William W. Fisher III\textsuperscript{1} and Talha Syed\textsuperscript{2}

\textbf{Infection: The Health Crisis in the Developing World and What We Should Do About It}  
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\textbf{Chapter 1: The Diseases}\textsuperscript{3}

A. Viral Diseases

Viruses are the smallest infectious agents. Lacking cell structure themselves, they survive and reproduce by invading the cells of other organisms. This section examines the subset of the infectious diseases rampant in the developing world that are caused by viruses.

1. HIV

The best known member of this group is the human immunodeficiency virus (HIV), the principal manifestation of which is Acquired Immune Deficiency Syndrome (AIDS). HIV is no longer quite as deadly as it was in the 1980s, but it still causes enormous suffering, the bulk of it in developing countries.

Today, roughly 35 million people in the world are infected with HIV.\textsuperscript{4} Each year, 4\% (1.5 million) of them die. This is significantly fewer than the 2.4 million who died during 2005, the peak year, but still an appalling number. Since 2001, the number of people who are newly infected with HIV each year has been declining, but it still exceeds 2 million, 250,000 of whom are children.\textsuperscript{5} The adult prevalence of the disease (as of 2011) is shown in the following map.\textsuperscript{6}

HIV is a retrovirus, which (unlike most viruses) stores its genetic information in the form of single-stranded RNA, rather than DNA. After it has invaded a host cell, the HIV virus uses an enzyme to generate DNA from the its RNA – a process known as “reverse transcription” because ordinarily RNA is “transcribed” from DNA. This modified DNA is then incorporated into the genome of the host cell, after which the virus is perpetuated by the replication of the host-cell DNA. The principal host cells targeted by HIV are CD4+ T lymphocytes and related components of the immune system.

HIV is transmitted from one person to another in three main ways: through unprotected sexual relations; through sharing of needles or syringes (typically by intravenous drug users); and from mother to child during pregnancy, birth, or breastfeeding. In the 1980s and ‘90s, it was also sometimes transmitted through blood transfusions or organ transplants, but these methods are now rare. In many developed countries, the primary form of sexual transmission has been through male-to-male relations, but in most developing countries, the primary form has been through heterosexual relations.

The disease caused by HIV typically proceeds through three main phases. Roughly three weeks after transmission, the infected person begins to suffer from symptoms that resemble those associated with influenza: fever, tender lymph nodes, rashes, sores, diarrhea, and so forth. The underlying cause of these symptoms is a sharp drop in the concentration of CD4 lymphocytes in the person’s blood and intestinal mucosa and a resultant degradation of her immune system. Roughly nine weeks after transmission, this acute phase of the disease subsides. It is succeeded by a long period of clinical latency, during which the person’s CD4 count initially rebounds (in the blood, although not in the mucosa), then very slowly declines. The average duration of the latency period is 8 years, but can be as long as 20 years. Some infected persons never move beyond this phase. In most, however, latency gradually gives way to the set of debilitating and life-threatening symptoms known as AIDS. As the person’s CD4 count nears zero and her immune system deteriorates, she is beset by a
growing set of opportunistic infections and viral induced cancers. If untreated, she typically dies within 2 years.

Various schemas have been developed to mark the progress of the disease. With respect to developing countries, the most influential is the set of four “clinical stages” defined by the World Health Organization. Stage 1 is “asymptomatic” – corresponding roughly to the latency period described above. Stage 2 (CD4 count under 500) is characterized by “mild symptoms” (e.g., recurrent respiratory infections, herpes zoster, fungal nail infections); stage 3 (CD4 count under 350) by “advanced symptoms” (e.g., weight loss, chronic diarrhea, pulmonary tuberculosis, pneumonia); and stage 4 (CD4 count under 200) by “severe symptoms” (e.g., “wasting syndrome,” extrapulmonary tuberculosis, Kaposi’s sarcoma, disorders of the central nervous system). If a course of these drugs is administered soon enough, it usually slows dramatically the progress of the disease. In some cases, however, the patient either develops resistance to the drugs or suffers increasingly severe side effects. At that point, he or she is usually given so-called “second line” ARVs. These typically combine previously unused reverse transcriptase inhibitors with protease inhibitors (PIs), which impede the replication of the virus and the release of viral particles from the host cell into the bloodstream. PIs that target HIV include saquinavir (developed by Roche), ritonavir (developed by Abbott [renamed AbbVie]), indinavir (developed by Merck), nelfinavir (developed by Agouron Pharmaceuticals and Eli Lilly), and fosamprenavir (a variant of amprenavir, developed by GlaxoSmithKline). If the second-line drugs lose effectiveness, they are replaced by “third line” ARVs – sometimes grimly called “salvage regimens.”

No cure for HIV/AIDS currently exists. However, since the early 1990s, medicines have become available that can slow or halt the progress of the disease. These medicines are commonly known variously as “anti-retroviral” drugs (ARVs), less commonly as antiretroviral therapies (ARTs) or highly active antiretroviral therapies (HAARTs). The most effective are reverse transcriptase inhibitors, which impede the process, described above, by which modified DNA is generated from HIV RNA. Inhibitors of this sort include zidovudine (AZT), tenofovir (TDF), lamivudine (3TC), stavudine (d4T), and emtricitabine (FTC). Combinations (“cocktails”) of these drugs have proven to be more effective that single drugs; typically, they are administered in combinations of three.

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As yet, there is no effective vaccine for HIV. This is not for lack of effort. Of diseases we will be considering in this book, HIV has received by far the most attention from researchers, foundations, pharmaceutical firms, and governments. Much of that attention has focused on vaccine development. To date, more than 30 vaccine projects have

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7 For lists of the other symptoms that characterize each stage, see http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf, pp. 15-16 (adults) and 17-18 (children).
8 For a comprehensive catalogue of the ARVs used in developing countries, see MSF, "Untangling the Web of Antiretroviral Price Reductions, 16th Ed.," (2013)., pp. 16-46.
9 For a catalogue of the principal combinations of ARVs, see ibid., pp. 47-69.
proceeded to clinical testing. Of those, four have completed efficacy trials. Only one has shown any significant power to prevent HIV infections in humans, and the effect of that single candidate (known as RV-144) was modest (31% efficacy in a small group of Thai volunteers).\(^\text{11}\)

Several circumstances, in combination, explain this disappointing result: the fact that, in the overwhelming majority of cases, HIV infection does not result in protective immunity, which deprives researchers of the naturally generated antibodies that are ordinarily employed to design vaccines;\(^\text{12}\) the extraordinary genetic diversity among HIV strains and the speed with which the virus evolves in vivo;\(^\text{13}\) and the difficulty of inducing immune protection in the mucosa, where the virus commonly enters the body.\(^\text{14}\) Despite these impediments, work on the development of an HIV vaccine continues. Some of the current projects focus on mechanisms for slowing the progress of infections.\(^\text{15}\) But the holy grail remains a vaccine that (like those discussed in the Introduction) would protect people fully from infection.\(^\text{16}\)

In the absence of an effective vaccine, efforts to halt the AIDS pandemic have focused on reducing the frequency of transmissions of the HIV virus from one person to another. Strategies of these sorts include:

- encouraging use of condoms during sexual relations (which sharply reduces transmissions of the virus);\(^\text{17}\)
- male circumcision (which significantly reduces sexual transmissions from females to males, though not necessarily transmissions from males to females or males to males);\(^\text{18}\)

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\(^{12}\) See David A. Garber et al., Prospects for an AIDS Vaccine: three big questions, no easy answers, The Lancet Infectious Diseases Vol. 4 at 397 (July 2004). The significance of this circumstance is suggested by the fact that live-attenuated varicella zoster virus vaccine is the only vaccine ever to be developed for “pathogens that reproducibly establish lifelong infection in their hosts.” Id. at 399.

\(^{13}\) Several factors have been identified as particularly problematic to the antibody approach to vaccine development: (1) virus particles are difficult to neutralize, (2) the rapid evolution of the virus in vivo, (3) extraordinarily high levels of viral genetic diversity and (4) the down-regulation of MHC-1 molecules on the surface of infected cells. See id. at 399.

\(^{14}\) WHO, "Global Update on the Health Sector Response to HIV, 2014."


\(^{16}\) See Richard D. Klausner et al., The Need for a Global HIV Vaccine Enterprise, Science, Vol. 300 at 2036 (June 27, 2003); WHO, "Global Update on the Health Sector Response to HIV, 2014."

\(^{17}\) See Johnson et al., “The Effect of Changes in Condom Usage and Antiretroviral Treatment Coverage on Human Immunodeficiency Virus Incidence in South Africa,” 9 J R. Soc. Interface 1544 (2012). The current rates of condom use in the countries where HIV is most prevalent are reviewed in ibid., pp. 11-12.

• sexual-abstinence programs (the efficacy of which is as yet unproven);
• providing testing and medical services to sex workers and to intravenous drug users, who are much more likely to be HIV-positive than the general population;¹⁹
• providing sterile or disposable syringes to intravenous drug users;²⁰
• prophylactic administration of ARVs, especially to the infected partners in serodiscordant couples²¹ and to infected pregnant women (which, if begun early enough, nearly eliminates transmission of the virus to their children);²²
• testing blood supplies, to prevent transmission through infusions;²³ and
• the use of various precautions by health-care workers, to reduce transmissions from their patients.

Essential both to management of the disease in infected persons and to several of the transmission-prevention programs just described is the availability of ARV drugs. For the first five years after they became publicly available, most of those drugs were subject to patent protection (at least in developed countries), and the companies that held the patents to them charged high prices – typically between US $10,000 and 15,000 for a year-long course of first-line drugs. These prices placed the drugs beyond the reach of almost all infected persons in developing countries. Starting in 2001, the prices of first-line ARVs in developing countries began to drop sharply. A diverse combination of factors produced the decline: the patents on some of the drugs expired; the efforts of several pharmaceutical firms to prevent South Africa from imposing a compulsory license on their remaining patents produced a public-relations backlash, which in turn prompted the firms to offer to sell their products at low prices in poor countries; generic drug manufacturers in India (where pharmaceutical product patents were not available until recently) began producing ARV cocktails and selling them cheaply in other countries;²⁴ the government of Brazil used its bargaining power to extract major price concessions from some of the pharmaceutical firms; the Clinton Foundation (starting in 2002) and UNITAID (starting in 2006) began negotiating contracts with pharmaceutical firms to make cheap ARVs available in developing countries; after 2010, some other countries (such as Thailand, Indonesia, and Ecuador) followed South Africa’s lead in imposing compulsory licenses on ARVs still subject to patent protection; and eventually, some pharmaceutical firms began donating ARVs – or granting generics royalty-free licenses to produce them – in poor countries.

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¹⁹ See WHO, "Global Update on the Health Sector Response to Hiv, 2014.", Table 2.2.
²¹ WHO, Note 51
²² WHO, "Global Update on the Health Sector Response to Hiv, 2014.", Chpt. 3.
²³ WHO, Notes 58, 60.
The net effect of these disparate forces is that a year-long course of first-line drugs is now available in most low-income countries for roughly $140. This modest price has, in turn, enabled governments and NGOs to underwrite the cost of the first-line drugs, which in turn has facilitated a radical expansion of the set of people who have access to them. The percentage of HIV-positive people throughout the world who now receive ART is roughly 37% (up from 10% in 2006). (The percentage of children is lower: roughly 25%). Both numbers are rising.

All is not well, however. The prices of first-line ARVs in many middle-income countries, where a majority of HIV-positive people lives, are substantially higher than in low-income countries. Equally important, second and third-line drugs are not as inexpensive or as readily available. Currently, a year-long course of the former costs (even in poor countries) roughly $330, and a year-long course of the latter typically costs over $500 in low-income countries and several thousand dollars in middle-income countries. The result is that significant numbers of AIDS patients in whom the first-line drugs are no longer effective cannot afford their successors and die.

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27 Id.

28 See MSF, "Msf, Untangling Arvs.", p. 2.


30 See ibid., p. 7.
References


