2: Spectrum's estimates of ART coverage at baseline

ART coverage by single risk group		Baseline value (%)
Males		
	Not sexually active	48
	Low risk heterosexual	41.9
	Medium risk heterosexual	43
	High risk heterosexual	55.4
	Injecting drug user	48
	Men who have sex with men	47
Females		
	Not sexually active	48.4
	Low risk heterosexual	44
	Medium risk heterosexual	50.9
	High risk heterosexual	29.3
	Injecting drug user	55.1

HIV-modeling scenario: Using data from the Avahan program, we modeled a joint community-outreach campaign for HIV and STI screening among MSM and FSW over a five year period (2018 to 2023). Funded by the Indian AIDS initiative of the Bill & Melinda Gates Foundation, the Avahan project is one of the largest HIV prevention programs targeting high-risk groups including MSM and FSW globally.[10] The program was implemented within six Indian state, from 2004 to 2009. Based on reported levels of population coverage from Avahan during this period, we modeled an intervention scenario reaching 60% of MSM and 90% of FSW from 2018 to 2023, and further assumed that such program can provide an infrastructure for maintaining all improvements in ART/PrEP coverage over the subsequent five years (2024-2028).

To model potential impact on HIV-related outcomes, we assumed that this integrated intervention can successfully deliver ART to 81% of individuals with diagnosed HIV who are not currently on ART

(i.e., 90% linkage and 90% engagement). This corresponds to a 54% (60%*81%) and an 81% (90%*81%) reduction in the unmet need for ART among HIV-positive MSM and FSW accordingly (Figure 6). We modeled this effect as a linear increase in rate of ART coverage from 2018 to 2023, using an extended version of the Spectrum AIM module. In sensitivity analysis, we reduced the expected level of ART uptake to 40%, in line with assumptions in the South African model, and studies the impact of this change on projected epidemiological outcomes.

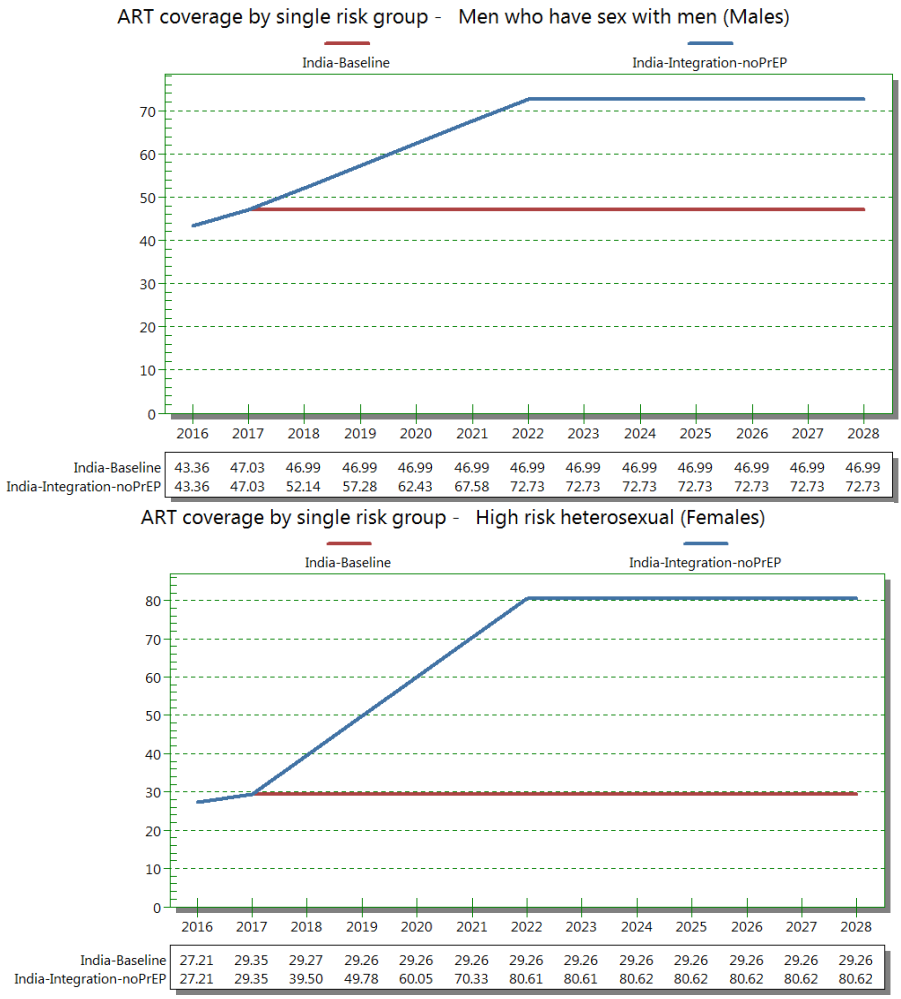

Figure 6: Assumed coverage of ART among MSM and FSW in each modeling scenario. The x-axis represents years, and the y-axis marks percent coverage for each program. The plotted values are further summarized within tables below each panel.

Furthermore, in order to estimate potential impact of PrEP, we modeled two additional scenarios for implementation of oral PrEP among MSM and FSW at low (10%) and high (30%) levels of coverage. In these scenarios, PrEP coverage was increased linearly from 2018 to 2023 (continued at fixed levels through 2028), and PrEP adherence was assumed at 50% for those on PrEP.

STIs-modeling scenario: Due to lack of representative data on incidence/prevalence of STIs among MSM and FSW in India, we limited our analysis to study the impact on integrated programs for screening and treatment of syphilis infection. Moreover, due to complexity of modeling the coepidemics of syphilis and HIV infections in India, we choses a simplified approach for estimating

the impact of intervention on program participants only and did not estimate the impact on secondary infections averted. Using an array of available estimates from the literature (see Table 3), we estimated the national prevalence of syphilis at 5.8% among FSWs and 3.5% among MSM, and assumed the same level of prevalence among those tested over the first 5 year of program in the integration scenarios.

Table 3. Estimates of Syphilis prevalence among FSW and MSM in India. Studies use a range of definition for reporting syphilis prevalence including % infected with syphilis, % with high syphilis titer and % with reactive syphilis serology.

Prevalence	Year	Population/Location	Reference
FSW			
2.40%	2011	Five districts in Karnataka state, India. 27-34 months after last one (R3)	Isac S, Ramesh BM, Rajaram S, Washington R, Bradley JE, Reza-Paul S, et al. Changes in HIV and syphilis prevalence among female sex workers from three serial cross-sectional surveys in Karnataka state, South India. BMJ Open. 2015 Mar 1;5(3):e007106.
3.40%	2007	Five districts in Karnataka state, India. 28-37 months after last one (R2)	Isac S, Ramesh BM, Rajaram S, Washington R, Bradley JE, Reza-Paul S, et al. Changes in HIV and syphilis prevalence among female sex workers from three serial cross-sectional surveys in Karnataka state, South India. BMJ Open. 2015 Mar 1;5(3):e007106.
5.90%	2005	Five districts in Karnataka state, India. 8-16 months after Avahan beginning (R1)	Isac S, Ramesh BM, Rajaram S, Washington R, Bradley JE, Reza-Paul S, et al. Changes in HIV and syphilis prevalence among female sex workers from three serial cross-sectional surveys in Karnataka state, South India. BMJ Open. 2015 Mar 1;5(3):e007106.
25%	2004	Mysore city-baseline	Reza-Paul S, Beattie T, Syed HUR, Venukumar KT, Venugopal MS, Fathima MP, et al. Declines in risk behaviour and sexually transmitted infection prevalence following a community-led HIV preventive intervention among female sex workers in Mysore, India. AIDS. 2008 Dec;22:S91.
12%	2006	Mysore city-post intervention	Reza-Paul S, Beattie T, Syed HUR, Venukumar KT, Venugopal MS, Fathima MP, et al. Declines in risk behaviour and sexually transmitted infection prevalence following a community-led HIV preventive intervention among female sex workers in Mysore, India. AIDS. 2008 Dec;22:S91.
11.89%	2010-11	Karnataka	Kumar SD, Kotresh, Prabhudeva, Narayanaswamy, Shetty B, Washington R. A study on Syphilis screening in Karnataka. Indian Journal of Forensic and Community Medicine. 2016;3(3):176.
6.6% (brothel), 2.9% (street based)	2007-2008	Mumbai and Thane in Maharashtra.	Gupte S, Daly C, Agarwal V, Gaikwad SB, George B. Introduction of Rapid Tests for Large-Scale Syphilis Screening Among Female, Male, and Transgender Sex Workers in Mumbai, India. Sexually Transmitted Diseases. 2011 Jun;38(6):499.
range 3.1% to 51.0%	2005-2007	Reported syphilis prevalence varies widely among female sex workers (FSWs) in India, ranging from 3.1% to 51.0%, depending on geographic location, sex worker (SW) typology, and laboratory definition of syphilis	Gupte S, Daly C, Agarwal V, Gaikwad SB, George B. Introduction of Rapid Tests for Large-Scale Syphilis Screening Among Female, Male, and Transgender Sex Workers in Mumbai, India. Sexually Transmitted Diseases. 2011 Jun;38(6):499.
5.4 per 100 person years	2000		Reynolds SJ, Risbud AR, Shepherd ME, Rompalo AM, Ghate MV, Godbole SV, et al. High rates of syphilis among STI patients are contributing to the spread of HIV-1 in India. Sex Transm Infect. 2006 Apr;82(2):121–6.
10.1%%	2008-2009	Hyderabad and Mumbai	Das A, Prabhakar P, Narayanan P, Neilsen G, Wi T, Kumta S, et al. Prevalence and Assessment of Clinical Management of Sexually Transmitted Infections among Female Sex Workers in Two

			Cities of India. Infectious Diseases in Obstetrics and Gynecology. 2011; Available from: https://www.hindawi.com/journals/idog/2011/494769/
6.66%	2005-2006	Surat city	Shethwala ND, Mulla SA, Kosambiya JK, Desai VK. Sexually transmitted infections and reproductive tract infections in female sex workers. Indian J Pathol Microbiol. 2009 Jun;52(2):198–9.
15.80%	2009	Nagaland, India	Mahanta J, Medhi GK, Paranjape RS, Adhikary R. Prevalence and correlates of sexually transmitted infections (syphilis, gonorrhea and chlamydia) among female sex workers (FSW) in a high HIV prevalence state of India. International Journal of Infectious Diseases. 2012 Jun 1;16:e335.
13% (9.3-17.9)	2005-2007	Mumbai (brothel based)	Indian Council of Medical Research, Family Health International. Integrated Behavioural and Biological Assessment: Repeated surveys to assess changes in behaviours and prevalence of HIV/STIs in populations at risk of HIV (Round 1). 2007. Available from: http://www.nari-icmr.res.in/pdf/IBBA/IBBA-NISR.pdf
14.6% (10.6-16)	2005-2007	Mumbai (street based)	Indian Council of Medical Research, Family Health International. Integrated Behavioural and Biological Assessment: Repeated surveys to assess changes in behaviours and prevalence of HIV/STIs in populations at risk of HIV (Round 1). 2007. Available from: http://www.nari-icmr.res.in/pdf/IBBA/IBBA-NISR.pdf
9.1% (5.9-13.8)	2005-2007	Thane (brothel based)	Indian Council of Medical Research and Family Health International. National Interim Summary Report: Integrated behavioral and biological assessment (IBBA), round 1 (2005–2007), National Interim Summary Report. New Delhi 2007. Available at: http://www.nari-icmr.res.in/IBBA/IBBA-NISR.pdf
4.7% (2.4-9)	2005-2007	Thane (street based)	Indian Council of Medical Research, Family Health International. Integrated Behavioural and Biological Assessment: Repeated surveys to assess changes in behaviours and prevalence of HIV/STIs in populations at risk of HIV (Round 1). 2007. Available from: http://www.nari-icmr.res.in/pdf/IBBA/IBBA-NISR.pdf
24.1	2006	Nagaland	Medhi GK, Mahanta J, Paranjape RS, Adhikary R, Laskar N, Ngully P. Factors associated with HIV among female sex workers in a high HIV prevalent state of India. AIDS Care. 2012 Mar;24(3):369–76.
5.4	2008	Karnataka	Beattie TSH, Mohan HL, Bhattacharjee P, Chandrashekar S, Isac S, Wheeler T, et al. Community Mobilization and Empowerment of Female Sex Workers in Karnataka State, South India: Associations With HIV and Sexually Transmitted Infection Risk. American Journal of Public Health. 2014 Aug;104(8):1516–25.
2.4	2008	Karnataka	Beattie TSH, Mohan HL, Bhattacharjee P, Chandrashekar S, Isac S, Wheeler T, et al. Community Mobilization and Empowerment of Female Sex Workers in Karnataka State, South India: Associations With HIV and Sexually Transmitted Infection Risk. American Journal of Public Health. 2014 Aug;104(8):1516–25.

10.8 (pre-Avahan intervention)	2005-2007	Andhra Pradesh	Rachakulla HK, Kodavalla V, Rajkumar H, Prasad S, Kallam S, Goswami P, et al. Condom use and prevalence of syphilis and HIV among female sex workers in Andhra Pradesh, India – following a large-scale HIV prevention intervention. BMC Public Health. 2011 Dec 29;11(Suppl 6):S1.
6.1 (post-Avahan intervention)	2009	Andhra Pradesh	Rachakulla HK, Kodavalla V, Rajkumar H, Prasad S, Kallam S, Goswami P, et al. Condom use and prevalence of syphilis and HIV among female sex workers in Andhra Pradesh, India – following a large-scale HIV prevention intervention. BMC Public Health. 2011 Dec 29;11(Suppl 6):S1.
3.2 (pre-Avahan intervention)	2005-2007	Andhra Pradesh	Rachakulla HK, Kodavalla V, Rajkumar H, Prasad S, Kallam S, Goswami P, et al. Condom use and prevalence of syphilis and HIV among female sex workers in Andhra Pradesh, India – following a large-scale HIV prevention intervention. BMC Public Health. 2011 Dec 29;11(Suppl 6):S1.
3.1 (post-Avahan intervention)	2009	Andhra Pradesh	Rachakulla HK, Kodavalla V, Rajkumar H, Prasad S, Kallam S, Goswami P, et al. Condom use and prevalence of syphilis and HIV among female sex workers in Andhra Pradesh, India – following a large-scale HIV prevention intervention. BMC Public Health. 2011 Dec 29;11(Suppl 6):S1.
15.8 (pre-Avahan intervention)	2005-2007	Maharashtra	Mainkar MM, Pardeshi DB, Dale J, Deshpande S, Khazi S, Gautam A, et al. Targeted interventions of the Avahan program and their association with intermediate outcomes among female sex workers in Maharashtra, India. BMC Public Health. 2011 Dec 29;11 Suppl 6:S2.
10.8 (post-Avahan intervention)	2009	Maharashtra	Mainkar MM, Pardeshi DB, Dale J, Deshpande S, Khazi S, Gautam A, et al. Targeted interventions of the Avahan program and their association with intermediate outcomes among female sex workers in Maharashtra, India. BMC Public Health. 2011 Dec 29;11 Suppl 6:S2.
4.2 (pre-Avahan intervention)	2005-2007	Maharashtra	Mainkar MM, Pardeshi DB, Dale J, Deshpande S, Khazi S, Gautam A, et al. Targeted interventions of the Avahan program and their association with intermediate outcomes among female sex workers in Maharashtra, India. BMC Public Health. 2011 Dec 29;11 Suppl 6:S2.
3.4 (post-Avahan intervention)	2009	Maharashtra	Mainkar MM, Pardeshi DB, Dale J, Deshpande S, Khazi S, Gautam A, et al. Targeted interventions of the Avahan program and their association with intermediate outcomes among female sex workers in Maharashtra, India. BMC Public Health. 2011 Dec 29;11 Suppl 6:S2.
9.7 (pre-Avahan intervention)	2005-2007	Tamil Nadu	Thilakavathi S, Boopathi K, Girish Kumar C, Santhakumar A, Senthilkumar R, Eswaramurthy C, et al. Assessment of the scale, coverage and outcomes of the Avahan HIV prevention program for female sex workers in Tamil Nadu, India: is there evidence of an effect? BMC Public Health. 2011 Dec 29;11(Suppl 6):S3.
2.2 (post-Avahan intervention)	2009	Tamil Nadu	Thilakavathi S, Boopathi K, Girish Kumar C, Santhakumar A, Senthilkumar R, Eswaramurthy C, et al. Assessment of the scale, coverage and outcomes of the Avahan HIV prevention program for female sex workers in Tamil Nadu, India: is there evidence of an effect? BMC Public Health. 2011 Dec 29;11(Suppl 6):S3.
1.1 (pre-Avahan intervention)	2005-2007	Tamil Nadu	Thilakavathi S, Boopathi K, Girish Kumar C, Santhakumar A, Senthilkumar R, Eswaramurthy C, et al. Assessment of the scale, coverage and outcomes of the Avahan HIV prevention program for female sex workers in Tamil Nadu, India: is there evidence of an effect? BMC Public Health. 2011 Dec 29;11(Suppl 6):S3.

0.5 (post-Avahan intervention)	2009	Tamil Nadu	Thilakavathi S, Boopathi K, Girish Kumar C, Santhakumar A, Senthilkumar R, Eswaramurthy C, et al. Assessment of the scale, coverage and outcomes of the Avahan HIV prevention program for female sex workers in Tamil Nadu, India: is there evidence of an effect? BMC Public Health. 2011 Dec 29;11(Suppl 6):S3.
10.8 (pre-Avahan intervention)	2005-2007	All three areas together	Adhikary R, Gautam A, Lenka SR, Goswami P, Ramakrishnan L, George B, et al. Decline in unprotected sex & sexually transmitted infections (STIs) among female sex workers from repeated behavioural & biological surveys in three southern States of India. Indian Journal of Medical Research. 2012 Oct 2;5–13.
5.0 (post-Avahan intervention)	2009	All three areas together	Adhikary R, Gautam A, Lenka SR, Goswami P, Ramakrishnan L, George B, et al. Decline in unprotected sex & sexually transmitted infections (STIs) among female sex workers from repeated behavioural & biological surveys in three southern States of India. Indian Journal of Medical Research. 2012 Oct 2;5–13.
2.1 (pre-Avahan intervention)	2005-2007	All three areas together	Adhikary R, Gautam A, Lenka SR, Goswami P, Ramakrishnan L, George B, et al. Decline in unprotected sex & sexually transmitted infections (STIs) among female sex workers from repeated behavioural & biological surveys in three southern States of India. Indian Journal of Medical Research. 2012 Oct 2;5–13.
2.1 (post-Avahan intervention)	2009	All three areas together	Adhikary R, Gautam A, Lenka SR, Goswami P, Ramakrishnan L, George B, et al. Decline in unprotected sex & sexually transmitted infections (STIs) among female sex workers from repeated behavioural & biological surveys in three southern States of India. Indian Journal of Medical Research. 2012 Oct 2;5–13.
MSM			
4	2008-2009	MSM (not involved in sex work) attending STI clinics in Mumbia and Hyderabad	Narayanan P, Das A, Morineau G, Prabhakar P, Deshpande GR, Gangakhedkar R, et al. An exploration of elevated HIV and STI risk among male sex workers from India. BMC Public Health. 2013 Nov 9;13:1059.
8.4% to 14.0%	2006-2007	four states in south India	Brahmam GNV, Kodavalla V, Rajkumar H, Rachakulla HK, Kallam S, Myakala SP, et al. Sexual practices, HIV and sexually transmitted infections among self-identified men who have sex with men in four high HIV prevalence states of India. AIDS. 2008 Dec;22 Suppl 5:S45-57.
6.5	2003-2004	Mumbai	Kumta S, Lurie M, Weitzen S, Jerajani H, Gogate A, Row-kavi A, et al. Bisexuality, Sexual Risk Taking, and HIV Prevalence Among Men Who Have Sex With Men Accessing Voluntary Counseling and Testing Services in Mumbai, India. J Acquir Immune Defic Syndr. 2010 Feb 1;53(2):227–33.
27	2004-2010	Kolkata	Garg T, Chander R, Jain A, Barara M. Sexually transmitted diseases among men who have sex with men: A retrospective analysis from Suraksha clinic in a tertiary care hospital. Indian J Sex Transm Dis. 2012;33(1):16–9.
0.8 (Belgaum) to 4.4 (Vijaywada)	2012-2013	12 cities nationwide	Solomon SS, Mehta SH, Srikrishnan AK, Vasudevan CK, Mcfall AM, Balakrishnan P, et al. High HIV prevalence and incidence among men who have sex with men (MSM) across 12 cities in India.

			AIDS. 2015 Mar 27;29(6):723–31.
26.92 (95% CI: 16.67, 40.35)	2013-2014	Delhi	Aggarwal P, Bhattar S, Sahani SK, Bhalla P, Garg VK. Sexually transmitted infections and HIV in self reporting men who have sex with men: A two-year study from India. Journal of Infection and Public Health. 2016 Sep 1;9(5):564–70.
1% (married MSM, RDS-adjusted)	2014	Mumbai	Mayer KH, Gangakhedkar R, Sivasubramanian M, Biello KB, Abuelezam N, Mane S, et al. Differing Identities but Comparably High HIV and Bacterial Sexually Transmitted Disease Burdens Among Married and Unmarried Men Who Have Sex With Men in Mumbai, India. Sex Transm Dis. 2015 Nov;42(11):629–33.
8.3% (unmarried MSM, RDS-adjusted)	2014	Mumbai	Mayer KH, Gangakhedkar R, Sivasubramanian M, Biello KB, Abuelezam N, Mane S, et al. Differing Identities but Comparably High HIV and Bacterial Sexually Transmitted Disease Burdens Among Married and Unmarried Men Who Have Sex With Men in Mumbai, India. Sex Transm Dis. 2015 Nov;42(11):629–33.
8.8 (pre-Avahan intervention)	2007	Maharastra	Ramanathan S, Deshpande S, Gautam A, Pardeshi DB, Ramakrishnan L, Goswami P, et al. Increase in condom use and decline in prevalence of sexually transmitted infections among high-risk men who have sex with men and transgender persons in Maharashtra, India: Avahan, the India AIDS Initiative. BMC Public Health. 2014 Aug 3;14:784.
1.1 (post-Avahan intervention)	2009	Maharastra	Ramanathan S, Deshpande S, Gautam A, Pardeshi DB, Ramakrishnan L, Goswami P, et al. Increase in condom use and decline in prevalence of sexually transmitted infections among high-risk men who have sex with men and transgender persons in Maharashtra, India: Avahan, the India AIDS Initiative. BMC Public Health. 2014 Aug 3;14:784.

4.2 Results

Figure 7 compares the projected number of new HIV infections among FSW and MSM in a set of modeled scenarios for expansion of ART in isolation (no PrEP), expansion of PrEP in isolation (no ART expansion), and finally expansion of ART and PrEP coverage together. Expansion of ART services has a significant impact on number of new infections among MSM, resulting in a 34% reduction over the next decade. Provision of PrEP at 10% or 30% coverage alone can not achieve similar results. However, combination of PrEP and ART can further reduce the HIV incidence among MSM by 46% at 30% PrEP coverage (blue line). Given the projected rapid decline in HIV incidence among FSW at baseline (black line), the interventions achieve smaller reductions in terms of HIV incidence. This is mainly driven by the underlying reduction in HIV prevalence among FSW in India, resulting in a small force of infection and therefore, limiting the impact of interventions for averting future transmissions. At a national level, expansion of ART services among FSW and MSM alone can reduce the number of new transmissions among the male and female population by 7% - corresponding to 51,250 new infections averted.

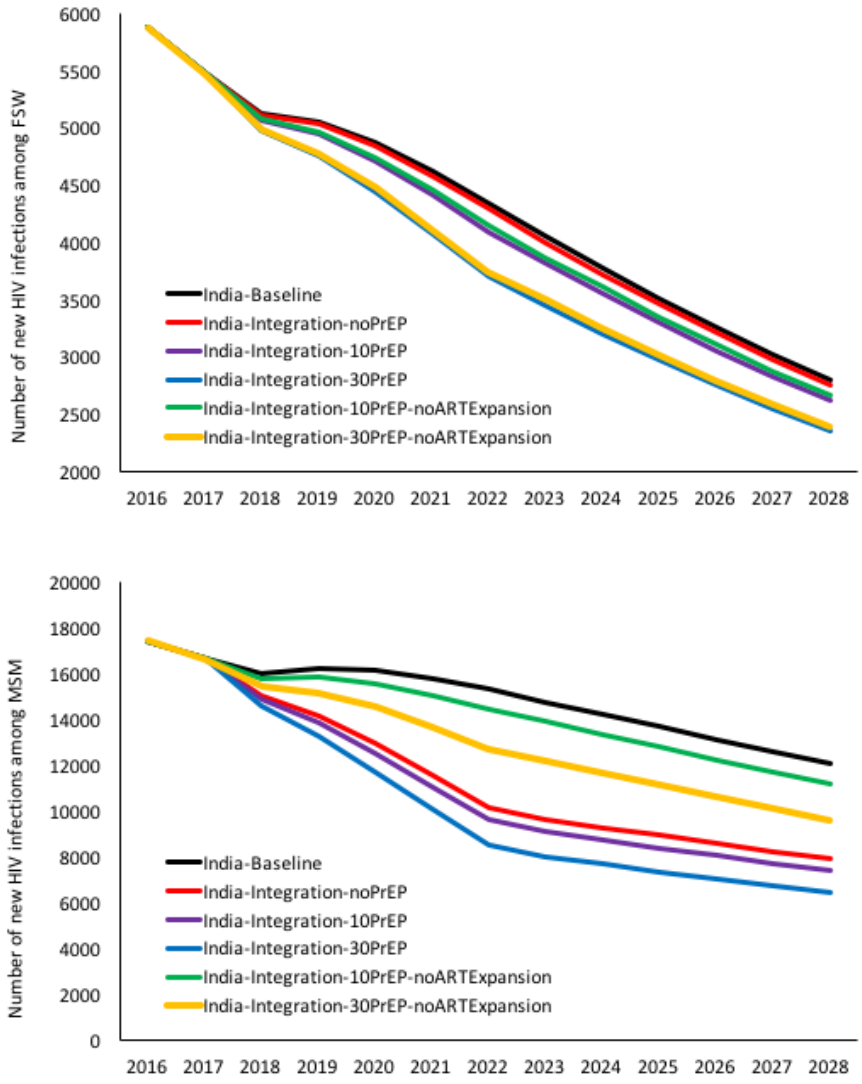

Figure 7: Projected impact of integration scenarios on number of new infections among FSW (top panel) and MSM (bottom panel). Each line represent a single modeling scenarios, comparing the projected number of new infections at baseline (black) with scenarios for expansion of ART services without PrEP (green) or with 10% (purple) or 30% (blue) PrEP coverage. The other two scenarios represent implementation of PrEP in isolation (no ART expansion) at 10% (green) and 30% (yellow) coverage.

4.3 Sensitivity analyses

We performed sensitivity analysis around the uptake of ART among MSM and FSW from the baseline value of 81% (90% linkage and 90% engagement in ART care) to a more conservative estimate at 40% (along with selected levels for the Kenya and South Africa models). Figure 8 compares the trend in number of new HIV infections among MSM and FSW under each scenario. The reduction in ART uptake by 50% results in similar reductions in impact of intervention, reducing the total number of HIV

infections averted from 43,737 (high uptake scenario) to 21,446 (low uptake scenario) among MSM and from 504 to 184 among FSW. At a national level, lower uptake reduces the impact on HIV incidence to a 3.2% reduction compared to baseline. Despite smaller impact, this intervention saves over 29,250 and 3,372 AIDS deaths among MSM and FSW respectively. This analysis highlights the sensitivity of the epidemiological impact of interventions on levels of uptake and essentially the program coverage ("number of people on ART") at any given scenario.

The base case scenario with 81% ART uptake among newly diagnosed MSM and FSW would avert over 2,700,000 DALYs. With 40% ART uptake, 1,300,000 DALYs would be averted. The cost per DALY averted would increase from $656 with 81% uptake to $1320 with 40% uptake. With lower uptake, the HIV impacts would still be highly cost effective relative to the per capita GDP of $ 6,571 in 2017.

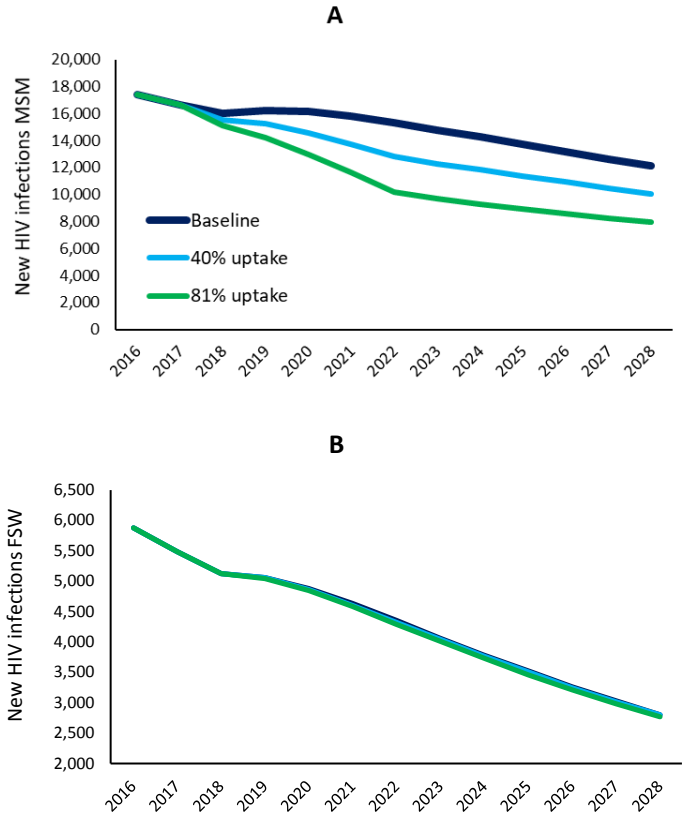

Figure 8. Projected impact of integration scenarios on number of new infections among FSW (top panel) and MSM (bottom panel).

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APPENDIX 3

Cost-effectiveness analyses for integrating health services for HIV and other health conditions in Kenya, Nigeria, and India

1 INTRODUCTION

The cost-effectiveness analyses of the modeling scenarios are based on the resources required to deliver the interventions, the impact of the interventions on healthcare utilization, and the impact of the interventions on death and disability expressed as disability-adjusted life years (DALYs). From the resources required and healthcare utilization (valued in 2016 USD) we estimate total costs from the healthcare perspective for each scenario. All costs and DALYs are estimated as incremental values, relative to a baseline of no additional intervention. From these values we calculate the incremental cost-effectiveness ratio (incremental cost per incremental DALY averted) in each setting. Intervention scenarios are often considered highly cost effective in a given country if the net cost per DALY averted is less than the per-capita gross domestic product (GDP). In conjunction with this commonly-used standard, it is essential to be cognizant of affordability, feasibility, and equity when evaluating these scenarios; thus, we present cost-effectiveness results for illustrative rather than prescriptive purposes.

Resources required: We consider first the resources required for HIV-related components (community-based HIV testing and linkage to treatment in Kenya; outreach, HIV testing and linkage to treatment for FSWs and MSM in India; PMTCT in Nigeria) and then estimate the additional resources required for integrated services (hypertension and diabetes screening and linkage to treatment in Kenya; syphilis testing and linkage to treatment in India; family planning coverage in Nigeria). The costs of these resources are derived from the literature, from the Spectrum model, and from the ImpactNow family planning module. Health care utilization: The Spectrum models estimate the number of people on ART each year, and person-year costs for ART in each country are applied to these estimates. For hypertension and diabetes in Kenya, the numbers of people newly receiving treatment are based on country-specific treatment rates. For HIV and STI treatment costs and effectiveness, we consider a ten-year time horizon (reporting each value in the year in which it occurs). By contrast, for hypertension, we consider a lifetime time horizon for both costs and DALYs, as much of the medical resource consumption and DALYs averted will occur after 2028. All lifetime costs and DALYs are discounted at 3% annually. For diabetes we could not identify per-case estimates of lifetime treatment costs and instead present costs per DALY averted based on population-level modeling.[1]

We limit our economic evaluation to a narrow scope of direct resource requirements plus healthcare utilization, reflecting the limited evidence base on integrated HIV interventions and a desire for transparency in this simplified analysis. As such, we adopt a healthcare perspective for these analyses and do not incorporate costs to clients, impacts on productivity, additional costs of health systems strengthening, or utilization of other services or other societal outcomes. Our estimates of cost-effectiveness may therefore be conservatively biased (to the extent that additional gains to society outweigh the additional costs). Health systems strengthening is necessary for delivery of these interventions and to respond to the health care demands they create.

2 PARAMETER ESTIMATES

Monetary values are presented in 2016 USD unless otherwise noted. For costs derived from other studies, the reported monetary value (typically in USD) were converted to local currency for the same year using year-specific World Bank official exchange rates. The local currency value was then updated to its 2016 value using country-specific World Bank deflator rates. The 2016 value in local currency was then converted to 2016 USD using year-specific World Bank exchange rates. We did not follow these procedures for Nigeria. For Nigeria, we found that intermediate conversion to the naira lead to substantial decreases in cost estimates. Instead we directly converted monetary values to 2016 USD using World Bank deflators for the U.S. To establish cost-effectiveness reference points, we used 2016 GDP per capita PPP (current international $) as reported by the World Bank at http://api.worldbank.org/v2/en/indicator/NY.GDP.PCAP.PP.CD?downloadformat=excel (accessed 22 February 2018).

Parameter	Value	Source	Comments
Kenya			
Intervention costs			
Community engagement and HIV testing	$21.03	Chang et al., 2016[2]	
Supplemental screening for hypertension & diabetes	$1.19	Chang et al., 2016[2]	
HIV-related healthcare costs and DALYs			
ART costs/year	$149.00	IHME[3]	
HIV-related DALYs	model output	Spectrum	
NCD-related healthcare costs and DALYs			
Lifetime hypertension cost moderate risk	$149.00	Ngalesoni et al., 2017 [4]	
Lifetime hypertension cost high risk	$486.25	Ngalesoni et al., 2017 [4]	
Lifetime DALYs averted with hypertension treatment moderate risk	1.02	Ngalesoni et al., 2017 [4]	
Lifetime DALYs averted with hypertension treatment high risk	1.56	Ngalesoni et al., 2017 [4]	
$/DALYs averted with standard glycemic control for diabetes	$944.00	Ortegon et al., 2012 [1]	Appendix 6, intervention DM-2
Nigeria			
Intervention costs			
HIV screening for pregnant women	$22.06	PEPFAR, 2012[5]	
PMTCT for HIV-positive pregnant women	$496.28	PEPFAR, 2012[5]	
Family planning (FP) per year	$3.48	Health Policy Project[6]	Based on FP mix in ImpactNow model
HIV-related healthcare costs and DALYs			
ART costs/year	$330.99	PEPFAR, 2014[7]	
HIV-related DALYs	model output	Spectrum	
Family planning-related healthcare costs and DALYs			
Maternal & infant healthcare costs averted per person-year of contraceptive use	$3.15	Health Policy Project[6]	Based on FP mix in ImpactNow model

DALYs averted per person-year of contraceptive use	0.35	Health Policy Project[6]	Based on FP mix in ImpactNow model
India			
Intervention costs			
Respondent-driven sampling with HIV testing	$20.33	Solomon et al., 2017[8]	
Syphilis screening for FSWs and MSM	$3.50	Korenromp et al., 2017[9]	Inclusive of service delivery
Syphilis treatment for FSWs and MSM	$9.30	Korenromp et al., 2017[9]	Inclusive of service delivery
Pre-exposure prophylaxis per person-year	$91.00	Stover et al., 2016[10]	Updated with TDF/3TC costs from MSF, 2016[11]
HIV-related healthcare costs and DALYs			
ART costs/year	$126.06	PEPFAR, 2014[7]	
HIV-related DALYs	model output	Spectrum	
Syphilis-related DALYs			
DALYs per prevalent case of syphilis	0.64		Calculated using the method by Korenromp et al., 2017,[9] see text

3 KENYA

3.1 Intervention costs

Chang et al.[2] provide a cost analysis of hybrid mobile multi-disease testing conducted in Western Kenya and Uganda as part of the SEARCH study. Reported HIV related costs were $20.5 USD (2014) per person, with a range of $18.9 to $21.6, and with the majority of costs related to the community health campaign. The reported joint cost for hypertension and diabetes screening was $1.16, with no range reported. This value reflects the marginal cost of screening given the expenditure of HIV-related costs. The authors also estimate at cost of $0.90 for malaria screening, although we did not include this intervention component in our modeling. The authors also provide a breakdown of resources required and their costs in an appendix.

3.2 HIV medical care costs and DALYs

The cost of HIV care in Kenya was based on those reported by Sharma et al., 2018,[12] which in turn are based on a 2014 report by the Institute for Health Metrics and Evaluation.[3] The IHME report estimated an annual cost per ART patient in Kenya in 2011 of $195 (in 2011 USD) or 16,167 (in 2011 Kshs). In contrast, *The Cost of Comprehensive HIV Treatment in Kenya,*[13] estimated annual costs of $240.33 and $116.71 for ART and pre-ART patients, respectively, in 2011 USD. For ART patients, ARV costs were $112.74. As less expensive regimens are becoming available in Kenya, we concluded that the IHME estimate would be closer to ART costs during the modeling period. Both persons on ART and HIV-related DALYs for each year and each scenario were obtained from Spectrum.

3.3 Hypertension and diabetes medical care costs and DALYs

Ngalesoni et al.[4] estimate the cost of hypertension treatment and DALYs averted in Tanzania using Markov models. They provide estimates for 8 risk groups (based on diabetes status and categorized into low, moderate, high and very high risk) defined by total cholesterol, systolic blood pressure, smoking, and sex for individuals. For each group, they estimate the intervention costs and DALYs averted for 2

different drug regimens. In our analyses, we categorized Kenyan adults into moderate or high risk based on blood pressure and assuming risk profiles of non-diabetics. This assumes a more conservative effect on DALYs averted than including the "very high risk" category based on smoking status or including comorbidity with diabetes. For adults at moderate and high risk of cardiovascular disease, respectively, the discounted lifetime cardiovascular disease healthcare costs without medical primary prevention are estimated at $1,353 and $1,512, the incremental costs of medical primary prevention are $149 and $486, the discounted DALYs averted are 1.02 and 1.56, and the incremental costs per DALY averted are $146 and $312. For both lifetime medical care costs and DALYs, Ngalesoni et al. report values discounted at 3% per annum.

The proportion of adult Kenyans falling into these groups was estimated based on the Kenya STEPwise Survey for Non Communicable Diseases Risk Factors 2015 Report,[14] a nationally representative survey with biometric measurements among Kenyans 18-69 years of age. Based on this survey, 23.8% (95% CI = 21.4-26.2) of adult Kenyans have hypertension (SBP ≥ 140 and/or DBP ≥ 90 mmHg or currently on medication), including 15.4% prevalence of moderate hypertension and 8.4% (95% CI = 7.3-9.6) prevalence of severe hypertension (systolic blood pressure >=160 mm Hg and/or diastolic blood pressure >=100 mm Hg).

3.4 Results

With an estimated 4.51 million individuals 15 years of age or older screened in 2018, the costs for community mobilization and HIV testing would be $56.8 million and the cost of NCD testing $3.2 million. In 2018, the number of people on ART would increase by 67,000 at an additional cost of $16.9 million, and these numbers would increase in 2028 to 659,000 additional people on ART and $346.3 million in additional treatment costs. Through 2028, the HIV-related components of the community health campaign would avert 6.5 million DALYs at a discounted cost of $1,480 million, equivalent to $227 per DALY averted, and highly cost-effective.

We estimate that 590,000 individuals with moderate or high blood pressure not currently on treatment would be identified in 2018. Assuming an uptake of hypertension treatment at 23% and discounted incremental lifetime healthcare costs of $149 and $486 for moderate-risk and high-risk hypertension treatment, the hypertension screening and treatment would avert 160,000 DALYs at a cost of $37.2m, corresponding to $232 per DALY averted. Over the 10-year modeling scenario, the population would increase as would the costs and benefits, reaching $49.8m and 215,000 DALYs averted in 2028.

Assuming a prevalence of 2.2% for diabetes among adult Kenyans, we estimate that blood glucose screening in conjunction with the HIV community health campaign would newly identify 53,000 individuals with diabetes, at a marginal cost of $54 per case identified. With standard glycemic control for individuals with diabetes, the cost per DALY averted is approximately $944. As with the HIV-related components, the hypertension and diabetes components of the intervention are estimated to be highly cost-effective.

4 NIGERIA

4.1 Intervention costs

Cost of screening of pregnant women and cost of PMTCT for HIV-positive pregnant women were derived from the PEPFAR *Report on Pilot Expenditure Analysis of PEPFAR Programs in Six Countries*.[5] The cost

estimates are averages of expenditures across facility types, and the report provides a discussion of variation in costs across types of facilities. Family planning costs are based on the Health Policy Project[6] ImpactNow model, which is a Microsoft Excel workbook that calculates a variety of outcomes including family planning costs, subsequent medical care utilization, and DALYs for specific countries with user-supplied scenarios and the ability to change a variety of parameters. As of this writing, the program can only project outcomes through 2020. For these analyses, the family planning intervention was modeled through 2020, and the costs and DALYs per person-year of contraceptive use were used to project outcomes through the end of the modeling period based on the hypothesized proportion of women with contraceptive coverage with and without the intervention and the projected number of women of reproductive age. We relied on the ImpactNow default values for the mix of contraceptives used in Nigeria (i.e., the proportion of women using various methods) and for the per-year cost of those methods. The later was derived from the Guttmacher Institute *Adding It Up* report.[15]

4.2 HIV medical care costs and DALYs

Per-person annual ART costs are from the *PEPFAR Annual Treatment Report*.[7] Both persons on ART and HIV-related DALYs for each year and each scenario were obtained from Spectrum.

4.3 Family planning costs and DALYs

As described above, the Health Policy Project ImpactNow model was used to estimate the costs and consequences for family planning. For health and medical outcomes, we relied on the default values for Nigeria in the ImpactNow model.

4.4 Results

Increasing access to PMTCT would require $31.3m in 2018, including $17.3m in screening costs and $14.0m in PMTCT costs. With full scale-up in 2023, $172.2m would be required to identify and deliver PMTCT to an additional 142,000 HIV-positive pregnant women. Although the number of women receiving PMTCT would decrease through 2028, the costs would increase slightly to $181.0m due to the larger number of pregnant women requiring screening due to decreasing HIV prevalence. From 2018 to 2028, the scale-up of PMTCT would avert 8.6m DALYs at a cost of $169 per DALY averted and would be highly cost-effective.

An increase from 16% to 31% in contraceptive use would require an additional investment of $4.8m in 2019, increasing to $27.4m in 2023 with greater coverage and population growth, and then increasing to $32.3m in 2028 with continued population growth. Approximately 90% of the increased investments would be offset by maternal and infant healthcare costs averted through family planning. DALYs averted per year would increase from 484,000 in 2019 to 3.2m in 2028, with a total of 22.9m DALYs averted. Increased access to family planning is highly cost-effective and approaches the cost-saving threshold, with a net cost of approximately $0.95 per DALY averted.

5 INDIA

5.1 Intervention costs

We considered two approaches to providing HIV and STI services to FSWs and MSM in India. The Avahan Initiative has been successful in reducing HIV risk among these populations, and it has done so with a comprehensive intervention. Among FSWs, the incremental cost per infection averted was estimated at

$785 and the incremental cost per DALY averted was estimated at $46. [16] The Avahan Initiative was multifaceted and included HIV testing, peer education, STI treatment and management, condom promotion, and a variety of activities for community mobilization, advocacy, and changing the enabling environment, with an overall cost per client per year of $231.[16] The second approach we considered was reaching MSM and FSWs through respondent-driven sampling (RDS), whereby MSM and FSWs are incentivized to visit program sites and refer others to service sites, where they would receive HIV and STI testing and treatment.[8] The estimated cost per person tested for HIV in this approach is of approximately $20. Although this RDS approach has not been evaluated on a large scale, we preferred if for our modeling scenario as it may be more affordable for achieving high levels of coverage and because the multifaceted mechanisms of HIV and STI risk reduction in Avahan would necessitate far more complex simulation models.

Solomon et al., 2017,[8] provide estimates of cost per HIV-positive MSM tested, inclusive of RDS costs and HIV testing costs, and the resulting HIV prevalence. From these figures we estimated the costs of RDS and HIV testing regardless of HIV status at $20.33 per person. Korenromp, et al., 2017,[9] provide estimates of syphilis testing and treatment costs for FSWs and MSM were estimated at $3.50 and $9.30.

5.2 HIV medical care costs and DALYs

ART costs were estimated at $126.06 per person-year, based on costing from the India National AIDS Control Program.[17] PrEP costs of $91 per person-year were based on Stover et al., 2016,[10] with updated drug cost estimates for TDF/3TC [11]. Stover et al. estimated that with lower drug prices, PrEP costs should decrease to around $95 per person-year with approximately $50 in drug costs, $30 in service delivery costs, and $15 in testing costs. Médecins Sans Frontières[11] has identified the lowest cost of generic tenofovir disoproxil fumarate/lamivudine as $46 per person per year, corresponding to an estimate of $91 for PrEP per person-year. Both persons on ART and HIV-related DALYs for each year and each scenario were obtained from Spectrum.

5.3 Syphilis DALYs

We did not identify any syphilis-related DALY estimates specific to India, and DALYs per prevalent syphilis case (0.64) were calculated using the method by Korenromp et al., 2017.[9] In brief, the global DALYs for syphilis in 2013 estimated in the Global Burden of Disease study[18] was divided by the global prevalence of syphilis in 2014 estimated by Newman et al., 2015,[19] thus yielding a global average of the number of DALYs per prevalent case.

5.4 Results

In the intervention scenarios, recruitment and HIV testing and referral costs would be $34.1m in 2018 and increase to $190.4m in 2028. With 81% ART uptake among those diagnosed, ART coverage would increase over the base case by 55,000 in 2018 and by 107,000 in 2028. Overall, the program with testing and treatment but without PrEP would be highly cost-effective, averting 2.7m DALYs at $656 per DALY averted, with an incremental cost of $1,797m over the base case cost of $1,315m. Neither of the PrEP scenarios (10% or 30% coverage) would be cost effective, with an incremental cost of $21,531 - $58,812 per DALY averted vs. the no PrEP scenario. While PrEP may not appear cost-effective among MSM and FSWs at a national level, it may prove cost-effective in regions of the country where incidence is particularly high in these populations.

The addition of syphilis screening and treatment to the HIV testing and treatment but no PrEP scenario would likely be highly cost-effective. In 2018, the program would test 1.68m individuals and diagnose and treat 76,000 cases at an incremental cost of $6.6m. At an estimated 0.64 DALYs per prevalent case, we estimate averting 49,000 DALYs in the first year at $135 per DALY averted. The total cost of testing each year would increase with the scale-up of coverage. With 60% coverage among MSM and 90% coverage among FSWs in 2022, the total syphilis testing cost for 2022 would be $16.9m. A maximum estimate of treatment costs in 2022 is $1.6m, assuming, pessimistically, no decrease in syphilis prevalence as a result of previous years of testing.

In sensitivity analyses we examined the cost of recruitment and HIV testing with per-person costs similar to Avahan. In this scenario, the costs for HIV testing and treatment with no PrEP would be $217.6m in 2018, $1,124.5m in 2022, and $1,188.8m in 2028. Overall, the cost per DALY averted would be $3765. We reiterate that this sensitivity analysis does reflect more substantial costs for the intervention, but it does not reflect the comprehensive nature of the Avahan intervention and should not be construed as an economic evaluation of the Avahan Initiative.

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APPENDIX 4

Modeling harm reduction interventions on people who inject drugs in Russia: assessing the dual benefit on HIV and fatal overdose prevention

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Background

The aim of this modeling exercise was to assess the impact of scaling up harm reduction and antiretroviral therapy (ART) on HIV transmission and fatal overdose among PWID in two different epidemic settings in Russia.

HIV epidemiology among PWID in Omsk and Ekaterinburg

Official data from the Russian government indicate that several regions within the Ural and Siberian Federal Districts have among highest rates of new HIV diagnoses.[1] Despite their geographic proximity, the burden of HIV in key populations, such as people who inject drugs (PWID) differs substantially. For illustrative modeling purposes, we selected Ekaterinburg, Russia's fourth largest city located in the Ural Federal district with a stable, high prevalence epidemic among PWID and Omsk, a major city in the Siberian Federal District with evidence suggestive of a growing epidemic.

In Omsk, cross-sectional studies indicated that HIV prevalence among PWID was approximately 9%[2] [95%CI 5-14%] in 2009, however by 2011 it nearly doubled to 17%[3] [95%CI 12-22%], reaching 19.4% in 2014.[4] This evidence of increasing HIV burden is supported by an increase in new HIV diagnoses among PWID in the Omsk oblast administrative region (not shown).

In Ekaterinburg, cross-sectional studies identified a high but stable HIV burden among PWID in Ekaterinburg, of 64% [95%CI 59-70%] in 2007 to 59% [95%CI 51-66%] in 2011 and 65% [95% CI: 61-71%] in 2014.[3] Additionally, a WHO surveillance study was conducted in 2001 in Ekaterinburg where the HIV prevalence among PWID was 34% [95%CI 25-45%] among 82 PWID, indicating that HIV prevalence increased in the early part of the decade but stabilized thereafter.[5]

Statistical analyses to inform the model

To inform the model parameterization, we performed statistical analyses of three cross-sectional surveys performed among PWID in Ekaterinburg (in 2007 and 2014) and Omsk (2009) .[3] Respondent driven sampling (RDS) was used to recruit 300-350 PWID in each site for each study. The domains of the interview administered research study included: sociodemographic characteristics, drug use behaviors, sexual partners and condom use, STI and TB diagnoses, HIV testing and knowledge, referral to medical services, interaction with HIV prevention programs. Rapid HIV and hepatitis C virus (HCV) testing was performed at both sites, for both years. Full details of the analysis methods and findings can be found in our companion paper.[6] Briefly, these analyses highlighted important heterogeneity among the PWID population in terms of history of incarceration (in both Ekaterinburg and Omsk) and sex (in Ekaterinburg). Consequently, we stratified the model by these factors and calibrated to HIV prevalence data among these groups (see Table S1)

Modeling methods

Technical Model Description

We developed a dynamic, deterministic compartmental model of HIV transmission among PWID (model schematics in Figure S1 and S2) incorporating injecting and sexual transmission among PWID. PWID enter due to injecting initiation and exit due to cessation of injecting or death (overdose, HIV-related death, or non-HIV background mortality). The model was stratified by HIV disease stage and ART status (uninfected [stage x], acute [stage h], latent [stage y], pre-AIDS [stage b], AIDS [stage a], latent ART [stage l], pre-AIDS ART [stage w], AIDS ART [stage z]), risk (low/high, denoted by superscript i=0 for low, 1 for high), sex (denoted by superscript j=0 for males, 1 for females) and harm reduction access (off/on, denoted by subscript k=0 for off, 1 for on). The HIV stages are characterized by an initial high

viraemia phase of acute infection (average duration $1/\gamma$), a longer latent phase of low viraemia (average duration $1/\kappa$), a short phase of high viraemia pre-AIDS (average duration $1/\tau$), and a short phase of AIDS where we assume PWID are too ill to contribute to HIV transmission (average duration $1/\theta$). Due to higher viraemia levels, those in the acute and pre-AIDS stages have heightened sexual and injecting transmission compared to individuals in the latent phase (cofactors ε and ι, respectively). PWID can be recruited onto ART once they enter the longer latent ART stage or later, upon which they have a reduced HIV-related death rate (cofactor ν for the latent and pre-AIDS stages, and ρ for the, AIDS stage). We assume individuals on ART have reduced sexual and injecting transmission (cofactors ω_{inj} and ω_{sex} for injecting and sexual transmission, respectively). Individuals can drop out of ART, at a rate $\delta_{k,}$ dependent on intervention status and type.

Based on multivariable log-binomial regression analyses, the model was stratified by sex and incarceration history in both settings. A certain proportion of individuals (denoted $p_{prisoon}$) are high risk (have a history of prison) on entry into injecting (the remainder ($1-p_{prison}$) are low-risk with no history of incarceration. PWID can move from low to high risk (become incarcerated) at a rate (r). Being high risk is assumed to change an individual's risk of injecting HIV transmission by a cofactor RR^{high} compared to low risk. Similarly, p_{sex} denotes the proportion of entrants by sex ($p_{sex}=p_{females}$ for females and $p_{sex}=(1-p_{females})$ for males), and being female alters an individual's risk of injecting HIV transmission by a cofactor RR^{female} compared to males. We assume proportional mixing by risk and sex.

Individuals can cycle on and off a harm reduction intervention (Figure S2), which is defined differently for each scenario (recruited at a rate η, drop-out at a rate ζ). The harm reduction scenarios explore scale-up of: high coverage needle/syringe program (NSP) only (defined as receiving one or more sterile syringes per injection), OAT only, or a combined NSP and OAT program (in other words, PWID are recruited onto a program providing both high coverage NSP and OAT). For each harm reduction scenario,

the harm reduction intervention is assumed to reduce an individual's risk of injecting HIV transmission compared to those no on harm reduction by RR_k. Therefore, RR_0=1, and RR_k varies depending on intervention examined (NSP, OAT, or NSP+OAT). Hence, we assume NSP, OAT, and NSP+OAT reduce an individual's risk of injecting HIV transmission compared to no NSP (cofactors $RR_{NSP,}$ RR_{OAT}, and $RR_{BOTH,}$ respectively). We also assume OAT (alone or in combination with NSP) reduces the risk of ART drop out compared to those not on OAT by 23% (cofactor ψ_k where by definition ψ_0=1, and ψ_k varies by intervention, such that ψ_{NSP}=1 and ψ_{OAT}= ψ_{BOTH}=mean 0.77), and risk of fatal overdose by 71% (cofactor Ψ_k by definition $\Psi_0 = 1$ and Ψ_k varies by intervention, such that $\Psi_{SEP} = 1$ and $\Psi_{MAT} = \Psi_{BOTH}$ =mean 0.29). ART recruitment is modeled at a rate α_k where α_0=α_c and $\alpha_1 = \chi_{INT}\alpha_c$. Here, we incorporate the impact of OAT interventions on increasing recruitment to ART (by a factor fold $\chi_{OAT=}$ χ_{BOTH}).[7] Individuals can drop out of ART, at a rate δ_k where $\delta_{0=}$ δ_c and $\delta_{1=}$ $\psi_{INT}\delta_c$, where we assume interventions incorporating OAT reduce ART drop out by a factor ψ_{OAT} .[7] We assume NSP only has no impact on ART drop out ($\psi_{NSP=0}$) or ART recruitment ($\chi_{NSP=0}$). We additionally incorporate a heightened risk of overdose in the first 4 weeks entering or leaving OAT based on data from a systematic-review and meta-analysis. Hence, we incorporate death for a small proportion of those entering OAT (proportion m_{enter}) , where $m_{enter} = \mu_1$ x OD_{prev} x ($RR_{ODonOAT} - 1$) x (4/52) . Here, μ_1 is the background overdose mortality rate, OD_{prev} is the protective overdose prevention benefit while being on OAT, and RR_{OD} is the risk of overdose within the first four weeks of initiating methadone. We multiply all of this by the duration at risk which is 4 weeks / 52 weeks per year. Similarly, when coming off the intervention, we incorporate death for a small proportion of those exiting OAT (m_{exit}) where $m_{exit} = \mu_1$ x ($RR_{ODoffOAT} - 1$) x (4/52) . The inflow of susceptible PWID was replaced by the number of PWID (N) who ceased from injecting or died due background (non-HIV, non-overdose) mortality.

Model Equations:

For low-risk PWID off harm reduction (where superscript *i*=0 for low-risk (never incarcerated), 1 for high-risk (ever incarcerated) and superscript *j*=0 for males and 1 for females):

$$\frac{dx_0^{0j}}{dt} = \Omega(t)(1-p_{prison})p_{sex} + (1-m_{exit})\zeta x_1^{0j} - x_0^{0j}\left(\lambda_{inj}^{0j} + \lambda_{sex}\right) - x_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta x_0^{0j} - r x_0^{0j}$$

$$\frac{dh_0^{0j}}{dt} = (1-m_{exit})\zeta h_1^{0j} + x_0^{0j}\left(\lambda_{inj}^{0j} + \lambda_{sex}\right) - \gamma h_0^{0j} - h_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta h_0^{0j} - r h_0^{0j}$$

$$\frac{dy_0^{0j}}{dt} = (1-m_{exit})\zeta y_1^{0j} + \gamma h_0^{0j} - \kappa y_0^{0j} + \delta_k l_0^{0j} - \alpha_k y_0^{0j} - y_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta y_0^{0j} - r y_0^{0j}$$

$$\frac{dl_0^{0j}}{dt} = (1-m_{exit})\zeta l_1^{0j} + \alpha_k y_0^{0j} - \nu\kappa l_0^{0j} - \delta_k l_0^{0j} - l_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta l_0^{0j} - r l_0^{0j}$$

$$\frac{db_0^{0j}}{dt} = (1-m_{exit})\zeta b_1^{0j} + \kappa y_0^{0j} + \delta_k w_0^{0j} - \alpha_k b_0^{0j} - \tau b_0^{0j} - b_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta b_0^{0j} - r b_0^{0j}$$

$$\frac{dw_0^{0j}}{dt} = (1-m_{exit})\zeta w_1^{0j} + \nu\kappa l_0^{0j} + \alpha_k b_0^{0j} - \delta_k w_0^{0j} - \nu\tau w_0^{0j} - w_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta w_0^{0j} - r w_0^{0j}$$

$$\frac{da_0^{0j}}{dt} = (1-m_{exit})\zeta a_1^{0j} + \tau b_0^{0j} + \delta_k z_0^{0j} - \alpha_k a_0^{0j} - \theta a_0^{0j} - a_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta a_0^{0j} - r a_0^{0j}$$

$$\frac{dz_0^{0j}}{dt} = (1-m_{exit})\zeta z_1^{0j} + \nu\tau w_0^{0j} + \alpha_k a_0^{0j} - \delta_k z_0^{0j} - \rho\theta z_0^{0j} - z_0^{0j}(\mu_1 + \mu_2 + \mu_3) - \eta z_0^{0j} - r z_0^{0j}$$

For low-risk PWID on harm reduction:

$$\frac{dx_1^{0j}}{dt} = (1-m_{enter})\eta x_0^{0j} - x_1^{0j}\left(\lambda_{inj}^{0j} + \lambda_{sex}\right) - x_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta x_1^{0j} - r x_1^{0j}$$

$$\frac{dh_1^{0j}}{dt} = (1 - m_{enter})\eta h_0^{0j} + x_1^{0j}\left(\lambda_{inj}^{0j} + \lambda_{sex}\right) - \gamma h_1^{0j} - h_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta h_1^{0j} - r h_1^{0j}$$

$$\frac{dy_1^{0j}}{dt} = (1 - m_{enter})\eta y_0^{0j} + \gamma h_1^{0j} + \psi_1\delta_k l_1^{0j} - \kappa y_1^{0j} - \alpha_k y_1^{0j} - y_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta y_1^{0j} - r y_1^{0j}$$

$$\frac{dl_1^{0j}}{dt} = (1 - m_{enter})\eta l_0^{0j} + \alpha_k y_1^{0j} - \psi_1\delta_k l_1^{0j} - \nu\kappa l_1^{0j} - l_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta l_1^{0j} - r l_1^{0j}$$

$$\frac{db_1^{0j}}{dt} = (1 - m_{enter})\eta b_0^{0j} + \kappa y_1^{0j} + \psi_1\delta_k w_1^{0j} - \alpha_k b_1^{0j} - \tau b_1^{0j} - b_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta b_1^{0j} - r b_1^{0j}$$

$$\frac{dw_1^{0j}}{dt} = (1 - m_{enter})\eta w_0^{0j} + \nu\kappa l_1^{0j} + \alpha_k b_1^{0j} - \psi_1\delta_k w_1^{0j} - \nu\tau w_1^{0j} - w_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta w_1^{0j} - r w_1^{0j}$$

$$\frac{da_1^{0j}}{dt} = (1 - m_{enter})\eta a_0^{0j} + \tau b_1^{0j} + \psi_1\delta_k z_1^{0j} - \alpha_k a_1^{0j} - \theta a_1^{0j} - a_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta a_1^{0j} - r a_1^{0j}$$

$$\frac{dz_1^{0j}}{dt} = \left(1 - m_{enter}\right)\eta z_0^{0j} + \nu\tau w_1^{0j} + \alpha_k a_1^{0j} - \psi_1\delta_k z_1^{0j} - \rho\theta z_1^{0j} - z_1^{0j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta z_1^{0j} - r z_1^{0j}$$

For high-risk PWID off harm reduction:

$$\frac{dx_0^{1j}}{dt} = \Omega(t)p_{prison}p_{sex} + r x_0^{0j} + (1 - m_{exit})\,\zeta x_0^{1j} - x_o^{1j}\left(\lambda_{inj}^{1j} + \lambda_{sex}\right) - x_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta x_0^{1j}$$

$$\frac{dh_0^{1j}}{dt} = (1 - m_{exit})\,\zeta h_1^{1j} + r h_0^{0j} + x_0^{1j}\left(\lambda_{inj}^{1j} + \lambda_{sex}\right) - \gamma h_0^{1j} - h_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta h_0^{1j}$$

$$\frac{dy_0^{1j}}{dt} = (1 - m_{exit})\zeta y_1^{1j} + r y_0^{0j} + \gamma h_0^{1j} - \kappa y_0^{1j} + \delta_k l_0^{1j} - \alpha_k y_0^{1j} - y_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta y_0^{1j}$$

$$\frac{dl_0^{1j}}{dt} = (1 - m_{exit})\,\zeta l_1^{1j} + r l_0^{0j} + \alpha_k y_0^{1j} - \nu\kappa l_0^{1j} - \delta_k l_0^{1j} - l_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta l_0^{1j}$$

$$\frac{db_0^{1j}}{dt} = (1 - m_{exit})\zeta b_1^{1j} + r b_0^{0j} + \kappa y_0^{1j} + \delta_k w_0^{1j} - \alpha_k b_0^{1j} - \tau b_0^{1j} - b_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta b_0^{1j}$$

$$\frac{dw_0^{1j}}{dt} = (1 - m_{exit})\,\zeta w_1^{1j} + r w_0^{0j} + \nu\kappa l_0^{1j} + \alpha_k b_0^{1j} - \delta_k w_0^{1j} - \nu\tau w_0^{1j} - w_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta w_0^{1j}$$

$$\frac{da_0^{1j}}{dt} = (1 - m_{exit})\,\zeta a_1^{1j} + r a_0^{0j} + \tau b_0^{1j} + \delta_k z_0^{1j} - \alpha_k a_0^{1j} - \theta a_0^{1j} - a_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta a_0^{1j}$$

$$\frac{dz_0^{1j}}{dt} = (1 - m_{exit})\zeta z_1^{1j} + r z_0^{0j} + \nu\tau w_0^{1j} + \alpha_k a_0^{1j} - \delta_k z_0^{1j} - \rho\theta z_0^{1j} - z_0^{1j}(\mu_1 + \mu_2 + \mu_3) - \eta z_0^{1j}$$

For high-risk PWID on harm reduction:

$$\frac{dx_1^{1j}}{dt} = (1 - m_{enter})\eta x_0^{1j} + r x_1^{0j} - x_1^{1j}\left(\lambda_{inj}^{1j} + \lambda_{sex}\right) - x_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta x_1^{1j}$$

$$\frac{dh_1^{1j}}{dt} = (1 - m_{enter})\,\eta h_0^{1j} + r h_1^{0j} + x_1^{1j}\left(\lambda_{inj}^{1j} + \lambda_{sex}\right) - \gamma h_1^{1j} - h_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta h_1^{1j}$$

$$\frac{dy_1^{1j}}{dt} = (1 - m_{enter})\eta y_0^{1j} + r y_1^{0j} + \gamma h_1^{1j} + \psi_1\delta_k l_1^{1j} - \kappa y_1^{1j} - \alpha_k y_1^{1j} - y_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta y_1^{1j}$$

$$\frac{dl_1^{1j}}{dt} = (1 - m_{enter})\eta l_0^{1j} + r l_1^{0j} + \alpha_k y_1^{1j} - \psi_1 \delta_k l_1^{1j} - \nu\kappa l_1^{1j} - l_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta l_1^{1j}$$

$$\frac{db_1^{1j}}{dt} = (1 - m_{enter})\eta b_0^{1j} + r b_1^{0j} + \kappa y_1^{1j} + \psi_1 \delta_k w_1^{1j} - \alpha_k b_1^{1j} - \tau b_1^{1j} - b_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta b_1^{1j}$$

$$\frac{dw_1^{1j}}{dt} = (1 - m_{enter})\eta w_0^{1j} + r w_1^{0j} + \nu\kappa l_1^{1j} + \alpha_k b_1^{1j} - \psi_1 \delta_k w_1^{1j} - \nu\tau w_1^{1j} - w_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta w_1^{1j}$$

$$\frac{da_1^{1j}}{dt} = (1 - m_{enter})\eta a_0^{1j} + r a_1^{0j} + \tau b_1^{1j} + \psi_1 \delta_k z_1^{1j} - \alpha_k a_1^{1j} - \theta a_1^{1j} - a_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta a_1^{1j}$$

$$\frac{dz_1^{1j}}{dt} = (1 - m_{enter})\eta z_0^{1j} + r z_1^{0j} + \nu\tau w_1^{1j} + \alpha_k a_1^{1j} - \psi_1 \delta_k z_1^{1j} - \rho\theta z_1^{1j} - z_1^{1j}(\Psi_1\mu_1 + \mu_2 + \mu_3) - \zeta z_1^{1j}$$

The inflow into the PWID population is defined as below:

$$\Omega(t) = (\mu_2 + \mu_3)N$$

The injecting force of infection is defined by the equations below, where $RR_k = RR_{NSP}$ for syringe exchange only, $RR_k = RR_{OAT}$ for OAT only, and $RR_k = RR_{BOTH}$ for OAT+NSP and RR^{female} is the increased risk of transmission among females compared to males.

$$\Pi^{ij} = \varepsilon h_0^{ij} + y_0^{ij} + \iota b_0^{ij} + \omega_{inj}\left(l_0^{ij} + w_0^{ij} + z_0^{ij}\right) + RR_k\left(\varepsilon h_1^{ij} + y_1^{ij} + \iota b_1^{ij} + \omega_{inj}\left(l_1^{ij} + w_1^{ij} + z_1^{ij}\right)\right)$$

$$\Gamma^{ij} = (x_0^{ij} + h_0^{ij} + y_0^{ij} + l_0^{ij} + b_0^{ij} + w_0^{ij} + z_0^{ij} + RR_k(x_1^{ij} + h_1^{ij} + y_1^{ij} + l_1^{ij} + b_1^{ij} + w_1^{ij} + z_1^{ij}))$$

For males:

$$\lambda_0^{00}{}_{inj} = \beta_{inj}\left[\frac{\Pi^{00} + RR^{female}\Pi^{01} + RR^{high}(\Pi^{10} + RR^{female}\Pi^{11})}{\Gamma^{00} + RR^{female}\Gamma^{01} + RR^{high}(\Gamma^{10} + RR^{female}\Gamma^{11})}\right]$$

$$\lambda_0^{10}{}_{inj} = RR^{high}\lambda_0^{00}{}_{inj}$$

$$\lambda_1^{00}{}_{inj} = RR_k \lambda_0^{00}{}_{inj}$$

$$\lambda_1^{10}{}_{inj} = RR^{high} RR_k \lambda_0^{00}{}_{inj}$$

For females:

$$\lambda_0^{01}{}_{inj} = RR^{female} \lambda_0^{00}{}_{inj}$$

$$\lambda_0^{11}{}_{inj} = RR^{female} RR^{high} \lambda_0^{00}{}_{inj}$$

$$\lambda_1^{01}{}_{inj} = RR^{female} RR_k \lambda_0^{00}{}_{inj}$$

$$\lambda_1^{11}{}_{inj} = RR^{female} RR^{high} RR_k \lambda_0^{00}{}_{inj}$$

The sexual force of infection is defined as

$$\lambda_{sex} = \beta_{sex} \left[\frac{\varepsilon\left(h_0^{ij} + h_1^{ij}\right) + y_0^{ij} + y_1^{ij} + \iota\left(b_0^{ij} + b_1^{ij}\right) + \omega_{sex}\left(l_0^{ij} + w_0^{ij} + z_0^{ij} + l_1^{ij} + w_1^{ij} + z_1^{ij}\right)}{N} \right]$$

Model calibration methods

The model was calibrated to two cities with differing epidemic profiles in Russia: Omsk (moderate but expanding HIV epidemic) and Ekaterinburg (high but stable HIV epidemic). Estimates and uncertainty bounds for parameters used in the models are found in Table -S1. We used Latin Hypercube Sampling to generate 100 randomly sampled parameter sets from most model parameters from their underlying uncertainty distributions. For each setting, the model was calibrated to multiple time-points of HIV prevalence among PWID, stratified by sex and incarceration history if available (in 2001, 2007, 2011, 2014 for Ekaterinburg and 2009, 2011, 2014 for Omsk), the estimated proportion of incident HIV infections related due to sexual risk (in 2007 for Ekaterinburg, and 2009 in Omsk), the ART coverage in 2014, and the proportion of PWID who were high risk (ever incarcerated) in 2007 and 2009 in Ekaterinburg and Omsk, respectively. This was achieved through varying the initial PWID population size in 1996, the seed HIV prevalences among PWID in each group in 1996, the sexual HIV transmission rate in the latent stage, the injecting HIV transmission rate in the latent stage, the ART recruitment rate,

and the transition rate from the low-risk to high-risk group (never incarcerated to incarcerated). For each parameter set, the model was calibrated to the data using a global optimization solver (*fmincon* with the *multistart* function in MATLAB) and by minimizing the sum log likelihood of the calibration points based on the distributions shown in Table S1.

Model parameterization

All parameters used in the model with their sample uncertainty bounds are found in Table S2.

Injecting cessation rate: The average duration of injecting until final cessation in Russia is highly uncertain. A published study on self-reported behavioral data reported a mean of 9.1 and 8.5 years of injection duration, in Omsk and Ekaterinburg, respectively.[2] However, since these data were cross-sectional, these point estimates do not include the period from the survey until injection cessation (or death). PWID from a cross-sectional study from St Petersburg reported a similar duration of injecting to Omsk and Ekaterinburg, of a mean of 10 years.[2] However, previous modeling work from St. Petersburg estimated the duration of injection until final cessation in St. Petersburg to be 30 years, based on model calibration to HIV incidence and prevalence data.[8] We accounted for the high uncertainty in this estimate by sampling uniformly from 1/35 – 1/5 (5-35 years injection duration).

Overdose rate: We estimated the overdose mortality rate to be approximately 2%, based on published estimates from PWID in St. Petersburg[9,10], as we did not have any estimates from Omsk or Ekaterinburg. We sampled from 0.5% - 3.5% to include the global estimate of the crude mortality rate for PWID (0.62%)[11] and the likely higher rate in Russia attributed to 1) the lack of opioid agonist OAT[12] and 2) restrictions on PWID accessing naloxone from pharmacies[13] and poorly equipped ambulances and trained staff to administer it.[14]

Overdose-related mortality on and off opioid agonist OAT: As highlighted in a recent systematic review and meta-analysis, individuals off methadone have a 4.80-fold (2.90 to 7.96) increased risk of mortality due to overdose.[15] However, the overdose-related mortality rate within the first four weeks of initiating methadone is 3.5 per 100,000 person-years and 4.2 per 100,000 person-years in the first four weeks after discontinuing methadone. By comparison, the overdose-related mortality rate while on

methadone is 2 per 100,000 person-years. Since no pooled rate ratios were provided on the increased risk of opioid overdose mortality for the first four weeks entering methadone and the first four weeks after exiting methadone, we sampled from the all-cause mortality pooled rate ratios for this period ($RR_{odonOAT}$ = 1.97, 95% CI: 0.97 – 4.10; $RR_{odoffOAT}$ = 2.38, 95% CI: 1.51 – 3.74).

ART coverage: Self-reported data from the 2014 study in Ekaterinburg revealed that 26% of HIV-positive PWID were currently on ART. We assumed ART scale-up to PWID began in 2006[16], in conjunction with Global Fund support, to reach 26% coverage among HIV+ PWID by 2014. No data on ART were available in Omsk, so we assumed similar coverage as in Ekaterinburg, which agreed with estimates of viral suppression among HIV+ PWID hospital patients in St. Petersburg (30%) in 2014-2015.[17]

Proportion of new infections due to sexual transmission: It is challenging to estimate what proportion of infections are due to sexual versus injecting transmission, however information regarding HIV/HCV coinfection epidemiology can shed insight as HCV is transmitted predominantly through injecting transmission, whereas HIV is transmitted through sexual and injecting transmission. We utilized findings from a previously published dynamic coinfection model of HIV and HCV transmission among PWID[18], which estimated the proportion of HIV transmission due to sexual transmission in various settings with different values of HIV/HCV coinfection prevalences and HIV/HCV prevalence ratios (the overall HIV prevalence divided by the overall HCV prevalence). See our companion paper for more details.[6]

Efficacy of ART on injection related transmission: No study has directly evaluated the efficacy of ART as prevention for injection related transmission. However, findings from a previous modeling study estimated ART efficacy to be a 44% reduction in transmission, but with high uncertainty.[19] Similarly, a 49% reduction in HIV transmission was observed in the Bangkok tenofvir pre-exposure prophylaxis trial that was conducted among 2,413 PWID.[20] Thus, we estimated the relative reduction in injection related

transmission to be between 25% and 75% which is approximately centered around the estimate from the modeling analysis (50%) and consistent with ART adherence estimates among PWID.[21]

Model Scenarios

We additionally modeled the following intervention coverage scenarios:

- **Base Case:** No harm reduction and ART recruitment at current rates producing 26% ART coverage among HIV+ PWID in 2014 (counterfactual). We assume no baseline coverage of any harm reduction (OAT is illegal and there are only a handful of NSPs country-wide with minimal provision).[22]. ART coverage was calibrated to 26% in 2014, based on self-reported data on current ART use among HIV+ PWID in Ekaterinburg.
- **NSP 50%:** Scale-up of coverage of high coverage NSP only in 2018 to 50% of PWID within 3 years
- **OAT 25%:** Scale-up of coverage of OAT only in 2018 to 25% of PWID within 3 years
- **OAT 50%:** Scale-up of coverage of OAT only in 2018 to 50% of PWID within 3 years
- **OAT+NSP 50%**: Scale-up of coverage of combination OAT and high coverage NSP in 2018 to 50% of PWID within 3 years
- **OAT+NSP (50%) plus integrated ART** (recruited 3-fold higher than the base case within harm reduction): Scale-up of coverage of combined OAT and high coverage NSP in 2018 to 50% of PWID within 3 years, and scaled-up ART to HIV-infected PWID within harm reduction at a rate 3-fold higher than the base case ART recruitment rate. This scenario assumes PWID who initiate ART while on combined harm reduction can remain on ART after dropping out of harm reduction (OAT+NSP), but PWID in the community experience elevated ART dropout rates compare to PWID on OAT+NSP.

Outcomes

We projected the HIV prevalence among PWID and HIV incidence among PWID from 1996-2028. We additionally estimated the proportion of new HIV infections and fatal overdoses averted by calculating the cumulative difference between the base case and the intervention scenario for each model run from 2018 – 2028, divided by the expected number of events in the base case scenario. We present all results as medians and 2.5-97.5% intervals.

Sensitivity analyses

We perform several sensitivity analyses to test the impact of model assumptions. First, we examine the impact on our HIV infections and overdoses averted in each of our scenarios with a persistent proportion of the population who does not access harm reduction (25%), for example due to unsuitability to OAT (such as if a stimulant injector) or other barriers. Additionally, we examine the impact of incorporating lower non-drug related mortality rates of 0.22% per year (age-specific mortality rate of aged 20-24) for Russia, compared to the base-case which assumes a 2% mortality rate.

Results from Modeling

Base-Case scenario:

The model projections for the median and 2.5-97.5% intervals for overall HIV prevalence and incidence among PWID at base-case can be found in Figure S3. The model calibrated well to overall HIV prevalence as well as by sex and risk group (not shown, see our companion paper for further details and full model calibration results[6]).

Intervention scenarios:

Intervention coverage: The coverage of harm reduction interventions (NSP only, OAT only, or NSP+OAT) reach steady state quickly and remain near the target coverage at 5 years (Figure S4). In the

base case, overall ART coverage reached 32% and 28% in 2018 in Omsk and Ekaterinburg, respectively. When we included the impact of OAT on increasing ART recruitment, coverage reached approximately 50%, 38% overall, and 54%, 41% among PWID on the intervention, and 46%, 34% among PWID in the community in Omsk and Ekaterinburg, respectively. In the scenario with ART scale-up (3 times the base case rate), coverage reached approximately 70%, 57% overall, 77% and 64% among PWID on the intervention, and 61%, 48% among PWID in the community in Omsk and Ekaterinburg, respectively. The discrepancy in ART coverage is due to the reduced odds of ART discontinuation if on OAT.[7] Hence, these scenarios highlight the substantial benefit that integrated ART within harm reduction services could have not only on PWID while on harm reduction, but also after harm reduction drop out. They also highlight the value of integrated OAT and ART on increasing ART retention and therefore coverage.

Sensitivity analyses:

We assumed that all PWID in both settings would be equally likely to access the harm reduction intervention, however it is probable that not all PWID would be able to access the harm reduction intervention nor obtain any benefit (e.g. PWID who only inject amphetamine-type-stimulants would not benefit from opioid agonist OAT). Thus, as a sensitivity analysis, we assumed that 25% of PWID would never access the harm reduction intervention, while still maintaining the same coverage. Results are shown in Figure S5. Overall, the relative change in the proportion of HIV cases and fatal overdoses averted was affected minimally (<15%). The relative change from the baseline scenarios was approximately 8% for all scenarios in this sensitivity analysis. Similar findings were observed with respect to overdose averted, with the largest relative change found in the 25% OAT scenario (15% in sensitivity analysis versus 17% in the baseline, -11% relative change). Additionally, we examined the impact of reducing the background mortality rate (μ_2) from 2% to 0.2% (Figure S6). Overall, this reduction in the background mortality rate minimally affected the proportion of HIV cases averted in Omsk (<3% relative change), with negligible change in Ekaterinburg. Compared to the original scenarios with a 2% background mortality rate in Omsk, slightly less impact was observed in scenarios with a 0.2%

mortality rate in Omsk (NSP: 33% vs. 36%, OAT 25%: 16% vs. 17%, OAT 50%: 34% vs. 36%, NSP+OAT (50%) 46% vs. 48%, and NSP+OAT+ART scale-up 52% vs. 53%). Minimal changes were observed in the proportion of fatal overdoses averted (<1% across all scenarios).

Model limitations: The model is limited by uncertainty in the underlying parameters. Where possible, we have used local data or Russian data. Where these estimates were unavailable, we utilized estimates from similar regions or low-middle income country settings. To incorporate this uncertainty in the model projections we perform a probabilistic uncertainty analysis and propagating this uncertainty in the fitting to the future projections, presenting the model projections in terms of means and 95%CIs. For full discussion of model limitations please see the companion paper.[6]

Estimating the cost of NSP provision: A study conducted by the World Bank estimated the cost per needle/syringe exchanged to be $0.38 [in 2017 USD]. The number of PWID in Russia has been estimated to be 1.88 million (1.5-2.2 million)[2], thus assuming 50% coverage, the number of PWID needed to be covered would be 0.94 million. Behavioral data from in Omsk and Ekaterinburg revealed that daily injection was common.[3] Thus, assuming that one clean syringe is needed per injection per day, then the cost of providing 50% of PWID in Russia would be 0.94 million PWID x $0.38 per clean syringe x 365.25 days = $130,467,300 (range: $104,096,250 – $152,674,500) per year.

Table S1: Calibration parameters and distributions for the log-likelihood calculation. 95% CI are the computed Wald confidence limits from survey data.

	Omsk, Russia	Ekaterinburg, Russia	Distribution for the log-likelihood calculation	Reference
HIV prevalence among PWID in 2001		34% (23.7% - 44.6%)	beta	[5]
HIV prevalence among male PWID in 2007		60.6% (53.6% - 67.7%)	beta	Data
HIV prevalence among female PWID in 2007		70.5% (62.0% - 79.1%)	beta	Data
HIV prevalence among male PWID in 2009	8.5% (5.1% - 11.9%)		beta	Data
HIV prevalence among female PWID in 2009	9.0% (2.9% - 15.0%)		beta	Data
HIV prevalence among ever incarcerated PWID in 2009	12.7% (7.1% - 18.2%)		beta	Data
HIV prevalence among never incarcerated PWID in 2009	5.8% (2.6% - 9.0%)		beta	Data
HIV prevalence among PWID in 2011	16.7% (12.9% - 20.8%)	58.5% (53.4% - 63.8%)	beta	[3]
HIV prevalence among male PWID in 2014		58.2% (52.0% - 64.4%)	beta	Data
HIV prevalence among female PWID in 2014		77.9% (70.9% - 85.0%)	beta	Data
HIV prevalence among ever incarcerated PWID in 2014		70.3% (64.4% - 76.2%)	beta	Data
HIV prevalence among never incarcerated PWID in 2014		56.6% (48.4% - 64.9%)	beta	Data
HIV prevalence among PWID in 2014	19.4%		beta	No sample size provided so assumed similar to GF study (N=350)[4]
ART coverage among HIV+ PWID in 2014	26%	26%	beta	Data from Ekaterinburg but assumed similar coverage in Omsk
Proportion of PWID with a history of incarceration	40.9% (35.7% - 46.0%) in 2009	37.7% (32.2% - 43.2%) in 2007	beta	Data
Proportion of incident infections attributed to sexual transmission among PWID	8-28% in 2009	7-27% in 2007	uniform	Estimated from HIV/HCV coinfection survey data and modeling[18]

Table S2: Model parameters

Parameter	Mean and 95%CI of generated distribution	Sampling distribution and parameters (if not sampled, then blank)	Reference/notes
Average duration of injection until final cessation in years ($1/\mu_3$)	20 (5.8-34.2)	uniform (min=5, max=35)	See text. Assumed longer duration than self-reported current average duration injecting, consistent with modeling estimates from St. Petersburg[8]
Proportion of PWID who are female (p_{female})	0.36 (0.31, 0.41) - Ekaterinburg 0.25 (0.21, 0.30) - Omsk	Beta (alpha=136, beta=244) in Ekaterinburg Beta (alpha=89, beta=261) in Omsk	Estimated from Ekaterinburg and Omsk data
Proportion of PWID in high-risk group (ever incarcerated) at entry to injecting (p_{prison})	0.15 (0.11, 0.19) - Ekaterinburg 0.10 (0.07, 0.13) - Omsk	Beta (alpha=45, beta=255) in Ekaterinburg Beta (alpha=35, beta=315) in Omsk	Estimated from Ekaterinburg and Omsk data
Opioid overdose mortality rate per year (μ_1)	0.020 (0.006-0.034)	uniform (min 0.005, max 0.035)	Estimated 2%/year in St Petersburg.[9,14]
Non-overdose mortality rate per year (μ_2)	1/50		Estimated assuming injection initiation at 20 years and life expectancy at 70[23]
Injection-related infection rate per year in latent phase (β_{inj})	varied to fit model		
Sexual-related infection rate per year in latent phase (β_{sex})	varied to fit model		
Seed HIV prevalences in 1996 (by risk and sex in Ekaterinburg and risk only in Omsk due to minimal differenes in sex)	varied to fit model		
Relative risk of injecting related HIV transmission if in high-risk group compared to low risk (RR^{high})	varied to fit model		
Relative risk of injecting related HIV transmission if female compared to male (RR^{female})	varied to fit model		
Rate from low risk to high risk group (r)	varied to fit model		
ART recruitment rate at baseline in the community (α_c)	varied to fit model		
Cofactor increase in HIV transmission probability during: Initial acute phase of high viremia (ε)	14.5 (3.7 – 25.5)	uniform (min=3, max=26)	[24,25]
Cofactor increase in HIV transmission probability during: pre-AIDS phase of high viremia (ι)	4 (1.2 - 6.8)	uniform (min=1, max=7)	[24,25]
Duration of initial period of high viremia in years ($1/\gamma$)	0.24		[24]
Duration of latent period of viremia in years ($1/\kappa$)	8.38		[24,26]
Duration of pre-AIDS period of high viremia in years ($1/\tau$)	0.75		[24,26]
Duration of AIDS period in years ($1/\theta$)	0.83		[26]
Intervention effectiveness			

Relative injection-related transmissibility while on ART compared to latent phase (ω_{inj})	0.50 (0.26 – 0.74)	uniform (min=0.25, max=0.75)	[19,21]
Relative sexual-related transmissibility while on ART compared to latent phase (ω_{sex})	0.07 (0.02 – 0.21)	lognormal (mean= -2.66, sd=0.58)	[27]
ART discontinuation rate per year when not on OAT (δ_c)	6.5% (3%-10%)	uniform (min 3%, max 10%)	assumed similar to European data[28,29]
Cofactor reduction in HIV mortality rate if initiating ART in latent or pre-AIDS stage (ν)	0.27 (0.20 – 0.33)	uniform (min 0.2, max 0.33)	[29]
Cofactor reduction in HIV mortality rate if initiating ART in AIDS stage (ρ)	0.51 (0.39 – 0.62)	uniform (min 0.38, max 0.63)	Assumed 90% reduced efficacy of ART on mortality if initiating at AIDS stage compared to latent stage[30]
Relative HIV injection transmission risk if on NSP only compared to no NSP (RR_{NSP})	0.42 (0.21 – 0.81)	lognormal (mean=-0.42, sd=0.22)	Pooled estimate from higher quality studies in Europe[31]
Relative HIV injection transmission risk if on OAT only compared to no OAT (RR_{OAT})	0.46 (0.31 – 0.68)	lognormal (mean=-0.78, sd=0.19)	[32]
Relative HIV injection transmission risk if on OAT+NSP compared to no OAT or NSP (RR_{BOTH})	product of RR_{NSP} and RR_{OAT}		similar procedures as in[8]
Relative risk of ART discontinuation if on OAT compared to no OAT (ψ_{OAT} and ψ_{BOTH})	0.77 (0.63-0.95)	lognormal (mean=-0.26, sd=0.11)	[10]
Relative increase in ART recruitment if on OAT compared to no OAT (χ_{OAT} and χ_{BOTH})	1.69 (1.32-2.14)	lognormal (mean=0.52, sd=0.12)	[7]
Rate of leaving harm reduction intervention per year (ζ)	0.45 (0.36 –0.54)	uniform (min=0.36, max=0.54)	Assumed similar average duration on OAT as in other lower/middle income settings[33]
Relative risk of fatal opioid overdose if on OAT compared to no OAT (Ψ_{OAT} and Ψ_{BOTH})	0.21 (0.12 – 0.35)	lognormal (mean=-1.57, sd=0.26)	[15]
Relative risk of death within the first four weeks of entering OAT compared to on OAT ($RR_{odonOAT}$)	1.97 (0.93 – 4.00)	lognormal (mean=0.68, sd=0.37)	[15]
Relative risk of death within the first four weeks of exiting OAT compared to off OAT($RR_{odoffOAT}$)	2.38 (1.53 – 3.75)	lognormal (mean=0.87, sd=0.23)	[15]

Figure S1. Model schematics for HIV progression and ART model components among PWID. The model is additionally stratified by the components in Figure S2. All stages are stratified by injecting risk (indicated by superscript i, where i=0 for low risk and 1 for high risk), sex (superscript j, where j=0 for males and 1 for females) and intervention status (indicated by subscript k, where k=0 for off and k=1 for on).

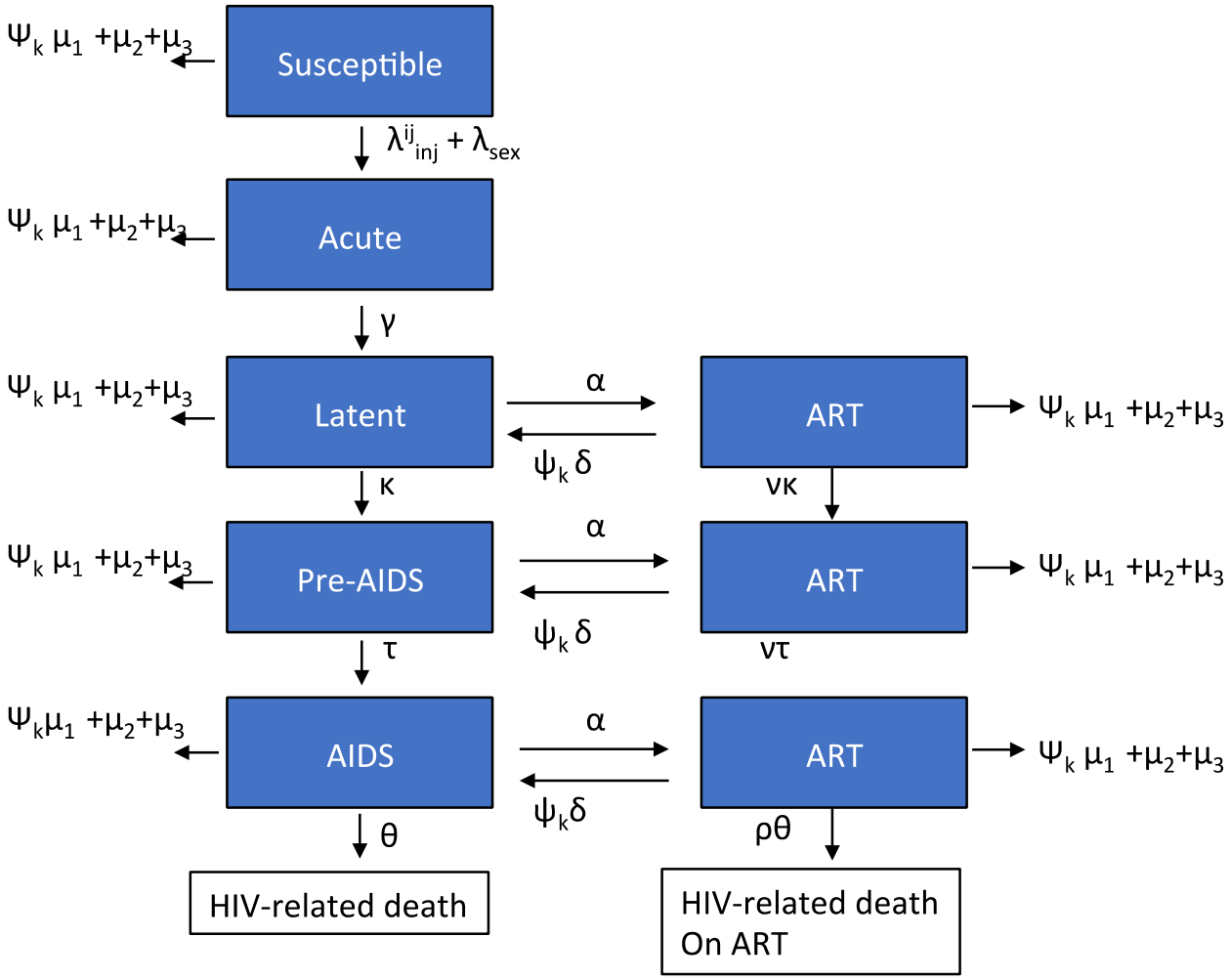


Figure S2. Model schematic for stratification of model based on (A) harm reduction program status and (B) risk. If recruited onto harm reduction with OAT, then a proportion of PWID die when transitioning on and off OAT (see text for details).

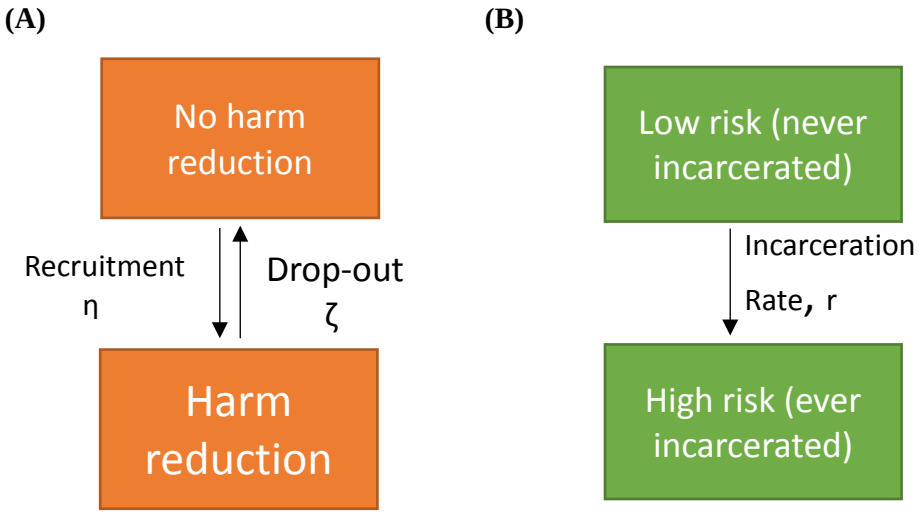


Figure S3: Model projections for the median (solid black line) and 2.5-97.5% (dashed gray lines) intervals for HIV prevalence (A-B) and incidence (C-D) at base-case in Omsk and Ekaterinburg. Black circles are observed data.

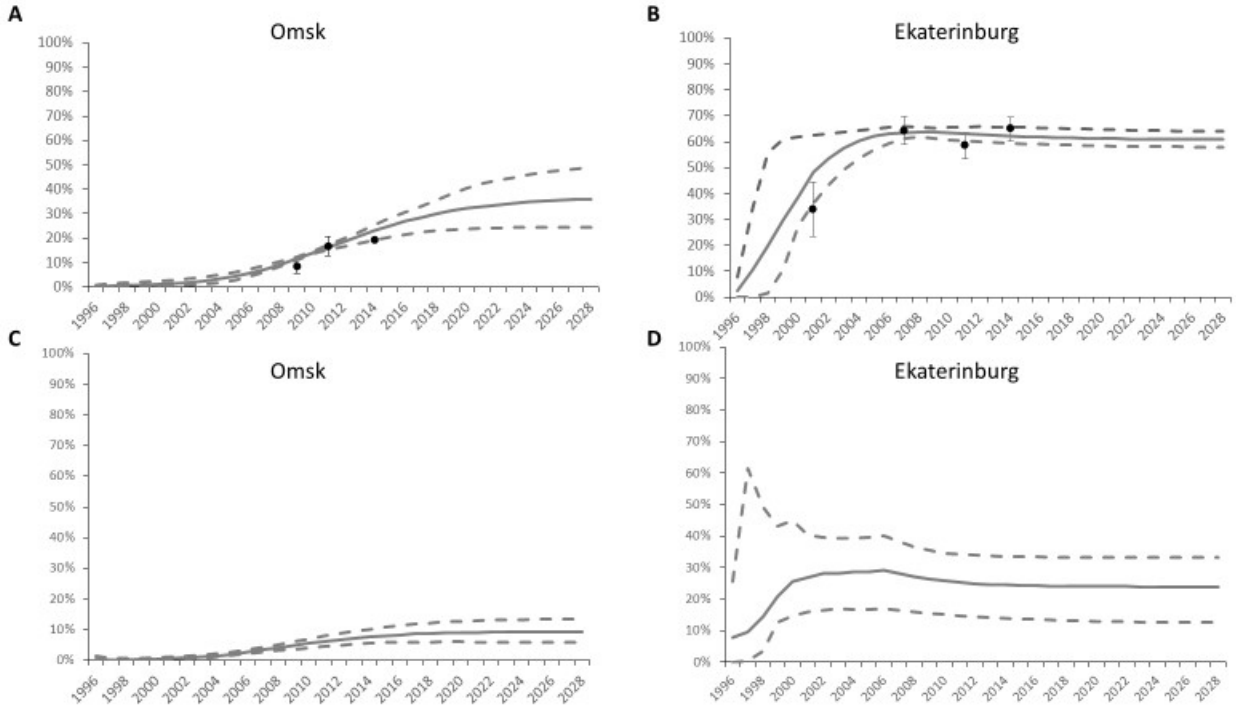
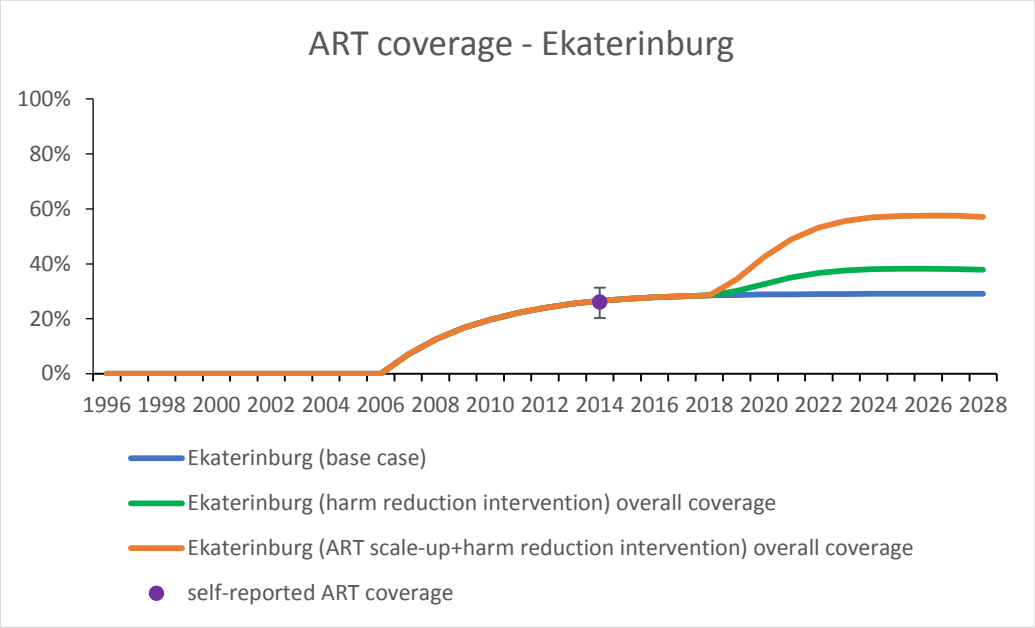


Figure S4: Model projections of median proportion of HIV+ PWID on ART in (A) Ekaterinburg and (B) Omsk.

(A)



(B)

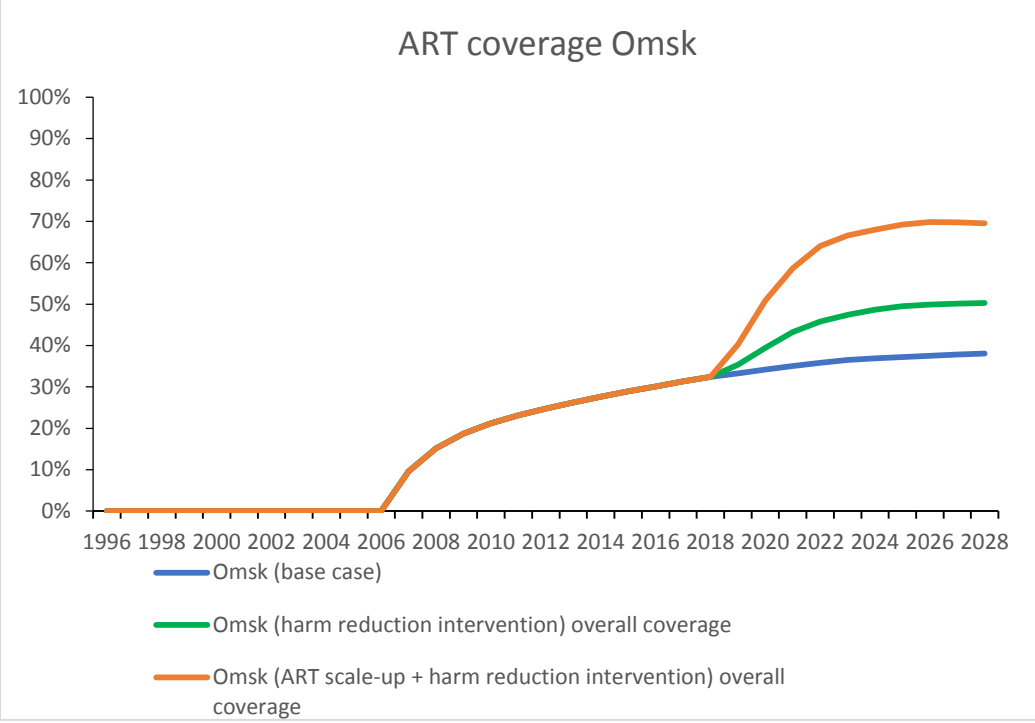


Figure S5: Sensitivity analysis comparing intervention impact between scenarios where all PWID can access harm reduction intervention (A-B) and if 25% of PWID would never access harm reduction intervention (C-D).

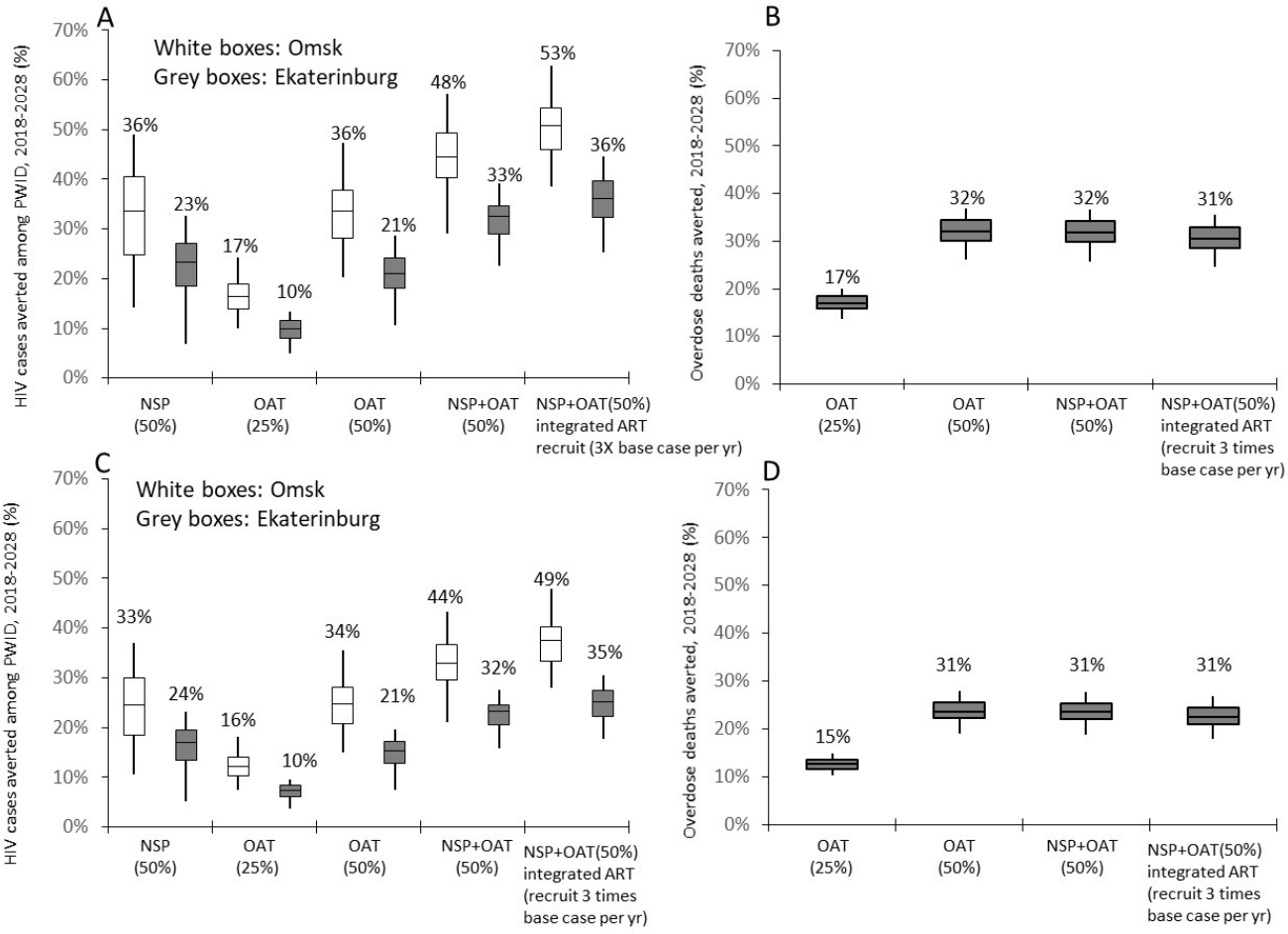
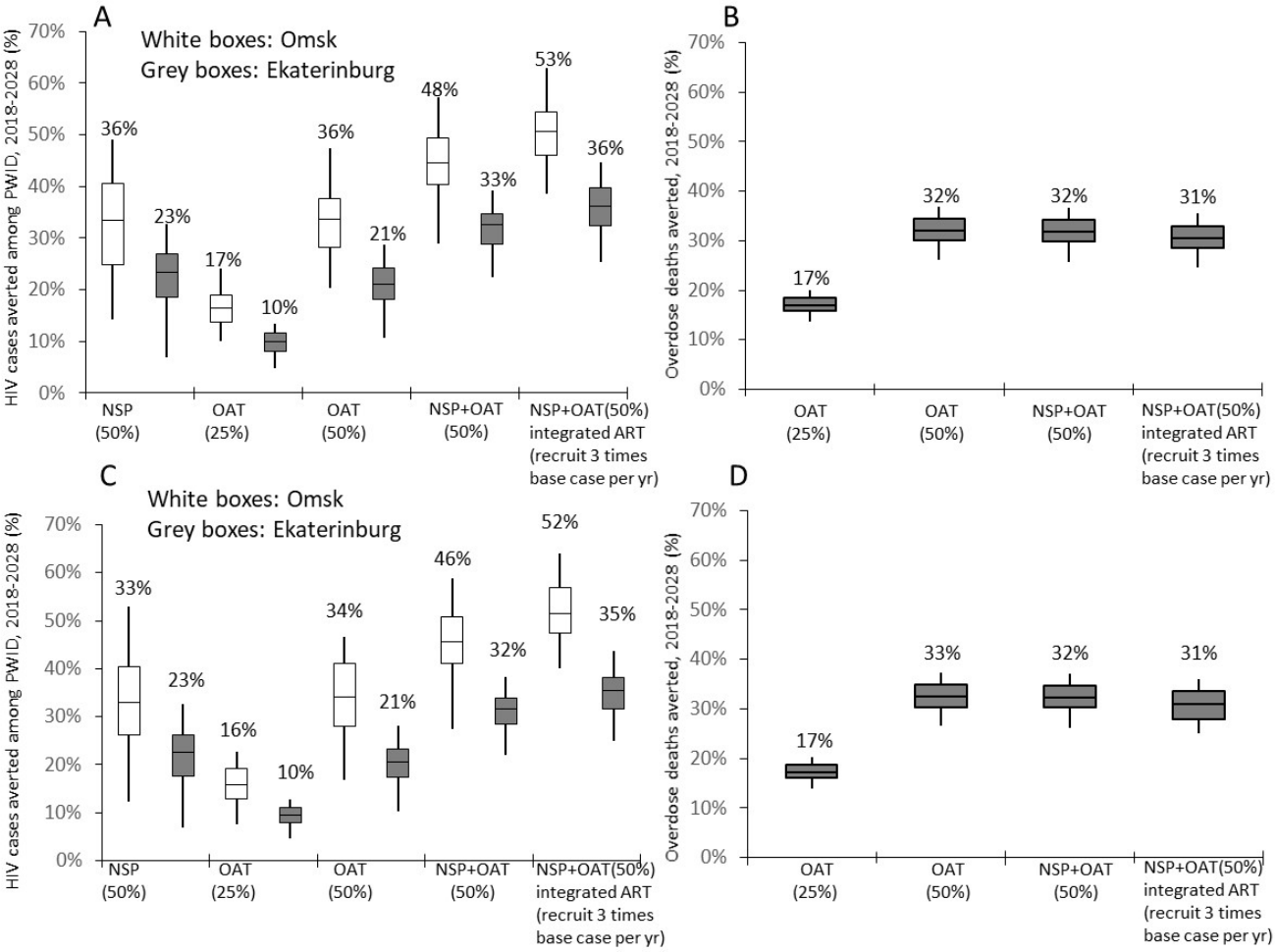


Figure S6: Sensitivity analysis comparing intervention impact between scenarios with a background mortality rate of 2% (A-B) and 0.2% background mortality rate (C-D).



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APPENDIX 5

Additional materials and governance and finance

National health assemblies

Effective governance incorporates institutional mechanisms that facilitate and respond to the input of the people and communities affected by these decisions. This is especially imperative in the case of health governance, which has a direct impact on people's lives and well-being and is integrally related to the economic and social conditions in which people live.

Participatory national health assemblies are potentially transformative vehicles for building broad-based support for health, informing the evolution and functioning of health systems, and creating people-centred health systems. Popular health assemblies are a decades-old innovation, but their salience has increased in recent years as a result of growing grassroots energy on health. In Thailand, the National Health Assembly convenes diverse parties to guide health policy-making, including government, civil society, academic experts, health workers and the private sector. In South Africa, a People's Health Assembly led to a call to action to achieve universal, comprehensive health access.[1]

Although these national assemblies have their greatest impact at country level, where they are able to influence national approaches to health, they also have the potential to have worldwide impact. Together, participatory national assemblies can aid in the emergence of a genuine, people-powered global movement for health, generating new awareness of the critical role of health in the broader development agenda.

Innovative financing for sustainable health

Although normal budgeting processes for domestic financing and international health assistance offer substantial potential for increasing resources for health, they also have inherent limitations, including year-to-year variations in budgeting priorities and uncertainties associated with changing political priorities. Sustainable health requires sustainable, reliable sources of financing. Innovative financing approaches have the potential to unlock major, renewable sources of funding for health programmes at both the global and national levels.

Innovative tax levies can bolster financing for health. These include taxes on alcohol, tobacco or high-sugar beverages, which could generate a new, reliable revenue stream for health programmes and promote healthy behaviours at the same time.[2] [3] More than half of Unitaid's budget derives from a marginal levy on airline tickets, pioneered by France; currently, 10 countries participate in the airline tax scheme, which could generate even greater resources were other countries to join.[4] Special taxes on corporations or high-wealth individuals have generated resources for social development projects in multiple countries.[5] Other potential taxation options for include the collection and earmarking of fees for use of mobile telecommunications.

At the global level, imposition of a marginal tax on financial transactions has long been studied as a possible mechanism for generating funding for global health and development. Proponents of such a tax also argue that it would discourage financial speculation. Although financial transaction taxes exist in several countries, governments in some high-income countries have resisted proposals to levy such a tax. At the global level, a financial transaction tax could help finance new mechanisms to ensure access to medicines and other global health goods.

Where national debt profiles permit, strategic borrowing may support national efforts to build health systems and accelerate progress towards universal health coverage. The Global Fund, for example, is working to leverage blended financing schemes that combine grants and loan buy-downs to generate concessional financing to developing countries for health programmes. Regional development banks can play an especially useful role in expanding financing for health in low- and middle-income countries.

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APPENDIX 6

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