Supplementary material

1. Model of the natural history of HPV-related cervical disease in Kenya

1.1 – Technical details

The modelling framework used in this study has been previously presented.[1,2] This supplementary material outlines key modifications to the model structure. Additional details on the basic model architecture can be found in the supplements by Smit et al.[1,2] Briefly, this is an individual-based model of the entire Kenyan population, simulating births, HIV infection, disease progression and treatment.

Demographic processes, specifically age composition at the start of the model and age-specific fertility and age-and-sex-specific mortality rates were based on data from the United Nations World Population Prospect, accounting for changes over time.[3] Projections from 2018 onwards assume medium variance in fertility and mortality rates.

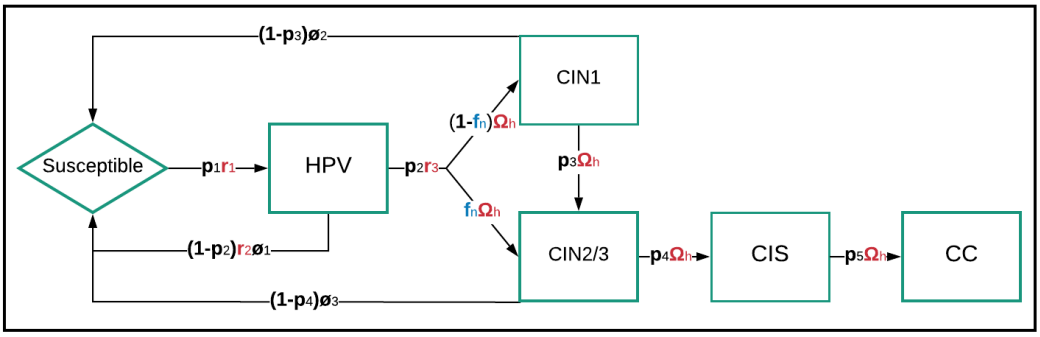
Age-and-sex-specific HIV incidence rates (including paediatric infection) and ART initiation rates by CD4 count were taken from the official UNAIDS (The Joint United Nations Programme on HIV and AIDS) estimates for Kenya, accounting for historic changes in ART eligibility criteria.[4] Parameters for CD4 count at seroconversion, CD4 count progression rates and mortality by CD4 count have been described previously and are based on estimates for Sub-Saharan Africa.[1,5] Projections of the number of new HIV-infections and people starting ART assume that HIV incidence to remains stable at 2017 levels and that ART coverage increases steadily to reach a level of coverage consistent with 90:90:90 targets by 2020.

To simulate invasive cervical cancer disease in Kenya, a validated natural history model of HPV infection and progression through mutually exclusive stages of related cervical disease (i.e. HPV infection, CIN grade 1, CIN grade 2/3, carcinoma in situ (CIS) and CC) was used (Figure) and incorporated into the main model. The model simulates new events of HPV infection among women between 15 and 65 years of age and transition to cervical disease stages probabilistically, while explicitly accounting for differences by HIV status and age.

Perez-Guzman PN, *et al. BMJ Global Health* 2020; 5:e001886. doi: 10.1136/bmjgh-2019-001886

Figure S1. Natural history model of HPV disease and progression to cervical cancer. Transition probabilities and rates vary by age and HIV status, as shown in blue and red annotations, respectively. Spontaneous recovery is possible from HPV and CIN stages.

Abbreviations: human papillomavirus (HPV); cervical intraepithelial neoplasia (CIN); carcinoma in situ (CIS); invasive cervical cancer (CC).



Spontaneous clearance of disease is possible amongst individual with either HPV infection, CIN 1 or CIN 2/3 (Figure S3, blue arrows). Upon clearance, individuals can become re-infected with HPV probabilistically, accounting for their individual risk by age and HIV status. The model assumes no-gained immunity amongst individuals clearing cervical disease, no vaccination coverage, and does not account for distinctions of infection by different HPV genotypes. Finally, the model assumes that women before the age of 26 had a risk of 'instantaneous' transition from HPV infection to CIN 2/3, based on evidence from cohort data showing that a fraction of young women will present high-grade cervical abnormalities shortly after (i.e. <3.3 years) the start of their sexual lives [6].

Four simplifying assumptions of the difference in the natural history of HPV by HIV status were made:

- HIV-positive women had a higher risk of HPV infection,
- HIV-positive women had a lower probability of HPV infection clearance,
- HIV-positive women had a higher risk of progression from CIN 1 to CIN 2/3 lesions
- HIV-positive women on antiretroviral therapy (ART) for 2 or more years were assumed to have the same probabilities and rates of transition than HIV-negative women.

Model parameters (Table S1) including transition probabilities and rates of transition were established by fitting simultaneously to available age- and HIV-specific prevalence of data of HPV (any genotype), related cervical disease, and the standardized incidence rate amongst HIV-positive women compared to HIV-negative women (Table S2). Results of the model fit are presented in the section below.

Table S1. HPV model parameters.

*Where ranges are specified, values were randomly drawn from a uniform distribution. Values represent, as specified, either an individual's overall probability of transitioning from one disease state to another; if applicable, the yearly rate at which such transition will take place; or the risk ratio given pre-existing HIV status compared to no pre-existing HIV status

**Cumulative (lifetime) probability of HPV infection among HIV-negative women.

HPV model parameters			
Parameter	**Description**	**Value***	**Reference**
p	Overall probability *p* of progressing between stages:		
	1. Susceptible to infected**	66%	[7]
	2. HPV to CIN (any grade)	30%	Fitted
	3. CIN 1 to CIN 2/3	50%	[8]
	4. CIN 2/3 to CIS	75%	[8]
	5. CIS to CC	100%	Assumed
r	Risk ratio *r* of transitioning between stages given HIV:		
	1. Susceptible to HPV	1.47	[9]
	2. HPV to susceptible	0.5	[9]
	3. HPV to CIN (any grade)	1.3	[10]
f_n	Probability *f* of transition straight from HPV to CIN 2/3 by HIV status and age *n*:		
	1. Among HIV-negatives <26 years old	7.6%	[11]
	2. Among HIV-positives <26 years old	15%	Assumed
	3. Among women ≥26 years old	0%	Assumed
Ø	Yearly rate of clearance Ø:		
	1. HPV to susceptible	0.2 to 2	Fitted
	2. CIN 1 to susceptible	0.93 to 1.5	[12]
	3. CIN 2/3 to susceptible	0.67 to 2.11	[12]
Ω_h	Yearly rate of progression Ω, depending on HIV status *h.*		
	Regardless of HIV status:		
	1. HPV infection to CIN (any grade)	1 to 5	[12,13]
	Among HIV-negative or HIV-positive on ART for 2+ years:		
	2. CIN1 to CIN 2/3	0.1 to 0.33	[11–13]
	3. CIN 2/3 to CIS	0.0416 to 0.33	Fitted
	4. CIS to CC	0.0125 to 0.33	Fitted
	Among HIV-positive not on ART or on ART for <2 years:		
	5. CIN 1 to CIN 2/3	0.2 to 0.5	[11–13]
	6. CIN 2/3 to CIS	0 to 0.1	Fitted
	7. CIS to CC	0 to 0.02	Fitted

Table S2. Data of HPV-related burden of cervical disease in Kenya.

*Collated through systematic review and meta-analysis, as detailed in Smit et al. 2019 [14]

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; CC, invasive cervical cancer; SIR, standardised incidence ratio; WHIV, women with HIV.

Data	Value (95%CI)		Setting (reference)
	Overall population	HIV-positive women only	
Prevalence of any HPV infection, without cervical abnormalities, by age*:			Kenya [15–20]
- **15 to 24**	0.319 (0.208 to 0.429)	0.696 (0.428 to 0.965)	
- **25 to 29**	0.329 (0.187 to 0.472)	0.643 (0.445 to 0.841)	
- **30 to 34**	0.291 (0.168 to 0.415)	0.582 (0.285 to 0.878)	
- **35 to 39**	0.338 (0.14 to 0.535)	0.6 (0.393 to 0.808)	
- **40 to 65**	0.279 (0.141 to 0.419)	0.56 (0.348 to 0.773)	
Prevalence of CIN 2/3 lesion by age*:			Kenya [15,16,21]
- **15 to 24**	0.039 (0.002 to 0.078	0.033 (0.007 to 0.058)	
- **25 to 29**	0.075 (0.043 to 0.108)	0.133 (0.1 to 0.15)	
- **30 to 34**	0.092 (0.054 to 0.131)	0.084 (0.063 to 0.094)	
- **35 to 39**	0.104 (0.054 to 0.154)	0.086 (0.067 to 0.094)	
- **40 to 65**	0.057 (0.026 to 0.087)	0.082 (0.037 to 0.1)	
CC incidence per 100,000 person-years:		Not available	Kenya [22]
- **15 to 19**			
- **20 to 24**	0.1		
- **25 to 29**	0.6		
- **30 to 34**	2.8		
- **35 to 39**	11.4		
- **40 to 44**	25.0		
- **45 to 49**	62.6		
- **50 to 54**	77.4		
- **55 to 59**	124.5		

- **60 to 64** - **65 to 69** - **70 to 74** - **75 and older**	148.2 150.4 190.7 150.9 122.2		
SIR of CC between WHIV and HIV-negative women	2.3 to 6.6		United States [23,24]

3. Model checks

As detailed in Smit et al. 2019,[14] a number of model checks were carried out to ensure our modelling framework accurately recreated key demographic (Figure S2), HIV-related (Figure S3) and cervical disease-related (Figure S4) processes and epidemiological trends. Please consult the consult supplementary material of Smit et al. 2019 for technical details on this model adaptation and results on the predicted present and future burden of cervical cancer and other non-communicable diseases by HIV status in Kenya.[14]

Figure S2. Comparison of demographic output from the model to United Nations World Prospect (UNWPP)data for Kenya and to data from the Kenyan National Bureau of Statistics (KNBS). Total annual Kenyan population compared to UNWPP from 1050 and 2017 of A) both sexes ; B) women; C) men; Population by age and sex, with extreme in horizontal bars illustrating differences between model and UNWPP in D) 2015; and E) 2035; and F) Annual population projections from 2015 to 2035 compared to KNBS.

Source: UNWPP and KNBS.[3,4]

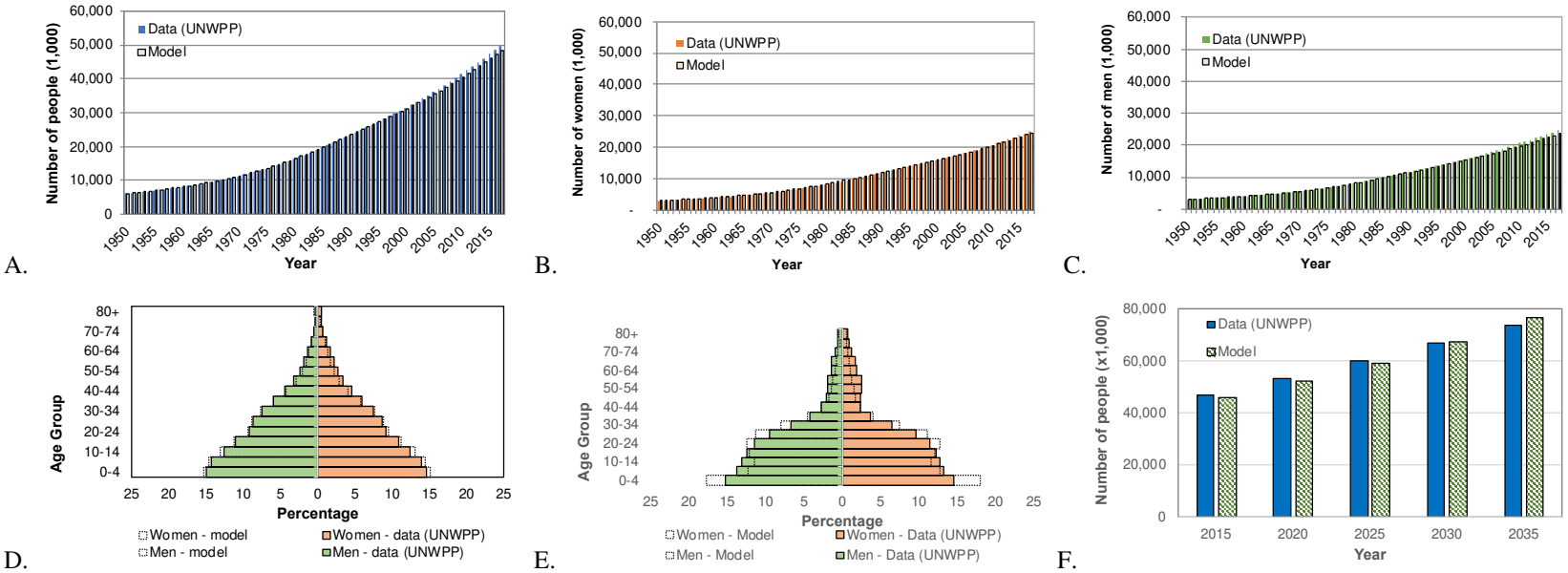
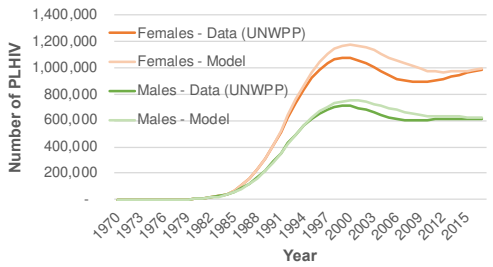
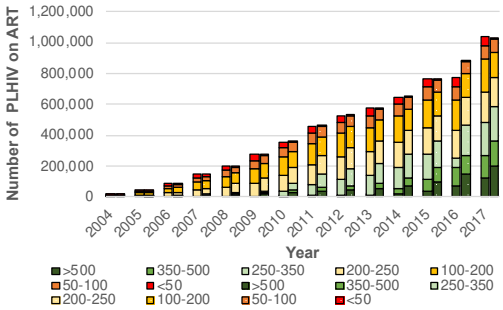


Figure S3. Comparison of HIV related outcomes as generated by the model to UNAIDS data for Kenya. A) Annual number of new infections and B) Annual number of HIV-positive people start treatment by CD4 count.

Source: UNAIDS [4]



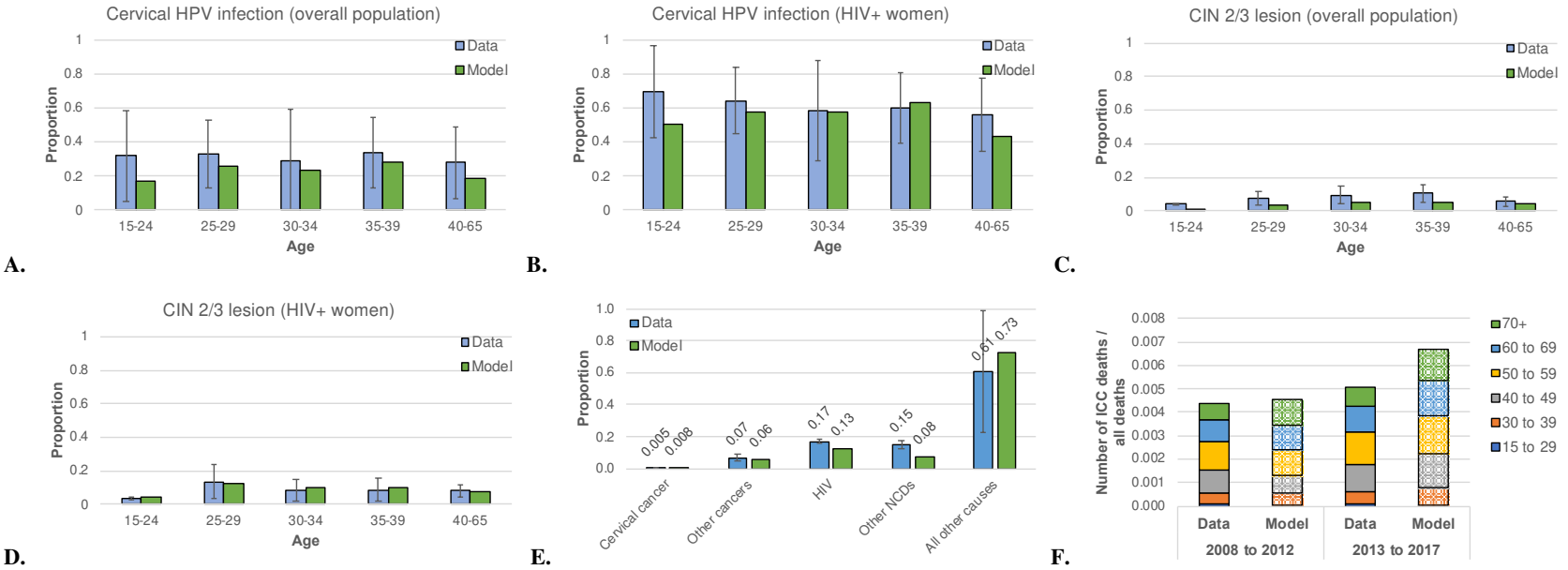
A.

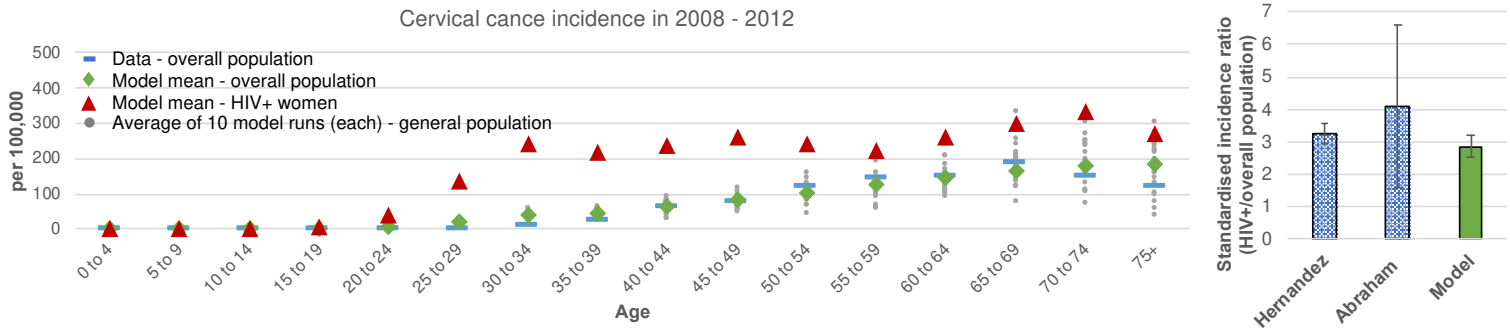


B.

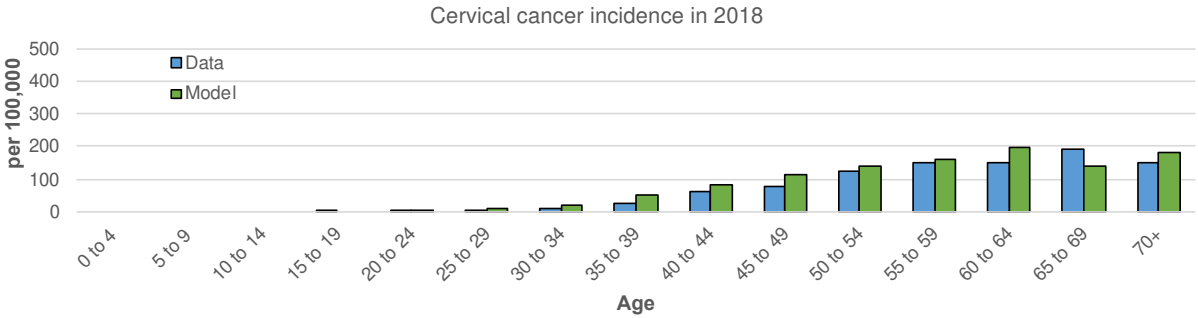
Figure S4. Comparison of cervical disease related outcomes as generated by the model to available data from Kenya.

HPV prevalence in A) the general population in 2001 and B) HIV-positive women in 2006 and prevalence of CIN 2/3 lesions in C) general population in 1997 and D) HIV-positive women in 2013 as collated by the systematic review and meta-analysis; E) Cause-specific mortality in the general population in 2017; F) invasive cervical cancer (CC) mortality compared to GBD estimates for Kenya; G) CC incidence in the overall population and in HIV-positive women from 2008 to 2012 on the left, and standardised incidence rate (mean and 95% CIs) of CC between HIV-positive and negative women compared to American multi-cohort data on the right; I) CC deaths in the overall population from 1990 to 2040. Data sources: for A-D epidemiological studies pooled in original systematic review and meta-analysis, as reported in Smit et al. 2019;[14] for E, F and I estimates for the country from the Global Burden of Disease;[25] also for I and for H, estimates for the country from Globocan;[26,27] for G, CC incidence for 2008 to 2012 corresponds to data from the Nairobi cancer registry for the specified years, as reported in Cancer Incidence in 5 continents version XI,[28] and cancer incidence ratios are as reported in two population-based studies from the United States.[23,24]

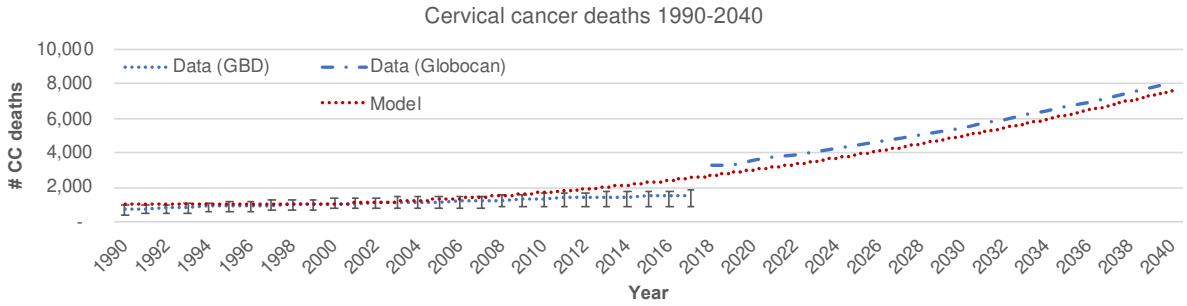



Cervical cance incidence in 2008 - 2012
Data - overall population
Model mean - overall population
Model mean - HIV+ women
Average of 10 model runs (each) - general population
per 100,000
Age
0 to 4
5 to 9
10 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 59
60 to 64
65 to 69
70 to 74
75+
Standardised incidence ratio (HIV+/overall population)
Hernandez
Abraham
Model

G.


Cervical cancer incidence in 2018
Data
Model
per 100,000
Age
0 to 4
5 to 9
10 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 59
60 to 64
65 to 69
70+

H.


Cervical cancer deaths 1990-2040
Data (GBD)
Data (Globocan)
Model
CC deaths
Year

I.

4. Additional results

Below, Table and Table summarise health outcomes and numbers of screening and treatment interventions among WHIV in care in Kenya from 2020 to 2040, as predicted by the model.

Table S3. Predicted health outcomes among WHIV in care in Kenya from 2020 to 2040.

*Predicted SIR of CC between WHIV and HIV-negative women assumes incidence among the latter remains stable at 2008-2012 levels, as per model validation above.

Abbreviations: ASI, age-standardised incidence; CIN, cervical intraepithelial neoplasia; Cryo, cryotherapy; HIV, human immunodeficiency virus; HPV, human papillomavirus; CC, invasive cervical cancer; LEEP, loop excision electrical procedure; SIR, standardised incidence rate; VIA, visual inspection with acetic acid; WHIV, women with HIV.

	Health outcomes	2020 to 2024	2025 to 2029	2030 to 2034	2035 to 2039
Status quo	**HPV prevalence**	54.7%	52.0%	50.0%	48.4%
	CIN 2/3 prevalence	6.9%	5.4%	4.9%	4.4%
	CC cases	15,120	18,643	21,875	30,478
	CC deaths	6,608	9,194	11,860	14,042
	ASI of CC	237	231	228	218
	SIR*	6.3	6.1	6.1	5.8
VIA-Cryo only	**HPV prevalence**	51.3%	46.2%	44.6%	43.4%
	CIN 2/3 prevalence	4.4%	3.4%	3.6%	3.5%
	CC cases	12,135	12,209	13,916	20,066
	CC deaths	6,644	8,216	8,532	9,334
	ASI of CC	195	160	148	143
	SIR*	5.2	4.2	4.0	3.8
VIA-Cryo plus LEEP	**HPV prevalence**	51.5%	46.2%	44.7%	43.5%
	CIN 2/3 prevalence	4.4%	3.5%	3.6%	3.4%
	CC cases	12,452	11,907	13,890	20,187
	CC deaths	6,502	8,354	8,254	8,961
	ASI of CC	201	157	146	144
	SIR*	5.3	4.1	3.9	3.8
DNA-Cryo plus LEEP	**HPV prevalence**	51.2%	45.9%	44.4%	43.2%
	CIN 2/3 prevalence	4.3%	3.3%	3.5%	3.4%
	CC cases	12,379	11,804	13,542	19,574
	CC deaths	6,750	8,350	7,820	8,548
	ASI of CC	197	156	143	141
	SIR*	5.2	4.1	3.8	3.7

Table S4. Predicted screening and treatment outcomes among WHIV in care in Kenya from 2020 to 2040.

All numbers shown are x1,000. Phase I refers to the period from 2020 to 2022 and phase II from 2023 to 2040.

*Refers to number of cryotherapy treatments administered for a false positive screening test result.

**Resfers to number of individuals experiencing adverse effects associated with LEEP treatment (e.g. bleeding, perforation, fistula)

Abbreviations: Av/year, average number per year; CIN, cervical intraepithelial neoplasia; Cryo, cryotherapy; LEEP, loop excision electrical procedure; LTFU, losses to follow-up; VIA, visual inspection with acetic acid.

		Screening tests (x1,000)						**Cryotherapy (x1,000)**					**LEEP (x1,000)**					**LTFU (x1,000)**				
		True +	True -	False +	False -	Total	Av/year	Successful	Failed	Unnecessary*	Total	Av/year	Successful	Failed	Adverse**	Total	Av/year	Screening	LEEP	With CIN2+	Total	Av/year
Phase I	VIA-Cryo only	161	449	232	95	937	312	80	71	232	383	128	-	-	-	-	-	-	-	-	-	-
	VIA-Cryo plus LEEP	146	448	231	86	912	304	48	20	231	299	100	28	7	4	38	12	-	34	34	34	11
	DNA-Cryo plus LEEP	289	314	250	57	910	303	51	15	260	326	109	29	7	4	39	12	228	34	87	261	87
Phase II	VIA-Cryo only	204	5,522	2,857	121	8,704	484	127	75	2,857	3,059	170	-	-	-	-	-	-	-	-	-	-
	VIA-Cryo plus LEEP	215	5,526	2,856	128	8,725	485	109	47	2,856	3,011	167	23	6	3	32	2	-	28	28	28	2
	DNA-Cryo plus LEEP	920	4,216	3,353	181	8,670	482	116	35	2,997	3,147	175	23	6	3	31	2	2,165	27	110	2,193	122

5. Sensitivity analyses

Reduced losses to follow-up and/or enhanced screening technologies for same-visit screening and treatment

We assessed the effect of reducing the probabilities of loss to follow-up on predicted health outcomes of the *DNA-Cryo plus LEEP* scenario. Baseline probabilities were of 25% during screening with HPV-DNA and of 49% from screening to treatment with LEEP, if required, as informed by in-country reports from CC screening and treatment programmes. We first adjusted these probabilities, to 0% and 49%, respectively, to simulate the adoption of enhanced technologies for either same-visit screening and treatment with HPV DNA or VIA with enhanced sensitivity to that of HPV DNA. We then set the probabilities of LTFU to 0% and 24.5%, respectively, to simulate both programmatic efforts to minimise LTFU from screening to LEEP alongside the adoption of enhanced technologies. Both of such enhanced technologies have been reported to be successfully used in SSA settings in recent years.[7–13][7–12][29–31] Lastly, we reduced both probabilities by 50% (i.e. to 12.5% and 24.5%, respectively), to simulate programmatic efforts to minimise LTFU without the adoption of said enhanced technologies.

Three-yearly screening during phase II

We explored the potential effect of spacing out the intervals of CC re-screening in phase II from yearly to 3-yearly in both health outcomes and screening and treatment outcomes. While national guidelines currently in place in Kenya recommend the former interval, WHO guidelines state 3-yearly screening with HPV-DNA is appropriate, even among WHIV.

Increased coverage

We explored the impact of increasing target yearly CC screening coverage from 70% to 100%, of the 87% willing to undergo screening, on our outcomes of interest in both health outcomes and screening and treatment outcomes. We considered this scenario as potentially attainable in the long term, as the population of WHIV in care are, by definition, regularly accessing care.

'Improved' vs 'worsened' HIV epidemic from 2020 to 2040

As detailed in the main manuscript, our modelled scenarios assumed HIV incidence to remain constant at 2017 levels and ART coverage to increase steadily to achieve the 90:90:90 goals by 2020, remaining steady at 90% thereon. We explored deviations from these assumptions in two scenarios, one with an 'improved and another with a 'worsened' HIV epidemic. For the former, we linearly decreased HIV incidence by 10% from 2020 to 2040, compared to 2017 levels, and increased ART coverage to 95%. For the 'worsened' scenario, we increased HIV by 10% and decreased ART coverage by 5%, correspondingly.

Of note, we did not change baseline intervention parameters of LFU, re-screening interval or target coverage. Moreover, there was only a marginal change in the predicted target population (i.e. those aged 18 to 65) by 2040, from 1.57 million in the baseline scenario used for sensitivity analyses (i.e. *DNA-Cryo plus LEEP*) to 1.45 in the *improved epidemic* scenario and 1.61 in the *worsened epidemic* scenario. We therefore do not present screening and treatment outcomes, as these were proportional deviations from the baseline predictions above.

Table S5. Predicted health outcomes of sensitivity analyses.

*Predicted SIR of CC between WHIV and HIV-negative women assumes incidence among the latter remains stable at 2008-2012 levels, as per model validation above.

Abbreviations: ASI, age-standardised incidence; CIN, cervical intraepithelial neoplasia; Cryo, cryotherapy; HIV, human immunodeficiency virus; HPV, human papillomavirus; CC, invasive cervical cancer; LEEP, loop excision electrical procedure; LTFU, losses to follow-up; SIR, standardised incidence rate; VIA, visual inspection with acetic acid; WHIV, women with HIV.

	Health outcomes	2020 to 2024	2025 to 2029	2030 to 2034	2035 to 2039
Enhanced technologies + reduced LTFU to LEEP	**HPV prevalence**	49.4%	42.5%	41.3%	40.5%
	CIN 2/3 prevalence	3.2%	2.4%	2.9%	3.0%
	CC cases	9,897	7,195	8,377	13,201
	CC deaths	6,210	6,001	5,536	5,902
	ASI of CC	168	100	90	93
	SIR*	4.4	2.7	2.4	2.4
Reduced LTFU only (12.5% and 24.5%)	**HPV prevalence**	50.3%	43.3%	41.7%	40.7%
	CIN 2/3 prevalence	3.2%	2.4%	2.9%	3.0%
	CC cases	11,369	8,247	9,297	14,166
	CC deaths	6,451	7,172	6,062	6,506
	ASI of CC	175	113	100	99
	SIR*	4.7	3.0	2.6	2.6
Enhanced technologies only	**HPV prevalence**	50.2%	43.2%	41.7%	40.8%
	CIN 2/3 prevalence	3.3%	2.5%	2.9%	3.0%
	CC cases	11,392	8,099	9,365	14,034
	CC deaths	6,678	8,074	6,796	6,258
	ASI of CC	186	114	102	99
	SIR*	5.0	3.0	2.7	2.6
Re-screening at 3-yearly intervals (phase II)	**HPV prevalence**	51.2%	45.9%	44.4%	43.2%
	CIN 2/3 prevalence	4.3%	3.4%	3.5%	3.4%
	CC cases	12,427	11,722	13,870	19,662
	CC deaths	6,587	8,314	8,398	8,886
	ASI of CC	199	155	146	140

	SIR*	5.4	4.1	3.9	3.7
100% of 'willing' WHIV target coverage	**HPV prevalence**	51.2%	46.0%	44.5%	43.3%
	CIN 2/3 prevalence	4.3%	3.4%	3.6%	3.5%
	CC cases	12,095	11,957	13,677	19,858
	CC deaths	6,429	8,326	8,513	8,929
	ASI of CC	195	157	145	142
	SIR*	5.1	4.2	3.9	3.7
Improved HIV epidemic	**HPV prevalence**	51.6%	46.4%	45.0%	43.8%
	CIN 2/3 prevalence	4.3%	3.4%	3.6%	3.5%
	CC cases	12,291	11,715	13,759	19,250
	CC deaths	6,264	8,155	8,326	8,842
	ASI of CC	200	157	150	140
	SIR*	5.3	4.2	4.0	3.7
Worsened HIV epidemic	**HPV prevalence**	51.2%	45.7%	44.2%	42.9%
	CIN 2/3 prevalence	4.2%	3.3%	3.4%	3.4%
	CC cases	12,383	11,843	13,493	20,187
	CC deaths	6,581	8,291	8,509	9,261
	ASI of CC	197	157	142	143
	SIR*	5.2	4.2	3.8	3.8

Table S6. Predicted screening and treatment outcomes in sensitivity analyses.

All numbers shown are x1,000. Phase I refers to the period from 2020 to 2022 and phase II from 2023 to 2040.

*Refers to number of cryotherapy treatments administered for a false positive screening test result.

**Resfers to number of individuals experiencing adverse effects associated with LEEP treatment (e.g. bleeding, perforation, fistula)

Abbreviations: Av/year, average number per year; CIN, cervical intraepithelial neoplasia; Cryo, cryotherapy; LEEP, loop excision electrical procedure; LTFU, reduced losses to follow-up; Tec, enhanced technologies; VIA, visual inspection with acetic acid.

		Screening tests						**Cryotherapy**					**LEEP**					**LFU***				
		True +	True -	False +	False -	Total	Av/year	Successful	Failed	Unnecessary	Total	Av/year	Successful	Failed	Adverse	Total	Av/year	Screening	LEEP	With CIN2+	Total	Av/year
Phase I	Tec+ LTFU	299	350	279	59	987	329	69	21	380	469	156	58	14	7	80	24	-	23	23	23	8
	LTFU	295	336	266	58	955	318	60	18	319	397	132	50	13	6	69	21	119	21	48	139	46
	Tec	296	343	273	58	970	323	69	21	373	463	154	38	10	5	48	16	-	46	46	46	15
	3-y	288	314	250	56	909	303	50	15	259	325	108	28	7	3	35	12	227	34	88	261	87
	100%	311	345	273	62	992	331	54	16	283	354	118	31	7	4	42	13	248	36	94	284	95
Phase II	Tec+ LTFU	966	4,669	3,713	190	9,537	530	166	50	4,395	4,611	256	39	10	5	54	3	-	16	16	16	1
	Tec	1,006	4,619	3,674	197	9,497	528	166	49	4,351	4,567	254	44	11	6	55	3	-	53	53	53	3
	LTFU	931	4,468	3,556	183	9,137	508	139	42	3,691	3,872	215	31	8	4	43	2	1,141	12	52	1,153	64
	3-y	919	4,211	3,349	180	8,659	481	115	35	2,990	3,140	174	23	6	3	29	2	2,166	28	111	2,194	122
	100%	908	4,435	3,526	178	9,046	503	110	32	3,131	3,273	182	21	5	3	28	1	2,262	25	101	2,286	127

6. STRESS guidelines checklist

To ensure transparency and reproducibility of our modelling analyses, we adhered to recommendations from the *Strengthening the reporting of empirical simulation studies: Introducing the STRESS guidelines*.[32] Table below key items specified from these guidelines for agent-based simulations.

Table S7. STRESS-ABS guidelines checklist.

Abbreviations: ABS, agent-based simulation; CC, cervical cancer; CD4, CD4+ T lymphocites; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; LTFU, losses to follow-up; NA, not applicable; SSA, Sub-Saharan Africa; STRESS, Strengthening the reporting of empirical simulation studies; UNAIDS, Joint United Nations Programme on HIV and AIDS; UNWPP, United Nations World Population Prospects.

Item	Comment	Relevant figures or tables
Purpose of the model	The purpose of this model was to provide a robust demographic and epidemiologic framework capable of representing the whole population of a Sub-Saharan country and its age-and-HIV related burden of HPV-related cervical disease. The model was used to quantify the real-world potential impact of different CC screening and treatment options, and explore key CC screening and treatment option variables that could affect the overall impact on health outcomes and resource needs the health system will need to account for.	NA
Model outputs	• Age-and-HIV specific prevalence of HPV cervical infection, CIN 2/3 lesions, CC incidence (only age-specific for the overall population) and standardised incidence ratio of CC by HIV status. • Demographic composition of the Kenyan population and their HIV epidemic. • Overall and, for the case of CC, age-specific mortality. • CC outcomes: number of cases, deaths and age-standardised incidence from 2020 to 2040. • Care engagement: number of individuals screened, treated and cured (from CIN) from 2020 to 2040. • Number of screening tests performed, treatment interventions administered and LTFU.	Figures S2 to S4 and Tables S3 to S6
Experimentation aims	The model performed a scenario-based analysis: • VIA-Cryo only: where screening was done with VIA and, for those with a positive test, treatment with Cryo. VIA and Cryo were performed on the same visit and used pragmatically (i.e. regardless of Cryo-eligible or not), as the only technologies available • VIA-Cryo plus LEEP: where, added to the above, LEEP was	Figure 1B (main manuscript)

	available for individuals with Cryo-ineligible lesions, which was assumed to need referral to a specialised clinic • HPV-DNA-Cryo plus LEEP: where screening was done with HPV-DNA testing, which was assumed to require two visits (i.e. one for testing and another to collect results). Cryo was performed at collection of results on women who tested positive with HPV-DNA and were Cryo-eligible. LEEP was available for Cryo-ineligible lesions, upon referral to a specialised clinic • Enhanced technologies: where testing was assumed to be done with either same-day HPV-DNA testing or digitally enhanced VIA (with increased sensitivity to that of HPV-DNA testing). Treatment was performed with either Cryo during the same visit or LEEP upon referral, given Cryo-eligibility	
Model and scenarios logic, and algorithms	Model and scenarios logic are described in the main manuscript in text and figures. Briefly, the base model simulated probabilistically key stages of the natural history of HPV cervical infection and progression through to CC. Model parameters were drawn from the literature, were available, or calibrated by exploring plausible ranges and fitting simultaneously to available Kenyan epidemiological data. Simulated scenarios adhere to Kenyan guidelines for CC screening and treatment among WHIV, as described above.	Figures 1A (main manuscript), S1, and Tables S1 and S2
Components	The model recreates the entire Kenyan population from 1950 to 2017 at the national level (i.e. without geographic distinction). Each agent is an individual, with the population being modelled at a fraction of 1/100 of the actual size, entering the model at birth and followed through to death. Demographic events (e.g. births and deaths) are assigned probabilistically, based on age-specific fertility and age-and-sex-specific mortality rates for Kenya, as reported by UNWPP, and accounting for changes over time. HIV-related events (e.g. HIV-infection, including paediatric infections), and access to antiretroviral therapy (ART), accounting for historic changes in CD4 eligibility, are also simulated probabilistically based on data from UNAIDS for Kenya. CD4 count at seroconversion, disease progression and mortality are based on modelling estimates for SSA. HPV-related cervical diseases states for females are modelled as described above. Each demographic and disease-state attribute is recorded for each individual and analysed at the end of the simulation in 2040. Forward projections from 2017 to 2040 assume: a UNWPP medium variant in fertility and mortality; that HIV incidence remains stable at 2017 levels; that ART coverage reached UNAIDS 90:90:90 targets by 2020 and remains stable thereafter.	NA
Data sources	Domain (references): • Demography [3,4] • HIV epidemic and access to ART [4]	Table S2

	• HIV disease progression and mortality [33] • HPV-related cervical disease • Cause specific mortality [25] As detailed in section 1 of this supplement, data on the HPV-related cervical disease in Kenya was collated through an original systematic review and meta-analysis with random effects model. No further pre-processing of the data was carried out.	
Input parameters	Input parameters for demography were as described above. For the natural history of HPV-related cervical disease and the scenarios modelled, parameters were drawn from the literature and are summarised in tables above.	Tables S1 and S2

Assumptions	Specific assumptions on the natural history model of HPV-related cervical disease are discussed in the main manuscript. Briefly:
	• New HPV infections occur between the ages of 15 and 65
	• All females are assumed to be susceptible to HPV (i.e. no baseline immunity, natural or acquired), even when they recover from an HPV infection event or CIN stage
	• Compared to HIV-negative women, WHIV are assumed to have:
	  • Higher risk of HPV infection
	  • Lower probability of recovering from HPV infection
	  • Higher risk of progression from HPV to CIN stages
	  • Conversely, if on ART for 2+ years, WHIV were assumed to have the same natural history of disease as HIV negatives
		NA

Initialisation	The model starts in 1950, by recreating the Kenyan population as per UNWPP estimates for the country. From 1950 to 2017, model outputs were compared yearly against UNWPP estimates and, for the case of HIV, this was done from 1970 to 2017 against UNAIDS data.	NA
Run length	The model runs from 1950 to 2040.	
Estimation approach	The model is stochastic. All outcomes were analysed drawing the mean from 100 model runs for each output for each one of the scenarios and sensitivity analyses described above.	NA
Programming language and software	The model was programmed using C++ language in the Mac free-access software Xcode Version 8.3.3	NA

Random sampling	Random numbers were generated using the standard C++ library. Integers used the function
	RandomMinMax(int min, int max);
	
	Doubles used the function
	randfrom(double min, double max){
	  double range = (max - min);
	  double div = RAND_MAX / range;
	  return min + (rand() / div);
	}
		NA

Model execution	The model is object orientated. The timeframe resolution is of a month.	NA
System specification	The model was run on a MacBook Air with macOS Sierra 10.12.6, 1.6 GHz Intel Core i5 processor, 4GB 1600 MHz DDR3 memory.	NA
Computer model sharing statement	Upon request, the model code can be accessed through an online repository.	NA

References

1 Smit M, Olney J, Ford NP, *et al.* The growing burden of non-communicable disease among persons living with HIV in Zimbabwe. *Aids* 2018;**0**:1. doi:10.1097/QAD.0000000000001754

2 Smit M, Perez-Guzman PN, Mutai KK, *et al.* Mapping the current and future non-communicable disease burden in Kenya by HIV status: a modelling study. *Clin Infect Dis* Published Online First: 2019. doi:10.1093/cid/ciz1103

3 United Nations, Department of Economic and Social Affairs PD. World Population Prospects - Population Division - United Nations. 2017.

4 AIDSinfo | UNAIDS. 2016.http://aidsinfo.unaids.org/

5 Mangal TD. Joint estimation of CD4+ cell progression and survival in untreated individuals with HIV-1 infection. *Aids* 2017;**31**:1073–82. doi:10.1097/QAD.0000000000001437

6 Rodriguez AC, Burk R, Herrero R, *et al.* The natural history of human papillomavirus infection and cervical intraepithelial neoplasia among young women in the Guanacaste cohort shortly after initiation of sexual life. *Sexually Transmitted Diseases* 2007;**34**:494–502. doi:10.1097/01.olq.0000251241.03088.a0

7 Chesson HW, Dunne EF, Hariri S, *et al.* The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sex Transm Dis* 2014;**41**:660–4. doi:10.1097/OLQ.0000000000000193

8 Goldie SJ, Kuhn L, Denny L, *et al.* Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. *JAMA* 2001;**285**:3107–15. doi:10.1001/jama.285.24.3107

9 Looker KJ, Rönn MM, Brock PM, *et al.* Evidence of synergistic relationships between HIV and Human Papillomavirus (HPV): systematic reviews and meta-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. *J Int AIDS Soc* 2018;**21**:e25110. doi:10.1002/jia2.25110

10 Liu G, Sharma M, Tan N, *et al.* HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *AIDS* 2018;**32**:795. doi:10.1097/QAD.0000000000001765

11 Rodriguez AC, Burk R, Herrero R, *et al.* The natural history of human papillomavirus infection and cervical intraepithelial neoplasia among young women in the Guanacaste cohort shortly after initiation of sexual life. *Sex Transm Dis* 2007;**34**:494–502. doi:10.1097/01.olq.0000251241.03088.a0

12 Schlecht NF, Platt RW, Duarte-Franco E, *et al.* Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. *J Natl Cancer Inst* 2003;**95**:1336–43. doi:10.1093/jnci/djg037

13 Castle PE, Rodríguez AC, Burk RD, *et al.* Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study. *BMJ* 2009;**339**:b2569. doi:10.1136/bmj.b2569

14 Smit M, Perez-Guzman PN, Mutai KK, *et al.* Mapping the current and future non-communicable disease burden in Kenya by HIV status: a modelling study. *In review* 2019.

15 Temmerman M, Tyndall MW, Kidula N, *et al.* Risk factors for human papillomavirus and cervical precancerous lesions, and the role of concurrent HIV-1 infection. *Int J Gynaecol Obstet* 1999;**65**:171–81. doi:10.1016/s0020-7292(99)00043-0

16 De Vuyst H, Steyaert S, Van Renterghem L, *et al.* Distribution of human papillomavirus in a family planning population in nairobi, kenya. *Sex Transm Dis* 2003;**30**:137–42.

17 Yamada R, Sasagawa T, Kirumbi LW, *et al.* Human papillomavirus infection and cervical abnormalities in Nairobi, Kenya, an area with a high prevalence of human immunodeficiency virus infection. *J Med Virol* 2008;**80**:847–55. doi:10.1002/jmv.21170

18 Luque AE, Hitti J, Mwachari C, *et al.* Prevalence of human papillomavirus genotypes in HIV-1-infected women in Seattle, USA and Nairobi, Kenya: results from the Women's HIV Interdisciplinary Network (WHIN). *Int J Infect Dis* 2010;**14**:e810-814. doi:10.1016/j.ijid.2010.03.016

19 De Vuyst H, Parisi MR, Karani A, *et al.* The prevalence of human papillomavirus infection in Mombasa, Kenya. *Cancer Causes Control* 2010;**21**:2309–13. doi:10.1007/s10552-010-9645-z

20 De Vuyst H, Mugo NR, Chung MH, *et al.* Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. *Br J Cancer* 2012;**107**:1624–30. doi:10.1038/bjc.2012.441

21 Greene SA, Vuyst HD, John-Stewart GC, *et al.* Effect of Cryotherapy vs Loop Electrosurgical Excision Procedure on Cervical Disease Recurrence Among Women With HIV and High-Grade Cervical Lesions in Kenya: A Randomized Clinical Trial. *JAMA* 2019;**322**:1570–9. doi:10.1001/jama.2019.14969

22 Bray F, Colombert M, Mery L, *et al.* Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. 2017.http://ci5.iarc.fr/CI5-XI/Default.aspx (accessed 2 Sep 2019).

23 Abraham AG, D'Souza G, Jing Y, *et al.* Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. *J Acquir Immune Defic Syndr* 2013;**62**:405–13. doi:10.1097/QAI.0b013e31828177d7

24 Hernández-Ramírez RU, Shiels MS, Dubrow R, *et al.* Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV* 2017;**4**:e495–504. doi:10.1016/S2352-3018(17)30125-X

25 Institute for Health Metrics and Evaluation. Global Burden of Disease - Kenya (2017). 2017.

26 Globocan. Cancer tomorrow. http://gco.iarc.fr/tomorrow/home (accessed 13 Nov 2019).

27 Globocan. Cancer today. http://gco.iarc.fr/today/home (accessed 20 Sep 2019).

28 Bray F, Colombet M, Mery L, *et al.* Cancer incidence in five continents, volume XI. Lyon: 2017.

29 Parham GP, Mwanahamuntu MH, Kapambwe S, *et al.* Population-Level Scale-Up of Cervical Cancer Prevention Services in a Low-Resource Setting: Development, Implementation, and Evaluation of the Cervical Cancer Prevention Program in Zambia. *PLOS ONE* 2015;**10**:e0122169. doi:10.1371/journal.pone.0122169

30 Vassilakos P, De Vuyst H, Combescure C, *et al.* A Smartphone-Based Approach for Triage of Human Papillomavirus-Positive Sub-Saharan African Women: A Prospective Study. *JMIR mHealth and uHealth* 2017;**5**:e72. doi:10.2196/mhealth.6697

31 Umulisa MC, Franceschi S, Baussano I, *et al.* Evaluation of human-papillomavirus testing and visual inspection for cervical cancer screening in Rwanda. *BMC Women's Health* 2018;**18**:1–8. doi:10.1186/s12905-018-0549-5

32 Monks T, Currie CSM, Onggo BS, *et al.* Strengthening the reporting of empirical simulation studies: Introducing the STRESS guidelines. *Journal of Simulation* 2019;**13**:55–67. doi:10.1080/17477778.2018.1442155

33 Mangal TD. Joint estimation of CD4+ cell progression and survival in untreated individuals with HIV-1 infection. *Aids* 2017;**31**:1073–82. doi:10.1097/QAD.0000000000001437

34 Temmerman M, Tyndall MW, Kidula N, *et al.* Risk factors for human papillomavirus and cervical precancerous lesions, and the role of concurrent HIV-1 infection. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 1999;**65**:171–81.

35 H. DV, S. S, L. VR, *et al.* Distribution of human papillomavirus in a family planning population in Nairobi, Kenya. *Sexually Transmitted Diseases* 2003;**30**:137–42. doi:http://dx.doi.org/10.1097/00007435-200302000-00009

36 R. Y, T. S, L.W. K, *et al.* Human papillomavirus infection and cervical abnormalities in Nairobi, Kenya, an area with a high prevalence of human immunodeficiency virus infection. *Journal of Medical Virology* 2008;**80**:847–55. doi:http://dx.doi.org/10.1002/jmv.21170

37 Luque AE, Hitti J, Mwachari C, *et al.* Prevalence of human papillomavirus genotypes in HIV-1-infected women in Seattle, USA and Nairobi, Kenya: Results from the Women's HIV Interdisciplinary Network (WHIN). *International Journal of Infectious Diseases* 2010;**14**:e810–4. doi:10.1016/j.ijid.2010.03.016

38 De Vuyst H, Rita M, Andrew P. The prevalence of human papillomavirus infection in Mombasa , Kenya. *Cancer Causes and Control* 2010;**21**:2309–13. doi:10.1007/s10552-010-9645-z

39 De Vuyst H, Mugo NR, Chung MH, *et al.* Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. *British Journal of Cancer* 2012;**107**:1624–30. doi:10.1038/bjc.2012.441

40 de Vuyst H, Steyaert S, Renterghem LVAN, *et al.* Distribution of human papillomavirus in a family planning population in Nairobi , Kenya. *Sexually Transmitted Diseases* 2003;**30**:137–42.

41 Greene SA, De Vuyst H, John-Stewart GC, *et al.* Effect of cryotherapy vs loop electrosurgical excision procedure (LEEP) on cervical disease recurrence among women with HIV and high-grade cervical lesions in Kenya: a randomized clinical trial. *In review* 2019.

42 Hernández-Ramírez RU, Shiels MS, Dubrow R, *et al.* Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *The Lancet HIV* 2017;**4**:e495–504. doi:10.1016/S2352-3018(17)30125-X

43 Abraham A, Strickler H, Jing Y, *et al.* Invasive cervical cancer risk among HIV-infected women: A North American multi-cohort collaboration prospective study. *Journal of Acquired Immune Deficiency Syndromes* 2013;**62**:405–13. doi:10.1097/QAI.0b013e31828177d7.Invasive