HIV and the Pathogenesis of AIDS

THIRD EDITION
To Sharon, for her continual support and encouragement.
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Preface

It hardly seems possible that nearly 10 years have passed since the second edition of this book was written. It is fitting to complete this third edition on the 25th anniversary of the recognition of AIDS in the world (1981). It has been quite a task, but also a pleasure, to cover the past decade of scientific articles in many different areas of HIV/AIDS research and to select those that have contributed the most notable new information to the field. Most of the new knowledge has added incrementally to the past information that was established in the first 15 years of research on this major human epidemic and was covered in the second edition. For this reason, several of the early quite definitive original articles in each topic remain cited in the book, but subsequent articles confirming the findings without adding much new information were deleted. They can be found in the first or second editions of this book.

New knowledge in basic and clinical research, as well as epidemiology and social science, has helped improve our understanding of HIV/AIDS and has provided novel approaches in prevention and treatment. The most recent contributions to these fields are cited in each chapter. Features of AIDS pathogenesis, including aspects of the HIV-1 and HIV-2 isolates involved; the cells infected; the consequences of this infection; and the host immune response to HIV are discussed in this book. Moreover, potential approaches for therapy and a vaccine for the prevention of HIV infection and AIDS are considered. Because of the interactions among the various chapters, readers are directed in the text to various sections in the book that cover the topic in greater detail. As an example, R5 and X4 subtypes are introduced very early in the book, before their definition in the text (Chapter 4). The term HIV is used generically to indicate observations with HIV-1 and HIV-2.

The Pioneers in HIV Research cited in the book are individuals who were actively involved in HIV research from the early 1980s (1981-83) and who continued to contribute to the field. Many of them have served as mentors to a large number of currently active HIV/AIDS investigators.

Among the major additions to our knowledge of HIV over the past decade has been the elucidation of intracellular controls of HIV replication that have
been identified by genetic studies. APOBEC3G and TRIM5a, which block HIV replication, provide approaches for novel antiviral therapies (Chapter 5). The identification of genetic markers for susceptibility to HIV infection and determinants of the clinical course has been greatly expanded (Chapter 13). Moreover, for therapy, the development of decoys for cell surface proteins, including chemokine coreceptors used for entry, has resulted in an emphasis on entry inhibitors along with virus fusion inhibitors that can serve as new targets for the anti-HIV drug armamentarium (Chapter 14).

Clinical trials have clarified to some extent what drugs to use in initiating therapy and take into consideration the potential toxicities of the treatments. In many cases, protease inhibitors are now avoided because of the clinical disorders particularly linked to these drugs. The use of combination therapy with one pill taken once daily has certainly enhanced the adherence of individuals on drug therapy and hopefully will limit development of virus resistance (Chapter 14). In this regard, the timing for the initiation of drug administration in chronically infected people is now better appreciated. The threshold for beginning highly active antiretroviral therapy (HAART) has been raised so that individuals who are healthy but have CD4+ cell counts of >250 cells/ml may not need therapy; viral loads are not as important in the decision for treatment (see Table 14.3). At the same time, the initiation of therapy in primary infection still requires further evaluation. Some results have suggested that treatment prior to seroconversion can be of clinical benefit to the HIV-infected individual (Chapters 4 and 14). Currently, ongoing studies are evaluating if and when one could stop HAART (i.e., structured treatment interruption [STI]) and permit the patient to be treatment-free for a while. STI for chronic infection has thus far not been encouraging, but in patients treated during acute infection, the procedure may be possible (Chapter 14).

Whereas 10 years ago I was surprised that viral latency was not as well researched as it had been in the first 5 years of this epidemic, more recently this topic has received further attention (Chapters 5 and 14). The interest stems from the discovery of residual virus-infected cells that remain in individuals who are on very effective anti-HIV therapy. Not surprising to those working with retroviruses, an agent like HIV, which becomes part of the genetic machinery of the cell, cannot be eliminated with the drugs currently available. Although the present anti-HIV treatments can make progeny viruses noninfectious (protease inhibitors) or not replicative competent (reverse transcriptase inhibitors), they still leave cellular reservoirs of the virus, even at low numbers, that can rebegin the infectious cycle and give rise to resistant strains (Chapter 4). Thus, approaches targeting a variety of cellular reservoirs need to be given continued attention (Chapters 5 and 14).

Also very important over the last 5 years has been the appreciation of the importance of innate immunity both as the first response to HIV (Chapter 9) and for its likely role in preventing infection in exposed seronegative individuals (Chapter 13). This arm of the immune system certainly plays a role, along with adaptive immunity, in maintaining virus control in several untreated healthy individuals infected for more than 25 years. This feature is dramatically illustrated in long-term survivors or long-term nonprogressors (Chapter 13). More knowledge of the immune system has led to further, though not sufficient, attention to immune system-based therapies, particularly using cytokines (e.g., interleukin-2 and interferon α) and dendritic cell approaches (Chapter 14).
Vaccine development has received greater emphasis over the past 10 years but has not yet revealed an approach for effective prevention of HIV transmission (Chapter 15). Completion of the first phase III trials provided important information on various legal, social, and public health issues and procedures that are needed to establish an effective vaccine trial, although they did not show efficacy. Other phase III and phase II trials are in progress, keeping this important topic in the forefront of clinical studies. Nevertheless, it is obvious to most investigators that a vaccine will not be available in the very near future. Thus, education on how to prevent the infection as well as the use of antiretroviral drugs in low-resource countries should help limit transmission (Chapter 3) and reduce the spread of the epidemic.

Other advances since 1997 that have improved our understanding of HIV pathogenesis and treatment include the following:

1. Additional HIV-1 clades have been identified in the M (main) group of HIV-1 (K and L), and clades E and I have now been recognized as recombinant viruses (Chapter 1). In addition, the O (outlier) clade has been found to have many representatives. The past decade has also revealed a new group (N [non-M, non-O]) that has had very few isolates in human populations; they most resemble the chimpanzee isolate. Thus, HIV as a zoonotic infection has been further emphasized (Chapter 1). Importantly, HIV appears to be continually evolving perhaps with founder viruses entering human populations with specific genetic features and immune responses (Chapters 1, 7, 8, and 13).

2. Several HIV-2 isolates have been found, and more extensive classification of this subtype has been established, with five new groups (notably not clades) recognized (Chapter 1).

3. The increasing incidence of recombinant viruses indicates that dual infection and superinfection can occur (Chapter 4). Recombination brings new types of viruses to human populations. Some of these may carry resistance to anti-HIV immune responses and therapies. For that reason, this ongoing viral process must be considered in curtailing the epidemic.

4. The role of immune activation in HIV pathogenesis has received much more appreciation, particularly in its induction of cell loss by cytokine-induced apoptosis (Chapters 5 and 13).

5. The field of HIV research has helped to redefine subsets of CD4+ and CD8+ T cells which reflect their naïve, or memory, status, whether activated or resting (Chapters 4, 8, and 11). The varying abilities of R5 and X4 viruses to infect subsets of cells have been shown to influence the pathogenic pathway (Chapters 4 and 13). It has become evident that HIV can infect resting T cells through cytokine exposure or the nature of the particular resting cell subset. The virus infects, integrates, and then can become latent in these cells.

6. Novel new functions of viral accessory genes are now highlighted (Chapter 7). The vast number of intracellular activities seems too large to be attributed solely to each of the viral proteins, but these pleiotropic functions are impressive. Targeting these viral gene products or the cellular proteins involved in their function offers new directions for therapy.

7. As noted above, great progress has been made in identifying genetic factors that are associated with the susceptibility of individuals to infection and a clinical course, reflecting either very rapid progression or long-term survival (Chap-
These observations give further support to the importance of both innate and adaptive immunity as targets for approaches to control HIV infection.

8. In the field of adaptive immunity, various different functioning subsets of cytotoxic T cells can now be distinguished, which helps to explain why tetramer-positive or HIV-specific CD4+ and CD8+ cells may be detected (e.g., by Elispot or intracellular cytokine production) but may not function as cytotoxic cells (e.g., lack perforin) (Chapters 11 and 13).

9. Some new information has been obtained in our understanding of neutralizing versus enhancing antibodies. Monoclonal antibodies with exquisite epitope selectivity have helped define regions in the viral envelope that can elicit broadly reactive humoral responses. The recognition that the removal of certain regions of the viral envelope (e.g., V2) may increase sensitivity of viruses to neutralization and help in the induction of neutralizing antibodies may provide novel approaches for vaccines (Chapter 10). Nevertheless, some broadly reactive antibodies have been found to cross-react with normal cellular proteins. Thus, how to induce virus-specific antibodies with strong neutralizing activity against a variety of diverse HIV groups and clades remains a challenge.

10. HIV neuropathogenesis has been further explored. Although new observations are limited, there is a greater acceptance of other cell types (e.g., astrocytes or oligodendrocytes) besides macrophages/microglia that can be infected by HIV and contribute to central nervous system disorders (Chapter 8).

11. The field of HIV enteropathy is better appreciated than it was 10 years ago, with the recognition of massive CD4+ cell infection and destruction in the gastrointestinal tract early in infection (Chapters 4 and 8). Infection of other organs such as the kidney and the compartmentalization of viruses in various tissues (e.g., the brain or testes) where they can undergo independent evolution have been noted (Chapters 4 and 8). Thus, having an absence of detectable virus in the blood does not necessarily indicate that there is no infectious virus elsewhere in the body, particularly in the gastrointestinal tract and genital fluids (Chapters 2 and 3).

12. In HIV-related cancers (Chapter 12), greater knowledge has been gained on the viruses associated with the malignancies (e.g., KSHV/HHV8, EBV, HPV) and HAART has reduced the incidence of most of these cancers. Several important steps, from infection to tumor development, remain to be elucidated.

13. Microbicides have been emphasized for prevention of HIV infection (Chapters 2 and 3). The progress in this field has not been dramatic, although clinical trials of diaphragms to block transmission via the cervical canal may provide encouraging results. Currently, it appears that microbicides that cover the vaginal wall and prevent contact with HIV-infected cells and the free virus would be the best approach. In this way, the antiviral compounds will not induce lesions in the vaginal and anal canals that could enhance virus infection.

14. In vaccines, the use of DNA as a vaccine approach has been less encouraging because it does not induce good humoral immunity and induces only limited cellular immunity. Prime/boost approaches continue to show promise, although the use of two different modalities has not been as popular as it was several years ago (Chapter 15).

15. Within the past 3 years, a greater emphasis has been given to the development of an AIDS vaccine through funding from the Bill and Melinda Gates Foundation, the National Institutes of Health, the International Agency for Vac-
cine Initiative (IAVI), and other international organizations. With this new support, one can hope for advancements and development of an effective vaccine in the very near future. In addition, further attention to the immune system and treatment strategies to harness immune responses against HIV should receive even greater emphasis.

Since 1998, the pandemic of HIV infection has continued to increase, with several additional countries (e.g., India, China, Nigeria, and Russia) experiencing the speed with which this infection can spread (Table A). The factors that are associated with the emergence and spread of the AIDS epidemic remain the same (Table B). Fears of similar large epidemics in countries such as Indonesia are surfacing. Education is the immediate approach available, and a vaccine is a vital necessity. It can be estimated that a new infection takes place in the world every 7 seconds and a death from HIV infection occurs every 10 seconds. In 1996, it was projected that by the year 2000, over 100 million individuals would be infected by HIV-1 or HIV-2 (2794). Because of the introduction of HAART, the number is now estimated to be about 40 million people infected with HIV worldwide (http://www.unaids.org) (Figure A) (Table A), and 22 million persons have died.

In the United States 40,000 new cases were reported in 2005. In 2006, 1 million people in the United States were living with HIV/AIDS (660). In the first edition of this book, 1 in 250 Americans was estimated to be infected by HIV.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of infected persons (millions)</th>
</tr>
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<tbody>
<tr>
<td>India</td>
<td>6.5</td>
</tr>
<tr>
<td>South Africa</td>
<td>5.5</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>4.1</td>
</tr>
<tr>
<td>Nigeria</td>
<td>3.6</td>
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<tr>
<td>Mozambique</td>
<td>1.8</td>
</tr>
<tr>
<td>Kenya</td>
<td>1.7</td>
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<tr>
<td>Zimbabwe</td>
<td>1.7</td>
</tr>
<tr>
<td>USA</td>
<td>1.3</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>1.0</td>
</tr>
<tr>
<td>China</td>
<td>1.0</td>
</tr>
</tbody>
</table>


Table A Number of HIV-infected persons (2006)*

Table B Factors conducive to the emergence of the AIDS epidemic

- Migration of carriers into cities – increased interpersonal contacts
- Poverty, prostitution
- International travel
- Sexual behavior
- Intravenous drug use
- Receipt of blood and blood products
including 1 in 100 males and 1 in 800 females. That number has not changed appreciably, indicating that either the prediction in 1993 was too high or the rate of new infections has stabilized. Nevertheless, the total number of U.S. cases of HIV infection since AIDS was recognized in 1981 has now reached nearly 2 million. More than 500,000 Americans have died from the disease. It is estimated that 275,000 people in the United States are HIV infected but have not been tested and identified. Until 1996, AIDS in the United States was the leading cause of death among young people, both male and female, between 25 and 44 years of age. Death from AIDS has now decreased because of the success of the antiviral therapies (Chapter 14). However, since 1992, non-Hispanic blacks, Hispanics, and women have accounted for increased proportions of AIDS cases. In 2005, women represented 25% of all U.S. adult cases reported. Currently, less than half of the new AIDS cases in the United States result from transmission by homosexual and bisexual men (45%) (660).

Papers published on HIV and AIDS have increased at a rapid rate. As of December 2006 (2952), a total of about 250,000 articles have been written on this subject since the initial report on AIDS in 1981 (652). The number of papers published on HIV and AIDS peaked at 19,721 in 1996. For this edition, about 5,000 have been cited.

To gain a perspective on the changes in our knowledge of HIV/AIDS and emphasis in research, readers are recommended to read the Prefaces to the first and second editions of this text. Criteria for AIDS as defined by the Centers for Disease Control are found in Appendices I and IV. The well-known relationship of CD4+ cell number to the risk of opportunistic infections and cancer is shown in Appendix V. The research conducted by my co-workers and myself was supported by grants from the National Institutes of Health, the California State
Universitywide Task Force on AIDS, the American Foundation for AIDS Research, the Campbell Foundation, and the James B. Pendleton Charitable Trust. In addition to my gratitude to those who provided helpful suggestions and advice on the initial text in *Microbiological Reviews* and the other editions of this book, I want to thank the following individuals for their assistance with the present edition: Lena Al-Harthi, Marcus Altfeld, Brigitte Autran, Edward Barker, David Blackbourn, Susan Buchbinder, Rick Bushman, Dennis Burton, Michael Busch, Andrew Carr, Mary Carrington, Cecilia Cheng-Mayer, Mario Clerici, Deborah Cohan, Suzanne Crowe, Tony Cunningham, Andrew Davison, Steven Deeks, Lisa Demeter, Josef Eberle, Lawrence Fong, Donald Forthal, Donald Francis, Robert Garry, Stephen Goff, Marie-Lise Gougeon, Carl Grunfeld, Phalguni Gupta, Ashley Haase, Beatrice Hahn, Marc Hellerstein, Walid Heneine, James Hoxie, Shiu-lik Hu, Rachel Kaplan, Paul Klotman, Bette Korber, Donald Kotler, Alan Landay, Nathaniel Landau, Michael Lederman, Alexandra Levine, Paul Luciw, Francine McCutchan, Preston Marx, Susan Moir, Laura Napolitano, Philip Norris, Jorge Oksenberg, Nancy Padian, Joel Palefsky, Tristram Parslow, David Pauza, Matija Peterlin, John Phair, Vicente Planes, Lynn Pulliam, Jacqueline Reeves, Edward Robinson, Mario Roederer, Robert Seder, Haynes Sheppard, Robert Siliciano, Gregory Spear, Leonidas Stamatatos, Ralph Steinman, Jeffrey Ulmer, Eric Verdin, Robert Winchester, and John Zaunders. I thank Julie Winters and Pamela Lacey for their help in editing and production, Krista Preckel for her assistance, Ann Murai for her excellent help with the manuscript, and particularly Kaylynn Peter for her close attention and overall handling of this book.

I hope this newly revised text will continue to be a helpful resource for researchers, clinicians, health care providers and students, who are all part of the important group dedicated to finding a solution to this devastating epidemic.
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