Why study evolution? An incentive for Charles Darwin (1859) was that understanding evolution can help us know ourselves. “Light will be thrown,” he wrote, “on the origin of man and his history.” The allure for Theodosius Dobzhansky (1973), an architect of our modern view of evolution, was that evolutionary biology is the conceptual foundation for all of life science. “Nothing in biology makes sense,” he said, “except in the light of evolution.” The motive for some readers may simply be that evolution is a required course. This, too, is a valid inducement.

Here we suggest an additional reason to study evolution: The tools and techniques of evolutionary biology offer crucial insights into matters of life and death. To back this claim, we explore the evolution of HIV (human immunodeficiency virus). Infection with HIV causes AIDS (acquired immune deficiency syndrome)—sometimes, as shown at right, despite triple-drug therapy.

Our main objective in Chapter 1 is to show that evolution matters outside of labs and classrooms. However, a deep look at HIV will serve other goals as well. It will illustrate the kinds of questions evolutionary biologists ask, show how an evolutionary perspective can inform research throughout biology, and introduce concepts that we will explore in detail elsewhere in the book.

Multidrug therapies have, for some patients, transformed HIV from fatal to treatable. Such therapies work best for conscientious patients, but still may fail. The data below are from 2,800 patients on triple-drug therapy (Nachega et al. 2007).

A Case for Evolutionary Thinking: Understanding HIV
HIV makes a compelling case study because it illustrates public health issues likely to influence the life of every reader. It is an emerging pathogen. It rapidly evolves drug resistance. And, of course, it is deadly. AIDS is among the 10 leading causes of death worldwide (Lopez et al. 2006; WHO 2008).

Here are the questions we address:

- What is HIV, how does it spread, and how does it cause AIDS?
- Why do therapies using just one drug, and sometimes therapies using multiple drugs, work well at first but ultimately fail?
- Are human populations evolving as a result of the HIV pandemic?
- Where did HIV come from?
- Why are untreated HIV infections usually fatal?

While one of these questions contains the word evolution, some of the others may appear unrelated to the subject. But evolutionary biology is devoted to understanding how populations change over time and how new forms of life arise. These are the issues targeted by our queries about HIV and AIDS. In preparation to address them, the first section covers some requisite background.

1.1 The Natural History of the HIV Epidemic

AIDS was recognized in 1981, when doctors in the United States reported rare forms of pneumonia and cancer among men who have sex with men (Fauci 2008). The virus responsible, HIV, was identified shortly thereafter (Barré-Sinoussi et al. 1983; Gallo et al. 1984; Popovic et al. 1984). Nearly always fatal, HIV/AIDS was devastating for those infected. But few physicians or researchers foresaw the magnitude of the epidemic to come (Figure 1.1).

Indeed, many were optimistic about the prospects for containing HIV (Walker and Burton 2008). Smallpox had been declared eradicated in 1980 (Moore et
al. 2006), and vaccines and antibiotics had brought many other infectious diseases under control. In 1984 the U.S. Secretary of Health and Human Services, Margaret Heckler, predicted that an AIDS vaccine would be ready for testing in two years. Actual events have, of course, played out rather differently.

HIV has infected over 65 million people (UNAIDS 2010, 2012a). Roughly 30 million have died of the opportunistic infections that characterize AIDS. The disease is the cause of about 3.1% of all deaths worldwide (WHO 2008/2011). AIDS is responsible for fewer deaths than heart disease (12.8%), strokes (10.8%), and lower respiratory tract infections (6.1%)—common agents of death among the elderly. But it causes more deaths than tuberculosis (2.4%), lung and other respiratory cancers (2.4%), and traffic accidents (2.1%).

Figure 1.1 summarizes the global AIDS epidemic. The map reveals substantial variation among regions in the number of people living with HIV, the percentage of the population infected, and the proportion of infected individuals who are women versus men versus children. The graphs show that the number of people infected has peaked in some countries but continues to climb in others.

The epidemic has been most devastating in sub-Saharan Africa, where 1 in 20 adults is living with HIV (UNAIDS 2008). Worst hit is Swaziland, with 26% of adults infected, followed by Botswana at 24%; Lesotho, 23%; and South Africa, 18%. Across southern Africa, life expectancy at birth has dropped below 50, a level last seen in the early 1960s (Figure 1.2a). The good news is that the annual rate of new infections in sub-Saharan Africa has been falling for over a decade (UNAIDS 2012). This has meant that the global rate of new infections has been falling as well (Figure 1.2b).

In developed countries, overall infection rates are much lower than in sub-Saharan Africa (UNAIDS 2008). In western and central Europe, 0.3% of adults are infected. In Canada the rate is 0.4%, and in the United States it is 0.6%. For certain risk groups, however, infection rates rival those in southern Africa. Among men who have sex with men, the infection rate is 12% in London, 18% in New York City, and 24% in San Francisco (CDC 2005; Dodds et al. 2007; Scheer et al. 2008). Among injection drug users, the infection rate is 12% in France, 13% in Canada, and 16% in the United States (Mathers et al. 2008).

**How Does HIV Spread, and How Can It Be Slowed?**

A new HIV infection starts when a bodily fluid carries the virus from an infected person directly onto a mucous membrane or into the bloodstream of an uninfected person. HIV travels via semen, vaginal and rectal secretions, blood, and breast milk (Hladik and McElrath 2008). It can move during heterosexual or homosexual sex, oral sex, needle sharing, transfusion with contaminated blood products, other unsafe medical procedures, childbirth, and breastfeeding.

HIV has spread by different routes in different regions (Figure 1.3, next page). In sub-Saharan Africa and parts of south and southeast Asia, heterosexual sex has been the most common mode of transmission. In other regions, including Europe and North America, male–male sex and needle sharing among injection drug users have predominated. Certain activities are particularly risky. For example, data on men who have sex with men in Victoria, Australia, show that having receptive anal intercourse with casual partners without the protection of a condom is a dangerous behavior. Individuals who report practicing it are nearly 60 times as likely to be infected with HIV as individuals who do not report practicing it (Read et al. 2007).
Clinical studies in which volunteers are randomly assigned to treatment versus control groups have identified medical interventions that reduce the rate of HIV transmission. Use of antiviral drugs, for example, lowers the risk that infected mothers will pass the virus to their infants by about 40% (Suksomboon et al. 2007). Antivirals are similarly effective in reducing transmission among men who have sex with men (Grant et al. 2010). Circumcision reduces the risk that men will contract HIV by about half (Bailey et al. 2007; Gray et al. 2007). Antiviral vaginal gels are comparably beneficial for women (Abdool Karim et al. 2010).

The value of encouraging people to change their behavior is less clear. Behavioral change undoubtedly has the potential to curtail transmission. Consistent use of condoms, for example, may reduce the risk of contracting HIV by 80% or more (Pinkerton and Abramson 1997; Weller and Davis 2002). And there are apparent success stories. In Uganda, for instance, a campaign discouraging casual sex and promoting condom use and voluntary HIV testing is thought to have substantially reduced the local AIDS epidemic (Slutkin et al. 2006; but see Oster 2009). On the other hand, the results of randomized controlled trials have been somewhat disappointing. A study of over 4,000 HIV-negative men who have sex with men in the United States offered extensive one-on-one counseling to members of the experimental group and conventional counseling to the control group (Koblin et al. 2004). As hoped, the experimental subjects engaged in fewer risky sexual behaviors than the controls. However, the rates at which the experimentals versus the controls contracted HIV were not statistically distinguishable.

There is clearly no room for complacency. The graph in Figure 1.4 tracks the number of new infections each year among men who have sex with men in the United States. After falling from the mid 1980s to the early 1990s, the annual number of new infections has since been rising steadily. The same thing seems to be happening elsewhere (Hamers and Downs 2004; Giuliani et al. 2005). Results of surveys suggest that the introduction of effective long-term drug therapies, which for some individuals has at least temporarily transformed HIV into a manageable chronic illness, has also prompted an increase in risky sexual behavior (Crepaz, Hart, and Marks 2004; Kalichman et al. 2007).

**What Is HIV?**

Like all viruses, HIV is an intracellular parasite incapable of reproducing on its own. HIV invades specific types of cells in the human immune system. The virus hijacks the enzymatic machinery, chemical materials, and energy of the host cells to make copies of itself, killing the host cells in the process.
The life cycle of HIV (1, upper left) HIV’s extracellular form, known as a virion, encounters a host cell (usually a helper T cell). (2) HIV’s gp120 surface protein binds first to CD4, then to a coreceptor (usually CCR5; sometimes CXCR4) on the surface of the host cell. (3) The HIV virion fuses with the host cell; HIV’s RNA genome and enzymes enter the host cell’s cytoplasm. (4) HIV’s reverse transcriptase enzyme synthesizes HIV DNA from HIV’s RNA template. (5) HIV’s integrase enzyme splices HIV’s DNA genome into the host cell’s genome. (6) HIV’s DNA genome is transcribed into HIV mRNA by the host cell’s RNA polymerase. (7) HIV’s mRNA is translated into HIV precursor proteins by host cell’s ribosomes. (8) A new generation of virions assembles at the membrane of the host cell. (9) New virions bud from the host cell’s membrane. (10) HIV’s protease enzyme cleaves precursors into mature viral proteins, allowing the new virions to mature.

HIV is a parasite that afflicts cells of the human immune system. HIV virions enter host cells by binding to proteins on their surface, then use the host cells’ own machinery to make new virions.
almost every step. This is why HIV, and viral disease
in general, is so difficult to treat. It is a challenge to
find drugs that interrupt the viral life cycle without also
disrupting the host cell’s enzymatic functions and thus
cauing debilitating side effects. Effective antiviral ther-
api es usually target enzymes specific to the virus, such
as reverse transcriptase and integrase.

How Does the Immune System React to HIV?
A patient’s immune system mobilizes to fight HIV the
same way it moves to combat other viral invaders. Key
aspects of the immune response appear in Figure 1.6.

Sentinels called dendritic cells patrol vulnerable tis-
sues, such as the lining of the digestive and reproduc-
tive tracts (Banchereau and Steinman 1998). When a
dendritic cell captures a virus, it travels to a lymph node
or other lymphoid tissue and presents bits of the virus’s
proteins to specialized white blood cells called naive
helper T cells (Sprent and Surh 2002).

Naive helper T cells carry highly variable proteins
called T-cell receptors. When a dendritic cell presents a
helper T cell with a bit of viral protein that binds to the
T cell’s receptor, the helper T cell activates. It grows
and divides, producing daughter cells called effector
helper T cells. Effector helper T cells help coordinate
the immune response.

Effector helper T cells issue commands, in the form
of molecules called cytokines, that help mobilize a va-
riety of immune cells to join the fight. They induce B
cells to mature into plasma cells, which produce anti-
bodies that bind invading virions and mark them for
elimination (McHeyzer-Williams et al. 2000). They
activate killer T cells, which destroy infected host cells
(Williams and Bevan 2007). And they recruit macro-
phages (not shown), which destroy virus particles or kill
infected cells (Seid et al. 1986; Abbas et al. 1996).

Most effector helper T cells die within a few weeks.
However, a few survive and become memory helper
T cells (Harrington et al. 2008). If the same pathogen
invades again, the memory cells produce a new popu-
lation of effector helper T cells.

How Does HIV Cause AIDS?
As we noted earlier, HIV invades host cells by first
latching onto two proteins on the host cell’s surface.
The first of these is CD4; the second is a called a core-
ceptor. Different strains of HIV exploit different core-
ceptors, but most strains responsible for new infections
use a protein called CCR5. Cells that carry both CD4
and CCR5 on their membranes, and are thus vulner-

Figure 1.6 How the immune system fights a viral infec-
able to HIV, include macrophages, effector helper T cells, and memory helper T cells (Figure 1.7).

The progress of an HIV infection can be monitored by periodically measuring the concentration of HIV virions in the patient’s bloodstream and the concentration of CD4 T cells in the patient’s bloodstream and in the lymphoid (immune system) tissues associated with the mucous membranes of the gut. A typical untreated infection progresses through three phases.

In the acute phase, HIV virions enter the host’s body and replicate explosively. The concentration of virions in the blood climbs steeply (Figure 1.8). The concentrations of CD4 T cells plummet—especially in the lymphoid tissues of the gut. During this time, the host may show general symptoms of a viral infection. The acute phase ends when viral replication slows and the concentration of virions in the bloodstream drops. The host’s CD4 T-cell counts recover somewhat.

During the chronic phase, the patient usually has few symptoms. HIV continues to replicate, however. The concentration of virions in the blood may stabilize for a while, but eventually rises again. Concentrations of CD4 T cells fall.

The AIDS phase begins when the concentration of CD4 T cells in the blood drops below 200 cells per cubic millimeter. By now the patient’s immune system has begun to collapse and can no longer fend off a variety of opportunistic viruses, bacteria, and fungi that rarely cause problems for people with robust immune systems. Without effective anti-HIV drug therapy, a patient diagnosed with AIDS can expect to live less than three years (Schneider et al. 2005).

The mechanisms by which an HIV infection depletes the patient’s CD4 T cells and undermines the patient’s immune system are complex. Despite a quarter century of research, they remain incompletely understood (Pandrea et al. 2008; Douek et al. 2009; Silvestri 2009). The simple infection and destruction of host CD4 T cells may explain their precipitous loss during the acute phase of infection. But the immune system has an impressive capacity to regenerate these cells. Furthermore, during the chronic phase no more than one CD4 T cell in a hundred is directly infected. There must be more to the story.

Figure 1.9 (next page) outlines key events thought to lead from HIV infection to AIDS (Appay and Sauce 2008; Pandrea et al. 2008; Douek et al. 2009; Silvestri 2009). HIV’s attack on the CD4 T cells in the gut (top) initiates a vicious cycle. This attack not only destroys a large fraction of the patient’s helper T cells, it also damages other tissues in the gut that help provide a barrier between gut bacteria...
and the bloodstream. The weakening of this barrier lets bacteria and their products move (translocate) from the gut into the blood (Figure 1.9, upper right).

The translocation of bacterial products into the blood triggers a high level of immune activation, to which the HIV infection itself also contributes (Biancotto et al. 2008). As we saw in Figure 1.6, activation of the immune system induces B cells and T cells to proliferate. This aggressive immune response has benefits, at least temporarily. For example, the anti–HIV killer T cells it yields help restrain HIV’s replication. This and the production of new helper T cells allow the patient’s concentrations of CD4 T cells to recover somewhat (Figure 1.8). But in the case of HIV, a strong immune response comes with heavy costs. The reason is that HIV replicates most efficiently in activated CD4 T cells. In other words, the immune system’s best efforts to douse the HIV infection just add fuel to the fire.

A major battleground in the ongoing fight between HIV and the immune system is the patient’s lymph nodes (Lederman and Margolis 2008). The lymph nodes are, among other things, the places where naive T cells are activated. Chronic infection and inflammation eventually damages the lymph nodes irreversibly and exhausts the immune system’s capacity to generate new T cells. As the patient’s T-cell concentrations inexorably fall, the immune system loses its ability to fight other pathogens. The ultimate result is AIDS.

How might HIV be stopped before it leads to AIDS? The obvious answer is to prevent it from replicating. The first drug to do so, azidothymidine, or AZT, was approved for therapeutic use in 1987 (De Clercq 2009). Clinical experience with AZT, and every antiviral developed since, brings us to the first of our organizing questions. Why do single drugs offer only temporary benefits?