Supplementary Digital Content to manuscript:

Ageing with HIV in South Africa

General model structure

We used STDSIM, a stochastic microsimulation model of the transmission and control of HIV and other STIs [1-3]. The model simulates the life course of individuals in a dynamic network of sexual contacts. Events like partnership formation or the acquisition of infections are the result of random processes, determined by probability distributions. Therefore, the results of the model are subject to stochastic variation. It is necessary to perform multiple runs and average the results to diminish the stochasticity in predictions.

The model consists of four modules: *demography*, *sexual behavior*, *transmission and natural history*, and *interventions*. The demography module implements the processes of birth, death, and migration. Processes for initiation and dissolution of sexual relationships, for mixing according to age preference, for sexual contacts within relationships and for sexual contacts between clients and sex workers are defined in the sexual behavior module. In the transmission and natural history module, transmission probabilities per sexual contact are specified for HIV and other simulated STIs. Finally, the interventions module specifies the timing and effectiveness of control measures in curbing transmission or enhancing survival. More details about the general model structure can be found in van der Ploeg *et al* [1], Korenromp *et al* [2], and Orroth *et al* [3]. The modeling of antiretroviral therapy (ART) is new with regard to these papers, and will be explained below.

Modeling ART

HIV stages and CD4+ cell counts

HIV infection is modeled in 6 consecutive stages: an acute stage (10 weeks), 2 asymptomatic stages (125 weeks each), 2 symptomatic stages (120 weeks and 80 weeks respectively), and an AIDS stage (40 weeks) (figure S1). The resulting survival time after infection, in the absence of treatment, is on average 10 years. This is consistent with observed data [4] the same as in previous STDSIM studies [3, 5], and nearly equal to the 11 years recently assumed in the modeling study by Granich *et al* [6]. Transmission probabilities are increased by a factor of 15 during the acute stage, 3 during the symptomatic stages and 7.5 during the AIDS stage, relative to the asymptomatic stages [3, 5]. The durations of the acute, asymptomatic and symptomatic stages are assumed to be exponentially distributed, whereas a Weibull distribution with a shape parameter 2 is used to describe the AIDS stage [3].

Initial CD4+ cell counts of HIV negatives are randomly drawn from a lognormal distribution with median 7.02 (equivalent to 1116 cells/µL) and a standard deviation of 0.303, which has previously been used by Granich *et al* and Williams *et al* [6, 7]. For each individual, this initial value is multiplied by x, the relative CD4+ cell count, which starts at 1 and continuously decreases during HIV progression (red line in figure S1). Analogous to Granich *et al* [6] and Williams *et al* [7], we assumed a rapid decline of x to 0.75 during the acute stage, followed by a linear decrease during the remaining stages until $x = 0.005$, after which the individual dies of AIDS [6, 7].

ART

At a rate $r_h(i)$, patients can visit a clinic and get a CD4+ cell count test. These health seeking rates can be varied per HIV stage (figure S1). When the CD4+ cell count is equal to or below a given threshold (e.g. 200 or 350 cells/µL), ART is initiated, and the patient moves to the corresponding ART stage (figure S1). The durations of the HIV stages on ART are three times that of the ART-naïve HIV-infected, based on a study by Walensky *et al*, who used randomized trials and observational cohorts to

assess the survival of HIV-patients on ART [8]. ART is assumed to decrease infectivity of HIV by 92%, based on a meta-analysis by Attia *et al* [9]. This value was also used in a recent modeling study by Dodd *et al* [10] and is the same as recently found by Donnell *et al* [11]. Patients stop treatment permanently at a rate r_d (annual dropout rate).

Baseline quantification of STDSIM

The model parameters were quantified to represent the Hlabisa sub-district of the Umkhanyakunde District in KwaZulu-Natal (KZN), South Africa [12, 13].

Demography

We used location-specific fertility- and migration-rates in order to fit the demographic structure of the Hlabisa sub-district [14]. In recent years, fertility rates in the area have been declining [15, 16]. Therefore, we adjusted fertility rates in accordance with published values: 4.4 until 1992; 3.9 in 1992-1996; 3.3 in 1997-2001; and 2.8 from 2002 onwards [16]. We used age- and sex-specific in- and out-migration rates as published by the Africa Centre [14]. Background mortality rates (i.e. excluding HIV-related death) were based on Coale-Demeney life tables (table: *South 55*) [17]. These background mortality rates resulted in a slight overestimation in the size of the male population aged 50+. In order to adjust for this overestimation, we corrected all results of men aged over 50 by a factor 0.85.

Sexual risk behavior

We assumed an average age of sexual debut of 18 years for women and 20 for men, based on observational data [18]. The study area is characterized by significant amounts of circular migration with about 60% of the adult male population spending most nights away in urban areas, where they frequently have additional sexual partners, often including sex workers [14, 19, 20]. We therefore adopted rates of visits to commercial sex workers (CSWs) used in the STDSIM quantification for Kisumu (Kenya) [3], which has an HIV prevalence similar to that in our study population: ANC prevalence 34% in Kisumu [3] versus 36% in KZN [21] in 2000. In the model, these CSWs are subject

to the same ART roll-out as the rest of the population. All age- and sex-related patterns regarding partnership formation were left as they were in the *four cities* study [3]. However, to make the model reflect local data regarding HIV prevalence in the population aged 50+ [22], we assumed sexual behavior to remain at the same level from age 45 onwards, together with a 25% reduction in the frequency of sexual contacts within relationships for those aged over 50. The overall partner change rate ('promiscuity factor'), which reflects the tendency of individuals to become available to form new sexual relationships [2], was calibrated such that the model accurately reflects the trend in HIV prevalence as available from antenatal clinic (ANC) data (2000-2004) [21] and ACDIS sero-surveillance data in the population aged 15-49 (2004-2009) [12] and 50+ (2007 and 2008) [22]. This parameter needed to be increased by 10% compared to the quantification for Kisumu [3]. In 2004, the population prevalence in the ACDIS cohort was 0.6 (25%/41%) that of the ANC prevalence in KZN, and we therefore multiplied the ANC prevalences by this factor. The resulting fit of the HIV prevalence in the 15-49 and 50+ age groups is illustrated in Figure 1A of the main text.

Transmission and natural history

We modeled the following STIs: HIV, Chancroid, Gonorrhea, Chlamydia, Syphilis, and HSV-2. STIs other than HIV were included for two reasons: Firstly, these STIs act as co-factors for HIV transmission, and are therefore important in reproducing the baseline HIV epidemic as observed in Hlabisa. Secondly, they provide additional support regarding the goodness fit of sexual (risk) behavior as the number of recent sexual partners has limitations regarding reporting bias. All biological parameters (transmission probabilities, co-factor effects, and natural history) are the same as in the recent STDSIM application for the *Four cities study* [3, 23], and can be found in table 1 of Orroth *et al* [3]

Interventions

We assumed a linear increase in the rate r_h (i) of seeking and receiving voluntary counseling and testing for HIV, as a function of stage number i (i = 1 to 5), not including the acute stage (figure S1).

We estimated an intercept and slope by fitting the predicted distribution of CD4+ cell counts during the patient‘s first test to that recorded in the Hlabisa Treatment and Care Programme [13] (intercept = 0.1 tests/year, slope = 1.1). In the model we phased in ART in accordance with the timeline of the actual rollout among the 17 clinics in Hlabisa sub-district. Whenever a new health facility started distributing ART, we increased the number of patients seeking care by $1/17^{th}$. Furthermore, we assumed that clinics start at 50% capacity, and run at full capacity after 1 year. After 4 years of the ART program, 5% of the population that initiated ART was observed to be lost to follow-up [13]. Therefore, in the model we assumed an annual dropout rate r_d of 1.27% and we further assumed that these patients do not initiate ART again.

We assumed an increase in condom use in casual (non-marital) and sex worker contacts in 1998 (from 0% to 15%) and 2003 (from 15% to 25%), according to KZN data [24-26]. For the whole study period, we assumed that condoms were not used in steady (marital) relationships. In addition, we incorporated a slight improvement in STI treatment coverage based on the introduction of syndromic treatment guidelines in 1995 [27, 28] (Men: coverage of treatment for chlamydia- and gonorrhea-symptoms from 20% to 50%, syphilis- and chancroid-symptoms from 20% to 60%; Women: coverage of treatment for chlamydia- and gonorrhea-symptoms from 15% to 40%, syphilis- and chancroid-symptoms from 15% to 50%). We used the best available estimate of the KZN circumcision rate (26% in 2003) [26].

Results of fitting the model to data

Our model was able to accurately simulate the demographic structure, sexual behavior dynamics, and HIV and STI prevalence in the Hlabisa sub-district (figure 1A in the main text, and figure S2). The reported number of recent sexual partners of women is lower than predicted by the model (figure S2B). This is likely a result of underreporting, something that is commonly observed in studies on reported sexual risk behavior [30-33]. The prevalence of classic STIs, which is often viewed as a more

accurate indicator of risk behavior, accurately fits the data for women (figure S2C). There were no data available on the number of partners or STI prevalences in the population aged over 50 years.

As a consequence of the good fit of the underlying demography, risk behavior and co-factors, the predicted HIV prevalence is very close to that observed in the population aged 15-49 (within 0.3% to 0.9% between 2004 and 2009; figure 1A) and 50+ (within 0.4% and 0.3% in 2007 and 2008 respectively; figure 1A). Furthermore, the cumulative number of people initiating treatment in the model accurately reflects the actual treatment initiation numbers observed in the program (figure S2D). Finally, the model accurately fits CD4+ cell count distributions as observed in the Hlabisa Treatment and Care Programme, both at the time of initial testing (figure S2E) and one year after initiating ART (figure S2F).

References

1. van der Ploeg CPB, Van Vliet C, De Vlas SJ, et al. STDSIM: A microsimulation model for decision support in STD control. Interfaces **1998**; 28: 84-100.
2. Korenromp EL, Van Vliet C, Bakker R, De Vlas SJ, Habbema JDF. HIV spread and partnership reduction for different patterns of sexual behavior – a study with the microsimulation model STDSIM. Math Pop Studies **2000**; 8: 135-73.
3. Orroth KK, Freeman EE, Bakker R, et al. Understanding the differences between contrasting HIV epidemics in east and west Africa: results from a simulation model of the Four Cities Study. Sex Transm Infect **2007**; 83 Suppl 1: i5-16.
4. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JA. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? AIDS **2002**; 16: 597-603.

5. White RG, Orroth KK, Glynn JR, et al. Treating curable sexually transmitted infections to prevent HIV in Africa: still an effective control strategy? J Acquir Immune Defic Syndr **2008**; 47: 346-53.

6. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet **2009**; 373: 48-57.

7. Williams BG, Korenromp EL, Gouws E, Schmid GP, Auvert B, Dye C. HIV infection, antiretroviral therapy, and CD4+ cell count distributions in African populations. J Infect Dis **2006**; 194: 1450-8.

8. Walensky RP, Wolf LL, Wood R, et al. When to start antiretroviral therapy in resource-limited settings. Ann Intern Med **2009**; 151: 157-66.

9. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS **2009**; 23: 1397-404.

10. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. AIDS **2010**; 24: 729-35.

11. Donnell D, Baeten J, Kiarie J, Thomas K, Stevens W, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet **2010;** 375: 2092-2098.

12. Tanser F, Hosegood V, Bärnighausen T, et al. Cohort Profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. Int J Epidemiol **2008**; 37: 956-62.

13. Houlihan CF, Bland R, Mutevedzi P, et al. Cohort Profile: Hlabisa HIV treatment and care programme. Int J Epidemiol **2010** (Published ahead of print: Feb 12).

14. Muhwava W, Nyirenda M. Demographic and socio-economic trends in the ACDIS, monograph No 2. Mtubatuba, South Africa: Africa Centre for Health and Population Studies; 2007 (accessed April 30, 2010, at http://www.africacentre.ac.za/Default.aspx?tabid=105).

15. Camlin CS, Garenne M, Moultrie TA. Fertility trend and pattern in a rural area of South Africa in the context of HIV/AIDS. Afr J Reprod Health **2004**; 8: 38-54.

16. Moultrie TA, Hosegood V, McGrath N, Hill C, Herbst K, Newell ML. Refining the criteria for stalled fertility declines: an application to rural KwaZulu-Natal, South Africa, 1990-2005. Stud Fam Plann **2008**; 39: 39-48.

17. Coale AJ, Demeny P. Regional Model Life Tables and Stable Populations. New York: Academic Press; 1983.

18. McGrath N, Nyirenda M, Hosegood V, Newell ML. Age at first sex in rural South Africa. Sex Transm Infect **2009**; 85 Suppl 1:i49-55.

19. Lurie MN, Williams BG, Zuma K, et al. Who infects whom? HIV-1 concordance and discordance among migrant and non-migrant couples in South Africa. AIDS **2003**; 17: 2245-52.

20. Campbell C. Migrancy, masculine identities and AIDS: the psychosocial context of HIV transmission on the South African gold mines. Soc Sci Med **1997**; 45: 273-81.

21. UNAIDS. Epidemiological Fact Sheet on HIV and AIDS South Africa. Geneva: UNAIDS; **2008**. (accessed April 30, 2010, at http://www.unaids.org/en/CountryResponses/Countries/south_africa.asp)

22. Wallrauch C, Barnighausen T, Newell M. HIV prevalence and incidence in people 50 years and older in rural South Africa. S Afr Med J **2010**; 100: 812-4.

23. Carael M, Holmes KK. Dynamics of HIV epidemics in sub-Saharan Africa: introduction. AIDS **2001**; 15 Suppl 4: S1-4.

24. Demographic and Health Survey of South Africa. Pretoria: Department of health; 1998. (accessed April 30, 2010, at http://www.doh.gov.za/facts/1998/sadhs98/)

25. Colvin M, Abdool Karim SS, Connolly C, Hoosen AA, Ntuli N. HIV infection and asymptomatic sexually transmitted infections in a rural South African community. Int J STD AIDS **1998**; 9: 548-50.

26. Demographic and Health Survey of South Africa. Pretoria: Department of Health; 2003. (accessed April 30, 2010, at http://www.measuredhs.com/countries/country_main.cfm?ctry_id=55&c=South Africa)

27. Wilkinson D, Connolly AM, Harrison A, Lurie M, Karim SS. Sexually transmitted disease syndromes in rural South Africa. Results from health facility surveillance. Sex Transm Dis **1998**; 25: 20-3.

28. White RG, Moodley P, McGrath N, et al. Low effectiveness of syndromic treatment services for curable sexually transmitted infections in rural South Africa. Sex Transm Infect **2008**; 84: 528-34.

29. Todd J, Cremin I, McGrath N, et al. Reported number of sexual partners: comparison of data from four African longitudinal studies. Sex Transm Infect **2009**; 85 Suppl 1: i72-80.

30. Weinhardt LS, Forsyth AD, Carey MP, Jaworski BC, Durant LE. Reliability and validity of self-report measures of HIV-related sexual behavior: progress since 1990 and recommendations for research and practice. Arch Sex Behav **1998**; 27: 155-80.

31. Carael M, Cleland J, Adeokun L. Overview and selected findings of sexual behaviour surveys. AIDS **1991**; Suppl 1: S65-74.

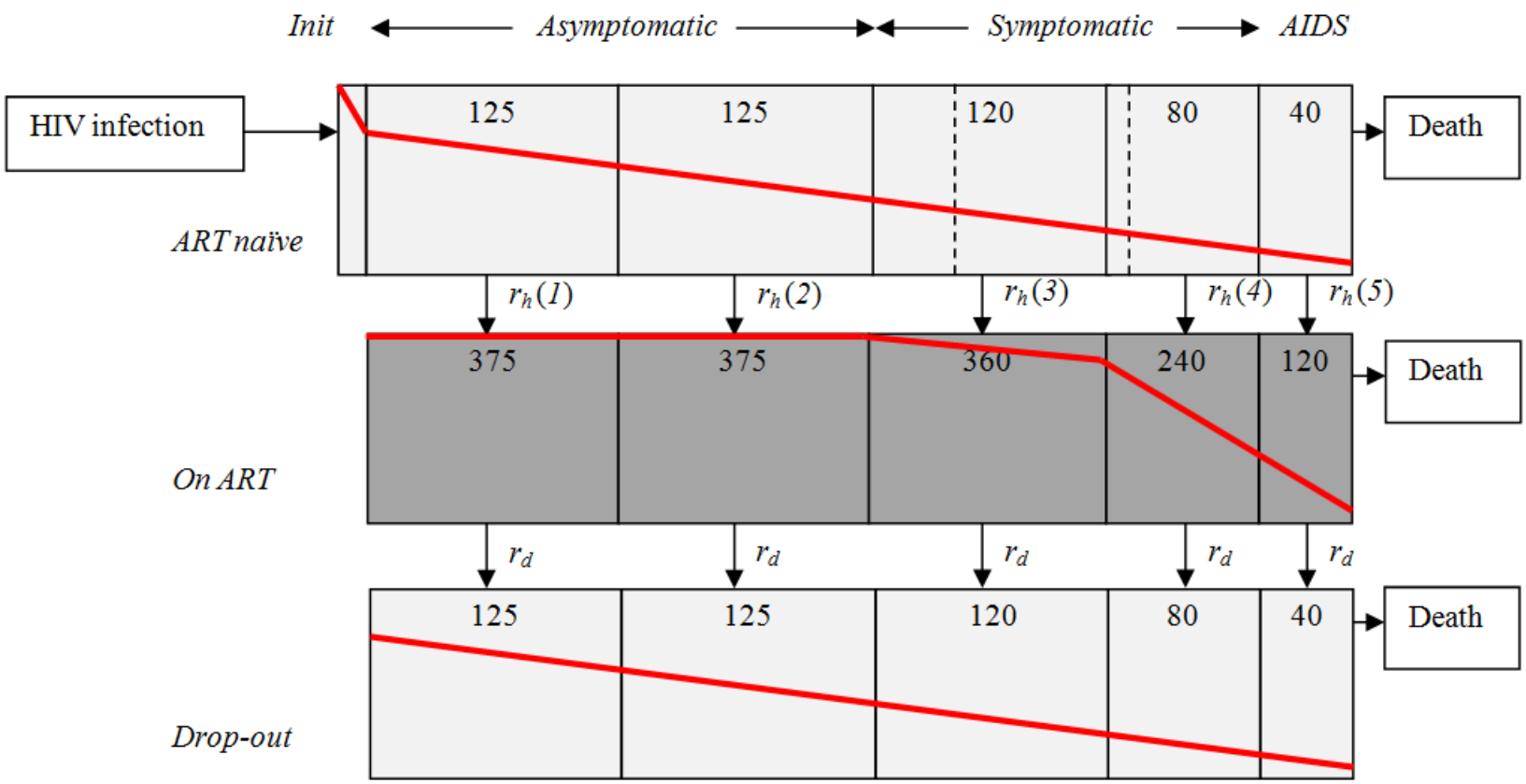
32. Nnko S, Boerma JT, Urassa M, Mwaluko G, Zaba B. Secretive females or swaggering males? An assessment of the quality of sexual partnership reporting in rural Tanzania. Soc Sci Med **2004**; 59: 299-310.

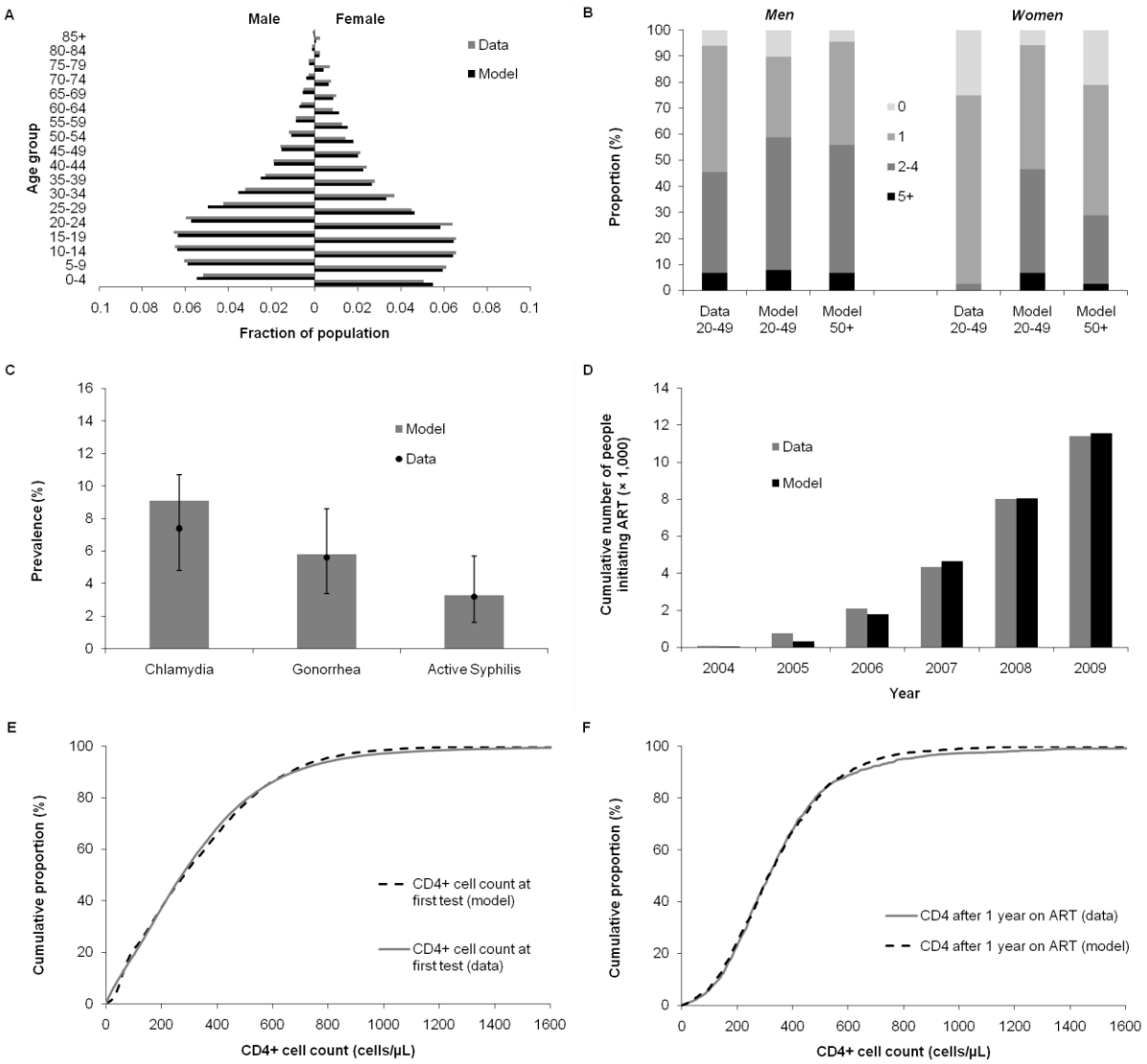
33. Lees S, Cook C, Vallely A, et al. Comparison of sexual behavior data collected using a coital diary and a clinic-based interview during a microbicide pilot study in Mwanza, Tanzania. Sex Transm Dis **2010**; ePub ahead of print: April 21 2010

Captions to figures

Figure S1. Model representation of HIV stages, CD4+ cell counts and ART. Each box represents an HIV stage with corresponding average duration in weeks. The red line in the boxes represents the relative CD4+ cell count *x*, which overall declines from 1 (top of the box) to 0.005 (close to bottom of the box). After infection patients enter in the acute phase of the ART naïve HIV infection and progress through five stages after which they die (*Death*). Parameters r_h (1) to r_h (5) are rates of successful health seeking behavior of HIV infected individuals in the corresponding ART-naïve stages. Health seeking behavior rates are assumed to increase linearly with stage number. Patients initiate ART when their CD4+ cell count is below a certain threshold (i.e. 200 cells/µL or 350 cells/µL). Parameter r_d is the dropout rate of patients on ART. The dashed vertical lines in the ART naïve boxes represent the average duration until HIV infected individuals reach CD4+ cell counts of 350 cells/µL (left) and 200 cells/µL (right), respectively.

Figure S2. Comparison of model predictions with data of the HIV-epidemic and ART rollout in Hlabisa sub-district of the Umkhanyakunde district in KwaZulu-Natal (KZN), South Africa. ***A:*** Modeled and actual demographic structure in 2006. Data derived from Muhwava & Nyirenda [14]; ***B.*** Total number of partners in the last 12 months in men and women aged 20-49 years and 50+ years in the model versus total number of reported partners in men and women aged 20-49 derived from Todd *et al* [29] ***C.*** Modeled and observed prevalence of classic STIs in women aged 15-49 in KZN. Data derived from White *et al* [28]. ***D:*** Cumulative number of people initiating treatment in the Hlabisa Treatment and Care Programme, model versus unpublished data [13]; ***E.*** Cumulative distribution of CD4+ cell counts at first test, model compared to data for 2007 to 2009. Data derived from the Hlabisa Treatment and Care Programme [13]. ***F.*** Cumulative distribution of CD4+ cell counts after 1 year on ART, model compared to data. Data derived from the Hlabisa Treatment and Care Programme [13].


Init
Asymptomatic
Symptomatic
AIDS
HIV infection
125
125
120
80
40
Death
ART naïve
$r_h(1)$
$r_h(2)$
$r_h(3)$
$r_h(4)$
$r_h(5)$
375
375
360
240
120
Death
On ART
r_d
r_d
r_d
r_d
r_d
125
125
120
80
40
Death
Drop-out


A
Male
Female
Data
Model
Age group
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
0.1 0.08 0.06 0.04 0.02 0 0.02 0.04 0.06 0.08 0.1
Fraction of population
B
Men
Women
Proportion (%)
0
1
2-4
5+
Data 20-49
Model 20-49
Model 50+
Data 20-49
Model 20-49
Model 50+
C
Prevalence (%)
Model
Data
Chlamydia
Gonorrhea
Active Syphilis
D
Cumulative number of people initiating ART (× 1,000)
Data
Model
2004
2005
2006
2007
2008
2009
Year
E
Cumulative proportion (%)
CD4+ cell count at first test (model)
CD4+ cell count at first test (data)
CD4+ cell count (cells/μL)
F
Cumulative proportion (%)
CD4 after 1 year on ART (data)
CD4 after 1 year on ART (model)
CD4+ cell count (cells/μL)