1 HIV Viral Load Working Group

The investigators who contributed HIV-1 plasma RNA viral load (VL) data to this project are listed in Table 1. The data include VL measurements from 25 studies of 44 sub-cohorts across the 7 geographic regions of North America, Europe, Asia, South America, West Africa, East Africa, and Southern Africa. The data reflect a total of 71,668 VL measurements from 17 different countries.

Table S1.1: HIV Viral Load Working Group.

Site by country	Investigators	Institution	City, Country
Burkina Faso	Nicolas Nagot, Helen A Weiss, Philippe Mayaud,Philippe Van de Perre,for the ANRS 1285 Study Group	Centre Muraz, LSHTM & University of Montpellier	Bobo-Dioulasso, Burkina Faso; London, UK; Montpellier, France
Denmark	Nicolai Lohse and Niels Obel for the Danish HIV Cohort Study	Aarhus University Hospital and Copenhagen University Hospital Rigshospitalet	Aarhus and Copenhagen, Denmark
India	Amita Gupta,Ramesh S. Paranjape,Madhuri Thakar,Nikhil Gupte,,Robert Bollinger	National AIDS Research Institute & the BJ Medical College; Johns Hopkins School of Medicine	Pune, India; Baltimore, USA
Kenya	Jared Baeten, Julie Overbaugh,Kishorchandra Mandaliya	UW & FHCRC Coast Provincial General Hospital	Seattle, USA; Mombasa, Kenya
	Grace John Stewart, Phelgona Otieno,, Julie Overbaugh, Dorothy Mbori-Ngacha	University of Nairobi & UW	Nairobi, Kenya; Seattle, USA
Malawi	James Kublin, Padmaja Patnaik, Irving Hoffman, Bill Miller Charles Jere, Richard Pendame, Terrie Taylor, Malcolm Molyneux	University of Malawi & UW UNC & Family Health International	Blantyre, Malawi; Seattle, USA; Chapel Hill, Research Triangle Park, USA
Malawi, Tanzania, Zambia	Taha Taha, Lynda Emel, Tom Fleming, Elizabeth Brown, Anthony Mwatha, Lei Wang, Moses Sinkala, George Kafulafula, Gernard Msamanga, Megan Valentine, Robert Goldenberg for HPTN 024 Team	SCHARP Malawi College of Medicine Lilongwe Clinical Research Muhimbili Univ., Muhimbili Med. Ctr. Centre for Infectious Disease Research in Zambia Family Health International	Seattle, USA; Blantyre, Malawi Lilongwe, Malawi; Dar es Salaam, Tanzania ; Lusaka, Zambia
	Aldo Lucchetti, Rosario Zuñiga, Jorge Sanchez	IMPACTA CTU	Lima, Peru

Peru	Connie Celum, Jared Baeten, Richard Zuckerman, Helen Weiss, Wil Whittington	UW	Seattle, USA
	Jorge Sanchez, Jesus Peinado, Juan Guanira	IMPACTA CTU	Lima, Peru
Senegal	Geoffrey Gottlieb, Stephen Hawes, Papa Salif Sow	University of Washington, University of Dakar	Seattle, Washington; Dakar, Senegal
South Africa	Gavin Churchyard, Katherine Fielding	Aurum Institute for Health Research & LSHTM	Johannesburg, South Africa; London, UK
	Sinead Delany, Nkuli Mlaba, Godspower Akpomiemie, Tim Clayton, Wendy Stevens Helen Rees, Philippe Mayaud	Reproductive Health & HIV Research Unit, Wits University & LSHTM	Johannesburg, South Africa; London, UK
	Gabriela Paz Bailey, David Lewis	US CDC & National Institute for Communicable Diseases	Atlanta, USA; Johannesburg, South Africa
Spain	Jordi Casabona for the PISCIS Study Group	Centre d'Estudis Epidemiolo` gics sobre ITS/VIH/SIDA de Catalunya	Barcelona, Spain
Tanzania	Wafaie Fawzi, Donna Spiegelman, Ellen Hertzmark, Ferdinand Mugusi, Gernard Msamanga, for the Tanzania Vitamin and HIV Infection Trial Team	Harvard & Muhimbili University College of Health Sciences	Boston, USA; Dar es Salaam, Tanzania
The Netherlands	Frank de Wolf and Colette Smit for the Dutch HIV Monitoring Foundation	Department of Human Retrovirology, Academic Medical Centre, University of Amsterdam	Amsterdam, The Netherlands
Uganda	Neil French and Christine Watera	MRC Programme on AIDS, London School of Hygiene and Tropical Medicine	Entebbe, Uganda and London, UK
Canada	D. William Cameron	University of Ottawa at The Ottawa Hospital	Ottawa, Canada
	Curtis L. Cooper	University of Ottawa at The Ottawa Hospital	Ottawa, Canada
USA, HOPS/ HIV Insight	John T. Brooks, Rose Baker	US CDC	Atlanta, USA
USA, MACS cohort	Alvaro Munoz, Lisa Jacobson	John Hopkins School of Public Health	Baltimore, USA
USA, 3 ACTG studies	Ronald Bosch for the ACTG trials group This study was supported in part by the AIDS Clinical Trials Group funded by the National Institute of Allergy and Infectious Diseases (AI 68636, AI 38858, AI 68634, AI 38855).	Harvard School of Public Health	Boston, USA
Various datasets	Christl A Donnelly	MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London	London, UK
Various datasets	Steve Self	Fred Hutchinson Cancer Research Center	Seattle, USA
Various datasets	Skillman, Thomas	Fred Hutchinson Cancer Research Center	Seattle, USA
Various datasets	Daniel Meade	Fred Hutchinson Cancer Research Center	Seattle, USA

2 Evidence for co-infections driving higher HIV-1 plasma RNA viral loads

Sub-Saharan Africa (SSA) has a high burden of infectious diseases other than HIV infection, including malaria, tuberculosis (TB), and helminthes among other tropical diseases, as well as high prevalence of herpes simplex virus type 2 (HSV-2). African populations have been found to have high levels of serum immune activation markers compared to developed countries [1-3], possibly from extended exposure to a range of pathogens. Over 70% of the 500 million clinical malaria infections that occur every year arise in SSA [4]. Mounting evidence suggests that HIV co-infections induce transient, but substantial increases in VL as a consequence of increased HIV replication associated with the immune response. Malaria induces a seven-fold increase in VL that lasts for 6 to 8 weeks following the acute illness [5, 6]. Active tuberculosis has been associated with 2.5-fold increase in VL [7-9]. Helminthic infections and leishmaniasis have also been linked to higher levels of VL, though not consistently [10-15]. Other studies have suggested a role for bacterial pneumonia episodes in increasing VL [9, 16]. In addition, a growing body of *in vitro* evidence suggests that co-infection with malaria [17, 18] and tuberculosis [19-21] can lead to substantially higher rates of HIV replication.

Herpes simplex virus type 2 (HSV-2), a sexually transmitted infection (STI), is also important given its high prevalence in SSA [22-24], persistence with frequent sub-clinical and clinical reactivation [25], and elevated levels of VL [26-30]. Reductions in VL of 0.25 to 0.53 $\log_{10}$ have been reported with HSV-2 suppressive therapy [31-37]. In addition to higher VL, symptomatic and asymptomatic recurrences of HSV-2 infection are associated with increased genital HIV-1 shedding among co-infected individuals [38-40]. This increase in genital HIV-1 plasma RNA viral load seen with HSV-2 co-infection places this STI in a special position compared to other non-STI co-infections, such as malaria and TB.

A recent systematic review and meta-analysis of existing evidence has found that acute malaria increases VL by 0.67 $\log_{10}$ copies/mL (95% CI: 0.15, 1.19), HSV-2 infection (seropositivity) by 0.18 $\log_{10}$ copies/mL (95% CI: 0.01, 0.34), and TB disease by 0.40 $\log_{10}$ copies/mL (95% CI: 0.13-0.67) [41]. There was also a trend towards decreased VL following malaria treatment (-0.25 log10 copies/mL, 95% CI: -0.59, 0.10), and HSV suppressive therapy (-0.28 log10 copies/mL, 95% CI: -0.36, -0.19), but there was no evidence of an association of tuberculosis treatment with VL reduction (-0.02 log10 copies/mL, 95% CI -0.19, 0.15).

3 HIV-1 plasma RNA viral load database and statistical analyses

3.1 General description of HIV-1 plasma RNA viral load database

We studied the effect of geographic region on viral load using data from 25 studies of 44 sub-cohorts of HIV infected but *antiretroviral therapy naïve* patients across 7 geographic regions. The studies include a total of 71,668 VL measurements. Data from each sub-cohort in every study consists of the average $\log_{10}$ VL for subjects in the following CD4 categories: < 200, 200-349, 350-499, and ≥ 500 cells/mm^3. The CD4 categories may contain VL measures for different individuals, or for the same individuals at different points in time.

We considered the effects of the following factors on $\log_{10}$ viral load: region (North America, Europe, Asia, South America, East Africa, West Africa, and Southern Africa) or country (South Africa); CD4 category; pregnancy; sex; HIV sub-type (the predominant sub-type in the local region); and assay (the predominant viral load assay used in the study). Table S3.1 includes a description of the sub-cohorts used in the VL analysis.

3.2 Statistical methods analyzing HIV-1 plasma RNA viral load database

Mean $\log_{10}$ HIV-1 plasma RNA viral load was modeled using a linear model that includes as predictors: region (North America, South America, Europe, West Africa, East Africa, Asia, South Africa, and the rest of Southern Africa), sex, CD4 category, pregnancy status, an interaction between CD4 category and sex, and an interaction between CD4 and pregnancy status. Let VL_{ij} denote the $\log_{10}$ VL in region *i* and CD4 category *j*. The model stipulates that

$$E(VL_{ij}) = \alpha_0 + \alpha_i + \beta_j + \gamma_j \text{Female} + \eta_j \text{Pregnant}$$

where α, β, γ and η are the parameters of the statistical model and *Female* and *Pregnant* are indicators of female and pregnant subcohorts. Studies with unknown pregnancy status were treated as not pregnant. The impact of this assumption was assessed using sensitivity analyses (see Section 3.4 below). The effects of viral sub-type and assay could not be statistically adjusted due to the high co-linearity with region. In future prospective studies use of the same viral load assay would be necessary to compare VL across regions. The model weights each observation by the sample size in that category in the study (i.e. CD4 category by sex category by pregnancy status). This weighting has the effect of up-weighting larger studies and down-weighting smaller studies. Robust standard errors are reported for the estimated model coefficients. These standard errors allow for correlation between observations from the same study (across sub-cohorts and CD4 categories).

Table S3.1: Summary of the characteristics of studies and sub-cohorts included in the regional HIV-1 plasma RNA viral load analysis.

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma RNA viral load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
1	1	Spiegelman[42-44]	East Africa	Tanzania	1995-2003	Supplements of Vit A &/or multivitamins	From antenatal clinics with VCT offered	53	<200	5.2	F	Target amplification by RT-PCR	P	A, C & D
								98	200-349	4.8				
								130	350-500	4.5				
								106	>500	4.3				
2	2	Spiegelman[42-44]	East Africa	Tanzania	1995-2003	Selenium supplements	From antenatal clinics with VCT offered	27	<200	4.5	F	Target amplification by RT-PCR	P	A, C & D
								32	200-349	4.1				
								22	350-500	4.0				
								27	>500	3.5				
3	3	Nagot[33]	West Africa	Burkina Faso	Aug 2004-Jan 2005	Suppressive valacyclovir	From a cohort of high-risk women, PLWHA and the University Hospital	78	<200	.	F	Target amplification by RT-PCR	NP	AG recombinants
								39	200-349	4.8				
								39	350-500	4.7				
								8	>500	4.0				
4	4	Lavreys[28]	East Africa	Kenya	1993-2001	Study of cofactors for HIV acquisition & subsequent viral load	Commercial sex workers attending a municipal clinic in Mombasa	131	<200	5.5	F	Target amplification by transcription-mediated amplification (TMA)	NK	A dominant & D
								.	200-349	.				
								.	350-500	.				
								344	>500	4.4				

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma viral RNA load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
5	5	Baeten[45]	East Africa	Kenya	Sept 1998-Jun 2000	Vit A supplements	HIV-positive women attending outpatient clinics at a General Hospital in Mombasa	173	<200	5.9	F	Target amplification by transcription-mediatedamplification (TMA)	NP	A dominant & D
								.	200-349	.				
								.	350-500	.				
								54	>500	4.7				
6	6	John Stewart[46]	East Africa	Kenya	Oct 2000-Jun 2005	HIV disease progression in breast feeding & formula feeding mothers	Pregnant women attending 4 Nairobi clinics with VCT offered	31	<200	5.4	F	Target amplification by transcription-mediated amplification (TMA)	NP	A dominant & D
								59	200-349	4.9				
								49	350-500	4.9				
								104	>500	4.2				
7	7	Delany[47]	South Africa	South Africa		Acyclovir suppression	From community or support groups for people living with HIV/AIDs in Johannesburg	0	<200	.	F	Target amplification by RT-PCR	NP	C
								71	200-349	4.4				
								90	350-500	4.0				
								138	>500	3.7				
8	8	Kublin[6]	Southern Africa	Malawi	Feb 2000 – Nov 2001	Malaria treatment	Through VCT on a tea estate in Thyolo District, Malawi	30	<200	5.2	M	Target amplification by RT-PCR	NP	C
								78	200-349	5.1				
								45	350-500	5.0				
								42	>500	5.1				

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma RNA viral load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
	9	Kublin[6]	Southern Africa	Malawi	Feb 2000-Nov 2001	Malaria treatment	Through VCT on a tea estate in Thyolo District, Malawi	31	<200	5.3	F	Target amplification by RT-PCR	NK	C
								51	200-349	5.0				
								58	350-500	4.7				
								50	>500	4.6				
9	10	Churchyard[48, 49]	South Africa	South Africa	May 1999-April 2002	Workplace & PEPFAR program	Health service of a gold mining company	2,411	<200	4.7	M	Signal amplification by branched DNA	NP	C
								923	200-349	4.2				
								3,334	350-500	3.8				
								628	>500	3.5				
9	11	Churchyard[48, 49]	South Africa	South Africa	May 1999-April 2002	Workplace & PEPFAR program	Health service of a gold mining company	2,696	<200	4.8	F	Signal amplification by branched DNA	NP	C
								1,187	200-349	4.0				
								654	350-500	3.6				
								648	>500	3.0				
9	12	Churchyard[48, 49]			May 1999-April 2002	Workplace & PEPFAR program	Health service of a gold mining company	32	<200	3.5	F	Signal amplification by branched DNA	P	C
								13	200-349	3.6				
								12	350-500	3.9				
								13	>500	3.3				
10	13	Brooks & Baker[50]	North America	United States	Jan 1992 – March	HIV outpatient visits	HIV clinics in the United States	1,327	<200	5.0	M	Target amplification by RT-PCR	NP	B

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma viral RNA load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
					1995									
								1,156	200-349	4.5				
								1,198	350-500	4.2				
								1,263	>500	3.9				
10	14	Brooks & Baker[50]	North America	United States	Jan 1992 – March 1995	HIV outpatient visits	HIV clinics in the United States	256	<200	4.9	F	Target amplification by RT-PCR	NP	B
								216	200-349	4.2				
								229	350-500	3.9				
								281	>500	3.5				
10	15	Brooks & Baker[50]	North America	United States	Jan 1992 - March 1995	HIV outpatient visits	HIV clinics in the United States	7	<200	3.9	F	Target amplification by RT-PCR	P	B
								19	200-349	3.5				
								9	350-500	4.0				
								12	>500	2.5				
11	16	Paz Bailey	South Africa	South Africa		Acyclovir therapy	Clinics in Gauteng Province, South Africa	121	<200	5.1	M	Target amplification by RT-PCR	NP	C
								120	200-349	4.9				
								69	350-500	4.7				
								59	>500	4.5				
12	17	Sanchez	South America	Peru		Sentinel Surveillance	Sentinel surveillance program	39	<200	4.7	M	Target amplification by RT-PCR	NP	B
								50	200-349	4.1				

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma viral RNA load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
								44	350-500	3.6				
								36	>500	3.1				
13	18	Sanchez	South America	Peru		HLA study	HAART national program	2	<200	3.1	M	Target amplification by RT-PCR	NP	B
								72	200-349	4.5				
								60	350-500	4.6				
								55	>500	4.2				
14	19	Goldenberg, Taha Mwatha & Donnell[51]	Southern Africa	Malawi	Jun 2001 – Feb 2003	Antibiotics to reduce mother to child transmission of HIV	Antenatal clinics with VCT offered	87	<200	4.8	F	Target amplification by RT-PCR	P	C
								83	200-349	4.4				
								47	350-500	4.4				
								53	>500	4.1				
14	20	Goldenberg, Taha, Mwatha & Donnell[51]	Southern Africa	Malawi	Jun 2001 – Feb 2003	Antibiotics to reduce mother to child transmission of HIV	Antenatal clinics with VCT offered	154	<200	4.8	F	Target amplification by RT-PCR	P	C
								210	200-349	4.6				
								163	350-500	4.4				
								196	>500	4.0				
14	21	Goldenberg, Taha, Mwatha & Donnell[51]	Southern Africa	Zambia	Jun 2001 – Feb 2003	Antibiotics to reduce mother to child transmission of HIV	Antenatal clinics with VCT offered	105	<200	4.7	F	Target amplification by RT-PCR	P	C
								171	200-349	4.4				

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma viral RNA load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
								156	350-500	4.2				
								153	>500	3.7				
14	22	Goldenberg, Taha, Mwatha & Donnell[51]	East Africa	Tanzania	Jun 2001 – Feb 2003	Antibiotics to reduce mother to child transmission of HIV	Antenatal clinics with VCT offered	95	<200	4.4	F	Target amplification by RT-PCR	P	A, C & D
								122	200-349	4.1				
								94	350-500	3.8				
								163	>500	3.5				
15	23	Celum[32]	South America	Peru		Valcyclovir suppression	Research organization in Lima, Peru	0	<200	.	F	Target amplification by RT-PCR	NP	B
								6	200-349	5.0				
								10	350-500	4.5				
								4	>500	4.1				
16	24	Celum[35]	South America	Peru		Valcyclovir suppression	Research organization in Lima, Peru	5	<200	4.7	M	Target amplification by RT-PCR	NP	B
								7	200-349	4.7				
								0	350-500	.				
								4	>500	4.2				
17	25	Munoz[52-54]	North America	United States	Mar 1984 - April 1985	Natural history of HIV	Cohort of MSM in the United States	1,145	<200	5.1	M	Signal amplification by branched DNA	NP	B
								1,172	200-349	4.6				
								2,501	350-500	4.3				
								5,130	>500	3.9				

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma RNA viral load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
18	26	de Wolf[55]	Europe	Netherlands		Amsterdam cohort - Natural history of HIV	Cohort of HIV-positive men followed in Amsterdam	4,891	<200	4.8	M	Target amplification by NASBA	NP	B
								5,937	200-349	4.4				
								5,138	350-500	4.3				
								4,302	>500	4.1				
18	27	de Wolf[55]	Europe	Netherlands		Amsterdam cohort - Natural history of HIV	Cohort of HIV-positive women followed in Amsterdam	1,189	<200	4.6	F	Target amplification by NASBA	NP	B
								1,425	200-349	4.2				
								1,106	350-500	4.0				
								1,185	>500	3.8				
18	28	de Wolf[55]	Europe	Netherlands		Amsterdam cohort - Natural history of HIV	Cohort of HIV-positive women followed in Amsterdam	78	<200	4.5	F	Target amplification by NASBA	P	B
								112	200-349	3.8				
								114	350-500	3.3				
								141	>500	3.1				
19	29	Cameron	North America	Canada	1995-2008	HIV outpatient clinic	HIV clinic data from Canada	70	<200	4.7	M	Signal amplification by branched DNA	NP	B
								70	200-349	4.5				
								157	350-500	4.3				
								279	>500	4.0				
19	30	Cameron	North America	Canada	1995-2008	HIV outpatient clinic	HIV clinic data from Canada	35	<200	4.6	F	Signal amplification by branched DNA	NK	B
								62	200-349	3.9				

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma RNA viral load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
								87	350-500	3.7				
								110	>500	3.6				
20	31	Cooper	North America	Canada		HIV outpatient clinic	HIV clinic data from Canada	157	<200	4.8	M	Signal amplification by branched DNA	NP	B
								99	200-349	4.3				
								60	350-500	4.3				
								35	>500	3.8				
20	32	Cooper	North America:	Canada		HIV outpatient clinic	HIV clinic data from Canada	48	<200	4.8	F	Signal amplification by branched DNA	NP	B
								24	200-349	3.6				
								7	350-500	4.5				
								7	>500	3.6				
20	33	Cooper	North America	Canada		HIV outpatient clinic	HIV clinic data from Canada	7	<200	4.3	F	Signal amplification by branched DNA	P	B
								6	200-349	3.6				
								7	350-500	3.6				
								8	>500	2.5				
21	34	Casabona[56]	Europe	Spain	Jan 2004-Oct 2005	Baseline data for a cohort starting ART	Cohort initiating ART among 10 hospitals in Spain	1,366	<200	4.9	M	RT PCR, bDNA, or NASBA	NP	B
								721	200-349	4.5				
								581	350-500	4.4				
								810	>500	4.0				
21	35	Casabona[56]	Europe	Spain	Jan 2004-Oct	Baseline data for a cohort starting ART	Cohort initiating ART among	379	<200	4.9	F	RT PCR, bDNA, or NASBA	NK	B

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma RNA viral load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
					2005		10 hospitals in Spain							
								231	200-349	4.2				
								182	350-500	4.0				
								297	>500	3.6				
22	36	Lohse[57]	Europe	Denmark	1995-2007	ART naïve HIV cohort	Population based cohort study	609	<200	5.2	M	Target amplification by RT-PCR	NP	B
								439	200-349	4.6				
								422	350-500	4.3				
								510	>500	3.9				
22	37	Lohse[57]	Europe	Denmark	1995-2007	ART naïve HIV cohort	Population based cohort study	242	<200	4.8	F	Target amplification by RT-PCR	NK	B
								182	200-349	4.2				
								131	350-500	4.0				
								218	>500	3.5				
23	38	Gupta[58]	Asia	India	Aug 2002-Jul 2004	Post partum women	Urban, public hospital in Pune, India	43	<200	4.9	F	Target amplification by RT-PCR	NP	C
								108	200-349	4.4				
								171	350-500	4.2				
								305	>500	3.8				
23	39	Gupta[58]	Asia	India	Aug 2002-Jul 2004	Post partum women	Urban, public hospital in Pune, India	43	<200	5.0	F	Target amplification by RT-PCR	NP	C
								125	200-349	4.5				
								139	350-500	4.2				

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma viral RNA load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
								306	>500	3.8				
23	40	Gupta[58]	Asia	India	Aug 2002-Jul 2004	Post partum women	Urban, public hospital in Pune, India	43	<200	4.8	F	Target amplification by RT-PCR	NP	C
								126	200-349	4.6				
								164	350-500	4.2				
								297	>500	3.8				
24	41	Bosch[59]	North America	United States		Cohorts in the ACTG randomized to ART – baseline data	Prospective cohort of individuals randomized in trials, United States	596	<200	5.5	M	Target amplification by RT-PCR	NP	B
								250	200-349	5.0				
								222	350-500	4.7				
								155	>500	4.4				
	42	Bosch[59]	North America	United States		Cohorts in the ACTG randomized to ART - baseline data	Prospective cohort of individuals randomized in trials, United States	110	<200	5.3	F	Target amplification by RT-PCR	NP	B
								64	200-349	4.7				
								51	350-500	4.5				
								49	>500	4.1				
25	43	Gottlieb[60, 61]	West Africa	Senegal	1994-2005	Cohort data HIV+ clinic participants at baseline	STD and Infectious Diseases Clinic	111	<200	5.2845	F	PCR assay (in house based upon Amplicor HIV-1 Monitor test, developed with Roche to include non-clade B types)	NP	
								91	200-349	4.5256	F		NP	AG recombination
								80	350-500	4.0010	F		NP	

Study #	Study ID	Principal Investigator	Region	Country	Study dates	Intervention (HIV-1 plasma RNA viral load at baseline or in placebo arm)	Study recruitment	Sample Size (N)	CD4 category	Average HIV-1 plasma RNA viral load (log_{10})	Sex	Viral load assay	Preg. Status	Regional sub-type
								111	>500	3.8142	F		NP	
								83	<200	5.3956	M			
								26	200-349	4.9765	M			
								17	350-499	4.4157	M			
								12	>500	3.8324	M			

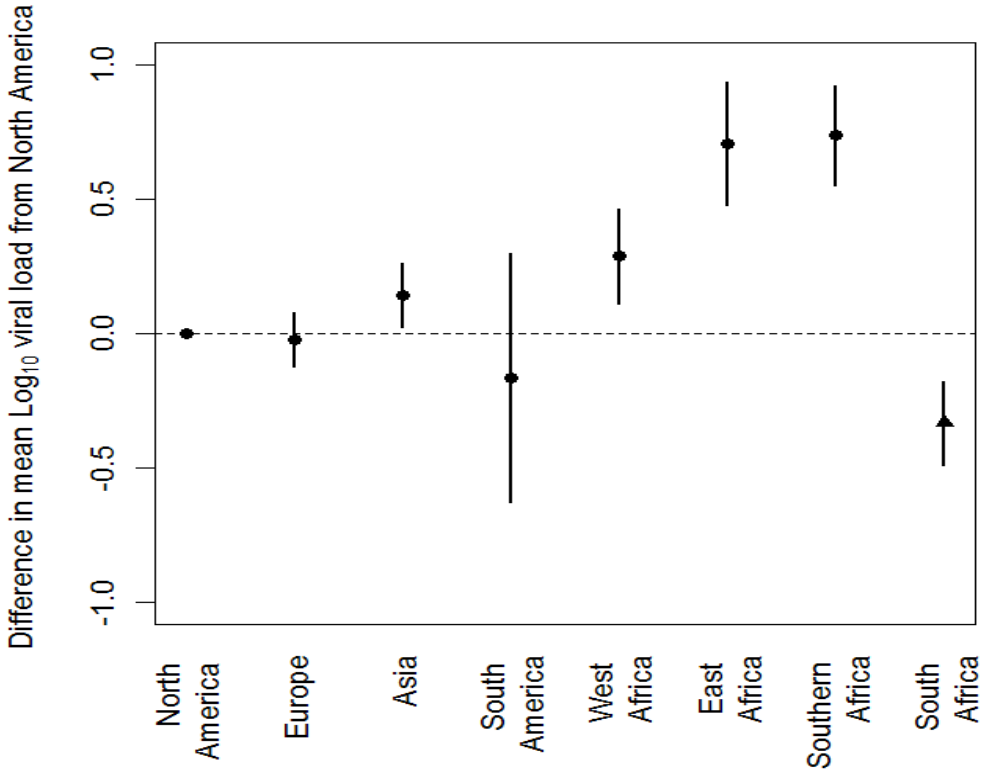
3.3 Summary of results of statistical analyses

We found that there are large and statistically significant differences in mean $\log_{10}$ VL between geographic regions, after adjusting for the effects of CD4 category, sex, and pregnancy status. North America serves as our reference region. We estimate that Europe and South America do not have significantly different mean $\log_{10}$ VL than North America (Europe: 0.02 lower, 95% CI: 0.12 lower to 0.08 higher; South America: 0.17 lower, 95% CI: 0.63 lower to 0.30 higher). West Africa, East Africa, and Southern Africa are estimated to have significantly higher mean $\log_{10}$ viral loads than North America (West Africa: 0.29 higher, 95% CI: 0.11 to 0.47; East Africa: 0.71 higher, 95% CI: 0.48 to 0.93; Southern Africa: 0.74 higher, 95% CI: 0.55 to 0.92). Of note, South Africa is estimated to have a significantly lower mean $\log_{10}$ viral load than North America (0.33 lower, 95% CI: 0.18 to 0.49) (see Section 3.5 below for further discussion). We estimate that Asia has a 0.14 higher mean $\log_{10}$ viral load than North America (95% CI: 0.03 to 0.26). The estimated differences in mean $\log_{10}$ VL from North America are shown in Table S3.2. The regional differences in mean VL compared to the North America are displayed in Figure S3.1.

Table S3.2: Estimated differences in mean $\log_{10}$ VL from North America.

	Estimated Difference in Mean Log_{10} VL from North America	**Standard Error**	**p-value**
North America	0.00	--	--
Europe	-0.02	0.05	0.66
South America	-0.17	0.24	0.49
Asia	0.14	0.06	0.03
West Africa	0.29	0.09	< 0.01
East Africa	0.71	0.12	< 0.01
Southern Africa	0.74	0.10	< 0.01
South Africa	-0.33	0.08	< 0.01

Figure S3.1: Estimated regional differences in mean $\log_{10}$ VL compared with the mean VL in North America.



3.4 Sensitivity analyses on the statistical modelling

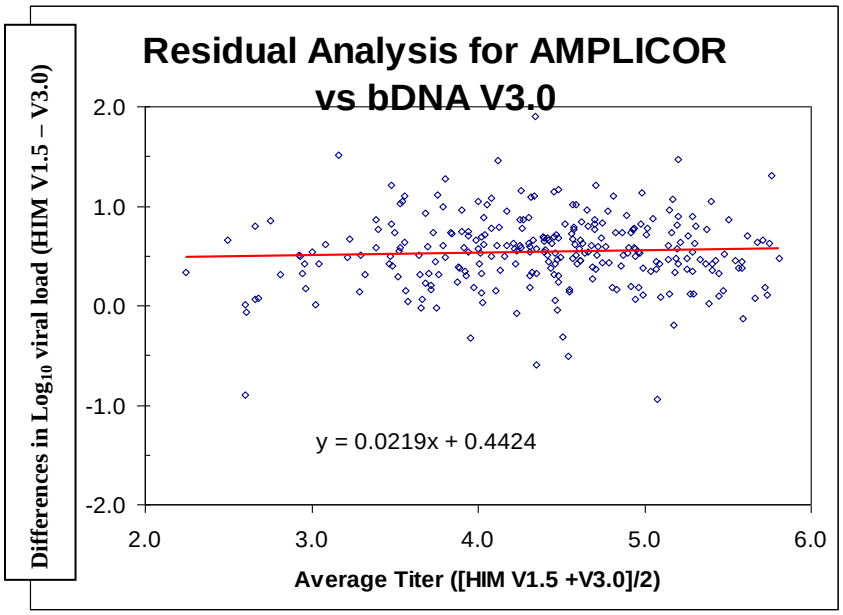
Sensitivity analyses were conducted to assess the robustness of the results to model mis-specification. First, we investigated the impact of the extreme $\log_{10}$ VL observations from South America (see Table S3.1). When these observations were omitted from the analysis, the results were qualitatively unchanged. Second, studies with unknown pregnancy status were excluded. This change resulted in very minor alterations in the estimated regional effects. Finally, we examined the effect of excluding the three sub-cohorts in South Africa where a specific bDNA assay was used (see Section 3.5 below).

3.5 Discrepancy of the data from South Africa

The VL data from South Africa include 5 sub-cohorts. For three of these cohorts, VL measurements were done at the same central laboratory using the branched DNA (bDNA) assay. These cohorts all showed lower VL data than the other South African cohorts, suggesting a systematic bias towards lower VL measurements. A South African study that compared the bDNA assay with a PCR assay found that for subtype C the 3.0 bDNA

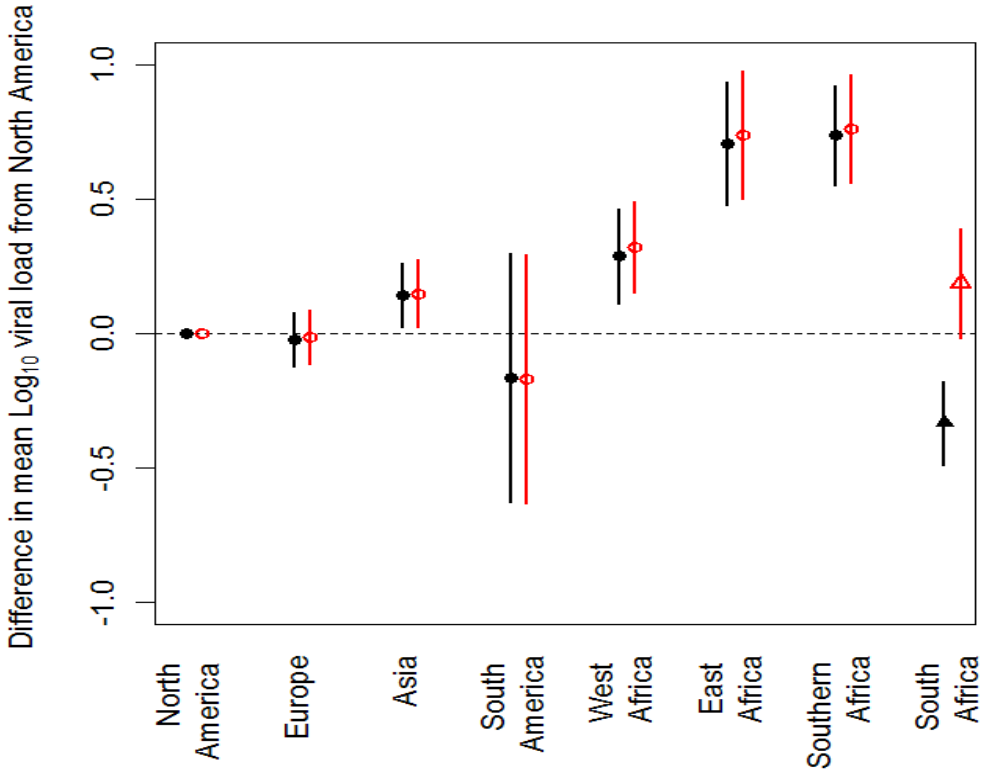
assay gave a 0.58 $\log_{10}$ lower viral load measure than the Roche 1.5 PCR assay (paired t-test, $p<0.001$, Figure S3.2) [62]. On the basis of these data, we hypothesized that the low level of VL in these three sub-cohorts from South Africa might be due to the VL assay used at this laboratory. It bears notice that, historically, commercially available RNA tests tended to be optimized to detect subtype B, the predominant HIV-1 subtype in North America and Europe, and were frequently suboptimal in detecting HIV-1 genetic forms or subtypes found in other parts of the world [63].

Figure S3.2: Differences in $\log_{10}$ VL between the bDNA V 3.0 and Roche Amplicor HIV-1 MONITOR (HIM) 1.5 PCR assay among subtype C HIV infections in South Africa [62].



We explored the impact of excluding these three sub-cohorts from our statistical analyses. Removing these three sub-cohorts left two South African sub-cohorts for which the PCR assay had been used. The estimated mean VL in South Africa increased, and the difference in estimated mean VL between South Africa and North America changed from a 0.33 lower mean VL (95% CI: -0.49 to -0.18) to a 0.19 higher mean VL (95% CI: -0.02 to 0.39). Figure S3.3 shows the estimated regional differences in mean VL excluding the three South Africa cohorts compared to the estimates obtained when including them.

Figure S3.3: Estimated regional differences in average $\log_{10}$ VL from North America before (black) and after (red) excluding the three sub-cohorts from South Africa.



4 Mathematical modeling formalism assessing the epidemiological impact of the VL effect

4.1 Model equations and description

A deterministic compartmental model was constructed through extension of earlier models [64, 65] to describe the HIV epidemic in sub-Saharan Africa in presence of the heightened VL effect. The model stratifies the population into compartments according to HIV sero-status and stage of HIV infection, sexual-risk activity group, and exposure to a biological cofactor (higher VL) that affects HIV infectivity. The model consists of a system of eight coupled nonlinear differential equations for each risk group:

$$
\begin{aligned}
\frac{dS(i)}{dt} &= \left(1 - f_B(i)\right)\mu N_0(i) - \mu S(i) - \Lambda_{HIV}^{S(i)} S(i) \\
\frac{dY_1(i)}{dt} &= \Lambda_{HIV}^{S(i)} S(i) - \mu Y_1(i) - \omega_{Y_1} Y_1(i) \\
\frac{dY_2(i)}{dt} &= \omega_{Y_1} Y_1(i) - \mu Y_2(i) - \omega_{Y_2} Y_2(i) \\
\frac{dY_3(i)}{dt} &= \omega_{Y_2} Y_2(i) - \mu Y_3(i) - \omega_{Y_3} Y_3(i) \\
\frac{dBS(i)}{dt} &= f_B(i)\mu N_0(i) - \mu BS(i) - \Lambda_{HIV}^{S(i)} BS(i) \\
\frac{dBY_1(i)}{dt} &= \Lambda_{HIV}^{S(i)} BS(i) - \mu BY_1(i) - \omega_{Y_1} BY_1(i) \\
\frac{dBY_2(i)}{dt} &= \omega_{Y_1} BY_1(i) - \mu BY_2(i) - \omega_{Y_2} BY_2(i) \\
\frac{dBY_3(i)}{dt} &= \omega_{Y_2} BY_2(i) - \mu BY_3(i) - \omega_{Y_3} BY_3(i)
\end{aligned}
\qquad (1)
$$

The index i stands for an i-sexual risk population where $i = 1, 2, 3, 4$ represent the low, low to intermediate, intermediate to high, and high risk groups, respectively. Here, $S(i)$ is the HIV susceptible population and $BS(i)$ is the HIV susceptible population that would experience the biological cofactor of heightened VL once it is infected with HIV, potentially due to a higher burden of co-infections and challenged immune response. $Y_\alpha(i)$ and $BY_\alpha(i)$ are the HIV infected populations without and with the biological cofactor, respectively. The index α marks the stage of HIV pathogenesis; $\alpha = 1, 2, 3$ stand for acute, latent, and late stages respectively. $N(i)$ is the population size, and $N_0(i)$ is the initial population size, of each i-risk group. N^{Total} is the total population size of all risk groups. Lastly, $f_B(i)$ is the fraction of the entering susceptible population that is exposed to the heightened VL biological cofactor for each i-risk group.

HIV pathogenesis is described by the three stages of acute, latent, and late and our model assumes negligible antiretroviral therapy coverage in the population. The progression of HIV is described by $\omega_{Y_{\alpha=1}}$, the rate of progression from acute to latent stage, $\omega_{Y_{\alpha=2}}$, the rate from latent to late stage, and $\omega_{Y_{\alpha=3}}$, the rate of HIV/AIDS disease mortality. μ is the birth (and death) rate. The rates $\Lambda_{HIV}^{S(i)}$ are the HIV forces of infection (hazard rates of infection) experienced by the susceptible populations ($S(i)$ and $BS(i)$). $\Lambda_{HIV}^{S(i)}$ is given by

$$\Lambda_{HIV}^{S(i)} = \rho_{S(i)} \times \sum_{j=1,2,3,4} \left(\begin{array}{l} \sum_{\alpha'=1,2,3} t_{Y_{\alpha'}(j)\to S(i)} G(i,j) \dfrac{\rho_{Y_{\alpha'}(j)} Y_{\alpha'}(j)}{\rho_{S(j)} S(j) + \sum_{\alpha''=1,2,3} \rho_{Y_{\alpha''}(j)} Y_{\alpha''}(j) + \rho_{BS(j)} BS(j) + \sum_{\alpha''=1,2,3} \rho_{BY_{\alpha''}(j)} BY_{\alpha''}(j)} \\ + \sum_{\alpha'=1,2,3} t_{BY_{\alpha'}(j)\to S(i)} G(i,j) \dfrac{\rho_{BY_{\alpha'}(j)} BY_{\alpha'}(j)}{\rho_{S(j)} S(j) + \sum_{\alpha''=1,2,3} \rho_{Y_{\alpha''}(j)} Y_{\alpha''}(j) + \rho_{BS(j)} BS(j) + \sum_{\alpha''=1,2,3} \rho_{BY_{\alpha''}(j)} BY_{\alpha''}(j)} \end{array} \right) \quad (2)$$

In these expressions, $\rho_{X(i)}$ describes the *effective* new sexual partner acquisition rate for each population variable $X(i)$. Note that we use the term effective rate of partner change, as opposed to rate of partner change, since this parameter does not merely reflect the actual rate at which individuals change their partners, but also represents other behavioral mechanisms that effectively enhance this quantity such as concurrency and topology of sexual networks [66-68], and variability in risk behavior [69].

The mixing among the four risk groups is dictated by the sexual-mixing matrix $G(i,j)$ that provides the probability that an individual in risk group i would choose a partner in risk group j [70]. It is given by the expression

$$G(i,j) = e\delta_{i,j} + (1-e) \frac{\rho_{S(j)} S(j) + \sum_{\alpha'=1,2,3} \rho_{Y_{\alpha'}(j)} Y_{\alpha'}(j) + \rho_{B(j)} B(j) + \sum_{\alpha''=1,2,3} \rho_{BY_{\alpha''}(j)} BY_{\alpha''}(j)}{\sum_{k=1,2,3,4} \left(\rho_{S(k)} S(k) + \sum_{\alpha'=1,2,3} \rho_{Y_{\alpha'}(k)} Y_{\alpha'}(k) + \rho_{B(k)} B(k) + \sum_{\alpha''=1,2,3} \rho_{BY_{\alpha''}(j)} BY_{\alpha''}(k) \right)} \quad (3)$$

Here, $\delta_{i,j}$ is the identity matrix and the parameter $e \in [0,1]$ measures the degree of assortativeness in the mixing. At one extreme, $e = 0$, mixing is fully proportional, while at the other extreme $e = 1$, mixing is fully assortative, as individuals choose partners only from within their risk group.

The parameters $t_{Y_\alpha(i)\to S(j)}$ and $t_{BY_\alpha(i)\to S(j)}$ stand for HIV transmission probability per partnership in a partnership between a member of the susceptible population $S(j)$ and a member of the HIV infected populations $Y_\alpha(i)$ and $BY_\alpha(i)$, respectively. They are expressed in terms of HIV transmission probability per coital act per HIV stage in this

partnership ($p^{HIV}_{Y_\alpha(i)\to S(j)}$), the frequency of coital acts per HIV stage in this partnership ($n_{Y_\alpha(i)\leftrightarrow S(j)}$), and the duration ($\tau_{Y_\alpha(i)\leftrightarrow S(j)}$) of this partnership, using the binomial model

$$t_{Y_\alpha(i)\to S(j)} = 1-\left(1- p^{HIV}_{Y_\alpha(i)\to S(j)}\right)^{n_{Y_\alpha(i)\leftrightarrow S(j)}\tau_{Y_\alpha(i)\leftrightarrow S(j)}} \quad (4)$$

$$t_{BY_\alpha(i)\to S(j)} = 1-\left(1- p^{HIV}_{BY_\alpha(i)\to S(j)}\right)^{n_{BY_\alpha(i)\leftrightarrow S(j)}\tau_{BY_\alpha(i)\leftrightarrow S(j)}} \quad (5)$$

Here

$$p^{HIV}_{BY_\alpha(i)\to S(j)} = 2.45^{\log\left(vl_{BY_\alpha}/vl_{Y_\alpha}\right)} p^{HIV}_{Y_\alpha(i)\to S(j)} \quad (6)$$

$$n_{BY_\alpha(i)\leftrightarrow S(j)} = \left(1-q_{Morb}\right) n_{Y_\alpha(i)\leftrightarrow S(j)} \quad (7)$$

$$\tau_{BY_\alpha(i)\leftrightarrow S(j)} = \tau_{Y_\alpha(i)\leftrightarrow S(j)} \quad (8)$$

In these expressions, $2.45^{\log\left(vl_{BY_\alpha}/vl_{Y_\alpha}\right)}$ is the enhancement in HIV transmission probability per coital act due to the heightened VL based on the Rakai study findings (HIV transmission probability per coital act increases by a factor of 2.45 with each $\log_{10}$ increase in VL) [71]. The parameter q_{Morb} describes the fractional decrease in coital frequency due to the presence of the heightened VL biological cofactor (to account for co-infection morbidity because the increase in VL is potentially due to co-infections).

We assume a constant birth rate in the model and we do not stratify the population according to sex. The best data on HIV transmission probability per coital act indicates that, in absence of male circumcision, there are no differences between HIV transmission probability per coital act from male to female and from female to male [72, 73]. The sources of the disparity in HIV prevalence among men and women appear to be primarily due to behavioral patterns such as age cohort mixing (young women with older men) [74].

4.2 Biological and behavioral input to the model

The model assumptions in terms of parameter values are summarized in Table S4.1 and S4.2 along with their references.

HIV transmission probabilities per coital act are extracted from the measurements of Wawer *et al* [73] in Rakai, Uganda by collapsing the sub-strata in their classification of incident, prevalent, and late stages into the three stages of acute, latent, and late as delineated in Ref [65]. There are, however, three distinctions from Wawer's analysis of the stages. We included in our definition of acute stage seroconversions those occurring in both members of an initially seronegative couple during the same follow up interval in the Rakai study and merged the rest of the seroconversions classified as incident stage with the latent stage [65]. This was done since the latter seroconversions would have likely occurred during latent infection rather than acute infection of the index partner. The second distinction is that we recalculated the transmission probabilities [65] using

the binomial model for the partnership transmission probability [75]. Lastly, for HIV transmission probability during acute infection we used recent re-analyses of the Rakai data [76, 77].

The durations of the acute, latent, and late stages are assumed to be 49 days (acute), 9 years (latent), and 2 years (late). These choices are based on the transmission probability classification in Wawer *et al.* [73], Pinkerton's analysis of the Rakai data for acute infection [77], the measured time from seroconversion to death in the Masaka cohort in Uganda [78], recent findings in the Mombasa cohort in Kenya [79], and recent compilation of data by UNAIDS indicating that the average duration from HIV acquisition to death in absence of antiretroviral therapy is about 11 years [80, 81].

The population is divided into four sexual-risk classes of low, low to moderate, moderate to high, and high risk groups. The risk groups are defined using the data of the Four City study [82]. Female sex workers and their male clients constitute the high risk group. Populations with more than one non-spousal, one non-spousal, and no non-spousal partnerships in the previous year characterize the intermediate to high, low to intermediate, and low risk groups, respectively. The duration of the sexual lifespan is set at 35 years to conform with the 15-49 years age groups that are typically used to define the sexually active population by the WHO as well as many HIV studies [83, 84].

We used the general population survey of the Four City study [83] to fit HIV prevalence levels in Kisumu, Kenya, the representative setting we adopted to assess the impact of the VL effect; and antenatal clinic surveillance data [85, 86] to fit the time series trends in HIV prevalence. Please note that antenatal surveillance data do not necessarily reflect the HIV population prevalence level [87], though they are valuable in describing prevalence trends. Our prediction for HIV prevalence in Kisumu appears to underestimate the epidemic since the general population survey for Kisumu found substantially lower prevalence than provided by the antenatal surveillance data.

Table S4.1: Model assumptions in terms of parameter values.

Assumption	**Parameter value**	**Sources**
Rate ratio increase in HIV per coital transmission probability per one-$\log_{10}$ rise in HIV viral load	2.45	[71]
Logarithmic increase in HIV viral load level in sub-Saharan Africa due to the HIV plasma viral load infectivity enhancement effect ($\log\left(vl_{BY_\alpha}/vl_{Y_\alpha}\right)$)	0.46	Statistical analyses of VL database with 20% reduction in estimated regional differences to account for potential systematic biases in comparing VL across regions
Reduction in coital frequency associated with	20%	Conservative assumption

the heightened VL (q_{Morb})

HIV transmission probability per coital act per stage of infection ($p^{HIV}_{Y_\alpha(i)\to S(j)}$):

Acute stage	0.0360	[73, 76, 77]
Latent stage	0.0008	[73]
Late stage	0.0042	[73]

Duration of each of HIV stages ($1/\omega_{Y_\alpha}$):

Acute stage	49 days	[73, 77]
Latent stage	9.0 years	[78, 80, 81]
Late stage	2.0 years	[73]

Frequency of coital acts per HIV stage ($n_{Y_\alpha(i)\leftrightarrow S(j)}$):

Acute stage	10.6 per month	[73]
Latent stage	11.0 per month	[73]
Late stage	7.1 per month	[73]

Fraction of the initial population size in each risk group ($N_0(i)/N_0^{Total}$):

Low risk	65.4%	[88]
Low to intermediate risk	22.9%	[88]
Intermediate to high risk	9.3%	[88]
High risk	2.5%	[89]

Effective new sexual partner acquisition rate ($\rho_{X(i)}$):

Low risk	0.1 partners/year	Representative values calibrated to the Kisumu epidemic
Low to intermediate risk	1.3 partners/year	*Ibid*
Intermediate to high risk	5.5 partners/year	*Ibid*
High risk	43.0 partners/year	*Ibid*

Duration of sexual partnerships ($\tau_{Y_\alpha(i)\leftrightarrow S(j)}$):		
Low risk with low risk	48 months	Representative value
Low risk with low to intermediate risk	36 months	*Ibid*
Low risk with intermediate to high risk	24 months	*ibid*
Low risk with high risk	12 months	*Ibid*
Low to intermediate risk with low to intermediate risk	24 months	*Ibid*
Low to intermediate risk with intermediate to high risk	12 months	*Ibid*
Low to intermediate risk with high risk	6 months	*Ibid*
Intermediate to high risk with intermediate to high risk	6 months	*Ibid*
Intermediate to high risk with high risk	1 months	*Ibid*
High risk with high risk	1 week	[89]
Degree of assortativeness (e)	0.224	Representative value calibrated to the Kisumu epidemic
Duration of sexual lifespan ($1/\mu$)	35 years	[65, 82]

Table S4.2: Effect of heightened VL on HIV transmission probability per coital act

Stage of infection	HIV transmission probability per coital act in absence of heightened VL effect	HIV transmission probability per coital act in presence of a heightened VL effect of size 0.58 $\log_{10}$	Percentage increase in HIV transmission probability per coital act in presence of a heightened VL effect of size 0.58 $\log_{10}$	HIV transmission probability per coital act in presence of a heightened VL effect of size 0.46 $\log_{10}$	Percentage increase in HIV transmission probability per coital act in presence of a heightened VL effect of size 0.46 $\log_{10}$
Acute	0.0360	0.0605	68%	0.0546	52%
Latent	0.0008	0.0013	68%	0.0012	52%
Late	0.0042	0.0071	68%	0.0064	52%

4.3 Population attributable fraction due to the VL effect

The population attributable fraction (*PAF*), the proportion of incident HIV infections that are due to increased infectivity with the heightened VL effect, is defined by the expression

$$PAF(t) = \frac{\text{Incidence of HIV arising from the HPVLIE effect at time } t}{\text{Total incidence of HIV at time } t} \quad (9)$$

while the cumulative PAF due to the VL effect since 1980 up to time t is defined as

$$PAF_{Cum}(t) = \frac{\text{Cumulative incidence of HIV arising from the HPVLIE effect from 1980 up to time } t}{\text{Total cumulative incidence of HIV from 1980 up to time } t} \quad (10)$$

4.4 Further results on modeling the epidemiological impact of higher HIV-1 plasma RNA viral loads in sub-Saharan Africa

4.4.1 Impact of the VL effect per risk group

Table S4.3 shows the impact of the VL effect on HIV prevalence and excess prevalence* in the different risk groups (measures evaluated at endemic equilibrium to avoid the intricacy of different time scales of the epidemic in the different risk groups).

The results indicate an inverse relationship such that the lower the risk, the higher the percentage increase in HIV prevalence due to the VL effect. This suggests that the VL effect has contributed to the general population epidemic in SSA by amplifying HIV transmission among the low risk population.

Table S4.3: The impact of the VL effect on HIV prevalence by risk group.

Risk group	HIV prevalence (%) No VL effect	HIV prevalence (%) VL effect	Excess prevalence (%)	Percentage increase in prevalence (%)
Low risk (general population)	9.2%	11.3%	2.1%	22.5%
Low to intermediate risk	52.4%	58.2%	5.8%	11.1%
Intermediate to high risk	66.5%	71.6%	5.1%	7.7%

* Excess prevalence is defined as prevalence in presence of the VL effect minus the prevalence in absence of the VL effect.

High risk	81.0%	84.6%	3.6%	4.4%
Total population	**18.8%**	**21.5%**	**2.7%**	**14.2%**

4.4.2 Impact of the VL effect assuming the full $\log_{10}$ increase in VL of 0.58

Figure S4.1 shows the prevalence and population attributable fraction, as in Figure 3 of the main text, but now assuming the full average $\log_{10}$ increase in VL of 0.58, the average $\log_{10}$ increase in VL found for the three regions of West Africa, East Africa, and Southern Africa without the 20% reduction assumed in consideration of the potential effects of uncontrolled variables that may affect the VL such as type of assay.

With the full $\log_{10}$ increase in VL and at the endemic equilibrium, the excess prevalence increases to 4.2% (versus 2.9% in Figure 3 of main text), the *PAF* at the epidemic peak increases to 21.2% (versus 14.4% in Figure 3 of main text), and the excess incidence rate[†] increases to 1.06 per 100 person-year (versus 0.69 per 100 person-year in Figure 3 of main text).

4.4.3 Impact of the VL effect assuming 20% faster disease progression with heightened VL

Figure S4.2 shows the prevalence and population attributable fraction as in Figure 3 of the main text, but assuming a 20% faster disease progression with the heightened VL. We examine this effect because the impact of coinfection-mediated increases in VL on HIV disease progression remains controversial. Although early evidence suggested accelerated progression to AIDS and death in SSA, potentially due, in part, to the high burden of co-infections [90], more recent evidence is mixed, with some supporting the view that co-infections may have limited impact on enhanced HIV disease progression [91, 92]. Despite the evidence that HIV patients at sustained lower HIV viral load, such as due to the CCR-5 delta 32 heterozygosity [93], have a slower disease progression [55, 94-99], available data on survival from HIV sero-conversion to AIDS or death [78, 100] suggest similar rates of progression in resource-rich and resource-poor settings in the absence of HAART, in the face of much higher co-infection rates and earlier progression towards symptomatic HIV disease [91]. More recent data from Karonga, Malawi [101] and Mombasa, Kenya [79] also support this view. However, the Partners in Prevention RCT of herpes suppressive therapy to reduce HIV transmission demonstrated a statistically significant 17% delay in HIV progression among HIV-1/HSV-2 co-infected participants receiving acyclovir [102]. It is not yet clear, however, whether this effect on disease

[†] Excess incidence rate is defined as incidence rate in presence of the VL effect minus the incidence rate in absence of the VL effect.

progression reflects suppression of HSV-2 effects or actually direct effects of acyclovir on HIV.

With the additional effect on disease progression and at the epidemic peak, the excess prevalence reduces to 1.4% (versus 2.9% in Figure 3 of main text), and the *PAF* reduces to 14.3% (versus 14.4% in Figure 3 of main text), but the excess incidence rate increases to 0.92 per 100 person-year (versus 0.69 in Figure 3 of main text). The incidence rate increases because, in order to fit the measured HIV prevalence in the presence of increased mortality due to faster disease progression, HIV incidence must be higher to generate enough infections to yield the measured HIV prevalence.

Figure S4.1: The time course of the HIV epidemic in Kisumu, Kenya in presence and absence of the VL effect, assuming the full average $\log_{10}$ increase in VL of 0.58 from the VL data. *(A)* HIV prevalence in presence of the VL effect compared to the prevalence in absence of the VL effect. *(B) PAF* (fraction of incident HIV infections) due to the VL effect.

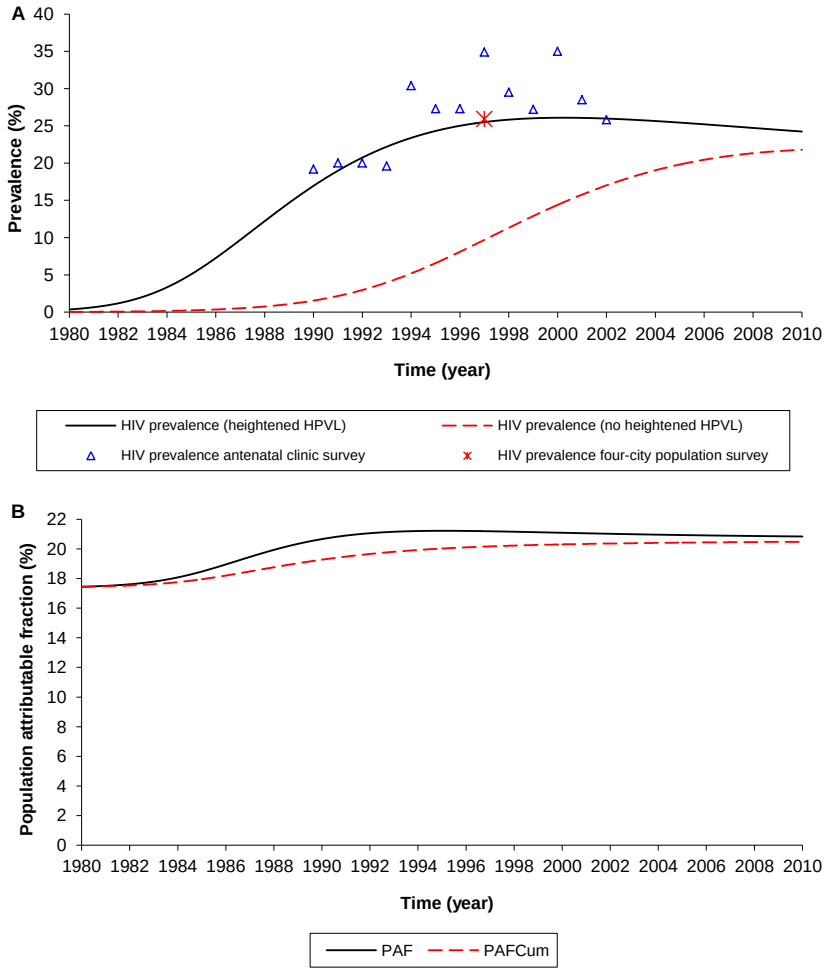
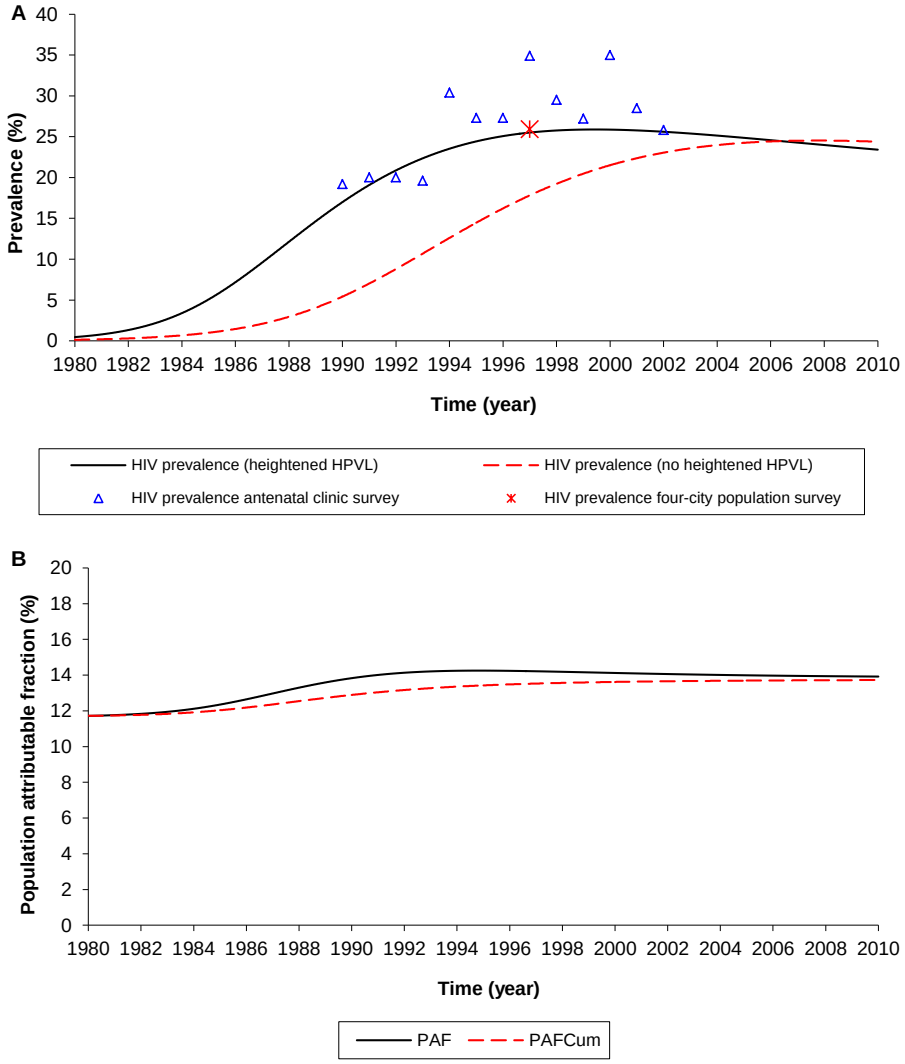


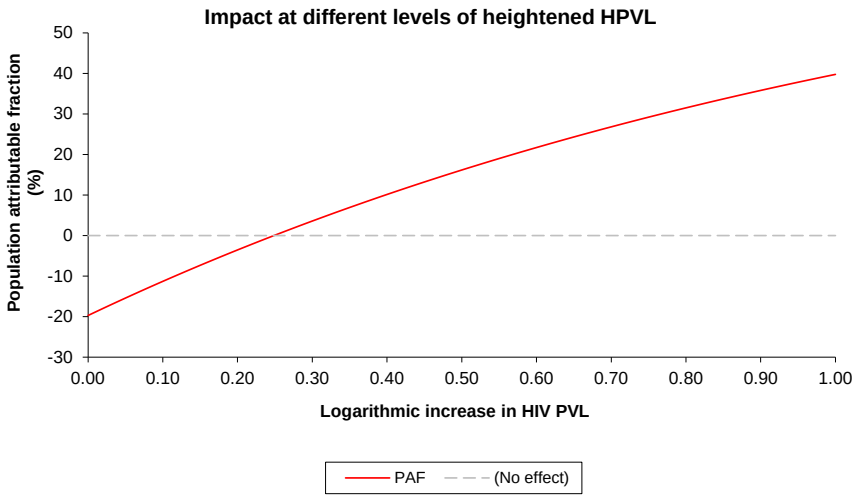
Figure S4.2: Time course of the HIV epidemic in Kisumu, Kenya in the presence and absence of the VL effect, assuming that the heightened VL effect accelerates disease progression by 20%. *(A)* HIV prevalence in the presence of the VL effect compared to the prevalence in absence of the VL effect. *(B) PAF* (fraction of incident HIV infections) due to the VL effect.



4.4.4 Impact of the VL effect at different levels of the heightened VL

Figure S4.3 shows the impact of the VL effect on the population attributable fraction at different levels of the heightened VL assuming a reduction in coital frequency of 20% with increased VL. A 0.25 $\log_{10}$ arithmetic increase in VL is needed to counter the assumed reduction in coital frequency of 20%. At one $\log_{10}$ increase in VL, the *PAF* is 39.9% (versus 14.2% at 0.46 $\log_{10}$ as in Figure 3 of main text).

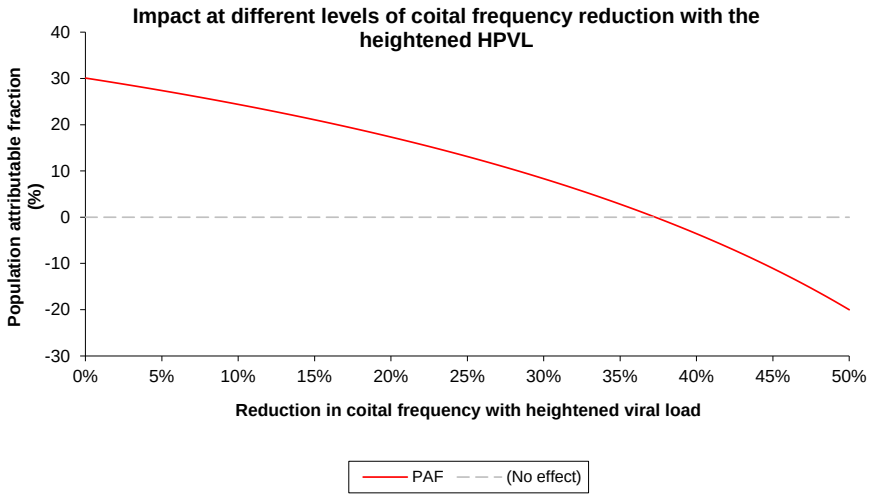
Figure S4.3: Impact of the VL effect on the population attributable fraction at different levels of the heightened VL assuming a reduction in coital frequency of 20% with increased VL.



4.4.5 Impact of the VL effect at different levels of sexual activity reduction with heightened VL

Figure S4.4 shows the impact of the VL effect on the population attributable fraction at different levels of sexual activity reduction (expressed in terms of reduction in coital frequency) with the heightened VL. A 34% reduction in coital frequency is needed to counter the effect of the 0.46 $\log_{10}$ increase in VL. Furthermore, if the full average $\log_{10}$ increase in VL were 0.58 $\log_{10}$, as suggested by the VL data, then a 41% reduction in coital frequency would be needed to counter the effect of the heightened VL.

Figure S4.4: Impact of the VL effect on the population attributable fraction at different levels of coital frequency reduction with the heightened VL.



4.5 Sensitivity and uncertainty analyses on the mathematical modeling predictions

Figures S4.3 and S4.4, as well as S4.2, show sensitivity analyses to the magnitude of the increase in $\log_{10}$ VL, reduction in sexual activity associated with the heightened VL, and shortening of the duration of latent infection (faster disease progression) associated with the heightened VL. Here we report on additional uncertainty and sensitivity analyses.

We performed two further kinds of uncertainty and sensitivity analyses to assess the robustness of our predictions for the impact of the VL effect on the key epidemiologic measures of interest, namely excess prevalence, excess incidence rate, and the *PAF*. First, we assessed the impact of uncertainty in the key parameters that directly drive the VL effect including $\log_{10}$ increase in VL and coital frequency reduction with the heightened VL. We did so by allowing $\pm$ 20% variation in each of these parameters (Figure S4.5).

Second, we examined the impact of uncertainty in the key structural parameters in the model, including the behavioral and HIV progression parameters used to parameterize the model (Figure S4.6). The biological inputs in our model, such as HIV transmission probabilities and HIV stage durations are set by empirical data, as described above. However, recent evidence suggests that the time from HIV infection to death can be as short as 7.5 years with infection with subtypes D and AD recombinant and multiple viruses [103, 104]. Conversely, recent compilation of data by UNAIDS suggests that the average duration from HIV infection to death in absence of antiretroviral therapy is about 11 years [80, 81], one year longer than earlier estimates [78]. Therefore, we included disease progression as one of the parameters in the sensitivity and uncertainty analyses and examined the impact of its variability within a range of $\pm$ 20% of the value used in the model. It is noteworthy that we examine here the impact of disease progression as a model structure parameter and not as an associated effect with the heightened VL. The latter is already addressed in Figure S4.2.

Though the behavioral input in our model is informed by empirical data, the ambiguity in the definition of what constitutes a sexual risk behavior introduces an element of uncertainty in the values of the behavioral parameters [65]. Sexual risk behavior is a complex phenomenon that cannot be directly observed and only indirect data are available on sexual activity [105]. The indirect nature of evidence, the private and sensitive nature of sexual behavior, the informational limitations of ego-centric sexual behavior data, and the non-random biases in sexual behavior reporting including social desirability and memory, can introduce elements of bias and uncertainty in available measures [106-111]. It is also challenging to precisely quantify risk behavior due to the multitude of facets of sexual behavior from partnership formation to contact with sex workers, heterogeneity in partner change rates, and assortative and age cohort mixing, among others. Network structure and concurrency of partnerships can further play a major role in shaping the risk of exposure to HIV [66-68, 112].

Therefore, we examined the sensitivity of our predictions to the following variations in the behavioral parameters: 1) overall $\pm$ 20% in all values of new sexual partner acquisition rates, 2) overall $\pm$ 20% in all values of duration of sexual partnerships, 3)

overall ± 20% in the fractions of the population in the low to moderate, moderate to high, and high risk groups, with the rest of the population allocated to the low risk group, and 4) ± 20% in the degree of assortativeness in the mixing between the risk groups.

Figures S4.5 and S4.6 show the results of the univariate sensitivity and uncertainty analyses for the Kisumu calculations of Figure 3 of the main text, but now at the endemic equilibrium to disentangle the temporal effects from the dynamic effects. The analyses were done by Monte Carlo sampling from the specified ranges of uncertainty using the uniform distribution for 1000 runs of the model for each parameter.

Our model predictions, as expected, are sensitive to variations in the direct drivers of the VL effect, namely the magnitude of the heightened VL and the level of sexual activity reduction associated with the heightened VL. However, our predictions for the excess prevalence and the *PAF* are largely robust to variations in the model structure parameters. Only the excess incidence rate shows some sensitivity to the partner change rates, durations of sexual partnerships, and the distribution of risk behavior in the population.

In conclusion, our predictions of a substantial impact for the VL effect are robust with respect to the variability and uncertainty in model structure parameters. The main drivers of the VL effect are undoubtedly the $\log_{10}$ increase in VL, as well as any assumed sexual activity reductions associated with the heightened VL.

Figure S4.5: Sensitivity and uncertainty analyses of the drivers of the VL effect including (*A*) $\log_{10}$ increase in VL and (*B*) coital frequency reduction associated with the heightened VL. These analyses are performed for the Kisumu calculations of Figure 3 of the main text, but at the endemic equilibrium.

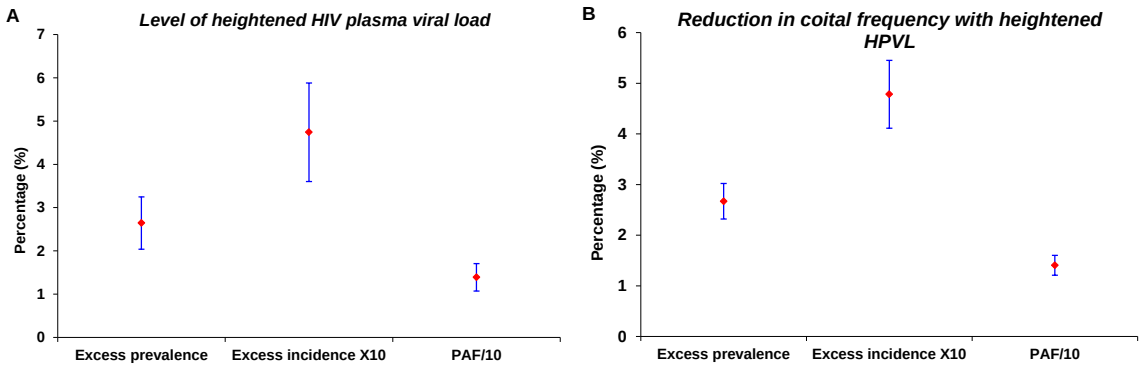
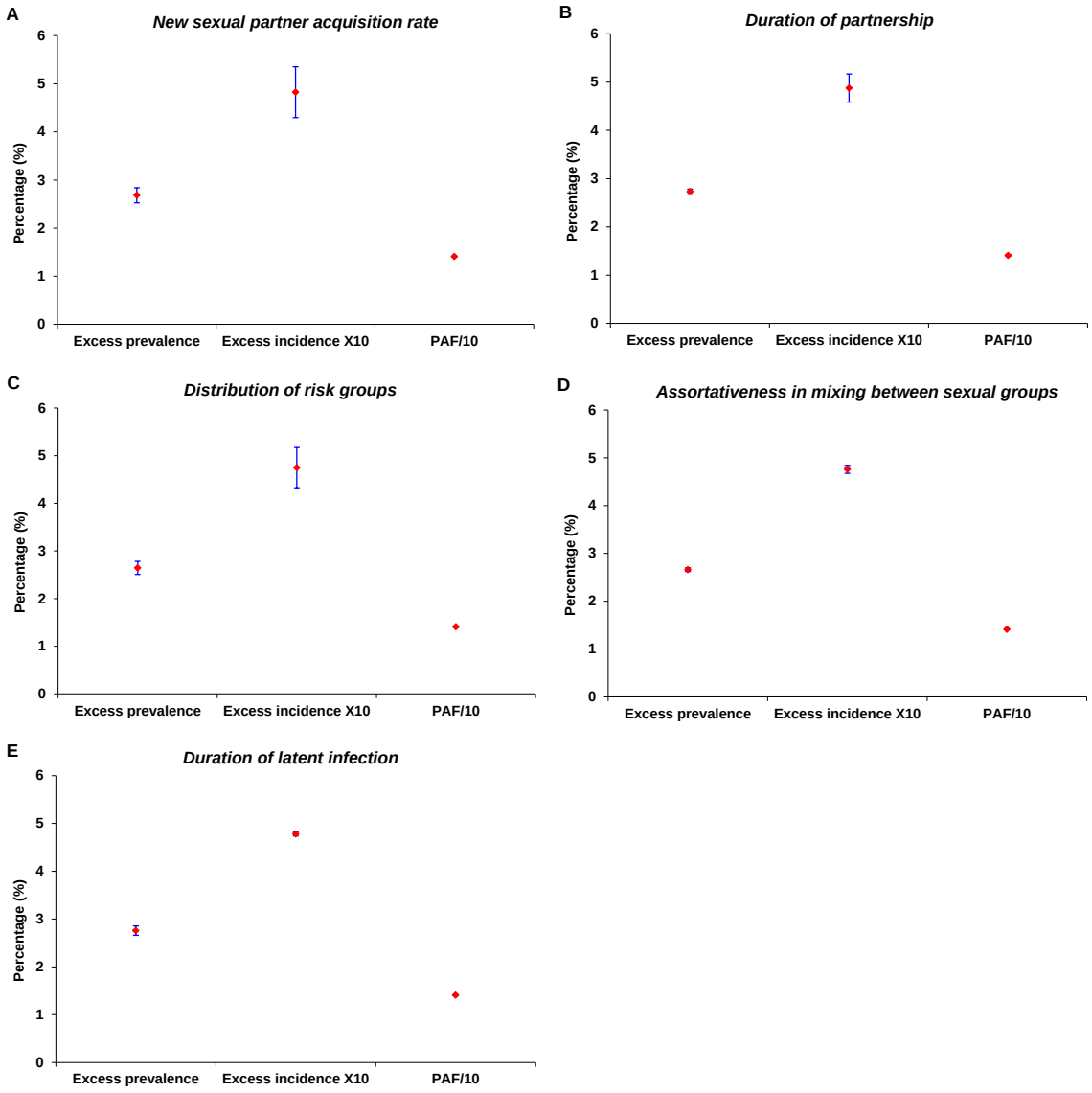


Figure S4.6: Sensitivity and uncertainty analyses of the model structure parameters including (*A*) new sexual partner acquisition rates, (*B*) duration of sexual partnerships, (*C*) distribution of the population among the risk groups, (*D*) assortativeness in the mixing between the risk groups, and (*E*) duration of HIV latent infection. These analyses are performed for the Kisumu calculations of Figure 3 of the main text, but at the endemic equilibrium.



REFERENCES

1. Rizzardini G, Piconi S, Ruzzante S, Fusi ML, Lukwiya M, Declich S, *et al.* Immunological activation markers in the serum of African and European HIV-seropositive and seronegative individuals. *Aids* 1996,**10**:1535-1542.
2. Kalinkovich A, Weisman Z, Leng Q, Borkow G, Stein M, Greenberg Z, *et al.* Increased CCR5 expression with decreased beta chemokine secretion in Ethiopians: relevance to AIDS in Africa. *J Hum Virol* 1999,**2**:283-289.
3. Cohen CR, Moscicki AB, Scott ME, Ma Y, Shiboski S, Bukusi E, *et al.* Increased levels of immune activation in the genital tract of healthy young women from sub-Saharan Africa. *AIDS* 2010,**24**:2069-2074.
4. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature* 2005,**434**:214-217.
5. Hoffman IF, Jere CS, Taylor TE, Munthali P, Dyer JR, Wirima JJ, *et al.* The effect of Plasmodium falciparum malaria on HIV-1 RNA blood plasma concentration. *Aids* 1999,**13**:487-494.
6. Kublin JG, Patnaik P, Jere CS, Miller WC, Hoffman IF, Chimbiya N, *et al.* Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *Lancet* 2005,**365**:233-240.
7. Goletti D, Weissman D, Jackson RW, Graham NM, Vlahov D, Klein RS, *et al.* Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. *J Immunol* 1996,**157**:1271-1278.
8. Toossi Z, Mayanja-Kizza H, Hirsch CS, Edmonds KL, Spahlinger T, Hom DL, *et al.* Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients. *Clin Exp Immunol* 2001,**123**:233-238.
9. Day JH, Grant AD, Fielding KL, Morris L, Moloi V, Charalambous S, *et al.* Does tuberculosis increase HIV load? *J Infect Dis* 2004,**190**:1677-1684.
10. Walson JL, Herrin BR, John-Stewart G. Deworming helminth co-infected individuals for delaying HIV disease progression. *Cochrane Database Syst Rev* 2009:CD006419.
11. Wolday D, Mayaan S, Mariam ZG, Berhe N, Seboxa T, Britton S, *et al.* Treatment of intestinal worms is associated with decreased HIV plasma viral load. *J Acquir Immune Defic Syndr* 2002,**31**:56-62.
12. Wolday D, Berhe N, Akuffo H, Desjeux P, Britton S. Emerging Leishmania/HIV co-infection in Africa. *Med Microbiol Immunol* 2001,**190**:65-67.
13. Berhe N, Wolday D, Hailu A, Abraham Y, Ali A, Gebre-Michael T, *et al.* HIV viral load and response to antileishmanial chemotherapy in co-infected patients. *Aids* 1999,**13**:1921-1925.
14. Brown M, Mawa PA, Joseph S, Bukusuba J, Watera C, Whitworth JA, *et al.* Treatment of Schistosoma mansoni infection increases helminth-specific type 2 cytokine responses and HIV-1 loads in coinfected Ugandan adults. *J Infect Dis* 2005,**191**:1648-1657.

15. Modjarrad K, Zulu I, Redden DT, Njobvu L, Lane HC, Bentwich Z, *et al.* Treatment of intestinal helminths does not reduce plasma concentrations of HIV-1 RNA in coinfected Zambian adults. *J Infect Dis* 2005,**192**:1277-1283.
16. Bush CE, Donovan RM, Markowitz NP, Kvale P, Saravolatz LD. A study of HIV RNA viral load in AIDS patients with bacterial pneumonia. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996,**13**:23-26.
17. Xiao L, Owen SM, Rudolph DL, Lal RB, Lal AA. Plasmodium falciparum antigen-induced human immunodeficiency virus type 1 replication is mediated through induction of tumor necrosis factor-alpha. *J Infect Dis* 1998,**177**:437-445.
18. Froebel K, Howard W, Schafer JR, Howie F, Whitworth J, Kaleebu P, *et al.* Activation by malaria antigens renders mononuclear cells susceptible to HIV infection and re-activates replication of endogenous HIV in cells from HIV-infected adults. *Parasite Immunol* 2004,**26**:213-217.
19. Zhang Y, Nakata K, Weiden M, Rom WN. Mycobacterium tuberculosis enhances human immunodeficiency virus-1 replication by transcriptional activation at the long terminal repeat. *J Clin Invest* 1995,**95**:2324-2331.
20. Shattock RJ, Friedland JS, Griffin GE. Phagocytosis of Mycobacterium tuberculosis modulates human immunodeficiency virus replication in human monocytic cells. *J Gen Virol* 1994,**75 (Pt 4)**:849-856.
21. Lederman MM, Georges DL, Kusner DJ, Mudido P, Giam CZ, Toossi Z. Mycobacterium tuberculosis and its purified protein derivative activate expression of the human immunodeficiency virus. *J Acquir Immune Defic Syndr* 1994,**7**:727-733.
22. Celum C, Levine R, Weaver M, Wald A. Genital herpes and human immunodeficiency virus: double trouble. *Bull World Health Organ* 2004,**82**:447-453.
23. Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr* 2004,**35**:435-445.
24. Wald A. Synergistic interactions between herpes simplex virus type-2 and human immunodeficiency virus epidemics. *Herpes* 2004,**11**:70-76.
25. Mark KE, Wald A, Magaret AS, Selke S, Olin L, Huang ML, *et al.* Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J Infect Dis* 2008,**198**:1141-1149.
26. Mole L, Ripich S, Margolis D, Holodniy M. The impact of active herpes simplex virus infection on human immunodeficiency virus load. *J Infect Dis* 1997,**176**:766-770.
27. Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis* 2002,**186**:1718-1725.
28. Lavreys L, Baeten JM, Kreiss JK, Richardson BA, Chohan BH, Hassan W, *et al.* Injectable contraceptive use and genital ulcer disease during the early phase of HIV-1 infection increase plasma virus load in women. *J Infect Dis* 2004,**189**:303-311.

29. Gray RH, Li X, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F, *et al.* Determinants of HIV-1 load in subjects with early and later HIV infections, in a general-population cohort of Rakai, Uganda. *J Infect Dis* 2004,**189**:1209-1215.
30. Serwadda D, Gray RH, Sewankambo NK, Wabwire-Mangen F, Chen MZ, Quinn TC, *et al.* Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: a nested case-control study in Rakai, Uganda. *J Infect Dis* 2003,**188**:1492-1497.
31. Dunne EF, Whitehead S, Sternberg M, Thepamnuay S, Leelawiwat W, McNicholl JM, *et al.* Suppressive acyclovir therapy reduces HIV cervicovaginal shedding in HIV- and HSV-2-infected women, Chiang Rai, Thailand. *J Acquir Immune Defic Syndr* 2008,**49**:77-83.
32. Baeten JM, Strick LB, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, *et al.* Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. *J Infect Dis* 2008,**198**:1804-1808.
33. Nagot N, Ouedraogo A, Foulongne V, Konate I, Weiss HA, Vergne L, *et al.* Reduction of HIV-1 RNA Levels with Therapy to Suppress Herpes Simplex Virus. *N Engl J Med* 2007,**356**:790-799.
34. Ouedraogo A, Nagot N, Vergne L, Konate I, Weiss HA, Defer MC, *et al.* Impact of suppressive herpes therapy on genital HIV-1 RNA among women taking antiretroviral therapy: A randomized controlled trial. *Aids* 2006,**20**:2305-2313.
35. Zuckerman RA, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, Zuniga R, *et al.* Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. *J Infect Dis* 2007,**196**:1500-1508.
36. Celum C, Wald A, Lingappa JR, Magaret AS, Wang RS, Mugo N, *et al.* Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010,**362**:427-439.
37. Delany S, Mlaba N, Clayton T, Akpomiemie G, Capovilla A, Legoff J, *et al.* Impact of aciclovir on genital and plasma HIV-1 RNA in HSV-2/HIV-1 co-infected women: a randomized placebo-controlled trial in South Africa. *Aids* 2009,**23**:461-469.
38. Mbopi-Keou FX, Gresenguet G, Mayaud P, Weiss HA, Gopal R, Matta M, *et al.* Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in african women: Opportunities for intervention. *Journal of Infectious Diseases* 2000,**182**:1090-1096.
39. McClelland RS, Wang CC, Overbaugh J, Richardson BA, Corey L, Ashley RL, *et al.* Association between cervical shedding of herpes simplex virus and HIV-1. *Aids* 2002,**16**:2425-2430.
40. Baeten JM, McClelland RS, Corey L, Overbaugh J, Lavreys L, Richardson BA, *et al.* Vitamin A supplementation and genital shedding of herpes simplex virus

among HIV-1-infected women: a randomized clinical trial. *J Infect Dis* 2004,**189**:1466-1471.
41. Barnabas RV, Webb EL, Weiss HA, Wasserheit JN. The role of coinfections in HIV epidemic trajectory and positive prevention: a systematic review and meta-analysis. *Aids* 2011,**25**:1559-1573.
42. Fawzi WW, Msamanga GI, Spiegelman D, Wei R, Kapiga S, Villamor E, *et al.* A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004,**351**:23-32.
43. Kupka R, Msamanga GI, Spiegelman D, Morris S, Mugusi F, Hunter DJ, *et al.* Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. *J Nutr* 2004,**134**:2556-2560.
44. Fawzi WW, Msamanga GI, Spiegelman D, Urassa EJ, McGrath N, Mwakagile D, *et al.* Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998,**351**:1477-1482.
45. Baeten JM, McClelland RS, Richardson BA, Bankson DD, Lavreys L, Wener MH, *et al.* Vitamin A deficiency and the acute phase response among HIV-1-infected and -uninfected women in Kenya. *J Acquir Immune Defic Syndr* 2002,**31**:243-249.
46. Otieno PA, Brown ER, Mbori-Ngacha DA, Nduati RW, Farquhar C, Obimbo EM, *et al.* HIV-1 disease progression in breast-feeding and formula-feeding mothers: a prospective 2-year comparison of T cell subsets, HIV-1 RNA levels, and mortality. *J Infect Dis* 2007,**195**:220-229.
47. Delany S, Mayaud P, Clayton T, Mlaba G, Akpomiemie G, Hira K, *et al.* Impact of HSV-2 Suppressive Therapy on Genital and Plasma HIV-1 RNA in HIV-1 and HSV-2-seropositive Women Not Taking ART: A Randomized, Placebo-controlled Trial in Johannesburg, South Africa. In: *14th Conference on Retroviruses and Opportunistic Infections*. Boston; 2008.
48. Fielding KL, Charalambous S, Stenson AL, Pemba LF, Martin DJ, Wood R, *et al.* Risk factors for poor virological outcome at 12 months in a workplace-based antiretroviral therapy programme in South Africa: a cohort study. *BMC Infect Dis* 2008,**8**:93.
49. Charalambous S, Innes C, Muirhead D, Kumaranayake L, Fielding K, Pemba L, *et al.* Evaluation of a workplace HIV treatment programme in South Africa. *Aids* 2007,**21 Suppl 3**:S73-78.
50. Moorman AC, Holmberg SD, Marlowe SI, Von Bargen JC, Yangco BG, Palella FJ, *et al.* Changing conditions and treatments in a dynamic cohort of ambulatory HIV patients: the HIV outpatient study (HOPS). *Ann Epidemiol* 1999,**9**:349-357.
51. Taha TE, Brown ER, Hoffman IF, Fawzi W, Read JS, Sinkala M, *et al.* A phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission. *Aids* 2006,**20**:1313-1321.
52. Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, *et al.* Effectiveness of potent antiretroviral therapy on time to AIDS and death in men

with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA* 1998,**280**:1497-1503.
53. Phair J, Jacobson L, Detels R, Rinaldo C, Saah A, Schrager L, *et al.* Acquired immune deficiency syndrome occurring within 5 years of infection with human immunodeficiency virus type-1: the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* 1992,**5**:490-496.
54. Jacobson LP, Munoz A, Fox R, Phair JP, Dudley J, Obrams GI, *et al.* Incidence of Kaposi's sarcoma in a cohort of homosexual men infected with the human immunodeficiency virus type 1. The Multicenter AIDS Cohort Study Group. *J Acquir Immune Defic Syndr* 1990,**3 Suppl 1**:S24-31.
55. de Wolf F, Spijkerman I, Schellekens PT, Langendam M, Kuiken C, Bakker M, *et al.* AIDS prognosis based on HIV-1 RNA, CD4+ T-cell count and function: markers with reciprocal predictive value over time after seroconversion. *Aids* 1997,**11**:1799-1806.
56. Caro-Murillo AM, Castilla J, Perez-Hoyos S, Miro JM, Podzamczer D, Rubio R, *et al.* [Spanish cohort of naive HIV-infected patients (CoRIS): rationale, organization and initial results]. *Enferm Infecc Microbiol Clin* 2007,**25**:23-31.
57. Sogaard OS, Lohse N, Gerstoft J, Kronborg G, Ostergaard L, Pedersen C, *et al.* Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis* 2008,**47**:1345-1353.
58. Gupta A, Gupte N, Sastry J, Bharucha KE, Bhosale R, Kulkarni P, *et al.* Mother-to-child transmission of HIV among women who chose not to exclusively breastfeed their infants in Pune, India. *Indian J Med Res* 2007,**126**:131-134.
59. Bosch RJ, Bennett K, Collier AC, Zackin R, Benson CA. Pretreatment factors associated with 3-year (144-week) virologic and immunologic responses to potent antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007,**44**:268-277.
60. Gottlieb GS, Sow PS, Hawes SE, Ndoye I, Redman M, Coll-Seck AM, *et al.* Equal plasma viral loads predict a similar rate of CD4+ T cell decline in human immunodeficiency virus (HIV) type 1- and HIV-2-infected individuals from Senegal, West Africa. *J Infect Dis* 2002,**185**:905-914.
61. Zheng NN, Kiviat NB, Sow PS, Hawes SE, Wilson A, Diallo-Agne H, *et al.* Comparison of human immunodeficiency virus (HIV)-specific T-cell responses in HIV-1- and HIV-2-infected individuals in Senegal. *J Virol* 2004,**78**:13934-13942.
62. Sim J, et. al. Log10 differences between viral load by assays (bDNA vs. PCR). In: *AIDS 2000*. Durban; 2000.
63. Emery S, Bodrug S, Richardson BA, Giachetti C, Bott MA, Panteleeff D, *et al.* Evaluation of performance of the Gen-Probe human immunodeficiency virus type 1 viral load assay using primary subtype A, C, and D isolates from Kenya. *J Clin Microbiol* 2000,**38**:2688-2695.
64. Abu-Raddad LJ, Longini IM, Jr. No HIV stage is dominant in driving the HIV epidemic in sub-Saharan Africa. *AIDS* 2008,**22**:1055-1061.
65. Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science* 2006,**314**:1603-1606.

66. Kretzschmar M, Morris M. Measures of concurrency in networks and the spread of infectious disease. *Mathematical Biosciences* 1996,**133**:165-195.
67. Morris M. Sexual networks and HIV. *Aids* 1997,**11**:S209-S216.
68. Watts CH, May RM. The influence of concurrent partnerships on the dynamics of HIV/AIDS. *Math Biosci* 1992,**108**:89-104.
69. May RM, Anderson RM. The Transmission Dynamics of Human Immunodeficiency Virus (Hiv). *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences* 1988,**321**:565-607.
70. Garnett GP, Anderson RM. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. *Philos Trans R Soc Lond B Biol Sci* 1993,**342**:137-159.
71. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li CJ, Wabwire-Mangen F, *et al.* Viral load and heterosexual transmission of human immunodeficiency virus type 1. *New England Journal of Medicine* 2000,**342**:921-929.
72. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, *et al.* Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001,**357**:1149-1153.
73. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, *et al.* Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005,**191**:1403-1409.
74. Gregson S, Nyamukapa CA, Garnett GP, Mason PR, Zhuwau T, Carael M, *et al.* Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet* 2002,**359**:1896-1903.
75. Rottingen JA, Garnett GP. The epidemiological and control implications of HIV transmission probabilities within partnerships. *Sex Transm Dis* 2002,**29**:818-827.
76. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. *J Infect Dis* 2008,**198**:687-693.
77. Pinkerton SD. Probability of HIV transmission during acute infection in Rakai, Uganda. *AIDS Behav* 2008,**12**:677-684.
78. Morgan D, Whitworth J. The natural history of HIV-1 infection in Africa. *Nat Med* 2001,**7**:143-145.
79. Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ, *et al.* Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. *J Infect Dis* 2005,**191**:546-553.
80. UNAIDS. UNAIDS Reference Group on Estimates, Modelling and Projections. 2007.
81. UNAIDS/WHO. *AIDS epidemic update 2007.* In.
82. Buve A, Carael M, Hayes RJ, Auvert B, Ferry B, Robinson NJ, *et al.* The multicentre study on factors determining the differential spread of HIV in four African cities: summary and conclusions. *Aids* 2001,**15 Suppl 4**:S127-131.

83. Buve A, Carael M, Hayes RJ, Auvert B, Ferry B, Robinson NJ, *et al.* Multicentre study on factors determining differences in rate of spread of HIV in sub-Saharan Africa: methods and prevalence of HIV infection. *Aids* 2001,**15 Suppl 4**:S5-14.
84. UNAIDS/WHO. *AIDS epidemic update 2006* 2006.
85. UNAIDS/WHO. *AIDS epidemic update 2004* 2004.
86. WHO/AFRO. *HIV/AIDS Epidemiological Surveillance Update for the WHO African Region 2002 Country Profiles* 2002.
87. UNAIDS/WHO. *Reconciling antenatal clinic-based surveillance and population-based survey estimates of HIV prevalence in sub-Saharan Africa* 2003.
88. Ferry B, Carael M, Buve A, Auvert B, Laourou M, Kanhonou L, *et al.* Comparison of key parameters of sexual behaviour in four African urban populations with different levels of HIV infection. *Aids* 2001,**15 Suppl 4**:S41-50.
89. Morison L, Weiss HA, Buve A, Carael M, Abega SC, Kaona F, *et al.* Commercial sex and the spread of HIV in four cities in sub-Saharan Africa. *Aids* 2001,**15 Suppl 4**:S61-69.
90. Dyer JR, Kazembe P, Vernazza PL, Gilliam BL, Maida M, Zimba D, *et al.* High levels of human immunodeficiency virus type 1 in blood and semen of seropositive men in sub-Saharan Africa. *J Infect Dis* 1998,**177**:1742-1746.
91. Morgan D, Mahe C, Mayanja B, Whitworth JA. Progression to symptomatic disease in people infected with HIV-1 in rural Uganda: prospective cohort study. *BMJ* 2002,**324**:193-196.
92. Jaffar S, Grant AD, Whitworth J, Smith PG, Whittle H. The natural history of HIV-1 and HIV-2 infections in adults in Africa: a literature review. *Bull World Health Organ* 2004,**82**:462-469.
93. Meyer L, Magierowska M, Hubert JB, Rouzioux C, Deveau C, Sanson F, *et al.* Early protective effect of CCR-5 delta 32 heterozygosity on HIV-1 disease progression: relationship with viral load. The SEROCO Study Group. *Aids* 1997,**11**:F73-78.
94. Geskus RB, Miedema FA, Goudsmit J, Reiss P, Schuitemaker H, Coutinho RA. Prediction of residual time to AIDS and death based on markers and cofactors. *J Acquir Immune Defic Syndr* 2003,**32**:514-521.
95. Hubert JB, Burgard M, Dussaix E, Tamalet C, Deveau C, Le Chenadec J, *et al.* Natural history of serum HIV-1 RNA levels in 330 patients with a known date of infection. The SEROCO Study Group. *Aids* 2000,**14**:123-131.
96. Rouzioux C, Hubert JB, Burgard M, Deveau C, Goujard C, Bary M, *et al.* Early levels of HIV-1 DNA in peripheral blood mononuclear cells are predictive of disease progression independently of HIV-1 RNA levels and CD4+ T cell counts. *J Infect Dis* 2005,**192**:46-55.
97. Mellors JW, Kingsley LA, Rinaldo CR, Jr., Todd JA, Hoo BS, Kokka RP, *et al.* Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med* 1995,**122**:573-579.
98. Mellors JW, Rinaldo CR, Jr., Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996,**272**:1167-1170.

99. Pedersen C, Katzenstein T, Nielsen C, Lundgren JD, Gerstoft J. Prognostic value of serum HIV-RNA levels at virologic steady state after seroconversion: relation to CD4 cell count and clinical course of primary infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997,**16**:93-99.
100. Morgan D, Malamba SS, Orem J, Mayanja B, Okongo M, Whitworth JA. Survival by AIDS defining condition in rural Uganda. *Sex Transm Infect* 2000,**76**:193-197.
101. Lagarde E, Auvert B, Carael M, Laourou M, Ferry B, Akam E*, et al.* Concurrent sexual partnerships and HIV prevalence in five urban communities of sub-Saharan Africa. *Aids* 2001,**15**:877-884.
102. Lingappa JR, Baeten JM, Wald A, Hughes J, Thomas KK, Mujugira A, *et al.* Daily acyclovir delays HIV-1 disease progression among HIV-1/HSV-2 dually-infected persons: a randomized trial. Partners in Prevention HSV/HIV. International AIDS Society Conference, Cape Town, Abstract WELBC102. 2009.
103. Kiwanuka N, Laeyendecker O, Robb M, Kigozi G, Arroyo M, McCutchan F*, et al.* Effect of human immunodeficiency virus Type 1 (HIV-1) subtype on disease progression in persons from Rakai, Uganda, with incident HIV-1 infection. *J Infect Dis* 2008,**197**:707-713.
104. Lutalo T, Gray RH, Wawer M, Sewankambo N, Serwadda D, Laeyendecker O*, et al.* Survival of HIV-infected treatment-naive individuals with documented dates of seroconversion in Rakai, Uganda. *AIDS* 2007,**21 Suppl 6**:S15-19.
105. Obasi A, Mosha F, Quigley M, Sekirassa Z, Gibbs T, Munguti K*, et al.* Antibody to herpes simplex virus type 2 as a marker of sexual risk behavior in rural Tanzania. *J Infect Dis* 1999,**179**:16-24.
106. Caldwell C. Quiggin (1989). J. Caldwell, P. Caldwell and P. Quiggin, The social context of AIDS in Sub-Saharan Africa. *Population and Development Review* 1989,**15**:185–234.
107. Lee RM, Renzetti CM. The problems of researching sensitive topics. *American Behavioral Scientist* 1990,**33**:510-528.
108. Wadsworth J, Field J, Johnson AM, Bradshaw S, Wellings K. Methodology of the National Survey of Sexual Attitudes and Lifestyles. *J R Stat Soc Ser A Stat Soc* 1993,**156**:407-421.
109. Morris M. Telling tails explain the discrepancy in sexual partner reports. *Nature* 1993,**365**:437-440.
110. Morris M. *Network Epidemiology: A Handbook for Survey Design and Data Collection*: Oxford University Press; 2004.
111. Cleland J, Boerma JT, Carael M, Weir SS. Measurement of sexual behaviour. *Sexually Transmitted Infections* 2004,**80**:ii1-ii90.
112. Ghani AC, Swinton J, Garnett GP. The role of sexual partnership networks in the epidemiology of gonorrhea. *Sex Transm Dis* 1997,**24**:45-56.