Incidence of HIV infection in rural KwaZulu-Natal

In the context of the epidemiology and impact of HIV/AIDS in South Africa

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Submitted in partial fulfilment of the requirements for the degree of
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Declaration

The research presented in the thesis represents original work by the author and has not been submitted in any form to any other university. Assistance received from others in the execution of the research has been duly acknowledged.

Eleanor Gouws, 15/11/2007

Eleanor Gouws

The thesis is dedicated to my parents and my husband

Acknowledgements

The thesis is the result of several years of research and I acknowledge the assistance and support of several people in the completion of the work.

I am deeply grateful to my supervisor, Professor Salim Abdool Karim, for advice, comments and suggestions on all aspects of the work presented in this thesis. His leadership in epidemiological research and commitment to finding ways to control the HIV epidemic in South Africa contributed greatly to the conceptualization and development of the work presented in this thesis. It was a privilege to work under his mentorship and the years of guidance and support are highly valued.

I thank Professor Champak Jinabhai for valuable comments and suggestions at various stages of the research and for allowing me to do this thesis through the Department of Community Health.

My greatest appreciation goes to Professor Brian Williams, who has taught me much of what I know about infectious disease modeling. His extensive knowledge of epidemiology, mathematics and statistics, but also his love for numbers and patterns has been a constant source of motivation. I thank him for his contribution to the development of the mathematical models, for advice and suggestions on epidemiology and statistical analyses, and for providing data from the Carletonville study to be included in the analyses. I greatly appreciate his generosity, enthusiasm and commitment to science, and above all I thank him for his support and encouragement while working on this thesis.

I thank Professor Quarraisha Abdool Karim for the advice, suggestions and comments on various parts of the research reported in this thesis, with specific reference to Chapter 5 and on the Hlabisa Vaccine Preparedness Study. Data from this study are used in several chapters and analysed in greater detail in Chapter 7.

I thank Dr Janet Frohlich for managing the Hlabisa Vaccine Preparedness Study between 1999 and 2002, the Hlabisa MRC staff and community educators for data collection and field work for this community based study, and Charmaine Pillay and Lorna Madurai for coordinating blood samples and laboratory work during this period.

The rural community of Hlabisa was the site where most of the Medical Research Council's research on HIV was conducted between 1990 and 2002. The area was identified in the late 1990s as a potential site for conducting future HIV intervention trials, and estimation of incidence rates became essential. Data from studies conducted in this area were used in the development of the models to estimate incidence, as well as in the validation of the laboratory method for incidence estimation. The initial development of the dynamical model and the laboratory method to estimate HIV incidence, as well as the Vaccine Preparedness Study were carried out while employed by the South African Medical Research Council and I thank the MRC for their support during this period.

I thank Dr Gita Ramjee from the Medical Research Council whose data on high risk groups (sex workers and truck drivers) in KwaZulu-Natal are included in the analysis in Chapters 5 and 6.

The data from national antenatal clinic surveillance conducted by the South African Department of Health are used in the analyses in several chapters. I acknowledge the contribution of the Department of Health in helping to understanding the trends and distribution of the HIV epidemic in South Africa.

Blood samples from Hlabisa were sent to the Viral and Rickettsial Disease Laboratory of the Department of Health Services in California to be tested for recent HIV seroconversion using the Standardized Testing Algorithm for Recent HIV Seroconversion. I thank Dr HW Sheppard for the laboratory analyses of these samples.

Funding for the Hlabisa Vaccine Preparedness Study was received from Family Health International, National Institute of Health, and the Southern African Fogarty AIDS Training Programme.

Support for this work was received from the Fogarty AIDS International Training and Research Programme through the Fellowship Programme.

Scientific publications and presentations related to this thesis

Scientific publications directly related to this thesis

1. Gouws E, Williams B. What are we doing about HIV/AIDS in South Africa? A review of the scientific literature. *South African Journal of Science* 2000; 96(6): 274-276. (Chapter 2)

2. Gouws E, Abdool Karim Q. HIV infection in South Africa: the evolving epidemic. In *HIV/AIDS in South Africa*. Eds SS Abdool Karim and Q Abdool Karim. 2005 Cambridge press, Cape Town. (Chapter 5)

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Relevant conference presentations

1. Gouws E, Williams B, Abdool Karim SS. Estimating HIV Incidence rates from age prevalence data. *South African Statistical Association Conference, Durban, 3-5 November 1999.*

2. Gouws E, Williams B, Colvin M, Sitas F, Ramjee G, Abdool Karim SS. Patterns of infection: using age prevalence and incidence data to understand the epidemic of HIV in South Africa. *XIII International AIDS Conference, Durban, 2000.*

3. Gouws E, Abdool Karim Q, Frohlich J, Abdool Karim SS. Preparing for phase III HIV vaccine trials: experiences from rural South Africa. *XIII International AIDS Conference, Durban, 2000.*

4. Zuma K, Gouws E, Williams B, Campbell C, Lurie M. Migrant women and HIV infection. *XIII International AIDS Conference, Durban, 2000.*

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9. Williams B, Gouws E. The association between HIV and *Herpes Simplex* Virus-2. *South African Statistical Association Conference, Johannesburg, 8-10 Nov 2000.*

10. Ramjee G, Gouws E. Targeting HIV prevention efforts on truck drivers and sex workers: implications for a decline in the spread of HIV in Southern Africa. *'AIDS in Context', International Conference, University of the Witwatersrand, Johannesburg, 4-7 April 2001.*

Field work related to this thesis

The author was Principal Investigator of the Hlabisa Vaccine Preparedness Study conducted in the rural community of Hlabisa, KwaZulu-Natal. In addition to determining the preparedness of the community to participate in future vaccine trials in the area, demographic and health data were collected, and blood samples were obtained to test for HIV infection. The survey included about 2300 men and women of age 15-54 years. Ethical approval for the study was obtained from the University of KwaZulu-Natal, Medical Faculty Ethics Committee.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
AIM	ART impact model
ANC	Antenatal clinic
ART	Antiretroviral therapy
ARV	Antiretroviral drugs
ASSA	Actuarial Society of South Africa
CDC	Centers for Disease Control and Prevention
DHS	Demographic and health survey
ELISA	Enzyme-linked immunosorbent assay
EPP	Estimation and Projection Package
HIV	Human immunodeficiency virus
HSRC	Human Sciences Research Council
HSV-2	*Herpes Simplex* virus-2
KZN	KwaZulu-Natal
MRC	South African Medical Research Council
OD	Optical density
RNA	Ribonucleic acid
PEPFAR	Presidents Emergency Program for AIDS Relief
PCR	Polymerase chain reaction
PMTCT	Prevention of mother-to-child transmission
STARHS	Standardized testing algorithm for recent HIV seroconversion
STI	Sexually transmitted infections
TB	Tuberculosis
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Session
USA	United States of America
VCT	Voluntary counseling and testing
WHO	World Health Organization

Abstract

South Africa has had one of the fastest growing HIV epidemics in the world and almost 30% of women attending public antenatal clinics (ANC) are currently infected with the virus. But as the epidemic is starting to level off and antiretroviral therapy (ART) is becoming increasingly available, few methods exist to determine the impact of ART or other interventions on the epidemic in South Africa. This thesis explores the epidemiology and dynamics of HIV infection and investigates the potential impact of ART.

Methods

Total and age-specific prevalence data are analysed in time and space and are used to investigate patterns of infection in men and women, urban and rural, and low and high risk populations. Dynamical models are developed to estimate incidence from age-specific prevalence and trends over time and are compared to laboratory-based estimates of recent HIV sero-conversion. Incidence is estimated in different populations in South Africa. A dynamical model is developed to estimate the impact of ART on the future course of the HIV epidemic.

Results

HIV prevalence varies geographically and by age, sex and race. The average female-to-male HIV prevalence ratio is 1.7 and prevalence peaks at an older age among men than women. The age at which prevalence peaks among women has increased from 23.0 to 26.5 years between 1995 and 2002. Four patterns of infection are identified: among pregnant women attending ANCs, among men and women in the general population, and among migrant workers. HIV incidence among ANC attendees peaked in the mid to late 1990s (at 6.6% per year nationally) with variation between provinces. Current estimates of HIV prevalence and incidence among the general population in South Africa (aged 15-49 year) are 18.8% and 2.4% per year, respectively. Age-specific incidence estimates from dynamical models and laboratory methods are in good agreement provided the window period for the laboratory method is increased. Over the next ten years the provision of ART could avert 1 to 1.5 million deaths depending on whether it is provided when the CD4 cell count falls to 200 or 350 cells/μl. By 2015 about 1.1 million people will be receiving ART but this will have little impact on the incidence of HIV and scaling up of prevention efforts remains urgent.

Conclusions

The thesis explores some of the determinants and patterns of HIV prevalence and incidence in South Africa in order to find better ways to manage the epidemic of HIV, monitor changes and evaluate progress in control efforts. In order to fight the epidemic we need to mobilize the best possible science in support of those people and communities affected by the epidemic.

CHAPTER 1 Introduction

> "HIV/AIDS is the greatest threat to life, liberty, and pursuit of happiness and prosperity in many African countries"
>
> Kevin De Cock, 2002[1]

The global epidemic

The acquired immunodeficiency syndrome (AIDS) was first identified in 1981 among homosexual men in the United States of America, and the human immunodeficiency virus (HIV) was identified as the cause of AIDS in 1984.[2] The virus has since spread throughout the world and HIV/AIDS has grown into one of the greatest epidemics in human history, having killed more than 25 million people[3] and threatening social and economic stability in the most affected regions.

The Joint United Nations Programme on HIV and AIDS (UNAIDS) estimated that at the end of 2005, 40.3 million (range: 36.7-45.3 million) adults and children worldwide were living with HIV,[3] while 3.1 million (2.8-3.6 million) died from AIDS in 2005. It is estimated that 4.9 million (4.3-6.6 million) new infections occurred in 2005, of which 700,000 (640,000-820,000) were among children under 15 years of age. Currently, about half of all new infections are among children and young people up to the age of 25 years. The epidemic is increasingly affecting women and as of 2003 women accounted for about 50% of all people living with HIV worldwide, and for 57% in sub-Saharan Africa.[4]

The epidemic affects different parts of the world differently and even within regions it progresses at different rates and at different levels of intensity. Estimates of national adult prevalence have remained below 1% in most countries in Asia, Oceania, West and Central Europe, North Africa, the Middle East, North America and Latin America, where transmission of the virus occurs mainly in concentrated groups of injecting drug users, men who have sex with men, and sex workers and their clients and partners.[3] In contrast, almost 8% of adults living in sub-Saharan Africa are infected with HIV, where the major route of HIV transmission is through heterosexual contact in the general population, with prevalence levels of around 20% or higher in most southern African countries. Despite increases in the number of people living with HIV in parts of East Asia, Eastern Europe

and Central Asia over the last three years, sub-Saharan Africa remains by far the most affected region in the world, accounting for 65% of all new infections and people living with HIV worldwide, and for 76% of all AIDS deaths.[5] At the end of 2005, it was estimated that 25.8 million people (23.8-28.9 million) were living with HIV in this region.[3]

In general, the HIV epidemic in sub-Saharan Africa appears to be levelling off.[6] Although no country in this region has escaped the virus, some are more affected than others. Southern Africa is the most affected part of Africa and the southernmost nine countries, where only 2% of the global population live, accounted for 30% of the total number of people living with HIV in 2004.[6] In contrast to the alarmingly high and sustained levels of HIV infection in Southern Africa, prevalence has stabilized in some countries in East Africa and has started to show a decline in some others. For example, the national prevalence in Uganda fell from 13% in the early 1990's to 4.1% at the end of 2003.[7] In West and Central Africa prevalence levels have remained stable at lower levels than in the rest of sub-Saharan Africa.

In developed countries HIV has been mainly concentrated in high risk groups, such as men who have sex with men and injecting drug users. In Western Europe, injecting drug users accounted for more than 10% of new infections in 2002.[6] While harm-reduction initiatives have resulted in falling transmission rates in this risk group, recent data from Western Europe have shown an increase in the number of infections among women. In the United States of America, men who have sex with men accounted for 45% and injecting drug users for 24% of all cases in 2003.[8] An increasing number of women and minorities are however becoming infected through heterosexual contact.

Standards of treatment and care have improved considerably, primarily in high-income countries, since the virus was first identified. The first antiretroviral drug, AZT, became available in 1987 while many other drugs have been developed since then.[9] Highly active triple combination therapies, available in high-income countries since 1996, have dramatically improved the quality of life and the life expectancy for many HIV infected people in these countries.[9] Although antiretroviral drugs do not cure AIDS, they reduce viral replication and thereby the level of the virus in blood and, in most cases, improve the patient's clinical status and prognosis substantially. Until recently, antiretroviral therapy (ART) was accessible mainly to people living in developed countries with the exception of

Brazil and Thailand where triple combination ART has been provided in the public sector since 1996 and 2000, respectively.[10,11] At the International AIDS conference in Durban, South Africa in 2000, there was a call for more serious efforts to provide HIV treatment to those in need in low-and middle income countries. Attention, resources and political commitment began to materialize after the United Nations General Assembly Special Session (UNGASS) in July 2001.[10] Resources for HIV and AIDS programs in developing countries have since increased substantially, with new resources becoming available through the Global Fund to Fight AIDS, Tuberculosis and Malaria, the World Bank, and several bilateral initiatives, including the USA government's President's Emergency Program for AIDS Relief (PEPFAR) initiative.[12] The World Health Organization (WHO) and UNAIDS launched the "3 by 5" strategy in 2003 which aimed to provide ART to 3 million people in low and middle income countries by 2005.[10] At the end of 2005, approximately 1.3 million people living in low and middle income countries had been receiving ART,[13] and although the target of 3 million people was not reached, the efforts to expand access to ART have helped to encourage countries to set their own treatment targets and to mobilize support. The positive change and commitment from countries and donors have provided a basis for moving forward towards the goal of providing universal access to treatment and care by 2010 for all those who need it.[14]

HIV/AIDS in South Africa

The first two cases of AIDS in South Africa were diagnosed among homosexual men in Pretoria in 1982.[15] During the next five years (1983–1988) this number had increased to over one hundred with high levels of mortality.[16] In 1988, the pattern of AIDS in South Africa revealed that 81% of patients were homosexual or bisexual, and 96% were men. However, by the end of 1989, several surveillance studies had confirmed the entry of HIV infection into the heterosexual population and although the prevalence was still low, alarming increases were predicted.[17-19] By January 1990 a total of 308 South African AIDS cases had been reported,[20] among whom two thirds were male homosexuals, 21% were heterosexuals with a male:female ratio of 1:1.2, 9% were haemophiliacs or recipients of blood products, and 3% were children.

Of great concern in the early 1990's was the extensive spread of HIV among attendees of public health sexually transmitted disease clinics and female family planning clinics, with

doubling times ranging from 6.5 to 10.7 months.[17] While no paediatric cases had been seen before 1987, a total of 73 had been reported by the end of 1990. Predictions based on mathematical models in the early 1990s[21,22] provided early warnings of the potential threat that HIV posed and suggested that infection levels could reach 20%-30% among the sexually active population in South Africa by 2000 to 2005.

In 1990, the Department of National Health and Population Development instituted an HIV surveillance programme based on annual surveys of women attending antenatal clinics in South Africa.[23] The data collected from these annual surveys have since been used to monitor the progress of the HIV epidemic in the heterosexually active population. In the past 15 years, the HIV sero-prevalence among antenatal clinic attendees increased dramatically from 0.8% in 1990 to 10.4% in 1995 and to 29.5% in 2004 (Figure 1.1). The total number of people infected with HIV in South Africa at the end of 2003 was estimated to be about 5.3 million (4.5 – 6.2 million),[4] the highest number of infections in any country in the world. With less than 1% of the world's population living in South Africa, the country currently accounts for about 14% of all people living with HIV. It is estimated that about 370,000 (270,000-520,000) people died from AIDS in South Africa in 2003[4] and that more than 1.2 million have died from AIDS since the start of the epidemic.[24] While HIV prevalence is starting to level off (Figure 1.1),[25] the number of people dying from AIDS continues to increase.

The HIV epidemic in South Africa is unevenly distributed. In KwaZulu-Natal, the province with the highest burden of infection, antenatal HIV prevalence increased from 1.6% in 1990 to 40.7% in 2004. During the same period, HIV prevalence in the Western Cape, the province with the lowest prevalence, increased from 0.1% to 15.4%. Proportionally, more females are infected than males and younger people are more likely to be infected than older people. The peak prevalence among women occurs between ages 20 and 29 years while it is shifted to older age groups (30-39 years) among men.[26]

HIV-1 is the dominant virus in South Africa while HIV-2 is rare. Phylogenetic studies on HIV-1 isolates from South Africa have shown that the subtype C virus is responsible for the majority of infections in South Africa,[27] while early studies on HIV-1 (from hereon called HIV) isolates from Cape Town showed that subtypes B and D were also found among homosexual and bisexual men.[28]

Until 2003, provision of care and treatment for HIV infected individuals was generally not available through the public health sector, and expensive treatment with antiretroviral drugs was limited to those who could afford it through the private sector. In 2003, the Government of South Africa announced its operational plan for comprehensive treatment, care and support[29] to those individuals with AIDS, through the public health sector, giving hope to many of those living with the virus.

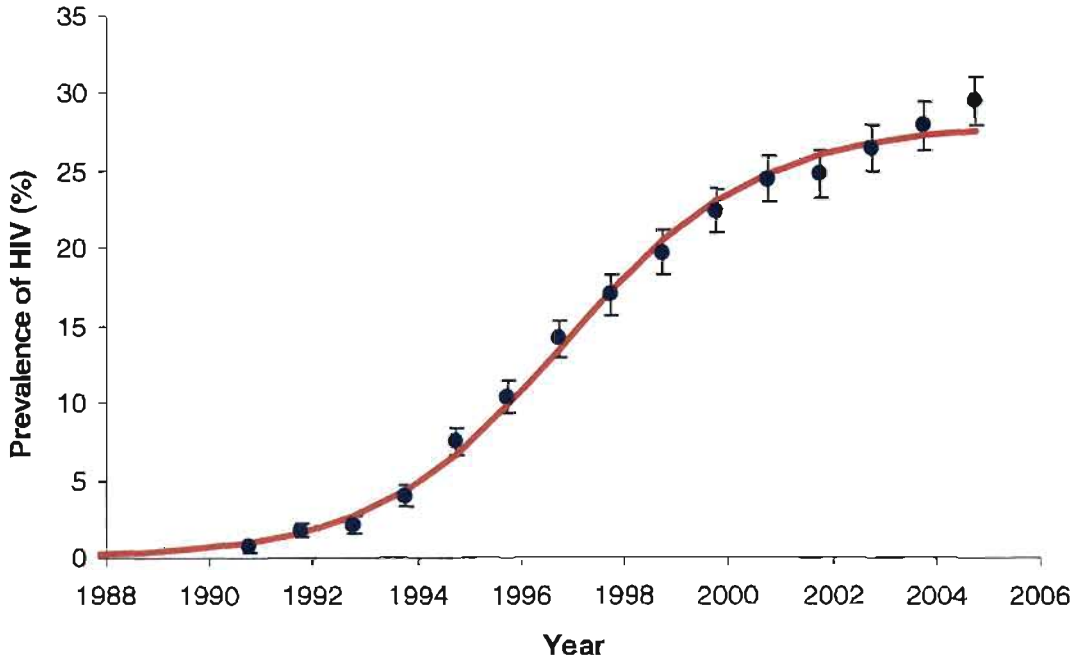


Figure 1.1 Increase in national HIV antenatal clinic prevalence from 1990 to 2004. (*Sources: Department of Health, Annual Antenatal Clinic surveillance reports*)

Despite a substantial scientific response to the HIV epidemic in South Africa, our understanding of risk factors for acquiring infection, and our knowledge of which interventions work and which do not, the prevalence data collected from antenatal clinics in 2004 still showed an increase. Our understanding of the dynamics of the infection, however, is limited. There is limited information on incidence and mortality, both of which are essential for monitoring future trends of the epidemic and in particular, to monitor the impact of interventions. Interventions such as the provision of antiretroviral therapy to those in need of treatment will have an immediate impact on mortality, while prevalence levels will show an increase. On the other hand, control measures expected to have a

public health impact, such as the control of sexually transmitted infections (STIs) or male circumcision might show an impact on prevalence only over several years, while their impact on incidence will appear almost immediately. In this thesis, prevalence data are used to study the epidemiology and dynamics of HIV infection in South Africa, with a particular emphasis on patterns of infection, the estimation of incidence from prevalence data, and the impact of antiretroviral therapy on future epidemic trends.

Objectives of the thesis

The aim of this thesis is to study the epidemiology, population dynamics and impact of the HIV-1 epidemic in South Africa through the analysis and modelling of existing prevalence data. Specific objectives are:

1. To study and analyse existing HIV prevalence levels and trends of infection among various population and risk groups in South Africa.
2. To use age-specific prevalence data to identify and compare patterns of infections among various groups in South Africa, including women attending antenatal clinics, men and women in urban and rural communities, commercial sex workers and migrant workers.
3. To compare estimates of prevalence among antenatal clinic attendees (who have been used as an indicator group for infection levels among the heterosexual population) with prevalence estimates among men and women from community studies.
4. To develop methods for estimating HIV incidence using time trends in prevalence and age-specific prevalence data.
5. To compare estimates of incidence using a mathematical model and a laboratory technique (the Standardized Testing Algorithm for Recent HIV Seroconverters).
6. To use the mathematical models to estimate incidence among various groups in South Africa.
7. To use existing prevalence data and assumptions about the provision of antiretroviral therapy to estimate the likely impact of antiretroviral therapy on future trends of the epidemic.

Description of the chapters

HIV-1 subtype B infection was introduced into the homosexual population in South Africa in the early 1980s while a second, independent, epidemic of HIV-1 subtype C infection started to evolve among the heterosexual population in the late 1980s. Once introduced, the spread of HIV among the heterosexual population was very rapid with an initial doubling time of less than 12 months.[30] In a 15 year period the HIV epidemic among public health antenatal clinic attendees grew from 0.73%[23] in 1990 to 29.5% in 2004,[31] and will have consequences far more serious than any other epidemic in the history of South Africa. The total number of people infected with HIV in South Africa in 2003 was estimated to be around 5.3 million, with estimated mortality rates of about 1000 people per day.[4] Accordingly, the scientific and public health response to HIV and AIDS has been substantial, and the efforts and resources devoted to the epidemic have been greater than for any other disease or epidemic. In Chapter 2, the state of the scientific knowledge on HIV infection and AIDS in South Africa is assessed. A MEDLINE search was conducted and a description is given of the scientific literature in response to the epidemic and how it has changed over time. In addition, a detailed summary is provided on the number of studies in the literature reporting on HIV prevalence and incidence in different population groups.

The epidemic of HIV infection threatens to overwhelm South Africa and if we are to deal with it effectively, we need to understand the underlying dynamics of HIV infection. Mathematical and statistical models are essential tools for understanding the population dynamics of an epidemic, and to study the factors that determine the course of infection in an individual, as well as those that determine the patterns of infection in a population. In Chapter 3, an introduction is given to mathematical models and its application in general to the HIV epidemic. The uses of models, types of models, and some basic concepts are discussed, and it is shown how simple models can be used to get a better understanding of the epidemic.

Knowledge of the HIV epidemic in South Africa depends greatly on the annual, anonymous surveys conducted by the Department of Health among antenatal clinic attendees, supported by data obtained from studies among high risk groups including migrant workers (mine workers and truck drivers) and commercial sex workers, several

surveys among attendees of family planning and sexually transmitted disease clinics, workplace surveys, surveys among hospital patients, students and blood donors, community based surveys conducted in two areas of South Africa, a rural area in KwaZulu-Natal and an urban setting in Gauteng, and two large, national population-based surveys on behavioural and socio-cultural determinants of vulnerability to HIV/AIDS. In Chapter 4 the data sets that are used in this thesis are described and in Chapter 5 a detailed description is given of the epidemic in space and in time. Prevalence data are described, ranging from the rapid spread of the HIV epidemic over time, to differences in gender, age and geographical area, while risk factors associated with prevalence levels are also discussed.

Age specific prevalence data obtained from various sources (antenatal clinics, community-based surveys, and studies among commercial sex worker and migrant workers) are used in Chapter 6 to investigate patterns of infection. Differences between the patterns of infection in men and women, and in urban and rural communities are investigated. The female-to-male prevalence ratio, estimated from community surveys, is shown to be around 1.7 while the prevalence peaks at an older age among men than among women. Differences in the patterns of infection between urban and rural populations are not significantly different. As the epidemic in South Africa is maturing, it is shown that the age of peak prevalence among women has shifted by 3.5 years from 23 in the mid-1990s to 26.5 years in 2002-2004. Four patterns of infection are identified: among women attending antenatal clinics, among men and women in the general population, and among migrant workers. The implications of these different patterns of infection for the spread and management of the epidemic in South Africa are considered.

Much of what we know about the HIV epidemic in South Africa is based on the analysis of data obtained from pregnant women attending antenatal clinics. It is therefore important to determine how accurately HIV prevalence among antenatal clinic attendees reflects prevalence in the community. In Chapter 7 this question is addressed by comparing HIV data collected from women aged 15 to 54 years as part of a community-based, cross-sectional study in Hlabisa between 2000 and 2002 with data collected independently among women attending antenatal clinics in the same district during the same time. It is shown that antenatal clinic prevalence in Hlabisa overestimates the prevalence in the general female population. A limitation of this study however, is that only 34% of women

in the community consented to having blood taken for HIV testing. Although potential biases are investigated, the results of this study cannot be regarded as conclusive and more studies are needed in South Africa.

The rate of increase in HIV prevalence among pregnant women attending antenatal clinics in South Africa has slowed over recent years. Good estimates of the incidence of infection will be of greater importance than prevalence for monitoring the epidemic over the next few years, for understanding the dynamics of the epidemic, and for estimating the number of new infections, all of which are essential for planning interventions. Direct estimates of incidence are difficult to obtain because of the cost, logistics and ethical problems of following people to HIV infection. However, incidence can be obtained indirectly from statistical and mathematical models. In Chapter 8, methods from which incidence estimates can be estimated are described. These include back-calculation methods, statistical methods, dynamical models, demographic models and laboratory techniques.

Data on the incidence of HIV infection in South Africa are very limited. The first estimates of HIV incidence in South Africa were calculated in 1999 by the author of this thesis, using statistical methods to assess the feasibility of conducting vaccine trials in Hlabisa.[32] This was followed in 2000 by a more sophisticated, dynamical model to obtain age-specific incidence from age-prevalence data.[33] In Chapter 9, a detailed description is given of the dynamical model to estimate incidence from age-prevalence data for specific application to South African data. This model is applied to data collected from women attending antenatal clinics in Hlabisa and shows an extraordinarily high average incidence rate of about 10% per year among this population. A second model is also developed to estimate incidence in the absence of age-specific data, using time trends in prevalence data only. This model is particularly useful for estimating incidence in the various provinces of South Africa for which antenatal clinic prevalence is not reported by age. The model confirms the high incidence rates among women attending antenatal clinics in Hlabisa.

In Chapter 10, the Standardized Testing Algorithm for Recent HIV Seroconversion (STARHS), a laboratory technique to estimate HIV incidence, is described. Estimates of HIV incidence using this method are then compared to the estimates obtained from the dynamical model described in Chapter 9. With some adjustment of the window period for the less-sensitive ELISA, good agreement is obtained in most of the age groups.

The methods described in Chapter 9 are applied to various HIV prevalence data sets in order to obtain estimates of HIV incidence for South Africa and these are reported by age, gender, geographical area and over time in Chapter 11. HIV incidence among national antenatal clinic attendees appears to have peaked in 1997 at 6.6% per year. Incidence estimates among antenatal clinic attendees in 2005 range from 2.5% per year in the Western Cape to 9.3% per year in KwaZulu-Natal (with a national average of 5.8% per year). The best estimate of HIV incidence for the general population in South Africa in 2005, using the antenatal clinic data adjusted for potential biases, is 2.4% per year.

Current mathematical models show that in 2003 alone, more than 350,000 deaths occurred in South Africa due to AIDS. In the absence of interventions, this is expected to continue to rise to about 500,000 deaths per year in the next 3-5 years, and to a cumulative number of more than 5 million deaths in the next ten years, with devastating consequences. In November 2003, the National Department of Health in South Africa announced an operational plan to provide comprehensive care, management and treatment for HIV/AIDS in the public health sector.[34] The plan considers 3 scenarios (assuming 20% antiretroviral (ARV) coverage, assuming 50% ARV coverage, and assuming 100% ARV coverage) in which between 200,000 and 1.2 million people would be receiving treatment by the end of 2008. To explore the impact of ARV on HIV incidence, prevalence and on AIDS deaths, a mathematical model is developed and described in Chapter 12. Through the use of the model, the consequences of providing ARV treatment at different levels of coverage and starting at different levels of $CD4^+$ T-lymphocyte counts (CD4 cell counts) are explored. The results show that while the provision of antiretroviral therapy, if given according to present guidelines, could save the lives of about one million people in the next 10 years, it is unlikely to reduce HIV transmission significantly in the population as a whole, and the need to find ways to reduce transmission remains urgent.

While much is known about the epidemic of HIV/AIDS in South Africa there is still much to learn. It is hoped that a better understanding of the dynamics of the epidemic based on the data presented and analyzed in this thesis will help us to find ways to deal with, manage and hopefully one day control, the epidemic of HIV that threatens to destroy so many lives in South Africa.

CHAPTER 2 HIV/AIDS in South Africa: A review of the scientific literature

> "The issues are so intense, the situation is so precarious for millions of people, the virus cuts such a swath of pain and desolation, that our voices, as well as your science, must be summoned and heard."
>
> Stephen Lewis, 2005[35]

Introduction

In order to assess the state of scientific knowledge on HIV and AIDS in South Africa, a MEDLINE search was undertaken on HIV and AIDS related articles through the National Library of Medicine at the National Institute of Health (PUBMED). The key words used in the search included *South Africa* and (*HIV* or *AIDS*). Journal articles, letters and editorials (excluding news related articles) published only in peer reviewed scientific journals were assessed. As at the end of 2005, 1664 scientific articles, letters or editorials on issues related to HIV and/or AIDS in South Africa had been published in scientific journals. The first HIV/AIDS related scientific paper, a report of two AIDS cases in South Africa, appeared in 1983 in the *South African Medical Journal*.[15] The total number of articles published each year increased slowly to a total of 31 in 1990, 76 in 1998, and 110 in 1999 (Figure 2.1). In 2000, the year during which the International AIDS Conference was hosted in South Africa, the number of scientific publications reached 205. In 2001 the total number of publications dropped to 141 but increased again to a total of 207 in 2005. The increase in the number of scientific publications over time is almost proportional to the increase in HIV prevalence, as reflected in Figure 2.1.

1983 to 1989

The first scientific paper concerned with HIV/AIDS in South Africa appeared in 1983 and reported on the first two cases of the acquired immunodeficiency syndrome among male homosexuals in South Africa.[15] During the next 6 years (1984-1989) 51 papers were published on HIV and AIDS in South Africa including several reports describing HTLV-III, HIV, AIDS and AIDS related conditions in particular risk groups.[17,36-38,39,40] One hundred and sixty-six cases of AIDS were seen in South Africa between 1982 and 1988,

with a mortality rate of 59%.[19] Of interest was the absence of HIV infection in sex workers, women attending sexually transmitted disease clinics and drug abusers in 1987.[41] Several epidemiological studies on the status and future growth of the AIDS epidemic were published[16] and in a three part series published in the *South African Medical Journal* in 1988, Ijsselmuiden and others emphasized the urgent need for, and proposed steps towards, a comprehensive strategy for the control of HIV infection.[42-44] In 1988 and 1989 the first papers appeared on medico-legal issues in caring for people with HIV infection,[45] the social impact of AIDS,[46,47] and AIDS education.[48-50] By the end of 1989, a number of surveillance studies had been presented and confirmed the entry of HIV infection into the heterosexual population in South Africa.[16,39,51,52] While the number of visits by male homosexual patients to HIV clinics reached a plateau in 1989, the number of visits from heterosexual patients began to increase. Although the prevalence of HIV infection was still low in the general population (probably less than 0.5%), an alarming increase in the number of AIDS cases in particular risk groups was predicted.[16,19] In the absence of a vaccine and effective treatment, an urgent call was made for safer sex practices through education.

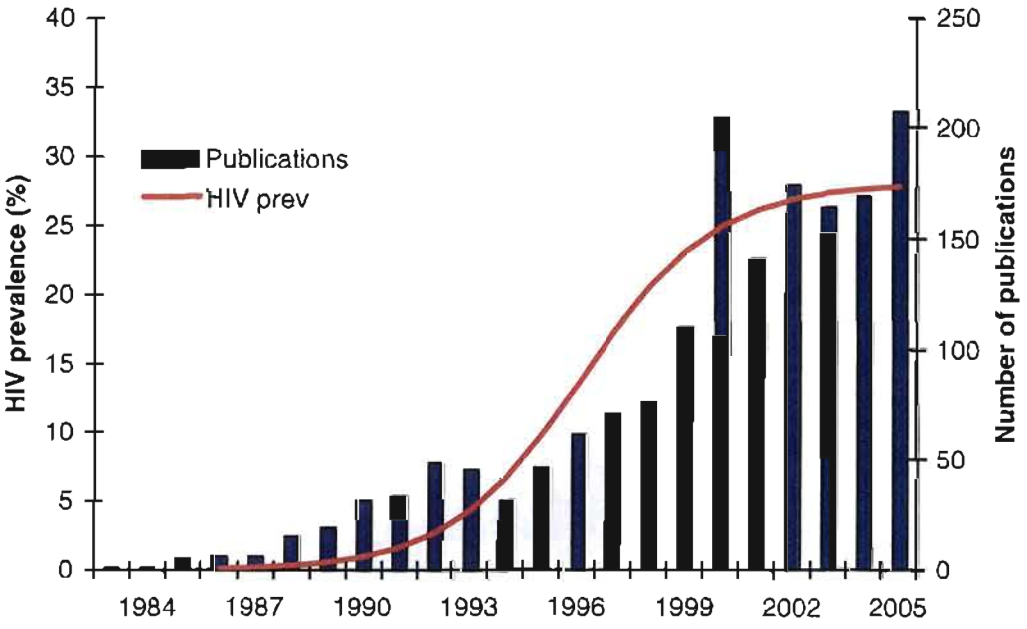


Figure 2.1 The total number of scientific publications in peer reviewed scientific journals that are concerned primarily with HIV/AIDS in South Africa (blue bars), and the HIV prevalence among antenatal clinic attendees in South Africa (red curve: logistic function fitted to observed antenatal clinic data).

1990 to 1994

Of great concern in the early 1990s was the extensive and continuing spread of HIV in urban heterosexual populations with the prevalence of HIV in some surveys doubling every 8.5 months.[53] Data on the prevalence of HIV data suggested that the spread of infection was far more extensive than suggested by the still low numbers of reported AIDS cases.[20] Of an estimated total of 122,951 HIV infected individuals in South Africa in 1991, 69% were from urban populations, 20% from rural populations and 7% from homosexual men.[54] Data from the National Department of Health's annual surveillance programme showed an increase in the point prevalence of HIV among first time antenatal clinic (ANC) attendees from 0.76% in 1990 to 7.6% in 1994, with wide geographical variation.[23,55]

Of 188 papers on HIV/AIDS published during this period, almost 20% were concerned with social and behavioural research. The majority of these dealt with knowledge, beliefs and practices among people in particular risk groups, such as youth, health care workers, STI and family planning clinic attendees, including reports on condom use and risk-taking behaviour.[56-64] Several papers dealt with ethical issues, including informed consent and confidentiality[57,65-68] and in four papers the question as to whether or not AIDS should be made a notifiable disease was discussed.[69-72] Several papers were published on the statistical analysis and modelling of the epidemic during this period. Current, short-term and medium-term predictions of the prevalence of HIV infection were presented. Although the forecasts were tentative, they indicated the seriousness of the HIV epidemic. Using a macro-simulation model, Schall predicted in 1990 that the AIDS epidemic could reach prevalences of 30% in the sexually active population by the year 2000 to 2005, which is close to the current prevalence among women attending antenatal clinics.[21,73] Similar predictions were made by Groeneveld and Padayachee using micro-simulation models.[22] Other areas that were well researched during this time included: AIDS-related conditions, including Kaposi's sarcoma, Donovanosis and HIV related cancers;[74-80] surveillance and epidemiological studies;[23,81-86] paediatric AIDS and HIV in children;[87] transmission of HIV, mainly through blood transfusion[84,88,89] and vertical transmission;[90-92] sexually transmitted diseases and their association with HIV;[93,94] and HIV and dental/oral research.[95-98] The relationship between tuberculosis (TB) and HIV was addressed in several papers[99,100] while some others dealt with the diagnosis of HIV.[101-104]

Surprisingly few papers were published on prevention strategies, with the exception of an adaptation of the Health Belief Model,[105] and the AIDS Educational and Training package, an education package designed to target low-literate groups in the workplace.[106] The evaluation of a school based education programme in Cape Town showed that although the program greatly improved students' knowledge in relation to HIV transmission and prevention, it had little effect on behavioural.[107] The evaluation of an education programme on HIV using puppetry and street theatre indicated that it could be more effective if incorporated into existing community-based education programmes.[108] One further study identified the need for prevention programmes to address AIDS related issues in juvenile correctional centres.[109]

There were several papers addressing factors associated with HIV including sexual behaviour,[63] poverty[110] and socio-economic determinants.[111] The first papers also appeared on migrant labour and HIV,[112] traditional healers and ancient beliefs,[113,114] geographic progression of disease illustrated by mapping the AIDS pandemic,[115] and the cost of adult AIDS inpatient care.[116] With the exception of molecular analyses of HIV-1 infections in India which were shown to be closely related to a sequence from a South African isolate, HIV-1NOF,[117] few papers were published on molecular biological or immunological aspects of the disease during this period. There was also a lack of papers on disease management and care of HIV infected patients.

1995 to 2000

The rising trend in HIV prevalence rates during this period was matched by an increase in the number of scientific publications (Figure 2.1), reaching a maximum number of 205 in 2000, coinciding with the International HIV/AIDS conference in Durban, South Africa. A total of 569 papers were published during this period. The prevalence of HIV infection among women attending antenatal clinics reached 23% in 1998, with the highest prevalence in KwaZulu-Natal (32%) and the lowest in the Western Cape (5.2%).[118] Using data from antenatal clinic surveys, extrapolated to the general population, it was estimated that 3.6 million South Africans were infected with HIV in 1998, up from an estimated 1.7 million in 1995. Of particular concern for public health professionals was the high prevalence among young women, aged 15 to 25 years.

South Africa joined the global effort to develop an effective AIDS vaccine and there was a substantial increase in the number of scientific papers on genetic, immunological and molecular biological aspects of the virus. Genetic analyses to determine HIV-1 subtypes in different risk groups in South Africa were reported in several publications.[28,119-123] Research suggested two different epidemics in South Africa: infection with HIV subtype B associated with homosexual transmission, and infection with subtype C associated with heterosexual transmission. Neutralization of HIV subtypes by antibodies and the implications for vaccine formulations were discussed.[124] While one article summarized the development of HIV-1 subtype C vaccines for southern Africa,[27] another reviewed an immunology-based approach to the design of an HIV-1 preventative vaccine, which will be of great importance to reduce the high rates of HIV-transmission in South Africa.[125] In addition to the genetic and molecular components of vaccine development and new prospects in vaccine research, papers started to appear on issues related to the country's preparedness to participate in HIV-1 vaccine efficacy trials,[126] including discussions on ethical considerations and informed consent.[127-129]

In countries with limited resources for diagnosis and management of the disease, absolute $CD4^+$ T-lymphocyte counts (CD4 cell counts) are generally used to monitor disease progression and to institute prophylaxis against opportunistic infections.[130] Studies were done locally to assess the correlation between HIV RNA levels, CD4 cell counts and progression to AIDS or death.[131-133] In addition, the role of surrogate markers (beta 2-microglobulin and CD4/CD8 ratio) was discussed in relation to predicting maternal HIV transmissibility and disease progression in infants.[134]

As in the previous period, a large number of papers were published on surveillance and estimating the size of the epidemic in different populations.[55,135-144] Two peer reviewed scientific papers on the national antenatal clinic surveillance, providing HIV estimates by province between 1993 and 1996, appeared in the South African Medical Journal.[55,141] Almost one quarter of all scientific papers published during this period were concerned with tuberculosis[145-151] and other HIV/AIDS-related illnesses, including *Pneumocystis carinii* pneumonia (PCP),[152,153] HIV-related cancers,[154,155] streptococcal diseases,[156,157] and meningitis.[158-161] Several papers were concerned with the association between sexually transmitted diseases and HIV,[162-164] while disease management and assessment of care for patients infected with HIV were also addressed.[165-170] Social aspects were still well

researched and included assessment of knowledge, attitudes and sexual behaviour,[171-176] children requiring social services,[177] impact of HIV on quality of life[178,179] and barriers to condom use.[180-183] Many papers dealt with ethics, informed consent, confidentiality and voluntary testing and counselling,[127,129,184-190] and whether AIDS should be made a notifiable disease.[191,192] Most of the papers on transmission of infection were concerned with determinants of mother-to-child transmission such as breastfeeding, antibody levels of the mother and mode of delivery,[193-198] while some were concerned with transmission of HIV through anal sex,[199] blood transfusions[200-202] and exposure of health care workers to blood and traumatized bodies.[203,204] Diagnosis and testing received some attention, including an evaluation of several antibody assays and rapid tests, dried blood spots and polymerase chain reaction (PCR).[121,205-208] Compared to the previous period, there was an increase in the number of papers dealing with prevention and public health interventions. Several papers were concerned with HIV in relation to sexual education and the evaluation of such programs.[209-213] Of the other papers on prevention, there were first reports on microbicide research,[214] papers on AIDS programmes at the workplace,[215-217] on antiretrovirals for pregnant mothers[218] and the cost-effectiveness of preventing mother-to-child transmission,[219,220] on child-feeding practices and a plea for dried milk formula,[221] and a call for universal precautions in health care settings.[204] Only one study assessing community based interventions was reported on.[222] A number of papers were concerned with paediatric HIV and AIDS, in particular with morbidity and mortality in children infected with HIV.[223-227] Papers were published on adult mortality, including a study on the survival differences between the two independent epidemics of heterosexual and homosexual infection in South Africa.[228,229] First papers (although only a few) appeared on the enormous potential problem of AIDS orphans.[230-232] Programs to provide antiretroviral treatment to individuals in need of treatment were not available in the public health sector in South Africa during this time and as a result, there were no papers on direct adult treatment of HIV in South Africa. However, treatment of sexually transmitted diseases, tuberculosis and HIV related cancer continued to receive attention.[165,233-235] One paper, through modelling, investigated the extent to which low-level use of antiretroviral (ARV) treatment could curb the AIDS epidemic in southern Africa.[236] Papers were also published on nutrition,[237] socio-demographic impact and demographic modelling,[238,239] HIV and infertility,[240] HIV among intravenous drug users,[241] pharmacokinetics and antiretroviral activity of AIDS drugs,[242]geographical presentation of HIV heterogeneity and proximity to roads in a rural district in South Africa,[243] and the origin of HIV.[244]

There were few papers on population dynamics and risk factors such as migrancy[245,246] and male circumcision[247] which are now known to play an important role in transmission of HIV in South Africa.

During 2000, a special edition on HIV/AIDS research in South Africa was published by the *South African Journal of Science*, presenting some of the varied contributions that science and South African scientists had made to our understanding of the HIV epidemic. The articles in the journal were grouped under the headings of origins, prevention, and treatment of HIV.

2001 to 2005

From 2001 to the end of 2005 a total of 855 papers were published in scientific journals. While prevalence data collected from the annual surveillance among antenatal clinic attendees between 2000 and 2002 indicated that the epidemic may stabilize at around 26%, the surveys in 2003 and 2004 showed an increase in prevalence to 27.9% and 29.5%, respectively. With morbidity and mortality increasing rapidly, the proportional number of articles that appeared in scientific journals on treatment, support and care for people with HIV/AIDS during this period increased significantly compared to previous years. While some papers described and evaluated the role of occupational health services and programs of care in the workplace,[248-250] some others assessed the cost of HIV/AIDS to businesses in South Africa.[251,252] The cost of a limited public sector antiretroviral programme was also assessed.[253] Papers on access to HIV treatment and care as a human rights issue appeared in several (medical and law) journals.[254-258] In anticipation of the South African government making ARV therapy available to those in need of treatment, papers started to appear on the first steps to providing ARV,[259-261] while some studies showed that adherence might not be a barrier to providing ARV therapy in South Africa.[262,263] A few papers were published on voluntary counselling and testing (VCT) as well as on the barriers to VCT.[264-267] In November 2003, the National Department of Health in South Africa announced an operational plan to provide comprehensive care, management and treatment for HIV/AIDS in the public health sector.[268] A potential problem in rolling out ARV therapy in coming years is the lack of resources in the public health care sector. Few papers however, were published on strengthening health systems for implementation of ARV therapy and an increase in studies related to the challenges of providing ARV therapy

in the public sector, such as delivery mechanisms and the challenges of retaining patients in long-term primary care, are anticipated in the next few years. A first report appeared on side effects, cardiovascular consequences, related to provision of antiretroviral treatment, [269] and their was a call for earlier initiation of ARV treatment.[270]

As AIDS related mortality continues to rise in South Africa, more papers have started to appear on estimated mortality rates and cause of death profiles through modelling and the analysis of vital registration data, and on maternal mortality.[271-279] Only one paper considered the impact of the HIV epidemic on the number of AIDS orphans in South Africa.[280] With the exception of the models described in this dissertation to estimate the incidence of HIV infection from prevalence data, very few papers reported estimates of HIV incidence. Two papers reported incidence estimates obtained directly from following a cohort of sex workers in KwaZulu-Natal,[281,282] while one other study discussed the estimation of incidence among young mothers using a combination of HIV antibody and RNA tests on dried blood spots.[283] In one further study the "detuned" ELISA technique was used to assess incidence of HIV among blood donors in South Africa.[284]

Several scientific papers were published on studies investigating the relationship between HIV and genital ulcer disease, including HSV-2.[281,285,286] Several reports on tuberculosis and HIV were published,[287-289] including the still growing burden of TB as a result of HIV,[290] drug-resistant TB in areas with high HIV,[291] maternal mortality associated with HIV-TB co-infection,[271] the vicious cycle of poverty,[292] and integrating TB and HIV care in primary care setting.[293-295] Further studies were published on preventing mother-to-child transmission,[296-299] including the first district-wide program for prevention of mother-to-child transmission (PMTCT),[300] health systems constraints to optimal coverage of PMTCT programmes,[301] and the benefits and risks of breastfeeding.[302-305] A study was published on assessing the sensitivity of paediatric HIV diagnosis in a primary health care setting using a clinical algorithm (the Integrated Management of Childhood Illnesses).[306] A few articles also appeared on rape and post-exposure prophylaxis,[307-309] an area which had been neglected in previous years.

Social and behavioural studies included factors associated with behaviour change and condom use,[310-317] gender violence,[318-321] 'survival' sex among commercial sex workers,[322-324] empowering women in the fight against HIV,[321,325] and alarming reports appeared on

unsafe sexual behaviour among youth in South Africa.[311,315,326] The effect of migration on HIV was assessed in four papers related to studies from rural KwaZulu-Natal and the mining town of Carletonville,[327-330]and one study on HIV prevalence among truck drivers in KwaZulu-Natal.[331]

Molecular and genetic research included a report on novel evolutionary analysis of full-length HIV type 1 subtype C molecular clones from Cape Town,[332] host and viral factors that impact on HIV-1 transmission and disease progression,[333] genotypic and phenotypic analysis of gag and env genes from subtype C and B isolates in South Africa,[334,335] and molecular and genetic characterisation and selection of HIV-1 subtype C isolates for use in vaccine development,[336,337,338,339,340] A review was also published on the development of HIV-1 subtype C vaccines for South Africa,[341] on ethical issues related to vaccine trials,[342,343] and on caring for HIV-1 vaccine trial participants.[344] Additional papers appeared on viral dynamics and CD4 cell counts,[345,346] and several were published on diagnostics, including the use of dried blood spots for surveillance purposes[347] and the evaluation of commercially available assays to test for HIV.[348-350]

In relation to research on prevention, the first results from a randomized controlled trial on male circumcision appeared from Orange Farm in the Gauteng province.[351] The trial showed a 60% reduction in the risk of acquiring HIV among circumcised men compared to uncircumcised men, and if these results are confirmed in further trials currently being conducted in Kenya and Uganda, male circumcision could have significant implications for HIV control in sub-Saharan Africa. Further research showed high levels of acceptability of male circumcision as a tool for preventing HIV infection in South Africa.[352] South Africa also contributed to research showing the beneficial effects of providing cotrimoxazole prophylactically to children infected with HIV in order to prevent opportunistic infections.[353]

During this period, the first national population-based survey to assess HIV prevalence was conducted by the Human Sciences Research Council (HSRC),[354-356] while the Reproductive Health Research Unit conducted another national survey among youth (aged 15-24 years) to assess HIV prevalence and related sexual behaviour.[357] Further research during this period included assessing the economic impact of HIV and AIDS,[358] STI care in the private sector,[359] care for health care workers with HIV,[250,360] prevalence among

adult patients in a tertiary hospital in KwaZulu-Natal[361] and among trauma patients in Johannesburg,[362] oral manifestations of HIV,[363,364] further reports on the effect of microbicides and the acceptability thereof,[282,365,366] intra-vaginal practices and susceptibility to HIV,[367] the impact of HIV infection on malaria,[368] the role of nutrition and micronutrients in HIV infection[369-371] including reports on the effects of herbal medicine in the treatment of HIV,[372] and a first report appeared on HIV policies and practices in South African prisons.[373]

Review of prevalence data

A separate PUBMED search was done to review the scientific literature in relation to the prevalence of HIV infection in South Africa, using the key words (*HIV* or *AIDS*), *prevalence* and *South Africa*. Papers reporting on prevalence of HIV infections in various populations or risk group were included, but papers reporting on secondary analysis of prevalence or providing summaries of existing prevalence data were excluded. An extensive number of papers reporting estimates of HIV prevalence were published between 1983 and December 2005, as summarized in Table 2.1. Where actual numbers or percentages were not provided in the papers, the figures in the table were derived using available data (e.g., calculating the total number of infected cases from the prevalence and the total sample size; or deriving the prevalence from the sample size and the number infected). Similarly, 95% confidence intervals were calculated, where not provided, assuming a binomial distribution in the case of small numbers or small prevalences, or assuming the normal approximation to the binomial in the case of large numbers.

Between 1983 and 1988 papers reporting on HIV prevalence or the number of AIDS cases in South Africa appeared almost exclusively in the South African Medical Journal, with the exception of one paper published in the *Transactions of the Royal Society of Tropical Medicine and Hygiene*.[41] HIV infection during this period was confined mainly to men who have sex with men, haemophiliacs and a high risk group of recurrent sexually transmitted infection (STI) clinic attendees. A study among sex workers in 1987 showed zero prevalence,[41] while a prevalence of 2.86% was found among recurrent attendees of STI clinics in 1988.[39] The introduction of the epidemic into the heterosexual population became apparent between 1988 and 1991 with several reports of HIV infection among attendees of STI or family planning clinics, mine workers and the general population

(urban and rural). In 1990 the then Department of Health and Population Development initiated annual anonymous HIV-prevalence surveys among antenatal clinic attendees, chosen as an indicator group for infection among the heterosexual population, to monitor the epidemic.[23,141] Since then numerous articles have been published on the epidemic among the heterosexual population, showing the rapid increase in prevalence over time and reporting on extraordinarily high prevalences in some populations. As summarized in Table 2.1, prevalences have been reported for public sector antenatal, family planning and STI clinic attendees, TB patients, hospital patients from general, paediatric or gynaecology wards, cancer patients, sex workers and their clients, rape victims, mine workers and migrant women, blood donors, corpses for autopsy, general populations (urban and rural), the workforce, health care workers, young people and children.

Review of incidence data

In contrast to the large amount of prevalence data published in the literature, very few papers have reported on the incidence of HIV infection. Incidence is more difficult to measure directly than prevalence because it requires following a cohort over time which is logistically and ethically difficult. Incidence however, can be indirectly estimated through mathematical or statistical models or the use of laboratory techniques. With the exception of the incidence estimates described in this dissertation (and published as a result), only one cohort study in South Africa where incidence was directly estimated from following a cohort of sex workers in KwaZulu-Natal was reported on in two scientific papers.[281,282] One further study used the UNAIDS models and prevalence data obtained from the national population based survey in 2002 to estimate incidence in the general adult population indirectly,[374] while one further study described the use of the "detuned" ELISA technique to estimate incidence among blood donors.[284] The estimated incidences in these different risk groups were 18.2% among sex workers followed between 1996 and 1998, 4.2% among the general adult population in 2002, 0.01% among low risk blood donors and 0.5% among high risk blood donors in 1999.

Modelling the epidemic

Despite the plethora of prevalence data in South Africa, few scientific papers have appeared in the public health literature using these data to model the dynamics of the epidemic. In the early years of the epidemic (1988-1992), two papers were published on the future projection of the epidemic by Schall[21,73] using a macro-simulation model, and one by Groeneveld and Padayachee using a micro-simulation model.[22] During the period 1993 to 2000, when the growth of the HIV epidemic in South Africa was very rapid, less than five scientific papers were found in the literature on modelling the epidemic. In 1990, Doyle and Millar gave a general description of an Actuarial Model with application to the HIV epidemic in South Africa in the *Transactions of the Actuarial Society in South Africa*[375], while two further publications appeared in journals on the application of the Doyle model.[376,377] Further applications of this model were summarized in formal company or organizational reports. Williams and Campbell in 1998 analysed the South African antenatal clinic data, using maximum likelihood methods, to investigate the magnitude and time course of the epidemic in the different provinces.[140] Since 2000, there has been an increase in the number of publications using mathematical models to understand the epidemic. Dorrington, Bradshaw and colleagues reported on the application of the Actuarial Society of South Africa (ASSA) model, specifically in relation to the current state and future projections of the epidemic, and on estimating the number of AIDS deaths in South Africa;[378,379] Wilkinson and Floyd developed a model to estimate the cost and cost-effectiveness of interventions in Hlabisa;[380] Rosen and colleagues applied models to estimate the cost of AIDS to companies;[252]Williams and Lurie developed a model to estimate the relative risk of infection for migrant and non-migrant men and women from their spouse and from partners outside the relationship;[330] Rehle and Shisana applied the UNAIDS methodology, using the antenatal clinic data and data from the first national population-based HIV survey by the HSRC, to make epidemiological and demographic projections of the epidemic in South Africa;[374] and Blower and co-workers from the University of California recently used uncertainty analysis to model the public health impact of disease modifying HIV vaccines in South Africa.[382] Further models are described in this dissertation to estimate the incidence of HIV infection from age prevalence data and to investigate the potential impact of antiretroviral therapy on future epidemic trends.

Table 2.1 Papers published in the peer reviewed literature on HIV prevalence in South Africa : 1983-2005. Unless provided in the paper, 95% confidence intervals (CI) were calculated from available data

Year Publ	Journal	Author	Population	Year of study	Sample size	Number of cases	Prevalence (%)	95% CI (or range)	Doubling time
1983	SAMJ	Ras et al.[15]	Men who have sex with men	1983		2 AIDS cases			
1985	SAMJ	Lyons et al.[17]	General population	1985	922	0	0	0-0.3	
1985	SAMJ	Sher[383]	Johannesburg	1983-1985		14 AIDS cases			
1985	SAMJ	Spracklen et al.[37]	Cape Town	1985		2 AIDS cases			
1986	SAMJ	Sher[384]	South Africa	1986		30 AIDS cases			
1986	SAMJ	Sher et al.[385]	Dental health care workers	1986			0		
1986	SAMJ	De Miranda et al.[386]	Drug abusers	1986	176	1	0.6	0-3.1	
1987	Trans R Soc Trop Med Hyg	Schoub et al. [41]	Sex workers in Johannesburg	1987	56	0	0	0-0.5	
			STI clinic attendees (women)	1987	240	1	0.4	0-2.3	
1988	SAMJ	Botha et al.[387]	Black South Africans	1988		2 AIDS cases			
1988	SAMJ	Schoub et al.[16]	White blood donors	1988	188365	15	0.008	0-0.1	
			Black blood donors	1988	167819	97	0.06	0.05-0.07	
1988	SAMJ	O'Farrell & Windsor[39]	Recurrent attendees of STI clinics	1988	140	4	2.86	0.8-7.2	
1989	Infection	Mertens et al.[388]	South African hospital	1982-83	211	0	0	0-1.4	
1989	Am J Epidem	Dusheiko et al.[389]	Male mine workers	1986	29,312	0	0	0-0.01	
1989	SAMJ	Sher[19]	General population - lab tests	1982-1988		1857 HIV cases			
			Blood donors	1982-1988	710,000	244	0.034	0.03-0.04	
1990	SAMJ	Padayachee & Schall[53]	South Africans	end 1989		54000		45,000-63,000	8.5m
1990	SAMJ	Schoub et al. [20]	Urban black men: STI clinic	1988-1989	4995	69	1.38	1.05-1.71	10.7m
			Urban black: women: STI clinic	1988-1989	2099	41	1.95	1.34-2.57	9.8m
			White men: STI clinic	1988-1989	926	13	1.40	0.59-2.21	7.6m
			Urban black: female family planning	1988-1989	2638	17	0.64	0.32-0.96	6.6m
			Black men in general population	1988-1989	6796	6	0.08	0.03-0.19	
			Black women in general population	1989	692	0	0	0-0.43	
			New blood donors in South Africa (White men)	End 1989	25043	8	0.03	0.01-0.06	15m
			New blood donors in SA (White women)	End 1989	16120	0	0	0-0.02	

			New blood donors in SA (Black men)	End 1989	19535	88	0.45	0.36-0.54	9m
			New blood donors in SA (Black women)	End 1989	13734	67	0.49	0.37-0.61	9m
1990	SAMJ	Ijsselmuiden et al.[390]	Mine workers	1986	750,000	14250	1.9	0.02-3.8	
1990	SAMJ	Friedman & Robertson[391]	Children	up to 1989		15 AIDS cases			
1990	SAMJ	Cohn et al.[392]	Haemophilia patients, JHB	1982-1984	198	6	3	1.1-6.5	
1990	SAMJ	Prior & Buckle[88]	Blood donors, Natal	1985-1989	587889	218	0.04	0.03-0.05	
1990	Trans R Soc Trop Med Hyg	Martin et al. [393]	Black female STI attendees	1988	1,224	15	1.2	0.6-1.8	
			Black male STI attendees	1988	2,482	21	0.8	0.5-1.2	
			White male STI attendees	1988	400	4	1	0.3-2.5	
			Black female family planning (FP) attendees	1988	1,459	4	0.3	0.02-0.6	
1992	Med Law	Grobbelaar[394]	White blood donors	1985-1990	102,724	0	0	0-0.003	
			Black blood donors	1985-1990	183,802	115	0.06	0 - 0.2	
1992	SAMJ	Schoub[54]	Urban black population in South Africa	1991		HIV cases: 85247			
			Rural black population in South Africa	1991		24474			8-10m
			MSM	1991		8175			
1992	SAMJ	Friedman & McIntyre[91]	Pregnant women, Baragwanath & Soweto clinics	end 1990	2200	18	0.82	0.44-1.19	7-21m
1992	SAMJ	Friedman et al.[85]	Pregnant women (ANC), Baragwanath hospital	End 1991	2912	30	1.0	0.64-1.36	
1992	Trans R Soc Trop Med Hyg	Schoub et al.[395]	Black adults STI attendees in Johannesburg	1990	272	15	5.5	2.8-8.2	
			Black adult FP attendees in Johannesburg	1990	148	2	1.4	0.2-4.8	
			Black adults general population (JHB municipality)	1990	246	2	0.8	0.1-2.9	
			Black blood donors (new donors) in Johannesburg	1990	117	1	0.7	0-4.7	
1992	AIDS	Abdool Karim et al.[82]	Rural black community, KZN	1990	5,023	60	1.2	0.9-1.5	
			Rural black women, KZN	1990	3206	52	1.6	1.2-2.0	
			Rural black men, KZN	1990	1683	7	0.4	0.1-0.7	
1993	SAMJ	Bhigjee et al.[396]	General population, Ngwelezane, KZN	1991	1,018	36	3.5	2.4-4.7	
1994	SAMJ	Kustner et al.[23]	National ANC attendees	1990	14,376*	70	0.76	0.57-0.96	12m
			National ANC attendees	1991	17,155*	167	1.49	1.21-1.58	
			National ANC attendees	1992	18,810*	326	2.69	2.29-3.09	
1994	SAMJ	Cronje et al.[397]	Rural women, OFS province	1991	468	2	0.4	0-0.97	
			Urban women, OFS province	1991	424	6	1.5	0.34-2.66	

1996	SAMJ	Wilkinson & Moore[398]	TB patients, Hlabisa hosp, KZN	1993-94	297	107	36.0	30.5-41.5
			Female TB patients	1993-94	124	57	45.9	37.1-54.7
			Male TB patients	1993-94	173	50	28.9	22.2-35.7
1996	Int J Gynaecol Obstet	Hoosen et al.[399]	Women with granuloma inguinale, King Edward KZN	1991-1993	110	18	16	9.2-22.9
1997	Br J Cancer	Sitas et al.[155]	Black cancer patients (HIV not origin), JHB		325	24	7.3	4.5-10.1
1997	SAMJ	Wilkinson & Davies[148]	TB patients, rural KZN	1995	839	237	28.3	25.3-31.3
1997	Int J Tuberc Lung Dis	Anastasis et al.[400]	TB patients in referral hosp, Durban	1991-1994	295	42	14.2	10.2-18.2
1997	J Acquir Immune Defic Syndr Hum Retrovirol.	Coleman & Wilkinson[139]	Rural ANC women, Hlabisa	1992	884	37	4.2	3.0-5.7
			Rural ANC women, Hlabisa	1993	709	56	7.9	6.0-10.1
			Rural ANC women, Hlabisa	1995	314	44	14.0	10.4-18.4
1997	Genitourin Med	Wilkinson et al.[401]	Women in rural KZN attending FP clinics	1997	189	44	23.3	17.9-30.1
1998	Int J Tuberc Lung Dis	Karstaedt et al.[402]	TB (pulmonary) cases in urban hosp, Soweto		412	185	44.9	40.1-49.7
1998	Sex Transm Dis	Ramjee et al.[403]	Sexworkers at truck stops in KZN Midlands	1996-1997	145	73	50.3	42.2-58.4
1998	SAMJ	Kustner et al.[55]	National ANC attendees	1993	16206	648	4	3.6-4.5
			National ANC attendees	1994	18630	1416	7.6	7.0-8.1
			National ANC attendees	1995	13741	1429	10.4	9.9-11.0
1998	SAMJ	Swanevelder et al.[141]	National ANC attendees	1996	15044	2136	14.2	13.5-14.9
			ANC women Western Cape	1996	1778	55	3.1	2.3-3.8
			ANC women Northern Cape	1996	1137	75	6.6	5.1-7.9
			ANC women Northern Province	1996	1407	111	7.9	6.2-9.7
			ANC women Eastern Cape	1996	2031	165	8.1	6.9-9.3
			ANC women Gauteng	1996	2156	334	15.5	13.6-17.4
			ANC women Mpumalanga	1996	2363	373	15.8	14.3-17.2
			ANC women Free State	1996	1483	260	17.5	15.6-19.4
			ANC women KZN	1996	1601	319	19.9	17.7-22.1
			ANC women North West	1996	1088	273	25.1	22.3-27.9
1998	Int J Tuberc Lung Dis	Connolly et al[404]	TB patients Hlabisa KZN	1993	297	107	36	30.5-41.5
			TB patients Hlabisa KZN	1997			65.9	
1998	AIDS	Jones et al. [405]	Streptococcus pneumonia patients, Baragwanath hosp	1996	178	83	46.6	39.3-53.9
1998	Int J STD AIDS	Wilkinson & Wilkinson[406]	STD clinic attendees, Hlabisa	1997	360	153	42.5	37.4-47.6

			ANC clinic attendees, Hlabisa	1997			25.9	
1998	Int J STD AIDS	Colvin et al.[102]	Rural community, Hlabisa, KZN	1995	228	24	10.5	6.5-14.5
1999	AIDS	Wilkinson et al.[407]	ANC clinic attendees, Hlabisa	1998	211	87	41.2	34.7-47.9
1999	Ann Trop Paediatr	Zwi et al.[408]	Children, paediatric wards Baragwanath hosp	1992			2.9	
			Children, paediatric wards Baragwanath hosp	1997			20	
1999	Int J Tuberc Lung Dis	Churchyard et al.[409]	Mine workers with TB	1993			15	
			Mine workers with TB	1996			45	
1999	Int J STD AIDS	Wilkinson et al.[410]	Gynaecological patients admitted to Hlabisa hosp	1997	196	82	42	35.1-48.9
1999	Am J Forensic Med Pathol	Du Plessis et al.[203]	Autopsied bodies, Medicolegal lab, Pretoria		263	29	11	7.2-14.8
2000	Sex Transm Dis	Chen et al.[153]	Men with GUD attending STD clinics in Durban, CT and JHB		558	220	39.4	35.4-43.5
			Men with urethritis attending STD clinics in Durban, CT and JHB		602	129	21.4	18.1-24.7
2000	J Trop Pediatr	Yeung [224]	Children admitted to Hlabisa hosp	1996-1997	281	72	26	20.9-31.1
2000	JAIDS	Wilkinson et al.[32]	ANC clinic attendees, Hlabisa	1997	2013	521	25.9	24-28
2000	Int J Tuberc Lung Dis	Madhi et al.[411]	Children admitted to Wits associated hospitals, JHB	1996-1997	161	68	42	34.4-49.6
2000	Clin Infect Dis	Madhi et al.[412]	Urban Black children (2-60m) admitted to JHB hosp with LRTI	1997-1998	1215	548	45.1	42.3-47.9
2000	J Trop Pediatr	Meyers et al.[413]	Children under 5 years admitted to tertiary hosp in Soweto		507	148	29.2	25.2-33.2
2000	Pediatr Infec Dis J	Johnson et al.[414]	Children (3m-4y) with gastroenteritis admitted to Baragwanath hosp		176	31	17.6	11.9-23.2
2000	Int J Cancer	Sitas et al.[154]	Cancer patients in 3 referral hops in JHB (excluding cancer with HIV as origin)	1995-99	4883	505	10.3	9.5-11.2
			Male patients	1995-99	288	24	8.3	5.7-12.1
			Female patients	1995-99	556	50	9.1	6.9-11.7
2000	SA J Science	Rees et al.[415]	Commercial sex worker in Johannesburg	1996-1998	278	125	44.9	39.2-50.8
2000	SA J Science	Williams et al.[222]	Commercial sex workers in Khutsong,Carletonville	1998	115	81	70.4	61.0-79.0
			General female population in Khutsong, Carletonville	1998	690	255	36.9	33.4-40.6
			General male population in Khutsong, Carletonville	1998	499	110	22.0	18.4-25.6
			Migrant mine workers in Khutsong, Carletonville	1998	897	260	28.9	26.0-31.9
2001	Int J Gynecol Cancer	Moodley et al.[416]	Cervical cancer patients at KEVIII hosp, Durban	1990-2000	672	141	21.0	17.9-24.1
2001	AIDS	Auvert et al[286]	Young men (14-24y) in Carletonville township	1999	723	68	9.4	7.3-11.5
			Young women (14-24y) in Carletonville township	1999	784	270	34.4	31.1-37.7

2001	Int J STD AIDS	Colvin et al.[361]	Adult medical inpatients, King Edward hosp, Durban	2000	507	274	54	49.7-58.3
2001	Stat Med	Williams et al.[33]	Women attending ANC in Hlabisa, KZN	1998	3163	1044	33.0	31.4-34.6
2001	Clin Infect Dis	Karstaedt et al.[417]	Patients with pneumococcal bacteremia at Baragwanath hosp	2001	161	108	67.0	59.7-74.3
2001	AIDS Patient Care STDs	Morris & Cheevers[418]	Men working in a sugar mill in KZN	1999	386	105	27.2	22.8-31.6
2001	Arch Dis Child	Pillay et al.[419]	Children admitted to Paediatric ward in academic hospital (KEVIII) in Durban	1998	160	100	62.5	55.0-70.0
2002	Sex Transm Dis	Ramjee & Gouws[331]	Truck driver clients of commercial sex workers in KZN	1999	310	174	56	50.5-61.5
			Sex workers at truck stops in Midlands, KZN	1996-1999	471	240	51	46.5-55.5
2002	JAIDS	Gouws et al.[420]	Women attending ANC in Hlabisa, KZN (age 14-44y)	1999	1717	680	39.6	37.3-41.9
2002	Int J STD AIDS	McPhail et al.[421]	Young men (14-24y) in Carletonville township	1999	230	18	7.9	4.4-11.4
			Young women (14-24y) in Carletonville township	1999	277	108	39.3	33.6-45.1
2002	Int J Tuberc Lung Dis	Jeena et al.[422]	Children (0-12 years) with proven TB from KE hosp, Durban	1998-1998	118	57	48.3	38.9-57.0
2002	Lancet	Rollins et al.[283]	Mothers attending rural immunization clinics in KZN	2000	1303	365	28.0	25.6-30.4
			Children (0-6weeks) born to HIV infected mothers	2000	102	14	13.7	7.3-20.7
			Children (6 weeks to 6 months) born to HIV infected mothers	2000	243	56	23.0	17.7-28.3
2003	AIDS	Lagarde et al.[352]	Men aged 19-29y in Westonaria, Gauteng	2001	482	53	10.9	8.2-13.8
			Women aged 14-25y in Westonaria, Gauteng	2001	302	91	30.1	24.8-35.2
2003	J Trop Pediatr	Zar et al.[423]	Children in Cape Town hospitalized with community acquired pneumonia		250	151	60.4	54.3-66.5
2003	J Clin Forensic Med.	Meel[424]	Rape victims attending Sinawe crisis centre in Transkei	2000-2002	243	22	9.1	5.4-12.6
2003	Vox Sang	Fang et al.[284]	South African blood donors – low HIV prev	1999	9077			
			South African blood donors - high HIV prev	1999	10632			
2003	Pediatr Infec Dis J	Grimwade et al.[425]	Febrile children in Hlabisa with malaria	2000	663	67	10.1	7.8-12.4
2003	Int J STD AIDS	Zuma et al.[328]	Migrant women in Carletonville	1998	150	69	46	38.0-54.0
			Non-migrant women in Carletonville	1998	551	191	34.7	30.7-38.7
2004	AIDS	Rosen et al.[252]	Workplaces in South Africa					7.9-25.0
2004	SAMJ	Evian et al.[426]	Formal sector workforces in South Africa	2000-2001	44000 (get number for SA)		14.5	14.1-14.9
2004	AIDS	Grimwade et al.[427]	Febrile adults at clinics and hospital inHlabisa	2000	613	180	29.9	26.4-33.4
2004	Sex Transm Dis	Myer et al.[428]	Women participating in Gynae screening study in Cape Town	2002	2897	387	13.4	11.8-4.2

2004	SAMJ	Shisana et al.[355]	Married people, South Africa	2002	2426	255	10.5	9.3-11.7
			Unmarried people, South Africa	2002	3664	575	15.7	14.5-16.9
			Adults (>15 years) in South Africa	2002	6090	826	13.6	12.2-15.1
2004	SAMJ	Shisana et al.[429]	South African health workers in four provinces, private and public sector	2002	721	113	15.7	12.2-19.9
2004	SAMJ	Connolly et al.[356]	General population in SA (HSRC study)	2002	8428	961	11.4	10.7-12.1
			Female general population (HSRC study)	2002	4656	596	12.8	11.0-14.7
			Male general population (HSRC study)	2002	3772	358	9.5	8.1-11.2
			Black general population (HSRC study)	2002	5056	652	12.9	11.3-14.6
			White general population (HSRC study)	2002	701	43	6.2	3.7-10.0
			Coloured general population (HSRC study)	2002	1175	72	6.1	4.5-8.3
			Indian general population (HSRC study)	2002	896	14	1.6	0.5-5.0
2004	JAIDS	Auvert et al.[430]	Community men and women from township in JHB	2001			21.8	19.2-24.6
2005	AIDS	Grimwade et al.[295]	Adults treated for TB in rural KZN	2001-2002	150	117	78	71-84
2005	Int J STD AIDS	Dunkle et al.[431]	Female sex workers in JHB		295	137	46.4	40.7-52.1
2005	BJOG	Mseleku et al.[432]	ANC attendees at Johannesburg hospital				29.4	
			ANC attendees at JHB hosp who initially refused routine testing		50	22	44.0	30.2-57.8
2005	SAMJ	Kagee et al.[433]	Muslims in the Cape Metropole		352	9	2.6	1.2-4.8
2005	AIDS	Pettifor et al[326]	Young women (aged 15-24 years)	2003			15.5	
			Young men (aged 15-24 years)	2003			4.8	

*Indicate samples received and not tested

Note: Where 95% confidence intervals were not provided in the paper, they were calculated here either assuming a normal approximation or the binomial distribution in the case of small numbers or prevalences.

Discussion

The scientific review in this chapter shows that there is a substantial literature covering many aspects of HIV and AIDS in South Africa. These include social, behavioural, epidemiological, clinical, molecular and genetic research. During the first period covered in this review, 1983 to 1989, the focus of the scientific research was on men who have sex with men, the group most affected by the epidemic during this period. However, by 1989 it became clear that the virus had been introduced into the heterosexual population and several papers debated the likely impacts of the epidemic and warned of the potential threat posed by HIV/AIDS to the South African society.

During the period 1990 to 1994 it became clear that the heterosexual epidemic was rapidly overtaking the homosexual epidemic in scale and importance and surveillance efforts to estimate the size of the epidemic in various populations and risk groups were described in several papers. The number of papers dealing with social and behavioural aspects of the epidemic increased steadily and important studies were published on the epidemiology and likely future growth of the epidemic. Predictions on the maximum size of the epidemic made by statisticians during this time have proved to be depressingly accurate.

During the third period under consideration, 1995 to 2000, research increased on all fronts and the number of papers in scientific journals reached a maximum in 2000. In particular, there was a dramatic increase in the number of papers dealing with the genetic and molecular aspects of the virus as South Africa joined the international effort to develop an effective AIDS vaccine. There was also an increase in interest in AIDS related diseases with numerous papers on tuberculosis and its association with HIV.

Trends during the third period continued after 2000, with an impressive number of publications in social, behavioural, epidemiological, clinical and molecular research areas. However, more emphasis was placed on issues related to providing treatment, care and support for patients with HIV or AIDS, an area of specific interest as the Government of South Africa announced its plan to provide antiretroviral treatment in the public health sector in 2003. South Africa also contributed significantly to international prevention efforts with research on the effect of cotrimoxazole in prevention of opportunistic infections in HIV infected children and the significant impact of male circumcision on

reducing the transmission of HIV from females to males. The first national population based surveys were also conducted in an attempt to estimate HIV prevalence in various population group (by region, men/women, children, young people) and to assess associated socio-economic and behavioural factors.

Finally, while there is an impressive amount of data on HIV prevalence in various risk groups in South Africa, there is a clear lack of estimates on HIV incidence, which is crucial for understanding the dynamics of the epidemic and for planning interventions. At a time when prevalence is starting to level off and mortality is rising, it is of particular importance to monitor changes in the number of new infections in various populations. In this thesis, methods are developed and described to estimate HIV incidence in various populations in South Africa, and to estimate the impact of ARV on future epidemic trends.

The scientific community has responded to the challenges of HIV/AIDS in South Africa with an impressive body of scientific literature, but more still needs to be done. Probably the greatest need however, is for social, epidemiological, clinical, biomedical and molecular scientists as well as policy makers and planners to work together to provide the intellectual support that will be needed if we are to deal with this devastating epidemic effectively.

CHAPTER 3 Mathematical modelling of HIV and AIDS

> "Understanding of the world in scientific terms is to build a model, to reduce apparent complexity to a set of simple rules. These rules constitute a theory. A theory may be verbal or in terms of mathematical equations, but a verbal theory is always incomplete. A mathematical theory provides a logical link between assumptions and conclusion. Thus, ultimately, the language of all natural sciences is mathematics. A verbal theory can be conveniently vague about its details and hide important assumptions. A mathematical theory is more transparent. It contains a clear list of assumptions, which are its ingredients generated by observation."
>
> Martin Novak and Robert May, 2000[434]

Introduction

Epidemiology is the study of diseases in populations rather than individuals. While clinicians are interested in disease in a particular person, epidemiologists are interested in knowing why some people get the disease while others do not. Epidemiologists are concerned with questions such as: If a vaccine is developed against HIV but it only gives 50% protection, what effect would this have on the epidemic of HIV? How many people will have to be vaccinated in order to control HIV? If condoms are to be used to reduce the incidence of HIV, do we need to ensure that everyone uses condoms? Mathematical modelling is an essential part of epidemiology because it provides a tool to help understand the biology and the dynamics of disease.

A central role of mathematical models in the study of epidemiology and control of HIV, as defined by Anderson and May, is to understand the interplay between the variables that determine the course of infection within an individual and those that determine the patterns of infection in communities of people.[435] Mathematical models have become an integral part of research related to infectious diseases, partly because of the non-linear dynamics of most infectious disease epidemics, and the role of epidemic theory based on mathematical models has been of great importance in seeking explanations for patterns of diseases.[436]

Brief history of mathematical modelling

One of the earliest examples of mathematical biology in history was published in 1202 in a book by the Italian mathematician Leonardo of Pisa (known as Fibonacci) which introduced the Hindu-Arabic decimal system to Western Europe. One of his examples,

regarded as the very beginning of mathematical biology, was: "How many pairs of rabbits can be produced from one pair, if every month each pair bears a new pair which from the second month on becomes reproductive?" Assuming that 1 month elapses before the initial pair reproduces, that there are no deaths, and that each pair reproduces regularly, the number of adult rabbit pairs being present in consecutive months is then given by the Fibonacci sequence: 1, 1, 2, 3, 5, 8, 13, 21,....[434]

The application of mathematical models to infectious diseases dates back to 1760 when Daniel Bernoulli developed a mathematical method to study the effect of variolation to protect against smallpox infection on life expectancy.[437] In 1840, William Farr fitted curves to data of smallpox epidemics in England and Wales.[435] At the beginning of the 20th century, Hamer and Ross developed mathematical equations to describe the spread of infectious agents within populations. Hamer first introduced the so-called "mass-action" principle for a deterministic epidemic model in discrete time in 1906,[438,439] in which the net rate of transmission of infection is proportional to the product of the densities of infected and susceptible individuals. This principle, which incorporates the principle of homogeneous mixing, has been the basis of most subsequent development in epidemic theory.[439] Ronald Ross, describing the spread of malaria in 1916, was the first to use the "mass-action" assumption in a continuous time model.[439] In 1927, Kermack and McKendrick laid the foundations for a theoretical framework of epidemiology, describing the form of equations most commonly used to characterize the typical general epidemic with susceptibles, $x(t)$, infecteds $y(t)$ and immunes $z(t)$.[439] They assumed a fixed population size $N = x(t) + y(t) + z(t)$ and used the homogeneous mixing principle for continuous time to derive the classical equations

$$dx/dt = b - \lambda xy,$$

$$dy/dt = \lambda xy - \gamma y,$$

$$dz/dt = \gamma y,$$

where people enter the model at a rate b, become infected at *per capita* rate λ which is determined by the contact rate times the prevalence of infection, and become immune at a rate γ. Fisher, in 1930, first described the "net reproductive value" for the parasite, a concept which has become central in discussing the population biology of an organism.[435] The basic reproductive rate, R_0, is the average number of successful offspring that a parasite is capable of producing. A parasite species must have $R_0 > 1$ in order to be able to

invade, and establish itself within a host population.[435] The concept has been discussed and developed by, amongst others, Macdonald in 1952 in the context of malaria transmission,[440] Dietz in the 1970's in studying the transmission and control of arbovirus disease and other infectious diseases,[441,442] York and co-workers in studying sexually transmitted infections, and Anderson and May in studying the dynamics and control of infectious diseases in humans.[435,443]

The literature concerned with mathematical epidemiology has grown rapidly over the last three decades, much of which has been concerned with probabilistic models, addressing the variation and elements of chance as important determinants of the spread of infection. In recent literature reviews it has been shown that the number of publications related to mathematical epidemiology increased from less than 10 in the period 1760-1855, to about 100 between 1856 and 1957, and to about 500 between 1958 and 1978.[435] Recent work has included studying control theory to epidemic models, the spatial spread of diseases, mechanisms underlying recurrent epidemic behaviour, heterogeneity in disease transmission, and extending threshold theory to more complex deterministic and stochastic models.[435]

Mathematical models applied to sexually transmitted disease epidemiology

Despite the early developments in mathematical models and epidemic theory, it is only during the last 30 years that mathematical models have been applied to sexually transmitted disease epidemiology. Following some early applications of mathematical models to describe the transmission dynamics of gonorrhoea in the 1970s[444], two influential publications by Yorke and Hethcote, supported by data, attempted to address issues of interest to health workers and introduced a number of essential concepts in sexually transmitted disease epidemiology.[445,446] These included the concept of the "reproductive number", already applied in other areas, as a measure of transmission success, the importance of asymptomatic infections in maintaining endemic infections, and the role of the "core group" of individuals with high rates of change in sexual partners to maintain transmission of disease in communities with both high and low rates of partner change.[436] The development of the conceptual/theoretical model of the transmission dynamics of sexually transmitted infections (STIs) in the early 1990s had a major impact and made mathematical models more accessible to many scientists.[447,448] Since then, the

conceptual model based on the basic reproductive number (R_0), has provided a framework for much of the research related to the dynamics of STI epidemiology.[449]

Mathematical models applied to HIV/AIDS

A number of models have been developed globally to investigate the dynamics and impact of HIV and AIDS, ranging from relatively simple extrapolation models to large, complex, macro- or micro-simulation models. Among the simple models that have been applied to most of the countries and regions in the world are the Estimation and Projection Package (EPP) model developed by the UNAIDS Reference Group on Estimates, Modelling and Projections to fit epidemic curves to data collected over time,[450] and the Spectrum (AIDS Impact Model) developed by Futures Group International, to estimate the demographic impact of HIV and AIDS.[451] The UNAIDS EPP model replaced the earlier model developed by WHO (Epi-Model) which was used to produce estimates of HIV in sub-Saharan Africa assuming that the HIV infection curve follows a gamma distribution.[452] Four major modelling efforts have been developed in relation to AIDS in developing countries, namely SimulAIDS, a Monte Carlo model of heterosexual transmission of AIDS, initially developed by Bertran Auvert and colleagues;[453] iwgAIDS, a complex continuous simulation model of known modes of transmission, developed by Steve Seitz and others with funding from the USA government;[454] a series of models to simulate the heterosexual spread of HIV, developed at Imperial College, London and Oxford University by Roy Anderson and colleagues;[455-458] and STDSIM, a micro-simulation model to describe the sexual transmission of HIV and STI's, developed at Erasmus University by Dik Habbema and colleagues with funding from the European Commission.[459,460]

Modelling the HIV epidemic in South Africa

In South Africa, models were developed in the early stages of the epidemic, and although the forecasts were tentative because of the lack of key data and the number of assumptions, they indicated the seriousness of the HIV epidemic. In the early 1990's, both Schall, using a macro-simulation model,[21] and Groeneveld and Padayachee, using micro-simulation models,[22] predicted that the prevalence of HIV could reach 30% in the sexually active population by the year 2000 to 2005, which is close to the current prevalence among women attending antenatal clinics. The Doyle-Metropolitan model, first described by Doyle and Millar in 1990,[375] was initially developed for use by Metropolitan Life to

investigate the demographic consequences of HIV in life insurance, health and pension applications. Application of the Doyle model in the early 1990s suggested that the number of AIDS cases could reach 800,000 in 2010.[376] The component population projection model, subsequently developed by the Actuarial Society of South Africa (ASSA model), has its origins in the Doyle-Metropolitan model and has been widely used to project the demographic impact, including mortality, of the HIV epidemic in South Africa.[461,462] The model is calibrated to the national antenatal clinic prevalence data and to estimates of mortality based on death data recorded by the Department of Home Affairs. The UNAIDS models have been used by some epidemiologists to estimate the current state of the epidemic (prevalence in adults and children, number of people living with HIV, number of AIDS deaths, and number of orphans)[4] and to make future projections of the epidemic in South Africa.[374] Models have also been used to estimate the cost and impact of HIV on businesses[252] and the cost effectiveness of intervention programs;[380] and a model has recently been described to predict the potential public health impact of disease-modifying HIV vaccines in South Africa.[382] Further models to describe epidemic trends and the impact of the epidemic in South Africa are described in this thesis.

Following an initiative by Brian Williams and colleagues to bring South African modellers together to investigate the dynamics of HIV/AIDS, TB and other diseases, the South African Centre for Epidemiological Modelling and Analysis (SACEMA) has been established with the support of the South African Department of Science and Technology.[463] This Centre of Excellence is the first national research institution of its kind in Africa and is dedicated to modelling disease transmission and progression, with a focus on South Africa's major health challenges.

The uses of mathematical models

The main purpose of mathematical models is to understand the dynamics of a disease, in terms of the interplay between those variables that determine the course of infection within an individual, and those that determine the pattern of infection in a population.[435] Mathematical models can be used to study disease transmission, to identify patterns of infection, and to help define the most important factors associated with the observed disease patterns. Models can be further used to explore the potential impact of behaviour

changes and interventions on the spread of disease, and to assess cost effectiveness of interventions or the economic impact of HIV in a workplace or country. Knowledge of the factors determining the patterns of infection and the potential impact of interventions can be used to model the future course of the epidemic in a population.

Mathematical models can help us to understand the demographic impact of HIV and AIDS in relation to mortality and morbidity, how HIV and AIDS will affect the demand for health services, or the productivity of labour, or how the dependency ratio will change and the impact this will have on social services. Finally, mathematical models can be used to inform policy and programmatic decisions related to the planning of adequate responses, targeting of medical and behavioural prevention strategies, and the provision of care and support in a community.

Modelling can be done in different ways. When statistical models are applied to epidemiological data we often begin by looking for associations between variables and then proceed to use regression or analysis or variance models to see if the values of one variable can be accurately predicted using others. The significance levels of the variables in these models can help to identify and rank the most significant associations, while the strength of the association can be specified in terms of odds- or risk-ratios. While statistical models can take the features of data into account (e.g., categorical or continuous measurement, random or fixed effects, linear or non-linear effects), conventional approaches to statistical analyses often assume linearity in data, and transformations are often applied to data in such a way that the transformed variables are linearly related with each other. Such transformations tacitly assume a particular form of the relationship, and therefore of the underlying dynamics, which may or may not be appropriate. An important limitation of statistical modelling is that it generally presents a static analysis of the data: one might consider the prevalence of HIV at several points in time and show that the prevalence is significantly higher or lower at later than at earlier times, but this does not take into account the dynamics of the disease over time; to do this we need to develop dynamical models based on difference or differential equations.

Dynamical models are designed to simulate an actual situation and are limited only by the imagination of the scientist building the model. They can be linear or non-linear, complex or simple, but they are usually designed to capture and describe the past (known) history of

the disease and to forecast the future (unknown) course of the disease. When developing models and interpreting model outcomes, it should be borne in mind that model estimates are always uncertain to some degree because they depend on the structure of the model, which is based on our assumed understanding of the epidemic, on the parameters included in the model, some of which are uncertain; and on the data sets used in the modelling exercise which contain further uncertainties.

Basic concepts in mathematical models related to HIV/AIDS

The simple epidemic

Transmission of HIV depends upon direct contact between infected and susceptible individuals. The simplest model of the population dynamics of HIV is shown schematically in Figure 3.1. People are born or become susceptible at a rate β, putting aside the issue of mother-to-child transmission, and the rate (λ) at which infections are acquired is proportional to the number of encounters between susceptible (S) and infected (I) people. In the case of HIV, the rate at which infection spreads in a population depends on the number of infected people, the number of susceptible people who are available to be infected, the rate at which these two groups make contact, the probability of transmitting HIV per sexual contact, and the life expectancy of infected people. In the simple model infected people die at a *per capita* rate δ, while the *per capita* background mortality rate (in the absence of disease) is μ.

Most mathematical modelling in biology consists in taking models conceptualised as in Figure 3.1, and formulating them in terms of differential equations which can be simulated on a computer.

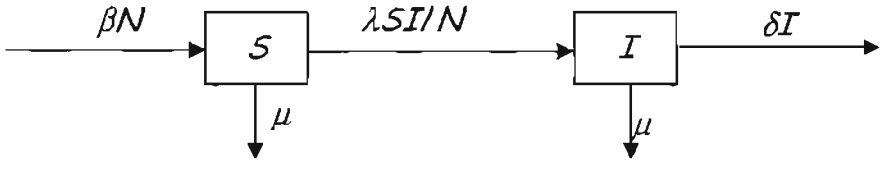


Figure 3.1 People are born or become susceptible at a per capita rate β, susceptible people become infected at a rate λ times the current prevalence (I/N), and people die of AIDS at a rate δ. The population growth rate, in the absence of disease, is the birth rate minus the background death rate μ.

Simulation models can be used to answer questions in relation to the HIV epidemic such as: How rapidly does the infection spread at the start of the epidemic when only a few people are infected and how does the spread of infection change later in the epidemic when many people are already infected? What happens later in the epidemic when infected people start dying? What happens if there are core groups of men or women who have many sexual encounters with other women or men? Once we know what has happened in the past, can we reliably forecast what we think will happen in the future? What percentage of the population need to use condoms with casual partners in order to significantly alter the course of the epidemic? If most sex workers use condoms will that have any impact on the spread of infection? What is the likely impact of providing anti-retroviral therapy to those in need on the future course of the epidemic? If we extend the life of people infected with HIV will that make the situation better (because they live for longer) or worse (because they infect more people)? If we had a vaccine, what sort of coverage would we need to bring down the overall rates of infection?

The Basic Reproductive Number

The rate and extent of spread of the epidemic can be derived from the *basic reproductive rate of infection* (R_0), defined as the average number of secondary cases of infection that arise from one infectious individual (primary case) in a susceptible population.[435] Essentially, it is a composite measure of transmission success in a particular community. The reproductive rate is influenced by three parameters: the transmission probability per partnership (β), the mean rate of sexual partner change (c), and the mean duration of infectiousness (D), and can be formulated as follows:

$$R_0 = \beta \times c \times D \qquad 3.1$$

Changes to any of the 3 variables, viz. β, c or D, will determine whether or not the infection will persist and how quickly it will spread. For an epidemic to persist in a population, R_0 must be greater than or equal to 1. The magnitude determines the likelihood, speed, and scale of the spread of infection. In order to eventually eliminate the infection R_0 must be reduced to less than 1. In South Africa we estimate that R_0 is approximately 7, as follows: From the analysis done in Chapter 5 of this thesis, the doubling time of HIV prevalence at the start of the epidemic is about 15 months. This means that each person with HIV infects one other person, on average, every 15 months (or 1.25 years). If the life

expectancy of an infected person is nine years then each person infected with HIV will infect 9/1.25 ≈ 7 people before they die, i.e., $R_0 \approx 7$. In order to eliminate the infection completely we need to reduce transmission by about seven times. Smaller reductions will, of course, lead to some decline in the prevalence.

Co-factors that will have an impact on one or more of the variables in Equation 3.1 include demographic factors such as age and gender, social factors such as sexual networking patterns and sexual practices, biological variables such as the presence of other sexually transmitted infections and male circumcision, and medical factors including the provision of antiretroviral drugs and the treatment of AIDS related opportunistic infections. For example, transmission of HIV will be more efficient when the male has an STI because shedding of HIV into semen increases in the presence of an STI and hence the partner is exposed to greater concentration of the virus.[464] A numerical example of how the epidemic growth could be reduced by managing STIs optimally is provided in Box 3.1. Using a condom reduces the transmission probability β, because the semen (and hence HIV) is contained in the condom and does not infect the sexual partner.

In order to reduce R_0 to less than 1, so as to control the HIV epidemic in South Africa, prevention efforts need to be scaled up, including control of STIs, promotion of condom use, reduction of high-risk sex and number of sexual partners, development of vaccines and microbicides, provision of antiretroviral drugs to prevent mother-to-child-infection, while access to treatment of HIV and other opportunistic infections should be ensured so that the lives of those who are already infected can be extended.

Box 3.1 Numerical example to show how co-factors may influence R_0

a. Reducing the rate of partner change

If each HIV infected individual reduces the number of sexual partners that he/she has whilst living with HIV by half then c in Equation 3.1 would become $c/2$ and $R_0 = \beta \times c/2 \times D$ so that the reproductive number R_0 would also be halved. If previously R_0 was 7, reducing the number of partners by half would reduce R_0 to 3.5.

b. Managing sexually transmitted infections

If we assume that about 20% of the adult population have at least one STI ($p = 0.2$) and that, on average, having an STI increases the chance of contracting HIV by a factor of 10, then the efficiency of transmission (β) becomes:

$$\beta = (0.2 \times 10) + (0.8 \times 1) = 2.8$$

If $R_0 = 7$ then, with the eradication of STIs, R_0 will become $7/2.8 = 2.5$.

Using models to understand trends in the epidemic of HIV in South Africa

The epidemic of HIV infection in South Africa, predominantly of subtype C, has reached extraordinarily high proportions and threatens to overwhelm the country. However, if we are to deal with it effectively, it is essential to first understand the basic dynamics of the infection. The surveillance systems and data on HIV infection rates in South Africa are among the best in the developing world, largely as a result of the efforts of the Department of National Health and Population Development who in 1990 started an annual programme to collect data on HIV prevalence among pregnant women attending antenatal clinics throughout the country.[23] Changes in the overall antenatal clinic prevalence of HIV over the last fourteen years (Figure 3.2) can be fitted to a logistic curve, described in Box 3.2.

The logistic curve gives a best estimate of the asymptotic prevalence (the value at which the epidemic is predicted to level off) of about 28% and an initial doubling time at the start of the epidemic of about 15 months (described in more detail in Chapter 5). Once the prevalence has levelled off, and depending on behaviour change and the impact of

prevention and interventions that reduce transmission of the virus, it is anticipated that the prevalence will eventually start to decline, as has been observed in countries such as Uganda (Figure 3.3, fitted to data obtained from UNAIDS, available at www.unaids.org). Once the prevalence of HIV begins to fall, a double logistic function can be used to describe the change over time, as explained in Box 3.2.

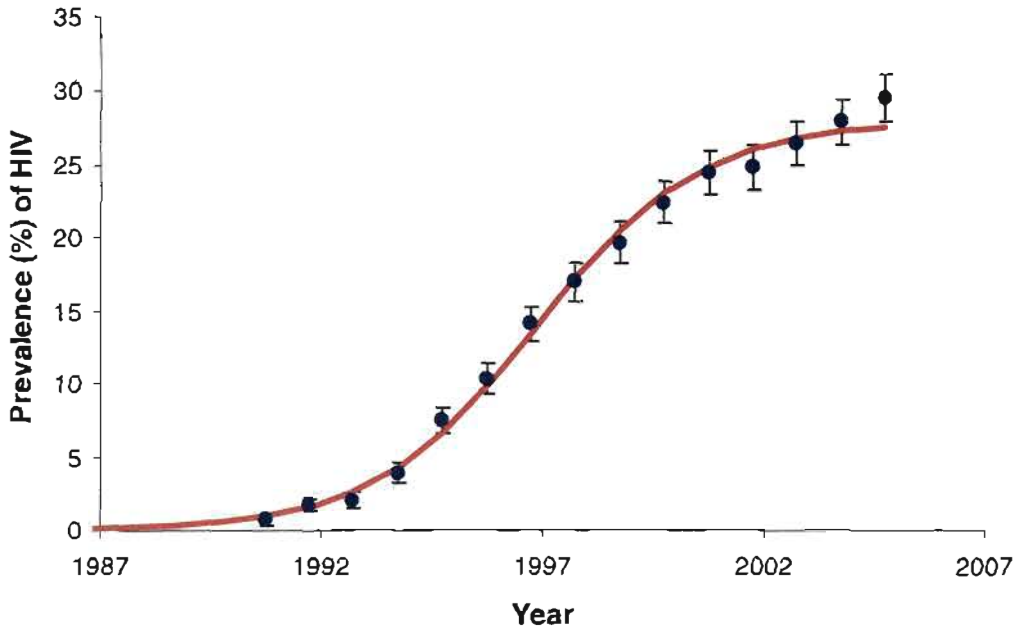


Figure 3.2 Prevalence of HIV infection from national antenatal clinic surveillance between 1990 and 2004. The early stages of the epidemic showed an exponential increase in HIV infection with a doubling time of 15.6 months (95% CI: 15.2–16.1). Fitted to a logistic curve, the HIV epidemic reached half its peak value between 1996 and 1997 and has an expected maximum prevalence of 28.3% (95%CI: 27.7-28.9).

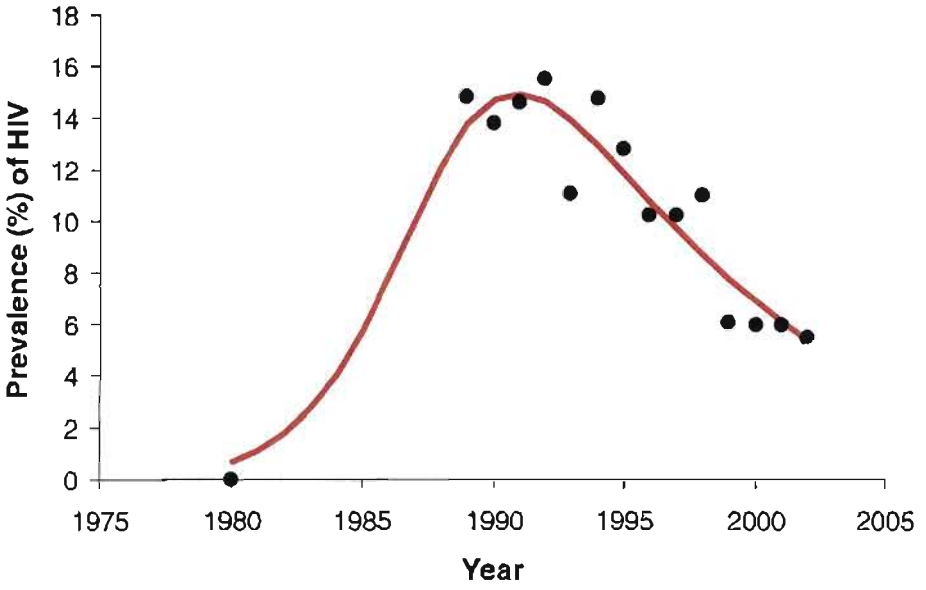


Figure 3.3 Double logistic curve fitted to prevalence data from Uganda, showing a decrease in the epidemic over recent years (source: curve fitted to UNAIDS data, available at www.unaids.org (Epi Fact Sheets))

Understanding the geographical distribution of infection is equally important and the provincial prevalences are discussed in Chapter 5. The patterns of infection vary strongly between men and women and with age (described in more detail in Chapter 6), and basic dynamical models should therefore be age-structured to allow for diversity in the behaviour and risk of different populations. The age-prevalence of infection among men and women is essential for determining the age and gender specific mortality and hence the future age structure of the population. The pattern of HIV age-prevalence has shown to be close to zero in young adolescents before the age of onset of sexual activity, then increases rapidly as sexual activity increases to a peak in the late 20's for women and early 30's for men, followed by a more gradual decrease in prevalence among older people. The function that has been shown to best describe the age prevalence of infection is the log-normal function of the form

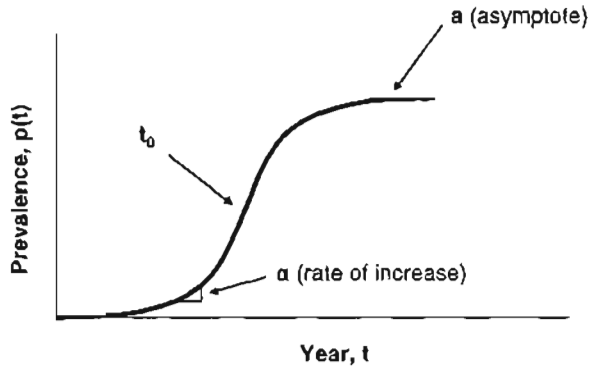
$$R(a) = \frac{N}{\sigma\sqrt{2\pi}(a-a_0)} e^{-(\ln((a-a_0)/m))^2/2\sigma^2} \qquad 3.2$$

with age a, off-set of sexual activity at age a_0, mean m, standard deviation σ and normalised to N, and is illustrated in Figure 3.4 using HIV prevalence data from antenatal clinics.

Box 3.2 Logistic or double logistic functions to model the change in the HIV epidemic over time.

When the prevalence is still increasing or showing signs of leveling off,
a logistic curve of the following form can be used to describe the epidemic:

$$p(t) = \frac{ae^{\alpha(t-t_0)}}{1+e^{\alpha(t-t_0)}}$$

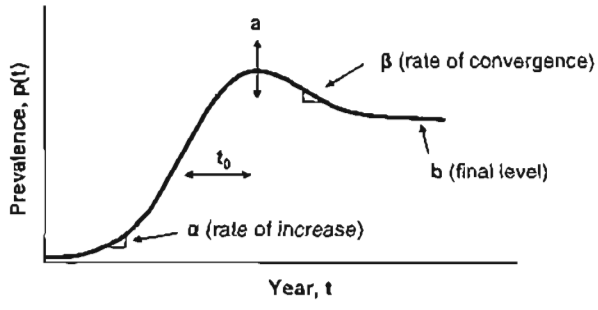


Where a = asymptote (i.e., the level at which the epidemic is expected to level off)
α = the rate of increase at the start of the epidemic
t_0 = the time at which the epidemic reaches half its asymptotic value

The doubling time at the beginning of the epidemic can be determined from α,
i.e., doubling time = ln(2) / α

When the prevalence shows evidence of a decline,
a double logistic curve of the following form can be fitted to the data:

$$p(t) = \left[\frac{e^{\alpha(t-t_0)}}{1+e^{\alpha(t-t_0)}}\right]\left[\frac{ae^{-\beta(t-t_0)}}{1+e^{-\beta(t-t_0)}}+b\right]$$



Where α = the rate of increase at the start of the epidemic
a = determines the peak value
β = the rate of convergence
b = final prevalence level
t_0 = shifts the curve backward or forward

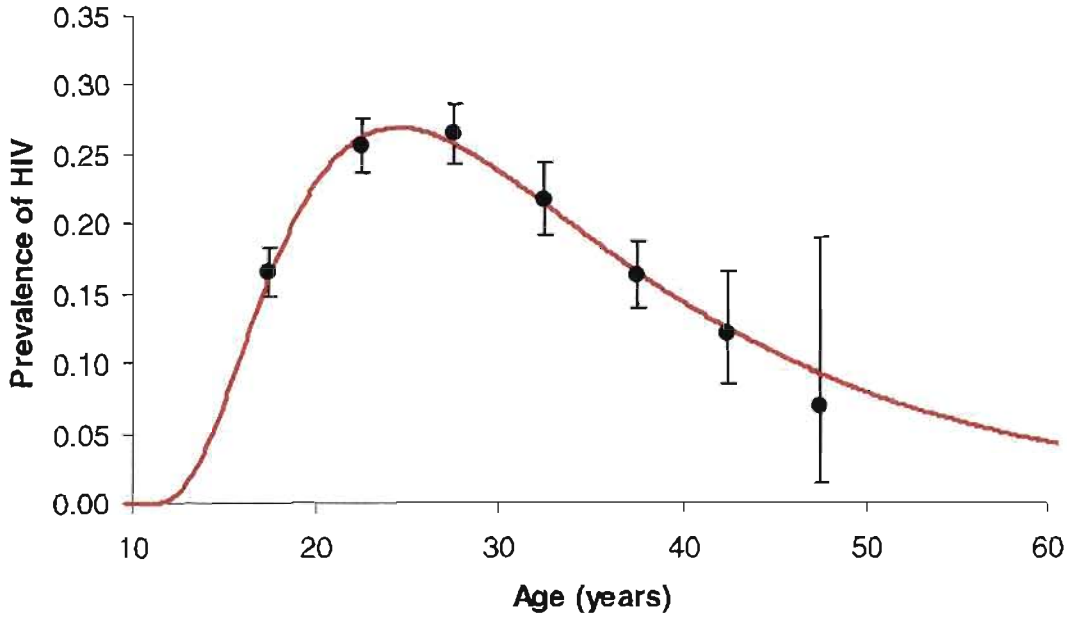


Figure 3.4 Age prevalence of HIV infection among women attending antenatal clinics in South Africa in 1999. Error bars are 95% confidence limits. The fitted curve is a log-normal function.

Given our current knowledge of the HIV epidemic, one can make an immediate, but approximate, estimate of the number of people infected with HIV in South Africa. From the antenatal clinic surveillance in 2004[31] it is known that about 29.5% of pregnant women were infected with HIV (Figure 3.2) and that the rates among adult men are about 75% of the rates in women.[26] Based on the United Nations Population Division population size estimates, it is assumed that the adult population (age 15-49 years) for South Africa was 24,349,000 in 2005.[465] If the antenatal clinic estimate is believed to give a reasonable estimate of the prevalence in adult women, then it is estimated that about 6.28 million adults are currently living with HIV. However, since the above data represent women attending public health clinics, it may exclude women from more affluent communities who are more likely to receive private health care, as well as women in deep rural areas who may visit traditional healers instead of public health facilities. In both these groups it is expected that HIV prevalence is lower than among those women attending public health clinics. If the antenatal prevalence estimate is adjusted down by 20%, the estimated number of adults (15-49 years) living with HIV is 5.03 million. This is within the range of the UNAIDS estimate of 5.1 million (range 4.3 to 5.9 million)[4] adults infected with HIV

in 2003, using more sophisticated models that make assumptions about the age-distributions, fertility reduction, the relative levels of HIV prevalence in women who use public antenatal clinics and those who do not, and survival rates.

Using mathematical models one can estimate the age-specific incidence of new infections, the most sensitive marker of transmission, from the slope of the prevalence curve, allowing for natural deaths and AIDS deaths and assuming a life expectancy after infection of 9 years, as will be described in Chapter 9. Similarly, the number of deaths can be estimated from models applied to HIV prevalence data, making assumptions about survival after infection with HIV. Future projections can be made about prevalence, incidence and deaths, as discussed in Chapter 12. Using vital registration data, the effect of HIV on adult death rates have become apparent over the last few years[279,466] and the Medical Research Council's Burden of Disease Research Unit showed that AIDS was the leading cause of deaths in 2000 in all provinces in South Africa with the exception of the Western Cape.[466] Nationally, in 2000, AIDS accounted for 30% of all deaths in South Africa and the number of AIDS deaths, using the ASSA model, was estimated to be 165,792.[466] It is further estimated that in 2010, AIDS will more than double the burden of premature mortality (as measured by *years of life lost* - YLL) experienced in 2000.

Many studies have speculated on the impact of HIV/AIDS on population growth. Most models suggest AIDS would only cause negative population growth in Africa if national HIV prevalence levels increased to 30-50% or if fertility rates decline sharply.[467] It is therefore possible that in South Africa, with very high levels of prevalence and declining fertility, the population may well cease to grow over the next ten to twenty years.

The importance of good demographic models cannot be over stated, for without such models it will be difficult to develop an effective response to the epidemic, to make sensible plans for the provision of health and welfare services, to manage the economic burden on the country's industries, or to assess the impact of interventions (including antiretroviral treatment, vaccines, increased condom use, management of sexually transmitted diseases, educational and behaviour change programmes, media campaigns, and so on). Fortunately, there is a considerable amount of data on HIV in South Africa (both from sentinel and site surveillance, and from community and national surveys), for without such data the best models in the world are no more than informed guesses.

Anderson and May pointed out in 1991[435] that despite the extent and sophistication of the mathematical literature, "the insights gained from theoretical work have, in general, had little impact on empirical approaches to epidemiological study and the design of public health policy", a consequence that they ascribe to the abstractly mathematical nature of the literature. They therefore stress that, "if theoretical work is to play a role in the solution of practical problems in disease control and in the interpretation of observed trends, a much greater emphasis must be placed on data-oriented studies."

The models that have already been developed in South Africa have given us powerful advocacy tools. They have helped us to start develop an understanding of the dynamics of the epidemic, and to do demographic projections of the epidemic, while economists have started to look at the economic impact of HIV on the workplace and at national level. But more is needed to explore and evaluate the impact of the wide range of existing and potential interventions, from antiretroviral treatment, vaccines and the impact of male circumcision to persuading adolescents to use condoms, and to inform the policy makers how to best address the challenges that face us.

CHAPTER 4 Sources of data on HIV infection in South Africa

> "All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time".
>
> Sir Austin Bradford Hill, 1965[468]

Introduction

Many HIV sero-prevalence surveys have been undertaken in South Africa over the past 15 years (Chapter 2, Table 2.1), providing important information on the course of the HIV epidemic and on factors that contribute to the spread of the epidemic. These sources include extensive and complete annual surveillance over time among pregnant women attending public health antenatal clinic surveys (national and provincial), surveillance among STI, family planning or TB clinics, some community based surveys such as those conducted in Hlabisa and Carletonville, and national population based surveys including those conducted by the HSRC (including all people older than 2 years)[469,470] and the Lovelife survey among youth.[357] These data sets can be used by epidemiologists and demographers to assess epidemic trends and to project the demographic impact of the epidemic, by health economists to study the economic impact of HIV on various aspects of society, by social scientists to investigate the impact of behaviour and behaviour change on the epidemic, and by statisticians and mathematical modellers to develop new analytical techniques and to try to understand the dynamics of the epidemic. In addition, these data can be used to evaluate the population level impact of interventions and to provide guidance to policy makers for prioritising and targeting interventions.

Some of the existing, publicly available, prevalence datasets have been used as part of this thesis to perform secondary analysis and modelling to further our understanding of the epidemiology, dynamics and impact of HIV infection in South Africa. The data sources used in the thesis are described below.

Data sources

Antenatal clinic surveys

National, annual, anonymous, antenatal clinic surveys

The rise in the number of HIV infections among heterosexual, voluntary blood donors during 1988 and 1989 prompted the Department of National Health and Population Development to initiate, in 1990, a national HIV surveillance programme based on anonymous, unlinked, cross-sectional surveys of pregnant women attending antenatal clinics in the public health sector throughout South Africa.[23] Only women who were attending the antenatal clinic for the first time in their current pregnancy were included in order to minimize the chance of the same woman being included in the study more than once.

Pregnant women were chosen as a proxy group for monitoring the spread of HIV in the heterosexual population because they represent a consistent subgroup that is easily accessible and it is assumed that they reflect the course of the HIV epidemic in the heterosexually active population.[23,471] All pregnant women attending antenatal clinics in the public health services routinely provide blood samples to be tested for syphilis, rhesus factor (Rh) and ABO blood grouping in order to prevent haemolytic disease in the newborn. After removal of personal identifiers, these blood specimens are used for the annual HIV surveys.

Notwithstanding several biases inherent in this population, the national, annual antenatal clinic HIV surveys conducted during October and November of each year provide the most reliable estimates of temporal trends of HIV infection in the general population, as well as the age-specific HIV prevalence and geographical distribution of HIV infection in South Africa.

The ANC surveys have been designed to minimize bias by ensuring large sample sizes in all provinces, using a consistent methodology and ensuring that the surveys are done at the same time every year. The sampling strategy for these surveys is intended to provide a geographically representative sample which allows the estimation of provincial HIV prevalence. Prior to changes in the sampling methodology in 1998, samples of approximately 2000 specimens per province were collected annually.[23,472] Because the

populations of the provinces vary across South Africa, the sample sizes also varied and the overall estimate was obtained by weighting the data accordingly. In 1998, the standard national protocol was modified by the Department of Health in collaboration with the Medical Research Council. The study methodology was strengthened, especially in regard to sampling and quality control, systematic cluster sampling was used with "probability proportional to size" techniques.[118,473] Standard operating procedures were developed for provincial coordinators, clinic nursing staff and laboratories involved in the surveys.

Annual reports have been published by the Department of Health since 1990, providing summaries of the national and provincial HIV prevalence, and producing HIV prevalence by five year age bands. The data from these surveys have been used to monitor the progress of the HIV epidemic in the heterosexually active population in South Africa.

Antenatal clinic surveillance in rural KwaZulu-Natal

The Hlabisa health district, situated in rural northern KwaZulu-Natal, covers an area of approximately 50km by 70km and is home to about 200,000 largely Zulu-speaking people. Hlabisa has a large male migrant population and a relatively stable female population (Figure 4.1). In addition to migrant labour, most people rely on subsistence farming and pension remittances. The district has a well developed clinical service, including fifteen fixed primary health care clinics, a mobile service, and the Hlabisa rural hospital.[474]

Research has been conducted by the Medical Research Council in Hlabisa since the early 1990s. From 1992 to 2002, repeat cross-sectional, anonymous, antenatal surveys were undertaken among antenatal clinic attendees in Hlabisa by the South African Medical Research Council, in the same months as the national ANC surveys.[32,139] They provide comparative data from a rural area that are consistent with the temporal trends in HIV infection in KwaZulu-Natal as observed in the national survey.

Specialized community-based surveys

Hlabisa: a rural community-based study

Between 1992 and 2002, most of the Medical Research Council's (MRC) HIV and STD research were conducted in the Hlabisa district, as described above. With a research structure already in place and HIV rates reflecting the rapid growth of the HIV epidemic in

the KwaZulu-Natal province, the province with the highest HIV prevalence, Hlabisa was identified by local and international organizations as a potential site for conducting future HIV vaccine trials. In 2000 and 2001, a large community-based study, the Vaccine Preparedness Study (with the author of this thesis as the Principal Investigator), was conducted to determine the preparedness of the community to participate in phase I, II and III vaccine trials. In addition, baseline demographic and health data were collected to assess the overall health profile of the community, and blood samples using dried blood spots were collected from consenting individuals to obtain community-based estimates of HIV prevalence. Data were collected from a total of 595 men and 1719 women aged 15 to 54 years.

The age distribution for men (n = 89,440) and women (n = 106,749) in the Hlabisa population, using census data from Hlabisa, is shown in Figure 4.1. Men and women, but especially men, often leave to seek work outside the district so that the curve for men falls substantially below the curve for women between the ages of 20 and 30 years.

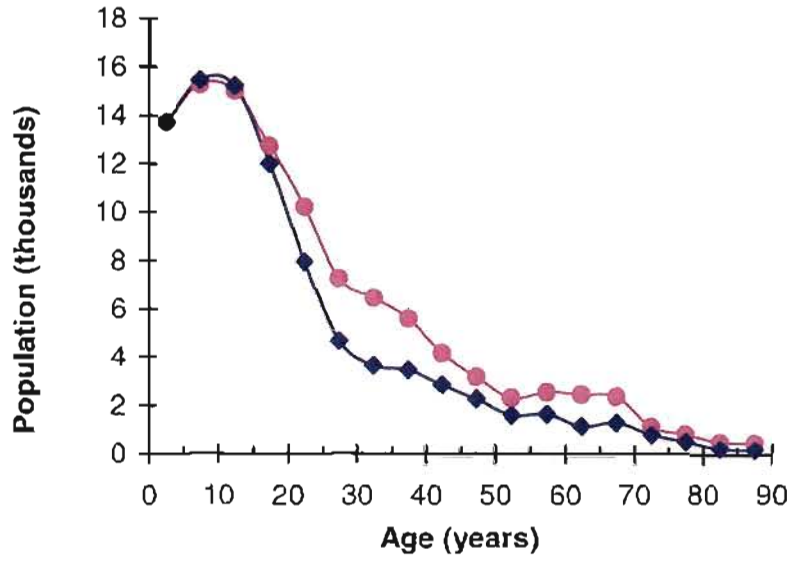


Figure 4.1 The age distribution of men (blue diamonds) and women (pink dots) in Hlabisa using census data

Early community-based surveys in rural KwaZulu-Natal

Three cross-sectional, anonymous, community based surveys were conducted in a rural area of northern KwaZulu-Natal in conjunction with the Malaria Control Programme between 1990-1992.[82] The purpose of these surveys was to determine the prevalence of

HIV infection and to monitor temporal trends of HIV in a predominantly rural population in the early stages of the epidemic. In addition, these surveys provide data on age and gender differences in HIV infection and are the only surveys in South Africa to provide population-based data for this early period of the HIV epidemic. The trends in HIV prevalence in these surveys are consistent with the provincial data from the national ANC surveys.[82]

Carletonville: an urban community-based study

The Carletonville Mothusimpilo ('Working-together-for-health') project was designed to demonstrate the feasibility of using sustainable interventions to reduce the transmission of HIV/AIDS in Carletonville, the largest gold-mining complex in the world.[222,310,475] In addition to the approximately 56,000 people living in the township of Khutsong, there are 70,000 migrant mineworkers living in single sex hostels without their wives or families who frequently visit sex workers operating in informal settlements in townships around the mines. The Mothusimpilo project was designed as a community based intervention with a strong biomedical and social evaluation component which would make it possible to identify and explore the contextual factors that influence the course of the epidemic and which can be used as markers of the effectiveness of the intervention. The intervention included community-based peer education, condom distribution, syndromic management of sexually transmitted infections and presumptive treatment for sex workers. A baseline survey was carried out in the general population in August 1998 while a follow-up survey was conducted in August 1999. The 1998 survey included a random sample of 1,185 men and women aged 13 to 59 years in the township of Khutsong, 899 mineworkers stratified by hostels, and 145 sex workers living in informal settlements or 'hotspots'. The 1999 survey in the Khutsong sample was limited to those aged 15 to 25 years to obtain more detailed information about this important risk group.[222] Information was collected on HIV and STI prevalence as well as on a range of social and behavioural determinants.

In addition to the published data, individual level data on HIV prevalence from the 1998 survey was made available by the Mothusimpilo project director, Prof B Williams, for inclusion in the analyses and modelling in this thesis.

National population based surveys to measure HIV prevalence

HSRC/ Nelson Mandela Foundation population-based surveys

In 2002, the Nelson Mandela Foundation in conjunction with the HSRC undertook the first national population-based survey on behavioural and socio-cultural determinants of vulnerability to HIV/AIDS and consenting people were tested for HIV infection.[469] The study provides data on HIV prevalence by geographic area, race, gender, age and other demographic and socio-economic factors.

The survey was repeated in 2005 and a total of 15,851 people older than 2 years of age were tested for HIV.[470] While oral fluids were used to test for HIV in 2002, the 2005 survey used dried blood spots for HIV testing. Bias is of particular concern in these surveys because of the very high level of household and individual non-response (about 35% in both surveys). The 2005 survey included HIV incidence testing using the BED capture enzyme immunoassay (EIA) developed by Centres for Disease Control and Prevention (CDC). However, at the time of this survey the BED assay still required further validation and calibration and data from several countries in 2005 suggested that the BED assays over-estimated incidence by a factor of 2 to 3. (Statement on BED available on the UNAIDS website.[476])

Other studies

Sex workers and clients at truck-stops in KwaZulu-Natal

The MRC has undertaken research with sex workers operating at truck-stops in the KwaZulu-Natal Midlands since the early 1990s.[477] Between 1996 and 1998, data were collected from commercial sex workers operating at truck-stops along the national road linking Durban to Johannesburg. At the time, there were an estimated 800 sex workers operating at the truck stops in the KwaZulu-Natal Midlands. Four hundred and seventy seven women were screened for HIV as a prerequisite for participation in a phase III multi-centre microbicide trial.[282,478] Of these, 198 HIV negative women were enrolled in the trial and followed up for an average of about three years to assess the effect of the microbicide (a nonoxynol-9 vaginal gel) on rates of HIV sero-incidence. To date, this has been the only cohort study in South Africa to obtain direct estimates of HIV incidence.[282] Clinical investigations were performed to identify sexually transmitted diseases and HIV status.

In 1998 a cross-sectional HIV seroprevalence study was undertaken with truck driver clients of sex workers at these truck-stops in order to compare the prevalence of HIV in sex workers and their clients. Ten sex workers were trained as field workers to collect socio-demographic data from their truck driver clients and to obtain a saliva sample to determine the HIV status of their clients.[331]

Workplace survey

Additional data on HIV infection in men and women by age, race and job category are available from an anonymous cross-sectional survey carried out among the workforce of a major South African parastatal company in 1999 in order to estimate the proportion of employees that were infected with HIV and to determine risk factors for HIV infection.[479,480] Of all of the sites in the country with more than one hundred employees, fifty percent were chosen for inclusion in the study using probability-proportional-to-size sampling. A set number of employees was then recruited at each site. The results of this study were used to make projections on future HIV prevalence levels, to estimate the economic and other impacts of HIV on the company and to provide a baseline against which to evaluate the company's HIV/AIDS programme. This study provided information on overall HIV levels among men and women from all the provinces in South Africa.

Discussion

The data sets described above are used in several of the chapters in this thesis. The ANC surveillance provides samples that are consistent over time so that good estimates of trends can be obtained. They also provide good overall national coverage, and provide estimates by age and geographical region. However, the use of these data sets is limited because the clinic and individual level data are not made publicly available. Only certain, limited analyses are published in official reports of the Department of Health. For example, the age distribution is given in bands of 5 years for the national sample but not by province, while infection rates by race group are generally not made available. The geographical distribution of HIV consists of a breakdown by province and no finer detail is provided on the spatial distribution of HIV within provinces (for example at district or clinic level), nor between urban and rural areas.

The specialized community-based surveys provide good coverage of the general population, including men, and provide detailed information on demographic factors (e.g., HIV prevalence can be obtained by one-year age categories for both genders), on social and economic factors, sexual behaviour and biomedical factors associated with HIV. The community-based studies described here covered a rural area in KwaZulu-Natal and an urban area in Gauteng.

Data sets on high risk groups, including sex workers in KwaZulu-Natal and in Carletonville, truck drivers operating between Durban and Johannesburg, and mine workers in Carletonville, are studied in this thesis to determine if the patterns of infection are different to those of men and women in the general adult population.

Together, these data sets can provide a clear picture of overall trends, and are used here to study the dynamics and the impact of the HIV epidemic in South Africa. Using the prevalence data collected over time and the age-specific distribution of infection, models are developed to estimate the incidence, to make projections about AIDS deaths and to assess the potential impact of antiretroviral treatment on the future course of the epidemic.

CHAPTER 5 Trends in the prevalence of HIV infection in South Africa

"What is not surrounded by uncertainty cannot be the truth."

Richard Feynman, 1976[481]

Introduction

This chapter explores the burden of HIV infection in particular populations at specific points in time as well as trends of infection over time. Using the data sources described in Chapter 4, the HIV epidemic in South Africa is analysed and described in relation to key events in the spread of HIV in South Africa from the first reported cases of HIV subtype B infections among men having sex with men in the early 1980s, haemophiliacs, and recipients of unscreened blood products to the current generalized, subtype C epidemic among the heterosexual population where the prevalence of HIV infection is starting to level off although morbidity and mortality are still increasing. Distinctive characteristics of the South African HIV epidemic are described ranging from the rapid spread of HIV infection, to differences in gender, age and geographic area. Risk factors contributing to the spread of the epidemic are discussed and the chapter concludes by describing the effect of HIV on morbidity and patterns of mortality.

Fundamental measures of the HIV epidemic

As the epidemic of HIV infection continues to grow in South Africa, it is important to understand the basic dynamics of the epidemic in order to deal with it effectively. It is necessary to know not only how much disease there is in a population at any time but also how the burden of infection and disease is changing with time. The two most fundamental measures of disease, in this regard, are prevalence and incidence.

Prevalence of HIV infection is defined as the proportion of individuals in the population who are infected with the virus at a given point in time (hence provides a measure of the cumulative risk of infection up to a cerain point in time), while the incidence of infection gives the rate at which *new* cases of infection are acquired during a given period of time. Definitions are provided in Figure 5.1.

Prevalence provides a snapshot view of the number of people currently infected with HIV and this is essential for understanding the health impact of a disease within a community, for assessing the demand for medical care, and for targeting and evaluating interventions, mainly for care and treatment. In contrast, incidence data provide information on current rates of new infections among individuals who were previously uninfected. Incidence data are therefore more sensitive than prevalence data to the current dynamics of disease transmission and are important for exploring causal theories concerning the course of the disease as well as for measuring the immediate or short-term impact of interventions.

In this and the following chapters, measures of both prevalence and incidence will be used to describe trends and characteristics of the HIV epidemic in South Africa. Where possible, 95% confidence intervals are calculated to indicate the range of values within which the population values are likely to fall. For prevalence estimates, these are based either on the binomial distribution or, in the case of large enough prevalence and sample size, the normal approximation to the binomial distribution.[a] In this chapter however, the focus is on HIV prevalence.

$$\text{Prevalence} = \frac{\textit{Number of individuals who are infected with HIV at a specific time}}{\textit{Number of individuals in the population at that point in time}}$$

$$\text{Incidence rate} = \frac{\textit{Number of new cases of HIV infection during a certain time period}}{\textit{Number of uninfected individuals in the population} \times \textit{time period of observation}}$$

Figure 5.1 Definition of prevalence and incidence rate

[a] The binomial theorem gives the probability of getting k successes out of n trials if the expected value is u as

$$P(k,n|u) = \frac{n!}{k!(n-k)!}u^k(1-u)^{n-k}$$

For given values of k and n the upper confidence bound on u is estimated as the value for which one would observe k or fewer success with probability 0.025 and use a similar argument to obtain the lower bound. If k and n are both sufficiently large, the 95% confidence interval can be estimated from the normal approximation to the binomial distribution as

$$p \pm 1.96\sqrt{\frac{p(1-p)}{n}}$$

The HIV epidemic in time and space

The first cases of AIDS in South Africa were diagnosed in 1982.[15] Up to 1987, the spread of HIV in South Africa occurred mainly among men who have sex with men and haemophiliacs receiving blood products (i.e., before the introduction of universal HIV-screening of blood products in 1985). Several surveys conducted between 1985 and 1987 in a diverse range of populations demonstrated that until 1987 HIV infection in the heterosexual population was rare[19,20] and zero prevalence was found in a rural community in 1985, among sex workers in the Transvaal in 1986 and among antenatal clinic attendees in KwaZulu-Natal in 1987. In a study conducted among 29,312 mine workers in South Africa in 1986, only 3 men tested positive for HIV infection.[389]

By 1989 however, several surveys had confirmed the entry of HIV infection in the general population,[16,39,51,52] and despite this relatively late introduction of the virus into the heterosexual population, South Africa experienced one of the fastest growing HIV epidemics in the world. Over a 14-year period from 1990 to 2004, HIV sero-prevalence (predominantly of subtype C) among antenatal clinic attendees in South Africa increased dramatically from 0.8% to 29.5%, as illustrated in Figure 3.2 (Chapter 3). The high infection rates in pregnant women also gave rise to a concomitant epidemic in the children born to HIV infected mothers.

In the early stages of the generalized heterosexual, subtype C epidemic, the prevalence rose exponentially with a doubling time of a little over one year and by 1994 had reached 10% among women attending ANCs.[141] Between 1994 and 1997 the prevalence of infection continued to rise rapidly,[118] with young women being at greatest risk of infection. Because of the long survival time for people infected with HIV (estimated median survival time of about 9 years)[450] and because the prevalence had increased so dramatically in only four or five years, morbidity and mortality remained low during this time.

Since the late 1990's, the rate of increase has slowed substantially and the overall HIV prevalence in the country as well as the age-specific and provincial data (Table 5.1) suggest that the prevalence is starting to level off. It is important to note, however, that the estimate based on the 2004 antenatal clinic surveillance was significantly above the fitted

logistic curve, suggesting that prevalence might still be increasing. More importantly is that while the prevalence may be increasing less rapidly, new infections are still arising but are more or less balanced by the increased mortality.

Table 5.1 HIV prevalence (%) among antenatal clinic attendees by province: 1990 to 2004

	Province									
Year	WC	EC	NC	FS	KZN	MP	LM	GT	NW	National
1990	0.06	0.44	0.20	0.59	1.61	0.38	0.26	0.66	1.05	0.73
1991	0.08	0.58	0.12	1.50	2.86	1.21	0.48	1.12	6.54	1.74
1992	0.25	0.96	0.65	2.86	4.50	2.23	1.05	2.53	0.94	2.15
1993	0.56	1.94	1.07	4.12	9.53	2.40	1.79	4.13	2.19	4.01
1994	1.16	4.52	1.81	9.19	14.35	12.16	3.04	6.44	6.71	7.57
1995	1.66	6.00	5.34	11.03	18.23	16.18	4.89	12.03	8.30	10.44
1996	3.09	8.10	6.47	17.49	19.90	15.77	7.96	15.49	25.13	14.17
1997	6.30	12.60	8.60	20.00	26.90	22.60	8.20	17.10	18.10	17.04
1998	5.20	15.90	9.90	22.80	32.50	30.00	11.50	22.50	21.30	22.80
1999	7.10	18.00	10.10	27.90	32.50	23.80	11.40	23.80	23.00	22.40
2000	8.70	20.20	11.20	27.90	36.20	29.70	13.20	29.40	22.90	24.50
2001	8.60	21.70	15.90	30.10	33.50	29.20	14.50	29.80	25.20	24.80
2002	12.40	23.60	15.10	28.80	36.50	28.60	15.60	31.60	26.20	26.50
2003	13.10	27.10	16.70	30.10	37.50	32.60	17.50	29.60	29.90	27.90
2004	15.40	28.00	17.60	29.50	40.70	30.80	19.30	33.10	26.70	29.50

Geographical distribution

There is considerable geographical variation in the distribution of HIV infection in South Africa with highest infection rates in KwaZulu-Natal on the east coast and the lowest in the Western and Northern Cape (Table 5.1 and Figure 5.2a). Between 1990 and 2004 the antenatal HIV prevalence increased from 1.6% to 41% in KwaZulu-Natal and 0.06% to 15.4% in the Western Cape.

One explanation for the wide variation in the geographical distribution of HIV infection is the uneven population distribution.[482] The distribution of people infected with HIV obtained by combining the provincial prevalence data with the population density is illustrated in Figure 5.2b. Although the Western Cape has low rates of infection, Cape Town has a large population and thus a high density of people infected with HIV. In contrast, while the overall infection rates in KwaZulu-Natal are high, the population is

patchily distributed and infections do not occur evenly through the province. In the former Transkei, to the north-east of East London, infected people are more evenly spread over a large area. The mining centres at Carletonville, Klerksdorp and Welkom show high densities of infected people as do the port cities of Port Elizabeth, Cape Town, East London and Durban and the major industrial and commercial centre of Johannesburg.

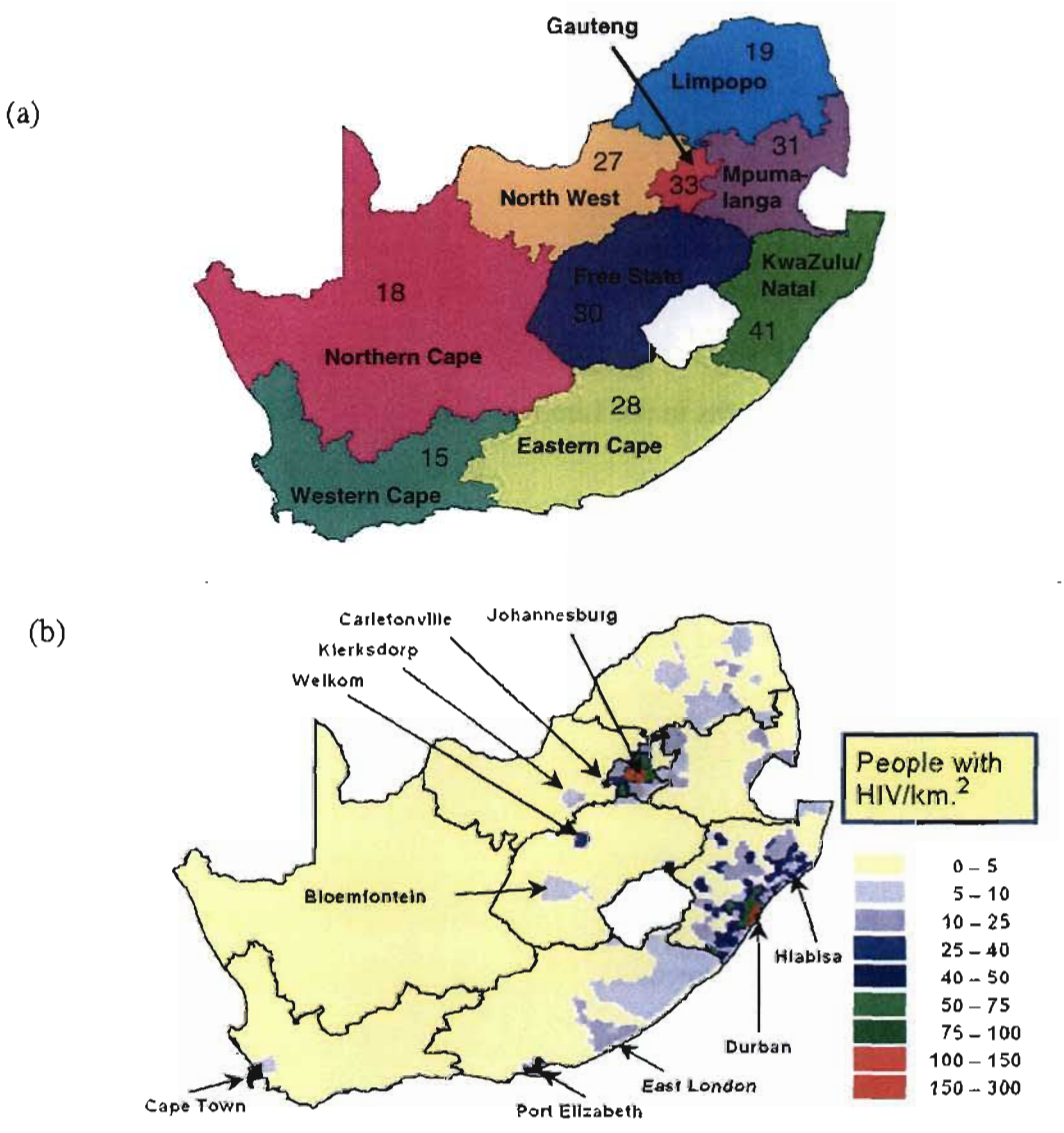


Figure 5.2 (a) Prevalence (%) of HIV infection among women attending antenatal clinics in the provinces of South Africa in 2004 (b) The number of people living with HIV infection per square kilometre

To estimate the asymptotic value (i.e., the value at which the epidemic is expected to level off) and the initial growth rate of the epidemic, logistic functions of the form described in Box 3.2 were fitted to the prevalence data from all provinces and the estimates obtained in this way are shown in Figure 5.3. Assuming exponential growth rate at the start of the epidemic, the initial doubling time was estimated nationally and for each of the provinces from the estimates of the initial growth rate, using

$$\textit{Doubling time}\ (\text{months}) = \frac{\ln(2)}{\textit{initial annual growth rate}} \times 12$$

While the overall doubling time at the start of the epidemic in South Africa was estimated to be around 15.6 months (95% CI 15.2 –16.1 months), the doubling time at provincial level varied from 10.5 months in the Limpopo province to 15.2 months in KwaZulu-Natal (Table 5.2).

Table 5.2 shows that the observed prevalence of HIV in 2004 in most provinces is close to the estimated asymptote and the observed prevalence in 2004 falls within the 95% confidence intervals of the asymptotic value for seven of the nine provinces, but with much higher rates in KwaZulu-Natal than elsewhere. The prevalence in the Western Cape is therefore likely to remain significantly below the current levels in the Eastern Cape and the levels there below that in KwaZulu-Natal. The asymptote for two of the nine provinces (Limpopo, and KwaZulu-Natal) were significantly higher than the estimated asymptotic value, indicating that the growth in 2004 was significantly greater than the expected estimate derived from the trend data.

Plotting the intrinsic doubling time against the asymptotic prevalence for the nine provinces in Table 5.2 shows that there was no significant correlation ($r = 0.43$, $p = 0.213$) so that asymptotic prevalence in a province cannot easily be predicted from the epidemic growth rate (Figure 5.4).

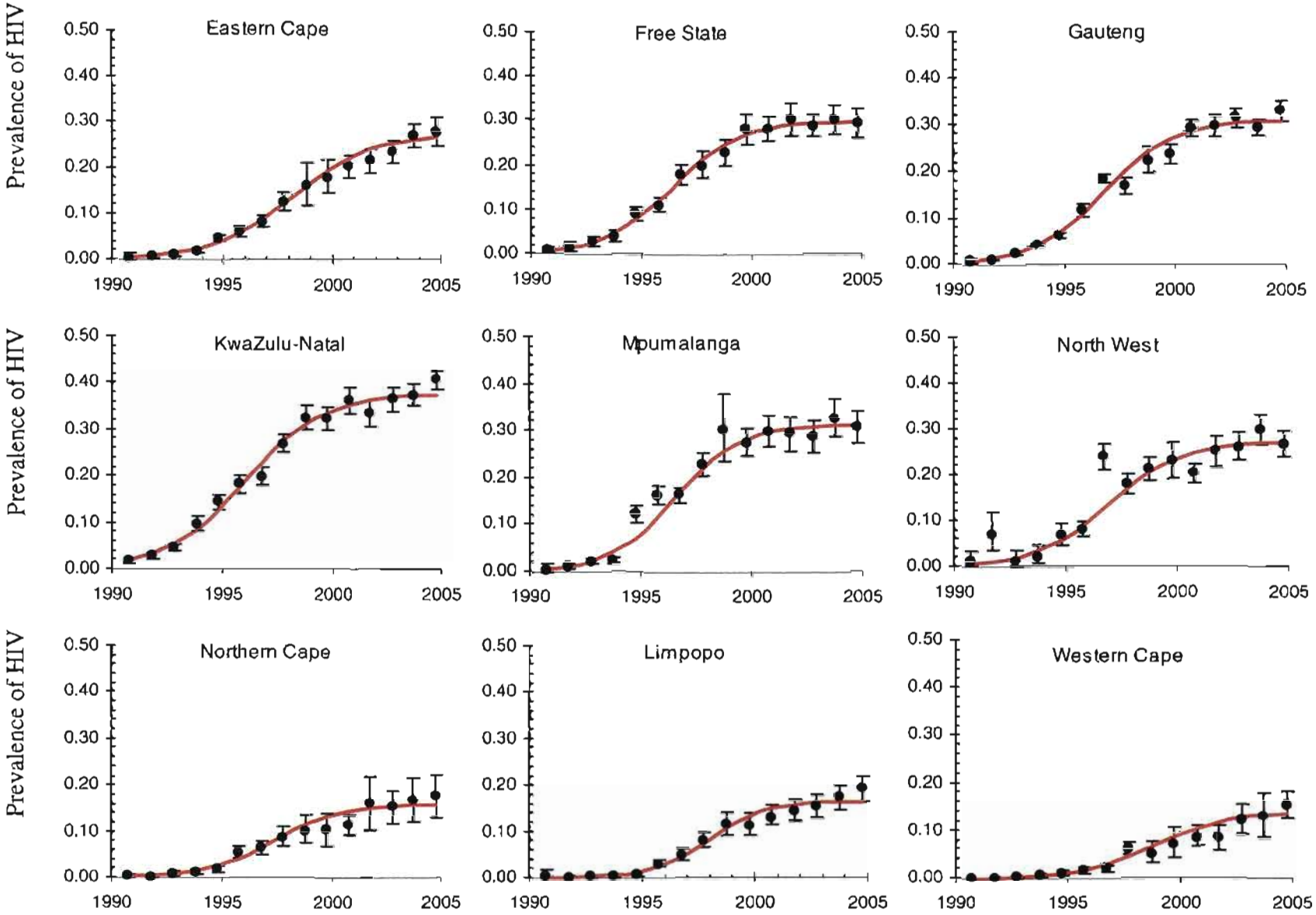


Figure 5.3 Observed HIV prevalence collected over time from antenatal clinics by province, plotted with 95% confidence intervals. Epidemic curves, assuming a logistic function, was fitted to data from each province.

Table 5.2 The 2004 HIV prevalence, the expected maximum (asymptotic) HIV prevalence estimated from logistic regression, and doubling times at the start of the epidemic (with 95% confidence interval) for data collected from antenatal clinic attendees by province.

Province	Prevalence (%) (95% CI)		Doubling Time (months)
	Prevalence (2004)	Asymptote*	
Western Cape (WC)	15.4 (12.5–18.2)	14.3 (13.0–15.6)	13.6 (11.8–16.2)
Eastern Cape (EC)	28.0 (25.0–31.0)	27.2 (25.5–28.9)	14.7 (13.5–16.3)
Northern Cape (NC)	17.6 (13.0–22.2)	15.7 (13.7–17.7)	12.6 (10.5–15.8)
Free State (FS)	29.5 (26.1–32.9)	29.8 (28.0–31.6)	13.1 (11.8–14.8)
KwaZulu-Natal (KN)	40.7 (38.8–42.7)	38.7 (37.6–39.8)	15.2 (14.2–16.4)
Mpumalanga (MP)	30.8 (27.4–34.2)	30.2 (28.7–31.7)	11.0 (10.1–12.2)
Limpopo (LM)	19.3 (16.8–21.9)	16.7 (15.6–17.8)	10.5 (9.4–12.0)
Gauteng (GT)	33.1 (31.0–35.3)	31.3 (30.1–32.5)	13.3 (12.3–14.4)
North-West (NW)	26.7 (23.9–29.6)	26.8 (25.1–28.5)	13.5 (11.6–16.3)
National	29.5 (28.5–30.5)	28.3 (27.7–28.9)	15.6 (15.2–16.1)

* The expected maximum prevalence (asymptote) is the prevalence at which the HIV epidemic is expected to level off in each province and is estimated by fitting a logistic curve to trend data with a variable asymptote using a weighted least squares fit.

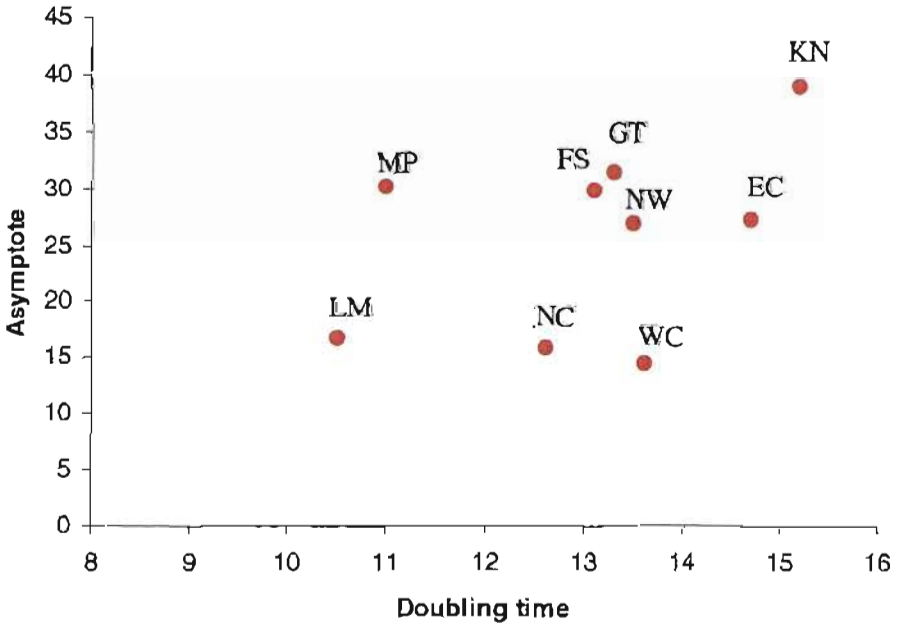


Figure 5.4 The asymptotic prevalence of the epidemic plotted against the initial doubling time (in months) by province

Age differences in HIV prevalence

Estimates of the prevalence of HIV by age in 1998 for national antenatal clinic attendees, two sentinel sites and selected risk groups in South Africa are summarized in Table 5.3. The age specific prevalence of HIV infection generally follows a log-normal distribution, as described in Chapter 3 and illustrated in Figure 5.5 using the data from antenatal clinic attendees in Hlabisa. The prevalence is close to zero among girls younger than 15 years and as people become sexually active, increases rapidly with age to a peak among 20-24 year old women, after which it declines slowly with age among older women.

In 1998, the national antenatal clinic surveillance data showed that 26.1% of women in the age group 20 to 24 years were infected with HIV, compared to a prevalence of 10.5% among women 40 years and older. In Hlabisa and Carletonville, 39.3% and 53.8% of 20-24 year old women, respectively, were infected in 1998, compared to 12.3% and 23.5%, of 40-44 year old women, respectively (Table 5.3).

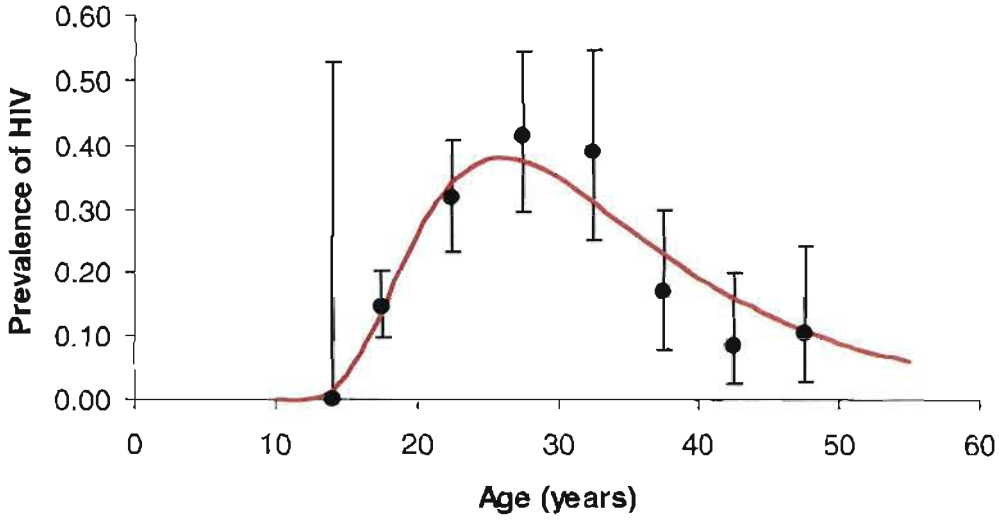


Figure 5.5 Age prevalence of HIV infection among women attending antenatal clinics in Hlabisa in 1998. Error bars are 95% confidence limits. The fitted curve is a log-normal function.

Table 5.3 Age-specific prevalence of HIV in various groups surveyed in South Africa in 1998. Numbers and percentages are shown in five year age groups for men and women.

Age (years)	Women										Men					
	National ANC		Hlabisa ANC		Carletonville Population		KZN* truck stops; sex workers		Carletonville Sex workers		Carletonville Population		KZN* truck drivers		Carletonville mine workers	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<15			7	0	30	0.0					31	0.0				
15 – 19	874	21.0	819	21.1	101	20.8	31	38.7			99	2.0				
20 – 24	1852	26.1	994	39.3	119	53.8	56	58.9			89	16.9	23	47.8	82	29.3
25 – 29	1634	26.9	608	36.4	117	58.1	41	68.3	14	92.9	59	42.4	61	50.8	167	28.1
30 – 34	1484	19.1	398	23.4	105	46.7	41	70.7	34	67.6	49	42.9	56	57.1	191	28.3
35 – 39	921	13.4	265	23.0	93	33.3	11	45.5	26	69.2	60	36.7	58	50.0	196	31.6
40 – 44	271	10.5	57	12.3	68	23.5	2	0.0	25	52.0	42	31.0	43	60.5	129	27.9
45 – 49	37	10.2	15	13.3	30	20.0	4	50.0	11	81.8	35	14.3	44	65.9	83	28.9
50 – 54			3	33.3	27	14.8			5	60.0	20	10.0	22	59.1	38	23.7
55 – 59											15	13.3			11	9.1

* KwaZulu-Natal

The age-specific HIV prevalence data nationally (Table 5.4) and from Hlabisa (Table 5.5) show the rapid increase in infection over time from 1992 - 2001 among all age groups and highlight the alarmingly high rate of increase among women under the age of 30 years.

In Hlabisa, the prevalence of HIV among 20-24 year old women increased from 6.9% in 1992, to 21.1% in 1995, 39.3% in 1998 and 50.8% in 2001 (Table 5.5). The rapid increase in prevalence in young women has been a major cause for concern.

Figure 5.6 shows that although prevalence increased dramatically over time the shape of the antenatal HIV age prevalence curves, fitted to a log-normal function, has remained much the same over a period of nine years, with peak prevalences among pregnant women occurring at around 24 years. In 1992, prevalence among pregnant women peaked at 3.7% at age 24.4 years, in 1995 it peaked at 14.2% among women aged 23.7 years, in 1998 it peaked at 27.7% among women aged 23.4 years, and in 2001 it peaked at 30.5% among women aged 24.3 years old.

Table 5.4 Temporal trends in the age-specific HIV prevalence (%) among women attending antenatal clinics in the annual national survey. Prevalence is presented as a percentage with 95% confidence intervals.

Age	1992	1995	1998	2001
15-19	2.4 (1.6–3.3)	10.3 (8.8–11.8)	21.0 (18.4–23.8)	15.4 (13.8–16.9)
20-24	3.5 (2.8–4.3)	14.3 (12.9–15.7)	26.1 (24.1–28.1)	28.4 (26.5–30.2)
25-29	1.8 (1.2–2.4)	12.1 (10.7–13.6)	26.9 (24.7–29.0)	31.4 (29.5–33.3)
30–34	1.8 (1.0–2.7)	9.1 (7.7–10.7)	19.1 (17.1–21.1)	25.6 (23.5–27.7)
35–39	1.6 (0.5–2.8)	6.7 (5.1–8.6)	13.4 (11.2–15.6)	19.3 (17.0–21.5)
40–44	0.1 (0–0.3)	4.5 (2.5–7.8)	10.5 (6.8–14.1)	9.1 (6.2–11.9)
45–49	0 (0–4.9)	2.5 (0.6–13.1)	10.2 (0.4–20.0)	17.8 (4.3–31.4)

Table 5.5 Temporal trends in the age-specific HIV prevalence (%) among women attending antenatal clinics in Hlabisa, northern KwaZulu-Natal.

Age group	1992	1995	1998	2001
20-24	6.9	21.1	39.3	50.8
25-29	2.7	18.8	36.4	47.2
30-34	1.4	15.0	23.4	38.4
35-39	0.0	3.4	23.0	36.4

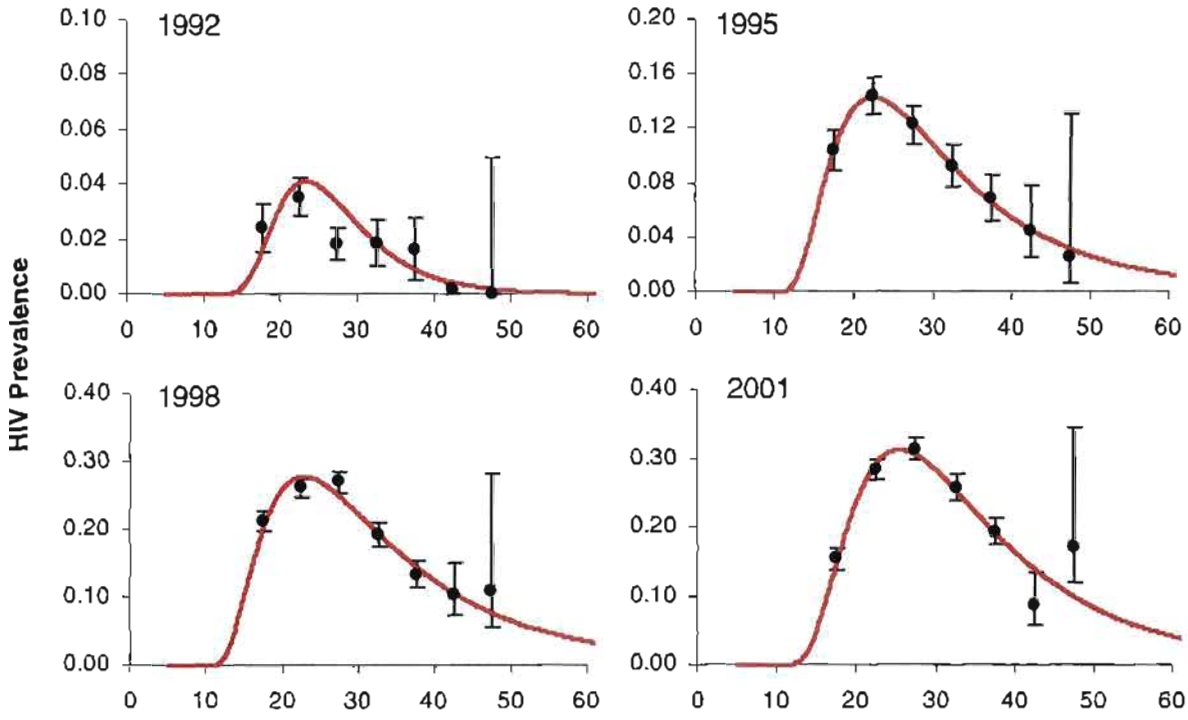


Figure 5.6 Age-prevalence curves showing temporal trends of the HIV epidemic among women attending national antenatal clinics.

Age and gender differences

Population-based surveys undertaken in rural KwaZulu-Natal during 1990-1992 showed that in addition to the rapid rise in HIV infection, there was a striking difference in the age distribution of HIV infection among men and women. Figure 5.7a illustrates the early rise of infection in young women between the ages of 15-19 years compared to the later rise of infection in men to a peak in the age group 25-29 years.

In Carletonville in 1998, the prevalence of infection was close to zero for both sexes before the age of 15 years but increased rapidly thereafter reaching 39.3% in 20-year old women but only 8.3% in 20-year old men (Figure 5.7b). The peak prevalence among women was 57.9% at 25 years of age and among men it peaked at 44.5% at 32 years of age. The median age at first sex was about 16 years for both men and women in Carletonville and the prevalence of infection increases rapidly thereafter.

The difference between the age-specific prevalence of infection in men and women is in part related to the age difference of sexual partners. Young women in South Africa often have male partners who are older than they are, which explains the shift to older ages of

infection in men compared to women (women have sex with men who are on average five years older than themselves). In addition, it has been shown in a systematic review of HIV-1 transmission probabilities that male-to-female transmission is on average higher (median 0.1% per sexual contact) than female-to-male transmission (median 0.07% per contact).[483] Factors that have explained the higher risk of infection among women compared to men in other African settings include the increased vulnerability of women around the age of puberty, rape and coercive sex, and dry sex.[484]

The age-specific prevalence of infection for rural men and women in KwaZulu-Natal in 1991 and for urban men and women in Carletonville in 1998, as illustrated in Figure 5.7, show that while there are important gender differences between men and women the shapes of the age-prevalence curves, reflecting the age-specific risk of infection, have not changed over time and are similar in urban and rural settings. Although the overall prevalence in the later urban survey is approximately ten times higher than in the earlier rural survey the shape of the age-prevalence curves for men and women are statistically the same. The national population-based survey carried out by the HSRC in 2005 show data that are consistent with the earlier observations on gender and age differences in HIV infection (Figure 5.8).[470]

The patterns of infection are investigated in more detail in Chapter 6, including an analysis of data on the age-specific prevalence of infection among men and women in urban and rural areas and among migrant men.

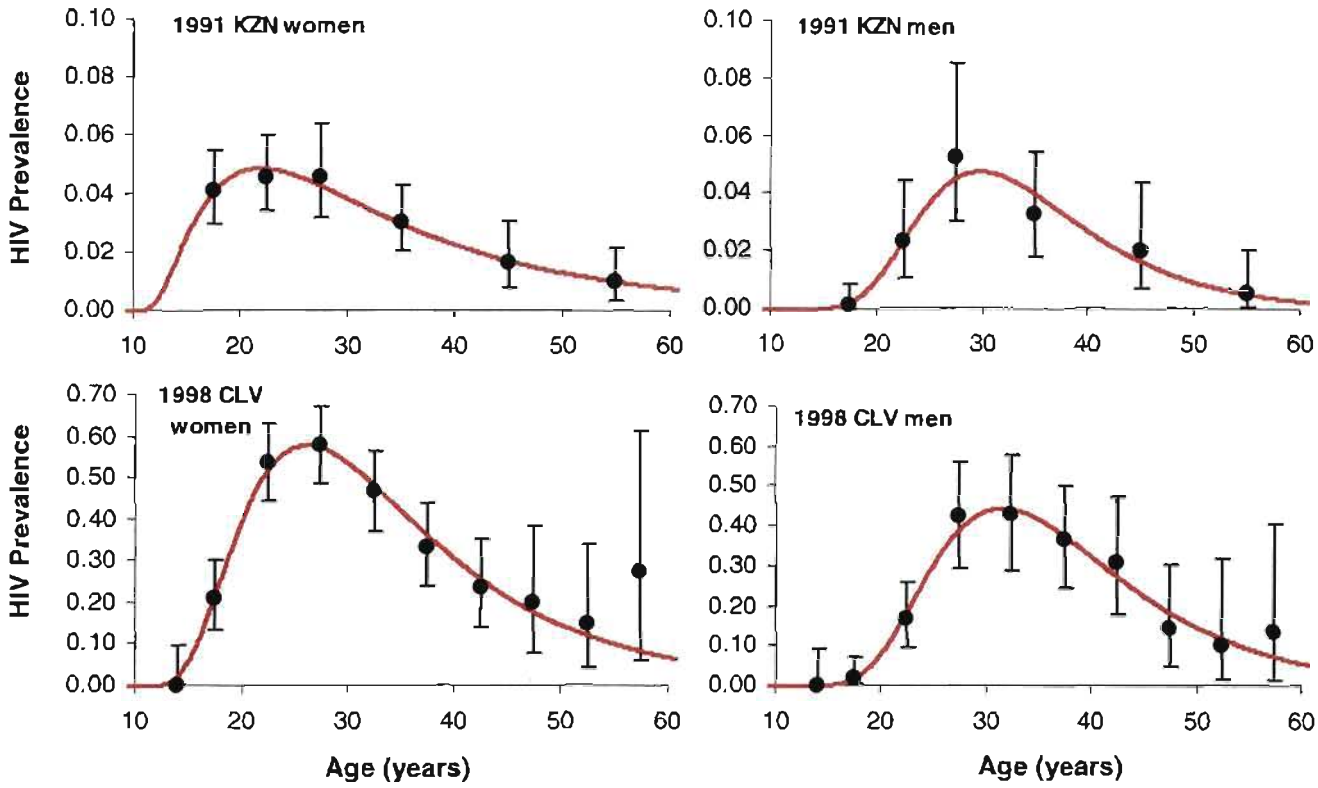


Figure 5.7 Age prevalence of HIV infection among men and women in a) Rural KwaZulu-Natal (KZN) in 1991 and b) Carletonville (CLV) in 1998.

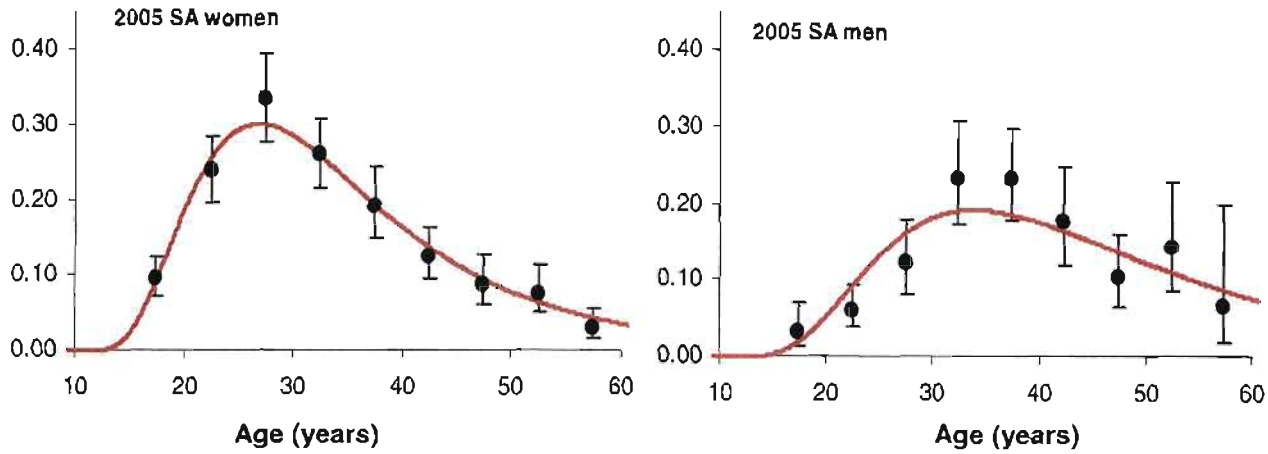


Figure 5.8 National prevalence of HIV by sex and age in 2005. Log-normal curves were fitted to data from the 2005 HSRC national population based survey.[470]

Racial differences

As in most countries, collection of data by race is politically sensitive, and few estimates are available on the racial distribution of HIV in South Africa. The majority of users of public sector health facilities in South Africa are Black Africans except in the Western Cape where the number of Black and Coloured women attending antenatal clinics are about equal. Most of the data collected from public sector facilities (including antenatal clinics) are therefore from Black women or, in the Western Cape, Black and Coloured women. Some data on the prevalence of HIV infection by race are available from early antenatal clinic surveillance (1991-1992),[23] from the recent national population-based surveys conducted by the HSRC (2002 and 2005),[469,470] and from the Lovelife survey of sexual behaviour and HIV among a national sample of almost 12,000 young people, aged 15 to 24 years in 2003.[485] In addition, HIV data are available from a large workplace survey in which specimens were collected in 1999 for HIV testing from more than 5000 workers in 175 sites across the nine provinces in South Africa.[480] These data are summarized in Table 5.6 and show that while HIV infection is prevalent in all race groups, the prevalence is significantly higher in the Black African population.

Table 5.6 HIV prevalence by race in South Africa, 1991-2005

	HIV prevalence (%) at national level with 95% confidence intervals				
Race group	ANC (1991) Pregnant women	ANC (1992) Pregnant women	Workplace (1999) Men and women	Lovelife survey (2003) Men and women aged 15-24 years	HSRC Survey (2005) Adult men and women (15-49)
African	1.84 (1.49-2.18)	3.22 (2.74-3.70)	13.9 (12.6-17.2)	11.8 (10.7-13.1)	19.9 (18.2-21.7)
White	0 (0-0.22)	0.09 (0-0.22)	2.1 (1.4-6.7)	2.0 (0.09-4.3)	0.5 (0.1-1.7)
Coloured	0.14 (0.02-0.26)	0.33 (0.12-0.54)	2.3 (0.8-12.2)	3.8 (2.7-5.5)	3.2 (2.1-4.5)
Indian	0.11 (0-0.31)	0.33 (0-0.7)	3.6 (0.9-17.3)	0.9 (0.2-3.6)	1.0 (0.2-2.3)

Using antenatal clinic data to obtain estimates of HIV in the general adult population

In addition to using the ANC data to determine epidemic trends over time and to analyse the geographic and age-specific distribution of the epidemic, this data can be used to obtain estimates of HIV prevalence among the general adult population in South Africa.

However, ANC data are biased estimators of the general adult population prevalence because the samples include only a select group of people (pregnant women attending public health services). HIV prevalence among women who attend public health services is generally estimated to be higher than prevalence among those who attend private health services. Furthermore, the distribution of HIV prevalence among pregnant women is likely to be different than the distribution among the general adult population. In order to correct for these biases the ANC prevalence estimates need to be adjusted. One way to do that is to firstly adjust for relative attendance rates at antenatal clinics and secondly to adjust for the difference in prevalence between pregnant women and the general adult population. Using this approach, the estimated adjustment factor is 0.64, as described in Appendix 5.1. The HIV prevalence among the general adult population can then be estimated by applying the correction factor to the ANC prevalence estimate, for example, for 2004 the estimated adult prevalence in South Africa is 29.5% ×0.64 = 18.9%.

Risk factors

Migration

One of the most important driving forces of the HIV epidemic in Southern Africa is the system of oscillating migration which increases people's risk of infection and when they become infected facilitates the rapid spread of the epidemic. "Influx control" laws during the apartheid era only allowed single, able-bodied people (mainly men) to migrate to the urban areas to sell their labour. Male migrants from other southern African countries also came to work in South Africa and in 1990 it was estimated that 2.5 million official - and many more unofficial - migrants were working in South Africa's mines, factories and on farms.[486] The migrant labour system has survived despite the change in Government in South Africa and as late as 1997 a study in rural KwaZulu-Natal found that 60% of adult men and 28% of women were away from their homes for most of the time.[246]

Migrant workers in southern Africa typically travel great distances to their places of work and return home infrequently, sometimes as seldom as once or twice a year. While away from home, these workers often live in single sex hostels. In a survey conducted in the early 1970s, Francis Wilson summarized the migrant/hostel system as leading to: "family break-ups, bigamy, prostitution, homosexuality, alcoholism, violence, corruption, venereal disease, tuberculosis and malnutrition".[487] This lifestyle results in men having more casual

partners[488] and more frequently visiting prostitutes.[489] Several studies have reported on the sexual practices of migrants and demonstrated that they are at significantly higher risk than non-migrants of having more sexual partners[490] and having an increased risk of acquiring sexually transmitted infections and/or HIV.[82,491,492] While many migrant workers visit sex workers in urban areas, they also maintain conjugal relationships in their rural home areas and can thereby contribute to the rapid geographical spread of the HIV epidemic.

A study in rural KwaZulu-Natal however,[330] highlighted the fact that it is not only the migrant men who are at risk of HIV but also the women that are left behind This study found that in 40% of discordant couples it was the wifes of migrant men who were HIV infected which indicates that these women must be having sex with men other than their husbands.

A risk factor analysis among women in Carletonville showed that migration, in addition to age, marital status, alcohol use, syphilis and gonorrhoea, were independently associated with HIV infection.[328] HIV prevalence was significantly higher among migrant women (46%) than non-migrant women (35%) (Odds ratio 1.61, 95% confidence intervals (CI): 1.1-2.3).

Often in disadvantaged areas women are pushed towards selling or exchanging sex for food and support as this is the only commodity that they have to sell in order to survive.[493] The practice of 'survival sex' increases the total number of partners that a women has as well as the probability of having concurrent partners, i.e., having more than one partner at the same time.

Migrancy almost certainly contributes to the spread of HIV prevalence by the nature of the sexual networking that it promotes. Although men in Africa may not have more total lifetime partners than men from other parts of the world, the impacts of a migrant lifestyle result in the tendency to have more concurrent partners. Concurrency, which increases the number of individuals linked to the sexual network at any one time, has been shown to potentially increase the size of the epidemic by a factor of 10 over a five year period if 50% of individuals have concurrent relationships as opposed to sequential but monogamous relationships.[494] Also, HIV infected people may be more infectious in the very early stages of their infection and in the terminal stages. Therefore, an individual who

becomes infected from a sexual contact and who has a concurrent partner is more likely to infect that concurrent partner (because the newly infected person is highly infectious) than a subsequent sequential partner (because the newly infected person is likely to be less infectious after a period of a few months).

Sexually transmitted infections

Sexually transmitted infections are an important co-factor in facilitating the spread of HIV. Evidence for the synergistic interaction between HIV and STI's came from epidemiologic studies that showed a higher prevalence of HIV among individuals who had a history of an STI that could not be explained by behavioural factors only.[495,496] Subsequent biological studies have shown that the shedding of HIV into genital fluids is increased both from genital ulcers[497] and from the inflammatory process associated with non-ulcerative STIs.[498] People who are HIV positive and have a sexually transmitted co-infection are therefore more likely to transmit HIV to their sexual partners than in the absence of STIs. Futher studies have shown that an STI not only makes people more *infective* but women with chlamydial infection or gonorrhoea may also be more *susceptible* to acquiring HIV because they have a disproportionate increase in CD4 cells in the endocervix and it is this cell line that is the target for HIV infection.[499]

A positive association between ulcerative disease, in particular *Herpes Simplex* virus-2 (HSV-2) and HIV has been found in several studies.[495,500] In a recent study, the impact of incident HSV-2 on the incidence of HIV-1 infection was investigated among commercial sex workers in KwaZulu-Natal.[281] This remains the only study in which follow up was done at sufficiently small intervals to clearly separate out the effect of incident and prevalent HSV-2 on the incidence of HIV-1. The results showed that the hazard ratio for incident HIV-1 seroconversion was 6.0 (95% CI: 2.6–14.0) times greater among women with incident than among women with prevalent HSV-2 infections. Immediately after HSV-2 sero-conversion women experienced a significantly increased risk of acquiring HIV, but the effect wanes with time since infection. Figure 5.9 (a) shows Kaplan-Meier survival curves for time to HIV seroconversion for women who were HSV-2 positive throughout the study (PP) (i.e., they were HSV-2 positive on entry), HSV-2 negative throughout the study (NN), and those who were HSV-2 negative on entry and positive on exit (NP). When treating HSV-2 as a time-dependent co-variate, all women who were HSV-2 negative up to the time when they seroconverted to HSV-2, or left the study, were

combined in a group called NT. All those who seroconverted to HSV-2 during the study were then considered in a second group (called PT) for whom incidence of HIV was measured from the time of HSV-2 seroconversion. The Kaplan-Meier curves for time to HIV infection for these groups are shown in Figure 5.9(b).

The presence of other sexually transmitted infections has been studied in detail and has shown to increase the probability of transmitting HIV.[483] The presence of an ulcerative STI (GUD), however, has been shown to be a more important co-factor of HIV infectivity than other STIs and in a prospective study of men visiting sex workers in Kenya, none of the men without GUD seroconverted to HIV compared to 16.2% of those with GUD, after only one contact-exposure to HIV.[501] Although effective management of STIs should have an impact on the transmission of HIV, it is still not understood how the control of STI's as a public health intervention will contribute to HIV prevention. Observational studies have not yet provided convincing evidence and results from two STI treatment trials in the 1990's gave conflicting results. In a community-based, randomized trial in Mwanza, Tanzania, syndromic management for patients with STI symptoms who were seeking treatment in clinics were offered to patients in the intervention arm. The intervention lead to a 38% reduction in the incidence of HIV (95% CI: 15%–55%).[502] However, a trial conducted in Rakai, Uganda, in which the entire adult population were given mass treatment with a broad spectrum antibiotic, showed no significant reduction in the incidence of HIV (incidence ratio 0.97, 95% CI: 0.81-1.16).[503] The reasons for the different impact in these two trials has been the subject of extensive debate.[504-507] The consensus seems to be that in the early stages of an epidemic of HIV the infections are concentrated in people with high-risk behaviour who are likely to have other STIs. STI treatment therefore has a significant impact on HIV. In the later stages of the epidemic, HIV infection is more wide-spread among people who are less likely to have other STIs and STI treatment therefore has less impact on the HIV epidemic.

The intervention project in the mining town of Carletonville included syndromic management of sexually transmitted infections and presumptive treatment for sex workers as part of the intervention, together with community-based peer education and condom distribution. Cross-sectional studies carried out in 1998 and 2000 indicated that the intervention did not have a significant impact on the control of STIs.[310]

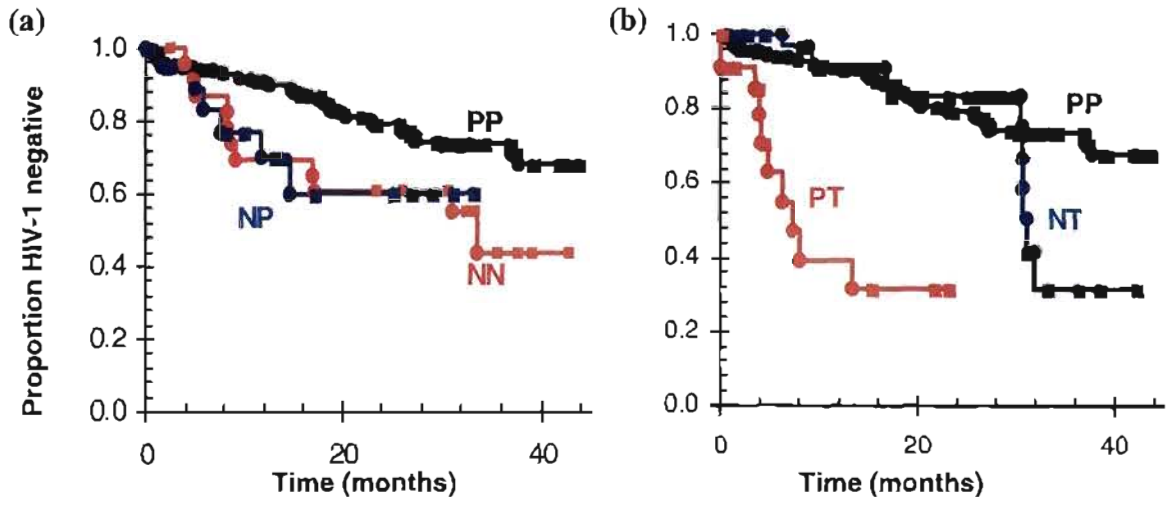


Figure 5.9 Kaplan-Meier curves for HIV-1 free survival: a) among those who were HSV-2 positive on enrolment (PP); HSV-2 negative throughout (NN); sero-converted to HSV-2 during the course of the trial (NP) and b) among those who were negative until they left the trial or seroconverted to HSV-2 (NT); and from the time at which they seroconverted to HSV-2 (PT). Dots indicate times at which women sero-converted, squares indicate times at which they were lost to follow up.

Male circumcision

Several observation studies have suggested that male circumcision might provide protection against HIV infection.[508] In a meta-analysis of 21 observational studies, most of which were cross-sectional studies, Weiss *et al.*[509] found that male circumcision reduced the risk of HIV acquisition in men by almost 50% (Relative risk 0.52, 95% CI: 0.40 - 0.68). A further review by the Cochran collaboration also showed strong epidemiological associations between male circumcision and prevention of HIV, in particular for high risk groups.[508] Observational studies however, may be limited by confounding and important factors such as religion and sexual practices are often not adequately adjusted for in these studies. In the absence of experimental studies, a causal relationship between male circumcision and protection against HIV infection could therefore not be established.

Results from the first randomized control trial on male circumcision were released in 2005. In the study carried out in Orange Farm, South Africa, Auvert and collegues showed that circumcision reduced the incidence of HIV-infection by 60% (95% CI: 32%–76%).[351] When controlling for behavioural factors, including sexual behaviour that

increased slightly in the intervention group, condom use, and health-seeking behaviour, the protection was 61% (95% CI: 34%–77%). Further trials are being conducted in Kenya and Uganda, with implications for policy and planning of prevention strategies. Implications of this finding for the promotion of male circumcision as a public health intervention to control HIV in sub-Saharan Africa have subsequently been explored using dynamical simulation models.[510] Assuming that full coverage of male circumcision is achieved over the next ten years, the results indicate that circumcision could avert 2.0 million (95% CI: 1.1–3.8 million) new HIV infections and 0.3 million (95% CI: 0.2–0.5 million) deaths over the next ten years in sub-Saharan Africa. In the ten years after that it could avert a further 3.7 million (95% CI: 1.9–7.5 million) new HIV infections and 2.7 million (95% CI: 1.5–5.3 million) deaths. In South Africa alone increasing male circumcision coverage has the potential to avert up to 144 thousand new infections each year.

The association between the prevalence of HIV and male circumcision is shown for countries in sub-Saharan Africa in Figure 5.10. Estimates of male circumcision rates[510] are plotted against the UNAIDS estimates of HIV prevalence for those countries,[4] showing lower rates of HIV infection in countries with high levels of male circumcision.

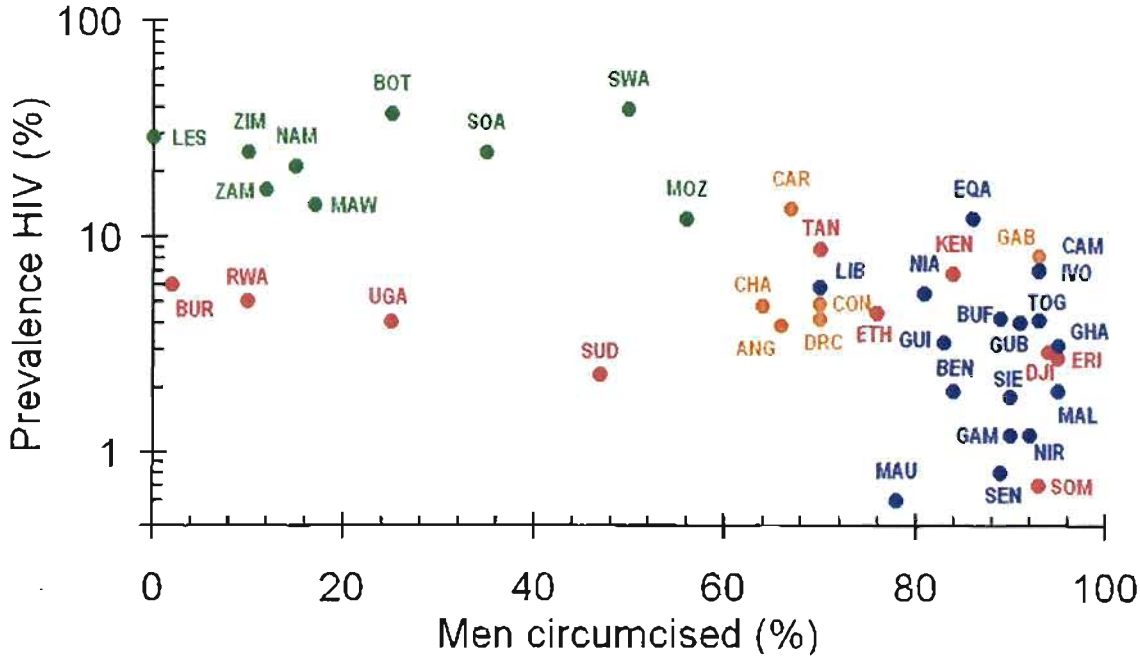


Figure 5.10 The relationship between the prevalence of HIV and male circumcision in sub-Saharan Africa. The percent prevalence of HIV[4] is plotted on a logarithmic scale against the estimated proportion of adult men who are circumcised.[510] Green, southern Africa; red, East Africa; orange, Central Africa; blue, West Africa.

Morbidity and Mortality

Morbidity

Given the long lag period between infection with HIV and progression to illness and death, it is only in the past few years that the disease burden has begun to have a serious impact on health facilities in South Africa.

As in other African countries, tuberculosis (TB) is the most common opportunistic infection associated with advancing HIV disease. It has been shown that HIV infection greatly increases a person's risk of infection with TB.[290] The risk of developing active TB infection among HIV positive patients is about five times higher than among HIV negative people, indicating the importance of HIV surveillance among TB patients. South Africa has one of the highest reported rates of TB in the world, estimated at close to 400 per 100,000 population[511] and the increasing burden of TB in South Africa has been attributed in part to the impact of HIV infection. In KwaZulu-Natal, the estimated number of TB cases in the year 2000 was 65,695, of whom 64.6% were HIV positive. Figure 5.11 illustrates how the TB burden in the rural community of Hlabisa has increased as the HIV prevalence has increased despite major advances and successes in TB control attained in this community in the early 1990s.[512] HIV prevalence among TB patients in the gold mines in Welkom rose from 15% in 1993 to 45% in 1996 ($p < 0.001$).[513] At the same time, the incidence of TB among goldminers in Welkom increased from 1174/100,000 in 1990 to 2476/100,000 in 1996. The increase occurred in the presence of a comprehensive TB control program applying the directly observed treatment, short-course (DOTS) strategy.

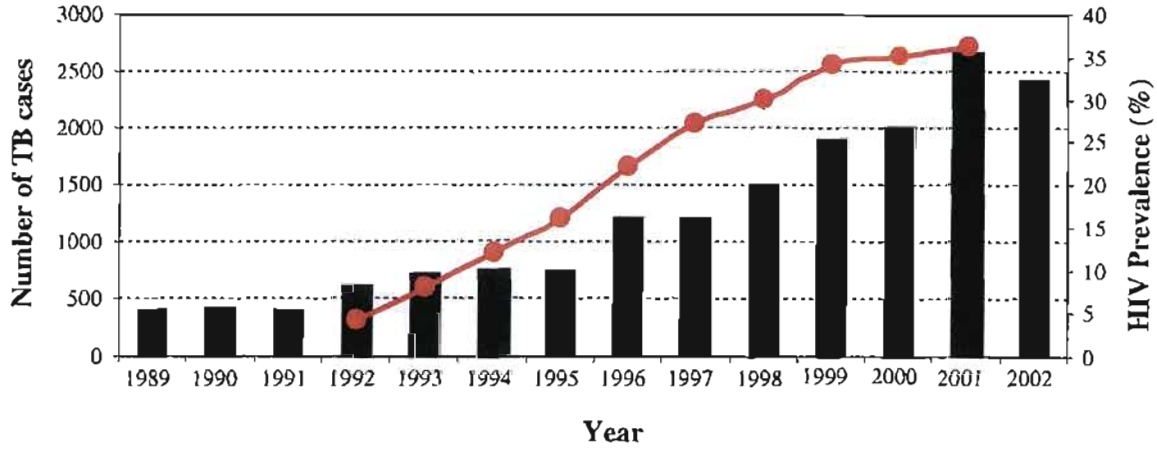


Figure 5.11 Tuberculosis caseload (from hospital records) and antenatal HIV prevalence in Hlabisa[514]

Mortality

The increase in adult mortality in the late 1990s, as estimated by the South African Medical Research Council (MRC), provides evidence of the impact of the HIV epidemic on the number of deaths in the country.[277] Analysis of South Africa's death registration data showed an increase in the total number of reported adult deaths of more than 65% between 1998 and 2003 (Figure 5.12), and in the case of women aged 20–49 years, an increase of more than 150% after adjustment of population growth and possible improvement in death registrations.[379]

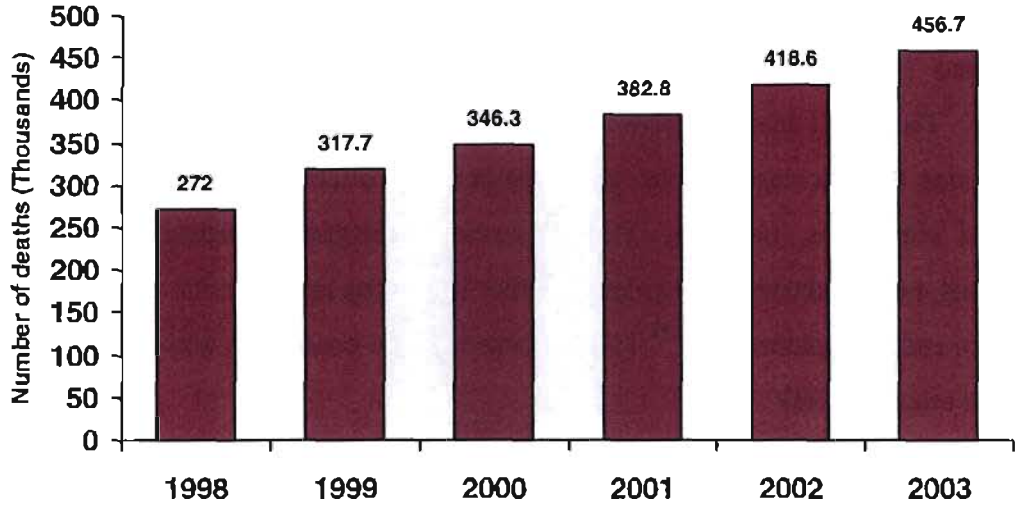


Figure 5.12 Number of registered adult deaths in South Africa, 1998 – 2003 (*Source: Bradshaw et. al. South African Medical Journal, 2004.*[379])

Given the limitations of the death registration data (including incomplete registrations, misclassification of cause of death, and delays in the production of mortality statistics),[277] the MRC undertook a national burden of disease study based on an analysis of all available data in an attempt to derive estimates of the underlying causes of death in South Africa.[466] The ASSA model was used to estimate overall mortality, population size and the number of deaths due to HIV/AIDS in each province. Estimates of the total burden of disease show that in 2000 HIV accounted for 30% of all deaths in South Africa, and HIV/AIDS was the leading cause of death in all provinces with the exception of the Western Cape.[466] In 2004, it was estimated that HIV was responsible for 44% of the total number of 701,000 deaths in South Africa, and 70% of the deaths in the age group 15-49 years.[24]

Statistics from the South African Government confirmed the large increase in mortality; 57% in the total number of deaths between 1997 and 2002 and an increase of 62% among people over the age of 15 years during the same period.[515] Although some of the increase can be explained by population growth and more complete reporting of deaths over time, this does not explain the substantial rise in the proportion of deaths among persons aged 25 to 49 years (Figure 5.13 – extracted from *Statistics SA* report[515]). In 1997, people in this age group accounted for 23% of all deaths, while in 2003 they accounted for 34%. Although death certificates often do not state HIV/AIDS as a direct cause of death, but rather record deaths related to HIV/AIDS as being due to associated opportunistic infections and diseases such as TB and pneumonia, the age and disease patterns provide strong evidence of the growing impact of AIDS. The report from Statistics SA shows that recorded TB deaths increased by 131% and influenza and pneumonia deaths by almost 200%. The MRC analysis showed that of 22 potential causes of death investigated, there were nine that increased in the same distinct age pattern and could be considered AIDS-related conditions, including TB, pneumonia, diarrhoea, meningitis, other respiratory diseases, non-infective gastroenteritis, other infectious and parasitic diseases, anaemia, and protein energy malnutrition.[279] The increase in these conditions accounted for 61% of total deaths related to HIV.

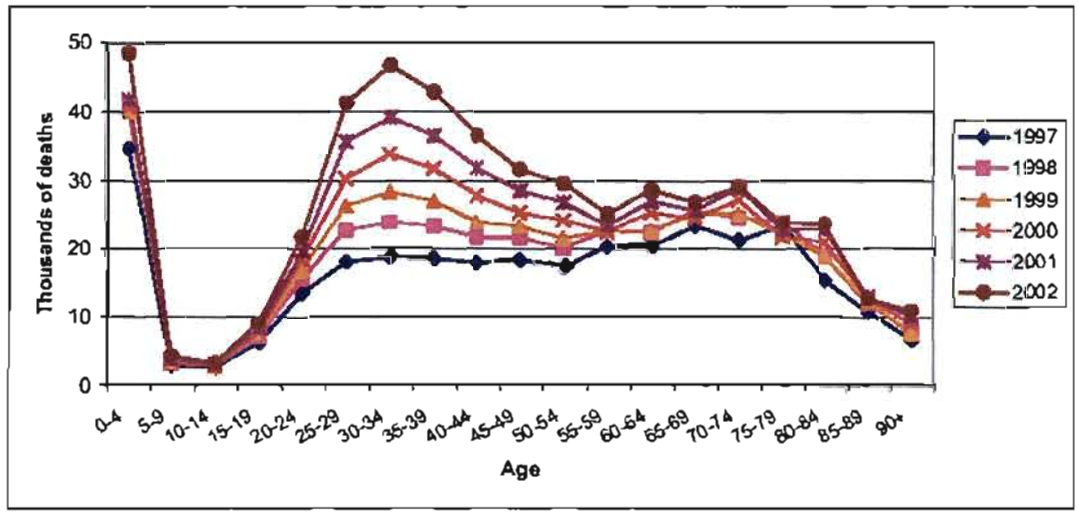


Figure 5.13 Distribution of deaths by age and year of deaths (1997-2002). (*Source: Statistics South Africa. Mortality and causes of death in South Africa, 1997–2003: Findings from death notification 2005*)

Further evidence of steep increases in AIDS related mortality is also provided from demographic surveillance and community/hospital surveys. Demographic surveillance conducted in Hlabisa, rural KwaZulu-Natal, confirmed a significant rise in adult mortality starting in the late 1990s, while in 2000 AIDS was the leading cause of adult death, being associated with 48% of all adult deaths. The risk of dying from AIDS was highest in women aged 25-39 years and men aged 30-44 years.[516] A study to investigate causes of child under-5 deaths in the North-West province showed that 31.4% of all deaths were caused by lower respiratory tract infections, 21% by AIDS, and 13.4% by sepsis. The percentage of those who died from AIDS and AIDS related conditions was 62%.[517]

Discussion

Cross-sectional data on HIV prevalence in South Africa are widely available, the most extensive being based on the annual surveillance system that was set up by the National Department of Heath and Population Development in 1990 to monitor the prevalence of HIV infection in pregnant women attending public health antenatal clinics. Many additional surveys have been conducted in South Africa over the last 15 years to provide essential information on epidemic trends, patterns of infection, and on factors that contribute to the spread of the epidemic.

South Africa has experienced one of the fastest growing HIV epidemics in the world and currently bears about 14% of the global burden of HIV infection. Estimates of prevalence have reached high levels and vary by age, gender and geographical area. Data collected in recent years show that the epidemic is starting to level off, an effect that more likely reflects the natural saturation of the epidemic than the impact of interventions. While the HIV prevalence is no longer increasing rapidly, the incidence of new infections is balanced by rising mortality rates.

The HIV epidemic in South Africa can be considered in different stages: before 1987 the epidemic was concentrated among men who have sex with men and recipients of blood products and was predominantly of subtype B. Once introduced into the heterosexual population, the prevalence of HIV subtype C started to rise exponentially reaching 4% in 1993. During the period 1994-1998 the prevalence of infection continued to increase rapidly among antenatal clinic attendees from 7.6% to 22.8%. Mathematical models show

that the peak incidence of infection occurred during this period, although AIDS-related mortality was still relatively low. Since 1998 the rate of increase in the epidemic has slowed substantially and prevalence data suggest that the epidemic is reaching a plateau. Mortality rates however, are still rising and the incidence of new infections are balanced by deaths.

In the current stage of the HIV epidemic, South Africa has had to deal with continued large numbers of new HIV infections, ongoing high mother-to-child transmission rates, rising morbidity, rapidly rising deaths, and an increasing number of orphans. Each of these factors demands effective and rapid interventions if the epidemic is to be brought under control. Finally, the high rates of new infections in young women highlight the importance of targeting interventions at youth, addressing gender inequalities, and the need for greater involvement of men. The increased risk of infection among migrant men, especially among older men, also needs to be addressed when designing interventions to manage the epidemic.

Appendix 5.1 Estimating HIV prevalence in the general adult population in South Africa by adjusting antenatal clinic HIV prevalence

Our knowledge of the HIV epidemic in South Africa is based primarily on the prevalence data that have been collected annually from pregnant women attending public antenatal clinics since 1990. This data can be used to obtain national estimates of HIV prevalence among the adult population in South Africa. However, ANC data are biased estimators of general population HIV prevalence because only pregnant women attending public health services are included in the sample. In order to correct for these biases it is firstly necessary to adjust for relative attendance rates at antenatal clinics (because HIV prevalence among women attending public health services is expected to be higher than among women attending private health services) and secondly to adjust for the difference in prevalence between pregnant women and the general adult population. Ideally, national population-based HIV prevalence surveys would be an unbiased sample of the general adult population but the response rate in the population based survey conducted by the HSRC in 2005 was low (combined household and individual response rate was 55%) and might therefore be biased.[470] If non-responders are more likely to be HIV positive than responders, then the HSRC survey is likely to underestimate the true population prevalence. One approach is therefore to start from the ANC estimates of prevalence, and to use the HSRC data to calculate correction factors. The two corrections factors needed to adjust the ANC data when estimating the national adult prevalence can be calculated as follows:

1. Adjusting for relative attendance rates at antenatal clinics

This adjustment requires that the ANC data are standardized for race because the race distribution of ANC attendees is different from the race distribution in the general population. Because the prevalence by race among ANC attendees is not available, the prevalence by race can be obtained from the 2005 HSRC survey, as shown in Table A5.1. The race distribution for the South African adult population (age 15-49 years), also shown in Table A5.1, can be obtained from the latest available Census data.[518] The correction factor is then estimated as the ratio of the unadjusted prevalence to the race-standardized prevalence (Table 5A.1).

Table 5A.1 Standardizing ANC data for race distribution

	Population distribution (SA Census)[518]	Adult (15-49 year) prevalence from 2005 HSRC survey[470]	Proportional ANC attendance distribution by race group	Standardized estimate of HIV prevalence	Ratio of unadjusted to standardized prevalence
African	79.3	19.9	0.87	17.31	
Coloured	8.8	3.2	0.09	0.30	
White	9.3	0.5	0.00	0.00	
Indian	2.5	1.0	0.03	0.03	
Total	100	16.2		17.6	0.92

2. Adjusting for prevalence in pregnant women versus prevalence among adults

To adjust for the difference between HIV prevalence in pregnant women and prevalence among adults in the general population, a correction factor based on the ratio of prevalence in these two population groups can be calculated using data from the 2005 HSRC survey, as 16.2/23.2= 0.7

Combined adjustment

The combined correction factor can then be estimated as the product of the two correction factors described above, i.e. 0.92×0.7 = 0.64.

Adjusted adult HIV prevalence in South Africa is therefore estimated to be 29.5% × 0.64 = 18.9%

The calculation of the correction factor as described above was endorsed by the Department of Health and UNAIDS at a meeting in the Department of Health in Pretoria in 2006.

CHAPTER 6 Analysing age prevalence data to understand the patterns of HIV infection in South Africa

> "For me, a hypothesis is a statement whose *truth* is temporarily assumed, but whose *meaning* must be beyond all doubt."
>
> Albert Einstein, 1918[519]

Introduction

Understanding the spread of the HIV epidemic in time and space is an essential step in trying to understand the dynamics of the epidemic, to make projections of the likely future course of the epidemic, to evaluate the impact of interventions and to find ways to deal with the epidemic effectively. In this chapter data are used on the age-specific risk of infection among various groups of men and women in an attempt to understand how patterns of infection vary with age, gender, geographic location, and migrancy status. The HIV prevalence data sets used in this analysis include data from women attending antenatal clinics in South Africa and in rural KwaZulu-Natal (Hlabisa), data on men and women from urban and rural community settings (rural KwaZulu-Natal in 1991, Hlabisa in 2000 and Carletonville in 1998), sex workers operating along the trucking route in KwaZulu-Natal and near the gold mines in Carletonville, mine workers from Carletonville, truck drivers visiting sex workers in KwaZulu-natal, and data from male and female employees of a large South African company in 1999. Different patterns of infection are identified among different risk groups and the implications for the spread and management of the epidemic in South Africa are considered.

Methods

In order to compare the different data sets it was first necessary to parameterize the data by fitting the age-prevalence data to suitable functions. In some cases the age-prevalence curve was statistically either constant or varied linearly with age. However, in most cases, including all the data collected from antenatal clinics and the general population, the age-specific prevalence increases rapidly between the ages of 15 and 30 and then declines more slowly with increasing age. A log-normal function with an age off-set, as described in Chapter 3, Equation 3.2, provides a suitable analytical function for fitting these data and

provided a good fit to all the data sets for which the age-prevalence of infection deviated from a straight line.

The shape of the age-prevalence curve is usually consistent with an onset of sexual activity in the early teenage years and a peak of sexual activity between the ages of about 20 and 30 years, and is supported by data on the age-incidence of pregnancy in Hlabisa, shown in Figure 6.1. These data were collected as part of an HIV seroprevalence survey of 3,163 women, age 15 to 49 years, attending antenatal clinics in Hlabisa between January and July 1998. Data from the 1996 census were used as the denominator and a log-normal function also provides a good fit to these data.

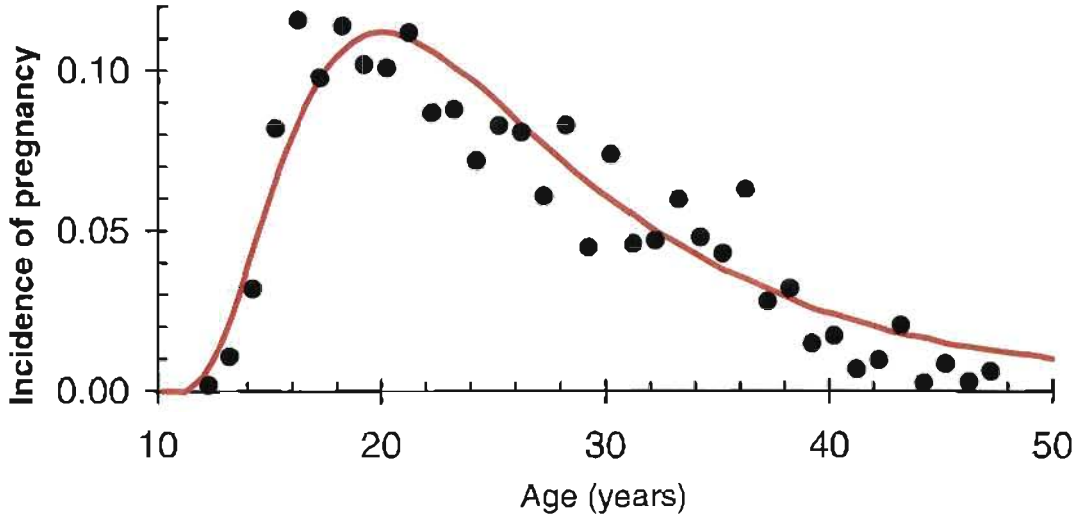


Figure 6.1 Fitted and observed annual fertility (for ages up to 50 years) estimated from the number of women attending antenatal clinics in Hlabisa. The curve is log-normal (Equation 3.1) with m = 14.9 years, a0 = 10 years, $\sigma = 0.629$ and N = 2.156. The incidence of pregnancy is shifted down by 0.75 years to allow for the 9 months gestation.

The log-normal curves were fitted to the data using a maximum likelihood procedure[520] with binomial errors. For the interpretation of the data the mode was more useful than the mean and the fits were done using the mode as one of the parameters. For a log-normal function the relationship between the mode and the mean is given by

$$mean = (mode - offset) \times e^{\sigma^2}$$

The *p*-values for goodness of fit, calculated using a χ^2 test of deviance, were used to assess the significance level of the model fit, and if greater than 0.05 it indicates that the fitted line does not differ significantly from the data.

The maximum likelihood procedure was also used to obtain the covariance matrices for the fitted parameters,[520] from which 95% confidence ellipses for the shape parameter and the mode were constructed and used in the comparison of the different fits. The mode gives the age at which the peak prevalence occurs, while the shape parameter, σ, is the standard deviation of the frequency distribution of the log-transformed data and determines the shape of the frequency distribution of the untransformed data. Only these two parameters were considered, and not the normalization parameter, since the prevalence of infection is expected to increase with time, while the only interest here was in the shape of the age-prevalence curves.

Data sources

The data used in this analysis came from a variety of sources, all of which are described in detail in Chapter 4. These included age-specific HIV prevalence data for:

- Pregnant women attending national antenatal clinics between 1995 and 2004;[25,31,118,472,473]
- Pregnant women attending antenatal clinics in Hlabisa in 1997, 1998, 1999, and 2001;[32]
- Men and women participating in a cross-sectional, anonymous, community based survey in rural KwaZulu-Natal in 1991;[82]
- Men and women taking part in the Vaccine Preparedness Study in the Hlabisa district in 2000;
- Men and women participating in a community based survey in an urban setting (Carletonville) in Gauteng in 1998;[222,310]
- Sex workers operating at truck stops along the national road between Durban and Johannesburg, in the KwaZulu-Natal Midlands, between 1996 and 1998;[331]
- Sex workers operating near the gold mines in Carletonville in 1998;[222,310]
- Truck drivers visiting sex workers along the trucking route in the KwaZulu-Natal Midlands in 1998;[331]
- Migrant mine workers working on the gold mines in Carletonville in 1998;[222,310] and

- Men and women participating in a large cross-sectional survey carried out among the workforce of a major South African company in 1999;[479,480]

Results

National ANC data

ANC data collected from national surveys between 1995 and 2004 are plotted by age in Figure 6.2, showing the dramatic increase in HIV prevalence in all age groups over time. The log-normal function provided a good fit to the age-prevalence data for each of the antenatal clinic surveys carried out between 1995 and 2004. The data and the fitted curves are shown graphically in Figure 6.3, and are provided in Table 6.1 together with the parameter values for the log-normal fits and the peak prevalence. The mode indicates the age at which the peak prevalence occured. The peak prevalence of HIV increased dramatically in all age groups, from an average of 14.2% in 1995 to 37.1% in 2004 (Figure 6.2). The prevalence in all ten surveys peaked among young women but shifted from age 22.4 years in 1995 to 26.7 years in 2004 (Table 6.1).

In order to compare trends over time in the location and shape of the age-distributions, Figure 6.4 shows 95% confidence ellipses for the two parameters of the log-normal distributions fitted to the data. The shapes of the curves for 1995, 1997 and 1998 were not significantly different but the ellipse for 1996 was quite different from all the other data sets with a much broader curve (σ = 0.825) and was therefore excluded from further consideration. It is clear from Figure 6.4 that the shapes of the age prevalence curves for HIV infection among antenatal clinic attendees have remained much the same over a period of ten years (excluding the data for 1996) as indicated by the parameter σ. However, the data show that the age at which the peak prevalence occurs has shifted over the period under consideration. Between 1995 and 1998, the peak prevalence occurred among young women aged around 23 years. By 1999-2000, the average age of the peak prevalence had shifted by about 1.5 years to 24.5 years, and by 2002-2004 it had shifted to an average of 26.5 years. The shapes of the curves for 2002, 2003 and 2004 were not significantly different. The observed changes are most likely the result of a maturing epidemic, reflecting possible saturation of the epidemic, although differences in the sampling procedure and other biases in the data may also have affected the shapes of the

curves. Over time the size of the confidence ellipses also became smaller because of smaller standard deviations related to higher prevalences and more precise data.

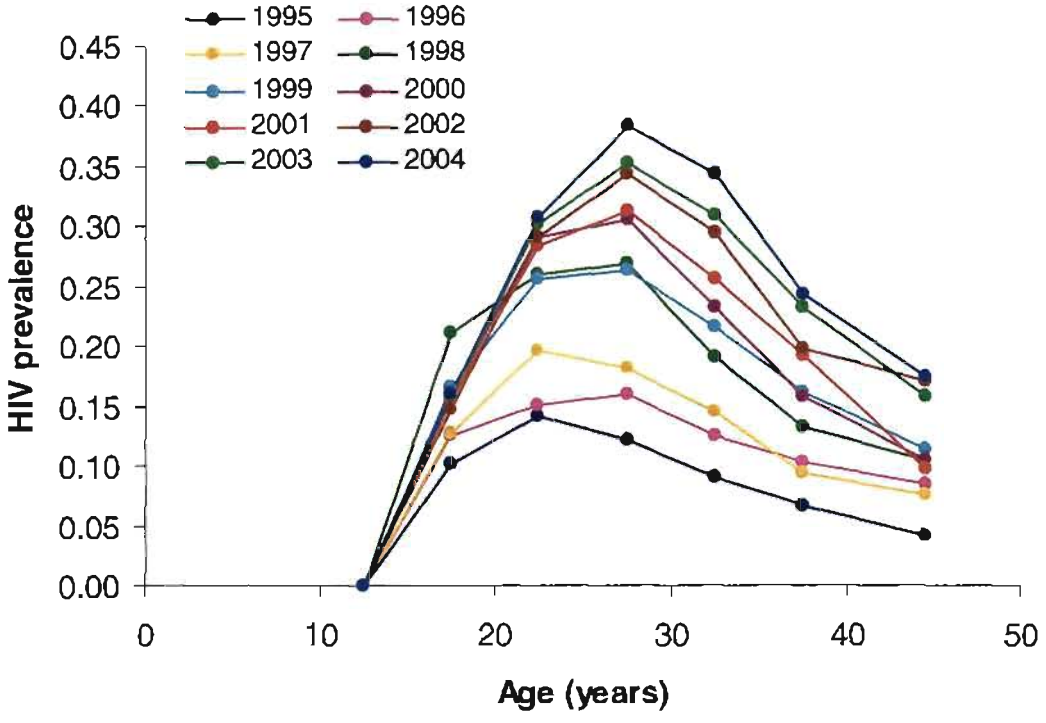


Figure 6.2 National antenatal clinic HIV prevalence data plotted by age for surveys carried out between 1995 and 2004.

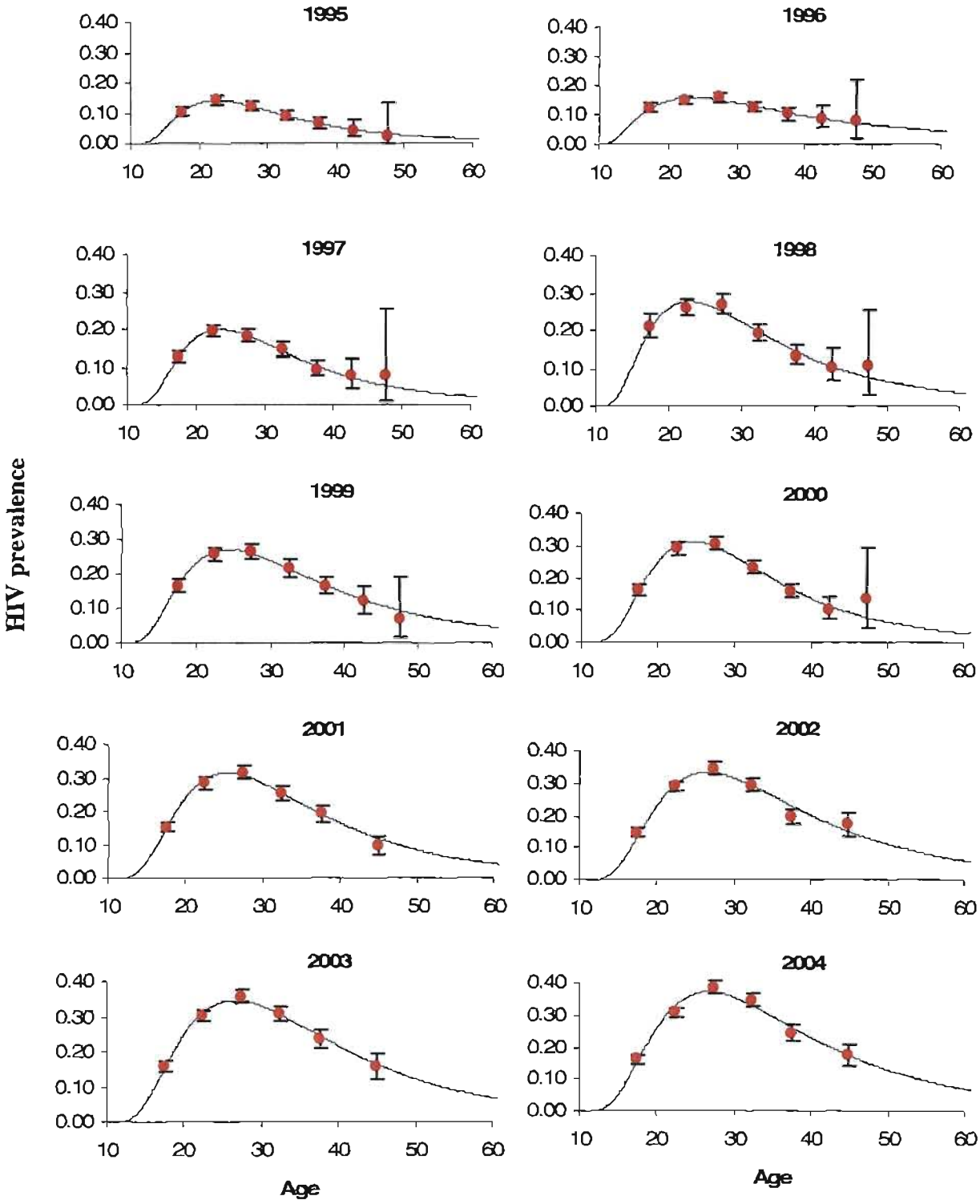


Figure 6.3 Age-prevalence of infection for women attending national antenatal clinics from 1995 to 2004 fitted to log-normal functions. The data, the parameters of the fits and the goodness of fit are given in Table 6.1. Error bars are 95% binomial confidence limits.

Table 6.1 Age-prevalence of infection among women attending national antenatal clinics. Parameter values of the log-normal fits, the observed and fitted prevalences for different age groups, and peak prevalences are provided.

Parameter values		Age	Prev	Fitted	Parameter values		Age	Prev	Fitted
1995					1996				
		15–19	0.103	0.103			15–19	0.126	0.123
N	3.417	20–24	0.143	0.142	*N*	6.135	20–24	0.150	0.157
Mode	22.447	25–29	0.121	0.123	*Mode*	23.375	25–29	0.160	0.150
σ	0.632	30–34	0.091	0.092	σ	0.825	30–34	0.125	0.129
m	18.564	35–39	0.067	0.065	*m*	26.426	35–39	0.104	0.108
p-value	0.996	40–44	0.045	0.045	*p-value*	0.366	40–44	0.087	0.088
Max prev	0.142	45–49	0.025	0.031	*Max prev*	0.158	45–49	0.081	0.072
1997					1998				
		15–19	0.127	0.127			15–19	0.211	0.202
N	5.031	20–24	0.197	0.197	*N*	7.442	20–24	0.261	0.277
Mode	23.497	25–29	0.182	0.182	*Mode*	22.765	25–29	0.269	0.248
σ	0.618	30–34	0.145	0.141	σ	0.671	30–34	0.191	0.194
m	19.766	35–39	0.095	0.102	*m*	20.029	35–39	0.134	0.144
p-value	0.884	40–44	0.077	0.072	*p-value*	0.089	40–44	0.103	0.105
Max prev	0.199	45–49	0.077	0.051	*Max prev*	0.277	45–49	0.108	0.076
1999					2000				
		15–19	0.165	0.163			15–19	0.161	0.157
N	7.880	20–24	0.256	0.262	*N*	7.534	20–24	0.291	0.301
Mode	24.449	25–29	0.264	0.257	*Mode*	24.543	25–29	0.306	0.296
σ	0.654	30–34	0.217	0.214	σ	0.565	30–34	0.233	0.231
m	22.152	35–39	0.162	0.166	*m*	20.013	35–39	0.158	0.165
p-value	0.810	40–44	0.121	0.125	*p-value*	0.245	40–44	0.102	0.113
Max prev	0.269	45–49	0.070	0.093	*Max prev*	0.312	45–49	0.137	0.076
2001					2002				
		15–19	0.154	0.149			15–19	0.148	0.143
N	8.437	20–24	0.284	0.295	*N*	9.749	20–24	0.291	0.302
Mode	25.357	25–29	0.314	0.306	*Mode*	26.309	25–29	0.345	0.331
σ	0.588	30–34	0.256	0.254	σ	0.598	30–34	0.295	0.288
m	21.698	35–39	0.193	0.192	*m*	23.326	35–39	0.198	0.228
p-value	0.142	40–49	0.098	0.118	*p-value*	0.001	40–49	0.172	0.148
Max prev	0.314				*Max prev*	0.333			
2003					2004				
		15–19	0.158	0.153			15–19	0.161	0.153
N	10.670	20–24	0.303	0.312	*N*	11.181	20–24	0.308	0.331
Mode	26.507	25–29	0.354	0.344	*Mode*	26.683	25–29	0.385	0.370
σ	0.616	30–34	0.309	0.305	σ	0.601	30–34	0.344	0.328
m	24.137	35–39	0.234	0.246	*m*	23.945	35–39	0.245	0.263
p-value	0.101	40–49	0.158	0.165	*p-value*	0.000	40–49	0.175	0.174
Max prev	0.346				*Max prev*	0.371			

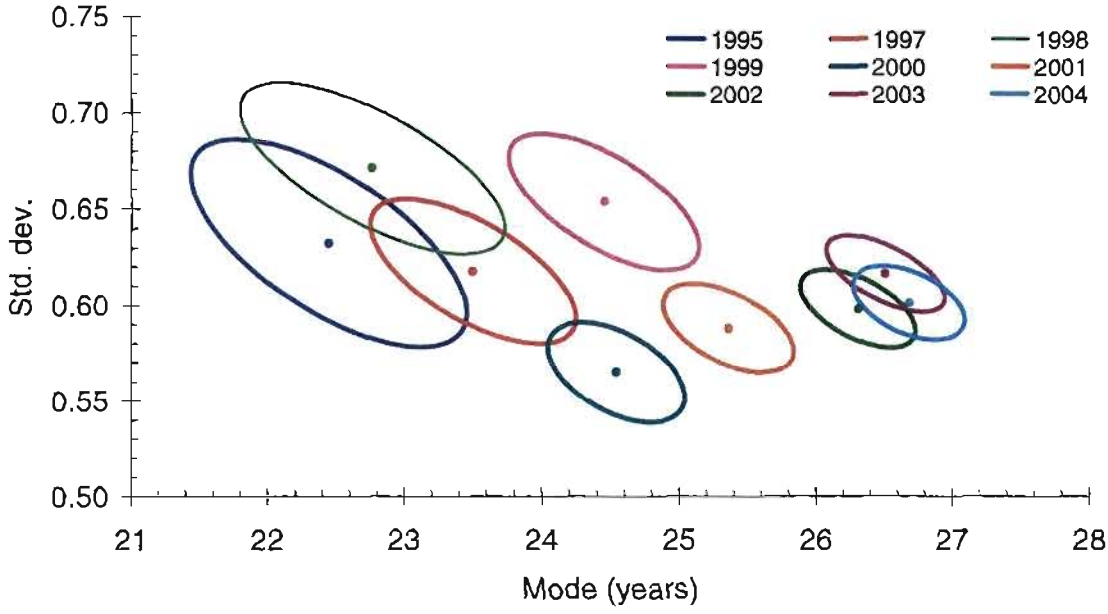


Figure 6.4 95% Confidence ellipses for the fits to the national antenatal clinic data between 1995 and 2004. The mode indicates the age at which peak prevalence occurred and the standard deviation indicates the width of the distribution of the log-normal curve.

Figure 6.5 shows the peaks in the age-prevalence curves for each ANC survey between 1995 and 2004 and the age at which these peaks occurred. While the peak prevalence increased from 14.2% in 1995 to 37.1% in 2004, the ages at which this occurred increased from 22.4 years to 26.7 years over the same period.

The increase in prevalence over time in each of the age groups (where age was grouped in categories of five years) was analysed and is shown for each age group in Figures 6.6 and 6.7. Logistic curves were fitted to the data. While the epidemic among the younger age groups (15-19 and 20-24 years) appears to have levelled off after 2000, the prevalence in the older age groups is still increasing. The data for the 15 to 19 year old age group suggests that the incidence is now fairly constant but at a high level. If very few women are infected before the age of 15 years and the prevalence in those aged 15 to 19 is about 15%, then this suggests an annual incidence of about 5-7% per year.

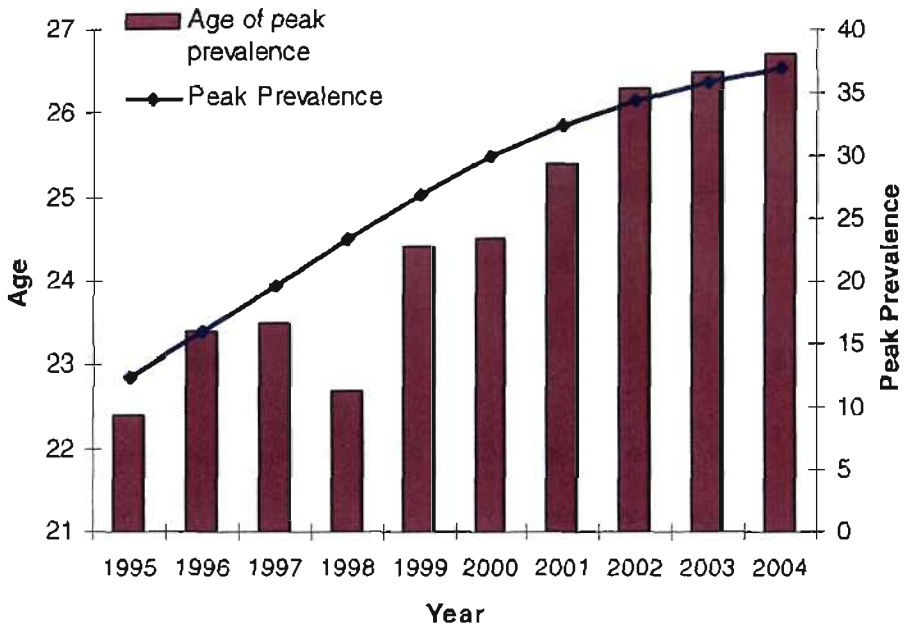


Figure 6.5 Age of peak prevalence (indicated by the mode in the log-normal fits) and the peak prevalence among national antenatal clinic attendees between 1995 and 2004.

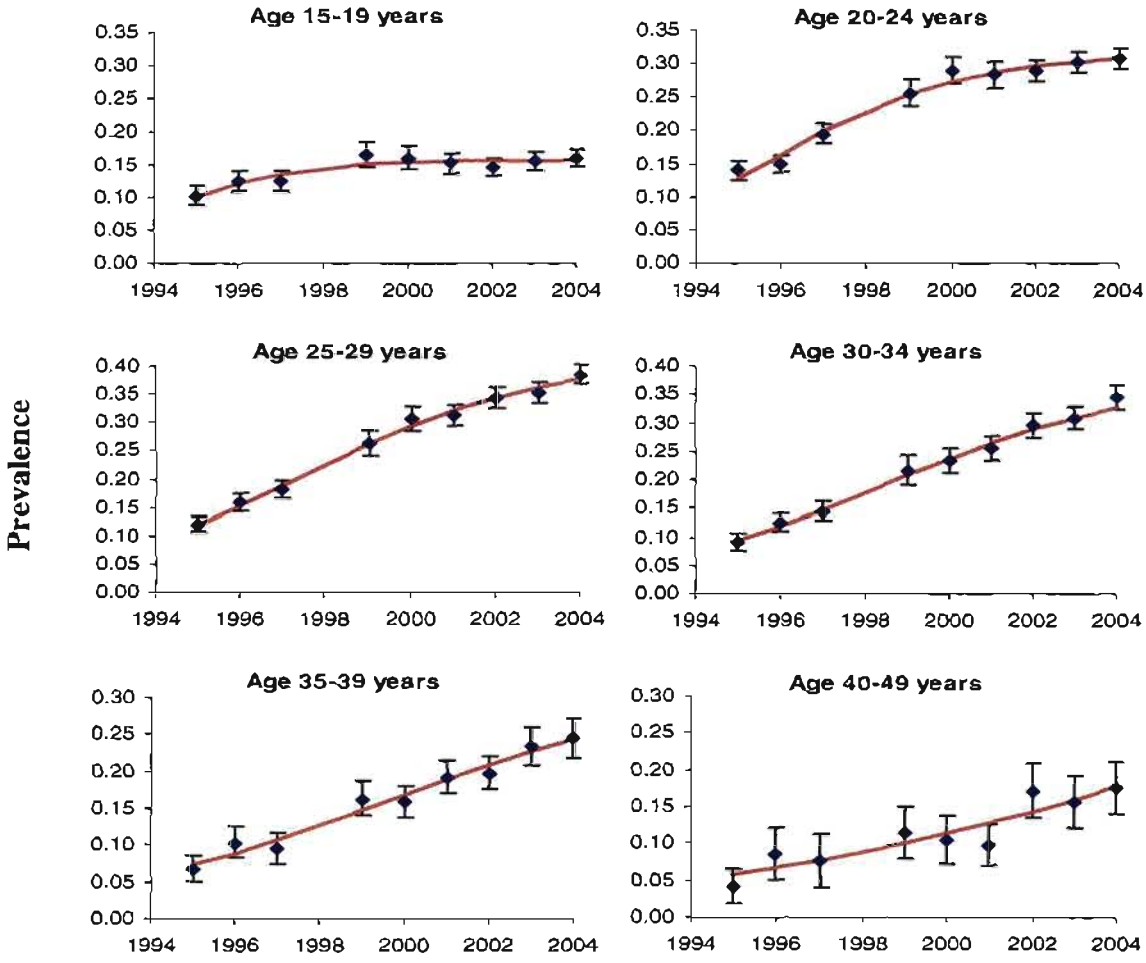


Figure 6.6 HIV prevalence plotted over time within age groups. Logistic curves were fitted to the data. Error bars are 95% binomial confidence intervals.

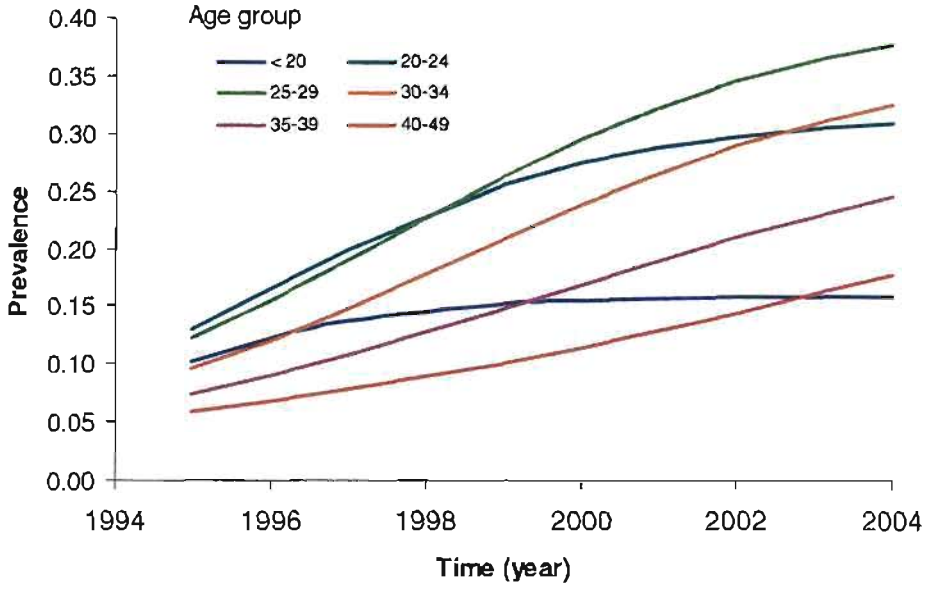


Figure 6.7 Comparison of change in HIV prevalence by age group among ANC attendees over time

Hlabisa ANC data

The shapes of the age-prevalence curves from antenatal clinic attendees in Hlabisa in rural KwaZulu-Natal between 1997 and 2001 (Figure 6.8) were similar to those for the national antenatal clinic surveys with the age of the peak prevalence shifting from 22.7 years in 1997 to 25.5 years in 2001 (Table 6.2). Log-normal distributions provided good fits to all four sets of data. HIV prevalence in Hlabisa in general reflects the high prevalences in the KwaZulu-Natal province. The peak prevalence among ANC attendees in this district increased from 34.3% in 1997 to 51.0% in 2001 (Figure 6.8).

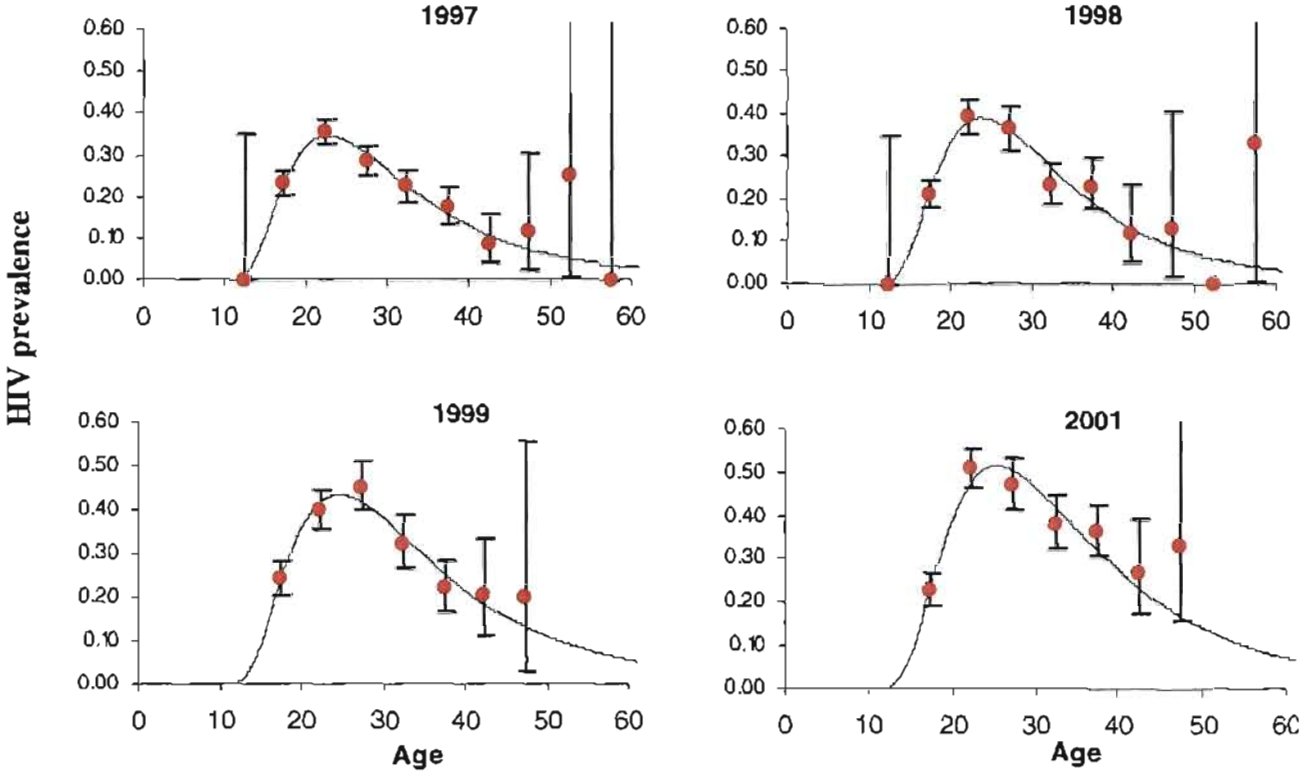


Figure 6.8 Age-prevalence data for women attending antenatal clinics in Hlabisa between 1997 and 2001, fitted to log-normal functions. Error bars are 95% binomial confidence limits.

Table 6.2 Age-prevalence of infection among women attending antenatal clinics in Hlabisa. Parameter values of the log-normal fits, numbers sampled and the observed and fitted prevalences.

Parameter values		Age	Total	Prev	Fitted	Parameter values		Age	Total	Prev	Fitte
1997						1998					
		10–14	7	0.000	0.010			10–14	7	0.000	0.00
N	8.140	15–19	1097	0.232	0.237	*N*	9.217	15–19	819	0.211	0.21
Mode	22.759	20–24	1491	0.355	0.345	*Mode*	23.977	20–24	994	0.393	0.38
σ	0.612	25–29	1005	0.285	0.302	σ	0.571	25–29	608	0.363	0.36
m	18.555	30–34	632	0.225	0.224	*m*	19.359	30–34	398	0.234	0.27
p-value	0.543	35–39	354	0.172	0.157	*p-value*	0.210	35–39	265	0.230	0.19
Max prev	0.343	40–44	113	0.088	0.107	*Max prev*	0.392	40–44	57	0.123	0.13
		45–49	26	0.115	0.073			45–49	15	0.133	0.08
		50–54	4	0.250	0.050			50–54	0		0.05
		55–59	1	0.000	0.034			55–59	3	0.333	0.03
		All ages	4730	0.272				All ages	3166	0.299	
1999						2001					
		15–19	661	0.244	0.237			15–19	179	0.229	0.24
N	11.633	20–24	797	0.400	0.420	*N*	14.012	20–24	185	0.508	0.48
Mode	24.634	25–29	539	0.453	0.416	*Mode*	25.509	25–29	89	0.472	0.50
σ	0.608	30–34	358	0.324	0.338	σ	0.588	30–34	73	0.384	0.42
m	21.170	35–39	199	0.221	0.253	*m*	21.922	35–39	44	0.364	0.32
p-value	0.170	40–44	58	0.207	0.183	*p-value*	0.662	40–44	15	0.267	0.23
Max prev	0.43	45–49	10	0.200	0.131	*Max prev*	0.51	45–49	3	0.333	0.16
		All ages	2622	0.342				All ages	588	0.384	

Community surveys

Three sets of data from community based surveys were available for analysis; one from a rural population in northern KwaZulu-Natal, carried out between 1990 and 1992;[82] the second from the Hlabisa community (Vaccine Preparedness Study), also in rural KwaZulu-Natal, carried out in 2000; and the third from the urban population of Carletonville carried out in 1998.[222] The age-specific prevalence curves for these populations are shown in Figure 6.9 using the data shown in Table 6.3. The infection rates in the later urban and rural surveys were approximately ten times higher than the rates measured in the earlier rural survey, and the fractional errors correspondingly smaller. Standard errors for the infection rates among rural men in 2000 were very large because of the small sample sizes in the various age groups. The patterns of infection are similar between the three sets of data with infection rates increasing more slowly among young men than among young women (Figure 6.9). Table 6.3 and Figure 6.10 show that the peak prevalence occurred at older ages among men than among women (about 7.5 years older among men in rural KwaZulu-Natal and about 5 years older among men in urban Gauteng). For rural women,

the age at peak prevalence shifted from 21.9 years in 1991 to 26.0 years in 2000; while it shifted from 29.8 to 33.3 years for men. Prevalence peaked among urban women in 1998 at age 26.1 years and among men at age 31.6 years. The ellipses indicate a narrower distribution (i.e., smaller standard deviation) for men than for women.

Data from the three community surveys were used to calculate the ratio of HIV prevalence among females to the prevalence among males. Figure 6.11 shows that the female to male prevalence ratio for all ages combined was about 1.7 in all three surveys. The female to male ratio among young people aged 15-19 years was much higher (20.5, 7.2, and 10.4, respectively, for rural KwaZulu-Natal 1991, rural KwaZulu-Natal 2000, and urban Gauteng 1998) than among older ages because of the much higher prevalence and vulnerability among young women compared to young men. At ages 25 to 49 the female to male prevalence ratio was about 1, while all three surveys indicate that prevalence was again higher among women aged 50+ than among men in this age group.

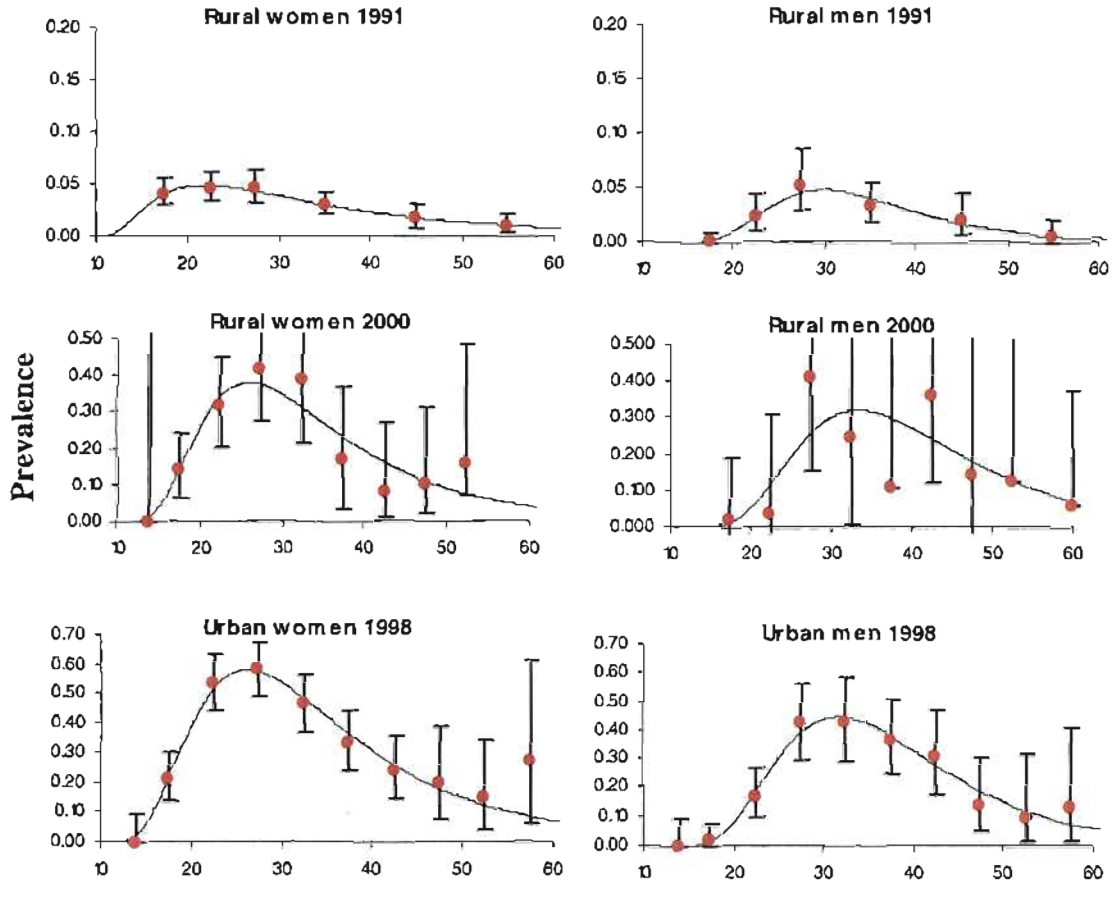


Figure 6.9 Age-prevalence curves for men and women in rural areas of northern KwaZulu-Natal in 1991 and 2000, and in the urban area of Carletonville in 1998. The data, parameters of the fits and the goodness of fit statistics are given in Table 6.3. Error bars are 95% binomial confidence limits.

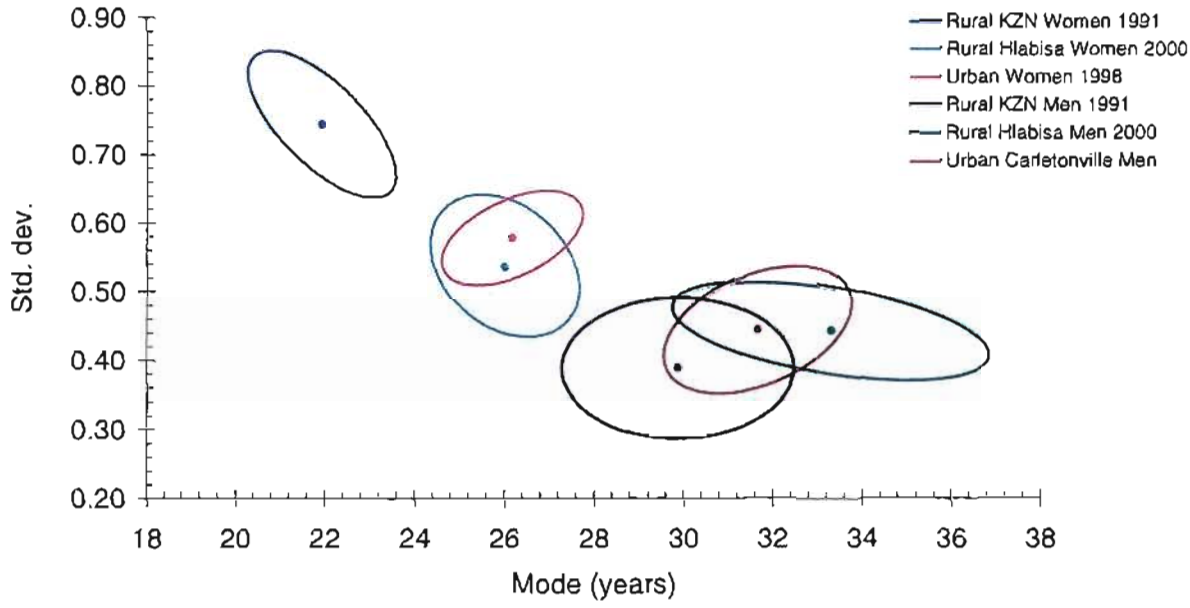


Figure 6.10 95% Confidence ellipses for the fits to the men and women from the community surveys conducted in 1991, 1998 and 2000.

Table 6.3 Age-prevalence of infection among men and women from three community surveys (rural KwaZulu-Natal in 1991 and 2000, and urban Carletonville in 1998). Parameter values of the log-normal fits, the observed and fitted prevalences, and peak prevalences are provided.

Parameter values		Age	Total	Prev	Fitted
Women rural KZN 1991					
		15-19	1095	0.041	0.040
N	1.436	20-24	1088	0.046	0.049
Mode	21.926	25-29	739	0.046	0.043
σ	0.745	30-39	1026	0.030	0.030
m	20.768	40-49	600	0.017	0.017
Chi2	0.937	50+	624	0.010	0.010
Max prev.	0.049	All ages	5172	0.034	
Women rural KZN 2000					
		< 15	4	0.000	0.011
N	9.492	15-19	180	0.144	0.141
Mode	26.018	20-24	114	0.316	0.342
σ	0.538	25-29	65	0.415	0.375
m	21.406	30-34	46	0.391	0.311
Chi2	0.201	35-39	53	0.169	0.229
Max prev.	0.380	40-44	48	0.085	0.160
		45-49	39	0.103	0.109
		50-54	31	0.161	0.074
		All ages	580	0.222	
Women urban 1998					
N	14.898	15-19	101	0.208	0.215
Mode	26.173	20-24	119	0.538	0.518
σ	0.546	25-29	117	0.581	0.573
m	21.799	30-34	105	0.467	0.483
Chi2	0.554	35-39	93	0.333	0.361
Max prev.	0.579	40-44	68	0.235	0.256
		45-49	30	0.200	0.177
		50-54	27	0.148	0.121
		55-59	11	0.273	0.083
		All ages	701	0.374	

Parameter values		Age	Total	Prev	Fitted
Men rural KZN 1991					
		15-19	643	0.002	0.002
N	0.993	20-24	385	0.023	0.023
Mode	29.871	25-29	305	0.052	0.045
σ	0.389	30-39	430	0.033	0.040
M	23.121	40-49	299	0.020	0.016
Chi2	0.720	50+	354	0.006	0.005
Max. prev.	0.047	All ages	2416	0.020	
Men rural KZN 2000					
N	9.078	15-19	50	0.020	0.012
Mode	33.294	20-24	25	0.040	0.119
σ	0.443	25-29	17	0.412	0.258
M	28.341	30-34	8	0.250	0.317
Chi2	0.228	35-39	9	0.111	0.297
Max. prev.	0.318	40-44	11	0.364	0.240
		45-49	7	0.143	0.179
		50-54	8	0.125	0.127
		>55	17	0.059	
		All ages	152	0.125	
Men urban 1998					
		13-14	31	0.000	0.000
N	10.939	15-19	99	0.020	0.017
Mode	31.646	20-24	89	0.169	0.181
σ	0.416	25-29	59	0.424	0.396
M	25.727	30-34	49	0.429	0.443
Chi2	0.962	35-39	60	0.367	0.37
Max. prev.	0.445	40-44	42	0.310	0.27
		45-49	35	0.143	0.18
		50-54	20	0.100	0.11
		55-59	15	0.133	0.07
		All ages	499	0.214	

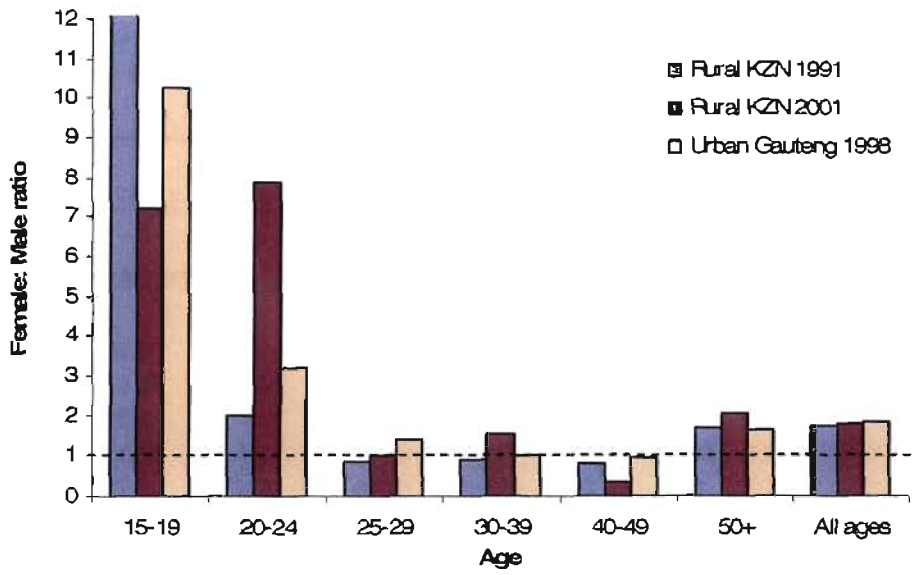


Figure 6.11 Ratio of female to male prevalence by age (and combined) for the three community surveys.

Migrant men

Two sets of data were available for migrant men: one for mineworkers from the Carletonville study[222] and the other for truck driver clients of sex workers in KwaZulu-Natal[331] and these are shown in Figure 6.12 and Table 6.4. For neither group did the age-prevalence deviate significantly from a constant, in contrast to all the other data sets, although the prevalence among the truck drivers (56.3%) was approximately twice the prevalence among the mine workers (28.6%).

Commercial sex workers

The age-prevalence of infection among commercial sex workers operating at truck stops in the KwaZulu-Natal Midlands and near the gold mines in Carletonville is shown in Figure 6.13 and Table 6.5. For the women operating out of truck stops the data differed significantly from a straight line (χ^2 test of deviance, p = 0.0013) and the log-normal function gave a statistically good fit, even though the number of sex workers in older age groups was small. However, for the women operating near gold mines in Carletonville the data did not differ significantly from a straight line but the sample size was small and the power to demonstrate differences correspondingly weak. The prevalence of infection among women operating near the mines in Carletonville was significantly higher (68.7%) than among the women operating along the trucking route in KwaZulu-Natal (50.0%).

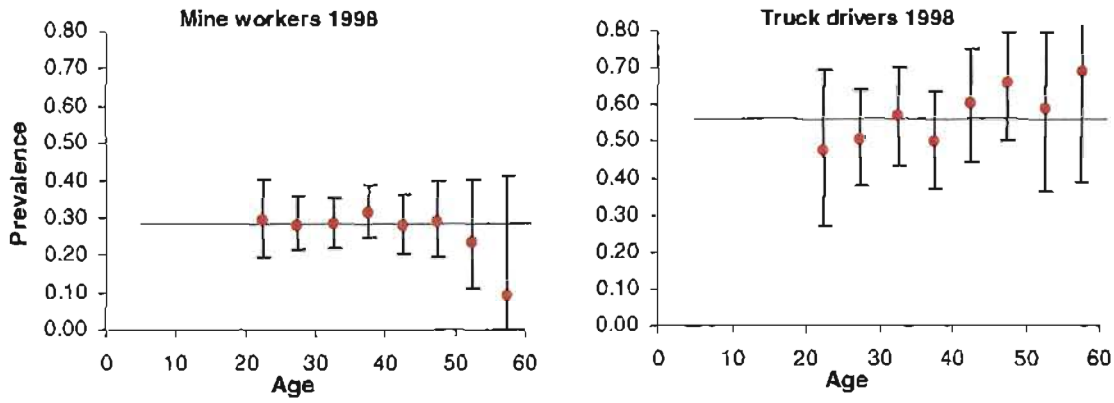


Figure 6.12 Age-prevalence data for mine workers in Carletonville and truck drivers in KwaZulu-Natal in 1998. The data and the parameters of the linear fits are given in Table 6.4. Error bars are 95% binomial confidence limits.

Table 6.4 Age-prevalence of infection among mine workers in Carletonville and truck drivers in KwaZulu-Natal. The parameter values of the linear fits and the observed and fitted prevalences are provided.

Parameter values		Age	Total	Prev	Fitted	Parameter Values		Age	Total	Prev	Fitted
Miners 1998						Truck drivers 1998					
		15-19	2	0.000	0.286						
Constant	0.286	20-24	82	0.293	0.286	*Constant*	0.562	20–24	23	0.478	0.562
P-value	0.506	25-29	167	0.281	0.286	*p-value*	0.502	25–29	61	0.508	0.562
		30-34	191	0.283	0.286			30–34	56	0.571	0.562
		35-39	196	0.316	0.286			35–39	58	0.500	0.562
		40-44	129	0.279	0.286			40–44	43	0.605	0.562
		45-49	83	0.289	0.286			45–49	44	0.659	0.562
		50-54	38	0.237	0.286			50–54	22	0.591	0.562
		55-59	11	0.091	0.286			55–59	13	0.692	0.562
		All ages	899	0.286				All ages	320	0.563	

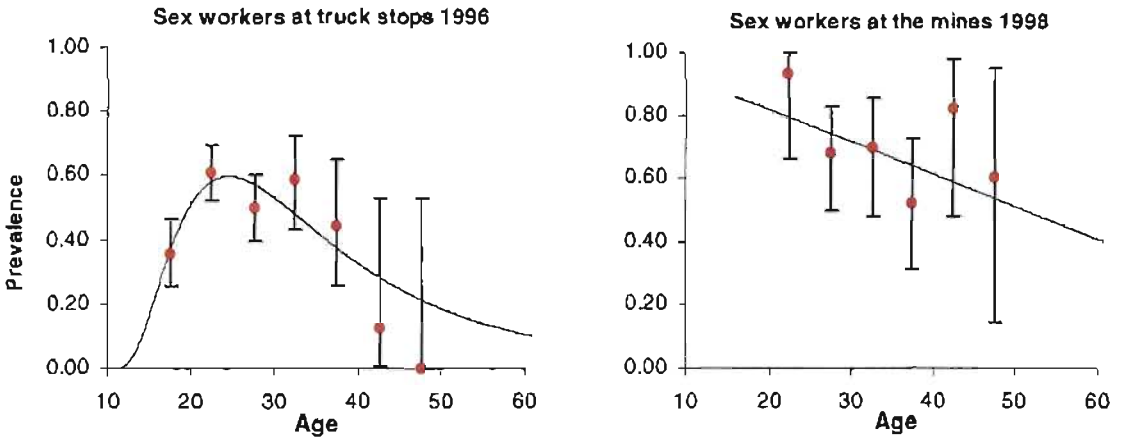


Figure 6.13 Age-prevalence for sex workers operating at truck-stops in KwaZulu-Natal and at a gold mine in Carletonville. The data, the parameters of the fits and the goodness of fit are given in Table 6.5. Error bars are 95% binomial confidence limits.

Table 6.5 Age-prevalence of infection among commercial sex workers operating at truck-stops in KwaZulu-Natal, and at a gold mine in Carletonville. Parameters values of the log-normal fit and linear fit, and the observed and fitted prevalences are provided.

Parameter values		Age	Total	Prev	Fitted	Parameter values		Age	Total	Prev	Fitted
Truck stop sex workers 1996						Mines Sex workers 1998					
		15-19	87	0.356	0.365						
		20-24	138	0.609	0.583			20-24	14	0.929	0.791
N	17.928	25-29	100	0.500	0.573	*constant*	1.020	25-29	34	0.676	0.740
Mode	24.480	30-34	48	0.583	0.479	*slope*	-0.010	30-34	26	0.692	0.689
σ	0.664	35-39	27	0.444	0.374	*p-value*	0.074	35-39	25	0.520	0.638
M	22.495	40-45	8	0.125	0.284			40-44	11	0.818	0.587
p-value	0.005	>45	4	0.000	0.214			45-49	5	0.600	0.536
Max. prev.	0.597	All ages	412	0.500				All ages	115	0.687	

Work place surveys

Figure 6.14 and Table 6.6 show the age-prevalence of infection from a national work-place survey carried out in a large parastatal company across the country. There were few women in the survey and the data for men were separated into those who live in hostels or camps and those who live in their own homes. For the men who live in hostels and camps the prevalence peaked at the age of 35.9 years, fairly similar to that among men in the community based surveys. For men living in hostels and camps the sample sizes were small so that the error bars were relatively large. The prevalences for men living in their own homes, however, were low and did not deviate significantly from a straight line. The average HIV prevalence among men living in their own homes was about one third (6.2%) of that among the men living in hostels or camps (18.1%).

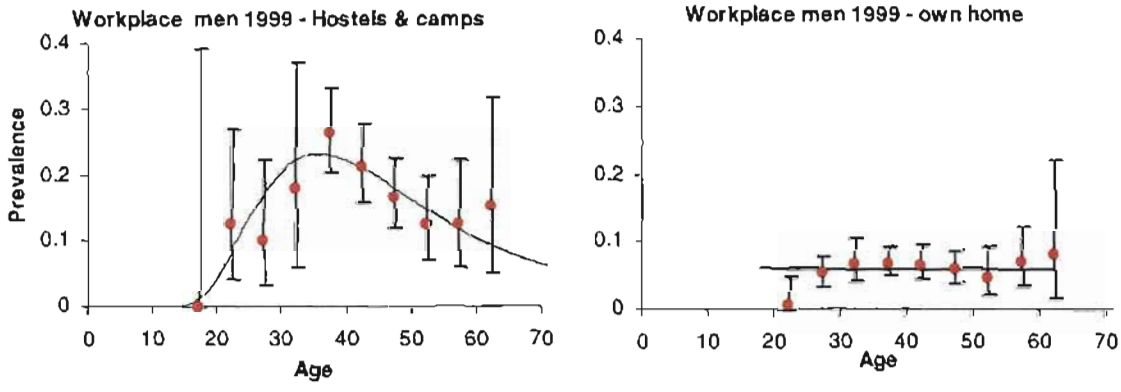


Figure 6.14 Age-prevalence for men working in a large parastatal industry in 1999, separated according to those who live in a hostel or a camp, or those men who live in their own home. The data, the parameters of the fits and the goodness of fit are given in Table 6.6. Error bars are 95% binomial confidence limits.

Table 6.6 Age-prevalence of infection among men working for a large parastatal, for those who own their own homes and those who live in hostels or camps. Parameter values of the log-normal fit and the linear fit, and the observed and fitted prevalences are provided.

Parameter	value	Age	Total	Prev	Fitted	Parameter values		Age	Total	Prev	Fitted
Workplace men living in hostels & camps 1999						Workplace men living in own home 1999					
		15-19	6	0.000	0.014			15-19	6	0.167	0.062
N	9.009	20-24	40	0.125	0.087	*constant*	0.062	20-24	112	0.009	0.062
Mode	35.976	25-29	49	0.102	0.174	*p-value*	0.110	25-29	459	0.054	0.062
σ	0.521	30-34	28	0.179	0.223			30-34	317	0.069	0.062
m	34.076	35-39	196	0.265	0.230			35-39	643	0.070	0.062
p-value	0.477	40-44	193	0.212	0.211			40-44	448	0.067	0.062
Max. prev	0.232	45-49	246	0.167	0.181			45-49	458	0.061	0.062
		50-54	113	0.124	0.148			50-54	165	0.048	0.062
		55-59	72	0.125	0.119			55-59	156	0.071	0.062
		61-65	33	0.152	0.093			61-65	37	0.081	0.062
		All ages	976	0.181				All ages	2801	0.062	

Comparisons between data sets

In order to compare the shapes of the age-prevalence distributions between various groups of data, 95% confidence ellipses for the fitted parameters were constructed; first for all women (Figure 6.15), then for all men (Figure 6.16), and finally for men and women in KwaZulu-Natal (Figure 6.17).

Figure 6.15 shows that data for women attending antenatal clinics are clustered, although there was a shift in the mode (age of peak prevalence) over time as the epidemic started to show signs of levelling off. The shapes of the curves for the ANC women were similar with similar distributions and the value of standard deviations did not vary much between antenatal clinic attendees, nationally as well as in Hlabisa. The data for women in the community survey in 1991 showed a wider distribution than for those in the community in 2000. The distribution for women in urban (1998) and rural (2000) communities did not differ significantly.

Data for men in South Africa (Figure 6.16) showed wider distributions for migrant mine workers than for men in the community. There were no significant differences between the distributions for men in the three community surveys although the mode shifted to older ages by about three years.

Figure 6.17 shows that data for women attending antenatal clinics in KwaZulu-Natal were clustered and that the shapes of the curves for women were similar not only for antenatal clinic attendees over different years, but also for women from community surveys and for female sexworkers. The mode for women in the community surveys shifted by about 4 years from 1991 to 2000; for men it shifted by about 3 years over the same period. The distributions for the men in the two community surveys were similar, while the distributions for the men were narrower (indicated by the smaller standard deviation) than for women.

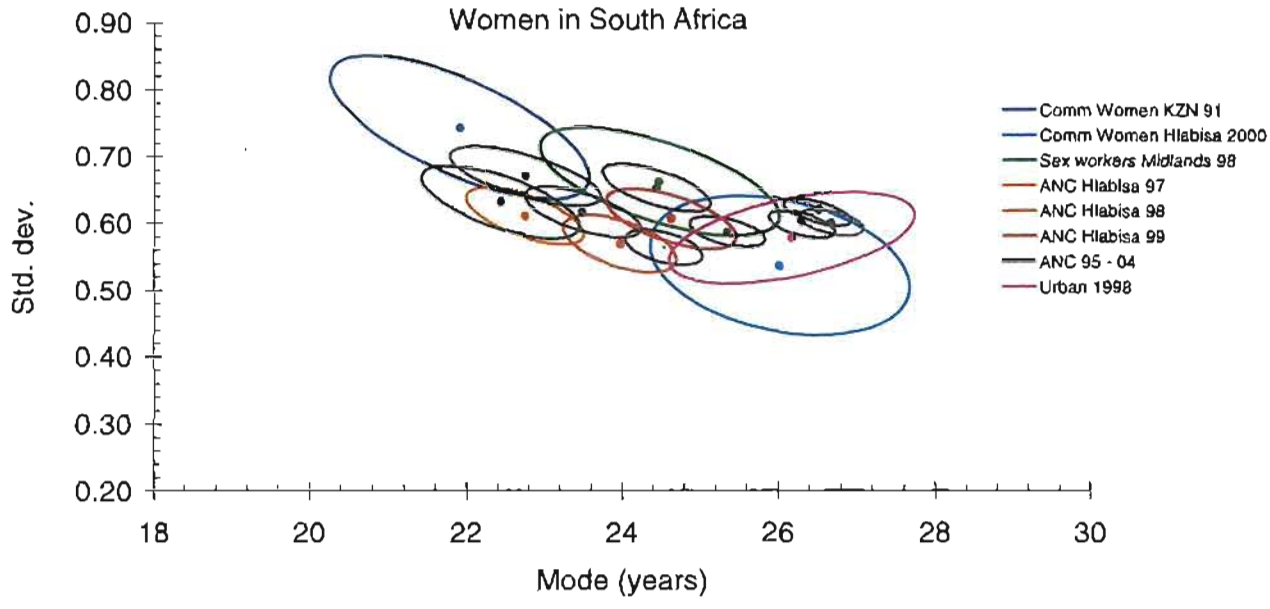


Figure 6.15 *95% Confidence ellipses for the fits to data sets on women in South Africa*

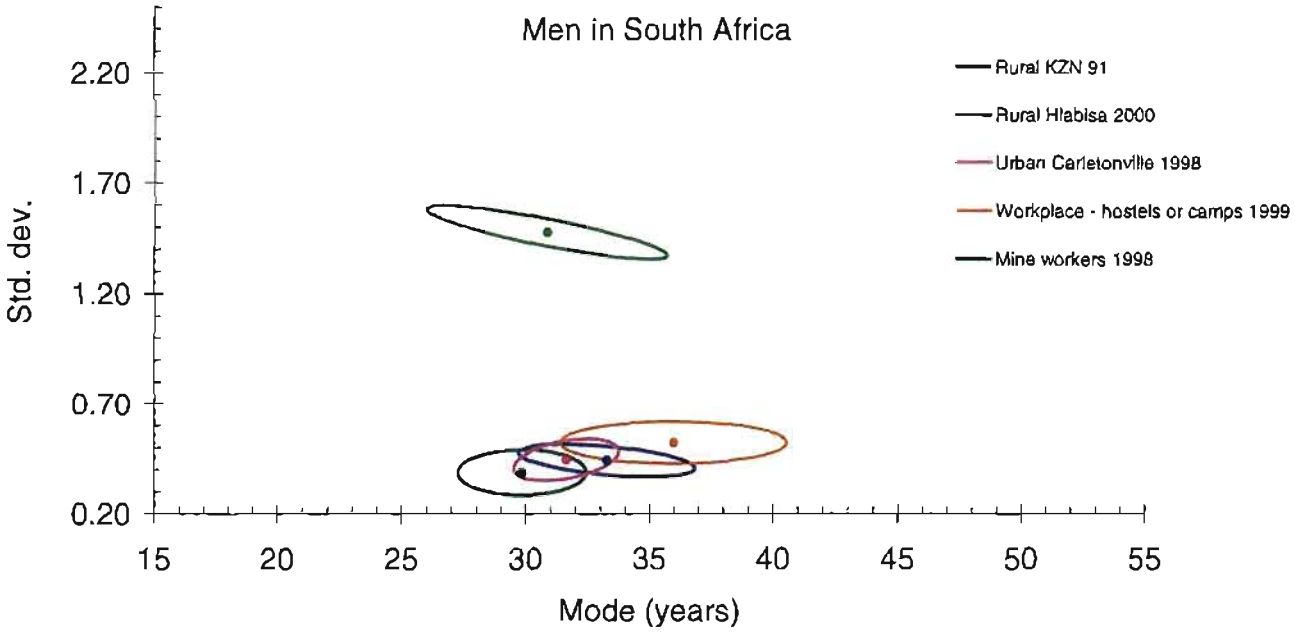


Figure 6.16 95% Confidence ellipses for the fits to data sets on men in South Africa

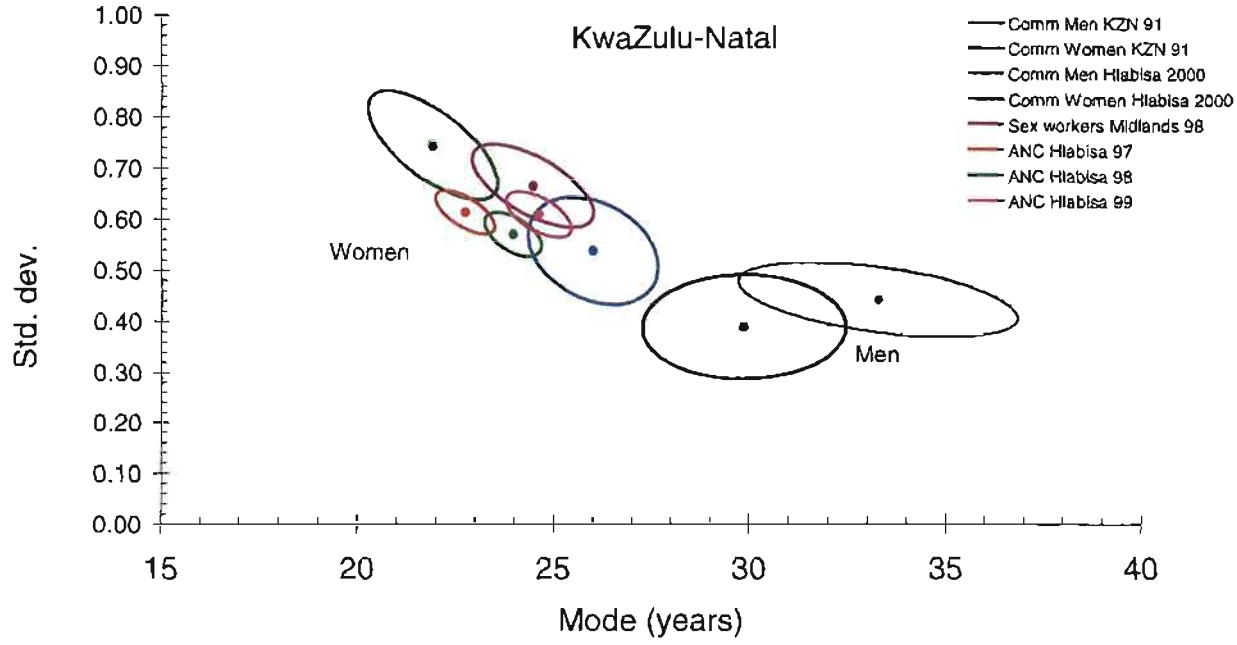


Figure 6.17 95% Confidence ellipses for the fits to data sets available for men and women in KwaZulu-Natal.

To illustrate the above observations in more detail Figure 6.18 shows a series of comparisons in which the curves are all scaled so that the area under each curve is one. This is done to facilitate the comparisons of the shapes of the curves since the average prevalence varies widely among the different data sets. Figure 6.18a shows first a comparison of the age-specific incidence of pregnancy (using fertility data from KwaZulu-Natal) and the average fit to the age-specific prevalence of HIV among women attending antenatal clinics in the years 1995, 1997 and 1998. Since the age-specific incidence of pregnancy gives a measure of sexual activity it also gives a measure of risk of infection although this will be confounded by the use of non-barrier methods of contraception. Nevertheless the curves are surprisingly similar. In Figure 6.18b the HIV prevalence data for women attending antenatal clinics are compared to the data for urban community women. Compared to the urban community survey data, antenatal clinic data appear to overestimate infection rates in younger women and underestimate infection rates in older women. The best comparison between men and women is based on the urban community survey carried out in Carletonville in 1998 and these data are shown in Figure 6.18c from which it is seen that the curve for men is shifted to older age-groups, as compared to women in the same community, by about five years. Finally Figure 6.18d shows a comparison of the fits to the data for urban men and migrant workers with the latter being essentially constant with age.

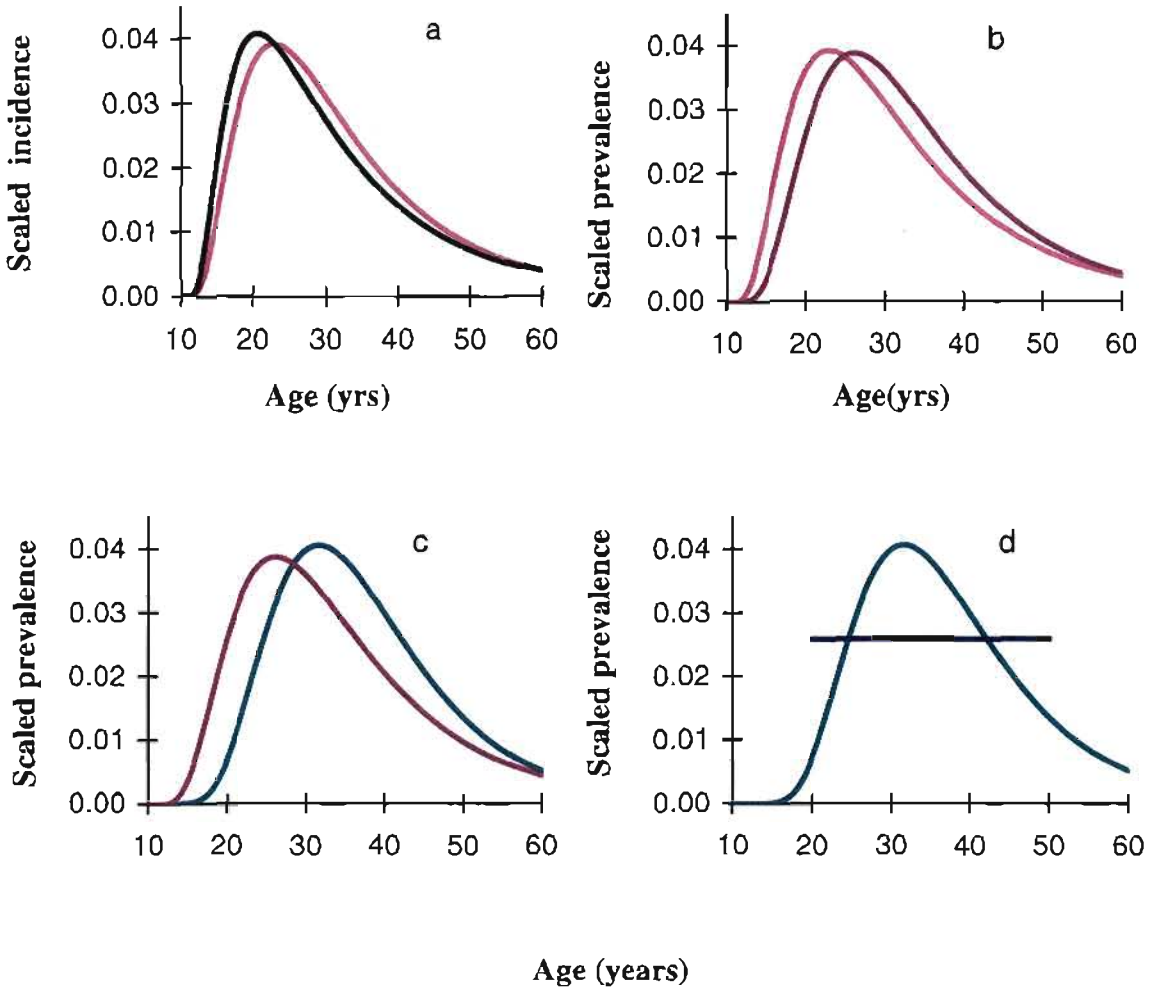


Figure 6.18 Age-specific incidence of fertility and age-specific prevalence of HIV infection. a) Left: fertility; right: women attending antenatal clinics. b) Left: women attending antenatal clinics; right: urban women. c) Left: urban women; right urban men. d) Curve: Urban men; straight line: migrant men. All the curves are scaled so that the area under the curve is one. The line for the migrant men is scaled by the same factor as the curve for the urban men.

Discussion

This chapter investigates patterns of HIV infection, reflecting the age-specific risk of infection, and how these patterns vary with age, gender, migrancy status and between urban and rural settings.

National antenatal clinic surveys provide data by age for women (at a national level) over time and show the rapid increase in HIV prevalence in all age groups over a ten year period (Figure 6.2). Although the shapes of the prevalence distributions by age remained fairly similar over time, the age at which the prevalence peaked shifted significantly to older age groups by about 3.5 years, from an average of about 23 years in 1995-1998 to an average of 26.5 years in 2002-2004 (Figure 6.4). As the epidemic is starting to level off, this is most probably a reflection of the ageing epidemic in South Africa. While the change in prevalence over time seems to be stabilizing among young women between the ages of 15 to 24 years, the prevalence in the older ages was still showing an increase in 2004 (Figure 6.6). In addition to the epidemic showing signs of leveling off, this could also be due to behavioural changes that are more likely to occur among younger women before it occurs among older women.

Data from three community surveys allowed comparisons between men and women and between urban and rural settings. Comparison between female and male prevalence show higher rates among females than males in all three surveys with an average female to male ratio of about 1.7 (Figure 6.11). This is very close to the ratio of 1.73 (prevalence of 20.2% among females and 11.7% among males, aged 15 to 49 years) obtained from the national population based survey conducted by the HSRC in 2005.[470] The three community surveys analysed here showed much higher prevalences among young women (15-24 years) than among young men (with an average female to male ratio for the three surveys of 12.7), while the female to male ratio in the age groups 25 to 49 years was about 1.

Analysis of the various data sources in this chapter revealed four main patterns of infection: among women attending antenatal clinics, among women in population surveys, among men in population surveys, and finally among migrant men. The pattern of infection does not appear to be changing substantially with time, although the peak prevalence is shifting to older age groups as the epidemic is maturing. Differences

between urban and rural populations were not significant. Data for men generally show narrower distributions (smaller values for the standard deviations in the log-normal fits) than for women, while the maximum prevalence for men occurs 5 to 7 years later than for women.

A number of important conclusions follow from this analysis. First of all, when the epidemic growth rate is very high, in particular in the early stages of the epidemic, the age-specific prevalence of infection gives an approximate measure of the age-specific incidence of infection and this is supported by the finding that the shape of these curves for particular populations between 1995 and 2004 does not vary greatly over time. Reliable estimates of the age-specific incidence of infection are essential for developing reliable demographic models to forecast the course of the epidemic and against which to assess the impact of interventions, and will be discussed in detail in further chapters in this thesis.

Comparing the age-specific prevalence of infection among women attending antenatal clinics with that of urban community women shows that the antenatal clinic data tend to overestimate the prevalence of infection among younger women and underestimate it among older women. The age-specific prevalence of infection among men is shifted up by about five to seven years as compared to that for women probably because males are usually older than their female sexual partners. The two data sets for migrant workers show a completely different pattern of infection with no significant variation with age. There are no very young migrant workers in the sample but these data suggests that among older migrant workers the risk of infection does not fall off in the way it does among all of the other groups for which data have been presented. It seems reasonable to suppose that migrant men, through the nature of their work, remain at high risk of infection as they get older since they do not have the social support provided in even the poorest of stable communities.

Finally, there were no significant differences between the data sets for people living in urban and rural areas as indicated by the results shown in Figure 6.10 so that the age-risk of infection does not appear to depend on whether or not people live in urban or rural areas. This, in turn, is probably a reflection of the high rate of circular migration between urban and rural areas in South Africa.[521]

The data presented here show alarmingly high prevalence rates among young women aged 15 to 24 years and prevalence rates of close to 60% in some groups of 25-29 year old women who are not commercial sex workers. Although the prevalence among women aged 15 to 24 years seems to be levelling off in most groups, much more work is needed to understand the reasons for these very high infection rates and to find ways to protect young women from becoming infected. It is of interest to note that in most of the data sets for women (antenatal clinic as well as community women), the prevalence tends to rise again among women aged 45 years and older, after having come down from its peak value in younger age groups. Although the sample sizes for women in this age group are generally small, this increase is observed almost consistently and needs to be further investigated. The data also highlight the increased risk of infection among migrant men, especially among older men, and this too must be taken into account when designing interventions to manage the epidemic. Finally, while the analysis in this chapter highlights the urgency of the HIV situation and the need to deal with the spread of infection effectively, it can also be used as a basis for predicting the future course of the epidemic, for planning effective responses and for evaluating the impact of interventions.

CHAPTER 7 Comparison between antenatal clinic and community based estimates of prevalence

> "At the time I read the report with great interest, but I never imagined I was looking at the first sign of an epidemic, that in just 20 years would have infected 60 million people, killed 22 million and achieved the status of the most devastating epidemic in human history"
>
> Peter Piot , 2001[522]

Introduction

Much of our understanding of the HIV epidemic in South Africa is based on prevalence data collected from surveillance among pregnant women attending public sector antenatal clinics. Antenatal clinic surveillance has been used to determine the overall HIV prevalence, age-specific prevalence, geographical variation and trends over time of HIV among women of reproductive age and hence to derive estimates of the overall burden of disease in the country.

In the mid 1980s, facility-based sentinel surveillance of HIV was recommended by the World Health Organization for monitoring the HIV epidemic, mainly because of easy access to people attending public health facilities.[471] In most countries in sub-Saharan Africa in which the HIV epidemic has spread into the general population, surveillance among pregnant women attending public sector antenatal clinics has since become the primary source of data on the spread of HIV.[523] In South Africa, antenatal clinic surveillance was initiated in 1990[23] and has since been conducted annually. Pregnant women are used as an indicator group for infection in the heterosexual population because they represent a readily accessible subgroup of sexually active adults from whom blood is routinely collected to test for syphilis or haemolytic diseases and among whom the trend of HIV infection is believed to mirror that in the overall adult population.[23]

In order to assess whether antenatal clinic prevalence accurately reflects community based prevalence in rural KwaZulu-Natal we compared data collected from a community based survey (the Vaccine Preparedness Study) in the rural community of Hlabisa between 2000 and 2002 to data collected independently from antenatal clinics in the same area from November 2001 to February 2002.

Methods

Community-based survey

HIV prevalence was measured as part of a community–based survey (the Vaccine Preparedness Study) conducted in Hlabisa, a rural district in KwaZulu-Natal, between February 2000 and March 2002. The purpose of the study was to determine the preparedness of the community for participation in future HIV vaccine and prevention trials, to collect key baseline demographic and health variables and to obtain community-based estimates of HIV prevalence. Interviews were conducted among 2314 adult participants, of whom 1719 (74%) were female. Hlabisa has a large migrant population and many men work and live away from home (e.g., working in factories in Empangeni or on the mines in Carletonville). The number of men who participated in the survey was therefore small (n =595).

Data on key demographic and health variables were collected by trained research assistants using standard questionnaires developed for men, women and households. Dried blood spots (DBSs) from a finger prick were collected on high-grade filter paper from each study participant who gave written, informed consent to having a blood sample taken. Pre-and post-test counseling were provided to those participants who wanted to know their results. Confidentiality was maintained by identifying blood specimens by bar code numbers only, while only two of the study investigators had access to the full data base. Samples were tested for HIV by the Virology Laboratory at the University of Natal in Durban using commercial third and fourth generation HIV ELISAs. Ethical approval for the study was obtained from the University of Natal Ethics Committee.

Antenatal clinic survey

Between November 2001 and February 2002 a survey was conducted, independently of the community-based survey, among women attending antenatal clinics (including fixed primary health care clinics, mobile clinics and the Hlabisa hospital) in the Hlabisa district. Blood samples that were routinely collected from pregnant women attending antenatal clinics for syphilis serology during this four-month period were used for anonymous HIV antibody testing. Only the age of the participant and the clinic numbers were recorded. Blood samples were analyzed at the University of Natal Department of Virology using a Uniform II (Vironostika) test for first line HIV and Abbott IMX as a confirmatory test.

Results

Response rates for HIV testing in the community-based survey were low and of the 1719 women (aged 15 to 54 years) who participated in the study, 34% consented to having a blood sample taken. Only 26% of the men (aged 15 years and above) consented to having a blood sample taken. Age-specific HIV prevalence data were therefore collected from 581 women and 154 men in the community. HIV prevalence is reported in Table 7.1 by age group for women and men in the Hlabisa community (2000-2002), and for women attending antenatal clinics (2001-2002).

Table 7.1 HIV prevalence by age for adult men and women in the community, and for women attending antenatal clinics in Hlabisa (2000-2002)

	Community men			Community women			ANC women		
Age	total	Prev (%)	95% CI	Total	Prev (%)	95% CI	total	Prev (%)	95% CI
15-19	50	2.0	0.1 -10.6	4	0.0	0.0 -52.7	3	0	0 -52.7
20-24	25	4.0	0.1 -20.4	180	14.4	9.6 -20.4	179	22.9	17.0-29.8
25-29	17	41.2	18.5 -67.1	114	31.6	23.2 -41.0	185	50.8	43.4-58.2
30-34	8	25.0	3.2 -65.1	65	41.5	29.4 -54.4	89	47.2	36.5-58.1
35-39	9	11.1	0.3 -48.2	46	39.1	25.1 -54.6	73	38.4	27.3-50.5
40-44	11	36.4	11.0 -69.2	53	16.9	8.0 -29.7	44	36.4	22.4-52.3
45-49	7	14.3	0.4 -57.9	48	8.5	2.5 -20.1	15	26.7	7.8-55.1
50-54	8	12.5	0.3 -52.8	39	10.3	2.9 -24.3	3	33.3	0.8-90.5
55-59	17	6.0	0.3 -28.8	31	16.1	5.4 -33.7			
Total	152	12.5	7.7 -18.8	580	22.2	18.8 -25.6	591	38.2	33.4-43.6

HIV prevalence among women

HIV prevalence data from 581 consenting women in the community were compared to data from 591 women attending antenatal clinics during the same time period for which HIV and age data were available (Table 7.1). In all but one age-group, HIV prevalence among women attending antenatal clinics was higher than among women in the general population. The overall HIV prevalence among women attending antenatal clinics (38.2%, 95% CI: 33.4–43.6%) was significantly higher than among women in the general population (22.2%; 95% CI: 18.8–25.6%, $p = 0.0001$). The overall prevalence of HIV in the two groups remained significantly different after standardizing the data to the age distribution of women aged 15 to 54 years in the general population in Hlabisa (31.3%

among antenatal clinic attendees versus 24.3% among women in the general population, $p = 0.0004$)

The prevalence data for the two groups were fitted to log-normal distributions using a maximum likelihood procedure and are presented in Figures 7.1 and 7.2. Although the data were collected over a short period of time it is important to determine the presence or otherwise of an overall time trend in the data because the ANC data were collected between November 2001 and February 2002 while the community data were collected between February 2000 and February 2002. The log-normal age-prevalence model for the community survey was therefore extended to include a linear time trend. The reduction in the deviance for the extended model was tested using a chi-square test and the trend was not significant ($p = 0.455$).

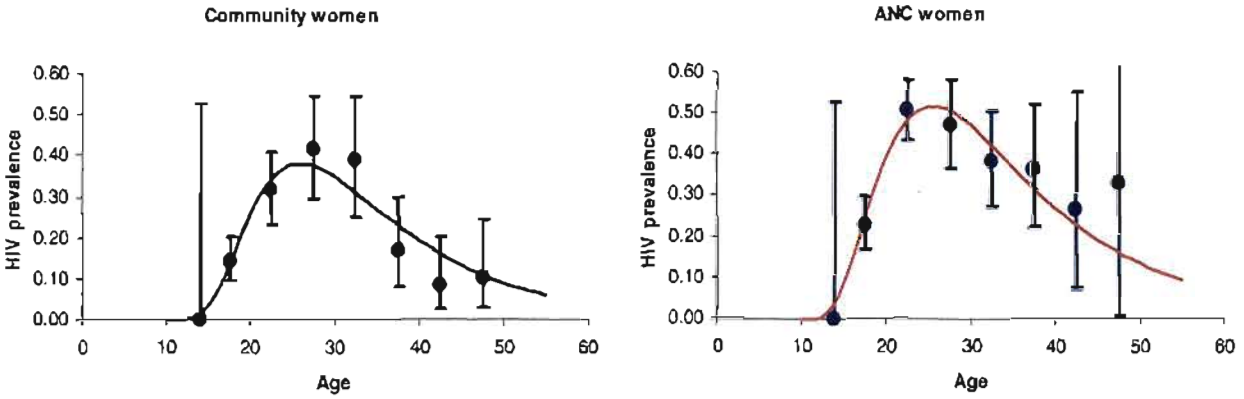


Figure 7.1 Log-normal curves fitted to the HIV prevalence data for women who attended antenatal clinics and women from the general population in Hlabisa between 2000 and 2002. Observed data points are plotted with 95% binomial confidence intervals.

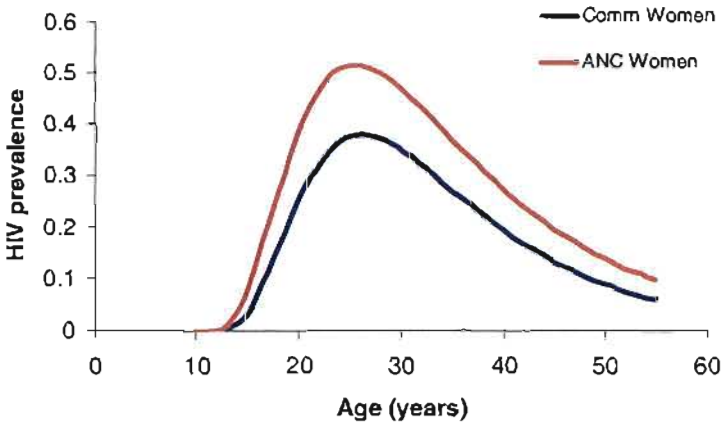


Figure 7.2 Log-normal curves fitted to the HIV prevalence data for women who attended antenatal clinics and women from the general population in Hlabisa.

Comparison of risk factors for HIV among women who did or did not consent to provide blood samples for HIV testing

Of concern in this study was the fact that only 34% of women in the community-based survey consented to having an HIV test done and it is therefore important to consider differences between those who consented and those who did not that might bias the data. Of those who refused having a blood sample taken, 61% gave the fear of knowing their status as the reason for refusal. A number of variables were compared between those who consented to having a blood sample taken and those who did not, including the proportion of women who had been diagnosed with a sexually transmitted infection in the last twelve months, the number who thought their husbands had had other sexual partners, age, marital status, age at first sex, the number of sexual partners they had had, the likelihood that women had changed their behaviour because of AIDS, and their perception of their risk of infection. The results, summarized in Table 7.2, indicate that the difference in HIV prevalence between women in the community and women attending antenatal clinics is unlikely to be explained by the effect of non-response in the community survey. Those who consented had their first sexual experience at a slightly younger age (17.0 years) and had more sexual partners (6.7% reported having more than 1 partner in the last 12 months) than those who refused to provide a blood sample (age at first sex 17.4 years; 3.5% had more than 1 partner in the past 12 months) so that, if anything, the prevalence of infection is likely to be lower among women who refused to participate leading to an even greater difference between the ANC and community based estimated than reported here.

HIV prevalence among men in the community

Of the 152 men who consented to having a blood sample taken, 12.5% (95% CI: 7.7-18.8%) were HIV positive. Fifty percent of the men who consented were younger than 25 years so that the samples of the men in the older age categories were small, and hence standard errors for estimates of HIV prevalence were large and confidence intervals were very wide. Figure 7.3 shows the HIV prevalence, with 95% confidence intervals, by age for men in the community, fitted to a log-normal distribution.

Table 7.2 Comparison of potential risk factors for HIV between those women who consented and those who did not consent to having blood taken for HIV in the Hlabisa community-based survey

Risk factor	Women who gave consent to have blood taken n = 587	Women who did not give consent n =1139	*p-value*
Percent ever tested for HIV	7.4%	5.5	0.127
Mean age in years (SE)	27.7 (0.47)	28.3 (0.32)	0.309
Percent currently married or in a stable relationship	76.9%	73.6%	0.134
Diagnosed with an STI in the last 12 months	3.8%	2.8%	0.251
Mean age at first sex in years (SE)	17.0 (0.10)	17.4 (0.09)	0.004
% Having more than 1 sexual partners in last 12 months	6.7%	3.5%	0.006
Thought husband had other sexual partners	60.8%	55.6%	0.149
% Never using condoms	77.7%	74.6%	0.163
Perception of risk			
No risk of HIV	44.7%	46.5%	0.265
Small risk	32.3%	27.8%	
Big risk	23.1%	25.7%	

Comparison between men and women in the community

Figure 7.4 shows the comparison of age-specific prevalence between men and women in the Hlabisa community. HIV prevalence among young women (age 15 to 24 years) were significantly higher than among men of the same age (2.7% vs 21.1%, respectively; χ^2 = 14.2, p<0.001). Differences in prevalence between men and women in older age groups were not statistically significant, mainly because of the small sample sizes and large standard errors (in particular for men). Log-normal curves fitted to the data show that for women in the community prevalence peaked at 35.4% at age 27 years and for men prevalence peaked 6 years later (at age 33 years) at 32.0%. In contrast, HIV prevalence among female antenatal clinic attendees peaked at 51.5% at age 26 years.

When combined, the overall adult HIV prevalence in the general population in Hlabisa was 20.2% (95% CI: 17.3-23.1%).

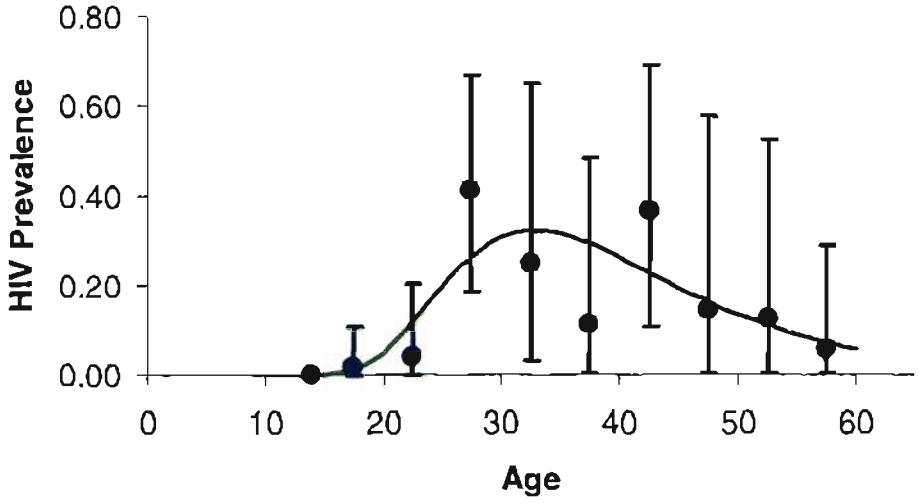


Figure 7.3 HIV prevalence among men in the Hlabisa community. Large 95% confidence intervals is a reflection of small sample sizes

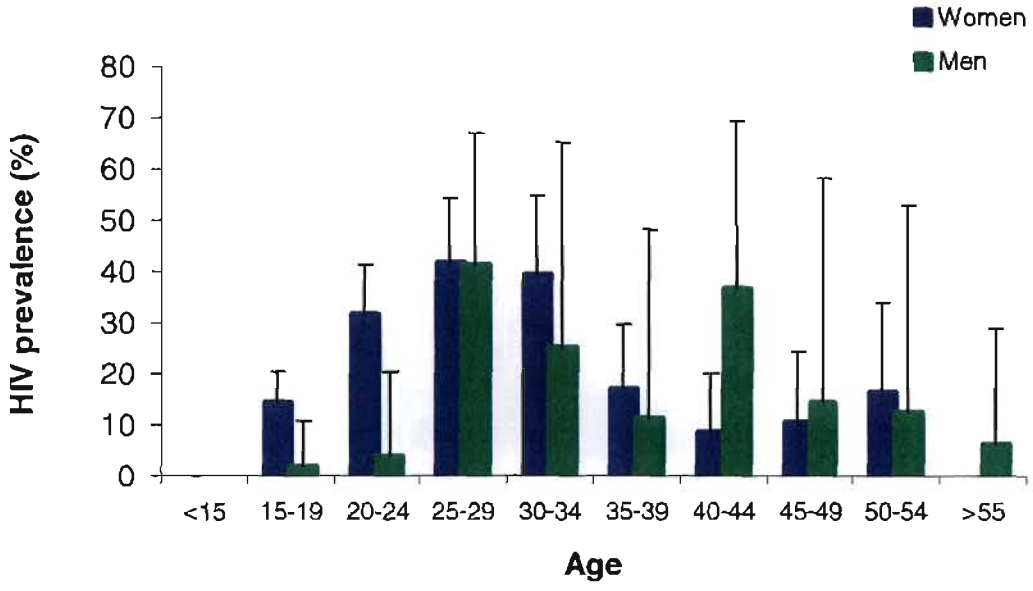


Figure 7.4 Comparison of age-specific prevalence between men and women in the Hlabisa Community

Discussion

Several studies conducted in sub-Saharan Africa have shown that HIV prevalence among antenatal clinic attendees is generally similar to adult female prevalence in the same community[524-526] in both high[527] and low[528] fertility populations. However, in a comparison of HIV prevalence in community-based and antenatal clinic surveys in Mwanza, Tanzania,[529] the prevalence among women attending antenatal clinics (3.6%) was lower than among women in the general population (4.7%, p = 0.025), but there was no difference between the two groups after adjustment for parity (4.6 versus 4.7%, p = 0.95). A comparison between HIV prevalence measured among adults in the community and HIV prevalence measured by sentinel surveillance in antenatal clinics in Yaounde, Kisumu and Ndola[530] showed that antenatal clinics underestimated HIV prevalence in the general female population (aged 15-49 years) in Yaounde (5.5% and 7.8%, respectively) and Ndola (27.3% and 31.9%, respectively), while prevalence among antenatal clinic attendees in Kisumu was similar to that of women in the general population (30.6% versus 30.1%, respectively). Factors identified to influence the difference in HIV prevalence between antenatal clinic attendees and the population included age, marital status, parity, schooling and contraceptive use.[530]

In contrast to these findings, the study in Hlabisa shows that antenatal clinic HIV prevalence over-estimates prevalence in the general female population (as well as in the general adult population). A major limitation of this study, however, is that two-thirds of the women in the community survey refused to give a blood sample to be tested for HIV. Differences in potential risk factors for HIV between those who consented to having blood taken and those who did not were considered (Table 7.2) but it was not possible to identify any potential confounding factors that might significantly bias the ANC estimate of prevalence upwards relative to the community estimate of prevalence.

In countries with generalized epidemics, the HIV prevalence among ANC attendees has been used as a proxy for prevalence in the general heterosexual population. When compared to the general adult population (men and women aged 15 to 49 years), a review of studies conducted in sub-Saharan Africa showed that prevalence among pregnant women is a good approximation to prevalence among the sexually active adult population (Appendix 7.1).[531] In all these studies, estimates of adult HIV prevalence (men and

women aged 15–49 years) from the community were compared to prevalence estimates from ANC attendees in the same locality over the same time period.[531] Of 14 comparisons in seven countries, only two showed a significant difference between ANC and community prevalence. Prevalence from the ANC sample overestimated community prevalence in 1997 in Kisumu, Kenya,[530] and underestimated community prevalence in 1999 in Zambia.[532]

In contrast to the above observations, however, population based surveys (including Demographic and Health surveys) conducted at a national level in several countries in sub-Saharan Africa over the last few years, have shown that national estimates of adult HIV prevalence are generally lower than those obtained from national antenatal clinic surveys (Table 7A, Appendix 7.1). In South Africa, for example, the population-based survey conducted by the HSRC in 2002[469] reported a national adult (aged 15-49 year) prevalence of 15.6%,(95% CI: 13.9-17.5%) compared to the national ANC estimate for the same year of 26.5% (95% CI: 25.5 – 27.6%). The prevalence among women from the population based survey of the same age group (15-49 years) was also significantly lower (17.7% among all women and 20.7% among Black African women) than the national ANC estimate. Similarly, HIV prevalence among adult women aged 15-49 years from the 2005 HSRC population-based survey[470] was significantly lower (20.2% among all women and 24.4% among Black African women) than the national HIV prevalence from antenatal clinics for 2004 (29.5%; 95% CI: 28.5-30.5). Both estimates may reflect sampling biases. For example, national population based surveys, by nature of their design, are more likely to exclude groups at higher risk of infection such as mobile populations living in hostels, sex workers and army recruits, and estimates from these surveys may underestimate the true prevalence in a population. In addition, non-response or absence from a household at the time of the survey may bias population based estimates. At the same time, antenatal clinic estimates may be biased upward because it represents pregnant women who attend public health services and exclude those who are not sexually active and those seeking private care, among whom the prevalence of infection might be lower. It is recognized that both antenatal clinics and national population based surveys have strengths and weaknesses and these are described in more detail in Appendix 7.2. Taken together, however, antenatal surveillance and population based surveys can provide complementary information and should both be considered when obtaining a national estimate of HIV prevalence.[533]

The prevalence measured among antenatal clinic attendees in the Hlabisa study is close to the reported value for the province of KwaZulu-Natal. However, the results reported here suggest that the ANC data might overestimate the actual prevalence among women by as much as 29% (95% CI: 5%–53%) which would have important implications for estimates of the total number of people infected with HIV in the country as a whole. Further studies are needed to investigate the relationship between the prevalence of HIV infection among women attending ANC clinics and among women and men in the general population and to understand the biases that operate in both and that might affect the estimates of HIV prevalence.

Appendix 7.1 Comparison between antenatal clinic prevalence and population-based prevalence of HIV

Table 7A Antenatal clinic prevalence and adult (men and women) community based prevalence. In part (a) HIV prevalence from community-based studies are compared with HIV prevalence from ANC women at the same locality over the same time period (adapted from Grassly *et al.*[531]). In part (b) national adult (aged 15-49 year for women and 15-54 years for men) HIV prevalence from population based demographic and health surveys (DHS) are compared with HIV prevalence estimates from national ANC surveys.

Location/community	Year	ANC prevalence	n	Population prevalence	n	Ratio ANC:Comm	95% CI
a. Community specific[531]							
Fort Portal Uganda	1995	18.4	477	22.9	875	0.80	0.64-1.01
Chelston Zambia	1995-96	26.1	532	25.7	1909	1.02	0.86-1.20
Chelston Zambia	1999	25.9	776	23	1768	1.13	0.97-1.30
Kapiri Mposhi Zambia	1995-96	12.6	422	16.7	760	0.75	0.56-1.02
Kapiri Mposhi Zambia	1999	8.3	300	16.7	724	0.50	0.33-0.75
Yaounde Cameroon	1997-98	5.5	1532	6.1	1913	0.90	0.69-1.18
Kisumu Kenya	1997-98	30.6	1480	25.9	1515	1.18	1.05-1.33
Ndola Zambia	1997-98	27.3	1021	28.4	1534	0.96	0.85-1.09
Urban Mwanza Tanzania	1990-91	11.7	1820	11.8	1184	0.99	0.76-1.08
Manicaland Zimbabwe	1998-2000	21.1	1215	22.5	9119	0.94	0.84-1.05
Manicaland Zimbabwe	2001-2003	19.2	1237	19.9	7153	0.96	0.85-1.09
Kagera Tanzania	1993	17.3	2816	18.1	653	0.96	0.80-1.15
Kagera Tanzania	1996	13	2893	12.9	1276	1.01	0.85-1.20
Karonga Malawi	1998-2001	10.4	2998	12.6	833	0.83	0.67-1.02
b. National DHS comparisons							
Burkina Faso[534]	2003	4.4	2422	1.8	7267	2.44	2.20-2.70
Cameroon[535,536]	2004	7.3	6745	5.5	9900	1.33	1.21-1.45
Ghana[537,538]	2003	3.6	13427	2.2	9144	1.64	1.47-1.80
Lesotho[539,540]	2004	27.0	4542	23.5	5043	1.15	1.08-1.22
Kenya[538,541]	2003	9.4	10616	6.7	6001	1.40	1.29-1.51
Mali[542]	2001	3.3	2662	1.7	6846	1.94	1.67-2.21
Rwanda[543]	1997	15.1	1368	11.1	4746	1.36	1.21-1.51
South Africa[25,469]	2002	26.5	16587	15.6	6080	1.70	1.63-1.76
Tanzania [544,545]	2004	8.7	17813	7.0	10747	1.24	1.16-1.33
Zambia[546,547]	2002	19	11975	15.6	3805	1.22	1.14-1.30

Appendix 7.2 Strengths and limitations of antenatal clinic surveillance and population-based surveys

Concerns about the representativeness and accuracy of national HIV estimates derived from antenatal clinic surveillance have led to an increased demand for more surveys and more data on the prevalence and distribution of HIV in the population. In recent years, several countries have included HIV testing in national population-based surveys. Technological developments, such as the use of dried blood spots for HIV sample collection and rapid HIV testing, have greatly facilitated the collection of biological data in population based surveys.

The strengths and limitations of antenatal surveillance and national population based surveys in countries with a generalized epidemic are discussed below.

Antenatal clinic surveillance

Although the main purpose of surveillance based on antenatal clinic attendees is to assess trends in HIV prevalence over time, antenatal clinic surveillance has also been used to estimate population levels of HIV because of the lack of data from other sources.

HIV surveillance in antenatal clinics has been implemented in more than 115 countries worldwide.[523] As in South Africa, these are usually based on anonymous, unlinked, cross-sectional surveys of pregnant women attending antenatal clinics in the public health sector. Only first time attendees are included in order to minimize the chance of any woman being included more than once. Blood is taken routinely from pregnant women for diagnostic purposes (e.g., to test for syphilis or rhesus factor). After removal of personal identifiers (with the exception of a few key characteristics such as age, parity, marital status, clinic location, or urban/rural residence) the blood is tested for HIV. Antenatal clinic surveys are usually done annually at the same time of the year to obtain an estimate of the point prevalence for that year but also to assess trends over time.

Strengths

- Antenatal clinics provide ready and easy access to a cross-section of sexually active women from the general population who are not using contraception. Blood is

drawn for routine testing for syphilis and a portion can be used for anonymous testing of HIV.

- In generalized epidemics, HIV testing among pregnant women is considered a good proxy for prevalence in the general population.
- Annual antenatal clinic survey data can be used to assess trends of the HIV epidemic over time.
- Data for pregnant women will reflect the prevalence in groups that may be of higher risk of infection because of their living arrangements (e.g. workers who live in hostels or army barracks) if there is regular unprotected sexual contact with women in the general population.
- Limitations of antenatal surveillance are recognized and acknowledged, and where possible, correction factors can be developed to overcome some of the limitations. (e.g., prevalence can be age-standardized using the age distribution of the general population).
- Geographical coverage (number and sample sizes of sites) of sentinel surveillance can be expanded, particularly in rural areas, to improve the representativeness of the samples

Weaknesses

- Most sentinel surveillance systems have limited geographical coverage, especially in smaller and more remote rural areas.
- Women attending antenatal clinics may not be representative of all pregnant women because many women may not attend antenatal clinics or may attend private clinics.
- The rate of contraceptive use in a country may affect the number of pregnant women
- Implementation of antenatal clinic based surveillance varies considerably between countries.[548] The quality of the surveys may vary over time depending on available resources.
- Antenatal clinic surveillance does not provide information about HIV prevalence in men. Because these surveys are conducted among pregnant women, estimates for men are based on assumptions about the ratio of male-to-female prevalence that are derived from community-based studies in the region. However, this ratio will vary between countries and over time.

Population based surveys including HIV testing

The demand by decision makers for better data on the burden of HIV/AIDS in countries and the limitations of antenatal surveillance systems with respect to geographical coverage, under-representation of rural areas and the absence of data for men, have led to an interest in including HIV testing in national population-based surveys. Population-based surveys can provide reasonable estimates of HIV prevalence for generalized epidemics, where HIV has spread throughout the general population in a country. However, for low-level and concentrated epidemics, these surveys will underestimate HIV prevalence, because HIV is concentrated in high risk groups and these groups are often not adequately sampled in household based surveys.

In recent years, the number of national population-based surveys that included collection of biological specimens for HIV testing has increased.[533] Many of these surveys covered women and men of reproductive ages (15-49 year old women and 15-59 year old men) and used dried blood spots for specimen collection. Some of the early surveys were designed for unlinked anonymous testing, where the HIV test results could not be linked to individuals, while more recent surveys have incorporated linked anonymous testing, where HIV test results can be linked to behavioral data without revealing the identity of any individual who has been tested.

Strengths

- In generalized epidemics, population based surveys can provide representative estimates of HIV prevalence for the general population, as well as for different subgroups, e.g., urban and rural areas, men and women, age groups and region or province.
- Results from population based surveys can be used as a means to adjust estimates obtained from sentinel surveillance systems.
- Population based surveys provide an opportunity to link HIV status with social, behavioral, and other biomedical information, thus enabling researchers to analyze in more detail the dynamics of the epidemic. Information from this analysis could lead to better program design and planning.

Weaknesses

- In population based surveys sampling from households may not adequately represent high risk and mobile populations. In low-level epidemics or epidemics where HIV is concentrated among high risk groups (e.g., sex workers, men who have sex with men, or intravenous drug users), population-based surveys will underestimate HIV prevalence.
- Non-response (either through refusal to participate or absence from the household at the time of the survey) can bias population based estimates of HIV. Collecting information on non-response can help in the process of making adjustments for non-response.
- Population based surveys are expensive and logistically difficult to carry out and cannot be conducted frequently. Typically, these surveys are conducted every five to ten years.

Combining data from sentinel and population based surveys

Sentinel surveillance and population-based surveys each have strengths and weaknesses but together provide complementary information. Sentinel surveillance provides samples that are consistent over time so that good estimates of HIV trends can be obtained. They can also provide good overall national coverage, and allow estimates to be generated by age and geographical location. Population-based surveys, on the other hand, provide much better coverage of the general population, including men, and can provide much more detailed information on social, economic, sexual behaviour and biomedical factors associated with HIV infection. Because of the cost, they can usually not be conducted regularly and therefore provide limited temporal coverage. However, in countries where both surveys have been conducted, analysis of combined data from sentinel surveillance and population-based surveys can provide a clear picture of both overall trends and geographical distribution of HIV as well as detailed information on potential risk factors and groups.

CHAPTER 8 Methods for estimating HIV incidence

"The purpose of models is not to fit the data but to sharpen the questions"

Samuel Karlin, 1983[549]

Introduction

In order to understand the dynamics of an epidemic we need to know not only how much disease there is in a population but also how it is changing with time. The two most fundamental measures of disease, in this regard, are prevalence and incidence, as defined in Chapter 5. While prevalence provides a measure of the cumulative risk of infection, the incidence of infection gives the rate at which new infections are acquired over a certain time period and is therefore a more sensitive measure of the current state of the epidemic. Prevalence data provide valuable information on the burden of disease and are essential for understanding the health impact of a disease within a community and for assessing the need for medical care. Incidence data, on the other hand, give a more immediate measure of the current infection rates and are therefore more sensitive to the changing dynamics of disease transmission, for making reliable projections into the future and for measuring the immediate impact of interventions on infection levels. Incidence data are also more useful than prevalence data for exploring causal theories, where the interest is focused on the rate of change of cases from the normal (disease-free) state to the diseased state. Furthermore, estimates of the risk of acquiring HIV infection are needed in order to establish a research infrastructure for designing clinical and vaccine trials. They are required for determining sample size and resource requirements, to evaluate the effect of interventions, and to identify populations with high transmission rates which could be targeted for future intervention trials.

While many estimates of the prevalence of HIV in South Africa are available in different risk groups from annual national antenatal clinic and other sentinel surveillance, community surveys, and studies among specific risk groups (Chapter 2, Table 2.1), few estimates have been made of incidence. In part this is because prevalence data are easier and less costly to collect than incidence data. Whereas prevalence data can be obtained from cross-sectional studies, it is more difficult to measure incidence. Ideally, one would follow a cohort of people for a year or more to determine the number who became newly

infected with HIV during the course of the study. However, very few cohort studies to obtain estimates of HIV incidence have been performed in South Africa because of the cost, logistics and the ethical considerations of following people to HIV infection.

Several indirect ways, including mathematical and statistical models, have been developed globally to obtain estimates of the incidence of HIV infection, many of which utilize cross-sectional prevalence data, without having to resort to cohort studies. In this chapter, a number of existing methods for estimating incidence are reviewed, and in the following chapter two new dynamical mathematical models are described to measure incidence from prevalence data, relying on both age-specific prevalence and on trends in prevalence over time. The models are used to derive estimates of incidence directly from cross-sectional HIV prevalence data in South Africa and are illustrated using data from Hlabisa in KwaZulu-Natal. In the chapters that follow a laboratory based method (the Standardized Algorithm for Recent HIV Sero-conversion) is also used to estimate incidence and results are compared to that of the mathematical models. Finally, the models are applied to other data sets from South Africa to further examine HIV incidence rates in the country.

Review of existing methods to estimate HIV incidence

Back-calculation methods

Back-calculation is a method for estimating past infections rates from AIDS incidence data and is useful for obtaining short-term projections of HIV incidence and estimating HIV prevalence.[550] The methods assume that trends in new AIDS cases reflect existing and past trends in HIV incidence. They require reliable estimates of the number of AIDS cases in the population over a period of time and a precise knowledge of the distribution of the incubation period, from which the incidence rate of HIV infection for some years earlier can then be estimated. Because of the need to have reliable estimates of AIDS incidence, back-calculation has been used mainly in developed countries. Methods of back-calculation have not been applied in South Africa because reporting of AIDS cases is voluntary and data are too incomplete to be of much use. The methods will therefore not be discussed in great detail in this chapter.

Statistical models using HIV prevalence data to estimate HIV incidence

Several statistical models have been developed to estimate incidence from cross-sectional age-prevalence data which are widely available in many countries from sentinel surveillance designed to monitor the progression of the HIV epidemic among particular risk groups such as pregnant women attending antenatal clinics, commercial sex workers, injecting drug users, sexually transmitted disease clinic attendees and blood donors.

Birth cohort methods

The simplest of these methods is based on the assumption that HIV incidence rates in the population are stable over time and that the prevalence in young people increases linearly with age. It further assumes that they have not been infected for long enough for significant numbers to have died, so that the slopes of the regression lines from repeated samples of birth cohorts provide crude estimates of HIV incidence.[551-553]

"Podgor and Leske" method

Various statistical models have been developed in order to estimate incidence after adjusting for mortality or cohort effects. For example, Podgor and Leske[554] developed a method for estimating incidence from age-specific disease prevalence, assuming a steady state, but allowing for differential mortality between people with and without disease. The method assumes that the overall prevalence, more specifically the force of infection, is constant and allows the incidence to be estimated over age bands.

The model used by Podgor and Leske is based on the functional relation between the cumulative incidence or risk (CInc) over a time Δt and the incidence per unit time (ID),

$$\text{CInc} = 1 - e^{-(\text{ID} \times \Delta t)}$$

where Δt is the elapsed time between the beginning and end of an age interval. Letting λ_1 be the mortality rate among people without disease, λ_2 the incidence of disease, and λ_3 the mortality rate among people with disease, they show that

$$\left[P_1(1-P_0)e^{-(\lambda_1+\lambda_2)} - P_0(1-P_1)e^{-\lambda_3}\right](\lambda_1+\lambda_2+\lambda_3) = (1-P_0)(1-P_1)\left(e^{-\lambda_3} - e^{-(\lambda_1+\lambda_2)}\right)$$

where P_0 is the prevalence at the beginning of the interval and P_1 is the prevalence at the end of the interval.[554] The model makes the assumption that the disease/infection is irreversible, that individuals with and without disease may have differential mortality rates that are assumed to be constant throughout the interval under consideration, and that the disease incidence and population composition remain constant during the time period being analysed. The main difficulty in applying this method to data from South Africa is that the prevalence has increased dramatically over time and is only now starting to approach a steady state.

Saidel and co-workers studied a cohort of initially sero-negative male volunteers in Burundi between 1990 and 1993.[555] They were able to measure the incidence of HIV directly and to validate the method developed by Podgor and Leske. The authors concluded that the method provided useful approximations of HIV incidence, particularly in countries where HIV prevalence has stabilized.

Dynamical models

Dynamical models simulate change over time in the incidence, prevalence and deaths due to a particular disease, in this instance HIV and AIDS. The simplest dynamical model which captures the essential aspects of these processes for HIV is described in Chapter 3, Figure 3.1, in which people enter the model at a rate β, susceptible people (S) become infected (I) at a rate λ times the current prevalence (I/N), and people die of AIDS at a *per capita* rate δ, while the *per capita* background mortality rate (in the absence of disease) is μ. The population growth rate, in the absence of disease, is the birth rate minus the background death rate μ. For other diseases it may be necessary to include latent class, recovery from infection, and so on. The rate at which HIV infection spreads at a population level depends on the number of infected people, the number of people who are susceptible to infection, the rate at which these two groups make contact, the probability that HIV is transmitted per sexual contact, and the life expectancy of infected people. Dynamical models can be formulated in terms of differential equations which can be simulated on a computer.

Many of the dynamical models related to HIV transmission that are described in the literature use data on age-specific prevalence of infection and data on the time trends in the average prevalence of infection together with assumptions about the form, age dependence and survivorship function for people infected with HIV. An example is described below.

Gregson et al. methods

Gregson and co-workers described two methods for estimating HIV incidence from age-specific prevalence data under stable endemic conditions (i.e. constant age-specific HIV incidence and HIV related mortality over time).[556] In their "cumulative incidence and survival" method they calculate the HIV prevalence at any given age as the cumulative incidence of new infections at each preceding age, adjusted for mortality. They assume a parametric form for the age specific risk of infection and assume that survival after infection with HIV follows a Weibull distribution. The model is fitted to the data using maximum likelihood methods. Their "constant prevalence method" is essentially the same but they do not parameterise the age specific risk of infection. The latter method is less tightly constrained than the former but gives substantially wider confidence limits. Under the assumption of stable endemic conditions, reasonable estimates of age-specific and cumulative incidence were obtained when applied to data collected from antenatal clinic attendees in Kampala, Uganda, between 1989 and 1990, while estimates of HIV incidence were sensitive to assumptions regarding the length of the survival period.

Demographic models

The main purpose of demographic models is to develop population projections in an attempt to answer questions about the demographic impact of HIV. Projections are usually based on current knowledge about population size and age structure, rates of birth, death and migration, and assumptions about how quickly these rates will change. Two such examples are described below:

UNAIDS/WHO methods

UNAIDS and WHO, with the guidance and recommendations of an external group of scientists and researchers (the UNAIDS Reference Group on Estimates, Modelling and Projections) have developed a set of methods and assumptions to model epidemic trends, to determine annual estimates of HIV prevalence in countries, and to make demographic projections of the epidemic.[450] For countries with generalized epidemics in which HIV is

firmly established in the general population, the Estimation and Projection Package (EPP) has been designed as a tool to construct national and sub-national (e.g., urban and rural, or provincial) epidemic curves, an essential step in the estimation of levels and trends in the epidemic and its impact.[557]

For each defined sub-epidemic, the EPP fits a simple epidemic model to a full set of HIV surveillance data points collected from sentinel surveillance sites over time. This produces an estimate of the time trend of adult HIV prevalence for each sub-epidemic, which are then combined (using population estimates assigned to the different sub-populations) to produce national prevalence estimates and trends. The EPP model incorporates population change over time and fits curves to epidemics by varying four parameters (shown in Figure 8.1): [557] the rate of growth of the epidemic (r); the start year of the epidemic (t_0); the fraction of the population considered to be at risk of infection at the start of the epidemic (f_0); and a behavioural response parameter which determines the final epidemic prevalence (ϕ). It further provides the user with the ability to apply prevalence adjustments to surveillance data, or to calibrate the curve using, for example, more representative data from national population based surveys.

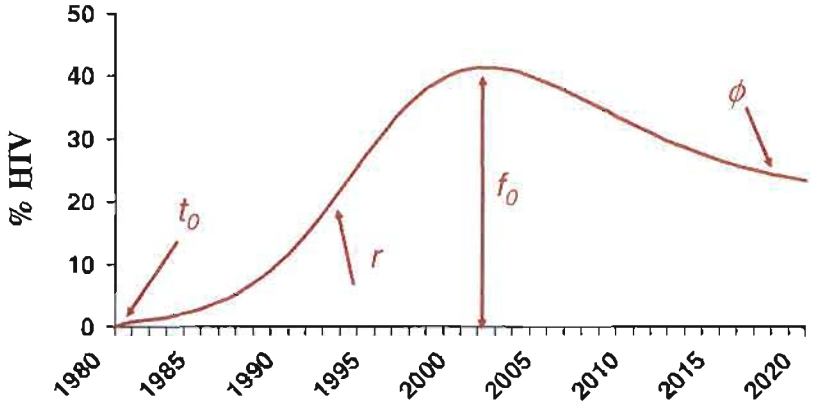


Figure 8.1 Parameters in the EPP model that are varied to produce the best fitting epidemic curve [557]

Once epidemic curves are produced in EPP, they are then incorporated into the SPECTRUM Projection Package, developed by the Futures Group, to generate estimates of national prevalence, incidence and mortality by sex and age groups.[451] The Spectrum module for HIV/AIDS projections uses the HIV prevalence curve produced in EPP

together with assumptions about the epidemiology of HIV, including the ratio of female to male prevalence, distribution of infection by age, the survival distribution (assumed to be a Weibull function), and the effect of HIV on fertility, to calculate HIV prevalence, incidence and mortality by age and sex. It also calculates the number of child infections occurring through infections from the mother, child deaths, and the number of orphans as a results of AIDS.[451]

The SPECTRUM projection package carries out the various calculations as follows:

i) The *number of adults* of age (a) and sex (s) that are infected with HIV in any year is calculated as

$$HIV_{a,s,t} = \text{adult population}_{a,s,t} \times \text{adult prevalence}_{a,s,t}$$

ii) The *number of new infections* is calculated as the total number of infections expected in year t minus the number of infections surviving from the previous year, where the number of infected people that survive from one year to the next is the number of infected in the previous year minus deaths from AIDS or other causes during the previous year, i.e.,

$$\text{New HIV infections}_{a,s,t} = HIV_{a,s,t} - (HIV_{a-1,s,t-1} - \text{AIDS deaths}_{a-1,s,t-1} - \text{non-AIDS deaths}_{a-1,s,t-1})$$

iii) The number of AIDS deaths is calculated as a function of the number of new infections in previous years and the rate of progression from infection to death:

$$\text{AIDS deaths}_{a,t-1} = \sum_{i=0}^{20} (\text{New HIV infections}_{a-i,t-i} \times \text{proportion dying from AIDS } i \text{ years after infection})$$

ASSA model

The Actuarial Society of South Africa (ASSA) has developed an age structured AIDS model which has been widely used in South Africa to investigate the demographic impact of HIV/AIDS in the different provinces, and from which prevalence, incidence and mortality estimates have been derived.[279,461,558] The ASSA AIDS and Demographic projection model is a cohort component projection model[b] which projects the demographic

[b] *In a cohort-component model initial populations for countries or regions are grouped into cohorts defined* by age and sex, and the projections proceeds by updating the population for each age-and sex-specific group according to assumptions about components of population change, such as fertility, mortality and migration. Each cohort survives to the next age group according to assumed age-specific mortality rates. Each cohort is treated as a homogenous group and average probabilities of birth, death and migration are used.

impact of the heterosexual HIV epidemic and has its origins in the Doyle-Metropolitan model, first described by Doyle and Millar in 1990 for use in life insurance, health and pension applications.[375] The model is concerned only with heterosexual and mother-to-child transmission and it allows for the effect of prevention and treatment programs.[559] The model is calibrated using the Department of Health's antenatal clinic prevalence data and mortality data from the Department of Home Affairs and is adjusted for under-reporting. The model splits the population into subgroups depending on risk factors associated with the mechanism of transmission of HIV, including age, behaviour group (high risk such as commercial sex workers, those who are significantly exposed to HIV through sexually transmitted infections or through engaging in risky behaviour, and those who are not significantly exposed to HIV), race and geography (provinces).[461] The model gives a good fit to the antenatal clinic survey data, allows one to make separate assumptions about men and women, model population groups separately, and to limit trends in mortality and fertility rates over time, limits in-migration, assumes that the HIV survival curve follows a Weibull distribution, allows for a bimodal distribution of paediatric HIV survival, and disaggregates a 'contagion matrix' in the model into more measurable and controllable parameters of heterosexual behaviour.

Laboratory methods

Laboratory methods have been developed for determining incidence through detecting and distinguishing recent HIV infections from long term infections. A variety of approaches and assays have been described in the literature. While some methods use the measurement of HIV p24 antigen or HIV RNA in the absence of HIV antibodies[560-563] (i.e., before antibody seroconversion) to indicate that an infection has been acquired recently, other approaches are based on qualitative and quantitative differences in the evolution of HIV antibodies following sero-conversion. An example is the use of a sensitive/less–sensitive serological algorithm to determine antibody levels and to infer the likelihood that an infection was recently acquired (standardized testing algorithm for recent HIV-1 seroconversion, or STARHS). To overcome some of the limitations of the sensitive/less-sensitive assays, which include variability in the window period and subtype-dependent performance, the BED-EIA was recently developed to detect HIV infection by measuring the increase in HIV immunoglobulin G (IgG) as a proportion of the total IgG following seroconversion.[564] These four types of assays (p24 antigen, HIV RNA, STARHS, and

BED-EIA) are the most advanced in terms of calibration, validation and application for measuring incident HIV-1 infections, and will be described in more detail below, while other methods have been proposed or are under development.[565]

p24 antigen and HIV-1 RNA

In 1995 Brookmeyer and Quinn[560] described the use of p24 antigen to determine HIV incidence in a cross-sectional study in which 1900 people were tested for HIV in India.[566] The approach is based on testing HIV negative individuals for HIV-1 antigen (p24) to identify individuals in the window period which corresponds to the time between exposure to HIV and appearance of detectable HIV antibodies. Detection of p24 antigen, prior to development of specific HIV antibodies indicates recent infection. The prevalence of p24 antigen together with the mean duration of the p24 antigen period (i.e., the time between the appearance of the p24 antigen and the appearance of HIV antibodies) can be obtained from a cross-sectional survey and under the assumption that the epidemic has reached a steady state, incidence can be obtained from the relation

$$p \approx I \times \mu$$

$$or \quad I \approx p / \mu$$

where I is the current HIV incidence rate, μ is the mean duration of the p24 antigen-positive pre-seroconversion period and p is the proportion of HIV seronegative individuals with p24 antigens. A confidence interval for the incidence rate can be calculated under the assumption that the number of individuals who are in the p24 antigen-positive pre-seroconversion period follows a Poisson distribution with expectation $n \cdot I \cdot \mu$, where n is the total number of individuals in the cross-sectional survey who tested negative for HIV antibodies and who were tested for p24 antigen.

The main source of uncertainty in this method is the estimation of the duration of the p24 antigen period, and large samples are required to obtain reliable estimates. The duration has been reported to be short, of the order of 1-2 weeks to about 1 month, which makes it difficult to capture enough people in this phase to obtain incidence estimates with reasonable confidence.[566]

The above concept has been extended to the more sensitive detection of HIV-1 RNA in antibody negative individuals with early infection, using specimen pooling and HIV RNA

reverse transcriptase-polymerase chain reaction (RT-PCR) tests.[563] HIV Nucleic acid-based testing has been widely used for blood bank screening in the United States.[563,565]

"Detuned" ELISA

The Standardized Testing Algorithm for Recent HIV Sero-conversion (STARHS) is based on a sensitive/less-sensitive enzyme-linked immunosorbent assay (ELISA). Generally, blood samples are tested for HIV using a standard ELISA. Those samples that test positive in the standard assay are re-tested, usually in triplicate, using a less-sensitive (LS) ELISA to discriminate between recent and old seroconverters. Samples that are positive on the standard sensitive ELISA and with standardized optical density below a certain prescribed cut-off value, are classified as recent infections.[567,568] After STARHS testing, the annual incidence *(I)* can be calculated as:

$$I = \frac{n}{(m+n)} \frac{365}{T} \times 100$$

where n is the number of infections classified as recent and m is the number of people who are HIV negative on the sensitive ELISA. The window period, T, is the mean number of days between the detection of sero-conversion using the two tests. The value of T and the appropriate optical density (OD) cut-off for the LS assay depends on the sensitivity of the LS assay and on the HIV-1 subtypes that are prevalent in the tested population. A window period of about 200 days for an OD cutoff of 0.45 has been recommended for HIV subtype C infection by the CDC. Chapter 10 reports on the use of the STARHS method and compare this method to a mathematical model developed to estimate incidence from age-prevalence data.

BED-Enzyme Immunoassay

The IgG-Capture BED-EIA was developed in the CDC laboratories in the USA to detect recent HIV seroconversion.[564,569,570] The BED-EIA indirectly measures the increasing proportion of HIV-IgG in a given blood specimen with respect to total IgG to determine the time that has elapsed since HIV infection. To overcome the problem of subtype-dependent performance (one of the limitations of the sensitive less-sensitive assays), the BED-EIA was designed by using a branched gp41 peptide with sequences derived from multiple subtypes (B, E and D) to achieve similar performances with different subtypes. The assay has been shown to be stable with minimal variation between runs of the assay.[564] The method has been applied to specimens from several cross-sectional studies to estimate

incidence, including populations from Uganda, Zimbabwe and Ethiopia, an injecting drug user population from Bangkok[571] and stored surveillance specimens from Cambodia (unpublished). Results from these countries were reported at a UNAIDS Reference Group meeting in December 2005 and indicated that the BED assay requires further validation and calibration before recommending it for routine testing.[476]

Discussion

A recent paper by Shelton *et al.*,[572] assessing trends in prevalence of HIV infection worldwide, emphasized the importance of estimating incidence but saw no easy way of doing this. Given the time lag between incidence and prevalence they conclude that "assessing prevention activities on the basis of prevalence is a perilous undertaking – literally 'behind the curve'." They further describe incidence as the gold standard for assessing prevention efforts. However, incidence is difficult to measure directly because of the logistical and ethical considerations when following people until sero-conversion and as a result, several methods have been developed to estimate incidence indirectly, some of which are described in this chapter.

Many of the existing mathematical models described in the literature ignore certain key epidemiological parameters, such as variables related to the primary route of transmission. A further limitation of many of the models is the assumption that the disease incidence and population composition remain constant over time. Many of the dynamical models described in the literature are therefore limited to stable epidemic conditions. Methods of back-calculation require good AIDS data and in countries such as South Africa where reporting of AIDS cases is voluntary, data are usually too patchy and incomplete to be of use.[573]

While statistical and mathematical models can be used to estimate population estimates of incidence they cannot be used to identify those individuals who have recently sero-converted. The advantage of laboratory methods for determining incidence is that it can be used to determine whether or not a specific individual infection has been acquired recently. Several laboratory methods based on either HIV antigen, RNA or HIV antibodies have been developed and some are still being tested. Limitations of the laboratory techniques

are mainly associated with poorly defined cut-offs and window periods for different viral subtypes.

Statistical and mathematical models are extremely important for estimating HIV incidence but because of assumptions regarding key parameters that cannot always be determined directly from raw data, there is always a degree of uncertainty around the estimates, and they should therefore be interpreted cautiously. However, Shelton *et al.*[572] point out that because the history of HIV is well understood, changing assumptions are unlikely to change overall pattens.

CHAPTER 9 Developing dynamical models to estimate HIV incidence using time trends and age-specific prevalence data in South Africa

> "Sensibly used, mathematical models are no more, and no less, than tools for thinking about things in a precise way"
>
> Roy Anderson and Robert May, 1991[435]

Introduction

Many of the models described in the literature to estimate HIV incidence ignore certain key epidemiological parameters such as variables related to the primary route of transmission, which in South Africa is via sexual activity. Many assume that the incidence and population composition remain constant over time. To overcome some of these limitations, and for specific application to the South African HIV epidemic an extended dynamical model has been developed for estimating HIV incidence rates in epidemic situations from data on age-specific prevalence and changes in the overall prevalence over time. The model allows for changing force of infection, age-dependence of the risk of infection and differential mortality. It uses maximum likelihood methods to obtain age-specific incidence rates while error estimates are obtained using a Monte Carlo procedure. To illustrate the model, the method is applied to data collected from women attending antenatal clinics in the rural district of Hlabisa in KwaZulu-Natal.

It is often the case, however, that age-specific prevalence data are not available, as in the case of the national antenatal clinic surveillance data reported by province. In the absence of such age-specific prevalence data, another model was developed to estimate incidence using only the trends in the prevalence of infection over time. In this chapter it is applied to time trend data from Hlabisa and in Chapter 11 it is applied to data from national antenatal clinic surveillance to obtain provincial estimates of HIV incidence.

The study population

Modelling HIV incidence rates is illustrated here using seroprevalence data on 590 women, age 15 to 49 years, who attended antenatal clinics in Hlabisa between December 2000 and February 2001. Hlabisa has a well developed clinical service and provides antenatal care

through the local hospital, village clinics and mobile clinics to about 95% of pregnant women in the district.[574] Between 1992 and 2002, anonymous HIV seroprevalence surveys were conducted annually among women attending antenatal clinics in the area. The antenatal prevalence, which mirrors the results for the whole province, increased from 4.2% in 1992 to 38.2% in 2001 (Table 9.1) and a logistic regression gave a good fit to the data with an intrinsic doubling time in the early stages of the epidemic of 15 months, as shown in Figure 9.1. The observed age-specific prevalence rates for 2001, which are used for illustrating the dynamical models are shown in Table 9.2 and Figure 9.2.

Table 9.1 Prevalence of HIV infection among antenatal clinic attendees, aged 15-49 in Hlabisa; 1992 – 2001

Year	n	Prevalence of HIV (95% CI)
1992	884	4.2% (3.0– 5.7)
1993	709	7.9% (6.0–10.1)
1995	314	14.0% (10.4–18.4)
1997	4731	27.2% (25.9–28.5)
1998	3166	29.9% (28.4–31.6)
1999	2623	34.2% (32.0–36.5)
2000	906	36.1% (32.9–39.2)
2001	590	38.2% (33.4–43.6)

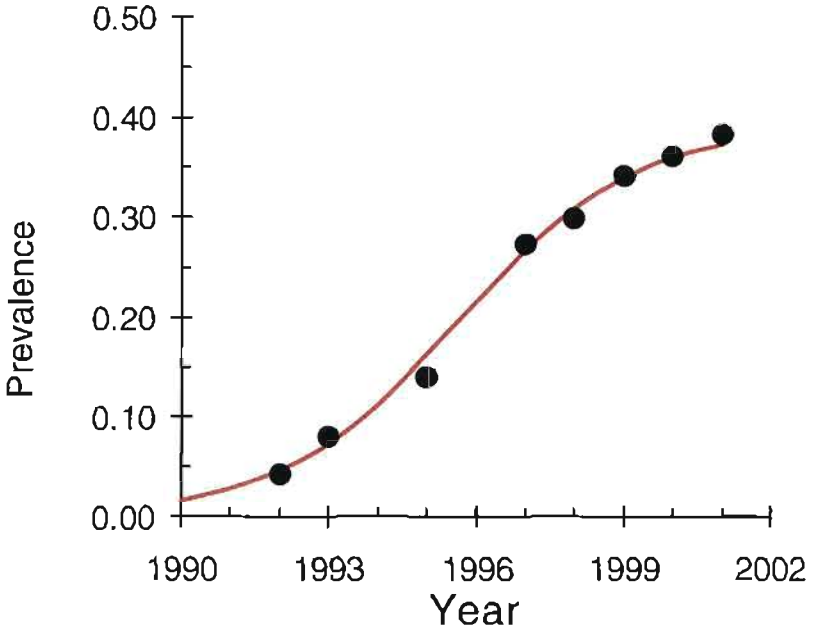


Figure 9.1 Prevalence of HIV among women attending antenatal clinics in Hlabisa fitted to a logistic curve. The doubling time at the beginning of the epidemic was 15 months and the asymptotic prevalence 39.2%

Table 9.2 The number of women in Hlabisa who were tested for HIV infection in 2001 and the number positive by age with the observed and fitted prevalence values.

Age	Total	Pos.	Obs.	Fitted	Age	Total	Pos.	Obs.	Fitted
14	1	0	0.000	0.037	32	16	5	0.313	0.419
15	8	2	0.250	0.083	33	10	4	0.400	0.397
16	24	5	0.208	0.145	34	8	2	0.250	0.375
17	41	6	0.146	0.214	35	13	5	0.385	0.353
18	52	16	0.308	0.284	36	11	5	0.455	0.332
19	54	12	0.222	0.348	37	3	2	0.667	0.311
20	41	17	0.415	0.403	38	9	2	0.222	0.291
21	41	21	0.512	0.447	39	8	2	0.250	0.272
22	29	12	0.414	0.480	40	6	3	0.500	0.254
23	40	24	0.600	0.502	41				0.237
24	34	20	0.588	0.515	42	6	1	0.167	0.221
25	19	11	0.579	0.519	43	1	0	0.000	0.206
26	21	12	0.571	0.516	44	2	0	0.000	0.192
27	12	4	0.333	0.508	45	2	1	0.500	0.178
28	13	6	0.462	0.495	46	0	0		0.166
29	24	9	0.375	0.479	47	0	0		0.154
30	24	13	0.542	0.460	48	0	0		0.143
31	15	4	0.267	0.440	49	0	0		0.133

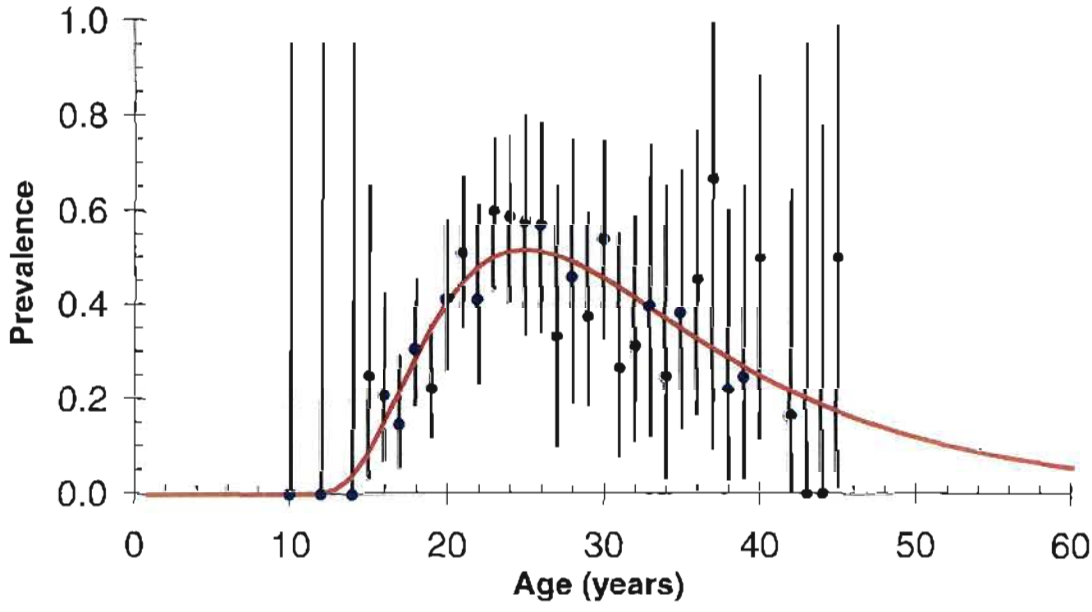


Figure 9.2 The age-specific prevalence of HIV infection fitted to the model described here. Error bars are 95% binomial confidence limits.

Model 1. Modelling the age-specific prevalence

The simplest way to estimate the age-specific incidence from age-specific prevalence data would be to assume that for newly infected young people, among whom the AIDS related mortality is still low, the slope of the prevalence curve gives an estimate of the incidence. This clearly does not apply in the older age groups and we can improve the estimate by making two corrections. The slope of the age-prevalence curve is the prevalence at age a at time t minus the prevalence at age $a-1$ at time $t-1$. To obtain the incidence, the prevalence at any age $a-1$ must be reduced by the amount by which the prevalence has increased and by the proportion of people who have died due to AIDS related diseases in the last year. The incidence at age a at time t, $I(a,t)$ is then

$$I(a,t) = P(a,t) - P(a-1,t)\frac{\overline{P}(t-1)}{\overline{P}(t)}e^{-\mu} \qquad 9.1$$

where $P(a,t)$ is the age-specific prevalence at age a at time t, $\overline{P}(t)$ is the average adult prevalence at time t, and μ is the AIDS related mortality per year. To get the incidence per susceptible person in the population the estimate given by Equation 9.1 must be divided by $1-P(a)$, the proportion who are susceptible at age a. To determine the age-specific incidence Equation 9.1 could then be applied to the age specific prevalence given in Table 9.2. However, while this approach would give reasonable estimates of the age-specific incidence it assumes that the survivorship function of those with HIV infection is exponential and it does not allow for the fact that infections in those of age a will have been acquired over several of the preceding years.

A more general model was therefore developed that allows one to relate $P(a,t)$, the prevalence of infection among women of age a at time t, to the incidence.[33] Details are given in Appendix 9.1 where it is shown that the prevalence in people of age a at time t is

$$P(a,t) = \frac{c(a,t)}{c(a,t) + s(a,t)} \qquad 9.2$$

where $c(a,t)$, the proportion of infected people, and $s(a,t)$, the proportion of susceptible people of age a at time t, are given by

$$s(a,t) = e^{-\int_0^a f(\hat{a},\hat{t})d\hat{a}} \qquad 9.3$$

$$c(a,t) = \int_0^a e^{-\int_{\tilde{a}}^{a}\mu(\hat{a},\tilde{a})d\hat{a}} f(\tilde{a},\tilde{t}) e^{-\int_0^{\tilde{a}} f(\hat{a},\hat{t})d\hat{a}} d\tilde{a} \qquad 9.4$$

In these equations $f(a,t)$ is the incidence of infection among those of age a at time t and $\mu(\hat{a},\tilde{a})$ is the AIDS related mortality of someone at age $\hat{a}$ who was infected at age $\tilde{a}$. Equation 9.3 gives the probability that a person who has reached age a remains uninfected. In Equation 9.4 the last term under the first integral sign gives the probability that a person remains uninfected at age $\tilde{a}$, the last but one term gives the probability that they became infected at age $\tilde{a}$, and the first term gives the probability that they then survived from age $\tilde{a}$ to their present age a. These events are summed over all possible ages at which the infection could have occurred. In Appendix 9.1 it is shown that this result does not depend on the background mortality rate.

The procedure is then to parameterise $f(a,t)$ and $\mu(\hat{a},\tilde{a})$, and use Equations 9.2 to 9.4 to get the best fit to the data and hence the best fit values of $f(a,t)$, the age specific incidence at time t. Because a parametric model is used the parameters can be varied in order to determine confidence bands and intervals for any derived functions or estimates.

Parameterising the model

In order to parameterise the age incidence function $f(a,t)$, it is assumed that the age and time dependence can be separated so that

$$f(a,t) = R(a)P(t) \qquad 9.5$$

where $R(a)$, the relative risk of infection with age is constant over time, and $P(t)$, the average adult prevalence is independent of age. If data were available on age matching of partners, on how sexual activity varies with age and so on, more sophisticated expressions could be used for $f(a,t)$.

In order to parameterise the age-risk function, which will be proportional to the age incidence under this model, a function is needed that approximately matches that of age-specific prevalence (Figure 9.2) and fertility (Chapter 6, Figure 6.1), i.e., a function that is zero, or very small, before the age of onset of sexual activity, increase rapidly as sexual activity increases and then decreases among older people. The log-normal function,

$$R(a) = \frac{N}{\sigma\sqrt{2\pi}(a-a_0)} e^{-(\ln((a-a_0)/m))^2/2\sigma^2} \qquad 9.6$$

with off-set a_0, mean m, standard deviation σ and normalised to N, has these properties.

It is also necessary to parameterise $P(t)$ which describes the change in overall prevalence with time. The available data were obtained from antenatal clinic surveys carried out over the past ten years. In the early years of the epidemic the prevalence of HIV infection increased exponentially[140] and a logistic function of time gave a statistically good fit to the overall prevalence. However, by 2000 it was clear that the epidemic was approaching a plateau and a logistic function with a variable asymptote was used to fit the overall prevalence data, as shown in Figure 9.1. Finally, the best form for the mortality as a function of time since infection, $\mu(a,\tilde{a})$, had to be decided on. The UNAIDS Reference Group on Estimates, Modelling and Projections, based on data from the CASCADE collaboration[575] and mortality data from Uganda[576,577],Thailand[578,579] and Haiti,[580]has been recommending the use of a Weibull survival distribution with a median survival time of 9 years for modelling AIDS deaths in developing countries in the absence of treatment.[450] The CASCADE collaboration[575] (providing an extensive analysis of time from HIV-1 seroconversion to AIDS and death in Europe, North America and Australia) showed that a Weibull survivorship gives a very good fit to available mortality data, and that survival declines linearly with age at infection, while it does not depend on gender or mode of transmission. For people infected with HIV at 10 years of age the median survival is 14.6 years, while for people infected at 60 years of age it is 6.2 years.[581] For all ages the shape parameter is close to 2.28. In this model the survival time was scaled to a median of 9 years at age 30, which thereafter declines linearly with age.

Fitting the data and estimating errors

A visual basic programme in an Excel spreadsheet was written to carry out the fitting procedure, as follows: The model given by Equations 9.2 to 9.4 is fitted to the data taking as inputs the age-specific prevalence of HIV, the fitted values of the prevalence over time and the survivorship, as described above. The parameters N, m, σ, and a_0 are then varied to obtain the maximum likelihood fit to the age-specific prevalence of HIV using binomial

error estimates.[520] The model gave a good fit to the data as shown in Figure 9.2. Using the parameter values to calculate $f(a,t)$ gives the age-specific incidence shown in Figure 9.3.

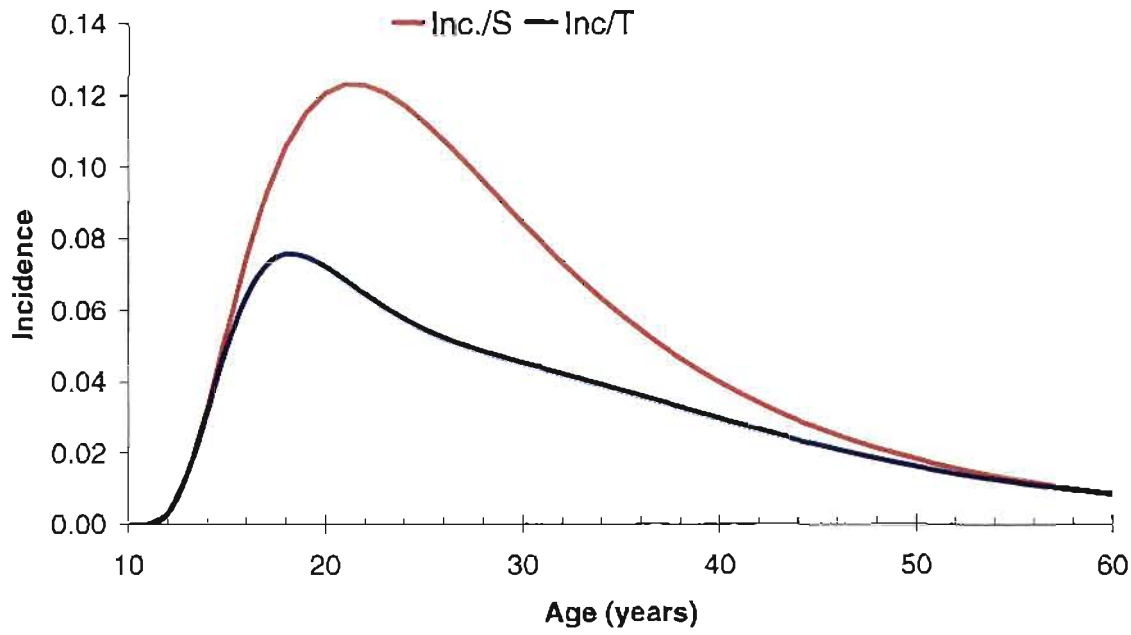


Figure 9.3 The age-specific incidence of HIV infection. Red line: incidence per susceptible; blue line: incidence per person alive at a given age both obtained using the model described in this chapter.

To determine confidence limits for estimates of the age-specific and mean incidence the Clayton and Hills method[582] was followed. They defined the 'supported range' for a set of parameter estimates as being the range of parameter values, $\tilde{\mathbf{p}}$,for which the deviance

$$D = -2\ln\left(\frac{L(\tilde{\mathbf{p}})}{L(\hat{\mathbf{p}})}\right) \qquad 7$$

exceeds a predetermined critical value, and where $\hat{\mathbf{p}}$ is the set of parameter values that maximise the likelihood, L. Since D asymptotically follows a χ^2 distribution with n degrees of freedom where n is the number of variable parameters in the model, setting the critical value for the supported range to $\chi^2_n(0.05)$ gave an approximate 95% confidence interval. To determine the corresponding confidence limits for the derived curve, the parameters $\tilde{\mathbf{p}}$ were varied over the parameter space to determine the family of curves corresponding to the supported range of the parameters. While the parameter space could be explored over a regular grid, a more efficient approach was to use a Monte Carlo

method. The maximum likelihood fit enabled the calculation of a covariance matrix of the coefficients.[17] Normally distributed random numbers were then generated from the multivariate distribution specified by the covariance matrix. For each set of parameters the deviance was calculated and tested to see if it falls within the supported range.

Having generated a sufficient number of runs for which the deviance fell within the supported range, typically about 1,000, the maximum and minimum values of the incidence at each age and of the overall incidence were determined for these runs. These extreme values then gave the estimated 95% confidence intervals for the curve and limits for the mean.[582] Figure 9.4 shows the age specific incidence of infection with 95% confidence limits.

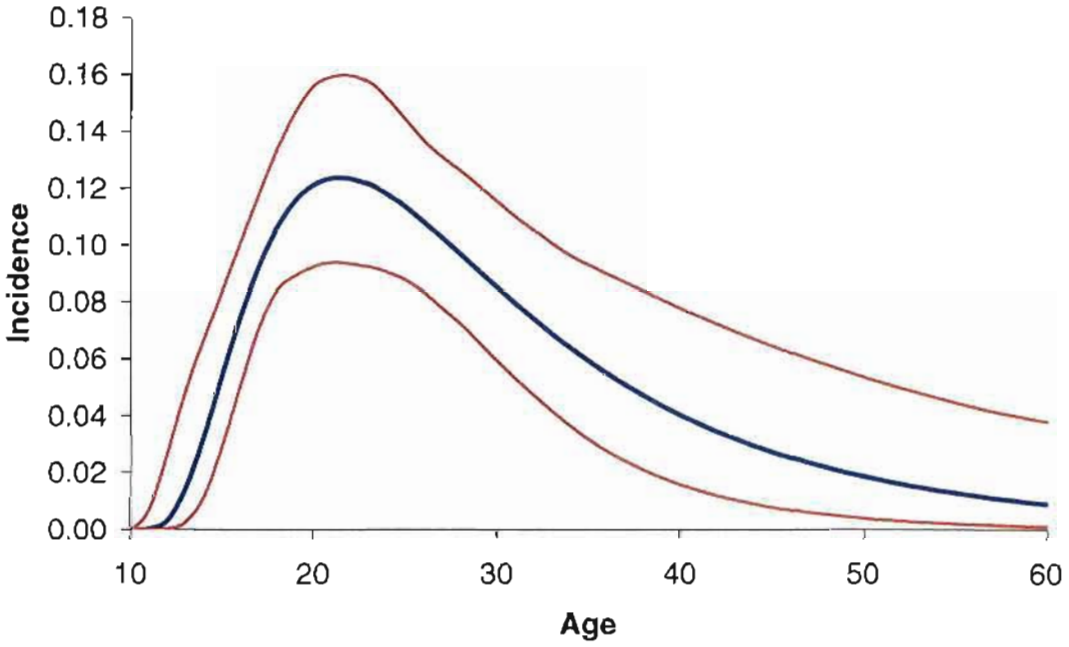


Figure 9.4 The annual age-specific incidence per susceptible with 95% confidence intervals.

Model 2. Estimating incidence using only time trends in prevalence

In the absence of age-specific prevalence data, incidence can be estimated using only the time trends in the prevalence of infection, i.e. from data such as those presented in Figure 9.1. If there were no deaths then the incidence would be given directly by the slope of the prevalence *(P(t))* curve so that

$$I_0(\tilde{t}) = \left.\frac{dP(t)}{dt}\right|_{\tilde{t}}$$

Assuming a Weibull survivorship, $W(t)$, the probability that people die a certain number of years after they are infected can be calculated by

$$M(t) = \frac{dW(t)}{dt}$$

Since deaths will lead to a decline in prevalence it is necessary to add to the estimate of incidence the decline in deaths due to all previous incident infections so that

$$I_1(\tilde{t}) = I_0(\tilde{t}) + \int_{-\infty}^{\tilde{t}} P(t)M(t-\tilde{t})dt$$

However, when time trends in prevalence among women attending ante-natal clinics are used to estimate the incidence in such women a correction must be made for the fact that the sample of women represents a narrow range of ages. For example, the age distribution of pregnant women in South Africa from the antenatal clinic survey in 2001 is shown in Figure 9.5 below. These data can be approximated reasonably well by assuming that women enter the sample at age 16 years and leave at a constant rate of ρ = 7% per year.

At any given time, therefore, infected women are leaving the sample (and being replaced by 16 year old women, none of whom are infected) at a rate ρ per year so that it is necessary to correct the incidence by this amount and a better approximation is

$$I_2(\tilde{t}) = I_1(\tilde{t}) + \rho P(\tilde{t})$$

This gives the incidence per person in the sample. To obtain the incidence per susceptible person the above equation is divided by the proportion of the population that are susceptible, which gives the equation

$$I_3(\tilde{t}) = I_2(\tilde{t}) / \left[1 - P(\tilde{t})\right]$$

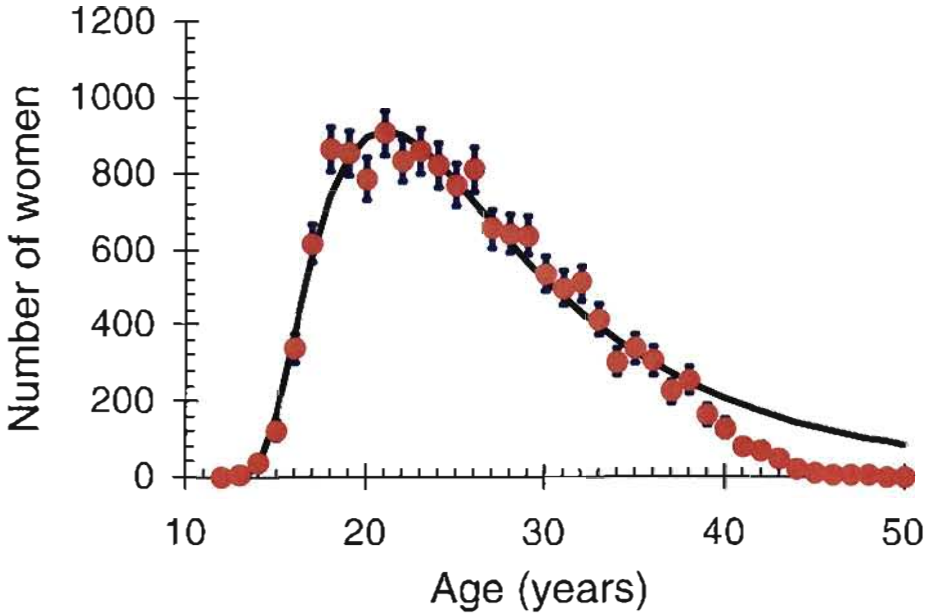


Figure 9.5 Number of women attending antenatal clinics in South Africa in 2001. The fitted curve is a log-normal function off-set by 12.7 years, with a mean at 23.4 years and a standard deviation of 0.691. A least squares fit was applied to the data up to the age of 40 years. Errors are 95% Poisson confidence limits (*Data source: Antenatal clinic data, Department of Health*)

Results

Model 1

A dynamical model using age-specific prevalence which allows for all past infections, changes in prevalence over time, and a Weibull survivorship probability for those infected with HIV, gave the results shown in Figures 9.3 and 9.4. The best estimate of the average annual incidence per susceptible in the Hlabisa ANC population aged 15–49 in 2001, standardised to a uniform age distribution, was 7.1% (5.5%–9.3% per year). Standardizing this result to the observed population distribution the average incidence per person was 8.1% (5.6%–11.3%), and standardizing to the age distribution of women attending antenatal clinics the average incidence per person was 9.9% (7.3%–13.1%). The annual incidence of infection per susceptible increased from 5.5% (2.9%–8.4%) at age 15 years to 12.3% (9.4%–15.91%) at age 21 years and declined to 2.0% (0.5%–5.6%) at age 50 years. Incidence by 5-year age groups are shown in Table 9.3.

Table 9.3 Estimated HIV incidence by age for women in Hlabisa in 2001 using *Model 1*

Age group	HIV incidence	95% confidence interval
10-14	1.0	0.4 – 2.9
15-19	8.9	7.0 – 11.0
20-24	12.1	9.5 – 15.7
25-29	10.2	7.8 – 12.9
30-34	7.4	5.2 – 10.5
35-39	5.1	2.7 – 8.1
40-44	3.5	1.4 – 6.8
45-49	2.3	0.8 – 5.7
50-54	1.6	0.4 – 4.8
55-59	1.1	0.2 – 4.1

Model 2

When applied to the Hlabisa time trend data shown in Figure 9.1, the HIV incidence using method 2 was 9.6%, which is very close to the incidence estimate of 9.9% using method 1 (standardized to the age distribution of the ANC population), confirming the extremely high incidence rates in this rural community in KwaZulu-Natal. Age-specific incidence rates cannot be obtained using method 2 because of the lack of age-prevalence data.

Discussion

In the absence of cohort studies to measure incidence directly, several methods have been developed for indirect estimation of incidence, some of which are described in Chapter 8. In this chapter, two new dynamical models are described that have been developed for specific application to the epidemic in South African which, at the time of developing the model, was still showing an increase in the levels of infection. The first model estimates incidence from age-specific prevalence data and changes in the overall prevalence over time. It allows for changing force of infection, age-dependence of the risk of infection, and an AIDS related mortality function that is both time and age dependent.

The second model was developed to estimate incidence from data on time trends in the prevalence of infection. This model is particularly useful for application to data sets where prevalence data are available over time, but age-specific data are not available, as sometimes the case for ANC data (e.g., national ANC surveillance data are reported by age

and by province, but provincial data are not provided by age).

The two dynamical models were developed and tested using data from antenatal clinics in Hlabisa, KwaZulu-Natal, and show extraordinarily high incidence rates among women in this rural area. There is considerable debate as to the extent to which antenatal clinic data under or over estimate the prevalence among all adult women. Since the antenatal clinic data include only women who are pregnant, and hence sexually active, the ANC surveillance may overestimate the population prevalence among younger women. At the same time, it may underestimate prevalence among older women, in whom HIV and other sexually transmitted infection could cause infertility. If this is indeed so the incidence estimates are likely to be too high for the younger women and too low for the older women. There is evidence from sub-Saharan African countries that HIV surveillance among women attending antenatal clinics provides a good approximation of the magnitude of the infection in the general population.[531] However, prevalence data from Hlabisa in 2000 to 2002 indicated that ANC prevalence might be overestimating estimates in the general population (Chapter 7), although this needs further investigation.

The two methods described here give estimates of overall HIV incidence among women in Hlabisa in 2001 that are very close; an average standardized estimate of 9.9% using the first model and an estimate of 9.6% using the second model. This gives us confidence in using both models as a way of estimating incidence indirectly.

Probably the most important limitation of the first model is the assumption of homogeneous mixing which allows us to separate the risk of infection into a term that depends only on age and a term that depends only on the overall population prevalence at a given time. Anderson and May[435] point out that heterogeneity in degrees of sexual activity tends to result in fewer infections. To obtain the same prevalence with heterogeneous mixing should therefore require higher incidences so that these estimates are more likely to be under estimates rather than over estimates.

The use of a log-normal age-risk function seems reasonable as it matches both the age-specific prevalence function and the age specific fertility. However, other functions will produce different estimates of incidence and it is important to consider the biases that may arise from the use of the log-normal distribution. If the age-risk function is either

monotonically increasing or constant with age, then the age-prevalence must be monotonically increasing so that the data exclude functions of this form. A normal distribution declines too rapidly at older ages and extends too far at younger ages. An off-set Weibull[583] distribution function, which like the log-normal is exponentially skewed to the right, also gives a good fit to the data but the difference between the estimated age-specific incidence for this model and for the log-normal model is less than 20% of the random errors, as estimated by the confidence inervals in Figure 9.4, so that the differences in the two functional forms change the estimates of incidence by considerably less than the uncertainty due to the random errors. With sufficiently precise data one could use the procedure outlined here to determine the form of the age-risk function. Direct measurements of the relative risk of infection as a function of age would also make it possible to define the age-risk function independently but the purpose of the procedure outlined here is to determine the age-specific incidence without having to do extensive cohort studies. Where such data are available it would nevertheless be interesting to investigate the functional form of the age-risk function which could then be used in analyses such as this. This analysis also shows the importance of collecting prevalence data for very young people. Since the prevalence at a given age depends on the cumulative risk up to that age, it is important to be able to determine the risk-function precisely for all younger ages.

In the absence of any good cohort data on survival time from HIV infection to death in South Africa, it seems reasonable to assume a Weibull survivorship function with median survival time of nine years (i.e., in the absence of treatment) in the model. This assumption is consistent with the UNAIDS Reference Group on Estimates, Modelling and Projections recommendation[450] which is based on data and findings from three major cohort studies on adult survival in Thailand,[578,579] Uganda[577] and Haiti,[580] and data from pre-ART era cohort studies in industrialized countries, including the CASCADE collaboration.[575] Few studies have been done in South Africa to assess the average survival time of adults after infection with HIV, with the exception of some studies in clinical settings to assess survival of patients from a certain clinical stage (e.g., onset of AIDS, or CD4 cell count below a certain level) after presenting to a clinic, showing that survival in untreated cohorts was similar to that of cohorts in the USA.[584,585]

It would clearly be desirable to obtain direct measures of incidence from cohort studies. To

obtain the same statistical precision as in this study (i.e. approximately 10% ± 2%, overall) from a cohort study would require approximately 1,600 HIV-negative people who would then be followed up for at least one year. In the absence of direct measures of incidence the next best approach may be to use laboratory methods which are further explored in Chapter 10. If it is assumed that a method such as this gives the number of people who have sero-converted in the last three months this would require a sample of about 6,400 people to obtain the same precision. Clearly, the approach suggested here is very attractive but, being an indirect measure, does rely on assumptions about the form of the age-risk function. Where direct measures of incidence have been made it would be very interesting to compare them with the results obtained using the method described here.

In summary, the analyses illustrated in this chapter provide useful measures of the incidence of infection which is a key aspect of the transmission dynamics of HIV infection. When applied to the Hlabisa data set, the procedures provide plausible estimates of age-specific incidence rates, which are essential for the planning of future studies in this area.

Appendix 9.1 Age-specific prevalence in terms of age-specific incidence

Let the probability, per unit time, that a susceptible person of age a becomes infected at time t be $f(a,t)$. Then, if the background mortality is $\delta(a,t)$, the proportion of people who are born susceptible and survive to age a at time t among those who are not infected with HIV,

$$s(a,t) = e^{-\int_0^a (f(\hat{a},\hat{t})+\delta(\hat{a}))d\hat{a}} \qquad \text{A1}$$

The proportion of cases who are infected at age $\tilde{a}$ to $\tilde{a}+d\tilde{a}$ at time $\tilde{t}$ to $\tilde{t}+d\tilde{t}$ and then survive to age a at time t,

$$c(\tilde{a},\tilde{t})\,d\tilde{a} = e^{-\int_{\tilde{a}}^{a}(\delta(\hat{a})+\mu(\hat{a},\tilde{a}))d\hat{a}} f(\tilde{a},\tilde{t}) e^{-\int_0^{\tilde{a}}(f(\hat{a},\hat{t})+\delta(\hat{a}))d\hat{a}} d\tilde{a} \qquad \text{A2}$$

where $\mu(\hat{a},\tilde{a})$ is the excess mortality due to HIV infection of someone who was infected at age $\tilde{a}$ and is now of age $\hat{a}$. In Equation A2, the last term is the probability of surviving and remaining uninfected up to age $\tilde{a}$, the last but one term is the probability of being infected at age $\tilde{a}$, and the first term is the probability of surviving with HIV from age $\tilde{a}$ to age a. The probability that a person is alive and infected at age a is obtained by integrating Equation A2 over all ages up to a so that

$$c(a,t) = e^{-\int_0^a \delta(\hat{a})d\hat{a}} \int_0^a e^{-\int_{\tilde{a}}^{a}\mu(\hat{a},\tilde{a})d\hat{a}} f(\tilde{a},\tilde{t}) e^{-\int_0^{\tilde{a}} f(\hat{a},\hat{t})d\hat{a}}\, d\tilde{a} \qquad \text{A3}$$

When using Equations A1 and A3 to determine the prevalence of infection the terms containing the background mortality $\delta(a)$ cancel giving Equations 2 to 4 in the text. To estimate the incidence requires parameterised expressions for $f(a,t)$ and $\mu(\hat{a},\tilde{a})$, so that the parameters can be varied to get the maximum likelihood fit to the age-specific prevalence as discussed in the text.

CHAPTER 10 Measuring the incidence of HIV in KwaZulu-Natal using a standardized testing algorithm for recent HIV sero-conversion (STARHS)

> "Equations are more important to me, because politics is for the present, but an equation is something for eternity."
>
> Albert Einstein[586]

Introduction

Cross-sectional measurements of HIV prevalence are carried out routinely and form the basis of epidemic forecasting models and impact assessments. Much more powerful analyses can, however, be done using measurements of age-specific incidence, as they provide information on the current rates of infection rather than the rates averaged over some time period. Reliable age-specific incidence data can make it possible to forecast the course of the epidemic with greater confidence, identify particular risk groups and assess the impact of interventions. As pointed out in previous chapters, incidence is best measured in cohort studies but these are expensive and time consuming, and raise many ethical problems. Several alternative, indirect, methods have been developed to estimate the incidence of HIV, including statistical and mathematical models as described in Chapters 8 and 9, and the use of novel laboratory techniques. The laboratory techniques include a variety of approaches that commonly rely on the properties of early HIV antibodies after seroconversion.[570] The sensitive/less-sensitive testing strategy (the "detuned" assay) was first developed by Janssens et al.[567] to provide a simple laboratory tool to detect recent seroconversion in a cross-sectional population. They observed that recently developed HIV tests could detect antibodies sooner than the older tests and created a test that is deliberately less sensitive so that the two tests would detect seroconversion at different times. The "Standardized Testing Algorithm for Recent HIV Seroconversion" (STARHS),[420,567,568,587] based on differential antibody titres in recent versus long-term infections, is the topic of this chapter.

In Chapter 9 it is shown that temporal or age-specific changes in HIV prevalence can be used to estimate the incidence of HIV infection. Such estimates generally depend on assumptions regarding the parametric form of the age-specific risk of infection, the survivorship as a function of the time since sero-conversion, and the overall change in

prevalence with time. Furthermore, these methods give population estimates of incidence and cannot be used to identify those individuals who have recently sero-converted. The advantage of laboratory methods for determining incidence, such as the STARHS method, is that it can be used to determine whether or not a specific individual infection has been acquired recently. The ability of the sensitive/less-sensitive testing strategy to differentiate persons with early infections from those with later infection is essential, not only to provide timely estimates of incidence in cross-sectional studies, or for the study of population dynamics and for guiding HIV prevention programs, but also for clinical care. Once antiretroviral therapy becomes widely available identification of individuals with early infection will become increasingly important, both to improve opportunities for providing early therapy and to prevent opportunistic infections.

The first aim of this chapter is to estimate the incidence of HIV infection among women attending antenatal clinics in rural KwaZulu-Natal using STARHS, which relies on the rise in HIV antibody levels over several months after infection so that those who have recently sero-converted have low antibody titres.[567] The second aim is to compare the STARHS estimates to estimates of HIV incidence independently obtained from age-specific prevalence using the mathematical model described in Chapter 9.

Methods

Study population

The data for this study were collected in 1999 in the Hlabisa district of northern KwaZulu-Natal as part of the MRC research in this area. Antenatal care in Hlabisa is provided by the local district hospital, ten community clinics and two mobile clinics where about 95% of pregnant women in the district receive antenatal care. Blood samples were taken from a random sample of 2,623 women, aged 15 to 49 years, attending antenatal clinics and tested anonymously for HIV-1 prevalence and incidence.

Laboratory methods

Serum samples were initially stored at 4^0C and were frozen at -20^0C within 48 hours. Frozen samples were shipped on dry ice to the Viral and Rickettsial Disease Laboratory, Department of Health Services, California for the independent assessment of early infection using the STARHS. Following HIV testing using a standard ELISA, the

STAHRS was applied using two HIV-1 ELISAs approved by the Food and Drug Administration (FDA). To make the ELISAs less-sensitive and so discriminate between recent and old sero-converters, the first ELISA (3A11, Abbott Laboratories, Abbott Park, Ill) was modified by a) increasing the initial sample dilution from 1:400 to 1:20,000; b) reducing the sample incubation time from 60 minutes to 30 minutes; and c) reducing the conjugate incubation time from 120 minutes to 30 minutes. The second ELISA (Vironostikaâ HIV-1 Microelisa, Organon Teknika, Raleigh, NC) was modified by a) increasing the sample dilution from 1:76 to 1:20,000; b) reducing the sample incubation from 100 minutes to 30 minutes while retaining the kit-specified conjugate incubation time of 30 minutes. Both assays were supplemented with HIV-1 LS-EIA calibrator plasma (CAL), low positive control (LPC), high positive control (HPC), and a proficiency/calibration panel made up of five specimens with pre-determined antibody levels, obtained from the Centers for Disease Control, Atlanta GA (CDC). Controls were run in triplicate and the standardized optical density (SOD) was calculated as SOD = (sample OD – average negative control OD)/(average CAL OD). Samples that were positive in the standard sensitive assay and had an SOD below 1.5 in the less-sensitive (LS) assay were re-tested in triplicate using the LS assay. The average SOD was then calculated as (average sample OD – average negative control OD)/(average CAL OD). Samples with an average SOD below the prescribed cut-off, 0.45 for subtype C, were classified as recent infections.

Comparison between the Abbott and Vironostikaâ ELISA

The study was started using the FDA approved Abbott ELISA. However, halfway through the study this assay was removed from the market because of an FDA ruling against Abbott and the Vironostikaâ assay was used instead. A subset of the samples (n = 240) were re-tested with both assays to establish the comparability of the results. Using a cut-off of 0.45 for classification of recent sero-converters, the two assays agreed on 95.4% (95% CI: 92.7 – 98.1%) of the total sample. Compared to the Abbott assay the Vironostikaâ assay had a sensitivity of 98% (95% CI: 96.2 – 99.8%) and a specificity of 94.7% (95% CI: 91.9 – 97.5%).

Statistical methods

STARHS technique

There is a time after infection with HIV that antibodies to the virus are not detected in a person. The appearance of detectable antibodies is called "sero-conversion". The time from sero-conversion on the sensitive test to sero-conversion on the less sensitive test defines the "window period".[588] Sero-conversion on the less-sensitive test means that the standard optical density (OD) measured by the test rises above a pre-specified cut-off. The window period varies from person to person, but the mean can be adjusted by varying the OD cut-off. If a specimen from an HIV-infected person tests positive on a sensitive test and negative (below the OD cut-off) on a less-sensitive test, one can conclude that the person was infected within a known time window.

After STAHRS testing the annual incidence, I, is calculated as:

$$I = \frac{n}{(m+n)} \frac{365}{T} \times 100$$

where n is the number of infections classified as recent (i.e., n people reacted to the sensitive but not to the less-sensitive ELISA) and m is the number of people who are HIV negative on the sensitive ELISA.[567] The window period, T, is the estimated mean number of days that would elapse between the detection of sero-conversion using the sensitive and the less-sensitive tests. The value of T depends on the sensitivity of the detuned test and the initial detuned ELISA was designed to give a value of 200 days using the cut-off recommended for HIV subtype C by the CDC. For the STARHS estimates of incidence, 95% confidence limits were calculated assuming binomial errors.

Mathematical model

The mathematical model described in Chapter 9 was used to estimate age-specific incidence from measurements of age-specific prevalence and changes in overall prevalence with time in an epidemic situation. To validate STARHS, the mathematical model was used, completely independently, to estimate the incidence of infection from prevalence data for the same blood samples.

Briefly, the model uses maximum likelihood methods to obtain age-specific incidence rates while error estimates are obtained using a Monte Carlo procedure. A simplifying, but not essential, assumption is that the risk of acquiring infection is determined by the product of

the force of infection, which is proportional to the overall prevalence at any time, and an age-risk function, which is determined by the likelihood that people will engage in high risk sex as a function of age, i.e.

$$f(a,t) = R(a)P(t)$$

where $R(a)$ is the relative risk of infection with age, and $P(t)$ is the average adult prevalence independent of age.

The age-risk function is assumed to be zero below a certain age because most data sets for South Africa show that the prevalence of infection among girls younger than 15 years is either zero or is very low. The prevalence of infection among girls older than 15 years increases rapidly, reaches a peak between the ages of 22 and 25 years, and then decreases with age. An off-set log-normal function (Chapter 9, Equation 9.6) has this general form and was therefore chosen to parameterize the age-risk function.

The function $P(t)$ describes the overall prevalence with time, which is available from the antenatal clinic surveillance data in Hlabisa from 1990 onward (shown in Chapter 9, Figure 9.1). In the early years of the epidemic the prevalence of HIV infection increased exponentially and a logistic function of time gave a statistically good fit to the overall prevalence. However, by 2000 it was clear that the epidemic growth rate was slowing and a logistic function with a variable asymptote has been used to fit the overall prevalence data.

A Weibull survivorship function was used to describe the median survival of people infected with HIV.[575] As described in Chapter 9, survival declines linearly with age at infection. In the model we assumed a shape parameter for all ages of 2.28, and a median survival time of 9 years.

Results

Data from which incidence rates were estimated are given in Table 10.1. Both methods, the STARHS and the mathematical model, were used completely independently, to estimate the age-specific incidence of HIV infection among women attending antenatal clinics in Hlabisa. The age-specific prevalence of HIV infection, $P(a,t)$, fitted to the model is shown in Figure 10.1 and shows that the prevalence of HIV infection increases rapidly

between the ages of 15 and 20 years, peaks among women aged 24 years and declines among older women. The log-normal function provided a good fit to the data. The average ANC prevalence in Hlabisa for 1999 was 34.2% (95% CI: 32.0 – 36.5%).

Table 10.1 Women attending antenatal clinics in Hlabisa who were tested for HIV infection in 1999. The number of HIV negatives, recent infections, and definite positives by age, followed by the HIV prevalence (%).

Age (yrs)	Negative	Recent	Positive	HIV prev (95% CI)
10–14	6	0	0	0.0 (0.0 – 39.3)
15–19	495	57	104	24.5 (20.9 – 28.6)
20–24	478	71	248	40.0 (35.7 – 44.7)
25–29	295	44	200	45.3 (39.8 – 51.3)
30–34	242	22	94	32.4 (26.8 – 38.9)
35–39	155	13	31	22.1 (16.5 – 28.5)
40–44	46	9	3	20.7 (11.2 – 33.4)
45–49	5	0	2	28.6 (3.7 – 71.0)

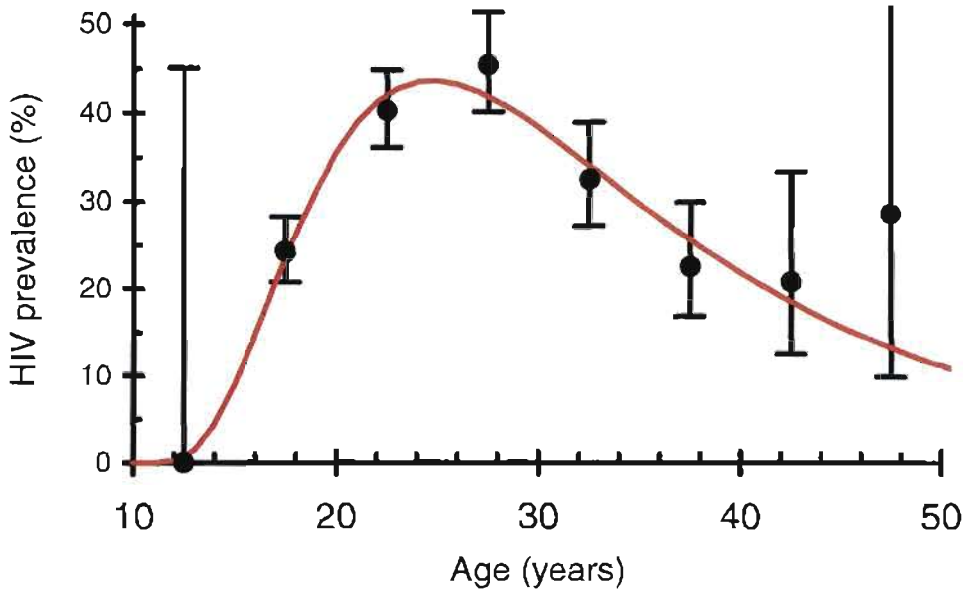


Figure 10.1 Age prevalence of HIV-1 infection among women attending antenatal clinics in Hlabisa in 1999. The curve was fitted to the data in one year age groups but the data are plotted in five yearly groups for clarity. Error bars are 95% confidence limits.

Using the model described above the annual age-specific incidence per susceptible with 95% confidence bands are shown in Table 10.2 and plotted in Figure 10.2. The STARHS estimates using the initial window period of 200 days provided age-specific estimates of incidence of the same shape, but 60% higher than the estimates obtained from the model. When scaled down accordingly, i.e., suggesting a window period of 320 days, the STARHS estimates of incidence (Table 10.2 and shown as dots in Figure 10.2) are similar up to the age of 40 years. Although the scaled estimates of incidence are similar to the model estimates, the STARHS method shows some uncertainty about the window period to be used for subtype C samples of HIV.

The estimates disagree significantly only in the estimate of incidence among 40 to 45 year old women. The prevalence curve suggests an upward trend after the age of 40 years but this is not statistically significant and the sample size is small. Furthermore, the STARHS provides an estimate of the incidence of infection among people aged 40 to 45 years that is almost as high as the prevalence (18.7% vs. 20.7%, respectively) in this group, suggesting that the STARHS estimate may be too high.

Table 10.2 Annual age-specific incidence of HIV infection estimated using STARHS and the age-prevalence model described in Chapter 9.

	STARHS incidence		Model incidence	
Age group	Incidence (%)	95% CI (%)	Incidence (%)	95% CI (%)
10–14	0.0	0.0 – 44.8	0.98	0.5 – 1.8
15–19	11.8	9.1 – 15.1	10.2	8.9 – 11.6
20–24	14.8	11.7 – 18.3	14.6	13.1 – 16.3
25–29	14.8	10.9 – 19.4	12.2	10.9 – 13.8
30–34	9.5	6.1 – 14.1	8.6	7.1 – 10.3
35–39	8.8	4.8 – 14.7	5.8	4.3 – 7.5
40–44	18.7	8.8 – 32.9	3.8	2.4 – 5.7

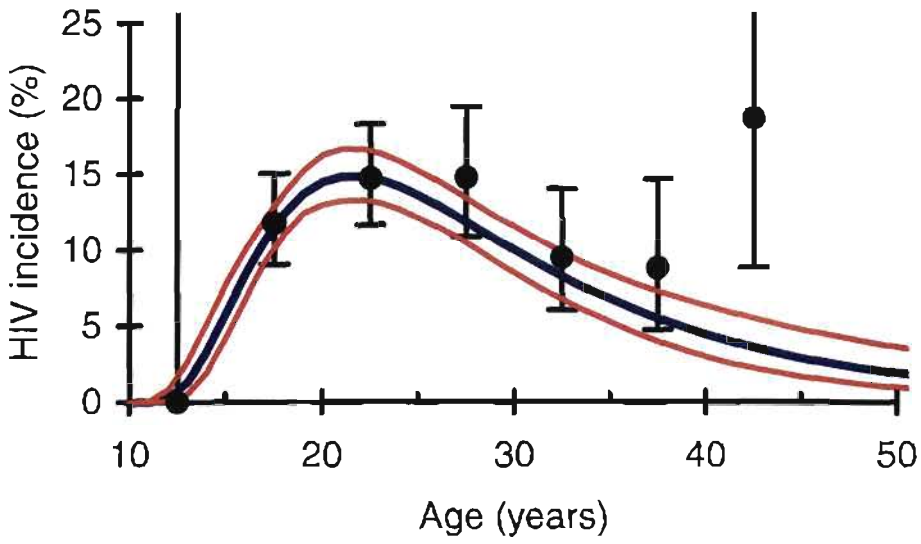


Figure 10.2 The annual age-specific incidence per susceptible. Heavy line: estimated from age-prevalence data; light lines: 95% confidence intervals. Dots: estimated from STARHS with 95% binomial confidence limits.

Discussion

The epidemic in South Africa has been among the fastest growing epidemics in the world and reliable incidence estimates are needed to understand the dynamics of the epidemic. Samples taken from women attending antenatal clinics in Hlabisa, rural KwaZulu-Natal, in 1999 provide the first estimates of HIV incidence using the STARHS in a South African population where subtype C is the dominant strain. The validity of the estimates is confirmed by comparing the STARHS results with incidence estimates based on modeling age-specific prevalence data. The annual incidence of infection, as estimated by the mathematical model, increases rapidly with age and reaches 15% in 22 year old women; the overall incidence of infection among women aged 15 to 49 years, standardized to the age distribution of women attending ANC in Hlabisa is 11.4% (95% CI: 9.9 – 13.0%).

The incidence rates reported here, which average 11.4% for 15-49 year old women and peak at 14.9% are much higher than rates reported in other comparable populations in Africa. A study of pregnant and post-partum women in Malawi found an annual incidence of 6.0% among women less than 20 years old with lower rates in older women.[589] Among women enrolled at delivery in a hospital in Kigali, Rwanda the annual incidence of HIV infection decreased linearly from 7.6% during the first six months post-partum to 2.5%

during the last six months of the three year follow up.[590] In a study of concordant and discordant couples in Uganda the annual incidence of infection was 0.82% for men and 0.87% for women when both partners were initially sero-negative but was 8.7% for men and 9.2% for women if the partner was already HIV-positive.[591] In a study conducted among male factory workers in Harare, Zimbabwe, the annual incidence of HIV infection was 3.0%.[592] In a cohort study of men in Bujumbura, Burundi, the annual incidence varied between 1.5% and 2.3% depending on the ages of the men.[555]

The extraordinarily high incidence rate of HIV infection gives cause for alarm. While young women below 30 years of age are experiencing the highest incidence rates, the incidence rates in women from 30 to 40 years are still between 5% and 10%. As will be shown in Chapter 11, the incidence rates reported here for 1999 were close to the peak rates for this epidemic, but it is essential that incidence rates are measured annually in order to monitor the epidemic trends.

The measured incidence in this South African population is very high but confirmed by two independent methods of estimation. The two methods agree for all but the oldest age group. The higher estimate of incidence among women aged 40 to 44 years using STARHS rather than the prevalence based model could indicate that the incidence is genuinely high among older women or that the STARHS tends to overestimate the incidence in older women. The overestimation in the older women could be related to a weaker immune system which in turn could affect the window period of the STARHS. The data however, are not sufficiently precise to resolve this issue, particularly for the oldest age group, and more extensive studies are needed.

The application of sensitive/less-sensitive assays to detect incident infections, following the initial report by Janssens *et al.*,[567] demonstrates that simple modifications in the assay protocol of commercial ELISAs can be used to detect recent HIV sero-conversion. Several laboratories in the United States have used versions of the less-sensitive ELISA to detect recent infections.[564] However, several reports indicated that there are limitations to this approach,[564,570] the most important of which include the significant variability of the window period and the dependence of the test on the particular subtype of HIV. Two studies using the 3A11-less sensitive and Vironostika-less-sensitive ELISA showed significant differences in the window period in subtypes B or E infected individuals from

Thailand.[593,594] The longer window period (270 to 350 days) in persons infected with subtype E were attributed to the use of subtype B derived antigens in the assays, indicating that other divergent HIV-1 subtypes from Africa and Asia are also likely to be different. This necessitated a change in seroconversion duration and the cut-off values to make it more applicable to areas of the world with multiple subtypes. The STARHS technique used in our analysis was designed to give a value of 200 days using the cut-off recommended for subtype C by the CDC. However, to make the estimates comparable to the model estimates, the window period had to be adjusted to 320 days, confirming the variability of the window period for different populations.

As a result of the limitations of the STARHS, in particular in relation to the poorly defined cut-offs and window periods in the circulating HIV subtypes, new tests have been developed, including those that detect recent HIV infection by indirectly measuring the increasing HIV IgG as a proportion of the total IgG following seroconversion, called the IgG-capture BED-EIA.[569,570,594] It is claimed that the format of the assay, which includes a multi-subtype derived antigen, allows reasonably high consistency and similar window periods in different subtypes. However, despite reasonable performance characteristics, results reported from several countries at a recent UNAIDS Reference Group meeting (Athens 2005) indicated that it is still an assay with limited applicability which requires further validation and calibration.[476]

Measurements of incidence should be carried out among other groups in South Africa to determine the current rate of new infections, to provide the basis for the design of effective interventions and to monitor the impact of such interventions as and when they are implemented. While cohort studies should be encouraged they are expensive, time consuming, difficult to carry out logistically and raise ethical problems. Laboratory techniques such as the sensitive/less-sensitive algorithm, the BED-EIA assay, p24 antigen and the HIV RNA assays, when properly applied, have the potential to provide estimates of incidence from existing programmes that conduct studies of HIV prevalence, but further research should be carried out to ensure the reliability and accuracy of these methods of measuring incidence across different settings and different viral subtypes. Laboratory techniques have the important advantage that they can be used to determine which individuals have recently sero-converted[595,596] while the estimates obtained by modeling age-specific prevalence data can only give a population estimate of the age incidence.

Because of the presence of divergent HIV subtypes and the need to monitor the impact of interventions, it is important to estimate incidence using a method that is robust, performs similarly in different subtypes and is widely applicable.

CHAPTER 11 HIV incidence rates in South Africa

> "The desire to understand the world and the desire to reform it are the two great engines of progress."
>
> Bertrand Russell, 1919[597]

Introduction

To fully understand temporal changes in the epidemic of HIV we need to know how incidence and mortality have changed over time. While incidence is difficult to measure directly for logistical and ethical reasons, mortality is difficult to measure directly because of the stigma associated with AIDS. Prevalence provides a measure of incidence and mortality averaged over the previous 5 to 10 years so that it is much more difficult to interpret immediate changes in the dynamics of the epidemic using prevalence than it is using incidence. Ideally, incidence rates should therefore be used to measure recent changes in the HIV epidemic.

Available data suggest that the HIV epidemic in South Africa is reaching stability: incidence is falling, prevalence appears to be levelling off, while mortality is still rising. Unlike estimates of the prevalence of HIV in South Africa that are available from annual national antenatal clinic surveillance, sentinel site surveillance, and studies among specific risk groups, few estimates of incidence are available. Very few cohort studies have been performed in South Africa because of the cost, logistics and the ethical considerations of following negative individuals until they seroconvert. More recently, a number of Phase III HIV prevention trials have been initiated with HIV infection as the endpoint and it is likely that more incidence data will become available in the near future. To date however, the only directly measured incidence data available are those collected from the UNAIDS sponsored Col-1492 Phase III microbicide trial among sex workers in KwaZulu-Natal.[282]

As described in the previous three chapters, several indirect methods, many of which utilize cross-sectional age-prevalence data, have been developed to estimate the incidence of HIV infection. These include back-calculation methods, statistical models, mathematical models, and several laboratory techniques.

Although statistical and mathematical models are extremely important for understanding the dynamics of the HIV epidemic, model estimates should be interpreted with care because there is always a degree of uncertainty around the estimates. The estimates depend both on the structure of the model and assumptions regarding the key parameters which cannot necessarily be determined directly from the raw data.

In this chapter the incidence rates obtained directly from the one cohort study conducted in South Africa among sex workers in KwaZulu-Natal are described. The two models that were developed and described in Chapter 9 are then applied to estimate incidence in several populations in South Africa for which cross-sectional prevalence data are available. These populations include the national antenatal clinic attendees (15-49 year old women), the rural community (male and female) of Hlabisa, and the urban community (male and female) in Carletonville, Gauteng. These populations are described in more detail in Chapter 4.

Incidence rates estimated directly from the UNAIDS sponsored phase III Col-1492 microbicide trial

A cohort of female sex workers operating at truck-stops along the national road linking Durban to Johannesburg was established in 1996, in preparation for a Phase III multi-centre microbicide (Col-1492) trial.[478] The mean age of 477 sex workers who were screened for possible participation in the trial was 25.1 years (range 15 - 48) with an average education of six years (range 0-16). The mean number of years as a sex worker was 2.5 years, ranging from one month to 31 years. On average they had four partners per day, and only 20% of women indicated that they used condoms more than 50% of the time. Baseline data on these 477 sex workers revealed a high HIV prevalence rate (51.3%; 95% CI: 46.7 – 55.8%).

A cohort of 198 HIV negative sex workers were then followed up as part of the microbicide trial for a period of about three years between 1996 and 1998 and represents the only data set in South Africa providing direct estimates of incidence from longitudinal data. The overall incidence rate per annum in this cohort study of women of mean age 25 years (range 15–48 years) was 18.2% (13.0%–23.0%), ranging from 16.8% in 1996/1997 to 20.0% in 1999 (Table 11.1).[282,598] This high incidence was not surprising given the

sexual risk, in terms of number of clients, low condom use and high incidence of other STIs, in particular HSV-2, that this cohort was exposed to.[281]

Table 11.1 HIV incidence rate in a cohort of sex workers participating in the Col-1492 microbicide trial in KwaZulu-Natal

Year	Number HIV+	Person-months of follow-up	HIV incidence rate (%) per year (95% CI)
1996/1997	14	996	16.8 (8–26)
1998	25	1644	18.2 (11–25)
1999	13	780	20.0 (9– 31)
1996-1999	52	3420	18.2 (13–23)

Estimating incidence rates indirectly

The following section presents incidence rates estimated indirectly using dynamical models developed and described in Chapter 9. Here the models are applied to data collected from the National and Hlabisa antenatal clinic surveys and the Carletonville community-based surveys using data on the age-specific prevalence of infection and time-trends in the average prevalence of infection to estimate age-specific incidence. Monte Carlo methods were used to estimate confidence limits for the projections.

Incidence rates estimated for South Africa

National and provincial estimates of incidence rates among antenatal clinic attendees for the period 1991 to 2005 are given in Table 11.2 and projected forward to 2010 in Figure 11.1. Incidence rates for the national ANC population peaked at 6.6% per year in 1997 while rates vary substantially between provinces, reflecting the differences in the spread of HIV between provinces. Incidence rates in most provinces peaked between 1996 and 1999, except in the Western Province where it peaked in 2000. As with the prevalence data, the highest incidence rates occurred in KwaZulu-Natal, reaching a peak in 1997 at 9.9% per year, while the lowest occurred in the Western Cape reaching a peak in 2000 at 2.9% per year. Both national and provincial incidence data suggest that the HIV epidemic in South Africa might be approaching a steady state and the forward projection indicate that the incidence among all pregnant women attending antenatal clinics in South Africa will remain at around 5.8% in the next five years.

The model-based estimate for the adult population (aged 15-49 years) of the same social class as the women attending antenatal clinics, is 3.8%. Further adjustment through application of the correction factor as calculated in Appendix 5.1, yields an incidence estimate for the general adult population (aged 15-49 years) in South Africa of 2.4%.

Table 11.2 Incidence estimates (%) for antenatal clinic attendees by year and by province 1990-2001

	WP	EC	NC	FS	KZN	MP	LM	GT	NW	National
1990	0.08	0.28	0.13	0.56	1.18	0.37	0.24	0.54	0.25	0.58
1991	0.13	0.47	0.24	1.02	1.97	0.81	0.41	0.92	0.56	0.97
1992	0.22	0.80	0.44	1.81	3.15	1.68	0.67	1.55	1.20	1.59
1993	0.36	1.31	0.79	3.04	4.79	3.28	1.06	2.52	2.45	2.50
1994	0.59	2.08	1.35	4.69	6.71	5.66	1.62	3.87	4.46	3.69
1995	0.94	3.13	2.11	6.42	8.49	8.03	2.30	5.47	6.68	4.99
1996	1.41	4.34	2.96	7.60	9.63	8.96	3.00	6.92	7.76	6.06
1997	1.97	5.44	3.56	7.83	9.93	8.22	3.51	7.80	7.19	6.59
1998	2.51	6.12	3.70	7.39	9.68	7.03	3.72	7.95	6.04	6.57
1999	2.88	6.26	3.46	6.81	9.28	6.26	3.65	7.63	5.26	6.27
2000	2.99	6.04	3.12	6.41	9.01	5.98	3.45	7.23	4.95	5.95
2001	2.89	5.73	2.88	6.25	8.91	5.99	3.27	6.95	4.93	5.75
2002	2.72	5.50	2.76	6.25	8.94	6.11	3.15	6.84	5.04	5.68
2003	2.57	5.39	2.73	6.33	9.04	6.26	3.10	6.85	5.17	5.69
2004	2.49	5.38	2.75	6.43	9.16	6.39	3.10	6.93	5.28	5.75
2005	2.45	5.41	2.79	6.52	9.26	6.49	3.12	7.01	5.37	5.81

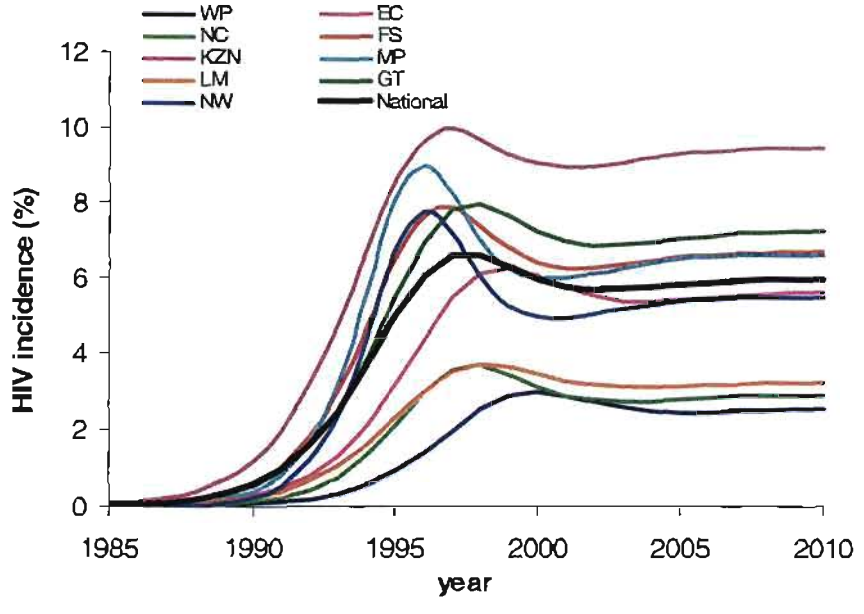


Figure 11.1 Estimates of incidence (percentage) from 1985 to 2010, by province, for women attending antenatal clinics in South Africa.

Incidence rates estimated for rural KwaZulu-Natal

Model estimates based on data collected annually from antenatal clinic attendees in the district of Hlabisa between 1992 and 2001, where the HIV prevalence rose from 4.2% in 1992 to 14.0% in 1995 and 36.1% in 2001, show a peak incidence of 10.3% in 1997 (Figure 11.2). As shown in Chapter 5 for HIV prevalence data, the estimated incidence rates for Hlabisa district are similar to those for the province of KwaZulu-Natal.

Estimates of annual incidence rates for Hlabisa using the two different models described in Chapter 9, are presented in Table 11.3. Model 1 was fitted to antenatal clinic data collected from 1997 to 2001 and estimates were derived from age-specific prevalence and changes in overall prevalence with time. Estimates of incidence were standardized using the age distribution of the Hlabisa female population attending antenatal clinics. The method described by Podgor and Leske in Chapter 8 was applied to estimate incidence in 1993 and 1995 because of the unavailability of age-specific data for these two years. Model 2 uses time trends in prevalence. The two sets of estimates are similar and both indicate that the epidemic in rural KwaZulu-Natal was approaching a steady state.

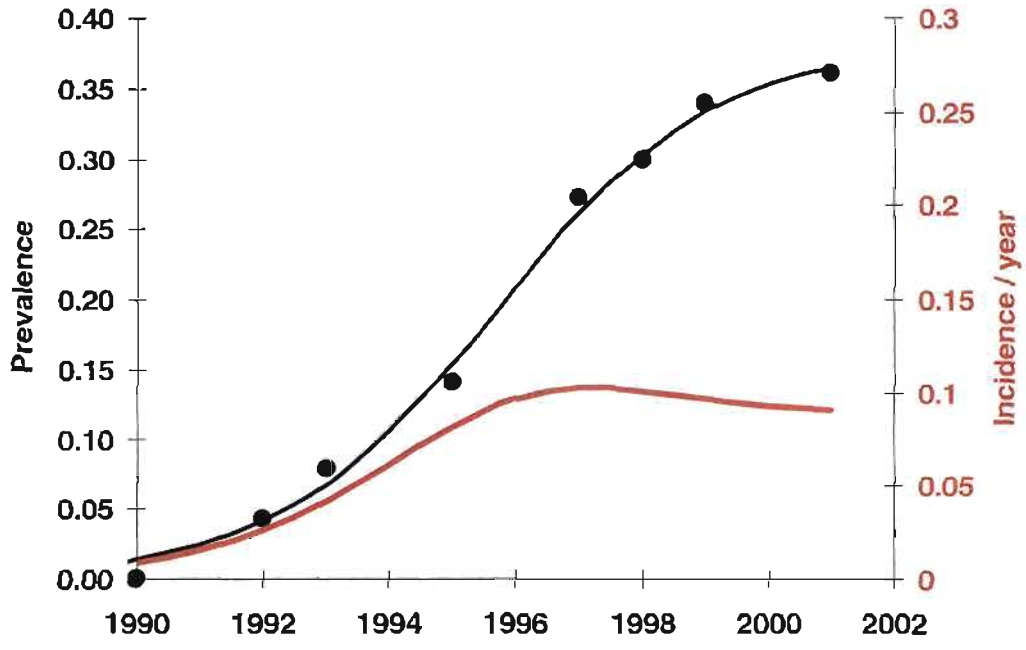


Figure 11.2 Temporal trends in prevalence and annual incidence among women attending antenatal clinics in Hlabisa.

The *age-specific* estimates of incidence for women attending antenatal clinics in Hlabisa from 1997 to 2001, using Model 1 in Chapter 9 with a Weibull survival distribution function, are presented in Table 11.4 and Figure 11.3, together with the corresponding prevalence data for this period. While age-specific estimates did not show dramatic changes between 1997 and 1999, estimates for 2001 were slightly lower. Similar to prevalence data, incidence peaked in the 20-24 year age groups at 13.1% in 1997, 14.6% in 1998, 14.6% in 1999, and 12.1% in 2001.

Table 11.3 Prevalence and estimated annual incidence of HIV infection among antenatal clinic attendees aged 15-49 years in Hlabisa, 1992 – 2001, using two different models. Model 1 uses age-specific prevalence and changes in overall prevalence with time, while Model 2 uses time trends in prevalence only.

			Estimated Annual Incidence	
Year	N	Prevalence of HIV (95% CI)	Model 1	Model 2
1992	884	4.2% (3.0– 5.7)		2.0%
1993	709	7.9% (6.0–10.1)	2.3	3.3%
1995	314	14.0% (10.4–18.4)	7.2	7.1%
1997	4731	27.2% (25.9–28.5)	10.6%	10.2%
1998	3166	29.9% (28.4–31.6)	10.5%	10.5%
1999	2623	34.0% (32.5–35.7)	11.4%	10.3%
2001	590	36.1% (32.9–39.2)	9.9%	9.6%

Table 11.4 Prevalence and annual incidence with 95% confidence intervals for women attending antenatal clinic in Hlabisa, by age 1997-2001

Age (years)	1997	1998	1999	2001
Prevalence				
10–14		0 (0–34.8)	0 (0–45.1)	0 (0–52.7)
15–19	23.2 (20.5–26.3)	21.1 (18.1–24.5)	24.2 (20.6–28.2)	22.9 (17.0–29.8)
20–24	35.5 (32.6–38.7)	39.3 (35.5–43.4)	40.2 (36.0–44.8)	50.8 (43.4–58.2)
25–29	28.5 (25.3–32.0)	36.4 (31.7–41.5)	45.3 (39.9–51.3)	47.2 (36.5–58.1)
30–34	22.5 (18.9–26.5)	23.4 (18.9–28.6)	32.5 (26.9–38.9)	38.4 (27.3–50.5)
35–39	17.2 (13.2–22.1)	23.0 (17.6–29.6)	22.4 (16.4–29.9)	36.4 (22.4–52.3)
40–44	8.8 (4.3–15.7)	12.3 (5.1–23.7)	20.7 (11.2–33.4)	26.7 (7.8–55.1)
45–49	11.5 (2.4–30.2)	13.3 (1.7–40.5)	28.6 (3.7–71.0)	33.3 (0.8–90.5)
Incidence				
10–14		0.75 (0.4–1.4)	0.98 (0.53–1.76)	1.0 (0.35–2.89)
15–19	11.1 (9.9–12.3)	10.0 (8.7–11.3)	10.2 (8.9–11.6)	8.9 (7.0–11.0)
20–24	13.1 (11.8–14.4)	14.6 (13.0–16.2)	14.6 (13.1–16.3)	12.1 (9.5–15.7)
25–29	10.1 (9.0–11.1)	11.5 (10.3–12.9)	12.2 (10.9–13.8)	10.2 (7.8–12.9)
30–34	6.8 (5.7–8.0)	7.4 (6.3–8.9)	8.6 (7.1–10.3)	7.4 (5.0–10.5)
35–39	4.5 (3.4–5.8)	4.5 (3.3–6.14)	5.8 (4.3–7.5)	5.1 (2.7–8.1)
40–44	2.9 (1.9–4.2)	2.6 (1.7–4.2)	3.8 (2.4–5.7)	3.5 (1.4–6.8)
45–49	1.9 (1.1–3.0)	1.6 (0.9–2.8)	2.5 (1.4–4.3)	2.3 (0.8–5.7)

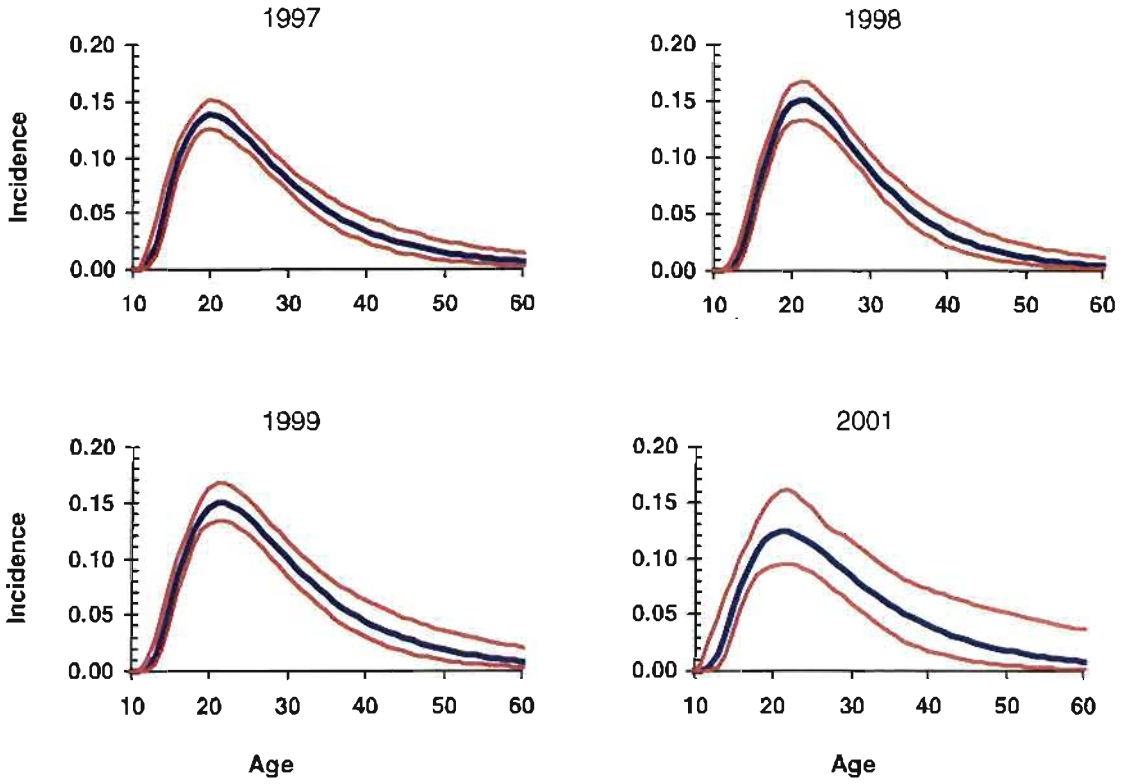


Figure 11.3 Age-specific estimates of HIV incidence per year for women attending antenatal clinics in Hlabisa in 1997, 1998, 1999 and 2001.

Estimated incidence rates by gender and age for an urban community in Gauteng

Using Model 1 in Chapter 9 with a Weibull survival distribution function, incidence rates were estimated from age-prevalence data collected from an urban mining community in Carletonville in 1998.[222] The overall incidence for men aged 15-49 years was 9.6% (assuming a flat age distribution) compared to 13.5% for women in the same age range. Age specific incidence rates for men and women are provided in Figure 11.4 and Table 11.5, and show a dramatic peak incidence of 22.8% among women aged 24 years and of 16.4% among men aged 30 years old. It is of interest to note that the incidence rate among young women in this community in 1998 was higher than that reported for the truck-stop sex worker population described above and this is of grave concern.

Table 11.5 Age-specific HIV prevalence and incidence for men and women in Carletonville in 1998

Age	Women		Men	
	Prevalence	Incidence	Prevalence	Incidence
10-14	0.5 (0.13–1.8)	0.52 (0.15–1.6)	0 (0 – 0.06)	0 (0 – 0.07)
15-19	18.7 (11.9–27.7)	10.7 (7.4–14.6)	1.73 (0.52–5.3)	1.3 (0.44–3.24)
20-24	48.7 (41.0–56.8)	21.5 (17.4–26.4)	17.1 (10.3–24.9)	8.5 (5.5–12.3)
25-29	55.6 (47.8–63.1)	21.3 (17.2–25.6)	37.6 (27.5–48.8)	15.3 (10.4–20.8)
30-34	49.4 (42.9–55.9)	16.6 (13.6–19.9)	44.1 (32.8–55.9)	15.7 (10.9–21.6)
35-39	38.5 (31.7–45.3)	11.6 (8.9–14.9)	39.1 (29.0–49.2)	12.4 (8.5–17.2)
40-44	27.7 (20.6–36.1)	7.9 (5.3–11.2)	29.6 (20.5–39.7)	8.5 (5.4–12.6)
45-49	18.9 (12.3–27.6)	5.2 (3.1 – 8.3)	20.0 (12.0–29.9)	5.5 (2.9–9.2)
50-54	12.6 (7.1–20.7)	3.5 (1.8 –6.3)	12.5 (5.8–23.2)	3.4 (1.3–7.1)
55-59	8.1 (4.0–15.7)	2.3 (1.1 – 4-8)	7.4 (2.5–17.5)	2.0 (0.6–5.4)

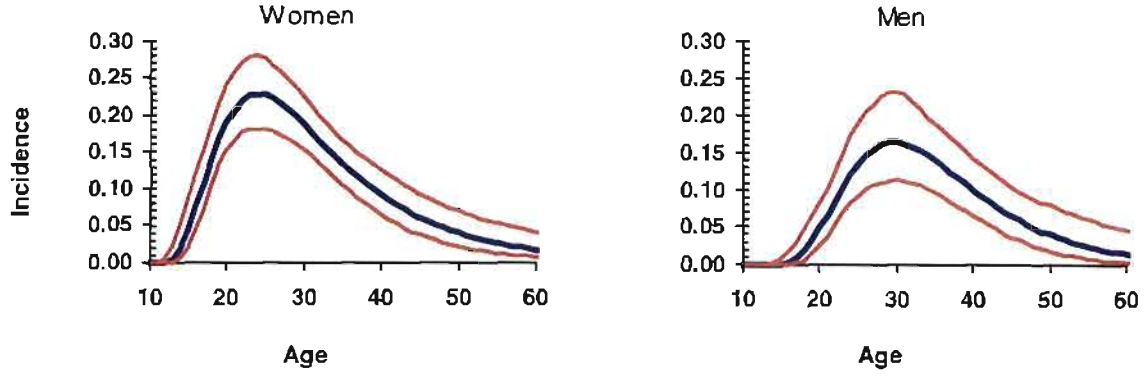


Figure 11.4 Age-specific incidence per year for women and men in the general population in Carletonville in 1998.

Discussion

South Africa has experienced one of the fastest growing HIV epidemics in the world and in 2002 more than 25% of women attending public antenatal clinics were infected with HIV. In order to understand the dynamics of HIV infection we need to know more about the current burden of disease, the rate of new infections and the rate of deaths, for which reliable estimates of prevalence and incidence are required. In this chapter, incidence rates were estimated indirectly from HIV prevalence data using dynamical models developed specifically for South Africa.

The annual incidence rate for women attending antenatal clinics in South Africa in 2005 was estimated to be 5.8%, ranging from 2.5% in the Western Cape to 9.3% in KwaZulu-Natal. National ANC indicence peaked at 6.6% in 1997. Extrapolating the ANC estimates to the general population, adjusting for racial differences and differences in prevalence between pregnant women and the general population, the annual incidence rate for the adult (men and women aged 15-49 years) population in South Africa in 2005 is estimated to be 2.4%. This is in agreement with the incidence estimate obtained from the Actuarial Society of South Africa (ASSA) model of 2.1% per year (Dorrington, personal communication).

The incidence estimates from two communities in South Africa demonstrate extraordinarily high levels of HIV infection in South Africa. The extremely high incidences among young men and women in both Carletonville and Hlabisa are a reflection of the very rapid rise in HIV prevalence after the onset of sexual activity. In Carletonville, HIV prevalence among young women in 1998 went up from 5% in 15-year olds to 56% in 25 year olds. Taking into account that many of the infections in this age group will be new infections, the high incidence estimates presented here are likely to be a true reflection of the rate at which young people acquire new infections. It should further be pointed out that Carletonville is a special case because it is a mining community with many male migrant workers working on the mines and living in single sex hostels, and hence the spread of HIV among young people is probably much higher than in other settings.

Age-specific incidence curves, similar to age-prevalence curves, show peak incidences among young people with a decline among older age groups. Young women aged 20 to 24

years are at highest risk of being infected with HIV, while infection rates among men peak at a later age (30-39 years). The shapes of the age-specific incidence curves are similar for urban and rural populations.

Data in South Africa suggest that the epidemic is starting to level off. Incidence estimated among national antenatal clinic attendees peaked in 1997 at 6.6% per year. The slight decrease in incidence after 1997/1998 probably reflects the natural course of the epidemic as it reaches a steady state. If there is no change in behaviour in the coming years, the epidemic curve is likely to stay steady. However, should the HIV transmission rate fall significantly as a result of natural behaviour change or effective interventions, this will first be seen in falling incidence, as incidence rates respond to change more quickly than does prevalence. Prevalence reflects the average incidence and mortality over the past 5 to 10 years, and a change in the epidemic will take a longer time period to manifest in estimates of prevalence.

The models described here and in previous chapters can be used to obtain good fits to the prevalence of infection and reliable estimates of the incidence of infection. However, in order to explore the biological and social factors that influence the course of the epidemic or to investigate the likely impact of different interventions, dynamic models based firmly on the knowledge of the natural history of the epidemic will be needed.

CHAPTER 12 The impact of anti-retroviral therapy on HIV incidence and AIDS related mortality in South Africa

> "It is our duty as children of the same God and citizens of the same planet to pool our energies and banish the scourge of AIDS from the headlines of our newspapers to the chapters of our history books once and for all"
>
> William J Clinton[599]

Introduction

While the benefits of providing combination antiretroviral therapy for the management of HIV disease are well established in developed countries (having resulted in a reduction in HIV-related deaths from 17 to 5 per 100,000 people in the United States of America[600]), access to ARV drugs in Africa has been limited. Of an estimated four million people who were in need of ARV treatment at the end of 2002, only about 1% were receiving treatment.[600] However, since the United Nations (UN) Member States made a declaration of commitment on HIV/AIDS at the 2001 Special Session of the UN General Assembly,[601] the global response to HIV/AIDS has grown significantly. The Global Fund to Fight AIDS, Tuberculosis and Malaria was established to provide low- and middle-income countries with additional funding for AIDS, TB and malaria; the World Bank provides large-scale grants through its multi-country AIDS Program; and the Government of the United States of America has set up the Presidents Emergency Fund for AIDS Relief (PEPFAR) which aims to provide treatment to 2 million HIV-infected people with anti-retroviral drugs by 2010.[602] The prices of first-line antiretrovirals have in the last few years been reduced substantially as a result of civil society advocacy, special pricing by pharmaceutical companies for low-income countries, increased generic competition and local production. Building on these developments the World Health Organization, together with UNAIDS and other partners, launched the "3 by 5" initiative in 2002 to mobilize support and expand access to antiretroviral treatment.[10,538,600] At the end of 2005, world leaders had committed themselves to "developing and implementing a package for HIV prevention, treatment and care with the aim of coming as close as possible to the goal of universal access to treatment by 2010 for all those who need it".[14]

With the introduction of cheap antiretroviral drugs, widespread treatment of HIV infected people, even in resource-limited settings, has become possible. In November 2003, the National Department of Health in South Africa announced an operational plan to provide comprehensive care, management and treatment for HIV and AIDS in the public health sector in South Africa.[34] The operational plan includes: a) strengthening prevention; b) providing prophylaxis and treatment for opportunistic infections and improving nutrition; and c) providing appropriate treatment for AIDS related conditions, including combination antiretroviral therapy for patients with CD4 cell counts less than 200 cells/μl. The plan assumes that 10% of about 5 million people infected with HIV are currently in need of antiretroviral therapy (ART). Between 2004 and 2008 the cumulative number in need of starting therapy is estimated to be around 1.9 million. The plan consider three scenarios, assuming 20% ART coverage, assuming 50% ART coverage and assuming 100% ART coverage, in which between 200,000 and 1.2 million people would be receiving treatment by the end of 2008.[34]

In light of these ambitious plans, it is important to explore the likelihood that targets will be met. Mathematical models can be used to explore the potential impact of various treatment strategies and to guide policy on the design of treatment programmes. In this chapter a simulation model is developed to explore the impact of ARV drugs on AIDS related mortality and also on HIV incidence, through the impact that the reduced viral load of people taking ARV drugs will have on transmission. The predictions of this model in the absence of treatment are firstly compared to those of previously published models and then the consequences of providing ARV drugs at different levels of coverage and starting at different levels of CD4 cell count are explored.

Methods

Epidemic models

Several attempts to model the course of the epidemic in South Africa have been published, including the ASSA model,[24,558] the UNAIDS EPP model,[557] and the Spectrum model developed by the Futures Group (also used as part of the UNAIDS package to estimate the demographic impact of HIV).[451] An extension of the model described in Chapter 9 to estimate incidence from time trends in the prevalence data and to estimate the impact of

antiretroviral treatment is decribed in this chapter, here referred to as the ART Impact Model (AIM).

The above models (ASSA, EPP and Spectrum) have been described in more detail in chapter 8. Briefly, the ASSA AIDS and demographic model is a cohort component-projection model designed to investigate the demographic impact of HIV in South Africa.[558] The model is fitted to the national antenatal clinic prevalence data and to mortality data from the Department of Home Affairs.[466] The population is separated into men and women, age groups, behavioural groups (high risk, including commercial sex workers; medium risk, including those with high rates of sexually transmitted infections and those who engage in risky behaviour; low risk, including those who are not significantly exposed), ethnic groups, and geographically by province. The model makes assumptions about mortality and fertility rates over time and about migration, which is important in the South African context.[558]

The EPP model is used by UNAIDS to make estimates and projections of HIV prevalence for each country in the world and is, of necessity, a simpler and more restricted model.[557] Four parameters are varied to obtain the best fitting epidemic curve to time series of HIV prevalence data. The first parameter determines the rate of spread of the epidemic, the second determines the proportion of the population considered to be at risk of infection and hence the peak prevalence, the third the behavioural response of the population and hence the long term epidemic trend, and the fourth parameter determines the timing of the epidemic.

The Spectrum model[451] is a demographic model and uses the prevalence curves developed in EPP together with a set of demographic and epidemiological assumptions, including the relative risk of infection for women relative to men, effects of HIV on fertility, mother-to-child transmission of HIV, survival time from infection to death, age patterns of prevalence, and effects and coverage levels of ARV, to produce age and sex-specific estimates of incidence, prevalence and mortality for adults and children (available at http://www.futuresgroup.com). The EPP and Spectrum models have been used in many countries in sub-Saharan Africa, including South Africa, to project future trends in HIV/AIDS.[4,374]

The basis for the AIM model is described in Chapter 9 and uses data on the time-trends in the average prevalence of infection together with assumptions about the form and survivorship function for people infected with HIV to project HIV incidence and mortality. Extending this model to include the impact of antiretroviral therapy is the focus of this chapter.

Data and model assumptions

Prevalence of infection

The most important set of data on trends of HIV infection in South Africa is from the Department of Health's annual HIV surveillance programme based on anonymous, unlinked, cross-sectional surveys of pregnant women attending antenatal clinics in the public health sector (described in more detail in Chapter 4).[23,31,118,141] Data on national and provincial HIV prevalence have been available annually since 1990 and most models on the course of the epidemic in South Africa rely primarily on these data.

In 2002 and 2005, national population-based HIV surveys were conducted in South Africa by the Nelson Mandela Foundation and the HSRC.[469,470] Complex, multi-stage sampling strategies were used to select individuals of whom about 10,000 in both surveys provided samples (saliva in 2002 and blood in 2005) to be tested for HIV, including males and females of all races, aged two years and older, from all nine provinces, including urban and rural areas. The data set has subsequently been used in some modeling exercises to adjust estimates of the HIV epidemic obtained from ANC surveillance.[374]

Life expectancy

Models which attempt to derive estimates of incidence or mortality from prevalence data all depend critically on estimates of the survival probability as a function of time for people infected with HIV. The UNAIDS Reference Group on Estimates, Modelling and Projections, using data from the CASCADE collaboration[575] and mortality data from cohort studies in Uganda[603], Thailand[579] and Haiti[580] recommend the use of a Weibull survival function with a median survival time after infection with HIV of 9 years for developing countries.[450,604] Williams *et al.*,[581] drawing on data from several cohort studies of survival and AIDS mortality, show that under optimal conditions the median life

expectancy, standardized to an age at seroconversion of 27 years, is 9 ± 1 years for those who receive no treatment, 10 ± 1 years if AIDS related opportunistic infections are treated effectively, 11 ± 1 years if ARV mono-therapy is also provided, 12 ± 1 years with dual therapy, and 18 ± 2 years with triple therapy, when initiated at an average CD4 cell count of about 350/μl. If combination therapy is provided at a CD4 count of 350/μl or more, it is therefore anticipated that life expectancy can be extended by an additional 9 years. Little data are available on the estimated increase in life expectancy if ART is started at 200 cells/μl, although the authors of the Government of South Africa's plan for comprehensive HIV care, management and treatment anticipate that this could add an additional 4 years to the life expectancy of HIV-positive people.[268] Under this scenario, it is further estimated that with an ART coverage of 20%, close to a million additional years of life in South Africa would be saved relative to the baseline scenario of not providing ART by 2010, with coverage of 50% an additional 2.3 million life years could be saved, and with 100% coverage an additional 5 million years of life relative to the non-ARV scenario over the period to 2010.[268]

Initiation of therapy

The prognosis for HIV infected patients who are starting ART is strongly related to the CD4 cell count at baseline.[34] While it has been shown that antiretroviral therapy initiated in patients with CD4 cell counts below 200/μl is associated with higher mortality as compared to those who start therapy at higher CD4 cell counts, the precise count at which to initiate therapy remains unclear.[605,606] Some recommendations are that therapy should start when the CD4 cell count falls below 350 cells/μl and it is argued that above this level the risk of 3-year clinical progression is low so that concerns about impact of antiretroviral regimens on quality of life, risk of serious adverse drug effects, and limitations on future treatment options generally outweigh the benefits of durable viral suppression.[607] The recommendation from the International AIDS Society-USA panel is that physicians and patients should weigh risks and benefits of starting antiretroviral therapy for CD4 counts in the range between 200 and 350/μl and above, and should make individualized informed decisions. Although the increased awareness of the activity and toxicity of antiretroviral therapy has shifted the initiation of therapy to a later time in the course of HIV disease, the International AIDS Society-USA panel recognizes that the availability of new drugs has broadened options for therapy initiation.[607] In 2003 the World Health Organization issued guidelines for the treatment of HIV-infected people in resource-limited settings

recommending combination antiretroviral therapy for people with AIDS (WHO clinical stage IV) regardless of CD4; WHO clinical stage III and CD4 less than 350/μl; or CD4 below 200/μl regardless of clinical stage.[538]

Infectivity

While there are many studies on the impact of ART on survival, the effect of ART on infectivity is less certain. ART is clearly associated with a decrease in the HIV-RNA viral load. With effective therapy it is estimated that viral load will be reduced by more than 90% within 8 weeks of treatment.[607] Successful suppression of viral replication is associated with viral loads below the reliable level of detection, i.e. less than about 50–200 copies/ml within the first 24 weeks.

The aim of combination ART is complete suppression of HIV replication. However, it is generally accepted that ART does not durably suppress HIV replication in 20-50% of treatment naïve patients and in up to 50–70% of treatment experienced patients.[608] There is evidence to suggest that continuing viral replication in the presence of therapy leads to drug resistance and viral rebound,[609] and new infections through transmission of drug resistant strains to individuals who have never been exposed to therapy are increasingly being reported, raising serious public health concerns.[608] Factors known to be associated with virological failure and the selection of drug-resistant variants include: sequential introduction of drugs (i.e., adding drugs to a patients treatment therapy as new drugs become available), inadequate drug potency, pre-existing resistance, non-adherence, poor drug absorption, drug interactions, altered intracellular metabolism of drugs, advanced disease stage, low baseline CD4 cell count, and high baseline plasma HIV-1 RNA concentrations.[609] The proportion of patients infected with drug-resistant HIV-1 in the USA has increased from less than 5% before 1991 to 10-22% in 1998–2000, althougb the trend may not be similar in other countries.[609,610] Despite publications on the rate of primary resistance, it is difficult to draw general conclusions,[608] in particular for Africa, where ART access to date has been limited.

A study of viral load as a function of adherence to therapy suggested that viral load declines by a factor of 10 for every 30% increase in adherence,[611] but with great variation. Hence, as adherence increases from zero to 100% the HIV-RNA viral load can fall by a

factor of 1000. In another study, Paterson and colleagues[612] suggested that the percentage of people with incomplete viral suppression increases from 22% at 95% adherence to 82% at less than 70% adherence. Gray *et al.* [613] in 2001 estimated that the unadjusted probability of transmission of HIV per sex act is 0.0011 (95% CI: 0.0008–0.0015). At viral loads greater than 38500/ml the probability of transmission per sex act is 0.0023, while at viral loads less than 1700/ml the probability per sex act is 0.0001 ($p = 0.002$). [613] We can therefore assume that with effective suppression of viral load through ART, an individual will make little contribution to transmission of HIV. However, in order to obtain effective suppression of viral load, high levels of adherence of people taking antiretroviral drugs have to be achieved.

Modelling the impact of ARVs

The AIM model described here is used to explore the impact of ART on survival. It is first noted that if there were no deaths then the incidence of infection (as described in Chapter 9) would be given directly by the slope of prevalence curve so that

$$I_0(\tilde{t}) = \left.\frac{dP(t)}{dt}\right|_{\tilde{t}} \qquad 12.1$$

If the probability that a person survives for t years is $W(t)$ then the probability per unit time that a person dies t years after being infected is

$$M(t) = \frac{dW(t)}{dt} \qquad 12.2$$

Since deaths will reduce prevalence the decline in deaths due to all previous incident infections need to be added to the estimate of incidence

$$I_1(t) = I_0(t) + \int_{-\infty}^{t} P(\tilde{t})M(t-\tilde{t})d\tilde{t} \equiv I_0(t) + P(\tilde{t}) \otimes M(\tilde{t})\big|_t \qquad 12.3$$

In Chapter 9 and 11, incidence rates were estimated using data on the prevalence of infection among women attending antenatal clinics. These estimates included a correction for the fact that the sample of women represents a narrow range of ages. In this chapter, it is assumed that the prevalence of HIV in pregnant women is a reasonable representation of the overall prevalence in men and women (i.e., from the same social class as women attending ANC), and this further correction is not applied to the incidence.

Finally, to obtain the incidence per susceptible person we divide by the proportion of the population that are susceptible to get

$$I_2(\tilde{t}) = I_1(\tilde{t}) / \left[1 - P(\tilde{t})\right] \qquad 12.4$$

Having estimated the incidence we then replace the Weibull survivorship with a Markov process with five stages. The model is illustrated and described in Figure 12.1. The rates at which susceptible people become infected is given by the incidence calculated from Equation 12.4, and the rates at which people move from one stage to the next, after being infected, are 0.44/year, for the first four stages. They die in the last stage at a rate of 2.0/year. If we assume that people spend equal times in the four classes, then the mean survival in the first four stages is 2.3 years and in the last stage 0.5 years.[c]

The numbers are chosen so that the survival in the last stage corresponds to the survival of people with late-stage AIDS and the survival in the first four stages is chosen to give the best fit to the assumed Weibull survival. The overall survival is then not significantly different using the Weibull or the Markov Model. The reason for this approach is that it is possible to intervene at any one of the four intermediate stages and to examine the impact on the epidemic.

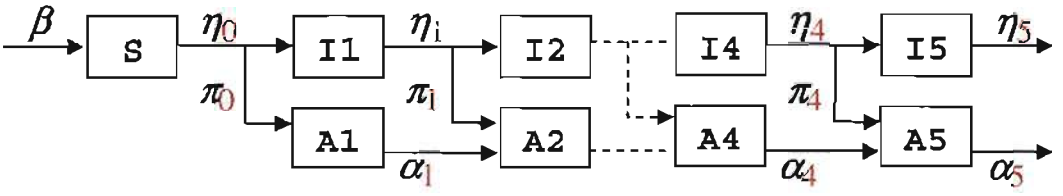


Figure 12.1 Model of HIV progression. People are born and enter into the susceptible class at a rate β; they become infected at a rate η_0 and of those who become infected a proportion π_0 are put on anti-retroviral treatment (A1) while the rest remain infected but not on treatment (I1). The people in these two classes then progress to the next class at rates η_1 and α_1 and of those that progress from the infected but untreated stage (I1) a proportion π_1 are put on anti-retroviral treatment. The median residence time in stage i is $1/\eta_i$ or $1/\alpha_i$ for untreated and treated people, respectively.

[c] If CD4 counts start at about 800/μl and fall linearly to about 200 after 9 years then we should have people spending about 150/(800-200)×9 years = 2.3years in stages 1, 2, 3 and 4

Having fixed the rates at which people progress from one stage to the next without ART ($\pi_i = 0$ for all i) the parameters α_i are then chosen to match what is known about survival on ART. Finally the model is run with different values of the parameters π_i corresponding to starting treatment at different CD4 cell counts. Setting $\pi_0 > 0$ would correspond to giving that proportion of the population preventive therapy or alternatively reducing incidence by that proportion; setting $\pi_1 > 0$ would correspond to putting that proportion of the people onto ART when their CD4 counts were about 500/μl; 350/μl or 200/μl, respectively.

Results

Changes in prevalence, incidence and mortality without ARVs

Four sets of models (ASSA[24], HSRC[374], UNAIDS[4], and the AIM model described here) have been used to project changes in the prevalence, incidence and mortality in the absence of widespread coverage with ART. Results from the AIM model are newly generated using the model described here, while results from the other models were taken from published reports. The model referred to as HSRC[374] used the EPP and Spectrum models applied to antenatal clinic data but adjusted the prevalence according to the national population based survey conducted by the HSRC[469](an adjustment factor set to the ANC prevalence/HSRC prevalence= 0.63 was used).[374] The UNAIDS estimates[4] were based on the application of EPP and Spectrum models to antenatal clinic data and prevalence was adjusted down by about 20% to account for the relative attendance rates at antenatal clinics. Estimates from the ASSA and AIM models were based on antenatal clinic prevalence data, also adjusted for potential difference in prevalence between the ANC population and the general population. For the AIM model, a female to male ratio of HIV prevalence of 1.7 was assumed, as calculated in Chapter 6. Results for 2003 are summarized in Table 12.1. Assuming a total adult (age 15-49 year) population of 24 million (UN Population Division estimates),[465] the models suggest that between 4 and 5 million adults were living with HIV at the end of 2003 and that adult (15-49 year) prevalence was about 20%. The HSRC estimates[374] for prevalence and number of people infected with HIV were lower than the other models because the estimates were adjusted according to the national household survey conducted in 2002 that produced a lower adult prevalence (15.6% in 2002) than the ANC estimate of 24.8% 2001. The HSRC and UNAIDS estimates of the number of AIDS

deaths in 2003 were similar at about 370,000, but slightly higher than the ASSA estimate of 311,000. The incidence for adults varied between 1.7% (HSRC), 1.9% (ASSA) and 2.3% (AIM). Both the AIM and HSRC models suggest that incidence peaked among adults (men and women) between 1996 and 1997 at a rate of just over 4% per year, and in the absence of treatment mortality is estimated to peak in 2008-2009 when about 500,000 people per year will die from AIDS.

Using the AIM model we estimated and projected the prevalence, incidence and mortality in each of the nine provinces in South Africa and in Figure 12.2 we show the results for KwaZulu-Natal (the province with the highest prevalence), the Western Cape (the province with the lowest prevalence) and for the country as a whole. Estimates for the other seven provinces (not shown here) all fall between the two provinces with the highest and the lowest burden. In the absence of successful interventions or significant behaviour change, the prevalence is expected to remain at the same level as the asymptotic prevalence for the foreseeable future. However, it is likely that as people experience the consequences of HIV directly in their own lives there might be some change in behaviour and it is also possible that effective prevention interventions may be implemented.

As seen in Figure 12.2, the incidence for adults (men and women) in most of the provinces peaked between 1995 and 1997. The decrease in incidence after 1995-1997 probably reflects the natural course of the epidemic as it reaches a steady state. In the absence of interventions, and if there is no change in behaviour in the coming years, the incidence is likely to remain steady, at around 2.8% for the national adult population, 3.8% in KwaZulu-Natal, and 1% in the Western Cape. In the event of no effective intervention, mortality is expected to peak among the national adult population in 2008 at about 2.8%, among the population in KwaZulu-Natal in 2008 at about 3.9%, and in the Western Cape in 2009 at around 1.0%, and will remain steady thereafter.

Table 12.1 Comparison of HIV estimates between different models in the absence of ART. The estimates are for the year 2003-2004 except for the peak incidence and mortality where the expected year is given. Total refers to the total population of the country. For 'Adults' and 'Women' the age group is indicated in column 1.

		Model			
		ASSA[24] (mid 2004)	HSRC[374] (2003)	UNAIDS[4] (2003)	AIM (2003)
Adults (age 15-49 years) living with HIV (millions)	Total	4.5	4.0	5.1	4.9
	Women	2.6	2.3	2.9	
HIV prevalence (%) (adults 15-49 years)	Total	11%	11%		
	Adults	18.5%	17%	21.5%	20.6%
	Women	20.2%			26%‡
HIV incidence (%) (adults 15-49 years)	Adults	1.9%*	1.7%		2.3%
	Women	1.7%*			
Mortality due to AIDS (k) (adults and children)	Total	311	376	370	399
	Women				
Peak incidence (year and %)	Year		1997		1996
	Adult		4.2%		4.3%
	Women				
Peak mortality (k/year)	Year	2010	2008		2009
	Total	500	487		523
Life expectancy	Total	51 years	46 years		

* Age 18-64 years; ‡ Public antenatal clinics;

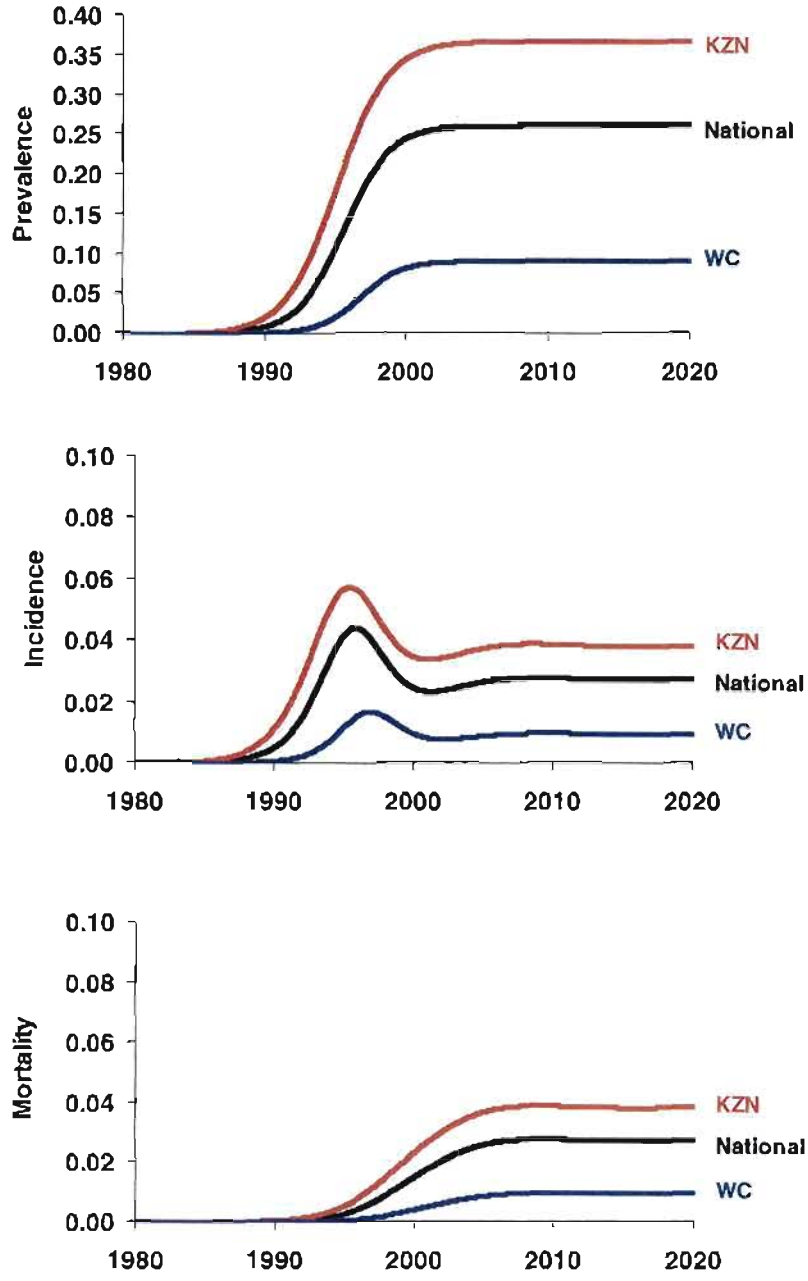


Figure 12.2 HIV prevalence, incidence and mortality in the worst and least affected provinces, and in the country as a whole.

Changes in prevalence, incidence and mortality with ARVs

Here the impact of providing ART on the prevalence and incidence of HIV and the mortality due to HIV/AIDS under different scenarios is considered. Firstly, the impact of putting 50% or 100% of the population on ART when their CD4 cell count falls to 200/μl or below, as proposed in the South African governments plan, is considered.[268] Secondly, the impact of putting 100% of the population on ART but starting at CD4 cell counts of 350/μl is considered. Throughout, the assumptions are made that of those people who are offered ART 80% are able to take them and comply fully, and that the interventions are introduced in 2005 and reach close to full coverage by 2010.

The results of these simulations are shown in Figure 12.3 and Table 12.2. In the absence of effective prevention measures or treatment programmes South Africa can expect about 5.1 million deaths and 4.9 million new infections in the ten year period between 2005 and 2014, and double that number in the next twenty years (Figure 12.3a). If 50% of the population are started on ART at 200 $CD4^+$ cells/μl in the next ten years (Figure 12.3b) there will be a short term improvement but this will soon be lost. About 500 thousand cumulative deaths and about 80 thousand new infections will be averted in the next 10 years and in 2015 about 560 thousand people will be receiving ART. The situation is much better if the proportion of the population being offered ART is increased to 100% (Figure 12.3c). In this case about one million cumulative deaths and about 150 thousand cumulative new infections will be averted; and in 2015 about 1.1 million people will be receiving ART. Starting therapy even earlier, at 350/μl (Figure 12.3d), will substantially reduce mortality, and about 1.5 million cumulative deaths can be averted, but there will be relatively little impact on the number of new cases averted which will increase to just over 150 thousand and the number of people who would be receiving treatment in 2015 will increase to 2.3 million. It is clear from Figure 12.3 and Table 12.2 that providing ART can reduce mortality quite substantially but the impact on incidence is much less, and mainly seen over the longer term.

The results from the above analysis show that ART will work in preventing deaths in the short term, particularly when given at a CD4 cell count of about 350/μl rather than at 200/μl. The main effect will be on mortality. However, even in the more optimistic

scenario, about 3.6 million AIDS related deaths will occur in the next ten years and about 7.7 million in the next twenty.

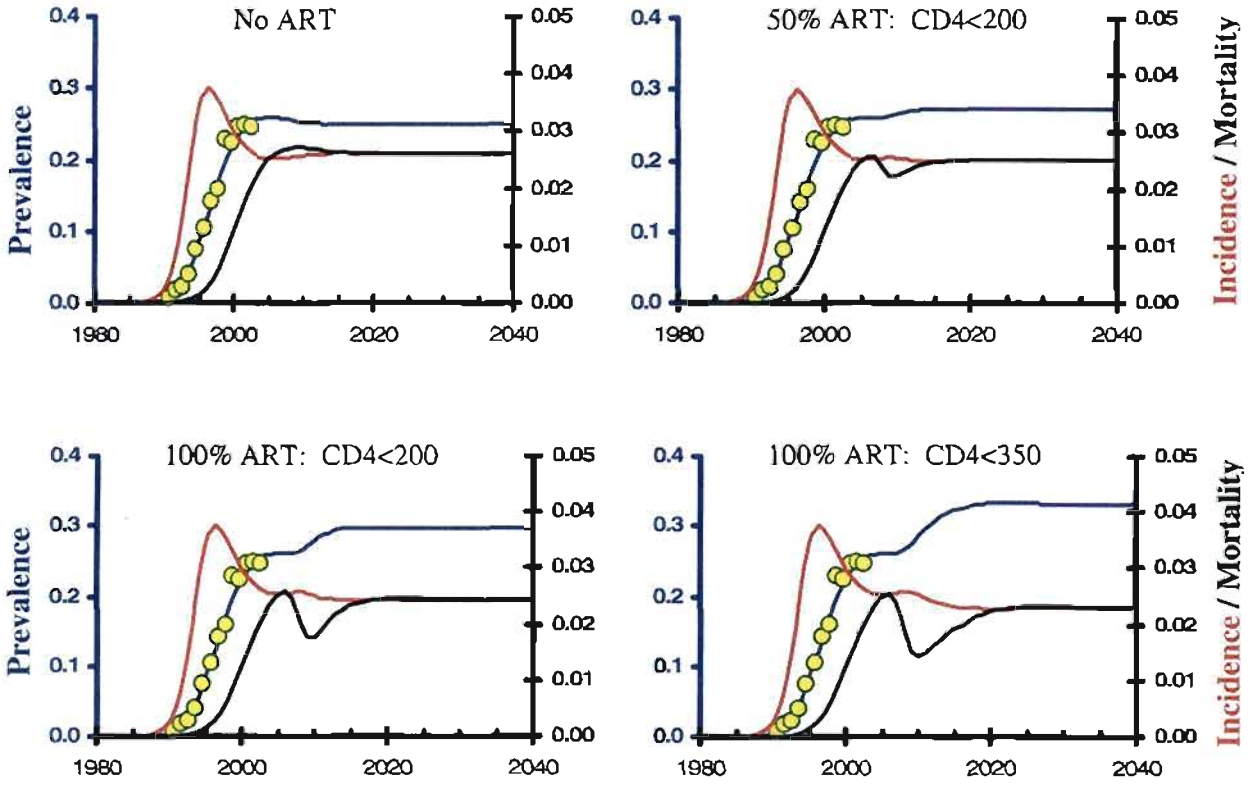


Figure 12.3 Fitted and projected prevalence, incidence and mortality (assuming 80% coverage of ART), for the following scenarios : a) No intervention; b) 50% with CD4 count<200 receive ART by 2010; c) 100% with CD4<200 receive ART by 2010; d) 100% with CD4 count < 350 receive ART by 2010. Prevalence among women attending antenatal clinics is indicated by the dots.

Table 12.2 The first part of the table gives the cumulative number of deaths and number of new cases (millions) that will arise over a ten year (2005 to 2014) and twenty year (2005 to 2024) period, as well as the number of people that will be on treatment at the end of these time periods. All figures are in millions. Four scenarios are considered; No ART; 50% of people are offered ART at a CD4 cell count of 200/μl or lower; 100% offered ART at CD4<200; and 100% offered ART at CD4<350/μl. The second part of the table gives the number of deaths and new infections averted (in millions) during the 10 and 20 year time period for the three treatment scenarios.

	2005-2014			2005-2024		
	Deaths	New cases	On treatment	Deaths	New cases	On treatment
Cumulative number (million)						
No ARV	5.07	4.90	0.00	10.04	9.89	0.00
200:50%	4.57	4.82	0.56	9.34	9.61	0.68
200:100%	4.08	4.75	1.11	8.67	9.34	1.33
350:100%	3.61	4.75	2.28	7.73	9.10	2.94
Numbers averted (million)						
200:50%	0.49	0.08		0.70	0.28	
200:100%	0.99	0.15		1.38	0.54	
350:100%	1.46	0.15		2.32	0.79	

Discussion

Cross-sectional data on HIV prevalence in South Africa is widely available, the most extensive are those from the annual surveillance which was set up by the National Department of Health in 1990 to monitor the prevalence of HIV infection in pregnant women attending public antenatal clinics.[23] Data on HIV prevalence collected from the national antenatal surveys have been widely used, not only to obtain estimates of the current burden of HIV infection in South Africa (prevalence, incidence and mortality), but also to model the future course of the epidemic. In this chapter estimates of prevalence, incidence, and mortality in the absence of antiretroviral treatment from four different models, including the ASSA[24], HSRC[374], UNAIDS[4] models, and the model developed and described here (AIM model), are firstly reported on. Differences in prevalence, incidence and mortality estimates from the models summarized in this chapter can be ascribed to differences in model input parameters and the structures of the models.

While prevalence and incidence appear to be leveling off, the next stage of the epidemic has been reached, with a steady increase in mortality rates. The AIM model estimates for 2003 show overall mortality rates of 2.3% among adults in South Africa, ranging from 3.1% in KwaZulu-Natal and 0.7% in the Western Cape. In the absence of effective interventions, these rates will continue to rise to a level of around 2.8% among the national population in 2008. Model estimates show that the epidemic is reaching equilibrium, with mortality estimates approaching the same level as incidence. In the absence of any effective future interventions or substantial changes in behaviour, it can be anticipated that these epidemic trends will remain at around the same levels in the foreseeable future, i.e. incidence and mortality will remain at about 2.8% per year.

In November 2003, the South African Government approved an operational plan for comprehensive HIV/AIDS care, management and treatment in the public health sector in South Africa,[268] with implications for future epidemic trends. In this plan, it was envisaged that there will be at least one service point in every health district across the country within one year and one service point in every local municipality within five years. These service points will give citizens access to comprehensive HIV/AIDS care and treatment, and will be integrated with intensified prevention and awareness campaigns. While prevention remains the cornerstone of the governments strategy, it is anticipated that approximately 50,000 new cases will start ART in 2003/2004, and that more than 1.4 million cases will be on ART by the end of 2009.[268] The provision of ART is expected to have a significant impact on mortality as well as on the transmission of HIV (i.e. incidence).

According to the Minister of Health, ART had been provided to 19,500 patients in over 103 sites nationally as at the end of October 2004.[614] Although the progress in implementation of the operational plan was initially slower than anticipated, there is a clear trend toward rapid scaling up of treatment availability and the number of people receiving ART at the end of 2005 (in both the private and public sector) had increased to around 200,000 (Department of Health, personal communication).

The simple differential equations model described in this chapter was developed to assess the impact of successful provision of ART on future HIV epidemic trends (prevalence, incidence and mortality). The model is based on past and existing trends of HIV

prevalence as observed through the surveillance of pregnant women attending antenatal clinics in the public health sector in South Africa.

Several assumptions were made in structuring the model. It was firstly assumed that in the absence of successful intervention, the median survival time for infected individuals, following a Weibull distribution, is approximately 9 years, depending on age. However, with the introduction of antiretroviral therapy we can expect an increase in survival, depending on the baseline CD4 cell count. For ART initiated at a CD4 cell count of 200/μl, life expectancy is expected to increase by an additional 3-4 years.[268] The additional increase in life expectancy when ART is provided at a baseline CD4 count of 350/μl, is expected to be about 9 years (i.e., total average survival after infection of about 18 years), depending on age.[581] Provision of ART to an infected individual earlier in the disease progression, i.e., at a CD4 cell count higher than 350/μl, may prolong life even further, but is generally not recommended in the developing world and must be weighed against the risk of toxicity, adverse events, problems with adherence and subsequent development of drug resistance.

Secondly, it was assumed that successful provision of ART is associated with suppression of viral load and therefore does not contribute to transmission of HIV, i.e. associated with a reduction in incidence. Virologically effective therapy should reduce viral load substantially within the first 2 – 8 weeks and for the majority of patients should decrease below detectable levels (<50 – 200 RNA copies/ml of plasma) by 16–24 weeks.[615] A study in Cape Town, conducted among an HIV positive cohort attending a public sector hospital and receiving ART through phase III studies, showed successful viral suppression in 66.1% of those patients who reached 48 weeks of therapy.[616] Predictors of virologic failure (i.e. >400 HIV RNA copies/ml) in this study included baseline viral load, three times daily dosing, incomplete adherence, age and dual nucleoside therapy. Among those who were ≥95% adherent at 48 weeks, 73.4% had a viral load of <400 copies /ml, compared with 61.0% of those whose adherence was <95% (p = 0.018).[616] In another study to assess the feasibility of implementing ART programs in Africa, 28 articles involving 14 African countries were reviewed and showed that a median of 73% of patients achieved undetectable viral loads by the end of the study period.[617] Further, even if viral load in all patients may not be reduced to undetectable levels, estimates by Gray *et al.*,[618] suggest that the transmission probability is reduced with a reduction in viral load and

that for viral loads below 1700/ml the transmission probability is almost negligible (probability per sex act is 0.0001).

In order to achieve successful reduction in viral load, good adherence is required.[607] In the model described in this chapter it is assumed that coverage, which here is a function of ART coverage, adherence and effective management, is 80% among infected individuals meeting the criterion for receiving ART. A study conducted among 289 patients attending a public sector hospital and receiving ART through phase III trials in South Africa,[619] showed adherence levels of the cohort of 93.5% and was hence not regarded as a significant barrier to successful antiretroviral therapy. In the study, ART was provided free and socio-economic status had no impact on adherence. The high level of adherence in the South African study was similar to the high levels of adherence found among 58 treatment-naïve patients receiving ART in Senegal (88% adherence),[620] and adherence levels of 95% or more for the majority of studies reporting on adherence levels in a review of 10 studies that documented ART use in Africa.[617] Given the South African governments commitment to provide free ART to all those in need of therapy by the year 2009, and the high level of adherence found in studies across Southern Africa, the assumption of 80% coverage in this model is reasonable, but can easily be changed once more data have become available.

While the government's treatment plan is aimed at providing antiretroviral therapy to those individuals with AIDS defining illness or with a CD4 cell count < 200/μl, the model described here predicts that provision of ART at this level will have a slight impact on mortality, but little effect is expected on incidence because treatment at this late stage will have a limited impact of transmission of the virus. If everyone with CD4< 200 is put on ART by 2010, we can expect a 10% decrease in mortality from 2.5% to about 2.25% in 2010 and a decrease in incidence of about 5% (from 2.5% to 2.38%). We can then expect an increase in prevalence over the next few years, to a level of about 30% in 2010. Under this scenario we can expect that about 1.1 million people will be receiving ART by 2015 and that about one million cumulative deaths and about 150 thousand cumulative new infections will be averted during the ten year period between 2005 and 2014. A more dramatic effect on mortality, incidence and prevalence is expected with provision of antriretrovirals earlier on in the progression of disease, i.e. at a higher CD4 cell count. If provided at a CD4 cell count of 350/μl, mortality is expected to decrease to a level of 1.8%

in 2010 (as compared to 2.25% when provided at a CD4 count of 200/μl), averting 1.5 million deaths, while incidence is expected to decrease to a level of 2.35% (from 2.5%). An even greater impact may be expected if ART is provided at CD4 cell counts higher than 350/μl, but provision of ART in this early stage of the disease is generally not recommended because antiretroviral regimens are very complex, have serious side effects linked to the activity and toxicity of current drugs, and pose difficulty with adherence, all of which have serious potential consequences such as the development of viral resistance.[615] At the same time, it has been shown that patients with early-stage HIV disease, lower viral loads and/or higher baseline CD4 cell counts have better virological response to therapy than later-stage disease.[609] Patient education and involvement in therapeutic decisions are critical and while treatment should be offered to all patients with symptoms of AIDS defining illness, recommendations for offering antiretroviral therapy to asymptomatic patients will require analysis of real and potential risks and benefits. [615] However, although the optimal time to initiate therapy remains imprecisely defined, it is recognized that the availability of new drugs constantly broaden options for therapy initiation and management of treatment failure.

Although the assumptions of the mathematical model in this chapter are based on the best available data, it is recognized that the model could be further improved as more accurate and reliable data become available. Good monitoring and evaluation of the massive task of providing ART to those meeting the eligibility criteria in South Africa will therefore be essential. Evaluation of the impact of ART will be essential, as will be the monitoring of circulating HIV-strains, survival rates, changes in CD4 cell count and HIV RNA viral load, adherence rates, side effects on ART, and assessing drug resistance and the effect thereof on future therapy options, all of which will also be required for future planning. Furthermore, while the continued annual surveillance of the antenatal clinic population for estimation of prevalence will be essential for monitoring the epidemic in the general population, the estimation of the annual incidence is going to be equally important for assessing the effect of ART on HIV transmission. Incidence is the best measure of impact because it shows the immediate impact of ART on the population and responds to change much quicker than prevalence (prevalence reflects the average incidence over the past 5 to 10 years, and a change in the epidemic will take a longer time period to manifest in estimates of prevalence).

In a review of the epidemiological impact of antriretroviral therapy predicted by mathematical models, Baggaley and colleagues[621] suggest that HIV transmission models should incorporate a realistic progression through stages of infection in order to realistically capture the timing of treatment initiation. Although it was suggested that further elaboration of models should include variables such as sexual behaviour and evolution of drug resistance, modeling exercises are dependent on the availability of setting specific surveillance and behavioural data, hence the importance of collection of such data in areas where large scale ART use is introduced.

Of the few studies in Africa to model the impact of antiretroviral therapy on HIV, Gray and colleagues[622] showed, using a stochastic simulation model, that ART could reduce but not interrupt transmission in Uganda and that the effective R_0 will remain above 1. It will therefore have minimal impact on the number of HIV-infected people and the number requiring treatment will increase substantially over time.

Of concern in African countries is that a small percentage of HIV infected individuals are believed to know their HIV status, and for the immediate future, most individuals may start receiving care only when they develop life-threatening, AIDS defining illnesses.[605]At an infectious disease institute in Uganda, the mean CD4 cell count at the start of ART was 63 cells/μl.[605] Starting treatment at this stage is unlikely to have a significant effect and many studies have shown that full immune reconstitution and survival rates are reduced if ART is started among patients with severe CD4 cell depletion.[623]

While Southern Africa has been the most severely affected region in the word, and several countries have reported prevalences exceeding 25%, the epidemic in eastern Africa appears to be declining,[624] showing that success is possible, even in the absence of ART. In Uganda there is evidence of a rapid reduction in the prevalence of HIV among women attending antenatal clinics. A cohort including the total adult population of a cluster of 15 neighbouring villages in a rural part of Masaka district in south-west Uganda has been followed since 1989.[625] The cohort was exposed to national health education messages. Seroprevalence among adults of all ages fell from 7.8% in 1989/1990 to 6.4% in 1998/1999, while incidence fell from 8.0 to 5.2 per 1000 person years during the same period.[626] The results demonstrated that an early, consistent and multisectoral control

strategy can reduce both the prevalence and incidence of HIV infection,[627] giving hope to AIDS control programmes elsewhere in Africa.

In 1996, Brazil became the first developing country to provide unrestricted, cost-free access to antiretroviral therapy to AIDS patients through its public health care system[628] with adherence rates between 41% and 69%.[629,630] Despite systemic deficiencies and individual obstacles, the introduction of ART was associated with a reduction in total mortality in Brazil between 1996 and 1999 of about 50%[631,632] (although it is recognized that it may not be exclusively ART-related) and a reduction in hospitalization rates from an average of 1.65 admissions per patient per year in 1996 to 0.28 per patient per year in 2001, with 358,000 hospitalizations being prevented.[632]

Given the political and multisectoral commitment, both of the above countries have shown that HIV can be successfully managed: Uganda using prevention techniques, and Brazil through the provision of universal access to ART. A comprehensive approach including both treatment and prevention will have an even bigger impact on the epidemic. These results give hope to millions of South Africans infected with HIV, entering a critical new phase of strong commitment from politicians and health professionals, community mobilization, more funding and scaling up of treatment and prevention programmes.

Chapter 13 Conclusions

> "In the face of the grave threat posed by HIV/AIDS, we have to rise above our differences and combine our efforts to save our people. History will judge us harshly if we fail to do so."
>
> Nelson Mandela, 2005

HIV continues to spread throughout the world, and almost every country is affected, although in different ways and in different degrees of severity. In 2005, it was estimated that around 40 million people were infected with HIV globally and that more than 25 million have died of AIDS since the beginning of the epidemic.[3] Almost 95% of those infected with HIV live in developing countries, the majority in sub-Saharan Africa. South Africa, with a total population of only 45 million people, currently accounts for almost 14% of the global number of infections and at 5.5 million has the highest number of people living with HIV in the world.[4]

In South Africa, HIV prevalence among national antenatal clinic attendees increased dramatically over a ten year period from 0.73% in 1990 to 24.5% in 2000. While data in 2001 suggested that the prevalence might be stabilizing, further increases have been observed since then and in 2004 the HIV prevalence among antenatal attendees was 29.5%.[31] While the provision of antiretroviral therapy (ART) to HIV positive people in need of treatment is expected to lead to an increase in prevalence, only 19,500 people (about 0.4% of the more than 5 million people infected with HIV) were estimated to be receiving ART at the end of 2004,[614] a figure too small to explain the observed increase in prevalence between 2001 and 2004. The increase in HIV prevalence over the last 15 years occurred despite a very substantial response by the scientific community, nationally and internationally, as shown in Chapter 2 of this thesis. Our knowledge covers all aspects of the HIV epidemic, including routes of transmission, trends in prevalence, the efficacy of interventions, social and behavioural aspects of the epidemic, HIV related illnesses, the association with sexually transmitted diseases and other risk factors, the molecular and genetic components of the virus, and the economic impact of HIV. However, relatively little research have been done in South Africa to understand the population level dynamics of the HIV epidemic. While prevalence data in South Africa have been well studied and have provided important information on the trends in the level of infection over time, from

which estimates of the total number of people living with HIV and hence resource needs can be estimated, prevalence on its own is not enough to understand the dynamics of the epidemics. In addition to overall estimates of prevalence, we need to understand how patterns of infection vary in space and between groups, and how they are changing with time. We also need to know more about the incidence of infection, that is to say the number of new infections that occur every year. Incidence provides an immediate measure of current infection rates and is therefore more sensitive to the dynamics of disease transmission, is more useful for projecting future epidemic trends, and gives more immediate measures to assess the impact of interventions. At equilibrium, an epidemic will have stable levels of prevalence while the number of new infections will be balanced by an equivalent number of deaths. In this thesis, the epidemiology and the dynamics of the HIV epidemic are studied in relation to prevalence and incidence, and new ways of estimating the incidence of infection indirectly are described. In addition, the impact of the provision of antiretroviral drugs on HIV prevalence, incidence and mortality is investigated.

HIV prevalence estimates obtained from cross-sectional studies in South Africa are widely available, as shown in Table 2.1. Some of these sources are described in more detail in Chapter 4 and were used in subsequent chapters to analyse prevalence levels in time and space and to derive estimates of incidence. In addition to extensive surveys among antenatal clinics in South Africa, data from three community surveys made it possible to compare the prevalence of infection among men and women and in urban and rural areas. Data are also available for certain high risk groups, including sex workers and migrant workers in KwaZulu-Natal and Gauteng province. In Chapter 5, data collected over a period of fifteen years were analysed to compare different stages of the epidemic, by province, gender, geographic area, and risk group (migrant workers and sex workers). Before 1987 the epidemic was concentrated mainly among men who have sex with men and recipients of blood products but in this thesis we focus on the distinct heterosexual epidemic which became established in the late 1980s. Although the prevalence of infection is still increasing, the rate of increase has slowed substantially, and the prevalence data suggest that the epidemic is starting to level off. Throughout this thesis logistic functions were used to describe the epidemic trends over time as described in Chapter 3; the three parameters of the logistic curve determine the intrinsic growth rate, the level at which the epidemic is likely to level off (the asymptote), and the time at which the epidemic reaches half its asymptotic value. In 2005, the logistic curve was also

introduced into the UNAIDS method for describing epidemic trends in countries where the epidemic is concentrated among high risk groups such as injecting drug users, sex workers, or men who have sex with men.[633]

In order to understand the natural history of the epidemic, and to design, target and evaluate interventions, data on the age-specific prevalence of infection among different groups of men and women were analysed in Chapter 6 to investigate patterns of infection. Differences in the age-specific risk of infection between antenatal clinic attendees, men and women in the community and in the workplace, urban and rural areas, migrant workers (including truck drivers and mine workers) and sex workers were investigated. It is shown that men in South Africa generally have lower levels of infection than women and prevalence peaks at an older age among men than among women. Three community surveys showed that the female to male ratio of HIV infection in South Africa is about 1.7. As the epidemic is maturing, the age at which the prevalence peaks among antenatal clinic attendees shifted by 3.5 years from 23 in 1995 to 26.5 years in 2004 while the level of peak prevalence during this period increased from 14.2% in 1995 to 37.1% in 2004. Four different patterns of infection were identified: among women attending antenatal clinics, among women in the general population, among men in the general population, and among migrant workers. Unlike data from several countries in sub-Saharan showing that HIV prevalence in urban areas is generally higher than in rural areas,[634] data from South Africa indicate that differences between urban and rural populations are not significantly different, so that the age-risk of infection does not appear to depend on whether people live in urban or rural areas. This result is likely to be a reflection of the high rates of circular migration between urban and rural areas in South Africa.

Understanding the trends in the HIV epidemic in South Africa depends largely on data collected annually from national antenatal clinic attendees in each of the nine provinces by the Department of Health. In countries with generalized epidemics, the prevalence among ANC attendees has been used as a proxy for the prevalence in the general heterosexual population, and several community based studies in Africa have shown that prevalence among pregnant women is indeed a good approximation for prevalence among the sexually active adult population.[531] In the first study to compare antenatal clinic estimates to community estimates in South Africa, described in Chapter 7, HIV prevalence among women from the general population in Hlabisa (measured through the Vaccine

Preparedness Study) was significantly lower (22.2%; 95% CI: 18.8 - 25.6%) than prevalence among women attending antenatal clinics in the same area in Hlabisa (38.2%; 95% CI: 33.4 - 43.6%), and the difference remained significant after standardizing the data to the age distribution of women in the general population in Hlabisa. A limitation of this study was that more than 60% of the women in the community survey refused to give a blood sample to be tested for HIV, and although differences in potential confounding variables between those who consented and those who did not cannot explain the lower prevalence in the community survey, further studies are needed to investigate the relationship between prevalence among women attending antenatal clinics and women and men in the general population and to understand the biases that operate in both groups.

Unlike prevalence data, estimates of incidence are not widely available because incidence is much more difficult to measure than prevalence. Measuring incidence directly is logistically difficult and raises ethical problems because cohorts of people need to be followed up over time to determine if and when they sero-convert to HIV. Incidence has been estimated directly from only one cohort study in South Africa (as part of a microbicide trial of sex workers in KwaZulu-Natal).[282] In Chapter 8, existing indirect methods for estimating incidence are reviewed, including statistical models, dynamical and demographic models, and laboratory techniques.

Because of the limitations of applying existing methods (most of which assume stable epidemics) to estimate incidence in the South African situation, two new dynamical models were developed and are described in Chapter 9 for estimating incidence indirectly from HIV prevalence data. In the first, an extended dynamical model was developed to estimate HIV incidence rates from data on age-specific prevalence and changes in the overall prevalence over time. The model allows for changing force of infection, age-dependence of the risk of infection and differential mortality. It uses maximum likelihood methods to obtain age-specific incidence rates while standard errors are estimated using a Monte Carlo procedure. The age incidence function is expressed as a function of the risk of infection with age and the change in the average adult prevalence over time. A log-normal function is used to describe the age-specific risk of infection: the function is very small (or zero) before the age of onset of sexual activity, increases rapidly thereafter as sexual activity increases, and then decreases more slowly among older people. The change in overall adult prevalence over time, for which antenatal clinic data showed an

exponential increase in the early years of the epidemic, is best described by a logistic function with a variable asymptote. A Weibull survival function with a median survival time of 9 years after infection with HIV, as recommended by the UNAIDS Reference Group on Modelling, Estimates and Projections,[450,604] is used. It is often the case that age-specific prevalence data are not available, and in the absence of such data, a second model was developed to estimate incidence (also described in Chapter 9). This model only uses trends in the average adult prevalence of infection over time and the same Weibull survivorship function is used to calculate the probably of death within any given number of years after infection. Both models were applied to HIV prevalence data obtained from antenatal clinic data in Hlabisa and show similar, but extraordinarily high incidence rates of up to 10% per year in this population.

In Chapter 10 incidence was estimated using a laboratory technique designed to identify people who have recently sero-converted (Standard Testing Algorithm for Recent HIV Sero-conversion), and these estimates were then validated by comparing them with incidence estimates obtained independently, for the same population, from the dynamical model described in Chapter 9. The technique involves assessing the HIV status of a sample using a sensitive ELISA; if positive, it is then tested using a less-sensitive ELISA and if negative on this latter ELISA, it can be concluded that the person became infected within a certain window of time. The STARHS method confirmed the very high incidence rates among the Hlabisa antenatal clinic attendees and highlights the particularly high risk of infection in young women aged 20-24 years among whom incidence rates were close to 15% in 1999. Two limitations of the sensitive-less sensitive ELISA technique are that standard optical density cut-offs and window periods are poorly defined and that the test is dependent on the particular subtype of HIV. Indeed, in the application of the method in this thesis, the window period had to be adjusted to obtain agreement with the model estimates; instead of using the cut-off of 200 days as recommended by the Centre for Disease Control and Prevention, the window period was adjusted to 320 days, which is close to the longer window period of 270 to 350 days found for subtype E infected individuals from Thailand.[594] New laboratory techniques that can be used to estimate incidence rapidly, reliably and accurately are still being developed. One of these detects recent HIV infection by measuring the increase in HIV immunoglobulin G (IgG) as a proportion of the total IgG following seroconversion. This IgG-capture BED-enzyme immunoassay (BED-CEIA) is designed to provide reasonably high consistency and similar

window periods for different subtypes[569] and is currently being validated and calibrated using data from studies conducted in several countries.

The two dynamical models used to estimate incidence from prevalence data were applied to different prevalence data sets from South Africa, including the national antenatal clinic data, data from rural KwaZulu-Natal (Hlabisa) and from an urban community in Gauteng (Carletonville). Estimates for the above data sets show very high levels of HIV incidence in South Africa, in all nine provinces, although with wide variation, as well as in urban and rural settings. As with the age-specific prevalence, the age-specific incidence rises rapidly to a peak among young people and then declines more slowly with age in older people. Young women aged 20-29 years are at highest risk of becoming infected while incidence among men peak at older ages (30-39 years). Shapes of age-specific incidence curves are similar for urban and rural populations. The data presented in Chapter 11 further indicate that incidence among antenatal clinic attendees in South Africa peaked in 1997 at a level of around 6.6%. The drop in incidence immediately after 1997/1998 is probably a reflection of the natural course of the epidemic reaching a steady state and in the absence of any behaviour change or effective intervention is expected to remain steady. In 2005, incidence among antenatal clinic attendees was estimated to be 5.8%, ranging from 2.5% in the Western Cape to 9.3% in KwaZulu-Natal. The best estimate of HIV incidence for the general population in South Africa in 2005, using the ANC data adjusted for potential bias (as described in Appendix 5.1), is 2.4%. Incidence responds to change in the epidemic much more quickly than does prevalence, and any change in the transmission rate as a result of behaviour change or effective interventions will be reflected in falling incidence before it is reflected in falling prevalence.

In addition to prevalence and incidence, mortality estimates are needed to understand the dynamics of the HIV epidemic, for planning the allocation of resources and for identifying vulnerable populations. Estimates of the impact of HIV on mortality, however, are not widely available and where such estimates have been made they have been a contentious issue in South Africa, partly because of the lack of reliable death statistics. An analysis by the Medical Research Council of cause-specific death rates for 1996 and 2000-2001 using vital registration data shows a substantial rise in mortality in both men and women in the age groups most affected by the HIV epidemic,[279] with the increase in mortality concentrated among young children, women aged 25-39 years and men aged 30-49 years.

The age pattern is consistent with the age pattern observed for HIV seroprevalence in South Africa, with an age lag. Results have been confirmed by Statistics South Africa and a report in February 2005[515] (available at http://www.statssa.gov.za) showed an increase of 57% in South Africa's mortality rate from 1997 to 2002. The group most affected were those in the economically productive ages of 30-34 years, in which the number of deaths more than doubled. Estimates of the total burden of disease show that in 2000, HIV/AIDS was the leading cause of death in all provinces with the exception of the Western Cape, and accounted for 30% of all deaths in South Africa.[466] In 2004, it was estimated that HIV was responsible for 44% of all deaths in South Africa, and 70% of the deaths in the age group 15-49 years.[24]

In Chapter 12, comparison of four different models to estimate the demographic impact of HIV show that the number of AIDS deaths in 2003 ranged between 300,000 and 400,000. Using antenatal clinic data, the model that was developed and described in this chapter (referred to as the ART Impact model model, AIM) shows that while prevalence and incidence are levelling off, mortality is increasing. The model estimates that annual mortality among adults in South Africa in 2003 was 2.3% and without intervention will increase to around 2.8% in 2008. As the epidemic reaches equilibrium, mortality estimates are approaching the same level as incidence and in the absence of any effective future interventions or substantial changes in behaviour, it can be anticipated that these trends will remain at around the same level for the foreseeable future.

The announcement by the South African Government to provide a comprehensive treatment and care programme to those in need of treatment has brought hope to many South Africans infected with HIV and facing death.[268] While prevention remains the cornerstone of the government's strategy, they have an ambitious plan to provide ART to more than 1.4 million people infected with HIV by the end of 2009. In order to estimate the impact of ART on future trends of the epidemic a 4-stage dynamical model was developed, making the following assumptions: 1) that survival for infected individuals follows a Weibull distribution with median survival time of 9 years in the absence of treatment; 2) that ART is associated with suppression of viral load and that people receiving it do not contribute significantly to transmission of HIV; and 3) that coverage (allowing for adherence and effective management) is 80% among infected individuals who meet the criterion for receiving ART. The model was firstly applied to the scenario

currently proposed in the government's strategy, namely that ART will be provided at a CD4 cell count below 200/μl; and secondly to assess the impact should ART be provided at a higher CD4 cell count (i.e., CD4 <350/μl). The model predicts that if everyone with CD4 < 200/μl is put on ART by 2010, mortality should fall by about 10%, from 2.5% to about 2.25%, and incidence should fall by about 5%. At the same time, because people remain infected when they are on ART, prevalence is expected to increase to about 30% in 2010 and about 1.12 million people will be receiving ART by 2015. Under this scenario, about one million cumulative deaths and about 150 thousand cumulative new infections will be averted over a ten year period. If ART is provided earlier on in the progression of disease a greater effect on mortality, incidence and prevalence is expected. If people are started on ART at a CD4 cell count of 350/μl mortality is expected to decrease from 2.5% to 1.8%/year in 2010 (by 28%), incidence to decrease from 2.5% to 2.35% by 2010 (by 6%), and 1.5 million deaths are estimated to be averted over a ten year period. Under this scenario, about 2.3 million people will be receiving ART by 2015.

The current recommendation by the World Health Organization for countries with limited resources is that ART should be provided to those with WHO clinical stage IV disease regardless of CD4 cell counts, WHO clinical stage III disease and CD4 less than 350/μl, or CD4 below 200/μl regardless of clinical symptoms.[130] However, the majority of published data support initiating ART when the CD4 cell count is below 350/μl (i.e. in the 200-350/μl range),[635] and WHO is currently reviewing its guidelines to determine if the universal CD4 threshold for provision of ART should be changed from 200 to 350/μl.

There is substantial variation in CD4 cell counts of HIV negative as well as HIV positive individuals and in a recent study by Williams et al.,[636] it has been shown that at a CD4 cell count of 200/μl the median life expectancy (in the absence of ART) of HIV-positive people in Zambia is 4 years, almost twice that of people in South Africa where it is 2.3 years so that the thresholds at which ART should ideally commence may be different in different settings. However, further studies and much better data on the factors that determine CD4 count distribution (in HIV positive and negative individuals), the patterns of decline of CD4 over the course of infection, and on the utility of CD4 as a prognostic indicator, would help to assess the stage of HIV epidemics in countries, the future demand for ART, and would help determine the most effective criteria for initiating ART.

A further problem related to the provision of antiretroviral drugs to those in need, on the basis of the WHO treatment guidelines,[130] is that CD4 cell count tests are often not available to help decide which people infected with HIV need treatment at the primary care level and eligibility for ART will have to depend on clinical staging by medical personnel. In a study conducted at two primary health care settings in South Africa (one in Soweto and one in an urban setting in Limpopo province) researchers compared CD4 cell counts with clinical staging among 2000 HIV positive adults, the majority of whom were seen and attended to by nurses.[637] Overall, 24% of patients classified with stage I and 46% with stage II disease (who would be regarded as ineligible for ART according to the WHO definition) had CD4 cell counts below 200 cells/μl^3. Hence, if ART is restricted to WHO clinical stages 3 and 4 exclusively, about 70% of patients would not have been given ART. One other study in South Africa reported that clinical disease stage is a stronger predictor than CD4 cell counts of the risk of both developing AIDS and death.[638]

The provision of universal access to ART in the public health sector through international initiatives such as WHO's 3×5 strategy[538] and the South African Government's comprehensive plan,[29,268] has given hope to individuals in low income countries. However, the roll-out was initially slow, globally[10] as well as nationally.[614] The goal of the comprehensive treatment plan of the government was to provide ART to 50,000 South Africans between 2003 and 2004,[268] but by the end of 2004, less than 20,000 people had received it.[614] By the end of 2005 however, greater progress had been made and about 200,000 people were estimated to be receiving ART through the private and public sector in South Africa. Athough WHO had not met its target of providing antiretrovirals to 3 million people globally (the estimated number on people receiving ART at the end of 2005 was 1.3million), much had been done to mobilize support and ongoing efforts to provide treatment has brought about positive change and has paved the way for greater advances towards the ultimate goal of universal access.[13]

Given the initial slow roll-out and the critically high and still rising prevalence in South Africa, the need to increase and extend prevention efforts is essential. Furthermore, the model presented in Chapter 12 shows that while scaling up of ART will have a significant impact on mortality, it will have less impact on the number of new infections. This result was confirmed by Salomon et al.[639] who applied an epidemiological model to sub-Saharan Africa and showed that while a treatment-centered strategy will reduce mortality in sub-

Saharan Africa by 9-13% over the next 15 years, it will have little effect on the number of new infections. However, a combined response of scaling up treatment and providing effective prevention programmes could reduce new infections by up to 55% and mortality by 27% by 2020. Combining treatment with prevention efforts will also substantially reduce the resources needed for future treatment.[639]

In developing countries, the delivery of antiretroviral therapy to those in need of treatment presents several challenges. Although millions of dollars are provided through international donors and local governments, the number of patients targeted for treatment are ambitious and African countries will find it difficult to provide the human resources, including personnel who can deliver required interventions, infrastructure, and financial resources to treat everyone who is in need.[640] With the increased availability of antiretroviral drugs, there will be an increased demand for HIV testing, counselling, drugs and care. In addition to the increased burden in hospitals, clinics and laboratories performing HIV tests, the workload of an already limited number of doctors, nurses, dispensers, pharmacists and counsellors will be increased and ways will have to be found to organize effective clinical teams for providing HIV care services.[605] Major training initiatives and the reorganization of health services will be required. To ensure good adherence among patients, a strong patient-centred approach was used in a study involving ART in an urban township (Khayelitsha),[38] including a comprehensive counselling infrastructure providing for one-on-one individual counselling with trained counsellors, and regular support groups.[641] A treatment access non-governmental organization, the Treatment Action Campaign, was active in the clinics included in the study and their activities contributed to the treatment literacy of patients. Although the study showed that ART can be provided in resource limited settings with good patient retention and clinical outcomes,[641] it will require lots of resources and staff to extend such an infrastructure to all areas in South Africa, and in particular to rural areas. It is further anticipated that monitoring the efficacy of antiretroviral treatment will be problematical because of the lack of available and reliable laboratory facilities to perform viral load and resistance testing.[605]

In relation to the development of antiretroviral drugs, much research has been done to find ways to introduce new drugs and drug classes, to reduce the costs of treatment, and to reduce toxicity and adherence burdens. Although drug regimes are being simplified and the number of pills that HIV infected individuals have to take per day has been reduced,

current therapeutic approaches can still not cure HIV. Currently, 32 new drugs are being tested in clinical trials (phase II or III), including nucleoside reverse transcriptase inhibitors and new classes of entry inhibitors (e.g. CCR5).[9] New approaches, targeted at eliminating HIV from latent infections of resting CD4 cells, have provided new hope for a potential cure in the future. In a recent study in San Francisco,[642] the use of valproic acid on four volunteers showed a significant decline of resting cell infection in three of the four participants. Although the research is still in its very early stages, the results suggest that eradication of established HIV infection might be achieved in a staged approached of firstly treating infected individuals with standard ARV drug regimens and for those in whom viral replication is suppressed, to then tackle latent viral infection with histone deacetylase inhibitors, intensified therapy, or both.[642]

Despite a massive effort to promote HIV prevention strategies including school-based programmes and peer education, voluntary testing and counseling services, outreach programmes for sex workers and their clients, encouraging condom use and reducing the number of sexual partners, workplace prevention programmes, media campaigns, and diagnosis and treatment of sexually transmitted infections, these interventions have had little impact on the epidemic trends of HIV in South Africa. More research is needed to establish the reasons for the lack of success to date and to develop methods of prevention that will be effective in reducing transmission. Three areas of prevention that could have a significance impact on the future course of the epidemic include vaccine development, microbicide development, and the impact of male circumcision on HIV, all of which are briefly discussed below.

Since HIV was identified as the cause of AIDS in the early 1980's, more resources have been spent on the search for a vaccine against the virus than on any vaccine effort in the history of infectious diseases.[643] The USA National Institute of Health alone invests about $500 million on HIV vaccine research each year, and more than 50 different formulations have entered clinical trials.[643] Yet, an effective vaccine that could potentially prevent millions of new infections is still a long way off, and David Ho, Director of the Aaron Diamond AIDS research centre told a symposium on HIV vaccines in 2005 that "we don't have a protective vaccine available today, and we don't expect to have a protective vaccine available in the foreseeable future."[644] There are several difficulties associated with developing an HIV vaccine, of which one of the biggest obstacles is the lack of a correlate

of protection. Futhermore, there are many different and diverse strains of the virus, the virus is not well controlled by the immune system during natural infection, it often manages to develop resistance to antiretroviral drugs and the host's immune response, superinfection with more than one strains of the virus occurs, and finally there is no good animal model to be used in experiments.[644] Because it is difficult to raise neutralising antibodies against HIV, research has shifted from envelope-based vaccines designed to induce neutralizing antibodies towards ways of promoting cellular immune response (also called cellular immunity, consisting mainly of helper T cells (CD4) cells and killer T cells (CD8 cells)), specifically targeting and eliminating HIV infected cells. Several vaccines being tested aim to stimulate the production of killer T cells, although cellular immunity also involve macrophages, cytokines and natural killer cells.[643] Despite these difficulties, the search for a successful HIV vaccine continues and new directions will continue to be explored. In 2003, the Global HIV Vaccine Enterprise was established by a group of 24 scientists, including the former director of the National cancer institute, Rick Klausner, and Nobel laureates Harold Varmus and David Baltimore.[645] The Enterprise was developed as an alliance of independent organizations committed to accelerating the development of a preventive vaccine for HIV through the implementation of a jointly developed scientific plan, mobilization of resources and greater collaboration among vaccine researchers worldwide. This led to several new activities having started in 2005, including a new NIH centre for HIV/AIDS Vaccine Immunology. However, in the absence of an effective vaccine, research must continue to focus on other prevention efforts and providing antiretroviral drugs to those in need.

At the same time, while large amounts of resources are being allocated to vaccine research an important aspect of this is the preparation of communities among which vaccine trials can be conducted. It is often forgotten that before such trials can be conducted one needs to spend several years not only educating communities about vaccine research but also collecting baseline data which are essential for the effective planning and execution of such trials. While one such study was conducted in Hlabisa, more are needed in South Africa.

Women in Africa have been disproportionately affected by HIV.[6] Currently available HIV prevention methods are often not feasible for women who live in resource poor settings, and they are often not in a position to negotiate condom use with their partners. One

approach, as an alternative or supplement to condoms, that would empower women to protect themselves and their partners, is the use of microbicides. Topical microbicides, that can be formulated as gels, creams, films or suppositories, are compounds that can be applied inside the vagina or rectum to protect the body's mucosal surfaces against sexually transmitted infections including HIV,[646] and unlike male or female condoms, provides a way of preventing infection that can easily be controlled by women. There are different ways in which microbicides act to prevent genital infections: some microbicides provide a physical barrier that keeps HIV and other pathogens from reaching the target cells; others act by enhancing the natural vaginal defence mechanisms by maintaining an acidic pH level which protects the vagina; others kill or disable pathogens by stripping them of their outer covering; and another class acts by preventing the virus from replicating after it has entered the cell.[647] Several microbicide products have been tested or are currently being evaluated in clinical research studies. In 2005, WHO reported that 23 products are in various stages of clinical development.[647] Many products, including Acidform, cellulose sulphate and tenofovir, are still being tested in Phase I safety and acceptability trials, while others are further along in the development pipeline, including Carraguard, BufferGel, PRO 2000, Savvy and Cellulose Sulfate, which are being tested in Phase IIb or III trials. Although some products, such as nonoxynol-9, have been shown to offer no protection against sexually transmitted diseases or HIV, evaluation of other potential microbicides should continue. Future research and challenges should include product formulation and delivery, as well as the development of combination products to inactivate the HIV virus and to inhibit STI pathogens simultaneously.[648]

Results recently released from the first randomised controlled trial on the effect of male circumcision on HIV transmission have produced new hope for prevention of sexually transmitted HIV. In the first of three randomized controlled trials conducted in Africa, Auvert and colleagues[351] showed that male circumcision reduced the transmission of HIV from women to men in Orange Farm, South Africa, by 60% (95% CI: 32% -76%). If these results, and similar findings in other observational studies,[508,509] are confirmed by the two other randomised trials currently underway in Kenya and Uganda, they will have profound implications for the prevention of HIV. Mathematical models to investigate the impact of male circumcision show that, if full coverage of male circumcision can be reached in South Africa over the next ten years, up to 144 thousand new infections can be averted each year.[510]

Finally, South Africa, in the current stage of the epidemic, has to deal with large numbers of new infections, rising morbidity and rising mortality. Life expectancy at birth for men dropped from 61.5 years in 1994 to 49 years in 2004, and is expected to fall to about 40 years in 2010 if the epidemic is not dealt with effectively in the next few years.[24] More than 1000 people are currently dying from AIDS in South Africa every day,[4] and in 2004, there were about 1 million orphaned childen with the number expected to increase in coming years. In addition to the loss of human life, the epidemic has enormous implications for the economy of the country, partly because the epidemic targets the young economically active population in South Africa. Not only does AIDS cause loss of labour, but is also causing an increase in labour costs and threatens the competitiveness of the South African industry.[252] HIV infection among the workforce is associated with increased cost related to sick leave, productivity loss, retirement, death, disability and medical benefits. In a study in six corporations in South Africa and Botswana between 1999 and 2002, it was found that the annual cost of AIDS to these companies ranged from 0.4% to about 6% of the wage bill.[251] In addition, HIV/AIDS is placing a heavy burden on health care services in the country. Already in 2000, more than 50% of patients admitted to a tertiary hospital in KwaZulu-Natal were infected with HIV, of whom more than 80% had AIDS.[361] Similarly, among children submitted to a paediatric ward in the same hospital over a four week period in 1998, 62.5% were infected with HIV.[419] And as the epidemic is maturing, more and more people will be needing care and support, not only clinical , but also psychological and palliative care,[649]and there will be an increased expectation for communities and families to provide this care at home.

South Africa is facing a catastrophe and much will have to be done to bring the HIV epidemic under control. In addition to rapidly scaling up antiretroviral therapy for those in need, comprehensive prevention packages to reduce new HIV infections need to be put in place urgently; prevention of mother-to-child programmes must be scaled up to reduce transmission of HIV to newborn babies; care services need to be strengthened to ensure the provision of prophylaxis and treatment of opportunistic infections and anti-retroviral treatment; social services for families who are affected by AIDS deaths need to be strengthened; programmes and social services to take care of orphans have to be established; social stigma associated with HIV/AIDS needs to be addressed so that more people can speak out about causes of illness and deaths, as Nelson Mandela did in speaking

about the death of his son due to AIDS in 2005; and most of all, political commitment is needed at all levels, not only to ensure that interventions are effectively implemented without any barriers, but also to acknowledge the scale of the problem and the need to increase the response to the epidemic. Finally, to track the future course of the epidemic and the impact of interventions, better understanding of the dynamics of the epidemic is still needed. This thesis is an attempt to understand the epidemiology of the epidemic in South Africa and to describe ways to measure it, including the development of models to obtain essential information. More analysis of this kind will be needed if we want to monitor future trends and evaluate the impact of interventions. In particular, the roll-out of antiretroviral drugs will have to be carefully monitored and evaluated in relation to adherence to treatment, adverse events, morbidity and mortality. Using dynamical models and the appropriate epidemiologic measures, we can assess whether interventions work or not, identify problems early, predict future trends and resource needs, identify those groups most at risk and most in need of treatment, care and support. Understanding the epidemiology of HIV, in turn, will help us find ways to deal with the epidemic. The fight against HIV and AIDS will only be won over the years, or even decades, ahead, but to ensure that we finally win this battle, we need to mobilize the best possible science in support of those people and communities affected by the epidemic.

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