CHAPTER 1

INTRODUCTION

Outline

1 CONTEXTUAL BACKGROUND

> It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair ...[1]

Charles Dickens' depiction of the human condition as it was in 1775 may, in equal measure, be applied to humanity's state in 2007 as the HIV and AIDS pandemic rages. Although therapeutic agents, able to slow down the progress of the disease significantly,[2] have been developed, the side effects, the exacting administration regimens and, most importantly, the cost of these agents, suggest their inadequacy as a long-term solution to combat the epidemic, especially in the developing world. Because of these drawbacks, for many in Africa, antiretrovirals offer a 'winter of

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1 Dickens (1964) 1.
2 See para 3.4 of ch 2 below.

despair' - it is as though they cannot afford to pay for 'life itself'[3] – even if elsewhere it is the 'spring of hope'.

Sub-Saharan Africa is, by far, the region that is the worst affected by the HIV and AIDS epidemic. Two thirds or 66.6 per cent of all adults and children with HIV globally live in sub-Saharan Africa, amounting to almost 25 million people.[4] Also, 2.1 million Africans died of AIDS in 2006, totalling almost three quarters or 72 per cent of all AIDS deaths globally.[5] Within sub-Saharan Africa, southern Africa is the worst off - one third or 32 per cent of all people living with the virus (PLWV) are in southern Africa and 34 per cent of all AIDS deaths in 2006 occurred in southern Africa.[6]

Within southern Africa, South Africa is experiencing one of the most devastating epidemics. A total of 5.5 million people in South Africa were living with the virus by the end of 2005 – the highest number of individuals infected by HIV in any single country in the world.[7] The level of HIV among women attending antenatal clinics in South Africa is at its highest yet – 30.2 per cent.[8]

Even though the Human Sciences Research Council's (HSRC) *South African national HIV prevalence, HIV incidence, behaviour and communication survey 2005*[9] puts South Africa's overall HIV prevalence rate lower than that estimated by UNAIDS, these percentages are still alarming.[10] In three provinces (the Eastern Cape, Free State and KwaZulu-Natal) the average life expectancy has fallen below 50 years.[11]

Despite their initial optimism and hope, scientists admit that the possibility of developing a cure for AIDS within the next decade remains remote. Furthermore,

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3 Cameron (2000) First Jonathan Mann Memorial lecture: 'The deafening silence of AIDS' XIII International AIDS Conference, Durban, 7 - 14 July. Also see para 2.3.2 of ch 5 below.

4 UNAIDS (2006) *AIDS epidemic update* 6. Also see para 3.3.4 of ch 2 below.

5 As above.

6 n 4 above, 3.

7 As above, 11.

8 As above; based on statistics supplied by the Department of Health, South Africa, 2006.

9 HSRC (2005) 'South African national HIV prevalence, HIV incidence, behaviour and communication survey 2005'.

10 HSRC 21 - 41. Different HIV prevalence studies yield different results. In 2004, the Department of Health published the 2004 National HIV and Syphilis antenatal sero-prevalence survey, which, based on a sample of 16 061 women at antenatal clinics across the country. This survey estimated that in 2004, 29.5% of pregnant women in South Africa were HIV positive and that a total of 6.29 million South Africans were living with HIV. The HSRC's survey, however, estimates that a lower total, 24.4%, were living with HIV. This lower estimate may be due to the different methodologies used by the two surveys - in this regard, see n 225 of ch 5.

11 n 4 above, 11.

although education and information programmes aimed at reducing the HIV infection rate are in place, these have had only limited success.[12] Experience teaches us that greater knowledge of the risk of HIV infection does not necessarily lead to individual behavioural change. If education and information programmes are to succeed, the individual must realise, first, that she is at risk and, second, she must be in a position to avoid the risk. Often, neither of these two preconditions required for the success of information and education programmes is present. Hence, as with many viral diseases, such as smallpox and poliomyelitis, the development of an effective vaccine offers the only hope of halting or slowing the HIV and AIDS epidemic.

Phase II clinical trials which have the purpose of establishing the efficacy of various candidate vaccines against HIV are underway in South Africa, and Phase III trials will start in the near future.[13] By definition, these trials involve human subjects. Thus, it is crucial that the existing ethical and human rights frameworks for the protection of research subjects be examined critically. As Charles McCarthy observes: 'We must develop ethical and legal answers that are as sophisticated as the science that develop the vaccine itself'.[14]

Although much attention has been paid to ethical guidelines governing clinical trials involving human subjects, generally, until very recently only limited work had been done on HIV vaccine trials, specifically. Similarly, scant attention has been given to issues relating to the human rights of HIV vaccine trial participants.

In the past, violations of the rights of participants in HIV-related clinical research by trial administrators were seen as violations of universal (medical) ethical principles and not as violations of the human rights of trial participants.[15] It is to be expected that this view should dominate, as clinical research is the domain of science and the medical profession: medical professionals, although well-versed in medical ethics, are relatively unfamiliar with human rights discourse.

In contrast to the traditional approach, this study places HIV-related human subject research within the context of the human rights discourse. The focus of the study is on preventive HIV vaccine efficacy trials in South Africa, seen within the context of HIV-related clinical research in Africa.

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12 Such as the ABC campaign in Uganda. See ch 2 below.

13 See para 4 of ch 2 and para 2.3.1 of ch 5 below.

14 McCarthy, quoted in Weisburd (1987) 131 *Science News* 329.

15 See for example, the debate regarding the supposed unethical nature of the short-duration AZT trials in Africa, discussed in ch 3 below.

The systems for protecting the interests of clinical research participants are analysed in terms of *concepts*: the study investigates norms related to human rights and bioethical discourse, and the implementation of each system.

2 SIGNIFICANCE OF THE TOPIC

Groups such as the HIV/AIDS Vaccine Ethics Group (HAVEG) have done valuable work in the delineation and scrutiny of ethical guidelines relating to HIV vaccine research, as well as building the capacity of non-governmental organisations (NGOs) working in the field. Because their focus is ethics, these groups concentrate on issues relating to the ethics of informed consent; the decision-making processes of trial participants; and cultural differences in the perceived voluntariness of trial participation. They rely on ethical guidelines expressed, for example, in the World Medical Association's Helsinki Declaration which governs biomedical research involving human subjects.

This study, by way of contrast, focuses on those aspects which relate to the human rights of trial participants. It investigates the protection afforded preventive HIV vaccine trial participants in South Africa by global, regional and domestic human rights instruments. As well, it surveys one of the major ethical concerns associated with HIV-related clinical trials in Africa – informed consent to participation. No similar study has been undertaken to date.

The value of the application of human rights discourse to the fields of medicine and clinical research has been advocated by various persons.[16] However, human rights discourse has not been used extensively to frame the rights of research subjects. In South Africa individual human rights are entrenched in a supreme constitution,[17] rendering the utility of such an approach self-evident.

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16 Such as the efforts of Jonathan Mann. See Mann *et al* 'Health and human rights' in Mann *et al* (eds) (1999) 7 - 20. Also see Macklin (2004) *Double standards in medical research in developing countries*. Macklin deals with the ethical controversies that surround research conducted in the developing world, and sponsored by the developed world. In ch 7, entitled 'Respecting, protecting and fulfilling human rights', Macklin advocates the utility of a rights-based approach to clinical research in the developing world, but sees human rights law as limited by its lack of realisation (she writes: 'As is true of the gap between the enunciation of ethical principles and their full realisation, a gulf exists between the human rights stipulated in or derived from these instruments and their full realisation. In developing countries generally, ... this gulf is the widest' (222)). On the whole, Macklin's study deals with the ethical concept of justice and the human rights norm of access to health care, and not with autonomy or informed consent (informed consent is touched upon in ch 5 of her work). Aspects of Macklin's work are discussed in chs 3 and 5 below.

17 Constitution of the Republic of South Africa 1996. See chs 4 and 5 below.

3 RESEARCH QUESTION

The thesis investigates the following research question:

> Do human rights afford more adequate protection to participants in preventive HIV vaccine efficacy trials in South Africa than that which is afforded by ethical guidelines, and what is the relationship between human rights and ethical guidelines in the protection of participants?

In order to answer the research question, it first must be established if it is more appropriate to rely upon human rights law rather than ethical guidelines to protect the interests of participants in HIV-related clinical research in Africa.

4 AIMS OF STUDY

The study centres on clinical trials to test the efficacy of a preventive HIV vaccine in South Africa. Preventive HIV vaccine testing is likely to take place in communities in which economic, medical, educational and other resources are stretched and where there is a high risk of HIV infection.[18] Because of the stigma attached to HIV infection and the victimisation of people who are (or are perceived to be) HIV positive, the rights of the participants in the various trials must be held sacrosanct, as must those of the community in which HIV vaccine trials are conducted.

The study has three primary aims.

- An investigation into the protection that ethical guidelines laid down by international and national bodies and adhered to by international and local ethical review committees, research institutions and researchers, afford HIV vaccine efficacy trial participants, in order to arrive at a comprehensive understanding of the extent of the protection afforded;

- An investigation into the protection international human rights instruments and the South African Constitution, 1996, afford to preventive HIV vaccine efficacy trial participants, in order to arrive at a comprehensive understanding of the extent of the protection afforded; and

- An investigation into the relationship between the different layers of protection afforded by human rights law and ethical guidelines to preventive

HIV vaccine efficacy trial participants in South Africa, in order to establish whether they are complementary or adversarial.

In addition, the study considers the following broader issues relating to **HIV clinical research in Africa**.

- The implications for clinical research in Africa of 'principlism' in bioethics and research ethics, embodied by Beauchamp and Childress' four principles-approach[19] and represented in international and national ethical guidelines and discourse;

- The limits of classical ethical discourse and the potential gains of employing human rights discourse in the protection of clinical research participants in Africa;

- The implementation of international human rights law in Africa;

- The clinical research endeavour as a means of accessing health care in the African context;

- The role of 'cultural relativism' in the application of 'universal' international ethical and human rights norms to research in developing countries. The issue is raised in the context of the debate over the use of placebo-controlled trials in Africa when an efficacious (but unsuitable) form of treatment has already been developed; and

- International collaborative research in the developing world and the potential for exploitation in this context.

These are the issues which are anticipated to be particularly contentious in relation to **preventive HIV vaccine efficacy trials in South Africa**.

- Informed consent - as an ethical guideline and as a human right embodied in international instruments, and in section 12(2)(c) of the South African

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18 See paras 5.4.1 and 5.4.2 of ch 2 and para 2 of ch 5 below.
19 See ch 3 below.

Constitution. In particular, the role of context in ensuring informed consent and the peculiar position of rural women as vaccine trial participants with regard to their economic and social vulnerability need to be taken into consideration in terms of whether their agreement is in compliance with ethical guidelines and human rights norms on informed consent;

- The nature and level of the risks which attach to the preventive HIV vaccine trial. These risks are scientific and social in nature, for example, the discrimination experienced by the participant consequent upon testing HIV positive on standard laboratory Elisa assays[20] according to the presence of vaccine-induced HIV antibodies in the trial subjects' blood, and stigmatisation because of perceptions that trial participants are at high risk for HIV infection;

- Whether preventive HIV vaccine efficacy trials should be classified as 'therapeutic' or 'non-therapeutic' research, and the implications of such a classification;

- The capacity of members of ethics committees to assess HIV vaccine efficacy trial protocols;

- Autochthonous collectivist notions with reference to ethical issues, such as voluntary consent in clinical trials; and

- Participation in HIV vaccine efficacy trials as a means of accessing health care in a setting where resources are stretched. This is problematic, especially in the case of the development of a therapeutic vaccine where such a programme represents the only chance of survival for HIV positive participants.

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20 See ch 2 below.

5 RESEARCH METHODOLOGY

The thesis is a theoretical study based on a literature review of the following:[21]

- A literature survey of the HIV virus, scientific progress in developing a HIV vaccine and the dangers inherent in participating in HIV vaccine research;
- A literature survey of relevant ethical principles - embodied in ethical rules and guidelines on clinical research;
- An analysis of the human rights which relate to clinical research, especially informed consent to participation in research, as well as instances in which these rights have been litigated nationally and internationally;
- A comparative literature study of relevant sections of selected African constitutions in order to arrive at an understanding of the scope of the protection provided to research participants in individual countries' constitutional frameworks;
- An analysis of the legal position regarding informed consent to research participation in South Africa, which includes an analysis of the common law, case law, legislation, ethical guidelines and human rights law;
- A brief analysis of a report on an empirical study of an informed consent process in a HIV vaccine efficacy trial in South Africa; and
- A critical scrutiny of the readability and comprehensibility of an informed consent document utilised in a HIV drug trial in South Africa.

In examining the protection afforded by bioethics and human rights to participants in clinical research, the thesis focuses on:

- the origins and normative framework of each system;
- the applications of each system as contained in their principles and norms;
- the implementation mechanisms of each system; and

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21 Additionally, while doing research at Yale University in the United States of America, I was able to interview members of NGOs and government, AIDS activists, academics, vaccine scientists and ethicists about some of the issues discussed in this study. On the whole, these interviews relate to the scientific background of the study.

- sanctions for non-compliance.

6 SCOPE OF STUDY

The aim of the study is to examine the protection afforded by ethical guidelines and human rights instruments to participants in HIV vaccine efficacy trials in South Africa. These are the steps taken in the study to achieve this goal:

- Positioning the study within a scientific context; in which the HIV virus is discussed, the course of the epidemic is delineated and the importance of clinical research aimed at providing an effective preventive vaccine is posited;

- Analysing the nature of ethical principles and the various enforcement mechanisms that exist internationally and locally, as well as presenting an overview of how these principles and mechanisms have served participants in HIV-related clinical research in Africa in the past;

- Analysing the nature of human rights and the various enforcement mechanisms that exist internationally and locally, as well as presenting an overview of the way in which these principles may be employed to serve participants in HIV-related clinical research in Africa;

- Scrutinising the scientific, political, economic and social contexts in which preventive HIV vaccine efficacy trials are likely to take place in South Africa and the risks that may be anticipated by trial participants; and

- Examining informed consent as an ethical and human rights imperative and analysing the manner in which the discourses of ethics and human rights ensure the informed consent of HIV vaccine efficacy trial participants in South Africa.

7 DIFFICULTIES AND LIMITATIONS OF STUDY

7.1 Difficulties

An evident difficulty for a layperson in the course of doing the scientific research for this study is coming to terms with the medico-scientific terminology. Vaccine science is a highly specialised field and, understandably, scientific journals do not make concessions to the lay reader. Because of the difficulty in comprehending scientific

texts, it has been a problem to read these texts critically. I have relied heavily on scientific colleagues for advice and information.

Further to this problem, HIV vaccine science is still developing, with the consequence that previously-held convictions and theories are being continually discarded. Scientific thought on suitable HIV-vaccine strategies, for example, is changing as more knowledge is gained about the human immune response to the virus.

A significant conceptual difficulty arises in attempting to impose a rights-based discourse on an ethical model. Rights and principles differ greatly in their origin and nature and are not easily interchangeable. The wariness of members of the medical profession in relation to a rights-based approach is symptomatic of this difficulty.

Related to this difficulty is the lack of a body of jurisprudence which utilises international human rights law to remedy abuses in clinical research in Africa.[22] The abuse of research participants is seen as a violation of ethical guidelines and not as an infringement of their human rights. Victims of abuse in Africa have attempted to take their case to court, but have not used human rights law as the basis for such litigation.[23]

7.2 Limitations

The study does not provide a number of things:

- An exhaustive epidemiological or public health-related analysis of HIV;
- Anything other than a representation of the science of HIV and vaccine research at the most basic (undergraduate) level – the aim is merely to introduce the reader to the scientific discourse on HIV in the context of its relevance to the thesis;
- A detailed examination of ethical guidelines and human rights instruments relevant to participants in *therapeutic* HIV vaccine efficacy trials;
- An investigation of issues related to the access of trial participants and their community to an effective vaccine once it has been developed – in terms of

22 See ch 5 below.

23 One exception to this is the case of the participants in the recent Trovan trials in Nigeria. See para 4.2.2 of ch 3 below.

the ethical value of justice and the human rights value entrenched in section 27 of the South African Constitution. This limitation is due to the focus of the thesis on informed consent in terms of the ethical value of respect for persons or autonomy, and the human rights value entrenched in section 12(2)(c) of the South African Constitution;

- A philosophical analysis of ethical theory, or an exhaustive account of modern ethical theory. It briefly investigates the traditional ethical theories that are the foundation of bioethical discourse. The challenges posed by the ethics of feminism and multiculturalism will be mentioned in passing, and particularly in chapter 5 below;

- A thorough-going philosophical analysis of ethics and human rights discourses within the context of post-modern philosophical thought;[24] and

- Finally, as no Phase III preventive HIV vaccine efficacy trials have yet been concluded in South Africa, chapter 5 of the thesis can present only an estimate of the problems likely to be encountered in these trials. For the same reason it was not possible to include a linguistic analysis of a consent document used in such a trial.

8 WORK ALREADY DONE IN THE FIELD

Until recently surprisingly little has been written on the role of ethics in HIV vaccine efficacy trials. Although ethical issues in clinical research have been dealt with extensively, to the extent of devoting entire journals to the issue,[25] vaccine efficacy trials have received little attention. This lack may be due in part to the fact that only a single candidate HIV vaccine has progressed to large-scale phase III clinical trials.[26] As was indicated above, the human rights of trial participants have not been attended to in the literature.

Scientific journals with articles on the science of HIV vaccine research are abundant. Vaccine strategies are examined and positive as well as negative research

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24 A number of post-modern philosophers, such as Alain Badiou, argue that human rights and ethical discourses merely serve to reinforce the individual's powerlessness. This contention falls outside of the scope of this study. See ch 6 below.

25 eg *Journal of Medical Ethics, Bioethics, Journal of Medicine and Philosophy, Kennedy Institute of Ethics Journal, Developing World Bioethics*, etc.

26 The VaxGen trial, see para 4.6 of ch 2 below.

results have been reported. However, these studies do not comment on the ethics of HIV vaccine research. An important analysis of current HIV vaccine science, (edited by Flossie Wong-Staal and Robert Gallo) is provided in a compilation of essays indicating current directions in HIV vaccine research. The first essay deals with the problems that have been encountered in HIV vaccine research.[27]

The pioneering work on ethical issues relating to HIV vaccine efficacy trials is that by Christine Grady, published in 1995, entitled *The search for an AIDS vaccine*. Grady's emphasis is on local[28] and international ethical guidelines relating to HIV vaccine research. By her own admission, she pays scant attention to issues specific to international vaccine efficacy trials.[29] Less thorough, is the work of Thomas Kerns, *Ethical issues in HIV vaccine trials*, published in 1997.

Specific to the African context, is a preliminary study by Nicholas A Christakis, entitled 'The ethical design of an AIDS vaccine trial in Africa', published as a Hastings Center Report in 1988.[30] Christakis touches on issues such as the design of a HIV vaccine trial, the selection of suitable subjects, risks and consent issues, the beneficent treatment of participants, ethical standards in cross-cultural perspective and maintaining research ethics in the face of such a devastating epidemic.

In 2000, UNAIDS published a guidance document, entitled *Ethical considerations in HIV preventive vaccine research*. Professor Robert Levine, a highly respected academic and ethicist, is one of the authors. Although the document provides a sound preliminary understanding of relevant issues, again, it focuses exclusively on ethics.

In South Africa, various preliminary explorations of ethical issues relating to HIV vaccine efficacy trials have been published, such as by Cathy Slack *et al*;[31] Lindegger and Richter[32] and Abdool Karim.[33]

The most thorough study of ethical issues relating to HIV vaccine efficacy trials in a South African context to date is that by Keymanthri Moodley - entitled 'HIV vaccine trial participation in South Africa – an ethical assessment', published in

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27 Nabel in Wong-Staal and Gallo (eds) (2002) 1 – 7.
28 Local to the United States of America.
29 Grady (1995) 10.
30 Christakis (1988) 18 *The Hastings Center Report* 31-37.
31 Slack *et al* (2000) 96 *SA J Science* 291.
32 Lindegger and Richter (2000) 96 *SA J Science* 313.
33 Abdool Karim (2002) 20 *CME* 588.

2002.[34] Moodley's study has a strong philosophical emphasis. She examines tensions which arise when developed countries sponsor research in the developing world. Specifically, she argues that in many societies in Africa, especially in rural regions, a moderate form of communitarianism exists in contrast to western liberal individualism. She explores concepts such as ethical relativism within the context of HIV vaccine efficacy trials in South Africa. However, although well-reasoned, Moodley's study focuses on ethics rather than on human rights.

A number of articles published recently deal with adolescent preventive HIV vaccine trial participation in South Africa in the light of new statistics[35] showing the increasing incidence of HIV infection in that age group.[36] The articles investigate the implications of the new National Health Act,[37] the Constitution and local and international ethical guidelines upon adolescents' vaccine trial participation and the notion of informed consent. By contrast, this thesis focuses on informed consent with respect to adults; the problems presented by adolescent participation are referred to in passing.

9 OUTLINE AND OVERVIEW OF CHAPTER CONTENT

The study consists of six chapters which are structured as follows:

In this chapter **(Chapter 1)** a general introduction is presented. The HIV/AIDS epidemic is examined as a public health issue and the argument for the importance of developing an effective vaccine is presented. Furthermore, the study is located within the South African context, so as to explore the peculiarities, if any, of the South African and African situation. It then will be possible to articulate the research question the study proposes and provide an outline of subsequent chapters.

Chapter 2: The Human Immunodeficiency Virus and the mechanics for developing an effective vaccine are dealt with here. The nature and functioning of retroviruses are discussed. The Human Immunodeficiency Virus is described as a sub-type of this group of viruses. The way in which a vaccine functions is traced and a distinction is

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34 Moodley (2002) 27 *J Med and Philosophy* 197. Also reprinted in Van Niekerk and Kopelman (eds) (2005) 160 – 178.

35 See HRC (n 10 above) 37.

36 See eg Van Wyk (2005) 68 *J Contemporary Roman Dutch L* 35; Strode *et al* (2005) 101 *SA J Science* 225; Slack and Kruger (2005) 96 *SA Med J* 269; Jaspan *et al* (2005) 95 *SA Med J* 685; Slack *et al* (2005) 95 *SA Med J* 682. On the scientific justification for adolescent participation, see Jaspan *et al* (2005) 95 *SA Med J* 785.

37 Act 61 of 2003.

made between preventive and therapeutic vaccines. Different research methodologies are outlined and possible strategies for the development of an effective HIV vaccine are explored.

Chapter 3: The origin and nature of ethical principles are examined. An analysis of the protection afforded by fundamental ethical principles, such as autonomy, informed consent, beneficence (including nonmaleficence), and justice, as they are embodied in various international and domestic documents, is presented. The protection afforded by international documents, such as the Nuremberg code, the International Ethical Guidelines for Biomedical Research involving Human Subjects, the Belmont Report and the Declaration of Helsinki will be scrutinised. Domestic documents, such as the Medical Research Council's Guidelines on Ethics for Medical Research of 1993 and the practices of Institutional Ethics Review Committees at different universities will be investigated. Examples of the abuse of research participants in Africa and elsewhere are discussed. The purview in this chapter is not limited to preventive vaccine efficacy trials in South Africa, but looks at clinical trials in Africa relating to HIV in general.

Chapter 4: In this chapter justiciable human rights are offered as an alternative means to protect the rights of participants in contrast to non-binding ethical guidelines. The origin and nature of human rights are explored. A critical examination of the protection international and domestic human rights documents and instruments offer is extended. The chapter additionally examines the implementation of international human rights law in Africa and South Africa. Again, the discussion in the chapter is not limited to preventive HIV vaccine efficacy trials in South Africa, but looks at clinical trials in Africa relating to HIV in general.

Chapter 5: The focus here is on informed consent in HIV vaccine efficacy trials in South Africa. The effectiveness of the ethical guidelines and human rights standards in South Africa for the protection of participants in HIV vaccine efficacy trials is considered. The chapter outlines the epidemiologic, scientific, political and socio-economic contexts in which HIV vaccine efficacy trials are taking place and are likely to take place in South Africa. In the first instance, the chapter highlights difficulties arising out of the use of non-binding ethical guidelines and the implications in a

South African context. In the second instance, the chapter debates the advantages of deploying human rights law in a South African context.

Chapter 6: Conclusion – a summary of the research findings. The research question that has been asked is revisited. A synthesis between the two systems is arrived at, rejecting the notion that either ethical guidelines or human rights on their own are able to function effectively to protect the interests of clinical research participants. Recommendations as to a discourse which will offer trial participants the maximum protection are offered with regard to the proposal in the thesis that the discussion with reference to an ethical discourse should be positioned more broadly than the limits of classical principlism allow.

Chapter 2, which follows, presents an examination of the scientific background to the discussion in subsequent chapters of ethical and human rights issues in relation to HIV-related clinical research and the search for an effective preventive vaccine against HIV infection.

CHAPTER 2

SCIENTIFIC FRAMEWORK: HIV/AIDS AND THE SEARCH FOR A PREVENTIVE VACCINE

Outline

1 INTRODUCTION

This chapter presents the scientific background to the discussion in subsequent chapters of ethical and human rights issues in relation to HIV-related clinical research and the search for an effective preventive vaccine against HIV infection.

The Human Immunodeficiency Virus (HIV) is characterised in the context of a general discussion of viruses as infective agents. The peculiarities of the HIV and AIDS syndrome, as well as the progress that has been made in its treatment, are investigated. The extent of the epidemic is outlined and it is argued that a vaccine offers the only chance of halting the spread of the epidemic.

Next a short history of the development of successful vaccines against pathogenic infections is given, and the focus is on challenges facing the development of a preventive HIV vaccine. In this section various options for candidate preventive HIV vaccines are explored.

Finally, clinical research, generally, and vaccine efficacy trials, specifically, are discussed. The discussion aims to provide the scientific setting for the third and fourth chapters that examine ethical issues associated with HIV-related research in Africa, as well as the setting for the fifth chapter which focuses on preventive HIV vaccine efficacy trials in South Africa. Throughout, the terms which relate to the HIV, vaccine development and clinical research are introduced and explained.

2 VIRUSES AND DISEASES

2.1 Viruses

A virus is the smallest form of life that is able to replicate – it is smaller than a bacterium and its measurement is taken in nanometres.[1] Viruses are totally dependent on living cells for their replication and existence. They can only replicate

inside cells, using the host cell's machinery for this process.[2] Viruses possess only one species of nucleic acid, either DNA or RNA.[3] The hereditary information of the virus is contained here.[4] Viral genomes commonly consist of ten to fifteen genes, but they may have as few as 3 or as many as 100 genes.[5] Viruses attach to cells by means of a receptor-binding protein; they exist in human, animal, plant, insect or bacterium cells and depend upon these cells for protein production.[6]

Viruses are classified into families according to whether their nucleic acid is RNA or DNA,[7] the number of strands they possess, and their polarity.[8] They may be divided further into sub-families[9] and genera.[10]

A virus is structured as follows:[11]

- a genome (sum total of genes);
- a capsid, which is the protein shell that surrounds and protects the DNA or RNA genome, and which acts as a vehicle to convey the virus from cell to cell and organism to organism; and
- an envelope, which is a loose, fragile lipoprotein membrane that covers the capsid. This envelope is acquired mainly from the host cell and in some cases viral proteins are added to the envelope.[12]

The replication cycle of a virus typically consists of the following elements:[13]

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1 Collier and Oxford (2000) 7. One nm is 1/100 000 of a cm. The smallest virus is more or less the size of haemoglobin molecules of red blood cells. The word virus is derived from Latin where it means 'poison' and 'slimy material'.

2 Collier and Oxford (n 1 above) 7; Cloete and Atlas (eds) (2006) 11; Nicklin *et al* (1999) 269. Because of this, some microbiologists view viruses as parasites of the host cells within which they replicate. Viral replication results in changes within the host cell, often causing its death (see Cloete and Atlas 11 – 12).

3 As above. DNA is **d**eoxyribo**n**ucleic **a**cid – the nucleic acid type where the linker molcule is deoxyribose sugar. RNA is **r**ibo**n**ucleic **a**cid – the nucleic acid type where the linker molecule is ribose.

4 Collier and Oxford 11; Cloete and Atlas 11.

5 Collier and Oxford 15; Nicklin *et al* (n 2 above) 279.

6 Collier and Oxford 7; Nicklin *et al* 282.

7 Nicklin *et al* 269; 285. Higher organisms consist of DNA.

8 Collier and Oxford 16. They may be either positive or negative stranded.

9 Depending on their gene structure; Nicklin *et al* 270.

10 Depending on antigenic and other biological properties (Cloete and Atlas 57; Nicklin *et al* 270).

11 Schoub (1994) 44; Nicklin *et al* 268; Cloete and Atlas 11 – 12. Because of their simplicity, viruses have no capacity to generate the energy that they need for processes such as replication. To carry out these processes, viruses make use of the host cell's machinery and biochemical facilities, sometimes, but not always, to the detriment of the host cell.

12 Not all viruses have such an envelope (Cloete and Atlas (n 2 above) 11); Nicklin *et al* (n 2 above) 270.

- attachment to the host cell surface;
- penetration into the cytoplasm;
- release of the viral genome within the infected cell;
- replication of viral nucleic acid and proteins;
- assembly of new virus particles; and
- their release from infected cells which may be accompanied by the acquisition of an envelope.

2.2 Viral disease

Viruses are classified as well according to their pathogenicity and virulence in causing disease.[14] Viruses vary in terms of the number of hosts they can infect, the tissues they infect,[15] and the mechanisms by which they are able to cause disease in the host.[16]

The typical spread of a virus in a host takes this route:[17]

- The virus enters the host (for example, via the respiratory tract, the gastrointestinal tract, conjunctiva, or via the genital tract).
- The virus then replicates in susceptible cells at the site of entry (called the site of inoculation).
- The virus manages to overcome the defence of local cells (at the site of inoculation), such as lymphocytes, macrophages[18] and interferon.
- The virus now spreads to other areas of the host via the bloodstream.
- The virus replicates further in a target area (localised or generalised).[19]

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13 Mackett and Williamson (1995) 15.

14 Schoub (n 11 above) 48. Pathogenicity is a comparison of the severity of disease caused by various viruses, while virulence is a comparison of the severity of disease caused by different strains of the same virus – eg HIV is more pathogenic than measles; HIV I is more virulent than HIV II.

15 Schoub 48. Tissue tropism. Possible target organs include the skin (herpes simplex virus), the lungs, the liver (hepatitis virus) and the central nervous system.

16 Pathogenesis.

17 Collier and Oxford (n 1 above) 30; Schoub 51 – 55; Cloete and Atlas 12; 18 – 20; Nicklin *et al* 307 – 309.

18 A macrophage, a type of helper-T cell, is a large immune system cell in the tissues that 'eats up' invading pathogens. The word 'macrophages' literally means 'big eaters' (Rick (2004) 85). Macrophages stimulate other immune cells by presenting them with small pieces of the invaders.

19 An example of a virus that attacks a localised target area is adenovirus conjunctivitis which causes eye infections, and a virus that attacks a generalised target area is measles.

- Finally, the virus leaves the host (sometimes called 'shedding' or 'budding') in sufficient quantities so that it may spread to another host (and so ensure its continued existence).

In humans, viral infections follow one of three basic patterns of disease (some, but by no means all, fatal):[20]

- Acute, non-persistent infections (influenza).
- Persistent infections with acute onset (HIV; herpes simplex).
- Insidious infections (sub-acute sclerosing panencepehalitis).

2.3 Resistance to infection: The human immune system

Over time humans have developed a complicated and efficient system of fighting infections caused by viruses and other organisms which is known as the human immune system.[21] The immune system is a complex system of cells, tissues and organs that protects the body against infectious agents and cancer[22] by means of different processes.[23] Scientists talk about 'non-specific' and 'specific' resistance to infection by the human immune system.[24] Before the discussion turns to a detailed description of the components and functioning of the specific and non-specific immune system, it is important to remember that certain general factors play a role in a person's resistance to infection.[25] These are:[26]

- mechanical or chemical barriers (such as the skin or a low PH balance in the stomach);
- fever (viruses find it difficult to replicate in temperatures above 37°C);
- age (for example, a younger person may not have acquired immunity to a certain disease because she has not yet been exposed to that disease; an older person may have a weakened immune system due to chronic illnesses and so on);

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20 Collier and Oxford (n 1 above) 34 – 36; Schoub (n 11 above) 53; Nicklin *et al* (n 2 above) 310 - 312.

21 Delves and Roitt (2000) 343 *New Engl J Med* 37; Nicklin *et al* 314.

22 Certain cancers are caused by viruses, such as cervical cancer, which is caused by the human papilloma virus. Viruses that transform cells and cause cancerous cells are called oncogenic viruses (Cloete and Atlas (n 2 above) 25.

23 Collier and Oxford (n 1 above) 38; Delves and Riott (n 21 above) 37.

24 As above.

25 Burton and Engelkirk (2000) 310 – 323; Collier and Oxford (n 1 above) 38; Schoub (n 11 above) 71 – 81.

26 As above.

- nutritional status (poor nutrition may exacerbate the severity of some infections);
- hormones (certain cancers 'feed off' hormones, for example oestrogen-positive breast cancers);
- genetic factors (some people are genetically predisposed to certain infections, while others may have a stronger immune system); and
- species resistance (for example, some viruses are able to infect humans only, others are able to infect all mammals).

As its name indicates, a non-specific immune response is a response by immune system cells that attack *any* infectious agent.[27] Non-specific immune system cells include:[28]

- phagocytes (that engulf and destroy infectious agents) consisting of:
  - macrophages[29] that generally engulf cells infected with viruses, such as monocytes,[30] tissue macrophages, and microglial cells;[31] and
  - neutrophils that generally attack foreign bacteria.
- mast cells, basophils and eosinophils that attack protozoa and large parasites such as worms.
- natural killer (cytotoxic) cells that attack virus-infected cells and tumour or cancer cells.

'Specific' immunity is characterised by:[32]

- the ability to launch an enhanced response against a specific antigen[33] (viruses or other micro-organisms) that has been encountered before; and
- the ability of the immune system to distinguish between its own molecules and 'non-self' molecules.

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27 As above.

28 Mackett and Williamson (n 13 above) 41; Burton and Engelkirk (n 25 above) 311 – 313; Nicklin *et al* (n 2 above) 314 - 315.

29 See n 18 above.

30 macrophages in blood.

31 macrophages in the brain.

32 Collier and Oxford (n 1 above) 39 – 47; Mackett and Williamson (n 13 above) 41 - 46.

33 An 'antigen' is any substance that is able to stimulate the immune system to produce antibodies, usually viruses and bacteria.

This system is considered 'specific' in that it consists of immune system cells that respond only to very specific foreign agents (molecular components of an infectious agent, such as a viral protein).[34] These are the two main components of specific immunity to viral infections.[35]

- Humoral (antibody-mediated, or resulting from the activity of antibodies) immunity which is produced by B-cells[36] (B-lymphocytes), which release masses of antibodies[37] into the bloodstream, in co-operation with antigen-presenting cells and T-lymphocytes.[38]
- Cell-mediated immunity (CMI) established by a variety of T-cells (T-lymphocytes), including particular helper, suppressor, and killer (cytotoxic) cells.

Antibodies act in protecting the body against viral attack in a number of ways. An antibody:[39]

- neutralises the virus by agglutinating (a process of glueing or clumping) the virions[40] and thus stops them from attaching to susceptible cells;
- acts as an opsonin, whereby it combines with virions and increases the ability of macrophages to destroy them;
- coats macrophages with specific antibody so that these macrophages are 'armed' to destroy those viral antigens that express that specific viral antigen;

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34 Burton and Engelkirk (n 25 above) 352.

35 Klein and Ho (2000) 22 *Clinical Therapeutics* 300; Rick (n 18 above) 78.

36 A B-cell (or B-lymphocyte) is one of the major classes of lymphocytes. They are white blood cells that are derived from the bone marrow and spleen. B-cells develop into plasma cells, which produce antibodies.

37 An antibody that is an infection-fighting protein molecule in blood and secretions, that tags, neutralises and destroys pathogenic microorganisms or toxins. Antibodies, also known as immunoglobulins, are made and secreted by B-lymphocytes in response to stimulation by the antigen. An antibody produced by a particular B-cell specifically recognises and binds to a particular foreign antigen (eg p24 protein of HIV).

38 A T-cell is a white blood cell that is critical to the body's immune response and can destroy cancer cells and cells infected with viruses, fungi and bacteria. These cells are also known as killer or helper T-cells or lymphocytes, and kill virus-infected cells, whereas antibodies target free-floating viruses in the blood. Killer (cytotoxic) T-lymphocyte (CTL) responses are suspected to be a correlate of HIV immunity.

39 Collier and Oxford (n 1 above) 43 – 44; Burton and Engelkirk (n 25 above) 336 – 339; Mackett and Williamson (n 13 above) 41.

40 The whole virus particle (nucleocapsid and outer envelope) is called a virion; Nicklin *et al* (n 2 above) 270.

- exerts antibody-dependent cellular cytotoxicity (ADCC), whereby it combines with the viral antigen expressed on the surface of the infected cell which it then kills; and
- interferes with the uncoating sequence[41] of the virus after the virus has entered a cell.

The body's B-cell (antibody) response acts to prevent the infiltration of cells by circulating virus. Once the virus is inside the cell, circulating antibodies specific to the virus cannot get at them and it is here that T-cells perform their function.[42]

T-cell response differs from the methods of B-cells. Whereas B-cells secrete antibodies into the general circulation, T-cells recognise virally infected cells and eliminate them.[43] Two types of T-cells exist.[44]

- CD4 cells (or helper T-cells), which are the regulators of the immune function, recruiting non-specific immune cells and stimulating the production of antibodies by B-cells.
- CD8 cells (or cytotoxic T-cells), which both kill virus-infected cells and release anti-viral cytokines in the blood.

The killer (cytotoxic) T-lymphocyte[45] (CTL) or CD8 cell binds directly to - and kills - cells carrying a foreign antigen that its receptor recognises, such as virus-infected cells and tumour cells.

Helper T-lymphocytes or CD4[46] (T4) cells are equally important. They play a central role in both humoral and cell-mediated immunity. They do not kill infected cells, but are necessary for the functioning of both B-lymphocytes and killer (or cytotoxic) T-lymphocytes.[47] They 'help' these cells to perform their function.

Immune responses to virus infections are sometimes complicated by the ability of some viruses to infect and damage the very cells that mediate this

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41 The virus literally takes off its coat, or envelope, in order to integrate itself with the host cell and replicate.

42 Klein and Ho (n 35 above) 300; Rick (n 18 above) 86; Mackett and Williamson (n 13 above) 41.

43 As above.

44 Klein and Ho (n 35 above) 300 – 301; Rick (n 18 above) 86.

45 See n 38 above.

46 CD4 is an abbreviation for 'cluster of differentiation 4', which refers to cell surface molecules that are used to identify stages of maturity of immune cells, for example CD4 cells.

47 Burton and Engelkirk (n 25 above) 335; Schoub (n 11 above) 71 – 81.

response. Finally, it is important to note that the mechanisms of the immune system's response vary according to the type of virus it is defending against.[48]

We now turn to the virus of interest to this study, the Human Immunodeficiency Virus.

3 THE HUMAN IMMUNODEFICIENCY VIRUS (HIV)

3.1 Classification

HIV is the virus that causes AIDS.[49] It is a lentivirus[50] and belongs to the family of viruses known as retroviruses.[51]

HIV consists of a RNA genome.[52] Inside the infected cell, reverse transcriptase[53] produces a DNA copy of HIV's RNA genome.[54] The virus then uses this DNA copy to replicate inside the invaded cell, producing a haploid double-stranded DNA provirus that gets inserted into the chromosomal DNA of the host cell.[55]

Once inside the host cell, the provirus may remain latent, especially in resting lymphocytes.[56] However, the moment these cells are activated, transcription and translation occur, and viral proteins assemble to form new virions.[57] Finally, the infected cell releases hundreds of new virions,[58] or viruses, which in turn are able to infect other cells.[59]

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48 Schoub (n 11 above) 81; Klein and Ho (n 35 above) 298; Cloete and Atlas (n 2 above) 22.

49 This scientific fact is questioned by only a few non-mainstream scientists and by misguided politicians. See Weiss and Weiss in Smith *et al* (eds) (2001) 147.

50 From the Greek *lenti* which means 'slow'. All lentiviruses produce slow viral diseases, and many affect the cells of the immune system (Schoub (n 11 above) 54).

51 Burton and Engelkirk (n 25 above) 424; Schoub 55; Klein and Ho 299. The scientific name is Retroviridae. Up until the mid-1970s, no member of the retrovirus family was known to occur in humans.

52 Weiss and Weiss in Smith *et al* (n 49 above) 127.

53 An enzyme unique to retroviruses. Nicklin *et al* (n 2 above) 303.

54 Schoub 81; Cloete and Atlas 22; Nicklin *et al* 303; Weiss and Weiss in Smith *et al* 127. Reverse transcriptase, as its name suggests it, causes the reverse of the normal transcription process (that involves the synthesis of RNA from a DNA template) in that it causes the synthesis of DNA from an RNA template.

55 Graham in Nelson *et al* (eds) (2000) 521 - 522; Nicklin *et al* 303. When incorporated into the host cell's DNA the virus can be transferred to each daughter cell when the host's cell divides.

56 Graham in Nelson *et al* 522.

57 As above.

58 a complete, infectious viral particle. Virions are released from host cell by means of 'budding' (Cloete and Atlas (n 2 above) 22.

59 Graham in Nelson *et al* (n 55 above) 522.

HIV is of medium size, more or less 100 – 150 nm in diameter.[60] It is roughly circular in shape, but may become oval or irregular because of the elasticity of the viral envelope.[61]

HIV's genome is composed of nine genes[62] which carry the code for the inner proteins, the envelope proteins and the enzymes.[63] Three of these genes carry the information needed to make key structural proteins for the new virions.[64] These three genes are called the *gag*,[65] *env*[66] and *pol*.[67] The six regulatory genes of HIV are *tat*, *rev*, *vif*, *nef*, *vpu* and *vpr*.[68]

HIV's replication rate is considered to be extremely high as it produces more or less 10 billion particles every day.[69] This replication rate may be compared with that of Hepatitis B which also replicates by means of reverse transcriptase, but which undergoes many fewer replications per unit of time.[70] This high replication rate and the fact that there is no proofreading mechanism during reverse transcription are responsible for HIV's high mutation rate[71] which has implications for anti-retroviral treatment and the development of a future vaccine.[72]

Upon infection HIV invades the dendritic cells[73] in the genital or oral mucosa of the infected person. These cells then fuse with CD4-lymphocytes (helper T-cells) and spread to deeper tissues.[74]

Helper T-lymphocytes are the ultimate target of the virus,[75] but HIV also infects the following cells:[76]

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60 Schoub (n 11 above) 56; Graham in Nelson *et al* 522.

61 As above.

62 Klein and Ho (n 35 above) 300.

63 As above. An enzyme is a protein produced by cells to accelerate a specific chemical reaction without itself being altered. Enzymes are generally named by adding '-ase' to the name of the substance on which the enzyme reacts, eg protease is an enzyme that acts on proteins.

64 Schoub 58; Graham in Nelson *et al* 522.

65 stands for group antigen.

66 stands for envelope.

67 short for polymerase (Schoub (n 11 above) 59 – 60).

68 Klein and Ho 300.

69 Perelson *et al* (1997) *Nature* 188; Klein and Ho 299. RNA viruses lack the 'proofreading' abilities of DNA viruses that enable them to correct mistakes.

70 Holmes (2003) 77 *J Virology* 3893; see also eg Coffin (1995) 267 *Science* 483.

71 Wodarz and Nowak in Domingo *et al* (eds) (1999) 199; Schoub (n 11 above) 65.

72 See para 4.5 below. Also see Meyerhans and Vartanian in Domingo *et al* (n 71 above) 87 – 88; Wodarz and Nowak in Domingo *et al* 199 – 200.

73 Dendritic cells are immune system cells with threadlike tentacles called dendrites used to enmesh antigens, which they present to T-cells. Langerhans cells, found in the skin, and follicular dendritic cells, found in lymphoid tissues, are both types of dendritic cells.

74 Burton and Engelkirk (n 25 above) 424.

- helper T-lymphocytes (they are in fact killed);[77]
- macrophages (the virus merely replicates inside macrophages without harming them);[78]
- dendritic cells; and
- nervous system cells.[79]

On looking at the types of cells that are infected, it becomes evident that HIV infects two systems in the body – the immune system and the nervous system.[80] Sources of HIV in a HIV-infected person are (amongst others):[81]

- semen (contains helper T-cells, macrophages);
- blood (contains T-cells, macrophages, dendritic cells);
- vaginal/cervical secretions (contain helper T-cells, macrophages);
- menstrual fluid (contents the same as blood); and
- breast milk (macrophages).[82]

The incubation period of the virus varies in accordance with various factors, such as the infected person's general state of health and nutrition.[83] If left untreated, about 90 per cent of all infected adults will develop AIDS within ten years to twelve years of infection.[84]

At present, two laboratory tests are used to establish the presence of HIV in the body:[85]

- An ELISA[86] HIV-antibody test.[87]
- Western Blot.[88]

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75 Klein and Ho (n 35 above) 299.
76 Schoub (n 11 above) 81 – 86.
77 which causes a failure of humoral immunity and cell-mediated immunity.
78 Also see Wodarz and Nowak in Domingo *et al* (n 71 above) 198.
79 The specific cells are still unclear.
80 Schoub 82 - 83.
81 Schoub 83; Lecture notes, Prof Robert Dubrow, Yale University School of Medicine.
82 Body fluids that are not sources of HIV include saliva, urine, tears, faeces and perspiration. These contain little or no live cells which makes it virtually impossible for HIV to be transmitted along these routes (Schoub 83).
83 Graham in Nelson *et al* (n 55 above) 524.
84 As above. Antiretrovirals seem to be able to (perhaps indefinitely) delay the onset of AIDS. See para 3.4 below.
85 Graham in Nelson *et al* 524. There are also so-called 'quick-tests' which are often used by public testing centres.
86 ELISA stands for enzyme-linked immunoabsorbent assay. This test detects antibodies based on a reaction that leads to a detectable colour change in the test tube.

An ELISA HIV-antibody test indicates the presence of HIV antibodies in the blood. The ELISA assay is 99.9 per cent accurate, but may at times give a false positive reading.[89]

A Western Blot test is used to confirm a positive ELISA. This test is more specific (as it detects antibodies to specific viral proteins), but also more complicated and therefore more expensive.[90] Tests that estimate the viral RNA load and CD4-count are important measures of the progression of the disease and of the effectiveness of anti-retroviral therapy.[91]

3.2 The natural history of HIV

There are different ways in which to categorise the progression of HIV infection.[92] Graham and Schoub categorise HIV's progress as follows:[93]

- primary infection (acute HIV syndrome);
- asymptomatic silent phase;
- initial symptoms;
- early immune failure; and, finally,
- AIDS or end-stage HIV infection.

3.2.1 Primary infection and acute HIV syndrome

Symptoms of acute HIV syndrome following infection usually appear within a few days to weeks after exposure to the virus, mostly two to four weeks after infection.[94] The symptoms of acute HIV infection last from a few days to a few weeks.[95] These

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87 used routinely.

88 a test detecting antibodies to specific viral components. This test is often used to confirm a positive ELISA, and is more expensive.

89 As it may react to other viral proteins than those belonging to HIV (Graham in Nelson *et al* 524; Schoub (n 11 above) 88 – 89.

90 A positive result on a HIV-antibody ELISA test may also be confirmed by doing two further ELISAs that use different HIV proteins (called a 'triple' ELISA).

91 The test which estimates viral RNA-load is also known as a polymerase chain reaction (PCR) test and measures the amount of HIV in the blood. The CD4-count measures the number of CD4-cells in the blood, which also indicates the progression of the disease.

92 The World Health Organization, for example, categorises the progression of HIV differently from that which is preferred by Graham and Schoub.

93 Graham in Nelson *et al* (n 55 above) 524; Schoub (n 11 above) 88 – 89. Also see Wodarz and Nowak in Domingo *et al* (n 71 above) 179 – 180 and Rouzine and Coffin in Domingo *et al* 225 – 226.

94 Weiss and Weiss in Smith *et al* (n 49 above) 137; Graham in Nelson *et al* 525.

95 As above. Also see Wodarz and Nowak in Domingo *et al* 197 – 198.

symptoms are flu-like[96] (also called 'viremia'), such as fever, rash, headache, generalised lymphadenopathy,[97] pharyngitis,[98] joint pain, weight loss, fatigue, lethargy, depression, night sweats, and various other symptoms.[99] Not everyone experiences all these symptoms, and the intensity of the symptoms varies from person to person.

Acute HIV syndrome occurs in 50 to 70 per cent of infected persons; during this stage of infection, laboratory findings show large quantities of HIV in the blood of the infected person, and also a suppression of helper T-lymphocytes.[100] Most important, seroconversion takes place during this stage: seroconversion is the point in time where a person 'converts' from a situation in which there is no production of HIV antibodies (HIV negative) to the production of HIV antibodies (HIV positive).

3.2.2 Asymptomatic 'silent' phase

During this phase of infection the body's immune system fights off the initial HIV onslaught and the person recovers from acute HIV syndrome.[101] There are now no overt symptoms of disease present and the person feels and appears healthy. There is a very low level of HIV in the blood at this stage (viral RNA load)[102] and this level remains relatively constant. The person's helper T-lymphocytes (CD4 cell) count returns to normal or near normal (600 – 1500 cells per ml of blood).[103]

Although this phase is often referred to as the 'silent' phase, an enormous struggle is being waged between HIV and the immune system.[104] Each day, approximately 100 million HIV particles are produced and are then destroyed by the immune system. Also, approximately two billion helper T-cells are destroyed and replaced.[105] Graham remarks that the main site is in the lymphoid tissue and not in the bloodstream as many lay people suppose.[106]

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96 Rouzine and Coffin in Domingo *et al* 226.
97 swollen lymph glands.
98 a sore throat.
99 Graham in Nelson *et al* 525; Rouzine and Coffin in Domingo *et al* 226; Weiss and Weiss in Smith *et al* 129.
100 Wodarz and Nowak in Domingo *et al* 197.
101 As above.
102 Viral RNA load is an important predictor of the progression of the disease.
103 Graham in Nelson *et al* (n 55 above) 525; Weiss and Weiss in Smith *et al* (n 49 above) 129; Wodarz and Nowak in Domingo *et al* (n 71 above) 198. Rouzine and Coffin in Domingo *et al* are of the opinion that the CD4-count returns only partially to its pre-infection level (226).
104 Weiss and Weiss in Smith *et al* 137.
105 This is 5% of the total helper T-cell population.
106 Graham in Nelson *et al* 525; Wodarz and Nowak in Domingo *et al* 198.

Eventually the immune system becomes exhausted and the viral load increases because HIV infects and damages the very cells that mediate the body's immune response.[107] It attacks and destroys CD4 or helper T-lymphocytes, which play a significant role in both humoral and cell-mediated immunity.[108] As a consequence, the CD4-count decreases.[109]

This phase may last from anything between one to fifteen years, but may be prolonged (perhaps even indefinitely) when triple-antiretroviral therapy is taken.[110]

3.2.3 Initial symptoms

The initial symptoms that an infected person shows during this stage are those of a lymphadenopathy syndrome.[111] Lymph glands in the neck, armpits and groin are enlarged. Wasting syndrome also sets in, and a person experiences weight loss, fever and night sweats. Some instances of neurological disease may also occur during this phase.[112]

3.2.4 Early immune failure

During this phase, because of the virus's gradual destruction of the body's immune system, the infected person suffers from relatively minor opportunistic infections caused by minor microorganisms.[113] These include candidiasis,[114] shingles[115] and hairy leukoplakia.[116]

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107 HIV infects and replicates in lymphocytes and macrophages and so destroys these cells which are crucial to the body's immune response.

108 See para 2.3 above.

109 Graham in Nelson *et al* 525; Wodarz and Nowak in Domingo *et al* 198; Rouzine and Coffin in Domingo *et al* 226.

110 As above. See para 3.4 below.

111 persistently enlarged lymph glands.

112 Graham in Nelson *et al* (n 55 above) 525.

113 As above. Opportunistic infections are infections that do not cause serious disease in persons who have a normal immune system.

114 Graham in Nelson *et al* 525. This is an infection by the *candida* fungus - a harmless infection that is kept in check by a healthy immune system. In HIV positive persons, the fungus causes thrush, esophagitis (it spreads down the esophagus) and vaginal candidiasis. It is treated with Mycostatin which controls the infection but does not eliminate it.

115 Graham in Nelson *et al* 525. This is caused by a reactivation of the varicella zoster virus (which causes chicken pox), which is dormant in the nerve cells. It causes a painful rash on the trunk of the person and can recur.

116 Graham in Nelson *et al* 525; Weiss and Weiss in Smith *et al* (n 49 above) 1138. Hairy leukoplakia is an infection caused by the Epstein Barr virus (mononucleosis

3.2.5 AIDS

Without anti-retroviral therapy, about 90 per cent of HIV infected persons will develop AIDS within ten to twelve years.[117] There is an upsurge in the viral load during this phase.[118] AIDS is a severe, life-threatening syndrome,[119] which represents the late clinical stages of HIV infection.[120] A medical definition of AIDS is that there is a helper T-lymphocyte-count of less than 200 cells per millilitre of blood.[121] This is because HIV has destroyed the HIV-infected person's helper T-cells (immunosuppression).[122] An infected person's immune system can no longer produce antibodies in response to T cell-dependent antigens and, thus, cannot cope with challenges from viruses, bacteria and fungi. People with AIDS die because of a variety of opportunistic infections which are able to take advantage of the weakened immune system. AIDS syndrome includes lymphadenopathy syndrome, wasting syndrome, neurological disease, opportunistic infections and various types of cancers. Major opportunistic infections include pneumocystis carinii pneumonia (PCP),[123] systemic mycosis,[124] cryptosporidium gastro-enteritis[125] and toxoplasmosis.[126] Opportunistic bacterial infections include mycobacterium tuberculosis[127] and mycobacterium avium-intracellulare.[128] Viral diseases include

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virus). It causes white plaques on the surface of the tongue and is not really seen in people other than those infected with HIV.

117 Weiss and Weiss in Smith *et al* 138.

118 Wodarz and Nowak in Domingo *et al* (n 71 above) 198; Rouzine and Coffin in Domingo *et al* 226.

119 AIDS is referred to as a 'syndrome' as it produces a group of symptoms.

120 Graham in Nelson *et al* (n 55 above) 525. Also see Wodarz and Nowak in Domingo *et al* 198 – 216 for a possible explanation of the evolutionary dynamics which are responsible for the transition from the asymptomatic period of the infection to AIDS.

121 As above; Wodarz and Nowak in Domingo *et al* (n 71 above) 198. A healthy, uninfected person has about 1000 CD4 cells per millilitre of blood (Wodarz and Nowak in Domingo *et al* 198).

122 Graham in Nelson *et al* 525.

123 As above. This infection was first identified in 1981 amongst men who have sex with men (MSM).

124 As above. This is caused by common soil fungi and results in devastating systemic infections.

125 Graham in Nelson *et al* 525. This is an infection of the gastro-intestinal tract that is caused by a protozoa. There is no cure for this disease. It causes prolonged, severe diarrhoea and weight loss. It occurs in 5% of AIDS patients.

126 Yet another protozoan disease, and although it can affect many organs, it often affects the brain and causes convulsions, disorientation and dementia. It is effectively treated by antibiotics.

127 Graham in Nelson *et al* 525. This is the most important infection amongst AIDS patients in Africa. It reactivates latent tuberculosis and is often multiple-drug resistant.

128 Causes a tuberculosis-like disease in the lungs.

cytomegalovirus (CVM)[129] and herpes simplex virus.[130] Cancers include Kaposi's sarcoma,[131] B-cell lymphoma[132] and cervical cancer.[133]

Other opportunistic diseases that sometimes are found in AIDS patients are: neurological disease,[134] HIV infection of the nervous system, which causes encephalopathy,[135] myelopathy[136] and peripheral neuropathy.[137] Previously, the diagnosis of HIV infection and AIDS was considered a death sentence,[138] but advances in anti-retroviral therapy have (indefinitely) extended the lives of many people living with HIV.[139]

3.3 An overview of the epidemiology of HIV and AIDS

3.3.1 Introduction

The purpose of this section is to describe the epidemiology of HIV/AIDS. Modes of transmission and risk factors are outlined. Finally, global trends in the epidemiology of HIV and AIDS are discussed, and emphasis is placed on the epidemic in sub-Saharan Africa.

3.3.2 Subtypes

Two subtypes of HIV have been identified, namely HIV I[140] and HIV II.[141] On the whole, the two subtypes have the same modes of transmission.[142] However,

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129 This is caused by a virus of the herpes family and causes severe pneumonia, blindness and gastro-enteritis. Antiviral drugs are used to control this infection.

130 Whereas this virus causes cold sores in persons who have a normal immune system, it causes very severe infections of the skin, mucus membranes and internal organs of AIDS patients.

131 This is the most common cancer associated with AIDS and is a cancer of the blood vessels that is very rare in persons with a normal immune system. It causes pink, purple or brown skin lesions. It is treated quite effectively with chemotherapy.

132 This is, as its name indicates, a cancer of the B-lymphocytes. Although it is treatable, there is no cure. It seems to be caused by the Epstein Barr virus.

133 Graham in Nelson *et al* (n 55 above) 525. This type of cancer is increasing in incidence and is caused by the human papilloma virus.

134 Graham in Nelson *et al* 525. This is caused by direct damage by the HIV virus which infects the nervous system and may cause a tumour in the brain.

135 of the brain – AIDS dementia.

136 of the spinal cord - weakness and paralysis of the lower limbs.

137 of peripheral nerves – loss of sensation and paralysis.

138 Without anti-retroviral treatment, death occurs between eighteen months and two years after onset of AIDS.

139 Graham in Nelson *et al* 525. These are the so-called 'long-term survivors'. See paras 3.4 and 3.5 below for some of the problems encountered in the long-term use of anti-retroviral therapy.

140 Weiss and Weiss in Smith *et al* (n 49 above) 129; Graham in Nelson *et al* 527; identified in 1983 and the more virulent of the two.

whereas HIV I-infection occurs worldwide, HIV II-infection is limited to West Africa and India.[143]

HIV I is subdivided into three groups or 'clades' - group M (major group), group O (outlier group) and N (non-M, non-O) - consisting of at least ten genetic subtypes or clades.[144] The three groups or clades each have a distinct genetic composition, making it possible to distinguish between the different groups. Some clades are found more frequently in certain parts of the world.[145] Recombination between different clades has also been documented.[146] Clade B predominates in industrialised Western countries, whereas clades A, C, D and E predominate in Africa and Asia.[147] In southern Africa, clade C predominates.

3.3.3 Modes of transmission

HIV is regarded as one of the less efficient viruses in its ability to be transmitted from one person to another.[148] For example, whereas the influenza virus is spread through environmental contact and is able to survive outside the host for some time, HIV is not spread through environmental contact and is unable to survive long outside the human body.[149]

HIV transmission varies in efficiency according to various factors such as viral load and route of transmission.[150] Transmission during a blood transfusion occurs in approximately 90 per cent of cases and vertical transmission occurs in approximately 30 per cent of cases.[151] Transmission rates during sexual intercourse vary between approximately 0.5 per cent and 1 per cent per exposure.[152] The rate of transmission

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141 Graham in Nelson *et al* 527; Weiss and Weiss in Smith *et al* 129; identified in 1986, and less virulent. For an interesting discussion on the similarities between HIV II and SIV, see Klein and Ho (n 35 above) 300. It appears that HIV II's genome shows a homology of 70% with SIV, while the genomes of HIV I and HIV II are only 40% similar. Because of the virus's high mutation rate, many biological variants exist, sometimes even within one infected individual (Graham in Nelson *et al* 525). See generally para 2.1 above. The two subtypes vary in their genetic composition.

142 Graham in Nelson *et al* 528 – 531.

143 As above, 528; Klein and Ho (n 35 above) 295.

144 Weiss and Weiss in Smith *et al* 129; Graham in Nelson *et al* 530. See also Van Harmelen and Williamson (2000) 20 *CME* 568 569 – 570.

145 As above.

146 As above.

147 As above.

148 Schoub (n 11 above) 91. Because of the variability of the virus, a relatively large mass of virus is required for successful transmission.

149 See below.

150 See Graham in Nelson *et al* 531 – 536 for more information.

151 As above, 527.

152 As above.

due to an accidental needle-stick injury is as low as approximately 0.3 per cent.[153] The targets for HIV infection and risk factors are discussed briefly below.

For transmission to occur live HIV must survive long enough to pass from an infected to an uninfected person.[154] HIV is very fragile outside the human body as it is quickly inactivated when exposed to air, light, soap and water.[155] Also, when semen or blood dries the infectivity of HIV is lost.[156] Finally, a relatively large mass of virus is required for successful transmission.[157]

HIV is not transmitted through environmental contact[158] and casual contact, such as shaking hands, hugging, living in the same household; sharing a bedroom, bathroom or telephone does not transmit the virus. HIV cannot penetrate intact skin[159] and is not transmitted through respiration.[160] As HIV cannot survive in water, waterborne transmission does not occur. Similarly, as HIV is rapidly inactivated in the stomach, it is not transmitted by ingestion in the gastrointestinal tract.[161] There are no documented cases of HIV transmission through insect bites.[162]

Targets for HIV infection are limited to:[163]

- blood;
- mucosal surfaces such as the vagina, the male urethra and the lining of the anus and the rectum;
- the target of HIV when passing from mother to child during breastfeeding remains unclear, but HIV is understood to pass in the mother's breast milk. Inflammatory conditions such as mastitis cause the presence of plasma-derived components and inflammatory cells in breast milk (such as HIV-1 infected lymphocytes).

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153 As above.

154 Transmission requires direct contact of:
- fluid or secretions containing HIV from an infected person; and
- susceptible cells of another person.

155 Schoub (n 11 above) 91.

156 Graham in Nelson *et al* 536.

157 As above. Several studies have shown that, generally, a high viral load is a risk factor for HIV transmission (see eg Garcia *et al* (1999) 341 *New Engl J Med* 394 and Gray *et al* (2001) 357 *The Lancet* 1149).

158 As above, 536.

159 As above.

160 As HIV is not present in the exhaled breath of the infected person.

161 Schoub 122.

162 As above, 122 - 123. HIV cannot replicate inside an insect as there are no CD4 cells inside an insect. Also, an extremely small amount of blood is transported by the insect and injected.

HIV is transmitted from person to person in the following ways (each is discussed more fully below):[164]

- direct sexual contact;
- sharing of needles and syringes by IDUs which are contaminated by HIV;
- transfusion of contaminated blood and blood products and organ donation;
- trans-placental transfer from mother-to-child;
- breastfeeding by HIV-positive mothers;
- needle-stick injury of health-care workers where needles are contaminated with HIV; and
- any other setting in which an uninfected person is in contact with an infected person's blood or fluids.[165]

a) Direct sexual contact

Sexual intercourse may result in damage or tears to the (mucosal) linings of the vagina or rectum, allowing HIV in semen to pass into the bloodstream of the uninfected person.[166] HIV contained in semen can directly infect the Langerhans cells or macrophages on vaginal or rectal mucosal surfaces.[167] Similarly, HIV in vaginal or cervical secretions can directly infect Langerhans cells or macrophages on the urethral mucosal surfaces or vaginal surfaces.[168]

Vaginal sexual intercourse is the most common mode of HIV transmission worldwide and is the most common mode of transmission in Africa.[169] Trauma to vaginal mucosal surfaces significantly increases the risk of transmission.[170] Male-to-female transmission is two to three times more efficient than female-to-male transmission.[171]

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163 Graham in Nelson *et al* (n 55 above) 531.

164 Graham in Nelson *et al* 531 - 537; see para 3.1 above for sources of HIV in the HIV-infected person.

165 Graham in Nelson *et al* 530.

166 Schoub (n 11 above) 96; Nicklin *et al* (n 2 above) 308.

167 Schoub 94 – 95.

168 As above.

169 Graham in Nelson *et al* 540.

170 As above.

171 Schoub 100. The biological explanation for this is the fact that, during heterosexual sexual intercourse, the vagina receives large volumes of semen which remain in contact with vaginal and cervical mucosa for a relatively long period of time. The penis/urethra has relatively brief contact with vaginal mucosa and retains only a thin film of vaginal or cervical secretions.

The most effective mode of HIV infection is through unprotected receptive anal intercourse.[172] Among men who have sex with men (MSM), a combination of receptive anal intercourse and a high number of sexual partners (who do not wear protection) is the most significant HIV risk factor.[173] The large number of macrophages in rectal mucosa transport HIV to the rich supply of lymphoid tissue in the lining of the rectum.[174] Rectal mucosa is also much thinner and, therefore, more susceptible to damage during sexual intercourse than the vagina.[175]

Oral sex performed on a man carries a very low risk of transmission.[176] There are no documented cases of instances where oral sex performed on a woman and wet kissing have transmitted the virus.[177]

Risk factors of a clinical nature for sexual transmission of the virus include:[178]

- unprotected sex;
- multiple sexual partners engaging in unprotected sex (of course, multiple sexual partners are not a risk factor *per se*, as long as protection is used during each sexual encounter);[179]
- high viral load in the infected partner;[180]
- sex during menstruation;[181]
- practices that cause trauma to the lining of the vagina or rectum, such as 'fisting';[182]
- the presence of other sexually-transmitted diseases at the time of sexual intercourse; [183]
- chronic, generalised infections at the time of sexual intercourse;[184]
- absence of male circumcision;[185] and

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172 Graham in Nelson *et al* 531; Schoub 96.
173 As above.
174 Schoub 96.
175 Graham in Nelson *et al* 531 – 532; Schoub 96.
176 Schoub 100 – 101.
177 As above. Sexual behaviour that carries no risk is dry kissing and mutual masturbation (as long as semen does not come into contact with broken skin). Also, the infection rate for women who have sex with women (WSW) is extremely low.
178 Graham in Nelson *et al* 532; Schoub 100 – 110.
179 Schoub 102.
180 As there is more viral material in the blood, there is a greater chance of the virus being transmitted to another person.
181 Schoub (n 11 above) 107 – 108.
182 As above, 97.
183 Such as genital ulcers.
184 Particularly TB. These are associated with a chronic activation of the lymphocytes, and also immunosuppression, which may enhance susceptibility.

- oral contraceptive and IUDs.[186]

b) Sharing of contaminated needles by injection drug users (IDUs)

In some countries, injection drug use (IDU) is responsible for more instances of HIV transmission than is sexual intercourse.[187] IDUs often share needles, syringes and other drug paraphernalia,[188] all of which are risk factors for the transmission of HIV.[189] Many IDUs also engage in risky sexual behaviours[190] and the drugs themselves are often immunosuppressive and therefore enhance the dug-user's susceptibility to infection.[191]

Prevention programmes among IDUs include needle or syringe exchange programmes, the non-prescription availability of needles and syringes in pharmacies and education programmes that encourage the use of bleach solutions to wash out syringes between use, if they are shared.[192]

c) Transfusion of contaminated blood, blood products and organ donation[193]

This mode of transmission is very infrequent in most developed countries because of thorough screening methods.[194] Also, clotting factor and other blood products are routinely subjected to heat treatment to inactivate HIV.[195]

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185 Schoub 107. Several studies have indicated that male circumcision decreases the risk of HIV transmission - see eg Quinn (2007) 20 *Current Opinion in Infectious Diseases* 38 – 38; Weiss (2007) 20 *Current Opinion in Infectious Diseases* 66 – 72; Roehr (2007) 334 *British Med J* 11.

186 As above. IUDs increase the woman's risk of infection, especially chlamydia. Mechanism of oral contraceptives not clear – may cause immunosuppression.

187 Such as Russia and Thailand.

188 The 'cooker' (equipment used to prepare the drugs) may be contaminated with HIV infected blood. During 'booting' – drawing a small amount of blood back into the syringe before injection – HIV can be transmitted to others who use the same syringe or needle. 'Shooting galleries', 'frontloading', 'backloading' and 'skinpopping' are other high risk practices associated with IDU (for more information, see Graham in Nelson *et al* (n 55 above) 532 – 533).

189 Graham in Nelson *et al* 533. HIV antibody testing of all donated blood, increased sensitivity of antibody tests, and other methods such as thorough screening of prospective donors on risk behaviour, contribute to lowering the chance of HIV-infected blood entering the blood supply.

190 Graham in Nelson *et al* 533.

191 Schoub 113.

192 Of course, programmes that treat drug addiction are very successful in preventing HIV transmission along this route.

193 The acquisition of HIV infection through blood donation has always been regarded sympathetically by the general public. Such infections are seen as 'innocent', whereas sexual transmission is considered less than innocent. Consider also the tendency to call HIV-positive children the 'innocent victims' of HIV. This tendency

The greatest potential risk for acquiring HIV infection through contaminated blood or blood products is at the time when the donor is in the 'window period', during which HIV-infected blood tests false-negative. This risk could be alleviated if use is made of repeat donors and through more sensitive screening tests.[196] The transfusion of contaminated blood and blood products is considered by some scientists to have been a major cause in establishing the epidemic in Africa.[197]

d) Transfer from mother-to-child (MTCT)[198]

HIV may be transmitted vertically to the foetus in utero, intra-partum (during delivery), or post-partum (by way of breastfeeding)[199] from a mother to a foetus or infant.[200] The risk of MTCT ranges from 13 per cent in Europe to 30 per cent in Africa, in accordance with the mode of transmission.[201] Vertical transmission is one of the most important routes of transmission of HIV in sub-Saharan Africa.[202]

Intrauterine or trans-placental infection takes place when the placenta is infected and infection spreads to the foetus.[203] Intra-partum infection takes place[204] when the baby passes through the birth canal and, therefore, is exposed to the mother's vaginal and cervical secretions. The virus is transmitted through intact mucosa or that which has been damaged because of abrasions and lacerations which often occur during birth. Postpartum infection occurs during breastfeeding.[205]

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reveals an element of hypocrisy, especially as such sentiment was rife in the late 1980s in South Africa when HIV infection was considered a 'gay disease'.

194 Graham in Nelson *et al* 534.

195 As above.

196 In the USA, the FDA recommended already in August 1995 that all blood and plasma donations be screened for p24 antigen that can detect HIV infection earlier than the routine ELISA antibody test. This test is also used in South Africa.

197 Opinion is divided on the role of contaminated blood and blood products in the transmission of the disease in Africa (also called 'parenteral transmission'). In this regard, see eg Gisselquist *et al* (2002) 13 *Intl J STD & AIDS* 657 and Walker *et al* (2003) 442 *Nature* 679.

198 Also known as perinatal, vertical transmission or MTCT.

199 Discussed in e) below.

200 Nicklin *et al* (n 2 above) 308; Graham in Nelson *et al* (n 55 above) 533; Schoub (n 11 above) 119.

201 Graham in Nelson *et al* 534; Schoub 119 – 120. This difference may be ascribed to differences in obstetric and breast-feeding practices, inherent factors in the study population and variances in the virulence of different strains of the virus.

202 When selected Caesarean section was combined with the administration of zidovudine (AZT) during the antepartum, intrapartum and neonatal periods, HIV transmission was reduced by about 85%.

203 Schoub 119. Estimated to amount to 23% of cases of MTCT.

204 Estimated to account for 65% of cases of MTCT.

205 Accounting for 12% of cases.

Risk factors for vertical transmission include:[206]

- most significantly, a high viral load in the mother at the time of giving birth or during pregnancy;
- if the mother suffers from sexually-transmitted infections at the time of giving birth or during pregnancy;
- prolonged rupture of the membranes (more than 4 hours prior to delivery);
- invasive obstetric procedures[207] during vaginal labour and delivery that causes tears / lacerations and increases bleeding;
- a premature infant; and
- breastfeeding, particularly if the mother has mastitis or breast abscesses.

Ways in which vertical transmission of HIV may be prevented include:[208]

- elective termination of pregnancy;[209]
- treatment for maternal sexually transmitted infections;
- zidovudine (AZT)[210] treatment

  given to the mother from the fourteenth week of pregnancy through to delivery

  given to the newborn for the first six weeks

  short courses of AZT (from 36 weeks through to delivery) have also been shown to be effective[211]
- short course treatment with Nevirapine[212] where a single dose is given in active labour and a single dose is given to the infant;
- caesarean section delivery before labour and before rupture of the membranes; and
- avoidance of invasive obstetric procedures during vaginal labour and delivery.

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206 Graham in Nelson *et al* 533 – 534.

207 For example, episiotomies.

208 Graham in Nelson *et al* (n 55 above) 533 – 534.

209 Of course this is not really a solution to the underlying problem.

210 In ACTG Protocol 076 (see ch 3), the ARV Zidovudine administered to a selected group of HIV infected women during pregnancy, labour and delivery and to their newborn infants, was shown to reduce the risk of perinatal HIV transmission by two thirds, compared to those mothers who received the placebo. In this regard see Connor *et al* (1994) 331 *New Engl J Med* 1173.

211 As above.

212 a protease inhibitor.

HIV positive mothers who breastfeed can pass on the virus to their babies.[213] Many of the breast-feeding infections may be due to the presence of the mother's blood in the milk because of cracked or injured nipples.[214] HIV transmission through breast-feeding remains an issue in developing countries, such as those in Africa, where poverty, lack of clean water and social prejudice prevent the use of formula feed.

e) Needle-stick injuries of health care workers[215]

The risk of contracting HIV from a deep, penetrating injury with a contaminated needle is about one in 300.[216] Needle-stick injuries represent a far greater risk than that of intact skin or membrane exposure to HIV infected blood.[217] Most health care workers today follow universal precautions, whereby all patients are treated as if they are HIV positive.[218]

3.3.4 The evolution of the epidemic

The HIV epidemic is understood to evolve with the initial infection of a core group, such as MSM, IDUs or sex workers, and spreads from that group to the general population. It is theorised by some that in South Africa the epidemic evolved from an initial (limited) epidemic among MSM and sex workers in the eighties, to the present (large-scale) epidemic of the entire population.[219]

International organisations, such as the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organisation (WHO), co-operate with local governments, networks of AIDS researchers and national AIDS programmes around the world to gather data which enables them to track and estimate the spread of HIV infection. Serosurveillance of so-called sentinel groups,[220] in which HIV antibody

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213 Schoub (n 11 above) 119.

214 As above.

215 The potential threat of HIV to health care workers has assumed 'panic proportions' (Schoub 113) and has caused much unfair discrimination against PLWHIV.

216 Schoub 114. Or about 0.3 %.

217 Graham in Nelson *et al* (n 55 above) 535; Schoub 113.

218 For an extensive discussion of this mode of transmission, see Schoub 113 – 115.

219 See Nelson in Nelson *et al* (eds) (2000) 97 and Schoub 116. This is not necessarily the correct view.

220 Groups who are thought to represent the spectrum of risk activities in a population. Sentinel groups are usually blood donors, pregnant women attending antenatal clinics, members of national armed forces, tuberculosis patients, persons who attend sexually transmitted disease clinics, sex workers, IDUs and MSMs (the last group is regarded as a sentinel group in areas where HIV is transmitted mainly along that route).

tests are performed on representative samples of each of these groups, enables bio-statisticians to track and monitor the epidemic.[221]

There exist two measures of the occurrence of HIV – HIV prevalence and HIV incidence. *HIV prevalence* refers to the proportion of persons in a specified population who are infected with HIV at a specified point in time.[222] *HIV incidence* refers to the proportion of persons in a specified population who are HIV negative who become newly infected with HIV over a specified period of time.[223]

As was pointed out in chapter 1, at the end of 2006 a total of 39.5 million people were estimated to be living with HIV/AIDS worldwide, of whom 37.2 million were adults, (17.7 million of whom were women) and 3.2 million were children under the age of fifteen.[224] Sub-Saharan Africa is the region hardest hit by the epidemic, and within sub-Saharan Africa, Southern Africa is the worst off - one third or 32 per cent of all PLWHIV live in southern Africa and 34 per cent all AIDS deaths in 2006 occurred in Southern Africa.[225]

The following table outlines the prevalence of HIV infection among the adult population of the world (ages 15 – 49):[226]

Sub-Saharan Africa	5.9%
North Africa and Middle East	0.2%
South and Southeast Asia	0.6%
East Asia	0.1%
Oceania	0.4%
Latin America	0.5%
Caribbean	1.2%
Eastern Europe and Central Asia	0.9%
Western Europe and Central Europe	0.3%
North America	0.8%
TOTAL	**1.0%**

The following table outlines the chief modes of HIV transmission worldwide:[227]

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221 Nelson in Nelson *et al* (n 219 above) 97.
222 As above.
223 As above.
224 UNAIDS (2006) *AIDS epidemic update* 1. See para 1 of ch 1 above.
225 As above, 3.
226 As above, 2.
227 As above, 5.

Sub-Saharan Africa	Hetero
North Africa and Middle East	Hetero, IDU
South and Southeast Asia	Hetero, IDU
East Asia and the Pacific	IDU, hetero, MSM
Latin America	MSM, IDU, hetero
Caribbean	Hetero, MSM
Eastern Europe and Central Asia	IDU
Western Europe	MSM, IDU
North America	MSM, IDU, hetero
Australia and New Zealand	MSM

The following table outlines the prevalence of HIV infection among adults in West and Central Africa in 2005:[228]

Senegal	0.9%
Mali	1.7%
Cameroon	5.4%
Central African Republic	10.7%
Cote d'Ivoire	7.1%
Nigeria	3.0%
Democratic Republic of the Congo	3.2%

The following table outlines the prevalence of HIV infection among adults in East Africa:[229]

Kenya	6.1%
Tanzania[230]	7.8%
Somalia	0.9%
Ethiopia	360 000 – 1 100 000
Uganda	6.7%

228 UNAIDS (2006) *Report on the global AIDS epidemic* 506. Only a few countries were included in the table.

229 As above.

230 Figure that of 2002. Not updated in 2005 report.

Finally, the following table outlines the prevalence of HIV infection among adults in Southern Africa:[231]

Botswana	24.1%
Lesotho	23.2%
Swaziland	33.4%
Mozambique	16.1%
Zimbabwe	20.1%
Namibia	19.6%
Malawi	14.1%
South Africa	18.8%

It is clear from the tables above that Southern Africa has the highest rate of HIV prevalence in Africa, and the world. If we combine this high prevalence rate with the fact that Southern African countries, generally, cannot afford expensive anti-retroviral (ARV) drugs, the picture for Southern Africans looks very bleak indeed, and the need for a preventive HIV vaccine becomes both urgent and self-evident.[232]

In the following pages, developments in the treatment of the disease will be examined.

3.4 Developments in the treatment of the infection

At present no drug exists that is able to eliminate HIV infection from the body, nor is there any drug that may indefinitely prevent the eventual onset of AIDS.[233]

At present, HIV/AIDS therapy consists of three major strategies. [234]

- Treatment of opportunistic infections.[235]
- Treatment of HIV-related cancers.
- ARV therapy.

Although there are many drugs which treat bacterial infections, relatively few drugs treat viral infections.[236] ARV drugs are designed to interfere with the viral replication cycle.[237] There are four classes of ARV drugs available:[238]

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231 As above.
232 See paras 3.5 and 4 below.
233 Schoub (n 11 above) 181.
234 Schoub 159.
235 As above.

- Nucleoside analogues or nucleotide reverse transcription inhibitors.
- Non-nucleoside reverse transcriptase inhibitors.
- Protease inhibitors.
- Fusion or entry inhibitors.

Each of these is discussed below.

3.4.1 Nucleoside analogs

AZT (Zidovudine) was the first drug to demonstrate a marked benefit in the treatment of AIDS patients.[239] AZT is incorporated into viral DNA by reverse transcriptase and terminates further viral DNA synthesis and viral replication;[240] upon initiating AZT therapy, the viral load drops ten to 100-fold. However, within a year the viral load returns to its original level as HIV becomes AZT-resistant due to the natural selection of AZT-resistant HIV-variants.[241] AZT is, thus, no longer the sole anti-retroviral drug given to HIV positive persons.[242] Other nucleoside analogs[243] include dideoxycytodine,[244] 3T3[245] and D4T.[246]

3.4.2 Non-nucleoside reverse transcriptase inhibitors (NRTIs)

These are drugs such as nevirapine (Viramune) and delavirdine (Rescriptor). As their name indicates, these drugs are aimed at interfering with HIV's reverse transcription enzyme.[247] After starting on a course of medication, most patients show an initial 1 000 to 10 000-fold decrease in viral load. However, once again

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236 Schoub 154. Antivirals that do exist are mainly those that treat infection by the herpes virus.

237 Schoub 157.

238 Schoub 157; Cloete and Atlas (n 2 above) 22.

239 Weiss and Weiss in Smith *et al* (n 49 above) 141; Rick (n 18 above) 33; Schoub 157; Cloete and Atlas 22; manufactured by GlaxoSmithKline.

240 Weiss and Weiss in Smith *et al* 141; the main toxic effects of AZT are anaemia and low white cell counts.

241 Weiss and Weiss in Smith *et al* 142; Wodarz and Nowak in Domingo *et al* (n 71 above) 214. In mono-therapy, HIV resistant to the drug may emerge within weeks.

242 Of course, with the exception of HIV positive pregnant women among whom AZT lowers the risk of transmission by 70%.

243 PLWV who are resistant to AZT are often not resistant to these.

244 ddC or zalcitabine.

245 Commercially known as Lamivudine.

246 Stavudine. For an extensive discussion of AZT therapy, see Schoub 181.

247 See para 3.1 above. HIV consists of a RNA genome. Inside the infected cell, reverse transcriptase produces a DNA copy of HIV's RNA genome. The virus then uses this DNA copy to replicate inside the invaded cell, producing a DNA provirus that gets

resistant HIV-variants are quickly selected. A single dose of nevirapine has been shown to be effective in reducing mother-to-child transmission of HIV. This fact is of great importance in the developing world.[248]

3.4.3 Protease inhibitors

These drugs inhibit the conversion of immature viral particles into mature viruses.[249] Protease inhibitors include saquinavir (Invirase), indinavir (Crixivan), ritonavir (Norvir) and nelfinavir (Viracept).[250] There is often an initial 1 000 to 10 000-fold decrease in the viral load. Once again resistant HIV-variants are quickly selected.[251]

3.4.4 Fusion or entry inhibitors

Fusion or entry inhibitors, as their name suggests, block the entry of the virus to a host cell.[252]

Because of drug resistance, triple combination therapy[253] has been introduced.[254] HAART[255] is such a triple therapy. HIV often mutates to a variant that is resistant to one drug, but it is less likely that it is able to mutate to a variant that is resistant to two drugs and even less to mutate to a drug that is resistant to three drugs.[256] The most effective combination has been found to be two nucleoside analogs and one protease inhibitor.[257]

Upon being administered HAART, the viral load in the blood of the majority of patients drops below detectable levels and stays at these levels for several years.[258] Even CD4-counts recover and AIDS symptoms and opportunistic infections disappear. When the viral load starts to increase again a new combination of drugs is used.

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inserted into the chromosomal DNA of the host cell. A drug that interferes with this enzyme, therefore, makes it impossible for the virus to replicate.

248 See ch 3 below.

249 They are also known as peptide mimics (Weiss and Weiss in Smith *et al* 314).

250 As above.

251 Wodarz and Nowak in Domingo *et al* 214. Variants resistant to one protease inhibitor are often also resistant to another protease inhibitor.

252 Cloete and Atlas (n 2 above) 22.

253 Also known as AIDS drug cocktails.

254 Wodarz and Nowak in Domingo *et al* (n 71 above) 214 – 215.

255 HAART stands for 'highly active anti-retroviral therapy'.

256 Wodarz and Nowak in Domingo *et al* 214; Rouzine and Coffin in Domingo *et al* 228. Often virus load stays below detectable levels for 2 – 3 years, or longer.

257 As above. Combivir is such a combination therapy.

258 Rouzine and Coffin in Domingo *et al* 226.

However, there are a number of uncertainties and limitations connected to HAART. HAART is not effective in all patients.[259] Also, the extent of the effectiveness is still unclear. HAART was introduced in 1996 and, seven years later, HIV-variants resistant to triple combination are appearing.[260]

There are many drawbacks to HAART. First, life-long therapy is needed.[261] Many patients find the side effects too severe to tolerate such long-term use.[262] It is difficult also to maintain complicated treatment schedules.[263] Strict treatment adherence is critical in preventing the development of drug-resistant variants.[264]

3.5 The need for an effective vaccine

In South Africa, particularly, government seems to lack political will in taking steps to combat the spread of the disease.[265] Because, on the whole, those who are infected tend to belong to a poorer socio-economic sector, they appear 'invisible' to those in power and, so far, the South African government has demonstrated a lack of clear leadership in their response to AIDS.[266]

Current options for the treatment of HIV infection have had limited success. The cost of caring for PLWV remains high, despite the efforts in South Africa of NGOs, such as the TAC, which have increased access to antiretrovirals.[267] As well, in

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259 It seems to be less effective in cases where the patient previously had mono-therapy such as AZT (in which case the patient is only really getting double therapy, not triple therapy).

260 Personal communication, Prof Robert Dubois, Yale University School of Medicine.

261 Weiss and Weiss in Smith *et al* (n 49 above) 317. This therapy is thus obviously not easily affordable in poorer countries, such as those in sub-Saharan Africa.

262 Weiss and Weiss in Smith *et al* 317.

263 In which the patient may have to take as many as 25 pills per day at very precise intervals. Also, there are special requirements connected to the administration of some of the drugs – Indinavir, for example, has to be taken on an empty stomach.

264 Weiss and Weiss in Smith *et al* 316.

265 For instance, the lack of political will in the provision of anti-retroviral therapy. See *MEC for Health, KwaZulu-Natal v Premier, KwaZulu-Natal: In re Minister of Health and Others v Treatment Action Campaign and Others* 2002 (5) SA 717 (CC), 2002 10 BCLR 1033 (CC). See also para 2.3.2 of ch 5 below.

266 See para 2.3.2 of ch 5 below.

267 In *MEC for Health, KwaZulu-Natal v Premier, KwaZulu-Natal: In re Minister of Health and Others v Treatment Action Campaign and Others* (n 265 above), the Constitutional Court found that in not providing Nevirapine in all public health facilities the state had not met its constitutional obligations. The Constitutional Court ordered that to do so, it should remove the restrictions preventing Nevirapine from being made available at public hospitals and clinics that are not research and training sites. It found that there was no reason why the state could not continue to collect data and closely monitor the use of Nevirapine at its chosen pilot sites. The Court stated that this should not prevent the state from providing the drug at other birthing institutions where facilities exist for doing so. The state was also ordered to take

public health care facilities, where antiretrovirals are made available to the public free of charge, PLWV have to meet certain criteria before they become eligible for treatment.[268]

The development of HAART has indefinitely prolonged the lives of countless PLWV, but this therapy is sometimes costly and difficult to administer. Further, new studies indicate that triple-therapy-resistant variants of the virus are developing.[269]

Current ARV therapies are in many instances toxic.[270] Because of this a viable alternative is urgently needed. Similarly, alternative methods for preventing the spread of the disease have met with only limited success. Although safe-sex-public awareness programmes and educational campaigns seem to have worked in some settings,[271] in others they have failed miserably as they neglect to address the underlying socio-economic and cultural issues responsible for the spread of the pandemic.[272]

Among the strategies being investigated to combat infection with HIV, are anti-HIV microbicides, male circumcision and pre-exposure prophylaxes.[273]

A number of microbicides against HIV are currently in Phase II and III clinical trials.[274] Microbicides, in the form of a cream or gel, are chemical products applied to the vagina.[275] An effective microbicide has advantages over male condoms, such as that it can be applied privately, and is in the control of the female sexual partner.[276] As yet, microbicides do not confer lasting protection, and it is assumed

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reasonable measures to extend testing and counselling throughout the public health sector to facilitate the use of Nevirapine.
Donor-funding and other strategies (such as the parallel importation of ARVs) have further lowered the cost of ARVs.

268 Such as a CD4-count of <200 cells per mm^3 irrespective of stage of illness; or WHO Stage 4 AIDS defining illness irrespective of CD4-count, AND patient expresses willingness to adhere to ART regimen (in the case of adults) (Department of Health (2006) 'ART Guidelines' 1 – 2).
In the private sector, one month's supply of the HAART drug Combivir costs R483.00, and Stocrin costs R198.00 (quote by Pharmavalu, Newlands, Pretoria, on file with author). The total cost of HAART in the private sector is therefore about R750.00 per month (which includes a dispensing fee).

269 Schoub (n 11 above) 182.

270 Weiss and Weiss in Smith *et al* (n 49 above) 145.

271 such as Uganda.

272 See ch 5 below, para 2.3.2.

273 And, of course, vaccines. See below.

274 Five are in large-scale trials, another 14 are in safety trials; see Ramjee (2006) 'Microbicides and other prevention technologies' Paper delivered at the XVI International HIV/AIDS Conference, Toronto, Canada, 13 -18 August 2006.

275 Early studies are also being undertaken on efficacy in rectal application (Ramjee 3).

276 See Ramjee (n 274 above) 4.

that a microbicide will need frequent re-applications.[277] In any case, it is not expected that microbicides confer total protection.

Results of previous studies have caused scientists to hypothesise that male circumcision may lower the HIV-infection rate among men.[278] This hypothesis was confirmed by a recent study which showed that male circumcision lowers the infection rate by up to 60 per cent.[279] Although a significant reduction in risk may potentially slow down the progress of the epidemic, circumcision cannot be considered a panacea: it (partly) protects only half of the population (men) and there are religious and cultural objections. More importantly, focussing on circumcision as a preventive strategy will erode the critical message that unprotected sex carries the greatest risk of infection – circumcision, therefore, could be counter-productive in fighting the epidemic: AIDS activists have floated the possibility that by causing people to relax their vigilance, and abandon the use of condoms, male circumcision will allow the disease to spread as rapidly as before.

Various clinical trials are investigating the efficacy of pre-exposure prophylaxes. These drugs (usually antivirals such as Tenofovir) need to be taken regularly, as often as once a day. The scientific and ethical problems associated with using pre-exposure prophylaxes as preventive means include monitoring the adverse effects[280] of the drugs and the implications arising out of the prescription of chronic medication for people in good health.[281]

Given the number of people globally who are infected with HIV, the absence of an effective, low-cost, non-toxic and long-term-efficacious treatment, the lack of hope for the development of a cure, the lack of effective prevention strategies and the prevalence of HIV among economically and socially powerless groups, it is absolutely critical that an effective preventive vaccine is developed. Because vaccines are generally safe, effective and inexpensive ways to prevent disease,[282] the development of an effective vaccine is currently our only hope to halt the spread of the epidemic.

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277 One method currently being developed is a vaginal ring containing microbicides. If successful, this method is expected to provide protection for up to 30 days at a time (Ramjee 9).

278 Quinn (n 185 above) 38 – 38; Weiss (n 185 above) 66 – 72; Roehr (n 185 above) 11. See para 4.2.2 (d) of ch 3 below.

279 Auvert *et al* (2005) 2 *PLos Med* e298.

280 See Ramjee (n 274 above) 17; some antiviral drugs, such as Tenofovir, have serious adverse effects (Ramjee 18).

281 See Ramjee 18.

282 Schoub (n 11 above) 183.

4 THE SEARCH FOR A VACCINE

4.1 Introduction

As indicated above, efforts to slow the spread of HIV have had limited success, and, therefore, it is not surprising that, lately, so much attention has been focussed on the development of an effective preventive vaccine for HIV.

Vaccines are powerful in the control and eradication of infectious disease. Smallpox was finally eradicated on 26 October 1977 because of a vaccine based on the vaccine first used by Edward Jenner in the 18th century.[283] Similarly, poliomyelitis, a devastating viral infection, is today close to eradication because of the use of a highly effective preventive vaccine.[284]

In the following pages, vaccine development will be placed in its historical context, types of vaccines will be discussed, challenges posed by the quest for an effective vaccine against HIV will be considered, and, finally, avenues of hope for the development of an effective vaccine against HIV will be explored.

4.2 A brief history of vaccine science

The beginning of the medical science of immunology is attributed to Emil Behring and Kitasato Shibasaburo who, in 1890, discovered antibodies.[285] However, as early as 1000 years before, a form of vaccination against smallpox was being practiced in Turkey, Greece, China and India.[286]

The first paper on inoculation was read by Dr Clopton Havers to the Royal Society of physicians in 1701.[287] He received a lukewarm response from the Society as little was known about the practice in the West.[288]

Almost twenty years later, during a time when smallpox was one of the most feared diseases in Europe, Lady Mary Wortley Montagu, who learned about the technique of inoculation while in Turkey, elicited the help of Charles Maitland in inoculating her daughter against smallpox in England.[289]

In 1721, Maitland carried out the first 'clinical trial' on inoculation. Six condemned prisoners were inoculated against smallpox on the understanding that

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283 As above, 182; Nicklin *et al* (n 2 above) 317. On 26 October 1977, a Somalian, Ali Maow Maalin, became the last person to be infected with wild smallpox.

284 Schoub 182.

285 Editorial (2000) 342 *New Engl J Med* 42 - 44.

286 As above. See also Mann (1999) 83.

287 As above, 84. Surely an unfair inducement to participation in a clinical trial. Medical and research ethics were at the time still in their infancy.

288 Mann (n 286 above) 83 – 84.

they would be given a reprieve if they agreed to the inoculation. The trial was successful and inoculation was practiced widely in England and Wales for the next fifty years, but not without casualties.[290]

In 1796, Edward Jenner, an English physician, made his contribution to the science of vaccination by discovering that cowpox lent immunity against smallpox, a discovery which would eventually lead to the eradication of smallpox.[291] Jenner observed that milkmaids who had previously been infected with cowpox, a very mild disease, seemed immune to smallpox. He started using fluid from cowpox lesions to vaccinate[292] against smallpox.[293] Around this time, the term 'vaccination' started being used by another English physician, called Dunning, to describe inoculation with cowpox. Soon vaccination became widely accepted, and vaccines for measles, poliomyelitis, rabies and anthrax were later developed as more was learned about the body's immune response.[294]

In 1881, Louis Pasteur, Emile Roux and Charles Chaimberland publicly immunised sheep, cows and a goat against anthrax and, in 1886, Richard Pfeiffer and Almoth Wright independently prepared heat-inactivated vaccines against typhoid.[295]

The next important milestone in the science of vaccination came in 1891 when passive immunisation against pneumococcal pneumonia was introduced by Georg Klemperer. Although his efforts were probably dangerous and ineffective, he was the first scientist to realise the importance of antibodies in immunity.[296]

In 1921, Camille Calmette and Alphonse Guerin administered an attenuated bacterial vaccine against tuberculosis to a newborn baby and, in 1955, salk-inactivated poliomyelitis vaccine proved effective.[297] In 1971, a live (attenuated) vaccine for measles, rubella and mumps was registered in the USA.

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289 As above.

290 As above, 84.

291 n 285 above, 45; Nicklin *et al* (n 2 above) 318; Mackett and Williamson (n 13 above) 5.

292 In this thesis, the terms 'vaccination', 'immunisation' and 'inoculation' are used interchangeably. See para 4.3 below for a definition of 'vaccination'.

293 As above; Cohen (1999) 7 *British Med J* 443; Mackett and Williamson 5.

294 Mann (n 286 above) 88. However, for a discussion of initial public resistance in England against compulsory vaccination programmes, see Mann 90 – 91.

295 Cohen (n 293 above) 443; Mackett and Williamson (n 13 above) 7.

296 n 285 above, 45.

297 The salk-inactivated vaccine was named for its discoverer, Peter Salk; Mackett and Williamson 5; see also Mann 95.

The first vaccine produced by DNA technology is the hepatitis B surface antigen vaccine. Instead of using proteins and polysaccharides this vaccine is based on sequences of DNA that encode microbial antigens that are injected.[298] This vaccine was licensed in 1981.[299] 1991 saw the first trial for DNA vaccines[300] for HIV.[301]

Another recent development in vaccine science is the use of engineered living carriers in the production of vaccines. Portions of the gene coding for the immunogenic protein of the virulent virus are inserted into relatively harmless 'carrier' organisms, such as the cold sore virus or salmonella typhimurium. In this way, a relatively harmless virus is used to introduce the immune system to the virus that is being vaccinated against.[302]

Technological advances have also brought the hope that, in the near future, vaccines will be developed to treat diseases such as diabetes, cancer and multiple sclerosis.[303]

4.3 A definition of vaccination

Vaccination is the artificial introduction of a viral antigen[304] in a modified form into the body in order to induce an immune response.[305] This viral antigen 'primes' the body's immune system not only to recognise the real virus when it is challenged by that specific virus, but also to destroy it. Because the immune system responds to the viral antigen, it is not necessary to introduce the entire virus to the body for immunity to be acquired. [306] Vaccines mimic the organism against which they protect, but they are not so much like that organism that they will cause the specific disease.[307]

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298 Cohen 445.

299 n 285 above, 44.

300 A DNA vaccine functions by directly injecting a gene or genes coding for a specific antigenic protein, resulting in direct production of such antigen(s) within the vaccine recipient in order to trigger an immune response. See para 4.4 below.

301 n 285.

302 Mann (n 286 above) 98.

303 Wilson (2003) 138 *Annals Internal Med* 857.

304 Nicklin *et al* (n 2 above) 317 - 318. An antigen is any substance that stimulates the immune system to produce antibodies. Antigens are foreign substances, such as invading bacteria or viruses, or sections of these substances. Also called an immunogen.

305 Rick (n 18 above) 77; Schoub (n 11 above) 184; Delves and Riott (n 21 above) 42.

306 Schoub 184.

307 Vaccine development therefore focuses on means to reduce the virulence factor of the virus while retaining the immunity stimulation (Rick (n 18 above) 78). Also see Schoub 184.

Vaccines are aimed either at causing sterilising immunity or, if that cannot be achieved, at controlling the infection.[308] Sterilising immunity protects so effectively against the pathogen that it completely prevents the host from being infected. In other words, all signs of the invading organism are cleared from the body.[309] This type of immunity is rarely achieved by vaccination.[310]

Vaccines that control infection are much more common. In this case, infection takes place, usually at the site of the pathogen's entry into the body, but before symptoms develop is quickly aborted by the immune response induced by the vaccine.[311]

When one thinks of vaccination one usually thinks of preventive vaccination. It is important to remember, however, that although vaccines, on the whole, are designed to prevent infection or disease (preventive vaccines), another class of vaccines exists, namely, for the *treatment* of disease (therapeutic vaccines).[312] As this thesis is concerned exclusively with the development of a preventive vaccine for HIV, therapeutic vaccines are not discussed.[313]

Today very effective immunisation programmes exist around the world; some have lead to the total eradication of the disease.[314] These programmes target, traditionally, childhood-onset diseases, such as measles, mumps, whooping cough and rubella; diseases that are mostly associated with teenagers and young adults, such as meningitis; and others, such as typhoid fever, Hepatitis A, B and C, anthrax, yellow fever, poliomyelitis and rabies.[315]

Vaccination to control pathogenic infections may be aimed either at protecting the individual against infection and disease[316] or at protecting the

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308 Schoub (2002) 20 *CME* 561; Van Harmelen and Williamson (n 144 above) 569.

309 As above.

310 As above.

311 As above.

312 Schoub (n 308 above) 561. One such vaccine, Remune, produced by the Trinity Medical Group, has been proven effective in maintaining key clinical markers in HIV+ trial participants one year after HAART was stopped ('Trinity announces Remune study results' *AIDS Weekly* 7 October 2002 21). For a comprehensive review of HIV-1 therapeutic vaccines, see Kinloch-de Loes and Autran (2002) 44 *J Infection* 152 – 159.

313 At present the search for a preventive vaccine enjoys higher priority than the search for a therapeutic vaccine. For information on the development of therapeutic vaccines, and the distinction between therapeutic vaccines and preventive vaccines, see Klein (2003) 21 *Vaccine* 616 – 619 and Schoub (n 308 above) 561.

314 Such the smallpox vaccine, see above.

315 Ada (2001) 345 *New Engl J Med* 1042 - 1044. This list is not exhaustive.

316 Such as vaccination of individuals who travel to certain areas, eg, yellow fever vaccination.

community as a whole by drastically reducing or eradicating the infection from the community.[317] In countries where wide-scale childhood immunisation programmes exist, population or 'herd immunity' is achieved.[318] The term 'herd immunity' refers to the protection of an entire community or population against a disease although only a portion of that population is vaccinated and, therefore, immune.[319] As a proportion of the 'herd' is immune, there are fewer infections and, thus, less chance of exposure for the unvaccinated individual.[320]

The effectiveness of a vaccine programme in controlling and eradicating disease depends on these factors.

- The infection must be limited to humans, leaving no animal reservoir to re-infect humans.[321]
- In the case of a viral vaccine, only a single strain or a few strains of the virus must exist and these should be genetically stable so that its antigenic properties remain more or less the same.[322]
- The virus must not persist in the infected host.[323]
- The vaccine used must be effective.[324]

More attention is given to these requirements and the likelihood of a candidate HIV vaccine being able to meet these requirements in paragraph 4.5 below.

The safety of vaccines has been a concern. Adverse reactions to vaccination include relatively mild reactions, such as swelling of the injection site and mild fever, and more serious reactions, such as seizures and encephalitis which could lead to brain damage.[325] The live (attenuated) oral poliovirus vaccine caused one case of paralysis per million doses of vaccine in the United States; only inactivated poliovirus vaccine is now used, as the cases of paralysis were due to the virus strain used in the vaccine reverting to its virulent state.[326]

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317 Such as organised programmes to eradicate polio and measles. Schoub (n 308 above) 562.
318 As above.
319 As above.
320 Schoub (n 308 above) 562.
321 Ada (n 315 above) 347.
322 Schoub (n 308) 562. See also para 4.5.1 below.
323 As above. In the case of HIV, the virus integrates itself into the host's DNA.
324 Ada (n 315 above) 347.
325 As above, 346.
326 As above. This is one of the documented problems when a live (attenuated) vaccine is used.

Because of these vaccine safety issues, vaccination programmes are not free from opposition among activists, politicians and the public.[327] Vaccines are given to healthy individuals in order to protect them against the risk of future infection. Clearly, the risk of future infection must be great enough to offset exposure to potentially adverse reactions to the vaccine. In the case of HIV, the risk and consequences of infection are great enough to offset this risk in many populations. An exposition on the risk-benefit analysis that is inherent in any decision to vaccinate, however, falls outside the scope of this thesis.

4.4 Types of vaccines

Vaccines may be divided into two major categories.[328]

- Inactivated (or killed) vaccines.
- Live (attenuated)[329] vaccines.[330]

4.4.1 Inactivated (or 'killed') vaccines

As their name indicates, inactivated or 'killed' vaccines are composed of viral material that has been inactivated so that they are unable to infect or replicate in the vaccinated person.[331]

Inactivated viral vaccines use either the entire virus that has been inactivated by means of chemical processes or heat, or parts of that virus, such as a surface antigen.[332] Vaccines utilizing parts of viruses are called subunit vaccines.[333]

Because they cannot replicate and revert to their 'wild'[334] type, inactivated vaccines are the safest type of vaccines. However, increased safety has its cost – these vaccines are often less successful in inducing immune response in the

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327 For a general discussion of, and empirical study on public attitudes to, vaccination programmes, see Ritvo *et al* (2003) 1 *J Immune Based Therapies and Vaccines* 3.

328 Rick (n 18 above) 78; Nicklin *et al* (n 2 above) 317 – 318; Schoub (n 308 above) 561.

329 Weakened or altered.

330 As above. 'Live' is used here to indicate that the virus has not lost the ability to reproduce and infect the host.

331 Nicklin *et al* (n 2 above) 318; Rick (n 18 above) 78; Schoub (n 11 above) 184; Schoub (n 308 above) 561; Klein and Ho (n 35 above) 306; Mackett and Williamson (n 13 above) 99.

332 Rick 78; Nicklin *et al* 319; Ada (n 315 above) 1043; Schoub (n 308 above) 561; Klein and Ho 306. Often, only the relevant immunogenic protein is synthesised by recombinant DNA technology.

333 Schoub (n 11 above) 184; Klein and Ho 306; Nicklin *et al* 319. By definition, a subunit vaccine is a vaccine that contains only part of that virus or other microorganism. HIV subunit vaccines produced by genetic engineering are called 'recombinant subunit vaccines'.

334 Original, infectious virus, as is found in the 'wild'.

vaccinated person and repeat vaccinations may be needed for optimum protection[335] as the immune response is shorter lived.[336]

A recent example of an inactivated vaccine is what is known as a recombinant subunit DNA vaccine. This vaccine uses genetically engineered DNA to produce a synthetic version of a viral surface antigen or it uses genetic material from the virus that cannot harm the vaccinated person.[337] Recombinant DNA vaccines are believed to be much more successful in inducing immunity than other inactivated vaccines.[338]

To enhance the immune response against inactivated vaccines, vaccine developers use adjuvants that can increase the type, strength and durability of immune responses against the pathogen.[339] Some adjuvants also stimulate mucosal immunity.[340] An example of an adjuvant is alum, which increases the strength of antibody responses generated by the vaccine antigen.[341]

In the case of killed subunit or recombinant vaccines it is the foreign protein contained in the vaccine that elicits an immune response and not any replicating activity (as killed viruses cannot replicate).[342]

4.4.2 Live (attenuated) vaccines

Again, as their name indicates live (attenuated) viruses are 'alive' and able to replicate in the vaccinated person.[343] They, however, are weakened by being genetically altered so that the new (vaccine) virus will not cause disease but will continue to stimulate the individual's immune system to recognise and defend against future attacks.[344] The process of changing the wild virus into the vaccine virus is called attenuation.[345]

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335 Rick 78; Schoub (n 11 above) 185; Nicklin *et al* 319.

336 Mackett and Williamson (n 13 above) 41; Wilson (n 303 above) 859; Rick (n 18 above) 78; Klein and Ho (n 35 above) 306. Often several administrations of the vaccine are needed to achieve long-lasting immunity.

337 Nicklin *et al* 319; Schoub 188; Rick 80. The recombinant DNA vaccine against for Hepatitis B is the only such human vaccine licensed to date.

338 Wilson 859; Nicklin *et al* 319.

339 Rick 82; NIH (2003) *Challenges in designing HIV vaccines* <http://www.niaid.nih.gov/factsheets/challenges/challvacc.htm> (30 August 2003).

340 As above.

341 As above.

342 Schoub (n 308 above) 561; Rick 82.

343 Mackett and Williamson 121; Rick 78; Nicklin *et al* (n 2 above) 318; Schoub (n 11 above) 184; Schoub (n 308 above) 561; Klein and Ho 307.

344 As above.

345 As above.

On the whole, live vaccines are much more successful than inactivated vaccines as they produce an immune response very like the one produced by the wild virus and because they provide longer-lasting immunity.[346] However, these advantages carry their own cost. Because live (attenuated) vaccines are able to replicate inside the vaccinated person's cells, they are able to revert to a wild (pathogenic) type and cause disease in the vaccinated person.[347] They also have a limited shelf life.[348]

As was suggested before, most of the successful vaccines used today are live vaccines. These vaccines have either been modified in cell culture (the measles, rubella and polio vaccines) or a close (less virulent) variant of the disease-causing virus has been used (such as in the case of smallpox using cowpox) in the production of the vaccine.[349]

The following table classifies some of the most important vaccines currently in use:[350]

Live vaccines	**Killed (inactivated) vaccines**
Trivalent oral polio (TOPV) Measles Mumps Rubella Yellow fever Varicella BCG	*a) Whole organism vaccines* Diphthera Pertussis (whole) Tetanus Trivalent inactivated polio (TIPV) Influenza (whole) Hepatitis A Rabies *b) Subunit vaccines* Heamophilus Influenza b Pneumococcal conjugate *c) Recombinant* Hepatitis B

346 Nicklin *et al* 318; Mackett and Williamson 121; Schoub (n 11 above) 184; Rick 78. They continue to reproduce inside the cells of the vaccinated person, thereby continually stimulating an immune response.

347 As above; Ada (n 315 above) 1055.

348 Rick 78.

349 Mackett and Williamson 124 – 125; Nicklin *et al* 318; Schoub (n 11 above) 184; Rick 78.

350 Table reproduced from Schoub (n 308 above) 562.

The following table shows some of the most important viral vaccines licensed for use in humans:[351]

Virus	Family	Type of vaccine	Disease (if different from virus)	Year identified	Year vaccine developed
Polio Oral Sabin vaccine Salk vaccine	Picornavirus	Live attenuated Inactivated	Poliomyelitis	1909	1957 1953
Measles	Paramyxovirus	Live attenuated		1954	1963
Mumps	Paramyxovirus	Live attenuated		1934	1967
Rubella	Togavirus	Live, partly attenuated	German measles	1962	1971
Rabies	Rhabdovirus	Inactivated		Discovered 1903; isolated 1960	1970
Influenza	Orthomyxovirus	Inactivated, subunit, and live attenuated		1933	1941
Hepatitis B	Hepadnavirus	Subunit	Serum hepatitis	1965	1986

This table illustrates that, on the whole, a lengthy period of time elapses from the moment that the viral pathogen responsible for a disease is discovered to the point where vaccine research produces a vaccine for that disease. The rabies virus was discovered in 1903, but the vaccine against rabies was only licensed in 1970. The poliovirus was identified in 1909, but the first vaccine became available only in 1953. Similarly, it took 34 years to develop the mumps vaccine.

The table similarly indicates that most viral vaccines currently in use are live (attenuated) vaccines. In the case of HIV such a vaccine is ruled out because of safety concerns.[352]

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351 Klein and Ho (n 35 above) 297.

352 See para 4.5.4 below.

More than twenty years have passed since the isolation and identification of HIV. There is, as yet, no vaccine available against HIV infection. The next section explores a few of the obstacles in the search for a preventive HIV vaccine.

4.5 Scientific challenges posed by the search for an effective preventive HIV vaccine

That clinical research is a long and difficult undertaking is shown by the fact that, although more than twenty years have passed since the first documentation of HIV in 1983, only a few vaccines have progressed to Phase III clinical trials. One such vaccine, produced by VaxGen, has proven a failure.[353]

From the discussion in paragraph 4.4 above, it should be clear at the outset that each type of vaccine (inactive or live) has its own drawbacks. Inactive vaccines are less able effectively to induce immunity, whereas live vaccines pose serious risk to the vaccinated person in that they mutate and cause disease.

HIV is an extremely complex virus and, therefore, vaccine development is difficult. An effective preventive HIV vaccine requires both a neutralising antibody response which will eliminate free virus and a killer (cytotoxic) T-lymphocyte (CTL) response which will eliminate virus-infected cells.[354]

An effective preventive vaccine to prevent infection by HIV should have the following qualities. It should be:

- safe;
- easy to administer;
- stable under adverse storage conditions;
- inexpensive; and
- capable of inducing long-lasting immunity, against a broad range of strains of HIV.[355]

A few of the most important scientific, logistic and economic obstacles in the way of developing a preventive HIV vaccine that meets these requirements are discussed below.

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353 Wilson (n 303 above) 857.

354 Van Harmelen and Williamson (n 144 above) 569; Klein and Ho (n 35 above) 304. The traditional method of developing a vaccine, in which the focus is on the stimulation of a strong antibody response, has proven ineffective in the case of HIV. Also see the discussion of the human immune system, para 2.3 above.

355 Graham and Wright (2003) 33 *New Engl J Med* 1331; Klein and Ho (n 35 above) 310.

4.5.1 Variation and mutation of HIV and other characteristics

Not only do a number of HIV subtypes exist, but great genetic variety is seen in strains isolated from the same individual.[356] The ability of HIV to mutate and recombine, and so escape the immune system, is likely to pose a serious obstacle to the successful development of a vaccine.[357] A successful vaccine against HIV, therefore, will have to protect against the emergence of resistant strains – in other words, it will have to protect even against a virus that is yet to evolve.[358] To many this seems a daunting task and one of the most significant obstacles in striving to develop a vaccine.

Initially, scientists thought that a subunit vaccine consisting of a HIV viral envelope protein, such as gp120, could provide immunity.[359] It was thought that the antigen contained in the vaccine would trigger the production of specific neutralising antibodies.[360] This assumption has been shown to be mistaken, as HIV simply evades the neutralising antibodies so generated. HIV coats itself in host-derived sugars when it buds out of an infected cell[361] and, as these sugars are seen as 'self' by the immune system, HIV is able to 'hide' from the immune system.[362]

The RNA of HIV is reverse transcribed into DNA that is integrated into the host genome. This makes it unlikely that any vaccine will be able to completely clear HIV infection.[363]

HIV infects helper T-cells, the very cells that orchestrate the immune system's response. It is difficult to design a vaccine that, to be effective, needs to activate the very cells that are infected by the virus.[364]

Certain viral proteins have adverse biological functions[365] that need to be inactivated before inclusion in vaccines. This has proven difficult to do.[366]

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356 Schoub (n 11 above) 189.

357 Graham and Wright (n 355 above) 1333. It seems that HIV is able to survive a great deal of sequence variation while still maintaining its ability to replicate and its structural integrity.

358 For a detailed discussion on this topic, see Lukashov *et al* in Wong-Staal and Gallo (eds) (2002) *AIDS vaccine research* 93 – 120.

359 Smith (2003) 2 *Med Immunology* 2.

360 Van Harmelen and Williamson (n 144 above) 569.

361 This process is called glycosylation.

362 Van Harmelen and Williamson 571.

363 As above, 573.

364 NIH (2003) *Challenges in developing AIDS vaccines* 1 <http://www.niaid.nih.gov/daids/vaccine/challenges.htm> (30 August 2003).

365 Such as stimulating tumour growth.

366 n 358.

Because of the virus's genetic diversity, a successful vaccine will have to stimulate not one but a broad range of neutralising antibodies against HIV. To date this has been impossible.[367]

4.5.2 A lack of models of protection to give clues to the mechanisms of immunity

Even though at the time little was known about human immunology, Edward Jenner was able to produce an effective vaccine against smallpox as early as the 18th century. What Jenner lacked in knowledge of the immune system, however, was made up for by the fact that he had a model of protection to study. Jenner was presented with a population of milkmaids who were protected from smallpox because of their prior exposure to cowpox. He had, literally, but to observe this group and draw conclusions about the cause of their resistance.[368]

In the case of HIV there exists no group of individuals who continue to be protected against HIV though they have repeatedly been exposed to the virus. A study of long-standing HIV negative sex workers in Nairobi has not provided clarity on the mechanism of their resistance.[369]

Although the role of neutralising antibodies and cytotoxic T-cells in the immune response against HIV has been documented, it is not known exactly which components of the immune response are necessary for protection from natural infection.[370]

4.5.3 Lack of experimental animal models to study the disease

Experimental animal models enable scientists to study infection and disease safely. Even though they do not always mimic human disease completely, animal models give important information on immune response and vaccine safety.[371] In the case of HIV very few animal models exist. The most successful animal model to date has

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367 Nabel (2001) 410 *Nature* 1002 1005.
368 As above, 1002.
369 Mackett and Williamson (n 13 above) 14; see Rowland-Jones *et al* (1998) 102 *J Clinical Investigation* 1785.
370 Mackett and Williamson (n 13 above) 14; Graham and Wright (n 355 above) 1331.
371 Wong-Staal and Gallo (n 358 above) iv. See also Pauza and Wallace in Wong-Staal and Gallo 287.

been that of the Rhesus macaque, in which infection with SIV[372] resulted in a syndrome very similar to AIDS.[373]

However, this animal model underscores the complexities of the interaction between retroviruses and their hosts, as neither the infection in animals nor the progression of the disease completely mimics HIV infection in humans. Structural and genetic differences between HIV and SIV make it difficult to transpose what has been learnt from animal studies to the human disease. [374]

4.5.4 Live (attenuated) HIV vaccines would be unsafe

The most successful vaccines that have been developed to date are live (attenuated) vaccines.[375] As was indicated above,[376] these vaccines consist of live viral material that is able to infect and replicate inside the host. In the case of a fatal infection, such as HIV, this poses a significant safety risk and, therefore, a live (attenuated) vaccine for HIV has been ruled out.[377] This approach, however, is being pursued in studies in animals and live (attenuated) mutant virus vaccines with deletions in the *nef* gene have been shown to have promise.[378]

4.5.5 The importance of logistics and economics

Although not scientific by nature, these obstacles to the development of a vaccine are significant. Vaccine trials are lengthy affairs and vaccine development is a costly exercise.

It takes almost 20 years from the moment a concept vaccine is produced up to the end of a Phase III vaccine trial. Many vaccines never make it to Phase III trials as they do not produce the necessary immune response *in vitro*.[379] Because of the long time frame involved, by the time a candidate vaccine finally reaches Phase

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372 Simian Immunodeficiency Virus.

373 In this regard, see Barouch *et al* (2002) 415 *Nature* 335 – 339. It is also important to remember that the animals that are needed in HIV vaccine experimentation are usually rare, protected species, unlike other laboratory animals such as rats and rabbits.

374 Graham and Wright 1333.

375 Klein and Ho (n 35 above) 306.

376 See para 4.4.2 above.

377 Smith (n 359 above) 1; Klein and Ho 306.

378 Graham and Wright 1334. In particular, see endnote 48 of their article. See also Klein and Ho 306.

379 'In vitro' refers to an artificial environment created outside a living organism (eg in a test tube) used in experimental research to study a biologic process or disease. 'In vivo' refers to the living body, or research done 'inside' a living organism.

III trials, scientific thinking may have changed no longer to reflect much hope that the vaccine antigen used in the vaccine will induce immunity successfully.

Thousands of volunteers at high risk for HIV infection are needed to take part in Phase III vaccine trials. This involves significant organisational and financial investment on the part of the pharmaceutical company. Often there is no expectation of a return on this investment.[380]

However, despite these obstacles, there do seem to be a few promising vaccine candidates. The next section explores a few of these possibilities.

4.6 Avenues of hope: various options for candidate preventive HIV vaccines

The disappointing results of the recently completed Phase III VaxGen candidate preventive HIV vaccine trial[381] have dampened many scientists' hopes that a successful preventive HIV vaccine will be found soon. However, scientists gain knowledge from clinical research; even failed trials.

Presently, despite our incomplete understanding of immunity to HIV and certain safety concerns, a number of candidate vaccines are entering Phase I and II trials, and a few are even entering Phase III trials. The results of completed Phase I and II trials give some room for optimism. The next section looks very briefly at a few of the candidate vaccines that are currently under investigation.

The following table summarises HIV vaccine strategies presently being investigated:[382]

Strategy	Description
Subunit vaccines	Recombinant viral proteins (eg *env*, p24, *tat*)
Live (attenuated) vaccines	Containing deletions of *nef* and/or *vpr* genes
Whole killed	Chemically inactivated HIV viruses
Peptide-based vaccines	Chemically synthesised HIV protein fragments and/or defined immunogenic epitopes
Pseudovirions	Non-replicating and non-infectious virus-like particles consisting of, for example,

380 Consider, for example, VaxGen's Phase III AIDSVAX trial. The trial was recently completed without any indication that the candidate vaccine that was tested provided protection against infection.

381 See McCarthy (2003) 361 *The Lancet* 755.

382 This table is taken from Bojak *et al* (2002) 7 *DDT* 36 39.

	gag, pol and *env*
Replicons	Non-HIV viruses engineered to carry genes encoding HIV proteins
Live bacterial vectors	Harmless bacteria engineered to carry genes encoding HIV proteins
Live viral vectors	Non-HIV viruses engineered to carry genes encoding HIV proteins, eg canary pox
DNA vaccines	Naked plasmid-DNA containing one or more HIV genes
Combined vaccines	Combination of different vaccines in a mixed modality immunisation schedule (eg DNA vaccines plus live viral vectors)

The following paragraphs mention specific candidate vaccines that are promising and that have entered clinical trials. (Also see chapter 5 for a more complete representation of the HIV vaccine trials being conducted in South Africa and around the world).[383]

Below, some important current candidate AIDS vaccines in Phase 1 and 2 clinical trials are classified according to vaccination approach, antigenic content and formulation:[384]

Vaccine antigens	**HIV strain of origin**	**Adjuvant, conjugate, or delivery system**
V3 (gp120) (a surface antigen)	Multiple	Alum, microspheres, IFA
Gp120 (surface antigen)	MN, SF-2	Alum, others
Gp 160	LAI, MN	Alum, alum + DOC
env *env, gag, pol*	LAI, MN LAI, MN	Vaccinia, canarypox[385]
Gp160, p24	MN	Virus- particle
P24	LAI	Self-assembling particle
gag (p24)	MN	Lipid conjugate

A vaccine developed by scientists at Oxford University and at the University of Nairobi is currently in Phase II trials in London and in Kenya. This vaccine, aimed at

383 Para 2.3.1 of ch 5.

384 This table is adapted from Graham and Wright (n 355 above) 1335.

385 Canarypox is a virus that infects birds and is used as a live vector in vaccine design as it is able to carry a large number of foreign genes. The canarypox virus cannot grow in human cells; an important safety aspect.

boosting cell-mediated immunity, consists of a number of the genes of HIV, such as *gag*, *pol*, *nef* and *env*. The vaccine is described as a 'prime boost' DNA vaccine.[386]

Another vaccine candidate soon to be entering clinical trials is Merck's 'HIV-1 gag replication defective adenovirus'. A cold virus that has been modified is used as a vehicle to deliver a fragment of the synthetically reproduced HIV-gene, called *gag*.[387] The Phase III trials of this candidate are to start in 18 cities around the world, including in South Africa.[388]

In March 2002, GlaxoSmithKline Biologicals announced the start of its first human trials of an adjuvant HIV vaccine, NefTat and gp 120.[389] This candidate vaccine succeeded in protecting rhesus monkeys against SIV, a virus similar to HIV.[390]

Another pharmaceutical company, AlphaVax, recently announced the start of the first human trials of its HIV preventive vaccine in the United States and South Africa.[391] The AlphaVax vaccine (called AVX101) uses a non-propagating form of an alphavirus vector[392] to express HIV genes.[393] It is hoped that these will elicit broad-based immune responses, including cellular immunity.[394]

The next section examines aspects of clinical research relevant to the thesis. Research methodologies to produce a vaccine are investigated and the structure of clinical trials used to develop a HIV vaccine is explained.

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386 Weidle *et al* (2002) 359 *The Lancet* 2264; 'AIDSVAX trial not the end of the story' *The Scientist* (Daily News) 28 February 2003.

387 The HIV Vaccine Trials Network *Press release 19 September 2003* <http://www.hctn.org/pressroom/press_releases.sht?id=36> (4 October 2003).

388 As above. Another candidate vaccine utilising the *gag* gene, is AVX101. This candidate vaccine has entered phase I trials in South Africa and the USA. AVX101 is an alphavirus replicon vaccine. See ch 5 below.

389 See 'GlaxoSmithKline Biologicals announces start of human trial of novel HIV vaccine' *AIDS Weekly* (2002) 11.

390 As above.

391 'Trials of new HIV vaccine begin in US, South Africa' *Biotech Week* 27 August 2003 42.

392 A 'vector' is a bacterium or virus that does not cause disease in humans and which is used in genetically engineered vaccines to transport genes coding for antigens into the body to induce an immune response.

393 n 388.

394 As above.

5 CLINICAL RESEARCH AND HIV VACCINE DEVELOPMENT

5.1 Introduction

In this section clinical research, generally, and vaccine efficacy trials, specifically, are explored in order to come to some understanding of the methodological framework underlying HIV-related clinical research. Problems and risks related to HIV vaccine efficacy trials are examined with a view to providing the scientific underpinning for the third, fourth and fifth chapters that focus on ethical issues and human rights issues in HIV-related clinical research and vaccine efficacy trials.

5.2 Clinical research

Levine defines the term 'research' to denote 'a class of activities designed to develop or contribute to generalizable knowledge'.[395] Such generalised knowledge consists of 'the theories, principles, or relationships (or the accumulation of data on which they may be based) that can be corroborated by accepted scientific observation and influence'.[396]

The term 'clinical research', in turn, refers to research 'involving human subjects, that is designed either to enhance the professional capabilities of individual physicians or to contribute to the fund of knowledge in those sciences that are traditionally considered basic ...'[397] Clinical research, thus, is research carried out on humans, and, by definition, therefore excludes research carried out on human blood or tissue samples[398] and research on animals.

The definition above also emphasises that the individual research participant might not benefit directly from the research that is being done – research may be undertaken to contribute to the 'fund of knowledge'. This is the case in clinical research aimed at testing a new drug, in which the participant is allocated to the control, or placebo, group. [399]

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395 Levine (1986) 3.

396 As above; Chen *et al* (2003) 138 *Annals Internal Med* 669. The term 'research' is often contrasted with the term 'practice'. 'Practice' relates to activities that are focussed on the individual patient or client with the aim of diagnosing, treating and curing that patient. The best interests of the individual patient are most important. In the case of research, the aim is to develop knowledge to help future patients.

397 Levine (n 395 above) ix; also see Rick (n 18 above) 4.

398 Rick 4. Even though these may often form part of research carried out on humans, for instance, where blood is drawn from participants to establish whether an immune response is present against a candidate vaccine.

399 A dummy treatment.

Furthermore, it is important to note that clinical research is sometimes carried out on healthy individuals who are exposed to risk solely to expand scientific knowledge.

The aim of clinical research is to benefit the individual or society as a whole. Without research on human subjects major medical breakthroughs would never have been achieved. Clinical research in the past has led to the development of drugs, such as antibiotics and antivirals, and procedures, such as heart and lung transplants. Clinical research is a necessity and the effects of neglecting such research would be disastrous. The World Medical Association's Declaration of Helsinki recognises the value of research for medical progress and the inevitability of that research having to include human participants: 'Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects'.[400]

The benefits of HIV-related research, generally, and of finding an effective preventive vaccine for HIV, specifically, are enormous, both to the individual and to society. Not only will the successfully vaccinated individual be protected against future infection by a deadly disease but, because of the 'herd' immunity, non-vaccinated members of society will be protected as the 'pool' of infection will have been decreased.[401] Clinical research to find a preventive vaccine is thus a necessity.

Two major types of clinical research may be distinguished.[402]

- Observational research.
- Experimental research.[403]

The two methods will be discussed briefly below.

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400 Declaration of Helsinki, adopted by the 18th World Medical Association assembly, Helsinki, Finland, in 1964, and revised subsequently, reprinted in Levine (n 395 above) 427.

401 See para 4.3 above.

402 Grimes and Schulz (2002) 359 *The Lancet* 57 - 58.

403 A third method, qualitative research, is also sometimes distinguished. Qualitative research attempts to interpret, or give meaning to, different phenomena. It studies participants in their natural surroundings and attempts to draw conclusions from these observations. With qualitative research the focus is on the research participants' interpretation of events, and not on that of the researcher. There is no attempt at objectivity - this method attempts to arrive at various, subjective interpretations of the world. A few qualitative research methods are focus groups, case study evaluation and qualitative interviews. As this method is rarely used in clinical research in a medical or scientific setting, it is not included in this discussion.

5.2.1 Observational research

Observational research involves the observation of a certain state or event without interfering.[404] This research method is clearly distinguishable from that of experimental research in which the effect of a specific intervention is studied. Observational research is sometimes referred to as epidemiological research, as this method is frequently used in epidemiological studies.[405] For example, observational research is frequently employed to determine the prevalence of diseases in a certain geographical area, the infection rate at a certain point in time, and so on.

Observational research is either descriptive or analytic.[406] Descriptive studies describe states or events without indicating their cause or effect. In descriptive studies there are no control or experimental groups.[407] Analytic studies, on the other hand, look for links between cause and effect in an attempt to arrive at an understanding of the interplay between different factors.[408] Analytic studies use a comparison or control group.[409] They are always quantitative in nature.[410]

Three types of analytic, observational clinical research methods exist, namely, cross-sectional studies; cohort studies; and case-control studies.[411] The direction in time of an analytic study determines its subtype.

A study that determines both exposures and outcomes at the same point in time is a cross-sectional study.[412] An example of a cross-sectional study is the measurement of the serum cholesterol levels of men admitted to hospital with myocardial infraction, compared to those at the hospital next door.[413]

Cohort studies compare two groups, whereby one group is exposed to risk and the other is not, and follow these groups.[414] For example, the study begins with an exposure (such as oral contraceptive use) and follows women for a period of time to measure outcomes (such as breast cancer).[415] In this way the ratio and rates of

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404 Foster (2001) 23; Grimes and Schulz (n 402 above) 58.
405 As above.
406 As above.
407 Grimes and Schulz (n 402 above) 58. A case report is an example of a descriptive study. When more than one patient, or 'case', is described, the study is known as a case-series report.
408 As above.
409 As above.
410 As above.
411 As above; Foster (n 404 above) 23.
412 Grimes and Schulz 58.
413 As above.
414 Foster 23.
415 Grimes and Schulz 58.

disease may be calculated.[416] Cohort studies may be either concurrent or non-concurrent.[417]

Case-control studies are the opposite of cohort studies. Case-control studies start with the effect or outcome (breast cancer) and look back in time to find a cause (oral contraceptive use).[418]

5.2.2 Experimental research

Experimental research attempts to exclude the weaknesses of observational research that affect its scientific validity, such as researcher and participant bias.[419] This is done through a clinical trial.

Clinical trials are 'organized studies to provide large bodies of clinical data for statistically valid evaluation of treatment'.[420] Such experimental research methods include randomised controlled clinical trials and non-randomised controlled trials.[421]

The randomised controlled clinical trial (RCCT) is the most widely used (experimental) research method.[422] A RCCT is used to 'compare the efficacy and safety of two or more interventions or regimes'.[423] This definition highlights the fundamental characteristic of the method – that it makes a comparison. For example, a new drug or treatment is compared to an existing drug or treatment, a placebo, or nothing at all.[424] Research participants receiving the existing (standard) drug or a placebo are referred to as the control group, while the participants receiving the new treatment are referred to as the experimental group.[425] Sometimes a RCCT compares different doses of the same drug.[426]

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416 Foster (n 404 above) 23.

417 Grimes and Schulz (n 402 above) 58.

418 Grimes and Schulz 58; Levine (n 395 above) 210; Foster 23.

419 Devereaux *et al* (2003) 413 *Clinical Orthopaedics and Related Research* 25 - 26.

420 Anderson (ed) (1998) 1E13. The International Conference on Harmonization (ICHJ) offers a more lengthy definition of a clinical trial:
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and / or other pharmacodynamic effects of an investigational product, and / or to identify any adverse reactions to an investigational product, and / or to study absorption, distribution, metabolism, and excretion of an investigational product with the object of ascertaining its safety and / or efficiency (Rick (n 18 above) 140).

421 Experimental designs that need mention but which do not really warrant inclusion as they are used in combination with RCCTs and non-randomised controlled clinical trials, are historical control data as a control in trials and dose-response design trials.

422 From now on referred to as RCCT.

423 Levine 185.

424 Foster 22.

425 As above.

426 As above.

An important characteristic of RCCTs is that they attempt to control for any chance of an outside (non-experimental) factor influencing the results of the trial. This is done by ensuring that the sample size is sufficiently large. The fact that the trial is often 'blinded', tries to exclude observer or participant bias.[427] In a 'double blind' RCCT, neither the researcher nor the participant knows who is given the 'real' intervention and who is receiving the standard care or the placebo.[428]

Randomisation also contributes to the elimination of outside influences.[429] Randomisation is the practice of allocating participants to different experimental groups by random selection.[430] In large trials the selection is done by computer.

Before research participants are randomised into different groups, efforts are made to ensure that they are as homogenous a group as possible. The eligibility criteria of trials attempt to ensure this. For example, only healthy persons of a certain cholesterol level or a certain age are included in a specific trial.[431]

RCCTs were initially designed to test new drugs[432] but are now used for a wide range of purposes, such as the study of existing drugs and the development of new surgical interventions.[433] This RCCT trial design is considered the approximate of the controlled experiment in basic science and is the 'gold standard' of clinical research.[434] The RCCT is of interest to this study as vaccine efficacy trials are conducted in this way.

When true randomisation is not used, the study design is that of a non-randomised controlled clinical trial. Instead of randomisation, another assignment scheme may be used, such as alternate assignment.[435] This study design is

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427 For example, a principle investigator whishing the trial drug to be proven effective may actively (and even subconsciously) select participants who stand a better chance of benefiting from the experimental regimen and ensure that those participants are part of the 'experimental' group; trial participants who know that a new drug is being tested on them may feel an 'improvement' in their condition which may be absent as they are part of a placebo group.

428 At the end of the trial, the trial is 'unblinded' to reveal who is receiving which intervention. This is also done where serious adverse events are reported. Also, for a discussion of some of the ethical implications of trials where placebos are used, see ch 3 below.

429 Such as a researcher allocating participants that she thinks may benefit most from the experimental treatment to the experimental group.

430 Levine 185.

431 As above.

432 As above.

433 As above. RCCTs are also used to test the efficacy and safety of new vaccines, see para 5.4 below.

434 Grimes and Schulz (n 402 above) 58.

435 As above.

considered less scientifically rigorous than that of a randomised controlled trial.[436] After the participants to a non-randomised control clinical trial have been assigned to the treatment and control groups the study resembles that of a cohort study.[437] The disadvantage of this trial design is that selection bias may occur.[438]

In the following section aspects of clinical research methodology significant to the development of new HIV drug regimens will be outlined, before attending to the design of clinical trials in the development of a preventive HIV vaccine.

5.3 Drug development through clinical research

This section explores the methodology of clinical research aimed at developing a new drug for the treatment of HIV and distinguishes vaccine efficacy trials from trials to develop other experimental drug regimens.

The development of a new drug or experimental treatment proceeds through the following phases. They are:[439]

- Basic research.
- Pre-clinical evaluation.
- Clinical trials (involving human trial participants).

5.3.1 Basic research

What this involves is research into the different attributes of the pathogen that produces the disease.[440] Thus, HIV's virulence, pathogenicity and infectivity have been established, as well as the exact mechanisms of the human immune response to HIV.[441] Knowledge gained from basic research leads to the identification of a drug strategy that, for example, it is suspected will be successful in lightening the burden of HIV-disease. The drug is then produced for pre-clinical testing.

5.3.2 Pre-clinical evaluation

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436 As above.
437 As above.
438 As above.
439 Levine (n 395 above) 6 – 7.
440 As above.
441 As above.

Pre-clinical testing is done to evaluate the drug's ability to treat the disease. Usually, such testing is done in vitro or on animals. In the case of HIV-related drug research the lack of a suitable animal model has hampered research.[442]

Animals are given the experimental drug or treatment, after which they are closely monitored. Not only are the animals' clinical responses examined during this stage but the levels at which the drug becomes toxic are also measured.[443]

Only once a drug has been shown successfully to elicit the required response in animals, as to be safe, is it tested on humans to ascertain its efficacy and safety.

5.3.3 Clinical trials

Clinical research to test drug safety and efficacy in humans is done by means of controlled clinical trials:[444]

- *Phase I: Clinical pharmacology*

This phase is intended to be the first introduction of the drug into humans and is aimed at determining levels of toxicity, the appropriate dosage and its safety.[445] Drug dynamic and absorption studies are performed during this phase. Normally, healthy volunteers are recruited during this phase.[446] Furthermore, usually no control group is included and only a limited number of participants are enrolled – from as few as 10 to about 100.[447] Subjects are monitored closely to check their tolerance to the drugs and any side-effects.[448] Depending on the complexity of the trial, the cost of a Phase I trial is estimated at around US$ 10 million.[449] The trial may last from several months to a year.[450]

- *Phase II: Clinical investigation*

This phase consists of controlled clinical trials to ascertain the effectiveness and relative safety of the developmental drug.[451] Only once a drug has passed through Phase I trials, and was proven safe and non-toxic, may it proceed to Phase II trials.

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442 See above.
443 Levine (n 395 above) 6.
444 As above. Not all drugs progress through all four phases. Most often the clinical trials of drugs are terminated during early phases when drugs are proven toxic or inefficacious.
445 Levine 6; Rick (n 18 above) 144.
446 Rick 144. However, in some instances, critically ill patients or with terminal diseases are presented with the option to be included in the trial after due consideration of the risk-benefit ratio.
447 Rick 144.
448 As above.
449 As above.
450 As above.

Phase II trials differ from Phase I trials as the effectiveness of the drug is also assessed. A series of doses of varying strengths may be given to participants.[452] Participants are randomised to a control group or an active group.[453] Once again a relatively small number of participants are enrolled – from about 50 participants to 500 participants.[454] Phase II trials result in the information needed to determine the effective dose and the dosing regimen with regard to frequency and duration.[455] The success rate of Phase I and II studies is around 30 per cent.[456] A Phase II trial may take one to two years and costs as much as US$20 million.[457]

- *Phase III: Clinical trials*

These are large-scale trials and may be controlled or uncontrolled.[458] The trials are most often RCCTs. This phase aims at establishing efficacy and the possibility of the existence of adverse effects, and uses the safe, effective dosage and administration schedule determined by the preceding phases.[459] Phase III trails are considered large-scale trails as they usually include thousands of participants.[460] These trials are usually conducted in different geographic locations (known as multi-centre trials).[461] The trial has to be methodologically sound in order for meaningful results to be presented at the end of the trial.[462] Statistical proof to show the efficacy of a drug or vaccine has to be established.[463]

- *Phase IV: Post-marketing clinical trials*

These trials are done after the new drug has been marketed to the public, and include clinical trails aimed at elucidating increased adverse reactions or events; testing of the drug in populations not previously included in the trials;[464] and trials to test drug efficacy for an indication other than what was initially tested for.[465]

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451 Levine 6; Rick 145.
452 Rick 145.
453 As above.
454 As above.
455 As above.
456 Rick 145.
457 As above.
458 Levine (n 395 above) 6 - 7.
459 As above.
460 Rick 145.
461 Rick 146.
462 As above.
463 Rick 147.
464 such as in children. Levine 6 – 7; Rick 147.
465 Levine 6 - 7.

Although they follow the same basic pattern as usual clinical trails to test drug efficacy, vaccine efficacy trials differ from drug efficacy trials in a few very important respects.

- Most important, in the case of trials to establish the efficacy of a new drug, the trial participants usually suffer from the particular disease the drug is being tested for - obesity drugs are tested on obese participants, cancer drugs are tested on cancer sufferers and new drugs to treat diabetes are tested on participants suffering from diabetes. This is not the case in vaccine trials. Vaccine trials are usually performed with healthy volunteers who may be at risk for contracting the disease[466] but who are otherwise healthy.
- Participants in a vaccine trial, thus, are taking part primarily to benefit their community or society and not themselves.[467] Of course, as a community that is at risk of HIV infection, they will ultimately benefit from the development of a successful vaccine.
- Because participants are healthy and are taking part in vaccine trials for the benefit of others, one would expect that they should be placed at a lower degree of risk than is expected of participants already suffering from a specific disease who are taking part in a trial to develop a new drug to better treat their own condition.
- Because vaccine trials utilise volunteers who are only at risk for contracting a disease and who are not sufferers of that specific disease, vaccine efficacy trials usually last longer and require more volunteers in order to be regarded as scientifically valid. [468]

5.4 Preventive HIV vaccine efficacy trials[469]

In turn, preventive HIV vaccine efficacy trials carry significantly greater risk to their participants than is the case with other vaccine efficacy trials. This section explores HIV vaccine efficacy trials, and attempts to establish exactly why participation in a

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466 Especially during Phase III trials. However, this risk may never materialise, as not all participants are ever exposed to the virus.

467 Even though they will benefit if a successful vaccine is developed.

468 Where everybody is a sufferer of a disease it is relatively easy to show that a certain drug works better than another. In the case of vaccine efficacy trials, because not all participants will be challenged by the pathogen, many more volunteers are required.

469 Only the stages of vaccine efficacy trials are discussed here – the process of gaining regulatory approval for conducting a human trial is discussed in ch 5, in which specific reference is made to this process in South Africa.

HIV efficacy trial poses greater risk than participation in any other vaccine efficacy trial. Finally, these risks are enumerated.

5.4.1 Stages and duration of HIV vaccine efficacy trials

Additional to the outline given in 5.3.3 above, the following applies to HIV vaccine efficacy trials in particular. Pre-clinical research to develop a new vaccine proceeds along the same pattern as indicated above.

- *Phase I: Clinical pharmacology*

As indicated above, this phase determines the levels of toxicity and appropriate dosage of the candidate HIV vaccine.[470] Human participants are exposed to the candidate vaccine for the first time during a Phase I trial. This phase lasts about eighteen months and requires a smaller number[471] of trial participants than subsequent phases.[472] Also, as efficacy is not at issue here, trial participants do not need to be at high risk of HIV infection. Phase I trials usually consist of ten to twenty patients or volunteers in each study arm.[473]

- *Phase II: Clinical investigation*

This phase attempts to determine the safety and effectiveness of the candidate HIV vaccine. Trials are done on larger numbers[474] of closely monitored participants, some of whom should be at high risk for infection. Phase II trials last 24 months.[475] The details of the immune response to the vaccine are studied during this phase.[476] This phase attempts to answer the question: Does the candidate vaccine produce the desired immune response?[477] These studies are mostly multi-centred.[478]

- *Phase III: Clinical trials*

These are large-scale, double blind, placebo-controlled, randomised clinical trials, aimed at finding out whether the candidate HIV vaccine is effective in preventing infection by HIV.[479] The possibility of the existence of adverse effects is also examined.[480] Large numbers of volunteers are used during this stage, usually more

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470 Abdool Karim (2002) 20 *CME* 588 589.
471 Fewer than a hundred, mostly twenty to 50 participants.
472 Abdool Karim (n 470 above) 588.
473 As above, 589.
474 100s of participants.
475 Abdool Karim 589.
476 As above.
477 As above.
478 As above.
479 Abdool Karim 589.
480 As above.

than a thousand.[481] The question to be answered is this: Is the candidate vaccine effective? Because the efficacy of the candidate vaccine needs to be established these volunteers should be at high risk for infection.[482] This aspect of Phase III clinical trials has important ethical implications which will be discussed later.[483]

5.4.2 Preventive HIV vaccine efficacy trials versus other vaccine efficacy trials

The most important differences between HIV vaccine efficacy trials and drug efficacy trials of vaccines for other diseases stem from the nature of the disease itself. The following comments are restricted to scientific and social aspects of HIV vaccine efficacy trials. Important ethical problems associated with HIV vaccine efficacy trials are dealt with subsequently.[484]

- *Stigmatisation of HIV/AIDS and its sufferers*

HIV/AIDS is not like any other disease. Despite many attempts to educate and inform the public, HIV/AIDS sufferers remain stigmatised. Because those at highest risk for HIV infection often belong to marginalised groups in society, such as IDUs, sex workers and MSM, HIV/AIDS is considered a shameful disease. Also, because HIV/AIDS is largely a sexually transmitted disease, and because sex is not discussed openly in many societies, HIV/AIDS is regarded as unmentionable.

HIV infection is regarded as avoidable. Unlike other viral diseases such as polio and measles, which are not really preventable in the true sense of the word, HIV infection is associated with promiscuity and sexual adventure. Politicians often refer to children as the 'innocent' victims of AIDS; adult victims, by implication, are not 'innocent'. It is likely that these assumptions about HIV/AIDS - perceptions that have created endless obstacles to effective prevention and treatment programmes - will influence the public's perception of HIV vaccine trials and their participants as well.

- *Severity of the disease*

HIV/AIDS is a potentially fatal disease. Any HIV vaccine efficacy trial, therefore, will need to conform to the highest safety standards in order to protect healthy participants against vaccine-related adverse effects. Fears of contracting HIV

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481 The VaxGen Phase III trial involved 5009 volunteers.
482 Abdool Karim 589.
483 See ch 5 below.
484 As above.

because of trial participation may inhibit participants form volunteering for preventive HIV vaccine efficacy trials.[485]

- *Natural history of infection*

Because it is a lenti-retrovirus, HIV infection does not advance along the same pattern of infection as other viruses. It is a slow, progressive disease. Because of its integration into the host cell's DNA and because of the high rate of error in the reverse-transcription process, HIV manages to escape the body's standard immune responses. A HIV vaccine design and efficacy trial will have to take cognisance of this fact.

- *The urgency of the need for an effective vaccine*

There is no room for error in the search for an effective preventive HIV vaccine. Each vaccine concept and trial takes years to deliver results. During this time many more people will be dying. Had HIV had not been a fatal disease, the need for an effective vaccine would not have been that urgent.

Because of their particular nature, HIV vaccine efficacy trials offer some benefits and pose specific risks for participants. These are mentioned below, paving the way for a detailed examination of the benefits and risks of participation (in chapter 5 below).

5.4.3 Advantages versus risks to participants: A preliminary overview[486]

In a setting where resources usually are stretched, the most important benefit of HIV vaccine trial participation is the fact that vaccine trial participants gain access to increased health care and attention. They are given treatment for STDs and counselling to reduce high-risk behaviour, possibly preventing infection in the future.

Risks borne by participants of HIV preventive vaccine efficacy trials are physical, psychological and social in nature and differ according to vaccine design and trial design.[487] Some risks are more serious than others.

Physical risks in HIV preventive vaccine trials include the possibility of adverse autoimmune reactions to the vaccine and the possibility that the participant will suffer from a worse infection should she ever become infected with HIV.[488] Other

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485 See paras 2.3.1 and 3.4.1 of ch 5 below.

486 Also see para 2.3.1 of ch 5 below for a more extensive discussion on the topic.

487 Some vaccines are safer than others, see para 4.4 above; and some trial designs may have more adverse effects, such as those using placebos, see ch 3 below.

488 Graham and Wright (n 355 above) 1335. See para 2.3.1 op ch 5 below.

risks are adverse reactions to the vaccine itself;[489] pain, skin irritations, fever, and malaise.[490] HIV vaccination may require repeated inoculations, each producing these adverse effects.

Live vaccines carry the risk that the vaccine virus may mutate sufficiently to revert back to its virulent form. Although pre-clinical research is being done on live vaccines, there is no indication that these vaccines will be tested on humans. Should this be, however, trial participants would be exposed to serious risk of harm.[491]

Finally, participation in a HIV preventive vaccine efficacy trial may result in immune tolerance which, in turn, will prevent the trial participant from being successfully immunised against HIV in the future.

Psychological risks to participants in HIV preventive vaccine efficacy trials include stress, anxiety and depression due to having to discuss intimate sexual matters with trial administrators, the stress inherent in being subjected to repeated HIV testing,[492] and also strain in the participants' sexual relations with others, especially when the participants' sexual partners (mistakenly) believe that the participants may infect others with the virus.[493]

After being vaccinated, participants may test HIV-positive on standard ELISA assays even though they are not infected with HIV. This could have serious consequences for participants' prospects of successfully taking out insurance, finding employment, and so on.[494] They may be perceived by a misinformed public to *be* HIV positive. Participants in Phase III trials are usually high-risk individuals and this perception may cause them to be stigmatised and discriminated against. The communities from which these participants are drawn may be similarly stigmatised.

6 CONCLUSION

This chapter aims to provide the scientific foundation for the ethical and rights-based analyses in subsequent chapters.

In order to do this HIV has been classified and described. The natural progression of the disease has been outlined and the peculiarities of the HIV and AIDS syndrome and progress made in its treatment have been investigated. It has

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489 Such as an allergic reaction to one of its components. See para 2.3.1 of ch 5 below.

490 UNAIDS (2000) *Ethical considerations in HIV preventive vaccine research* 28. See para 2.3.1 op ch 5 below.

491 See para 4.4 above.

492 UNAIDS (n 490 above) 29. See para 2.3.1 op ch 5 below.

493 As above.

494 As above. See ch 5 below on attempts to prevent this risk from materialising.

been pointed out that, although relatively effective, HAART is not a long-term solution to halting the epidemic.

It was argued that an effective HIV preventive vaccine is the only way of controlling and eradicating HIV. In order to arrive at a successful vaccine clinical research will have to be undertaken. Such clinical research, by definition, will involve human participants, exposing them to risks and adverse effects.

The sections on challenges posed by HIV vaccine development and on the problems and risks related to HIV vaccine efficacy trials show that there is a long road ahead in the search for an effective HIV preventive vaccine; a road along which science will have to be assisted by ethics and human rights principles.

The focus of some sections in this chapter has been on the scientific framework of HIV preventive vaccine efficacy trials. These sections have been included in preparation for the analysis in chapter 5, which focuses on preventive HIV vaccine efficacy trials in South Africa.

In the following two chapters there is a more general emphasis on HIV-related clinical research in Africa. As background to the more general discussion of clinical research in these chapters this chapter contains an overview of clinical research methodology.

The discussion turns to an examination of ethical issues with regard to HIV-related clinical research in Africa.