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A Supplementary Review of Existing HIV/AIDS Models with the View of Adopting/Adapting One or More Models for National and Provincial Population Projections in South Africa

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A supplementary review of existing HIV/AIDS models with the view of adopting/adapting one or more models for national and provincial population projections in South Africa.

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1. Introduction

This report is in essence a technical review of the literature on HIV/AIDS modelling. Such a review is necessary to make an informed decision about which approach to use in projecting prevalence of HIV/AIDS and for its subsequent use in population projections. As this is a vast topic, a practical approach has to be used in order to reduce on research time and to avoid duplication. The strategy adopted is to start off with an overview of reviews followed by a supplementary review. This strategy is used in the first part wherein the models are reviewed, in the second part wherein the empirical research findings are reviewed and in the third part wherein the existing software packages are reviewed.

The report starts by summarising existing published reviews, and supplements the summary by reviewing some additional works (omitted, missed out or glossed over) in those reviews. In summarising existing reviews, the report uses four pivots; a paper written by Palloni and Gliklich (1991) in the beginning of the 1990s (with over 100 references), one by Palloni (1996) in the mid-1990s (also with over 100 references), one by Foulkes (1998) (with over 350 references) and a last one by Karon *et al.* (1998). The section on empirical evidence accumulated on HIV/AIDS that inform modelling efforts, draws heavily from the paper written by Boerma (1998). Lastly the section on evaluation of existing software draws heavily on the paper by Stover (1997).

The report does not in any way, attempt to develop an HIV/AIDS model nor does it do an independent evaluation of existing software. The report is, and remains, a technical review. The author realises that he could have missed out many important and relevant models/software or review papers and hence does not claim that this is a definitive technical review on this subject.

2. Summary of selected published reviews

An excellent review of pre-1990 models is reported in Palloni and Glicklich (1991). The review cites references from most leading epidemiological, medical, public health and statistical journals. In their review, they classified existing models according to three criteria: the type of outcomes the models are designed to evaluate, the data they require and the nature of the assumptions (behavioural, epidemiological, medical) on which they rest. Using these criteria, they classify the models into four types: simple extrapolation models (type 1); models with postulated incubation period (type 2); models with postulated incubation period and modes of transmission (type 3) and models with behavioural assumptions (type 4). Chin and Lwanga (1991) used a similar typology in grouping models for HIV/AIDS. In the review paper, Palloni and Glicklich (1991) evaluated the models, pointing out some of their weaknesses. Table 1 gives brief description of these broad types of models and outlines some of their advantages and disadvantages. Palloni and Glicklich concluded that increased sophistication in modelling techniques alone would not yield very useful results without corresponding improvements in the quantity and quality of the data required by the models.

Table 1: Summary of typology of HIV/AIDS models described in Palloni and Glicklich (1991).

Type	Short description	Advantages	Disadvantages
I	These are models that focus on the size of the AIDS epidemic. The models attempt to fit a suitable pre-defined function to observed AIDS cases (new or cumulated). Future trends in number of new or cumulated AIDS cases are estimated by extrapolation.	1. The models can give fairly good results in the initial stages of the epidemic.	1. Many different functional forms can fit observed data well. However, these different functions differ substantively in their extrapolations, especially in the long term
II	The models introduce a distinction between new reported AIDS cases and unrecognised HIV infections. Through the use of back-projections, the combination of past reported AIDS cases and an incubation function, estimates are obtained for HIV infections. The models using this approach have many variants.	1. The models yield reasonably accurate short-term forecasts of HIV and AIDS	1. The models are quite sensitive to the assumptions made about the incubation period. 2. The longer-term forecasts are very sensitive to the shape of the incubation function and the functional representation for HIV infection.
III	These models make assumptions about the incubation period and modes of transmission (but without explicitly taking behaviour into account). The models aim to reproduce past trends in cumulative AIDS cases, to estimate unrecognised HIV infection and AIDS a) One variant of this model (by Bouard, 1987) is a renewal model analogous to a stable population model b) Another variant (by Artzrouni, 1988) breaks down the population into different states and proposes transitions between these states. c) The WHO model is another variant of this model. Its aim is to use the model to make short-term projections where data are poor.	1. The model is useful for showing the relationship between the force of transmission of HIV, the rate of growth of new HIV cases and HIV incidence	1. In one of the variants of the model, the results of the models are highly sensitive to the shape of the incubation function. 2. In one of the variants, the model relies on assumptions about the past time pattern of HIV, incidence, the accuracy of seroprevalence estimates derived from available data.
IV	These models are like type III models but they incorporate explicit behavioral, epidemiological and biologic assumptions. These assumptions are translated into parametric functions that control one of three elements: the number and type of groups in the population, the various states that persons may occupy; and the flow of persons between states and groups. Past trends are almost always used to calibrate some of the parameters used in the model. a) one subclass of the models are deterministic macro-models that represent behaviour of aggregates instead of individuals b) Another subclass is micro-models that use micro-simulation to represent individual behaviour.	1. Offers a holistic approach for capturing the effects of complex relationships and interactions.	1.These models require a large number of parameter and in most cases, are neither elegant nor parsimonious.

In subsequent publications, different aspects of this typology was clarified. For example, regarding type 1 models, De Angelis *et al.* (1998) clarify that these models were mostly based on fitting a curve on observed cases and extrapolating from the fitted model. While a certain method could fit the observed cases well, the fact that it does not incorporate additional epidemiological data makes it unable to predict abrupt deviations from current trends.

Many authors have contributed in clarifying on type 2 models and extending them further. Back-projection (or back-calculation) methods involve reconstructing the realised but unobserved HIV infection curve from AIDS data by using knowledge about the incubation distribution. The formula used for back-projections is expressed differently by different researchers. However, according to De Angelis *et al.* (1998), the essence of the back-calculation method is as follows:

$$AIDS\ diagnosis\ rate\ at\ time\ t = \int_0^t (HIV\ infection\ rate\ at\ time\ s) * p(incubation\ time = t - s)ds$$

where $p(.)$ denotes a probability density and the *incubation time* is the time between HIV infection and AIDS diagnosis.

Karon *et al.* (1998) express the back-projection method in a similar manner. They use the following equation:

$$a(t) = \int_0^t f(t-s)i(s)ds$$

Where $f(t)$ is the probability density function of the time from HIV infection to AIDS diagnosis, $I(t)$ is the (unknown) number of persons who were infected at time t and $a(t)$ is the number of AIDS cases diagnosed at time t (as obtained from AIDS surveillance).

Becker and Britton (1999) express the back-projection method in yet another manner. They use the following equation:

$$\boldsymbol{m}_t = \int_0^t \boldsymbol{\lambda}_{t-u}dF_D(u)$$

Where λ_t and μ_t represent the mean infection incidence and the mean removal incidence respectively at time t, D is the duration of the infectious period and F_D is its distribution function.

Irrespective of mathematical form of the equation, the back projection approach requires a fixed choice for the incubation distribution function and an assumption about the parametric form of the HIV incidence curve (Raab *et al.*,1994). In several studies, it is assumed that HIV infection could be represented as a Poisson process with intensity function μ_t and $F_D(u)$ is assumed known from past studies. Other distributions such as the Weibull distribution have been used several studies such as in the one by Gore *et al.* (1994). Starting with these assumptions, different researchers used different statistical approaches to obtain estimates of λ_t.

When doing AIDS projection for sub-national regions, additional challenges are met. Gore *et al.* (1994) recommend that regional projections of AIDS cases should be based, not on scaled back-projections but on the immunological monitoring of prevalent HIV-infected individuals. In other words, the projections should be a function of risk group size not of total population size.

Foulkes (1998) mentioned the recent advances/extensions on back calculation techniques with respect to the following areas:

> "… the development of a flexible linear model; the impact incubation period estimate; sensitivity analysis; lower bound estimation; the effect of censoring; short-term extrapolation; forecasting health care needs; stage-specific estimation; heterogeneity per contact probability; the effect of social mixing; Markov models; and variable infectiousness" (Foulkes, 1998:3)

Further clarification on type 3 HIV/AIDS models was given by Palloni (1996). He argues that a multistate framework could be used to describe most type 3 models. He summarised the multistate representation as shown in Figure 1.

Figure 1: Conceptualisation of type 3 models according to Palloni (1996).
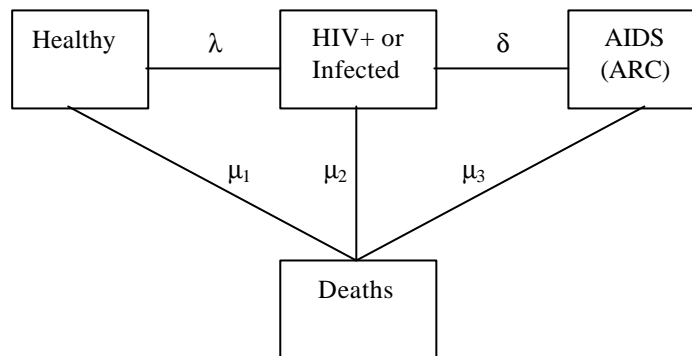
The Figure shows that at any time, any individual in a population may occupy one and only one of three possible states: healthy or susceptible (Healthy), asymptomatic-infected (HIV+ or Infected) and all those with AIDS related complex or full-blown AIDS (AIDS or ARC). The flows between the three non-absorbing states and between these and the absorbing state are governed by five transition rates, λ, δ, μ_1, μ_2 and μ_3. This framework is also applicable in multi-stage models. In such models, several sub-states are included between the state of being infected with HIV to being diagnosed with AIDS. For example, Aalen *et al.* (1997) proposed a Markov model for the development of AIDS and HIV diagnosis. The model comprises of 10 states. Three of the states refer to HIV infection before AIDS but before diagnosis. Three additional states refer to these stages of HIV infection but with diagnosis. One state refers to HIV infection with diagnosis and treatment. The remaining three states refer to AIDS (without diagnosis, with diagnosis, with diagnosis and treatment). This work builds on previous work by Aalen *et al.* (1994).

All projection models for HIV/AIDS use the multistate framework represented above (or a similar framework). The only difference between the models is the type of population and the behavioural heterogeneity they are designed to handle.

To proceed further, in the 1996 review paper, Palloni classified HIV/AIDS models into two broad types; the one dealing with forward projections and other dealing with backward projections. For both types, he discusses models ranging from the simplest to the most complex. Most of the models included in the earlier review of Palloni and Glickich were included in the review in addition to some post-1990 works. For the forward projection models, Palloni argues that from experience, simple functional representation of new AIDS cases are much less likely to capture the highly uncertain and variable course of the HIV/AIDS epidemic. For the backward projection models, Palloni maintains his argument that all variants of the model are highly sensitive to assumptions about the incubation period and to the functional form chosen to represent the trajectory of the AIDS cases. He supports his argument by an illustration of a backward projection model using AIDS data from the USA. His illustration also shows that the use of different sets of observations leads to a completely different HIV epidemic and a forecast of new AIDS cases.

A review paper by Karon *et al.* (1998) looked at the status of methods for estimating the prevalence of HIV in the USA. While the models used in the USA do not exhaust all the existing models, the models used in the USA would be indicative of the general direction of modelling of HIV/AIDS. The paper groups the existing methods used in the USA into three groups: those based on surveys of childbearing women; those based on national household surveys and those based on back-calculation. Each of these methods for estimating HIV prevalence has distinct strengths and weaknesses. One common feature is that for each of the methods, substantial adjustments to an estimate based on a well-defined statistical procedure must be made in order to include HIV-infected persons in population not covered by the data source on which the estimate is based (Karon *et al.*, 1998).

The authors arrive at the following conclusion:

> "Thus, there is substantial uncertainty associated with the HIV prevalence estimate obtained from each of these methods, and this uncertainty cannot be greatly reduced by more sophisticated statistical models or better data." (Karon *et al*., 1998:140).

In subsequent research efforts, attempts were made to incorporate the vexing phenomenon of uncertainty in the input parameters that go into the modelling of HIV/AIDS. This problem had been acknowledged since the development of the first generation of HIV/AIDS models. For example, Brouard (1991:89) made the following remarks:

> "…In an epidemic like AIDS the uncertainty about infectivity level creates great uncertainty for the growth rate because of the very short interval between two generations of infected people."

As another example, Palloni (1996:621) made the following remarks:

> "Our discussion of the demographic impact of HIV/AIDS reflects uncertainty about the past, current and future course of the epidemic."

One of the methodological strategies used to address uncertainty was to develop the model within a Bayesian framework. The idea of adopting a Bayesian approach to HIV/AIDS modelling was suggested in the works of Carlin and Gelman (1993) and Wild *et al*. (1993). Becker and Britton (1999) briefly mentioned about the importance of data augmentation methods such as Bayesian analysis using Markov chain Monte Carlo methods. In a very detailed study, De Angelis *et al*. (1998) developed a Bayesian formulation of the back-projection method and used it to project AIDS in England and Wales. The method uses a multi-stage Markov chain Monte Carlo method and allows for uncertainty in the model's input parameters and incorporates seroprevalence data.

3. Supplementary review of models

3.1 Model of Gregson et al. (1996)

Some models make no assumptions about the epidemiology of the HIV virus or the behavioural and socio-demographic determinants of its spread. The models simple propose a mathematical relationship between observed HIV prevalence with its incidence. One such method is the cumulative survival and survival (CIS) method proposed by Gregson *et al*. (1996). This model easily fits within the description of type 1 models.

The CIS method requires an age-dependent hazard function, $g(a)$, to be assumed such that the cumulative incidence of HIV infection up to age a, $I(a)$, is given by the expression:

$$I(a) = \int_0^a g(x) . e^{\int_0^x g(y)dy} \, dx$$

Where the hazard function, $g(a)$, is represented by a three-parameter model as follows:

$$g(x) = \begin{cases} \boldsymbol{a} \exp\left(\dfrac{-(x - U\boldsymbol{g})^2}{\boldsymbol{b}\left(\dfrac{U}{2}\right)^2} \right), & for L \le x < U \\ 0, & otherwise \end{cases}$$

Where α, β, and γ represent the level, spread and skewness of the age-specific model of infection. L and U are the upper and age limits beyond which HIV-1 incidence is negligible. The parameters α, β, and $\gamma > 0$ and $g(x) \in (0,1]$.

Upon application of the CIS method to data from male factory workers in Harare, Zimbabwe, the authors found broadly consistent estimates of HIV incidence (Gregson *et al*. 1998).

3.2 Model of Bongaarts (1989)

Bongaarts (1989) proposed a model of the spread of HIV infection and the demographic impact of AIDS. The model can best be described as a type 4 model. It was developed during the early stages of the epidemic, a time when uncertainty was very high in the parameters that go into models of HIV/AIDS. As a solution to this high uncertainty, he proposed a simulation model. The model can best be described as being epidemio-demographic in nature. A set of epidemiologic submodels of the various routes of HIV transmission in different sexual behaviour groups forms the core of the overall model. These submodels are then integrated within a demographic framework, along the lines of a cohort component projection model. In the model, the population is divided according to their risk of HIV infection (or sexual behaviour). For example, prostitutes and sexually mobile males are at high risk of HIV infection than faithful partners in marital unions. The model acknowledges the existence of other non-sexual modes of transmission but did not include them at the stage. The model also subdivided the population infected with the HIV virus into various states depending on the stage of the HIV infection, starting with asymptomatic (normal immune function) to AIDS related complex (ARC). Bongaarts argues for his proposed approach as follows:

> "The advantage of the proposed approach to modelling the progression from infections to AIDS are significant. It is now possible to assign different levels of infectiousness to individuals at different states of infection, and other relevant variables such as frequency of sexual contact and condom use can also be varied by stage. An important practical implication is that the entire model can be simulated as a Markov chain, which allows relatively simple and fast implementation on microcomputer.' (Bongaarts, 1998:110-111).

The model proposes a formula for computing HIV infection rates for groups of individuals with multiple partners and frequent partner change and another formula for groups of individuals with single partners and infrequent partner change. For ease of computation, simplifying assumptions are made and multipliers are used. On application of the model on simulated data, the following significant conclusion was reached:

> "Despite the fact that seroprevalence among adults reached 21 per cent in year 25, the annual population growth rate was reduced by 'only' 1.1 per cent". (Bongaarts, 1989:118).

While no further work has been done on the model, aspects of the model have been used in the development of the AIDS software used by the US Bureau of the Census (Bongaarts, 2000).

### 3.3 The model of Mariotto and Verdecchia (2000)

The model of Mariotto and Verdechhia (2000) is an extension and refinement of previous models that some Italian group of researchers, led by Arduino Vedecchia, have been working on since the 1980s. The main theme of the models is to estimate morbidity rates using largely mortality data. The model was applied for cardiovascular diseases by Verdecchia *et al*. (1984), applied to cancer morbidity by Verdecchia *et al*. (1985), applied to chronic diseases by Verdecchia *et al*. (1989), applied to HIV infection by Verdecchia and Mariotto (1995) and Mariotto and Verdecchia (2000). A distinct feature of these models is the use of the 'age-period-cohort' perspective in calculating the morbidity measures. The 1995 and the 2000 models are extensions of the back-calculation method. They make use of two convolution equations rather than one and the intensity function considered depends on both calendar time and age and consideration of the susceptible population. A main difference between the 1995 formulation and the 2000 one is that the former uses reported AIDS cases while the later assumes these are absent (or incomplete) and uses recorded AIDS deaths. Further details of the 2000 formulation are given below.

The model divides the population into HIV-free and HIV-infected and separates the deaths into AIDS deaths and non-AIDS deaths. The changes from one state (or substate) to another is mathematically represented by the following symbols:

μ(i,t) is the conditional probability of getting infected at age i in period t, being HIV-free

γ(i,t) is the conditional probability of an individual in the general population dying from AIDS at age i in period t, being alive

α_1(i,t) is the mortality rate of individuals aged i in period t, being alive

α_2(i,t) is the non-AIDS mortality rate of individuals aged i in period t, being HIV-free

β(i,t) is the non-AIDS mortality rate of individuals aged I who were infected at age j in period t

δ_1(i-j|j,t) is the conditional probability of developing AIDS at age i being infected at age j in period t

δ (i-j|j,t) is the conditional probability of dying from AIDS at age i being infected at age j in period t

δ_2(i-j|j,t) is the conditional probability of dying from AIDS at age i being diagnosed with AIDS at age j in period t

For the purpose of simplification, the relationship between these rates/probabilities and the different states is shown in the Figure below:

Figure 3: Conceptual framework of the model of Mariotto and Verdecchia (2000)
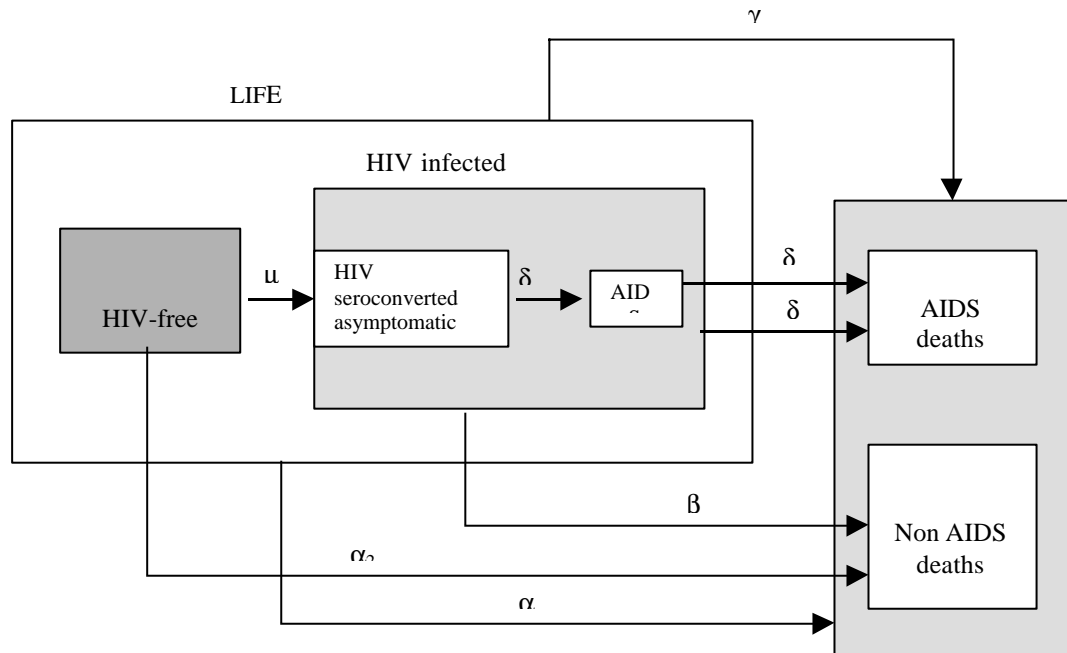
The parameters of the model are obtained as follows:

$$\boldsymbol{g}(i,t) = \sum_{j=0}^{i-1}\{1 - \boldsymbol{n}(j,p+j)\}\boldsymbol{m}(j,p+j)\boldsymbol{d}(i-j \mid j,p+j)S(i,j,p+j)$$

$$\boldsymbol{n}(i,t) = \sum_{j=0}^{i-1}\{1 - \boldsymbol{n}(j,p+j)\}\boldsymbol{m}(j,p+j)S(i,j,p+j)$$

where

$$S(i,j,p+j) = \exp\left\{-\sum_{l=j}^{i}[\boldsymbol{b}(l,j,p+j) - \boldsymbol{a}(l,p+l)]\right\}$$

The model assumes that the logit of the incidence function μ belongs to a family of polynomial functions of age, period i and cohort $p=t-i$, so that:

$$\log\left(\frac{\boldsymbol{m}(i,t)}{1-\boldsymbol{m}(i,t)}\right) = const + \sum_{k=1}^{k_1} a_k i^k + \sum_{k=1}^{k_2} b_k t^k + \sum_{k=2}^{k_3} c_k p^k$$

Where $\theta = (const, a_1, \ldots a_k, b_1, \ldots b_k, c_2, \ldots c_k)$ is a parameter vector to be estimated.

From the these equations and from the assumption that the number of AIDS deaths is assumed to be independently distributed as Poisson (with mean $N_{it}\boldsymbol{g}(i,t,\boldsymbol{q})$, where N_{it} is the population at age i and time t).

AIDS incidence at age i in period t is estimated as:

$$A(i,t) = \sum_{j=0}^{i} \{1 - \boldsymbol{n}(j, p+j)\}\boldsymbol{m}(j, p+j)\boldsymbol{d}_1(i-j \mid j, p+j)S(i, j, p+j)$$

where,

$$\boldsymbol{d}_1(d \mid j, t) = \int_{d-1/2}^{d+1/2} f_1(u \mid j, t) du$$

where, $f_1(d/j,t)$ is the density function of the AIDS incubation time d, for individuals infected at age j in year t (estimated from prior cohort studies).

When the method was applied to Italian data for reconstructing the HIV/AIDS epidemic, they obtained AIDS mortality data that were consistent with those obtained from back-calculating on the AIDS reported cases. The advantage of the method is its applicability in situations where AIDS registered cases are unavailable or are inconsistent.

3.4 Works of Ian Timaeus (various years)

Through various papers, Ian Timaeus has made significant contributions towards measuring the mortality impact of AIDS in countries with poor vital statistics. The impact of AIDS on mortality can only be properly assessed once there is a pre-AIDS mortality baseline against which to compare. But what is this pre-AIDS baseline? Such a question is very difficult to answer for many African countries. Timaeus (1992) contributed towards estimating (pre-AIDS) male adult mortality using paternal orphanhood data. In the original Brass method, the estimation of mean age at paternity (M) as well as male fertility had not been sufficiently addressed. Partly as a result of these, the original paternal orphanhood method had been found to give results as satisfactory as those from the maternal orphanhood method. Timaeus took account of these and other factors and obtained new sets of regression coefficients (from simulated data) for calculating male as well as female adult mortality. The simulated data was derived from the use of the relational logit model life table (using the General Standard) and the relational Gompertz model (using Booth's standard for females and the Paget and Timaeus' standard for males). The new regression coefficients for male mortality were found to perform better than the older Brass method especially at extreme levels of mortality.

In Timaeus (1997) the argument put forward is that AIDS might have changed the age pattern of mortality in a remarkable fashion. In the paper, he did not develop a specific model of HIV/AIDS but looked at its impact on age patterns of mortality. He addressed the practical situation found in most developing countries- where vital statistics is grossly deficient and mortality data has to be obtained through indirect demographic techniques. In the paper, Timaeus cautions against the use of indirect techniques in areas where deaths due HIV/AIDS is high. Firstly, the regression coefficients used in indirect demographic techniques (to convert data on survivorship of kin to life table indices of survivorship) were derived using model life tables that have different age patterns of mortality. Secondly, the model life tables are used for linking indices of survivorship over different age ranges. In the paper, he studied age patterns of mortality from the available data (drawing mostly upon DHS data)

9

and attempted to develop model life tables for Africa that would best capture the effect of HIV/AIDS. Timaeus reasons that the effect of HIV would have a strongly differentiated effect on age patterns of mortality. In the case of the (four) Southern African data sets analysed, Timaeus found no evidence that the age pattern of mortality was related to the overall level of mortality nor that it has changed over time. Timaeus proceeded to produce model life tables for various regions of Africa. He believed that these life tables represented African mortality patterns more accurately than the Coale-Demeny model life tables.

In Timaeus and Nunn (1997), the issue of indirect estimation of adult mortality (using orphanhood data) in populations affected by AIDS was addressed. The paper starts off by recognising an inherent limitation of the orphanhood method namely that the data on parents' survival can only be collected from those of their offspring who themselves remain alive. Even though the bias that arises from this has been found to be small, in population affected by AIDS, this bias is likely to be more severe. A model is developed which divides the female population into two groups, those HIV-free and those with HIV. The model is developed in such a way that it will feed into the conventional orphanhood method. Three crucial variables introduced in the model are as follows: F (undefined but mathematically related to $F(a,y)$ which is the age specific ratio of fertility of seropositive to seronegative women who gave birth a years ago at age y); h, the proportion of sereopositive mothers who transmit the virus to their children perinatally and P the seroprevalence rate for women seen at antenatal clinics. The model derives the following relationship:

$$\frac{S(a)}{S^*(a)} = \frac{1 - hP}{1 + \dfrac{1 - F}{F}P}$$

where $S(a)$ is the proportion still alive of women who would have given birth a years ago in the absence of any impact of HIV infection on fertility; $S^*(a)$ is the proportion of respondents aged a who report that their mother is alive.

Alternatively,

$$\frac{S(a)}{S^*(a)} = 1 - (1 - (1 - h)F)P^*$$

where P^* is a population-based estimate of seroprevalence among women of childbearing ages.

Using these equations and substituting values for F and P based on Ugandan data, Timaeus and Nunn estimate HIV-related selection bias and proceed to revise the regression coefficients for maternal orphanhood reported in Timaeus (1992). While the paper acknowledges the arguments put forward in Timaeus (1997) regarding the problem of accepting the (pre-AIDS) model age patterns of mortality underpinning the orphanhood regression estimates, the paper did not use recent age patterns of mortality (as reported in Timaeus, 1997) that sought to take AIDS into account.

The paper proposes an adjustment of orphanhood data for the bias introduced by additional AIDS mortality. The technique requires an estimate of the proportion of mothers who were infected at the time their children were born.

In Timaeus (1998), the impact of the HIV epidemic on mortality in sub-Saharan Africa was assessed using data from national surveys and censuses. While Timaeus acknowledges that the spread of HIV infection is not the only reason for the slowdown in mortality decline in Africa, the results showed clear split between those countries where one would expect significant HIV mortality by the time the data were collected and those where one would not. In Timaues (1999), the same investigation was further explored using in-dept analysis of few countries.

4. Research findings that add to modeling efforts

4.1 Work based on community studies

Boerma *et al.* reviewed various demographic indicators that capture the effect of HIV/AIDS. Among the indicators reviewed, the following seem to have the most merits. Under-fifteen mortality (broken down by under-five mortality and mortality between 5 and 15) ($_{15}q_0$); the probability of dying before age 60 among 15 year olds ($_{45}q_{15}$); the proportion of causes of deaths attributable to HIV/AIDS and the proportion orphaned (by one parent (single orphanhood) or by both parents (double orphanhood)).

Based on a review of literature on community studies, Boerma *et al.* summarise recent evidences as follows:

1. In developed countries mean survival time has been found to exceed 11 years. In Africa, median survival time could be between 8-10 years as observed in developed countries in the pre-treatment era.
2. Age at infection is an important determinant of survival.
3. There are important differences between developed countries and LDC with regards to HIV virus, mode of transmission, host immunological system even in the absence of HIV infection and the availability and quality of curative care for opportunistic and other infections.
4. The effect of HIV-2 infection on mortality is much smaller than for HIV-1.
5. Mortality among AIDS patients is not substantially different for HIV-2 and HIV-1
6. Survival time of patients with AIDS in LDC indicate shorter survival times, ranging from 5 to 9 months.
7. A proportion of HIV-infected deaths occurs before clinical AIDS. The proportion ranges from 20% to 50%. Only a small proportion of these non-AIDS deaths are due to competing causes and most can be attributable to impaired immunity in association with HIV infection.
8. Even prior to the AIDS epidemic, TB was considered the leading cause of death amongst adults in LDC. If untreated, about two –thirds of TB patients die, even in HIV-negative persons.
9. TB is the most common opportunistic infection in African patients who die from AIDS.
10. In one study it was found that $_{45}q_{15}$ was 24% amongst HIV-negative individuals and 61% among the whole population.
11. In the absence of HIV serostatus, increasing mortality trends cannot be conclusively attributed to AIDS.
12. In LDC, greater overlap exists between diseases associated with HIV infection and other common childhood diseases than in adults diseases, and this complicates the study of HIV/AIDS survival time. However data on the age at death of the children are sufficient to estimate survival time since the age at which most children become infected is much less variable than in adults.
13. In one study, the infant mortality rate in infants born to HIV-infected mothers was 163 per 1000 live births, compared to 34 per 1000 in infants born to mothers uninfected with HIV. However for infants with laboratory confirmed HIV, the IMR was 336 per 1000 live births.
14. In one study of the history of HIV in Africa, it was found that of the children with laboratory confirmed HIV, 34% had died at 1 year, 66% at 3 years and 75% at 5 years. The median survival was 21 months.

In a study of disease progression and survival in HIV-1-infected Africans in London, Del Amo (1998) found the following:

1. There was no difference in progression from prevalent HIV-1 infection to AIDS and from AIDS to death attributable to African ethnicity. To them, this suggested that the lower survival rates in sub-Saharan Africa resulted from lack of access to health care and from exposure to acute infections in the African environment.

2. Regarding the effect of age on disease progression, the study found that for every additional year of age, there was a 2% increase in the risk of progression to AIDS and a 4% increase in the risk of deaths after AIDS.

In a forty-year follow up study of the mortality in Gwembe, Zambia, Clark (1999) found the following:

1. Overall the mortality was similar to Coale-Demeny South model pattern and not 'terribly extreme'.

2. Probabilities of dying between ages x and x+n increased by 100% for females in age group 30-39 and 40-49 during 1985-1990 and increased by more than 100% for females in age groups 20-29 and 30-39 during 1990-1994. This increase in mortality which was absent in the 40 year study period suggests the impact of AIDS.

3. Probabilities of dying between ages x and x+n increased by 100% for males in age group 30-39 and 40-49 during 1985-1990 and increased by 50% for males in age groups 30-39 and 40-49 during 1990-1994. Again this increase in mortality suggests the impact of AIDS.

4. For females, age specific fertility rates did not show any change for the age group 15-24 and not a lot of change at older ages, over the period 1980-1994. However, for age group 25-29, there was big drop in the rates over the period 1980-1994. This drop is seen to be possibly AIDS associated.

5. For males, the age specific fertility rates did not change for age groups 15-29 and 50-69 over the period 1980-1994. However, for age group 30-44, there was big drop in the rates especially in the period 1985-1989. This drop is seen to be possibly AIDS associated.

4.2 Population-based studies

4.2.1 National surveys

In contrast to community-based studies, national surveys such as DHS are population-based. Such studies have also contributed to the body of knowledge on AIDS and mortality in developing countries. Bicego (1997) shows the importance of DHS sibling histories in estimating adult mortality in the context of AIDS in sub-Saharan Africa. Direct analysis of full sibling histories allows for a more recent, and therefore relevant, reference period than is now possible with indirect estimation techniques. In a prior study comparing direct and indirect estimates obtained from the sisterhood method, Rutenberg and Sullivan reached a similar conclusion:

> " We conclude that where the interest is in estimating in some detail the level, recent trends, and distribution of maternal deaths according to age and parity, the direct approach is a rich source of data on these issues." (Rutenberg and Sullivan, 1991:1679).

In the case of Abidjan, Code d'Ivoire, Bicego (1997) compared the DHS estimates for 1988-94 based on sibling history data with vital registration data over two periods, 1983-87 and 1988-1992. It was found that the DHS estimate was in line with the rising mortality (found to be AIDS-related) over those two periods.

4.2.2 Recorded causes of death

In a demographic study estimating the contribution of AIDS to general mortality in Brazzaville, Congo, Pictet (1998) found that, in 1996, AIDS was the leading cause of death among adults 15 years or older, with 25% diagnosed with AIDS. For infants less than one year, neonatal death was the leading cause, accounting for 47.6% of the total. AIDS was diagnosed in only 6% of the deaths. For children aged 1-4, malaria was the primary cause of death, accounting for 25% of the cases. AIDS was the second leading cause of death, accounting for 19% of all cases. For older children aged 5-14, the leading cause of death was malaria. Only four children died of AIDS in this age group. The study also found that AIDS was not prevalent after 65 years. The life tables computed for the population found that the difference in life expectancy at birth for the life tables with AIDS considered and without AIDS, were 4.3 years for females and 3.3 years for males.

5. Available software for estimating/projecting HIV/AIDS

For almost all the models reviewed above, some kinds of computer program were used to estimate the parameters of the model and obtain the results. These kinds of programs are more of tailor-made programs designed to solve only the problem at hand and might not be easily applicable for use in other

contexts. In this section, one only reviews those programs that have been developed for generic use. The programs/software falling in this category are few.

5.1 GPA's EpiModel

The EpiModel was developed by the WHO Global Programme on AIDS (GPA) for short-term forecasting of AIDS. The model has been described in Chin *et al.* (1989), Chin and Lwanga (1991). The main estimates and assumptions needed to run the model are as follows:

(a)   The year extensive spread of HIV infections started
(b)   HIV point prevalence
(c)   The year HIV prevalence was measured
(d)   The shape of the HIV incidence curve
(e)   The location of the reference year on the HIV epidemic (incidence) curve
(f)   The annual number of HIV-infected cohorts
(g)   Progression rates from HIV infection to AIDS

The EpiModel software simplifies these requirements further. A description of the model is given below:

> "EpiModel projects the past and future course of an AIDS epidemic based on three key assumptions: the year in which HIV infection first became widespread, the number of people alive with HIV infection in a recent year, and the shape of the infection curve. The model allows the user to select a curve type to describe cumulative HIV infections over time. Most projections assume a gamma curve (a type of S-shaped curve). A gamma curve is fitted to two points: (1) zero infections the year before HIV infection became well established in a core group, and (2) the current estimate of infections. The user decides where on the gamma curve the current year lies. If the user decides that the epidemic is still in its early stages, then the point representing the current year is placed in the early part of the S-curve, leaving the most rapid increase in infections to occur in the future. If the user decides that HIV incidence is currently at its peak, then the current year estimate is placed right in the middle of the S-curve. Similarly, if it is assumed that the epidemic has reached the endemic stage, then the current year estimate is placed near the top of the S-curve. Thus, the assumption about the current stage of the epidemic largely determines the future projection.

> While EpiModel does not produce an automatic projection of future prevalence, it does make it easier for users to prepare such an estimate." (Stover, 1997:12-13)

The Population Division of the United Nations makes use of EpiModel in making AIDS prevalence projections for inclusion in their population projections. The UN assumes that the peak incidence age, middle of the Gamma curve, is reached 12 years after the beginning of the epidemic (Stover, 1997).

5.2 AIDSTECH /AIDSproj/ AIM

AIDSTECH and AIDSproj are used for estimating HIV prevalence and for subsequently calculating AIDS cases and AIDS deaths. AIM is used to illustrate the future consequences of the epidemic. John Stover has developed them all wholly or partially. AIDSproj is an Excel spreadsheet software developed by Stover and incorporates AIDSTECH and the methodology in EpiModel as described in Chin and Lwanga (1991). Lastly, AIM was developed by Stover. AIM has been included as a module in integrated software, Spectrum, developed by Futures Group International. AIDSProj has similar features as EpiModel. One key difference between the two is that AIDSproj uses as input the prevalence of HIV as a percentage of all adults rather than the number of infections (as done in EpiModel). In this way, the projection of future prevalence does not rely on a population projection (since it is expressed as a percentage) (Stover, 1997). Further details of AIDSproj is given below:

AIDSproj is designed to facilitate the use of surveillance data from antenatal clinics to prepare estimates of national adult prevalence and to prepare projections of HIV prevalence. The program makes three sets of assumptions for the progression from HIV to AIDS. The FAST assumption is based upon the methodology used in EpiModel (Chin, 1996); the MEDIUM assumption is based estimates derived by Hendricks *et al.* (1996) and the SLOW assumption is based upon estimates derived by Buchbinder *et al.* (1996). The program adjusts for the fertility-inhibiting effects of HIV. The program adjusts the ANC data to account for male infections and for women over the age of 49. An important

aspect of the program is that it allows for the ANC input data to be provided according to regional breakdowns (depending on the number of ANC sites in the country).

5.3 iwgAIDS model

The iwgAIDS (Interagency Working Group on AIDS) model is a complex simulation model of the spread of HIV through a population as a result of the behavior of various population subgroups (Stanley *et al.*, 1989). The US Census Bureau approach to projecting HIV prevalence is based on this model. According to the authors of the model,

> "The IWG model is designed to provide qualitative insights into specific demographic and epidemiological questions about the epidemic. Demographic questions include the age pattern of infections and the effect of the epidemic on the age structure of the population (e.g. dependency ratios), on infant and child mortality and on overall population growth rates. Epidemiological questions include the relative importance of each infection route, how the virus spreads between age groups, the role that very-high-risk takers play in spreading the epidemic, how the epidemic spreads from urban to rural regions (why it appears to spread rapidly under some conditions and not spread at all under other conditions), the effect of other sexually transmitted diseases and the impact of interventions on the epidemic."
> (Stanley et. al., 1991:119).

The essential features of the iwgAIDS model is summarised below:

> "The iwgAIDS model … uses a deterministic system of differential equations to model behaviors affecting HIV transmission and the course of the disease. The model disaggregates the population in several dimensions, including sex, age, region, marital status and high-risk behavior. Groups are described in terms of a number of characteristics, including number of sexual contacts within and outside marriage, use of condoms, number of concurrent partners, number of blood transfusions and practice of breast-feeding. All major HIV transmission mechanisms and cofactors are simulated, including heterosexual transmission, perinatal transmission, blood transfusion, homosexual transmission and injections. The model includes a number of co-factors of HIV transmission, including ulcerative and inflammatory STDs, circumcision…"
> (Stover and Way, 1995:3)

5.4 Doyle model/ASSA500/ASSA600

The Doyle model, ASSA500 and ASSA600 models are interrelated and were all developed in South Africa. The Doyle model was produced by Metropolitan Life and was later adapted by the Actuarial Society of South Africa (ASSA) to produce ASSA500 and ASSA600 spreadsheet models. At the core of the ASSA models, the population is divided into four risk groups and three broad age groups. The initial population is then allocated into the various risk groups according to assumptions made and the proportions of the population at each age group. The HIV infection spreads in the population according to the specifications in the 'expected contagions' table. According to Dorrington (1998:16),

> "This table represents the average number of individuals of each risk group that an infected individual of one risk group would expect to infect in a year if he or she were the only infected individual in the population."

For each age and risk group there is a force of infection, which is used to derive an independent probability of infection at each age for each sex and risk group and each period in the projection. The computation of force of infection includes a parameter known as 'sexual activity index' defined as a composite measure of 'number of contacts', 'number of new partners' and 'ease of infection' (Dorrington, 1998). The model allows for AIDS deaths and normal deaths. The normal deaths and the probability of infection are used in a multiple decrement table that applies to the HIV-free lives. Also, the normal deaths and the AIDS deaths form a double decrement table applicable to HIV infected individuals. An S-shaped curve is used to model incubation period and a separate mortality assumption is made for AIDS deaths as a result of perinatal HIV infection. This perinatal infection is computed as a constant probability of death in each year of age. Lastly, the model made allowance for reduced fertility in the different risk groups. The model can be described as being close to a type 3 model.

While the ASSA500 could be described as an AIDS model (designed for use only among African/Blacks), the ASSA600 (for the whole of South Africa without breakdown by population group) adds in an elaborate population base estimation component that makes it both an AIDS as well as a demographic model. The model has been widely used in South Africa by various modellers and interest groups.

6. Comparative evaluation of software packages and computer programs

It is clear that the most of the existing software for estimating/projecting HIV/AIDS emerged from models whose theoretical basis had been outlined at the 1989 UN/WHO workshop held in New York. At that time, it was difficult to compare the results of these models. As Palloni and Glicklich (1991:40) noted:

> "Because these models are at different stages of development, it is difficult to compare their results. A more feasible task is to define their main features, compare them with those features which have been singled out as crucial for evaluating the further course of the pandemic and then assess the nature of their primary conclusions."

Palloni and Glicklich (1991) did such a comparative study of the main features. Subsequently, Stover (1997) and then Stover and Way (1998) took the work a few steps further.

6.1 Stover's evaluation

Stover reviewed the different approaches to incorporating AIDS into demographic projections. In his review, he covered the following approaches: the UN approach, the World Bank approach and the US Census Bureau approach. He did mention briefly the Population Council approach but did not include it in the comparison. He based his review on the results that the different approaches produced in projection the populations of different African countries. Stover noted that none of the projections assumed any connection between HIV prevalence and fertility rates. He noted that all fours sets of projections agree on one key point, namely that AIDS will not cause negative population growth in any country in sub-Saharan Africa. The results however showed very large differences in both 2010 and 2025 between the US Census Bureau projections and the UN and the World Bank projections. The Census Bureau projection showed a much larger effect of AIDS on population size than either the UN or World Bank. Stover attributes the differences between the results to the following factors:
- Adult HIV prevalence in the base year
- Projection of future levels of adult HIV prevalence
- length of the incubation period for adults and children
- perinatal transmission rate
- methodology for incorporating AIDS deaths into demographic projection
- length time from AIDS to death
- age and sex distribution of AIDS deaths
- start year of the epidemic

Of these, the most important were found to be: prevalence projections (56%), incubation period (27%), base year prevalence estimates (16%) and perinatal transmission rate (7%).

6.2 Stover and Way's evaluation

In a way, the review by Stover and Way (1998) is a subset of the Stover's (1997) review. Stover and Way (1998) reviewed the works of two leading institutions, UN and the US Bureau of Census and compared the results of 14 countries. The conclusions reached were similar to those in Stover (1997). For brevity the results of the evaluation is not reported here.

6.3 Unpublished evaluations

There are some excellent reports written, comparing different available HIV/AIDS software. Some of these reports are commissioned works or consultancy reports, and hence are not easily available. In some of these reports, other software which have their origins in the earlier-mentioned UN HIV/AIDS modelling workshop, are described. An example is the PRAY AIDS model which was developed from the work of Bulatao (1991) (SADC Secretariat, 2000).

7. Criteria for making appropriate selection for estimating/projection HIV/AIDS in South Africa

From the models reviewed above, it is clear that while some of the models pay close attention to the available data and how best to utilise them, for others, this is not the primary concern. Though unstated, for the latter set of models, the primary concern is the elegance of the model and its logical consistency. Issues of data were to be addressed later when they become available. The same remarks apply for software that were developed out of these models. In this regard, Pictet *et al.* (1998) write as follows:

> " [HIV/AIDS] (m)odels, however depend on a number of variables that are either difficult to measure, such as the duration of the incubation period, or currently unavailable, such as the sex and age-specific prevalence rates in the general population." (Pictet *et al.*,1998:2217).

However, in spite of uncertainties such as those identified above, short-term predictions (5-10 years) of the impact of AIDS can be reasonably derived from knowledge of the natural history of HIV infections and from seroprevalence data. Short-term projections at time *t* are virtually independent of the future trends and new HIV infections that will occur in time *t* and later (Chin *et al.*, 1989).

In the case of South Africa, a lot of data is already available, and has relevance to estimation of mortality due to HIV/AIDS and its projection. The practical course to follow would therefore be to concentrate on models/software that have a strong empirical basis. In this regard, the section below will review the available data followed by review of models/software that make use of similar sets of data.

8. South African context

8.1 Available data in South Africa

South Africa has a wide range of data sets that can be utilised to provide input for various aspects the HIV/AIDS modelling. Admittedly, the data sources are not all of the same quality. They nevertheless could assist in minimising uncertainties or resorting to unwarranted assumptions in HIV/AIDS modelling. Some of the main data sources are as follows:

1. Registered deaths based on vital statistics (up to 1996) and cause of deaths (up to 1995)
2. Annual national seroprevalence surveys (from 1990 to 1999)
3. Demographic and Health Survey (1998)
4. Cancer registry data (with 1995 being the latest year for which data is available).
5. Demographic Surveillance Systems (as in the Agincourt study)
6. Small scale studies (with results published mostly in the South African Medical Journal)
7. 1996 census
8. Other national surveys such as the OHS (with 1998 being the latest year for which data is available).

A lot could be said about the merits and demerits of each of these data sets but this is not the place to do so. Suffice to say that these data sets provide a wide range of variables that could be exploited by a careful analyst to inform HIV/AIDS modelling.

8.2 Missing data in South Africa

A crucial missing data in South Africa is the AIDS registry data. As AIDS is not a notifiable disease in South Africa, such a databank would be difficult to compile. Other surveys specifically designed to understand social networks and behaviours of individuals with respect to HIV/AIDS, if available at all, is not at a national level.

9. Synthesis

9.1 Summary

As at 1989, the WHO surveillance system for AIDS covered 177 countries and territories, and about 133,000 cases of AIDS had been reported from 143 of them (WHO, 1998). At this stage, knowledge of the HIV/AIDS dynamics was limited and not enough data had been collected. At this stage of the HIV/AIDS epidemic, it was necessary to formulate elaborate models for use in simulation. Such models assist in providing answers to the effects of different interventions. As the epidemic matured, and more knowledge is accumulated about the natural history of the epidemic and its social, demographic and epidemiologic determinants, more practical models were formulated. These models concentrated on maximising the utility of the available HIV/AIDS-related data and overcoming their shortcomings. The availability of AIDS registries prompted the development of back-calculation methods. The realisation, subsequently, that such registry data were affected by the problem of delay in reporting led to various extensions of the back-calculation method, to adjust for such delays.

In the case of South Africa, the absence of AIDS registries largely precludes the use of back-calculation methods. The limited small scale studies and prospective cohort studies coupled with the absence of a detailed attitude and behaviour survey preclude the use of models that include the use of hard-to-find data such as infectivity, transition probabilities from one HIV stage to another or from one risk group to another. Under such circumstances, the approach to be adopted should be to use the model which utilise most, if not all, of the existing HIV/AIDS related data sets. As mentioned above, these data sets are: recorded deaths, recorded causes of deaths, HIV prevalence (from antenatal clinic surveys). Two candidates for this are first the model by Marrioto and Verdecchia followed by AIDSproj.

The model of Mariotto and Verdecchia was specifically designed for countries lacking AIDS registry data. The model allows for adjustment of the registered deaths to allow for underreporting of deaths. The importance of recorded causes of deaths (in a developing country setting) in estimating HIV/AIDS mortality has been demonstrated in the Abidjan study by Garenne *et al*. It must be noted that the model of Mariotto and Verdecchia requires values for overall (normal) mortality. These can be derived from a life table constructed via one of two approaches. One approach is to use the registered deaths for the latest available year (1996) and adjust for underreporting using one of several demographic techniques designed for such tasks. The other approach is to construct life tables indirectly (using the census or survey data)- by combining infant and child mortality estimates (using Brass-type techniques) and adult mortality using the revised equations derived by Timaeus (1992). One problem with the use of the model by Mariotto and Verdecchia is that the model is not yet developed as software for more general use. As such, time would be needed for its full development and adaptation.

AIDSproj, as has been mentioned, incorporates HIV prevalence data and other data based on community studies. It has the advantage that it is already developed as software for wider use.

9.2 Suggested way forward.

In making selection of models for projecting HIV/AIDS prevalence, the preference has to be for models that maximise the available data in South Africa. A model, no matter how elegant or realistic, cannot be utilised if the necessary input parameters are not available. In view of the discussion above, Stats SA could use three strategies: short run, medium term and long run. In the short run, at least two issues could be addressed. First is the construction of life tables reflecting both pre-AIDS mortality and mortality during the AIDS era. Here, some of the works of Ian Timaeus could be drawn upon as well other indirect demographic estimation techniques. Second, AIDSproj could be made use of to obtain projections of HIV/AIDS prevalence and these rates could be fed other projection software/programs to prepare projections that incorporate HIV/AIDS. The different ways of preparing population projections incorporating HIV/AIDS have been discussed in Stover (1997). In the medium term, programs could be written to use the model of Mariotto and Verdecchia and adapt it where necessary. In the long term, the model of Mariotto and Verdecchia could be reformulated within a Bayesian framework to allow for uncertainties in all of the input parameters. This would fit in quite well with the Bayesian population projections that Stats SA would be preparing for its detailed population projections.

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