## Modelling the demographic impact of HIV/AIDS in South Africa and the likely impact of interventions

L. F. Johnson\* and R. E. Dorrington\*

\*Centre for Actuarial Research, University of Cape Town, South Africa

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#### Abstract

This paper describes how the AIDS and Demographic projection model of the Actuarial Society of South Africa (ASSA) models the demographic impact of HIV/AIDS on the South African population through modelling of sexual behaviour and the impact of interventions to change behaviour and provide antiretroviral therapy. Results of several scenarios are presented and discussed.

#### **INTRODUCTION**

South Africa is one of the few African countries with nationally representative HIV prevalence data and good vital registration data (Bradshaw, Laubscher, Dorrington *et al.* 2004; Department of Health 2004). However, these data cannot provide planners with a direct measure of the demographic impact of HIV/AIDS or an indication of the likely future evolution of the epidemic. For this, mathematical models, calibrated to these data, are necessary. These models, if appropriately constructed, can also be used to assess the likely effect of different prevention and treatment programmes, as well as likely needs for treatment and orphan care, etc., and are therefore an important tool in policy formulation.

A large number of mathematical models have been developed to simulate the impact of HIV/AIDS and the likely effect of prevention and treatment programmes. These models can be classified into two broad groups: individual-based stochastic simulation models, which randomly generate events such as infection and death for each individual in the population, or as 'population average' deterministic models, which divide the population into cohorts of individuals, and compute average numbers of events in each cohort on the assumption that all individuals in a cohort share the same characteristics.

Of the stochastic models that have been developed, most have focussed on simulating the effects of HIV prevention rather than treatment (Bracher, Santow and Cotts Watkins 2004; Korenromp, Van Vliet, Bakker *et al.* 2000; Robinson, Mulder, Auvert *et al.* 1995; Van der Ploeg, Van Vliet, De Vlas *et al.* 1998). Because of the heavy computational requirements associated with individual-based simulation, populations simulated are typically limited in size to 10 000 to 20 000 individuals. This results in a significant amount of stochastic variation, which makes it difficult to calibrate the model to HIV prevalence and mortality data (Korenromp, Van Vliet, Bakker *et al.* 2000). In addition these models require a fairly extensive range of assumptions as input.

Deterministic models tend to be used for larger populations and in situations where data for setting assumptions are quite limited. Many of these models have been used to illustrate the differences between the effects of HIV prevention and treatment programmes (Nagelkerke, Jha, de Vlas *et al.* 2002; Salomon, Hogan, Stover *et al.* 2005; Stover, Walker, Garnett *et al.* 2002). However, many of these models are based on very broad age divisions of the population, which makes them inappropriate for projecting the population over anything but short periods, and forces calibration to be crude. In some cases, the results of these simple deterministic models have been incorporated into cohort component projection models such as DemProj (Stover 2004), in an attempt to estimate the demographic impact of HIV/AIDS more accurately. However, Heuveline (2003) identifies a number of problems with this approach, including failure to allow for changes in the age profile of HIV cases over the course of the epidemic, difficulties in incorporating the effect of HIV on fertility, and difficulties in establishing parameters for a cohort component projection model in a hypothetical 'no AIDS' scenario.

The ASSA2002 AIDS and Demographic model is a combined cohort component projection model and HIV/AIDS model, developed by the Actuarial Society of South Africa to estimate the impact of HIV/AIDS in South Africa. The basic structure of the ASSA2000 version of the model has been described previously (Dorrington 2000). The objective of this paper is to describe how the basic cohort component projection model has been extended to model the demographic impact of HIV/AIDS, to describe how HIV prevention and treatment programmes are modelled, and to demonstrate the significance of these prevention and treatment programmes in demographic terms.

#### METHOD

The ASSA2002 model was developed from an earlier version of the model, ASSA2000, which did not allow for the effects of prevention and treatment programmes. The model is only concerned with heterosexual and mother-to-child transmission. It is assumed that the epidemic is started by the 'importing' of a number of infected individuals in 1985, a few years prior to the first reports of AIDS cases in the heterosexual population. Age-specific assumptions about the population profile in 1985, fertility, non-AIDS mortality and international migration are based on analyses of 1970, 1996 and 2001 censuses and the 1998 Demographic and Health Survey (DHS), and are not described here. Vital registration of adult deaths is estimated to be about 85% complete for the years 1996-2001 and thus provides a fairly reliable measure, in addition to the data on prevalence, against which to calibrate the model.

The model has been programmed both in Excel/VBA and in Visual C++, and the Excel/VBA version is freely available online (Actuarial Society of South Africa 2004). A separate model, which makes use of output from the AIDS and Demographic model, has been developed to estimate numbers of orphans from the ASSA2002 outputs, and is described elsewhere (Johnson and Dorrington 2001).

#### Modelling of sexual behaviour

Individuals are assumed to be at risk of acquiring HIV through heterosexual contact between the ages of 14 and 59. Within this age band, individuals are split into four

'risk groups': a 'PRO' group, which represents sex workers and their frequent clients; a 'STD' group, which represents individuals who are regularly infected with sexually transmitted diseases (STDs); a 'RSK' group, consisting of individuals who are at risk of HIV infection although not regularly infected with other STDs; and a 'NOT' group, comprising individuals who are not at risk of infection (either because they are not sexually active or because they are in long-term mutually monogamous relationships). The assumed relative sizes of these risk groups and their sexual behaviour characteristics are shown in Table 1.

	Female risk group				Male risk group				
	PRO	STD	RSK	NOT	PRO	STD	RSK	NOT	
% of 25-59 population in risk group in 1985	1%	20%	23%	56%	1%	20%	23%	56%	
Average annual number of new partners	250	12	1	-	233*	13*	$1^*$	-	
% of new partners in									
PRO group	0.75	0.2	0	-	$0.8^*$	$0.26^{*}$	0	-	
STD group	0.25	0.75	0.4	-	$0.2^{*}$	$0.71^{*}$	$0.47^{*}$	-	
RSK group	0	0.05	0.6	-	0	$0.04^*$	$0.53^{*}$	-	
Average # coital acts per									
partnership if partner is in									
PRO group	1	3	-	-	1	1	-	-	
STD group	1	13	50	-	3	13	45	-	
RSK group	-	45	95	-	-	50	95	-	
Condom usage adjustment factor	2	1.5	1	-	2	1.5	1	-	
Fertility adjustment factor	0.4	0.7	1	$1.12^{\dagger}$	-	-	-	-	

#### **Table 1: Characteristics of risk groups**

\* Determined to be consistent with female assumptions.<sup>†</sup> Determined to be such that the fertility adjustment factors, when weighted by the proportion of the sexually experienced population in each risk group, averaged to 1.

Where there are empirical data, these are used to set the order of magnitude of the parameters, otherwise parameter values are determined as part of the calibration process. The relative sizes of the risk groups are assumed to be the same for males and females, as are the relative frequencies of condom usage in each risk group. The assumed average annual numbers of partners, for males, and male preferences regarding the risk group of their partners, are determined to be consistent with the assumptions for females. Average fertility rates are assumed to apply to women in the RSK group, while women in the PRO and STD groups have fertility rates that are lower than the average by 60% and 30% respectively; this is to allow for the effects of higher contraceptive usage and STD incidence in these groups.

Rates of condom use are assumed to be higher in the PRO and STD groups, as condoms tend to be used more frequently in short-term casual relationships (Department of Health 1999; Van der Ryst, Joubert, Steyn *et al.* 2001; Williams, Gilgen, Campbell *et al.* 2000). The condom usage adjustment factors in Table 1

represent the factor by which the average age-specific rates of condom usage are multiplied to obtain age-specific condom usage rates in each risk group. The average age-specific rates for 1998 were set to be the same as those recorded in the 1998 DHS, and are shown in Table 2. Frequency of condom use appears to have increased substantially in recent years (Human Sciences Research Council 2002; Reproductive Health Research Unit 2004), and it is assumed that this is the result of social marketing programmes. In the absence of these social marketing programmes, it is assumed that condom usage would have remained constant at half the level observed in 1998, in all years.

Individuals become sexually active between the ages of 13 and 25. At age 14, it is assumed that 10% of individuals are sexually experienced, and 12% of the remainder are assumed to become sexually experienced in the next year. The annual probability of becoming sexually experienced is assumed to increase linearly with respect to age, until all individuals are sexually experienced at age 25. These assumptions were set to produce rates of sexual experience consistent with those observed in surveys (Department of Health 1999; Reproductive Health Research Unit 2004), and are shown in Table 2. The same sexual debut assumptions are used for males and females, as surveys do not suggest that there is a significant difference in sexual experience between males and females at young ages (Reproductive Health Research Unit 2004; Williams, Gilgen, Campbell *et al.* 2000). Individuals remain in the NOT group until they become sexually experienced, after which they either remain in the NOT group or get moved into the other risk groups. The model assumes that people do not change risk group after sexual debut.

Average rate of			Average	Age of male			
Age group	condo	n usage	% sexually	partners			
	1985	1998*	experienced	Average	Variance		
15-19	9.8%	19.6%	46%	24.31	19.80		
20-24	7.2%	14.4%	90%	28.84	25.24		
25-29	3.8%	7.6%	100%	32.95	49.43		
30-34	3.3%	6.6%	100%	37.63	55.10		
35-39	1.5%	3.0%	100%	42.69	70.99		
40-44	1.5%	3.0%	100%	47.04	66.86		
45-49	1.5%	3.0%	100%	51.45	56.05		
50-54	1.5%	3.0%	100%	$55.86^{\dagger}$	$45.24^{\dagger}$		
55-59	1.5%	3.0%	100%	$60.27^{\dagger}$	$34.43^{\dagger}$		

#### Table 2: Age-specific behavioural assumptions

\* Allowing for the effect of social marketing programmes. <sup>†</sup>Extrapolated from estimates at younger ages

Although individuals cannot move between risk groups after sexual debut, allowance is made for rates of partnership formation and coital frequencies to vary with age. For females, a sexual activity index is constructed using the formula

$$S_{x} = \sqrt{\frac{46(x-13)\exp(-0.005(x-13)^{2})}{\sum_{u=14}^{59} (u-13)\exp(-0.005(u-13)^{2})}}$$
(1)

where  $S_x$  is the multiple by which the average number of partners and the average number of coital acts per partnership increases at age x. The shape parameter (0.005) and position parameter (13) were set at levels that ensured patterns of HIV prevalence by age were as far as possible consistent with those observed in surveys (Department of Health 2004). The mean age of male partners and the variance of male partner ages were estimated from the 1998 DHS, for each five-year age band, and are shown in Table 2. For a woman aged x, the distribution of male partner ages, f(Y | x), is assumed to be gamma, with mean and variance determined from the values in Table 2:

$$f(y \mid x) = \int_{y-1}^{y} \frac{\lambda^{\alpha} (u-13)^{\alpha-1} \exp(-\lambda (u-13))}{\Gamma(\alpha)} du .$$
<sup>(2)</sup>

For a man aged y, the sexual activity index is calculated using the formula

$$S_{y}^{*} = \sqrt{46\sum_{x=14}^{59} f(y \mid x) S_{x}^{2} / \sum_{u=14}^{59} S_{u}^{2}},$$
(3)

and the proportion of female partners aged x is calculated as

$$f^{*}(x \mid y) = f(y \mid x) \frac{S_{x}^{2} / \sum_{u=14}^{59} S_{u}^{2}}{S_{y}^{*2} / \sum_{u=14}^{59} S_{u}^{*2}}.$$
(4)

#### **Modelling of HIV survival**

In the absence of treatment and other interventions, adult HIV survival is modelled using a four-stage model of HIV disease progression, with the four stages corresponding to the four stages of the WHO Clinical Staging System (WHO International Collaborating Group for the study of the WHO Staging System 1993). The effect of highly active antiretroviral treatment (HAART) is modelled by adding two stages to the basic four-stage model of HIV survival: stage 5 represents individuals currently on HAART, and stage 6 represents individuals who have discontinued HAART. Individuals are assumed to start treatment at the time of their first AIDS-defining illness, i.e. on moving from HIV stage 3 to HIV stage 4. For each of stages 1 to 4, a record is kept of the proportion of individuals who have received voluntary counselling and testing (VCT) and know their HIV status. All individuals who are on HAART or who were previously on HAART are assumed to know their HIV status. This model of disease progression is represented in Figure 1.

The total time from HIV infection to death in adults has been found to depend on the age at HIV infection (Collaborative Group on AIDS Incubation and HIV Survival 2000). AIDS mortality rates and proportions of individuals in each of the six disease stages are therefore calculated at each integer duration of HIV infection for three

infection ages: 19, 29 and 39. For other ages at infection, AIDS mortality rates and proportions in different stages, at integer durations of infection, are interpolated or extrapolated from those calculated at the three pivot ages. The mean time from HIV infection to death, in the absence of HAART, is assumed to be 12 years for individuals infected at age 19, 11 years for individuals infected at age 29 and 9.5 years for individuals infected at age 39 or older (median survival times are roughly half a year shorter). These assumptions are set to be consistent with survival rates in the developed world, as local studies do not suggest that HIV survival in South Africa differs substantially from that in the developed world (Badri, Bekker, Orrell *et al.* 2004; Maartens, Wood, O'Keefe *et al.* 1997).

Estimates of the proportion of adult HIV survival time spent in each of WHO stages 1 to 4, in the absence of HAART, are derived from application of simple Markov models to survival data collected from a number of settings (Davidse 2000; Deschamps, Fitzgerald, Pape *et al.* 2000; Longini, Scott Clark, Byers *et al.* 1989; Malamba, Morgan, Clayton *et al.* 1999; Morgan, Mahe, Mayanja *et al.* 2002; Morgan, Mahe, Mayanja *et al.* 2002). The estimated proportions, shown in Table 3, are used to estimate the mean time spent in each stage of disease, for each of the three pivot ages. The term spent in stage *t* of disease is assumed to follow a Weibull distribution, parameterized in terms of a median  $(m_t)$  and shape parameter  $(\phi_t)$ , both of which are related to the mean  $(\mu_t)$  by the following formulae:

$$\phi_{t} = \phi_{4} + b(\mu_{t} - \mu_{4})$$
(5)

$$m_{t} = \frac{\mu_{t} (\ln 2)^{1/\phi_{t}}}{\Gamma(1 + 1/\phi_{t})}$$
(6)

As equation (5) shows, the means and shape parameters for the different stages are assumed to be linearly related. Parameter  $\phi_4$  is set at 1, and parameter *b* is set at 0.35, in order to replicate the 'shape' of the survivor functions observed in the developed world (Collaborative Group on AIDS Incubation and HIV Survival 2000).



## Figure 1: Model of HIV disease progression in adults, incorporating the effects of HAART and knowledge of HIV status

As shown in Figure 1, individuals on HAART ultimately either discontinue treatment or die while on treatment. The probabilities of AIDS death and discontinuation of HAART in the first six months on HAART (0.0821 and 0.0914 respectively) are assumed to be particularly high. Thereafter, annual probabilities of AIDS death while on HAART and discontinuation of HAART (both 0.0584) are assumed to remain constant. After discontinuing HAART, individuals are assumed to experience the same AIDS mortality rates as untreated individuals in HIV stage 4. These assumptions result in a decline in AIDS mortality rates consistent with the 70 to 80% reductions in AIDS mortality rates observed after starting HAART in various studies (Jordan, Gold, Cummins *et al.* 2002; Murphy, Collier, Kalish *et al.* 2001; Palella, Delaney, Moorman *et al.* 1998). These and other studies (Badri, Bekker, Orrell *et al.* 2004) also suggest a 60 to 85% reduction in the incidence of opportunistic infections after starting HAART. It is therefore assumed that only 25% of individuals in stages 5 and 6 are classified as 'AIDS sick'.

As individuals enter the later stages of HIV disease, coital frequencies decrease due to increased morbidity (Hankins, Tran and Lapointe 1998; Ross, Van der Paal, Lubega *et al.* 2004; Terceira, Gregson, Zaba *et al.* 2003; Wilson, Gore, Greenblatt *et al.* 2004). The frequency of sex in stage *t*, expressed as a multiple of the frequency of sex in stages 1 and 2 (the asymptomatic stages), is set to vary according to the severity of symptoms in stage *t*. The assumed values of these multiples are shown in Table 3. Further changes in sexual behaviour are assumed to occur when HIV-infected individuals learn their HIV status through VCT programmes. Table 3 also shows the assumed reductions in the frequency of sex and in the proportion of coital acts that are unprotected in HIV-positive individuals who know their HIV status, based on studies by the VCT Efficacy Study Group (2000) and De Vincenzi (1994).

	% of total	Dolotivo	Effect of VCT			
	survival	fraguancy	Reduction	Reduction in		
	time spent	of sex	in frequency	% of sex acts		
	in stage <sup>*</sup>	OI SEX	of sex	unprotected		
WHO stage 1	27.0%	1	19%	36%		
WHO stage 2	19.8%	1	19%	36%		
WHO stage 3	35.8%	0.65	19%	36%		
WHO stage 4	17.4%	0.25	31%	53%		
Stage 5 (on HAART)	-	0.8	31%	53%		
Stage 6 (off HAART)	-	0.25	31%	53%		

#### **Table 3: Stage-specific parameters**

\* Assuming HAART is not available.

#### Modelling of sexual transmission

The parameter  $T_{iij}(y)$  is defined as the probability that an HIV-positive *y*-year old woman, in stage *t* of disease and in risk group *j*, transmits the virus to a partner in risk group *i* in a single act of sex. The parameter is calculated using the formula

$$T_{tij}(y) = r_{ij} \cdot I_t \left( 1 - \left[ 1 - \left( 1 - c_j(y) \right) R_t \right] e \right)$$

$$\tag{7}$$

where

 $r_{ij}$  is the average probability of transmission from an HIV-positive female in risk group *j* to an HIV-negative male in risk group *i*, in a single act of unprotected sex;

 $I_t$  is the factor by which  $r_{ij}$  is multiplied if the HIV-positive female is in stage t of disease;

 $c_j(y)$  is the probability that a sero-discordant couple use a condom when the index partner is aged y and in risk group j;

 $R_t$  is the factor by which the proportion of sex acts that are unprotected is multiplied in stage t of disease (taking into account the effect of knowledge of HIV status); and e is the probability that a condom is effective in preventing HIV transmission in a single act of sex (assumed to be 0.95).

A similar formula is used to define the probability of male-to-female transmission, with parameters  $T_{ij}^{*}(y)$ ,  $r_{ij}^{*}$  and  $R_{t}^{*}$  replacing  $T_{ij}(y)$ ,  $r_{ij}$  and  $R_{t}$  respectively.

On the basis of studies of HIV transmission in stable serodiscordant partnerships (Downs and De Vincenzi 1996; Gray, Wawer, Brookmeyer *et al.* 2001; Peterman, Stoneburner, Allen *et al.* 1988; Wiley, Herschkorn and Padian 1989), the parameters  $r_{33}$  and  $r_{33}^*$  are set at 0.001 and 0.002 respectively (these parameters apply when both partners are in the RSK group). To reflect the effect of STDs on HIV transmission, it is assumed that transmission probabilities are higher when both partners are either in the PRO or STD group ( $r_{11} = r_{12} = r_{21} = r_{22} = 0.005$  and  $r_{11}^* = r_{12}^* = r_{21}^* = r_{22}^* = 0.007$ ), or one partner is in the STD group and the other in the RSK group ( $r_{23} = r_{32} = 0.003$  and  $r_{23}^* = r_{32}^* = 0.0045$ ).

HIV transmission probabilities are assumed to vary according to the stage of disease, with transmission being most efficient in those stages with the highest average levels of viral load. Based on estimates of change in viral load over the course of HIV infection (Hubert, Burgard, Dussaix *et al.* 2000; Kassa, Rinke de Wit, Hailu *et al.* 1999), and an assumed 3-fold increase in HIV transmissibility per log increase in viral load (Fideli, Allen, Musonda *et al.* 2001; Quinn, Wawer, Sewankambo *et al.* 2000), the values of  $I_1$ ,  $I_2$ ,  $I_3$  and  $I_4$  are set at 0.5, 0.4., 1.5 and 2.9 respectively. It is assumed that HIV viral load on antiretroviral treatment is 1.76 log below that in stage 4 (Jordan, Gold, Cummins *et al.* 2002), and the value of  $I_5$  has therefore been set at 0.4 (=  $2.9 \times 3^{-1.76}$ ). After discontinuation of treatment, levels of infectiousness are assumed to return to those in untreated AIDS (i.e.  $I_6 = I_4$ ).

Probabilities of HIV infection are calculated at annual intervals. The probability that a female aged x, in risk group i, becomes infected in a given year is calculated as

$$1 - \left\{1 - a(x)\sum_{j=1}^{4} w_{ij}\sum_{y=14}^{59} f(y \mid x)\sum_{t=1}^{6} p_{tj}(y) \left[1 - \left(1 - T_{tij}^{*}(y)\right)^{n_{ij}S_{y}^{*}D_{t}}\right]\right\}^{P_{t}S_{x}}$$
(8)

where

a(x) is the factor by which the per-partnership transmission probability is multiplied in women aged *x*;

 $w_{ij}$  is the proportion of male partners who are in risk group *j* (Table 1);

 $p_{ij}(y)$  is the proportion of male partners (aged y and in risk group j) who are HIV-positive and in stage t of disease;

 $n_{ij}$  is the number of coital acts per partnership between a female in risk group *i* and a male in risk group *j* (Table 1);

 $D_t$  is the factor by which the coital frequency is multiplied in stage *t* of disease (taking into account the effect of disease symptoms and knowledge of HIV status);  $P_i$  is the average annual number of partners for a woman in group *i* (Table 1). A similar formula for the annual infection probability is used for males, with female parameters being replaced by male parameters.

Studies suggest that transmission probabilities are particularly high in women under the age of 25 (Carpenter, Kamali, Ruberantwari *et al.* 1999), possibly as a result of the high prevalence of cervical ectopy in young women (Plourde, Pepin, Agoki *et al.* 1994). The factor a(x) is therefore set to 1 for all women over the age of 25, and is increased at younger ages according to the formula

$$a(x) = \begin{cases} 1.1^5 \times 1.15^{20-x} & 14 \le x < 20\\ 1.1^{25-x} & 20 \le x < 25 \end{cases}$$
(9)

The factor a(x) is omitted in the calculation of female-to-male transmission.

#### Modelling vertical transmission and paediatric HIV survival

Two distinct patterns of mother-to-child transmission of HIV are modelled: intrauterine/intrapartum transmission (transmission before or during birth) and transmission through breastmilk. It is assumed that in the absence of intervention, 20% of HIV-positive mothers would transmit the virus to their child before or during birth (Coutsoudis, Pillay, Spooner *et al.* 1999; Dabis, Msellati, Meda *et al.* 1999; Nduati, John, Mbori-Ngacha *et al.* 2000), and 16% of the remainder would subsequently transmit the virus to their child as a result of breastfeeding (Miotti, Taha, Kumwenda *et al.* 1999; Nduati, John, Mbori-Ngacha *et al.* 2000). The age at infection through breastmilk is assumed to be uniformly distributed over the first year of life, with equal numbers of children infected through breastmilk in the first six months of life and in the second six months.

The modelling of paediatric HIV survival is similar to that of adult HIV survival, though there are two important differences. Firstly, the four-stage WHO clinical staging system for adults is replaced with a simple two-stage system (pre-AIDS and AIDS). Secondly, survival assumptions differ for children who are infected before or at birth and children infected through breastmilk, with children infected intrauterine/intrapartum being assumed to experience much more rapid disease progression. As in adults, the term spent in each of the non-antiretroviral stages is assumed to follow a Weibull distribution, and antiretroviral treatment is assumed to be started at the time that children experience their first AIDS-defining illness. In common with the adult survival model, the shape parameter for the Weibull distribution is set at 1 for the AIDS stage, and the distribution of survival times in the 'off treatment' stage is assumed to be the same as that for the untreated AIDS stage.

Assumptions about the term spent in each stage were set so that the aggregate paediatric HIV survivor function was consistent with that assumed by the UNAIDS Reference Group on Estimates, Modelling and Projections (2002). The UNAIDS survivor function is a double Weibull distribution, with 'fast progression' and 'slow progression' components (assumed to be appropriate to intrauterine/intrapartum infections and breastmilk infections respectively). For children infected before or during birth, the term spent in the pre-AIDS stage follows a Weibull distribution with median 0.5 years and shape parameter 0.7, and the median term in the AIDS stage is 0.3 years (Hussey, Reijnhart, Sebens *et al.* 1998). For children infected by breastmilk, the pre-AIDS survivor function is Weibull with median 7.8 years and shape parameter 5.5, and the median survival time in the AIDS stage is 0.93 years.

#### Modelling of prevention and treatment programmes

Five intervention programmes are modelled: VCT, mother-to-child transmission prevention (MTCTP), HAART, improved STD treatment, and social marketing. Assumptions are made about the year in which each programme is introduced and the proportion of the population that has access to the treatment or prevention service in each subsequent year (Table 4). These assumptions reflect the actual experience in South Africa to date, based on published and unpublished data discussed below.

VCT is assumed to result in a reduction in unprotected sex in individuals who test HIV-positive, as described previously. It is assumed that if VCT was readily accessible and well-publicized, 5% of adults at risk of infection would seek VCT per annum (Fylkesnes, Haworth, Rosensvard *et al.* 1999). It is further assumed that 80% of women receiving antenatal care agree to VCT if the service is offered to them as part of an MTCTP programme (Abdullah, Young, Bitalo *et al.* 2001). Adults also automatically receive VCT before starting HAART if they are not already aware of their HIV status. The proportions in the VCT row of Table 4 are the proportions of adults with access to VCT and awareness of the VCT programmes on offer, based on estimates of VCT access in the South African public sector in 2002 (Ramkissoon, Kleinschmidt, Beksinska *et al.* 2004).

The proportions in the MTCTP row in Table 4 are the proportions of pregnant women assumed to be offered MTCTP in each year, based on early reports (McCoy, Besser, Visser *et al.* 2002; Ramkissoon, Kleinschmidt, Beksinska *et al.* 2004). It is assumed that if women agree to VCT, all of those who test positive receive short-course antiretroviral treatment to prevent perinatal transmission of HIV. The regimen currently offered is the HIVNET 012 regimen, which is assumed to result in a 47% reduction in intrauterine/intrapartum transmission (Guay, Musoke, Fleming *et al.* 1999). It is also assumed that women participating in the MTCTP programme have a 50% lower risk of transmitting the virus to their child through breastmilk, as a result of the availability of formula milk to these mothers.

HAART is assumed to have benefits both in terms of improved survival and reduced HIV infectiousness, as previously described. The proportions in the HAART rows in Table 4 are the proportions of new AIDS cases starting antiretroviral treatment in each year. The assumptions prior to 2004 are based on historical estimates of numbers treated, mostly in the private health sector (McLeod, Achmat and Stein 2003). Much uncertainty exists, however, regarding the likely future pace and extent of antiretroviral treatment rollout. Two treatment scenarios are therefore considered: a 'constrained' scenario in which ultimately only 50% of new AIDS cases are able to access treatment, and an 'optimistic' scenario in which the percentage of new AIDS cases starting HAART rises to 90%.

Improved STD treatment in South Africa is mostly the result of syndromic management protocols in public STD clinics. This began in 1994, and by 1999 virtually all public STD clinics were following syndromic management guidelines (Dr D. Coetzee, Department of Public Health, UCT, personal communication). This improvement is assumed to result in a reduction in average HIV transmission probabilities: by 15% when both partners are in either the PRO or STD group, by 10% when one partner is in the STD group and the other in the RSK group, and by 5% when both partners are in the RSK group. The reductions assumed are thus commensurate with the STD prevalence rates in the different risk groups. The reductions assumed are also conservative, as there is little evidence of similar improvements in STD treatment in the private health sector, which treats roughly half of all STD cases (Schneider, Blaauw, Dartnall *et al.* 2001).

Social marketing is assumed to have resulted in increased condom usage, as previously described. Based on the significant improvements in condom usage that have been observed, it is assumed that condom usage is three times more common in individuals with high awareness and good knowledge of HIV/AIDS than in those who have little or no knowledge of the disease. The proportions in the 'Social marketing' row of Table 4 are the proportions of sexually active adults who are exposed to social marketing on a regular basis in each year. These were set to be such that the average rates of condom usage in 1998 and 2002 were roughly consistent with those estimated in surveys (Department of Health 1999; Human Sciences Research Council 2002).

Intervention	Year		Rates of phase-in								
	intro- duced	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Yr 7	Yr 8	Yr 9	Yr 10*
VCT MTCTP HAART	1995 2001	10% 10%	20% 40%	30% 60%	40% 80%	50% 90%	60% 90%	70% 90%	80% 90%	90% 90%	100% 90%
'Constrained' 'Optimistic' STD treatment Social marketing	2000 2000 1994 1994	2% 2% 10% 3%	4% 4% 30% 7%	6% 6% 50% 12%	8% 8% 80% 20%	17% 25% 90% 33%	25% 41% 95% 50%	34% 58% 95% 66%	42% 74% 95% 80%	50% 90% 95% 90%	50% 90% 95% 95%

#### Table 4: Rates of intervention phase-in

\* Rates of phase-in achieved by the  $10^{\text{th}}$  year are assumed to be maintained at the same level in all subsequent years.

In the analysis that follows, four intervention scenarios are considered:

- 'no intervention' scenario: no prevention or treatment programmes are assumed to be introduced,
- 'prevention only' scenario: assumes the same rates of intervention phase-in as in Table 4, except that there is no HAART rollout,
- 'constrained' and

• 'optimistic' scenarios: the levels of HAART rollout described previously are combined with the rates of phase-in for the other four interventions shown in Table 4.

The 'constrained' scenario corresponds to the default scenario in the publicly available ASSA2002 model.

#### Calibration

Model estimates of numbers of adult deaths, by sex and 5-year age band, are compared with empirical estimates of numbers of deaths for each year from 1996 to 2002. Similarly, model estimates of HIV prevalence in pregnant women using public antenatal clinics, by 5-year age band, are compared with those observed in the national antenatal clinic surveys, for each year from 1991 to 2002. In order to produce model estimates of prevalence in pregnant women attending public clinics, it is necessary to allow for both the effect of HIV on fertility and socioeconomic bias in the antenatal sample.

To obtain the age-specific fertility rate of an HIV-positive woman aged x, who has been infected for d years, the fertility rate in HIV-negative women of the same age is multiplied by a factor proportional to

$$A_x (1 - B_x)^d , \tag{10}$$

where  $B_x$  is the percentage by which fertility reduces per year of HIV infection, and  $A_x$  is a factor introduced to allow for the positive correlation between childbearing and risk of HIV infection at young ages. These parameters were set to be such that the ratios of antenatal prevalence to general female prevalence in each 5-year age band were approximately consistent with those ratios estimated from southern African surveys (Gregson, Terceira, Kakowa *et al.* 2002; Human Sciences Research Council 2002). Parameter  $B_x$  was set at 4% for all x.  $A_{14}$  was set at 1.5, with a 20% reduction in the difference between  $A_x$  and 1 for each year of increase in age.

The model estimates of prevalence in pregnant females were multiplied by 'antenatal adjustment factors' to allow for the under-representation of non-African women and women of higher socio-economic status in the public antenatal clinic survey. These factors were derived based on health-seeking behaviour data by age and race from the 1998 DHS, together with unpublished estimates of HIV prevalence by age, race and medical scheme membership, derived by the authors. The antenatal adjustment factors for the different 5-year age bands vary between 1.08 and 1.18.

#### RESULTS

Model estimates of HIV prevalence in antenatal clinics and numbers of deaths in the constrained scenario are compared with empirical estimates in Figures 2 and 3 respectively. The correspondence between observed and modelled antenatal

prevalence in recent years is close, with the model estimating a prevalence of 26.7% in pregnant women attending public clinics in 2003, just less than the prevalence of 27.9% observed in the survey. In earlier years, the correspondence is poor, due to the bias towards urban clinics in the early antenatal surveys, which was only corrected when new survey protocols were introduced between 1997 and 2000 (Department of Health 2001). Comparison of prevalence by age group show a levelling in the prevalence in the age groups 15-24 which is not matched by the model.

Estimates of numbers of deaths between the ages of 15 and 59 are close to those derived empirically, though there appears to be some over-estimation of mortality in males between the ages of 35 and 45 and in females between the ages of 25 and 45.



## Figure 2: Observed and modelled HIV prevalence in women attending public antenatal clinics

The confidence intervals published before 1998 did not allow for clustering and hence are incorrectly too narrow

The results of the ASSA2002 model for the four scenarios considered are shown in Figure 4. In the absence of interventions, it is estimated that the annual number of new HIV infections would have risen to 1.9% of the HIV-negative population by 1998 and thereafter declined (Figure 4b), due to decreasing numbers of HIV-susceptible individuals in the high-risk groups. Prevention programmes have led to some reduction in HIV incidence, but HIV incidence remains high at 1.2% in 2005 in the three intervention scenarios. The introduction of HAART is expected to have little impact on HIV incidence, with the difference in incidence in the 'prevention only' and 'optimistic' scenarios lying below 0.1% in all years. HAART is, however, expected to have a significant impact on HIV prevalence, due to the improved survival prospects of infected individuals. The effect of prevention programmes is to reduce HIV prevalence in 2005 from 12.8% of the total population to 11.1% of the population (Figure 4a). By 2020, the prevalence expected if prevention was not coupled with HAART (9.5%) is well below that which would be expected if prevention was coupled with a high level of HAART rollout (12.2%).



## Figure 3: Modelled and empirically derived estimates of male and female deaths in 2002/2003

Model estimates (solid diamonds) and empirically derived estimates (open squares) are shown for each 5-year age band in the 15 to 59 age group.

Figure 4c shows the increase in the crude mortality rate due to AIDS, or the percentage of the population dying due to AIDS in each year. By 2010, there is significant divergence between the four scenarios, with the increase in the crude mortality rate due to AIDS lying between 0.60% in the 'optimistic' scenario and 1.26% in the 'no intervention' scenario. Over the longer term, however, the differences between the three intervention scenarios diminish, due to the assumed limited duration of the HAART survival benefit. A similar trend is observed in respect of the life expectancy at birth (Figure 4d). In 2010, life expectancy would have been expected to be 46.3 years in the 'prevention only' scenario, 50.0 years in the 'constrained' scenario and 53.1 years in the 'optimistic' scenario. By 2020, however, the life expectancy in the 'optimistic' scenario is expected to exceed that in the 'prevention only' scenario by only three years.



Figure 4: HIV incidence, prevalence, and impact of HIV/AIDS on demographic indicators

The child mortality rate (number of deaths per 1000 births in the first five years of life) is also significantly affected by HIV/AIDS prevention and treatment. In the absence of intervention, this rate would be expected to rise by 32 per 1000 from 1990 to 2010 (Figure 4e). As a result of prevention programmes (mostly MTCTP), there is a reduction of almost 25 deaths per 1000 births in 2010 and subsequent years, relative to the 'no intervention' scenario. With the inclusion of HAART in the intervention package, even greater reductions in child mortality would be expected. In the 'constrained' scenario, the child mortality rate is expected to drop by a further 10 per 1000 from 2010.

Coinciding with the rise in AIDS mortality are rapid increases in the percentage of children whose mothers have died (maternal orphans). It is expected that by 2015, 16.4% of children under the age of 18 would be maternally orphaned in the 'no intervention' scenario (Figure 4f). Prevention programmes have little impact on rates of orphanhood, as reductions in orphanhood due to reduced adult mortality are largely

offset by increases in orphanhood due to lower rates of mother-to-child transmission. However, the introduction of HAART has a significant impact on orphan numbers. The proportion of children aged less than 18 who are maternally orphaned is expected to reach 11.7% by 2015 in the 'optimistic' scenario and 13.5% in the 'constrained' scenario.

Figure 5 shows trends in the age profile of newly infected individuals and trends in the morbidity profile of the infected adult population, for the 'no intervention' and 'optimistic' scenarios. In 1995, 30% of new HIV infections are estimated to have been acquired by infants, from their infected mothers, or by teenagers, through sexual exposure. As the epidemic progresses, a higher proportion of new infections occurs below the age of 20, due to 'saturation' of the epidemic at older ages. In the 'no intervention' scenario, it is estimated that 60% of new HIV infections occur below the age of 20 by 2020 (Figure 5a). This proportion is reduced to 53% in the 'optimistic' scenario (Figure 5b), partly because of reduced mother-to-child transmission, and partly because reductions in unprotected sex lead to longer intervals between sexual debut and HIV infection.



# Figure 5: Trends in the age profile of new HIV infections and the morbidity profile of adult HIV infections, for the 'no intervention' and 'optimistic' scenarios

Adult infections are grouped according to WHO clinical stage, with 'HAART' representing individuals who either are on treatment or have discontinued treatment.

The morbidity profile of the HIV-infected adult population also changes over the course of the epidemic. In 1995, 87% of all HIV-positive adults were in WHO stages 1 and 2, the asymptomatic stages of disease. This is expected to decline to 46% in the 'no intervention' scenario, and to 34% in the 'optimistic' scenario, by 2015 (Figures 5c and 5d). The proportion which is symptomatic and untreated (stages 3 and 4) in 2015 differs substantially between the 'no intervention' scenario (54%) and the 'optimistic' scenario (29%).

The morbidity profile in 2015 can be further analysed by age (Figure 6). Although Figure 2a shows similar aggregate levels of HIV prevalence in 2015 in the 'no intervention' and 'optimistic' scenarios, this masks significant differences between the two scenarios in terms of the age profile of the infected population. Below the age of 30, HIV prevalence is higher in the 'no intervention' scenario than in the 'optimistic' scenario, due to the impact of prevention programmes in the latter. Over the age of 30, however, HIV prevalence is higher in the 'optimistic' scenario, due largely to the greater survival under HAART and partly to the shifting of HIV incidence to the older ages. Most infections below the age of 25 are asymptomatic (WHO stages 1 and 2), as they are recently acquired. The need for HAART is likely to be greatest between the ages of 30 and 50, at over 10% of the population in this age band.



(a) Morbidity profile, 'no intervention' scenario

## Figure 6: Percentage of population infected by age, split by disease stage, in 2015, for the 'no intervention' and 'optimistic' scenarios

Adult infections are grouped according to WHO clinical stage, with 'HAART' representing individuals who either are on treatment or have discontinued treatment.

#### DISCUSSION

The ASSA2002 model confirms that HIV/AIDS is having a significant demographic impact in South Africa, although not as significant as is being predicted by the international agencies. Figure 7 compares the projected life expectancies of the ASSA model (constrained scenario) with those projected by the Population Division of the United Nations (2005) and the (2005) showing that whereas the ASSA model projects life expectancy levelling at around 50, the other models have it falling below 45 before rising again. Interestingly, while both models appear, broadly, to use the estimates of prevalence (and hence incidence) produced by the UNAIDS/WHO Reference Group on Estimates, Modelling and Projections, the US Census Bureau currently assumes 'no one will receive treatment', but assumes a decline in incidence of 50% from 2010 to 2050. The projections of the UN Population Division, on the other hand, assume from 2005 that treatment is introduced from 2005 at levels consistent with WHO estimates rising to a plateau in 2015 of between 20% and 85% 'depending on the current level of coverage'. Those on treatment are assumed to survive for a median of 4.5 years. In addition, the projections assume that there will be change in behaviour and lower recruitment to high-risk groups from 2005, which also help reduce the chance of infection.



Figure 7: Projected life expectancies at birth from three models

That only part of the difference is due to the impact of ART roll-out can be seen by the comparison of the numbers of adult deaths estimated by the models with those estimated from deaths recorded in 2002, as shown in Figure 8. The numbers from the other models imply that around half of all deaths were due to HIV/AIDS in 2002, when even the most rigorous searching through the cause of death data (Groenewald, Dorrington, Bradshaw *et al.* 2005) can only identify barely a third as being due to HIV/AIDS. Clearly the UN and US Census Bureau are exaggerating the number of deaths due to HIV/AIDS.



Figure 8: Comparison of estimates of the number of adult deaths (plotted at age in middle of age range)

The ASSA2002 model also demonstrates that the prevention and treatment programmes that have been and are being introduced can significantly modify this demographic impact. Even when interventions do not substantially alter HIV prevalence, they can result in a shift of HIV incidence from younger to older ages, as well as an extension of HIV survival, both of which reduce the years of life lost due to HIV/AIDS.

HIV prevention programmes appear to have had a modest impact on HIV incidence, with much of the reduction in HIV incidence taking place in the absence of prevention programmes. HAART is expected to have little impact on HIV incidence, but further sensitivity testing is necessary to test the robustness of this conclusion, particularly as the model does not currently assume any change in utilization of VCT or any change in sexual behaviour in HIV-negative individuals after HAART becomes available. Other models suggest that HAART will lead to a reduction in HIV prevalence (Boily, Bastos, Desai *et al.* 2004; Gray, Li, Wawer *et al.* 2003; Nagelkerke, Jha, de Vlas *et al.* 2002), reflecting a significant positive effect of HAART on HIV incidence. The ASSA2002 model predicts a less significant preventative benefit from HAART because it assumes a slower phase-in of the intervention and because it assumes HAART is initiated in later stages of HIV disease.

South Africa would still be experiencing significant declines in life expectancy had interventions not been introduced. Prevention programmes have not had significant effects on mortality in the short term, though MTCTP is estimated to have contributed significantly to declines in the child mortality rate. More immediate reductions in mortality are observed when HAART is introduced. However, as other models have shown (Salomon, Hogan, Stover *et al.* 2005), the difference in mortality rates between 'high HAART coverage' and 'low HAART coverage' scenarios diminishes over the longer term, due to the limited survival benefit from HAART. HAART has a more

sustained benefit in terms of levels of orphanhood, as HAART defers mortality in parents to those ages at which their children have ceased to be dependent on them.

The ASSA2002 model is unique in modelling the profile of the HIV-positive population by WHO clinical stage, and this model output has proved useful in assessing the burden of disease due to HIV/AIDS (Bradshaw, Groenewald, Laubscher *et al.* 2003) as well as the costs of treatment and care for HIV/AIDS. Although HIV prevalence rates and AIDS mortality rates appear to be levelling off in the 'constrained' scenario, this conceals the fact that an increasingly high proportion of infected individuals are either symptomatic (WHO stage 3 or 4) or on HAART. The need for treatment is greatest over the age of 25, while an increasingly high proportion of new infections are occurring below the age of 25. This suggests that prevention programmes need to be tailored to the youth, while treatment literacy and treatment screening would be particularly appropriate to older age groups.

A strength of the ASSA2002 model is that it is calibrated to both HIV prevalence data and vital registration data, and produces results roughly consistent with both. However, it is a weakness of the model that the sexual behaviour assumptions shown in Table 1 have been set arbitrarily in order to achieve this correspondence, with little empirical basis. Uncertainty analysis techniques need to be applied to determine whether other parameter combinations may give similar or better fits to the data. Another weakness of the sexual behaviour component of the model is that it does not take into account the asymmetries in sexual relationships between men and women. For example, individual-based simulations suggest that in settings in which commercial sex is common, the distribution of annual numbers of partners is very different for men and women (Korenromp, Van Vliet, Bakker et al. 2000). It is also debatable whether a group of individuals 'not at risk of infection' could comprise more than half of the sexually active population. This places a significant ceiling on the extent of HIV/AIDS 'saturation', particularly in the later stages of the epidemic and at the older ages. The sensitivity of the model results to the assumed proportion in the NOT group therefore needs to be further explored.

Another limitation of the model is that HIV transmission probabilities are calculated on an annual basis. This makes it impractical to allow for transmission dynamics that operate over short time periods. For example, the period of high HIV viraemia around seroconversion lasts for only a few months, but is potentially very significant in the spread of HIV (Pilcher, Tien, Eron *et al.* 2004). STDs are also often only of short duration, but play an important role in increasing HIV susceptibility and HIV infectiousness while present (Røttingen, Cameron and Garnett 2001). The modelling of the effect of improved STD treatment in ASSA2002 is therefore of necessity simplistic, and models with shorter time steps are needed to simulate the interactions between HIV and other STDs more accurately.

The ASSA2002 model is an example of how the effects of HIV/AIDS can be incorporated into a cohort component projection model. The model demonstrates that the age profile of new HIV infections changes over the course of the epidemic, and changes in response to prevention and treatment programmes. This suggests that the approach of deriving adjustments to a cohort component projection model from an independent HIV/AIDS model is problematic if it is assumed that the age profile of HIV cases is fixed, as Stover (2004) acknowledges. The ASSA2002 model also

demonstrates that there is significant age variation in HIV/AIDS prevalence, morbidity and mortality. HIV/AIDS models which are based on very broad age divisions may therefore be difficult to validate reliably against prevalence and vital registration data, and may also be less reliable in estimating treatment requirements.

#### REFERENCES

- Abdullah, M., Young, T., Bitalo, L., Coetzee, N. *et al.* 2001. "Public health lessons from a pilot programme to reduce mother-to-child transmission of HIV-1 in Khayelitsha", *South African Medical Journal* **91**:579-583.
- Actuarial Society of South Africa. 2004. *ASSA2002 AIDS and Demographic Model*. Available: <u>http://www.assa.org.za/default.asp?id=1000000050</u>
- Badri, M., Bekker, L. G., Orrell, C., Pitt, J. *et al.* 2004. "Initiating highly active antiretroviral therapy in sub-Saharan Africa: an assessment of the revised World Health Organization scaling-up guidelines", *AIDS* **18**(8):1159-1168.
- Boily, M., Bastos, F. I., Desai, K. and Mâsse, B. 2004. "Changes in the transmission dynamics of the HIV epidemic after the wide-scale use of antiretroviral therapy could explain increases in sexually transmitted infections", *Sexually Transmitted Diseases* 31(2):100-113.
- Bracher, M., Santow, G. and Cotts Watkins, S. 2004. "Assessing the potential of condom use to prevent the spread of HIV: a microsimulation study", *Studies in Family Planning* **35**(1):48-64.
- Bradshaw, D., Groenewald, P., Laubscher, R., Nannan, N. *et al.* 2003. "Initial burden of disease estimates for South Africa, 2000", *South African Medical Journal* **93**:682-688.
- Bradshaw, D., Laubscher, R., Dorrington, R., Bourne, D. E. *et al.* 2004. "Unabated rise in number of adult deaths in South Africa", *South African Medical Journal* **94**(4):278-279.
- Carpenter, L. M., Kamali, A., Ruberantwari, A., Malamba, S. S. *et al.* 1999. "Rates of HIV-1 transmission within marriage in rural Uganda in relation to the HIV sero-status of the partners", *AIDS* **13**(9):1083-1089.
- Collaborative Group on AIDS Incubation and HIV Survival. 2000. "Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis", *Lancet* **355**:1131-1137.
- Coutsoudis, A., Pillay, K., Spooner, E., Kuhn, L. *et al.* 1999. "Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study", *Lancet* **354**:471-476.
- Dabis, F., Msellati, P., Meda, N., Welffens-Ekra, C. *et al.* 1999. "Six-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial", *Lancet* 353:786-792.
- Davidse, A. 2000. "An analysis of the course of HIV infection using a Markov model." Unpublished thesis, University of Cape Town.
- De Vincenzi, I. and European Study Group on Heterosexual Transmission of HIV. 1994. "A longitudinal study of human immunodeficiency virus transmission by heterosexual partners", *New England Journal of Medicine* **331**:341-346.
- Department of Health. 1999. "South Africa Demographic and Health Survey 1998: Preliminary Report",

- Department of Health. 2001. *National HIV and syphilis sero-prevalence survey of women attending public antenatal clinics in South Africa: 2000.* Available: <u>http://www.doh.gov.za/docs/index.html</u>
- Department of Health. 2004. National HIV and syphilis antenatal sero-prevalence survey in South Africa 2003. Available: http://www.doh.gov.za/docs/reports/2003/hiv.pdf. Accessed 22 Sept 2004
- Deschamps, M., Fitzgerald, D., Pape, J. and Johnson, W. 2000. "HIV infection in Haiti: natural history and disease progression", *AIDS* 14:2515-2521.
- Dorrington, R. E. 2000. "The ASSA2000 suite of models," Paper presented at Actuarial Society of South Africa annual convention. Somerset West, October.
- Downs, A. and De Vincenzi, I. 1996. "Probability of heterosexual transmission of HIV: relationship to the number of unprotected sexual contacts", *Journal of Acquired Immune Deficiency Syndromes* **11**:388-395.
- Fideli, U. S., Allen, S. A., Musonda, R., Trask, S. *et al.* 2001. "Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa", *AIDS Research and Human Retroviruses* 17(10):901-910.
- Fylkesnes, K., Haworth, A., Rosensvard, C. and Kwapa, P. M. 1999. "HIV counselling and testing: overemphasizing high acceptance rates a threat to confidentiality and the right not to know", *AIDS* **13**(17):2469-2474.
- Gray, R., Wawer, M., Brookmeyer, R., Sewankambo, N. *et al.* 2001. "Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1discordant couples in Rakai, Uganda", *Lancet* 357:1149-1153.
- Gray, R. H., Li, X., Wawer, M. J., Gange, S. J. *et al.* 2003. "Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda", *AIDS* 17:1941-1951.
- Gregson, S., Terceira, N., Kakowa, M., Mason, P. *et al.* 2002. "Study of bias in antenatal clinic HIV-1 surveillance data in a high contraceptive prevalence population in sub-Saharan Africa", *AIDS* **16**:643-652.
- Groenewald, P., Dorrington, R. E., Bradshaw, D. and Laubscher, R. 2005. "Where are the AIDS Deaths in the South African Mortality Statistics," Paper presented at 2nd South African AIDS Conference. Durban, 7-10 June.
- Guay, L. A., Musoke, P., Fleming, T., Bagenda, D. *et al.* 1999. "Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial", *Lancet* 354:795-802.
- Hankins, C., Tran, T. and Lapointe, N. 1998. "Sexual behaviour and pregnancy outcome in HIV-infected women", *Journal of Acquired Immune Deficiency Syndromes* 18:479-487.
- Heuveline, P. 2003. "HIV and population dynamics: a general model and maximumlikelihood standards for East Africa", *Demography* **40**(2):217-245.
- Hubert, J., Burgard, M., Dussaix, E., Tamalet, C. *et al.* 2000. "Natural history of serum HIV-1 RNA levels in 330 patients with a known date of infection", *AIDS* 14:123-131.
- Human Sciences Research Council. 2002. South African national HIV prevalence, behavioural risks and mass media household survey 2002. Available: www.hsrcpublishers.co.za/hiv.html. Accessed 9 December 2002
- Hussey, G. D., Reijnhart, R. M., Sebens, A. M., Burgess, J. *et al.* 1998. "Survival of children in Cape Town known to be vertically infected with HIV-1", *South African Medical Journal* **88**(5):554-558.

- Johnson, L. and Dorrington, R. 2001. *The impact of AIDS on orphanhood in South Africa: a quantitative analysis.* Centre for Actuarial Research. Available: www.commerce.uct.ac.za/care/Monographs/Monographs/mono04.pdf
- Jordan, R., Gold, L., Cummins, C. and Hyde, C. 2002. "Systematic review and metaanalysis of evidence for increasing numbers of drugs in antiretroviral combination therapy", *British Medical Journal* **324**:1-10.
- Kassa, E., Rinke de Wit, T. F., Hailu, E., Girma, M. *et al.* 1999. "Evaluation of the World Health Organization staging system for HIV infection and disease in Ethiopia: association between clinical stages and laboratory markers", *AIDS* 13:381-389.
- Korenromp, E. L., Van Vliet, C., Bakker, R., de Vlas, S. J. *et al.* 2000. "HIV spread and partnership reduction for different patterns of sexual behaviour - a study with the microsimulation model *STDSIM*", *Mathematical Population Studies* **8**(2):135-173.
- Longini, I., Scott Clark, W., Byers, R., Ward, J. *et al.* 1989. "Statistical analysis of the stages of HIV infection using a Markov model", *Statistics in Medicine* **8**:831-843.
- Maartens, G., Wood, R., O'Keefe, E. and Byrne, C. 1997. "Independent epidemics of heterosexual and homosexual infection in South Africa survival differences", *Quarterly Journal of Medicine* **90**:449-454.
- Malamba, S., Morgan, D., Clayton, T., Mayanja, B. *et al.* 1999. "The prognostic value of the World Health Organisation staging system for HIV infection and disease in rural Uganda", *AIDS* **13**:2555-2562.
- McCoy, D., Besser, M., Visser, R. and Doherty, T. 2002. *Interim findings on the national PMTCT pilot sites: lessons and recommendations*. Durban: Health Systems Trust. Available: <u>www.hst.org.za/pubs/pmtct/pmtctinterim.htm</u>. Accessed 18 May 2004
- McLeod, H. D., Achmat, Z. and Stein, A. M. 2003. "Minimum benefits for HIV/AIDS in South African medical schemes", *South African Actuarial Journal* **3**:77-111.
- Miotti, P. G., Taha, T. E. T., Kumwenda, N. I., Broadhead, R. *et al.* 1999. "HIV transmission through breastfeeding: a study in Malawi", *Journal of the American Medical Association* **282**(8):744-749.
- Morgan, D., Mahe, C., Mayanja, B., Okongo, M. *et al.* 2002. "HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries?" *AIDS* **16**:597-603.
- Morgan, D., Mahe, C., Mayanja, B. and Whitworth, J. 2002. "Progression to symptomatic disease in people infected with HIV-1 in rural Uganda: prospective cohort study", *British Medical Journal* **324**:193-196.
- Murphy, E., Collier, A., Kalish, L., Assman, S. *et al.* 2001. "Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease", *Annals of Internal Medicine* **135**:17-26.
- Nagelkerke, N. J. D., Jha, P., de Vlas, S. J., Korenromp, E. L. *et al.* 2002. "Modelling HIV/AIDS epidemics in Botswana and India: impact of interventions to prevent transmission", *Bulletin of the World Health Organization* **80**:89-96.
- Nduati, R., John, G., Mbori-Ngacha, D., Richardson, B. *et al.* 2000. "Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial", *Journal of the American Medical Association* **283**(9):1167-1174.

- Palella, F., Delaney, K., Moorman, A., Loveless, M. *et al.* 1998. "Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection", *New England Journal of Medicine* **338**:853-860.
- Peterman, T. A., Stoneburner, R. L., Allen, J. R., Jaffe, H. W. *et al.* 1988. "Risk of human immunodeficiency virus transmission from heterosexual adults with transfusion-associated infections", *Journal of the American Medical Association* 259(1):55-58.
- Pilcher, C. D., Tien, H. C., Eron, J. J., Vernazza, P. L. *et al.* 2004. "Brief but efficient: acute HIV infection and the sexual transmission of HIV", *Journal of Infectious Diseases* **189**(10):1785-1792.
- Plourde, P. J., Pepin, J., Agoki, E., Ronald, A. R. *et al.* 1994. "Human immunodeficiency virus type 1 seroconversion in women with genital ulcers", *Journal of Infectious Diseases* **170**(2):313-317.
- Quinn, T., Wawer, M., Sewankambo, N., Serwadda, D. *et al.* 2000. "Viral load and heterosexual transmission of human immunodeficiency virus type 1", *New England Journal of Medicine* **342**:921-929.
- Ramkissoon, A., Kleinschmidt, I., Beksinska, M., Smit, J. *et al.* 2004. *National Baseline Assessment of Sexually Transmitted Infection and HIV Services in South African Public Sector Health Facilities*. Durban: Reproductive Health Research Unit, University of the Witwatersrand. Available: <u>www.rhru.co.za/images/Docs/6%20proof%20final15-01.pdf</u>. Accessed 13 February 2004
- Reproductive Health Research Unit. 2004. *HIV and sexual behaviour among young South Africans: a national survey of 15-24 year olds.* Joint publication of Reproductive Health Research Unit and loveLife. Available: <u>www.rhru.co.za/images/Docs/national%20survey%20RHRU.pdf</u>. Accessed 8 May 2004
- Robinson, N. J., Mulder, D. W., Auvert, B. and Hayes, R. J. 1995. "Modelling the impact of alternative HIV intervention strategies in rural Uganda", *AIDS* 9:1263-1270.
- Ross, A., Van der Paal, L., Lubega, R., Mayanja, B. N. *et al.* 2004. "HIV-1 disease progression and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda", *AIDS* **18**:799-804.
- Røttingen, J., Cameron, D. W. and Garnett, G. P. 2001. "A systematic review of the epidemiological interactions between classic sexually transmitted diseases and HIV: how much is really known?" *Sexually Transmitted Diseases* **28**:579-597.
- Salomon, J. A., Hogan, D. R., Stover, J., Stanecki, K. A. *et al.* 2005. "Integrating HIV prevention and treatment: from slogans to impact", *PLoS Medicine* **2**(1):e16.
- Schneider, H., Blaauw, D., Dartnall, E., Coetzee, D. J. et al. 2001. "STD care in the South African private health sector", South African Medical Journal 91:151-156.
- Stover, J. 2004. "Projecting the demographic consequences of adult HIV prevalence trends: the Spectrum Projection Package", *Sexually Transmitted Infections* 80(Suppl 1):i14-18.
- Stover, J., Walker, N., Garnett, G., Salomon, J. *et al.* 2002. "Can we reverse the HIV/AIDS pandemic with an expanded response?" *Lancet* **360**:73-77.
- Terceira, N., Gregson, S., Zaba, B. and Mason, P. R. 2003. "The contribution of HIV to fertility decline in rural Zimbabwe, 1985-2000", *Population Studies* 57(2):149-164.

- UNAIDS Reference Group on Estimates Modelling and Projections. 2002. "Improved methods and assumptions for estimation of the HIV/AIDS epidemic and its impact: recommendations of the UNAIDS Reference Group on Estimates, Modelling and Projections", *AIDS* 16(WHO-UNAIDS Report):W1-W14.
- United Nations. 2005. *World Population Prospects: The 2004 Revision, Highlights.* New York: Department of Economic and Social Affairs.
- US Census Bureau. 2005. *International Database*. Washington DC: International Programs Center. Available: <u>http://www.census.gov/ipc/www/idbnew.html</u>. Accessed 04 July.
- Van der Ploeg, C. P. B., Van Vliet, C., De Vlas, S., Ndinya-Achola, J. O. *et al.* 1998. "STDSIM: a microsimulation model for decision support in STD control", *Interfaces* 28:84-100.
- Van der Ryst, E., Joubert, G., Steyn, F., Heunis, C. *et al.* 2001. "HIV/AIDS-related knowledge, attitudes and practices among South African military recruits", *South African Medical Journal* **91**:587-591.
- Voluntary HIV-1 Counselling and Testing Efficacy Study Group. 2000. "Efficacy of voluntary HIV-1 counselling and testing in individuals and couples in Kenya, Tanzania and Trinidad: a randomised trial", *Lancet* **356**:103-112.
- WHO International Collaborating Group for the study of the WHO Staging System. 1993. "Proposed 'World Health Organization staging system for HIV infection and disease': preliminary testing by an international collaborative crosssectional study", AIDS 7:711-718.
- Wiley, J., Herschkorn, S. and Padian, N. 1989. "Heterogeneity in the probability of HIV transmission per sexual contact: the case of male-to-female transmission in penile-vaginal intercourse", *Statistics in Medicine* **8**:93-102.
- Williams, B., Gilgen, D., Campbell, C., Taljaard, D. *et al.* 2000. *The natural history* of *HIV* / *AIDS in South Africa: A biomedical and social survey in Carletonville.* Johannesburg: Council for Scientific and Industrial Research.
- Wilson, T. E., Gore, M. E., Greenblatt, R., Cohen, M. et al. 2004. "Changes in sexual behaviour among HIV-infected women after initiation of HAART", American Journal of Public Health 94(7):1141-1146.