Chapter 46

What HIV Has Taught About the Interactions Between Biology, Culture, and Other Evolving Systems

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THE INTERACTION OF EVOLUTIONARY SYSTEMS

Although our first understanding of the evolutionary process came from biology, we can define evolution more broadly as a gradual process in which something changes into a different and usually more complex or better form. A key to understanding evolutionary systems is the concept of an emergent property as a property of a collection or complex system not present in its component parts. As such, it could not have been predicted ahead of time. A simple example is saltiness, an emergent property of salt, present in neither sodium nor chloride on their own. The field of complexity science categorizes emergent properties into various types (Fromm, 2005) and recognizes such evolutionary processes work at many levels from cosmological, chemical, biological, cultural/political, commercial, scientific/technical/industrial, and regulatory amongst others (Fig. 46.1).

These forms of evolution operate over very differing time frames, and for this reason the emergent properties of older and slower forms of evolution are more likely to exert constraints and selective pressures on more recent or rapidly changing systems than the other way around. This hierarchy in no way implies the greater importance of one field over another but rather may provide guidance of the likely dominant directionality of the influences.

Life on earth is estimated to have begun about 3.5 billion years ago, marking the beginning of biologic evolution. A critical threshold was the emergence of language and collective learning that has only developed in man in the last 250,000 years. This has underpinned downstream evolutionary processes that have further accelerated the appearance of additional emergent properties.

Biological evolution has provided solutions to improve survival and reproductive success, and this has imbued us with strong instincts to nurture our families and insiders and defend against external threats. These instincts were selected for by threats that could be defended, or opportunities that could be exploited, in our environment when we were hunter-gatherers. As efficient as these evolutionary processes are at providing solutions to modifiable threats or exploitable

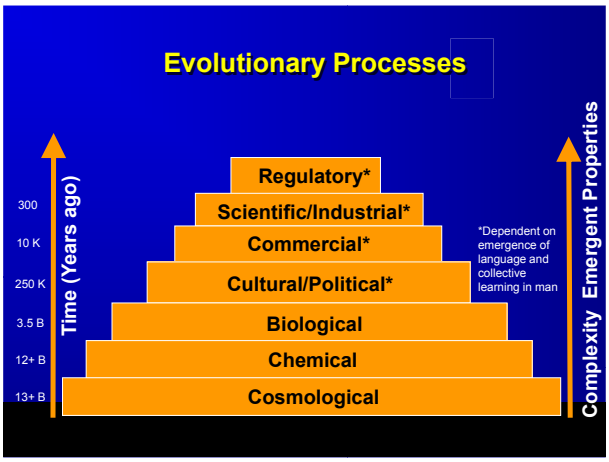

FIGURE 46.1 The pyramid of evolutionary processes: The universe has become increasing complex since its formation over 13 billion years ago. Out of this complexity, new properties have emerged such as language and collective learning in man over the last 250,000 years. This has critically underpinned cultural and other evolutionary processes that shape our world today.

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opportunities in our environment, they do so without simultaneously providing a rationale for why the solution worked. In other words, the human brain is highly adapted, individually and collectively, to empirically solve such problems in our environment, but we are prone to assign an erroneous post-hoc explanation for our success. This may cause a problem at a later time if we act on such assumptions. In contrast, the more painstaking, strictly logical, and deterministic scientific process, a more recent emergent system in evolutionary terms, provides understanding of how things work to facilitate design of solutions.

Language, collective learning, agriculture, industrialization, and globalization have also emerged as solutions to needs of our species, mitigating many of the modifiable threats of our hunter-gatherer past that shaped our instincts. These emergent properties have underpinned our accelerating collective progress and rendered some of our more primitive instincts, such as excessive food-seeking and other addictive behaviors, aggression, paranoia, anxiety, and similar traits unnecessary or maladaptive for most aspects of everyday life today (Fig. 46.2). Commercial and political evolutionary processes can very effectively find and exploit such instincts in an evolutionary arm race for profit as exemplified by the excesses evident in many of the most successful contemporary foods, computer games, social media, sports, entertainment, literature, media, and political strategies.

We have an instinct to move to safe, resource rich settings. Remarkably we live in one of the first generations in which the mass voluntary movement of people has become possible. We have therefore witnessed the establishment of remarkable genetic, ethnic and culture heterogeneity in the developed world and a major translocation of nearly 2 billion people from rural into urban centers in emerging nations. In our time, the basic needs of more people have been met, trade and globalization has increased, and information has come to flow more freely. Altruistic cultural mores have emerged as we have enjoyed an unprecedented period of safety, affluence, and relative peace. Unfortunately, we may not be free to enjoy this as the products of intense cultural and commercial evolution exploit more primitive instincts of old to recreate an environment that often feels as threatening as that of our hunter-gatherer past.

So, what can HIV teach about the interacting evolutionary systems that shape our world? Specifically, why did the HIV pandemic emerge when and where it did, and what can be learned from our response to HIV that might guide our response to other global challenges.

Why Did the HIV Pandemic Emerge When and Where It Did?

The chimp virus Simian Immunodeficiency Virus (SIVcpz) was first transmitted to human hunters or bush meat vendors, and mutated into HIV, in Cameroon at the beginning of the last century. Other species of monkey in East Africa have been found to have their own distinct stains of SIV but not get sick or die. Evolving to this mutual accommodation benefitted both the virus and host and gave these monkeys infectious disease missiles with the potential to annihilate a closely related species competing for local resources. It is of no surprise then that HIV, the greatest emerging infectious disease of our time, came from the monkey species most similar to us. We now know that chimps themselves hunted and ate these two smaller species of ape, red-capped mangabeys and greater spot-nosed monkeys, in west central Africa, and the SIVs from those two viruses recombined to create the hybrid virus SIVcpz that could infect their chimp predators and later man (Bailes et al., 2003).

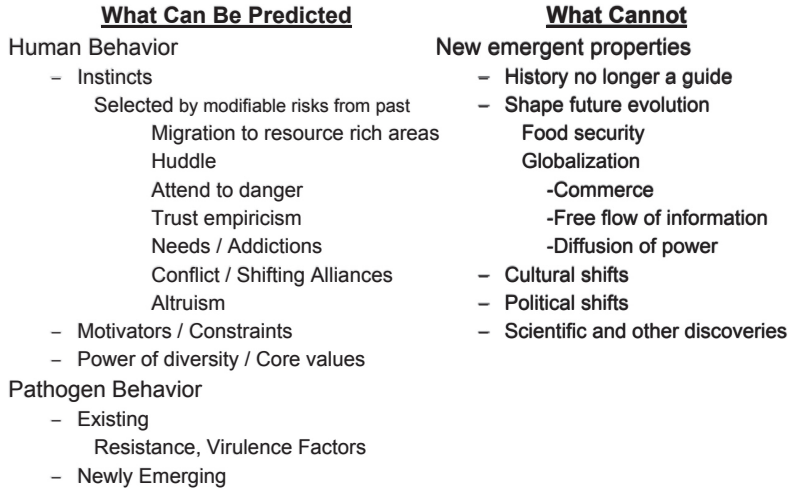

FIGURE 46.2 Predicting the Future: Human and Pathogen Behavior that may been predictable compared to emergent properties that could not have been predicted before they occurred.

Driven by the changes associated with colonialism, HIV is believed to have spread from the Cameroon from the 1920s by road, rail, and river links to the rapidly growing population of Kinshasa in the Democratic Republic of the Congo (DRC) and beyond (Faria et al., 2014). Demographic, cultural, and economic changes also drove increased sexual promiscuity and prostitution with an associated increase in the prevalence of sexually transmitted diseases, which are known to substantially increase the risk of transmission of HIV. Haitian professionals who went to the DRC in the 1960s probably carried the virus back to Haiti in 1964 before a single migration of HIV to the United States is believed to have occurred around 1969 (Gilbert et al., 2007). The rare cancer Kaposi's Sarcoma and infection *Pneumocystis jiroveci* pneumonia were first recognized in homosexual men with low $CD4^+$ T cell counts in New York and California in 1981 (Gottlieb, 1981). These and other unusual opportunistic infections and malignancies were used to define the Acquired Immunodeficiency Disease Syndrome (AIDS) in 1982, and before long, it was apparent the AIDS epidemic was spreading among hemophiliacs and others receiving blood products, intravenous drug addicts, and the infants of those with the syndrome.

There was much initial speculation as to the cause of AIDS until HIV was identified in 1983 (Gallo et al., 1983; Barré-Sinoussi et al., 1983). Why did this take so long? First, there is a latency period of several years between silent infection with HIV and the development of symptomatic AIDS. Second, unlike other viral epidemics such as Ebola, influenza, or SARS, standard laboratory tools of the time could not detect the virus. HIV antibody testing became available in 1984 allowing the identification of HIV-infected individuals before they developed AIDS.

MHC Coevolution With Herpes and Other Viruses

The herpes viruses are large DNA viruses that share more than 100 million years of coevolution with current hosts and have hitched their survival to the particular species they infect (McGeoch et al., 2006). The eight human herpes viruses (Herpes Simplex-1 and -2, varicella zoster, Epstein–Barr, cytomegalovirus, and human herpes virus-6, -7, and -8) have different primary target cells and sites of latency and are very efficient at establishing chronic infection (Virgin, 2009). Herpes and other DNA viruses coadapted with their vertebrate host are known to possess genes encoding molecules that show evidence of homology to molecules of their hosts presumably as a result of horizontal gene transfer (Barry and McFadden, 1997; Lalani and McFadden, 1999).

For most of our evolution, these lifelong infections were acquired early in life, and it has been proposed they provide broadly protective immunodominant epitopes and a form of natural immunization (Chiu et al., 2014). For example, the pp65 protein of rhesus cytomegalovirus (CMV) generates a T cell response that vigorously restricts viral replication during primary infection but has little impact on viral shedding. This appears to be an example of a viral protein that has evolved to benefit a chronic persistent virus by facilitating an acute immune response to avoid overwhelming the host in primary infection, while providing the host long-term benefit at an individual and population level (Malouli, 2014). This symbiotic coevolution has been disrupted since industrialization as infections such as Ebstein–Barr virus (EBV) are acquired later in life in the developed world, and it has been proposed that this is responsible for the increasing incidence of allergy and autoimmune conditions such as multiple sclerosis (Shapira et al., 2010).

The extraordinary polymorphism of major histocompatibility complex (MHC) Class I and II alleles provides protection to infectious diseases at a population level, but the individual only inherits a very limited MHC repertoire. So although every individual in the population inherits the same potential to generate the enormous number of different T cell receptors, the functional T cell repertoire is limited to those cells with T-cell receptors (TCRs) that bind the self HLA-peptide complexes present in the individual with moderate but not high affinity (Bontrop et al., 1995). The individual's human leukocyte antigen (HLA) Class II restricted T cell help, in turn, shape the B-cell repertoire and HLA Class I restricted T cell cytotoxicity.

The key event resulting in the evolution of the molecular components of antibody, TCR, and MHC molecules is believed to have occurred at the base of the jawed vertebrate evolution about 500 million years ago (Flajnik and Kasahara, 2010; Kaufman, 2010). Binding of functionally important and conserved epitopes in vertebrate proteins and chronic persistent infections such as herpes viruses has therefore shaped MHC and TcR coevolution. This phylogeny appears to be recapitulated in T cell ontogeny, where TCRs are first positively selected according to their capacity to recognize the functionally important and conserved host peptide bound by the particular HLA alleles inherited by the individual, and then further activated by conserved but subtly different epitopes from herpes viruses that bind to those same HLA alleles. Some TCR clonotypes are known to be produced more efficiently during V(D)J recombination (Venturi, 2006). This convergent TCR recombination is believed to contribute to the efficient production of TCR receptors that recognize immunodominant herpes epitopes in CMV and EBV. The HLA molecules are also tuned to efficiently recognize evolutionarily conserved and functionally important epitopes. Specifically, the HLA-A alleles and the HLA- B57/58 group target conserved elements of human herpes viruses and the human proteome most efficiently, while the HLA-B alleles target conserved elements of most RNA viruses, such as HIV, well (Hertz et al., 2011).

Human herpes virus infections facilitate the transmission of HIV and its replication in activated CD4 T cells. HIV infection, in turn, depletes CD4 T cells over time, which ultimately results in severe herpes simplex virus (HSV), CMV, EBV, and Kaposi's sarcoma-associated herpesvirus (or human herpes virus-8)-related AIDS diseases. Phylogenetic modelling that allows the strength of natural selection to vary across the viral phylogeny and gene alignment suggests that, after HSV-1 and chimp herpes virus (ChHV) co-diverged around 6 million years ago, ChHV was transmitted back to an ancestor of humans around 1.6 million years ago (Wertheim, 2014). Many HLA-restricted epitopes are shared between HSV-1, HSV-2, and ChHV, and many MHC alleles have been conserved between chimp and man. Similarly, human and chimp CMV are relatively conserved. For example, the HLA-DR7 restricted CMV epitope DYSNTHSTRYV (DYS) is completely conserved in humans and chimps, and human DYS-specific $CD4^+$ T cells not only recognize, and make an inflated response to, the epitope when presented by HLA-$DR7^+$ human cells but also recognize peptide-sensitized Patr-$DR7^+$ chimpanzee LCL (Elkington et al., 2004). The Patr-DR7 β chain differs from HLA-DR7 at only three amino acid residues. SIV and HIV productively infect and replicate in activate CD4 T cells, and infected cells are killed by cytotoxic T cells, and therefore SIVs have been adapting to the common prevalent MHC-restricted immune responses for at least 32,000 years. We can therefore surmise that when SIVcpz was transmitted to man, it found a favorable landscape of immunogenetics, coinfections, and prevalent immunodominant $CD4^+$ and $CD8^+$ T cell responses in the rapidly growing population in Kinshasa and beyond.

The principle of old and slow evolutionary processes setting the context of more recent and rapidly adaptable systems is well illustrated by HIV. The gradual evolution of the MHC over about 500 million years in vertebrates (Flajnik and Kasahara, 2010; Kaufman, 2010) and SIV over at least 32,000 years (Worobey et al., 2010) contrasts with HLA-restricted cytotoxic T cell selection of HIV escape mutations that can be observed within days of acute HIV infection (Price et al., 1997) and HIV adaptation to HLA-restricted immune responses at a population level (Moore et al., 2002; Kawashima et al., 2009) and decreased virulence (Payne et al., 2014) that becomes apparent within a few years. On the other hand, despite the enormity of the HIV pandemic over the last 35 years, we are yet to detect an effect of HIV on the distribution of HLA alleles in any population.

ANTIRETROVIRAL THERAPY IN TREATMENT AND PREVENTION

Azidothymidine (AZT or zidovudine), a nucleoside analog reverse transcriptase inhibitor that had been originally been developed as a potential anti-cancer drug, was licensed for the treatment of HIV in 1987. This approval occurred only 25 months after the drug was shown to be active against the virus in the laboratory, and it represents an unprecedented example of accelerated drug development. However, AZT rapidly induced resistance mutations in HIV, and the clinical benefits of monotherapy typically disappeared within 6–18 months. It was only with the advent of potent three-drug combinations in 1996 that durable suppression of HIV and avoidance of resistance became achievable, transforming HIV into a chronic manageable disease for those with access to therapy. Although seemingly self-evident, convincing evidence that treatment of HIV reduces transmission to others was not available until 2011 (Cohen et al., 2011), and in September 2015 the World Health Organization recommended treatment for all as soon after diagnosis as possible.

Preexposure prophylaxis with tenofovir-based ART also has demonstrated efficacy in the prevention of transmission, but availability has been limited in the developing world to date. Long-acting injectable anti-retrovirals such as cabotegravir or rilpivirine are being actively investigated and may find a role in the prevention or treatment of HIV in subjects that cannot access or adhere to contemporary oral ART regimens.

CULTURAL AND POLITICAL CONTEXT AND RESPONSE TO HIV

Denial, fear, and sometimes paranoia had a negative influence on the fight against AIDS in both the developed and developing world. There was limited awareness of AIDS in the early years, and it was 2 years into the epidemic before the first effective public health response was taken in the United States, exclusion of at risk individuals from donating blood. In 1985, Rock Hudson announced he had AIDS, and Elizabeth Taylor became the first celebrity to raise awareness of AIDS and funds for research. Despite knowing that HIV cannot be casually transmitted, Ryan White was barred from attending school in Indiana. In 1987, the United States banned HIV-positive travelers from entering the country. In that same year, activist groups mobilized and demanded more research and accelerated approval of drugs. 1990 was the year of the first gulf war, led by President George Bush senior against the regime of Saddam Hussein. The following year, Magic Johnson announced that he had HIV, doing much to increase understanding and acceptance of HIV. By 1992, HIV/AIDS was openly discussed for the first time at the US presidential conventions; Elizabeth Glaser addressed the Democratic and Mary Fisher the Republican convention. In 1994, Tom Hanks won the best actor Oscar for his role in Philadelphia, playing a lawyer fired because he was HIV-positive.

Denial also had significant negative impact on public health in many parts of the developing world. One of the

most tragic and extreme forms of denial was HIV/AIDS denialism as adopted by Thabo Mbeki during his presidency of South Africa between 1999 and 2008. His administration supported arguments that HIV was not the cause of AIDS and denied antiviral treatment to AIDS patients. His health minister advocated the use of unproven herbal remedies instead. It has been estimated these policies were to blame for more than 330,000 preventable deaths (Chigwedere et al., 2008). It has been proposed that the same tenacious antiestablishment attributes that drove Mbeki to fight Apartheid also contributed to his opposition to mainstream scientific evidence on HIV and ART (Gellman, 2000).

In 2003, President George W Bush led the second gulf war against the regime of Saddam Hussein. In the same year, he announced the President's Emergency Plan For AIDS Relief (PEPFAR) to provide access to prevention, care, and treatment programs in many of the developing countries in most need. In 2009, President Obama ordered 30,000 more troops to Afghanistan. In the same year, his administration authorized the Global Health Initiative with PEPFAR as a central component. As of September 2015, the program continues to support provision of ART to 9.5 million people, 8.9 million male circumcisions, prevention of mother to child transmission, training of healthcare workers, and support of orphans and vulnerable children.

SIZE OF THE HIV EPIDEMIC

In 2014, an estimated 36.9 million people were living with HIV, giving a global prevalence of 0.8%. By then, approximately 78 million people had been infected with HIV, and about 39 million people had died since the beginning of the epidemic.

CURRENT TARGETS AND PRIORITIES TO CONTROL THE HIV EPIDEMIC

UN AIDS has set the ambitious target that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained ART, and 90% of all people receiving ART will have viral suppression. Meanwhile, considerable research efforts continue to develop an effective preventative HIV vaccine and to find a functional cure for HIV that would allow patients to stop their HIV medications. It is hoped that it is not too long before these interventions become part of the multipronged prevention armamentarium that currently includes risk reduction measures, male circumcision, use of HIV medications to prevent infection, and treatment of those already infected to stop others becoming infected.

WHAT CAN BE LEARNED FROM OUR RESPONSE TO HIV?

HIV, like many infectious diseases, primarily afflicts disenfranchised out-groups, and HIV/AIDS has been, and often still is, associated with considerable fear and stigma. The early individual and collective response was often dominated by denial and avoidance, which sometimes progressed to fear, discrimination, and inappropriate actions, such as banning Ryan White from school or travelers entering the United States. However, once individuals became personally touched by the suffering of those they knew, as occurred for Elizabeth Taylor when she saw her friend Rock Hudson dying of AIDS, compassion and altruism triumphed. Although community response from the ground up has always been critical, celebrities, the media, and the arts have also lead the cultural and political evolution necessary for broader mobilization of support and resources. History has repeatedly shown that nations are far better prepared and resourced for war than they are to fight infectious diseases pandemics. It will ever be thus, as individual and collective behavioral adaptations leading to success in physical conflict have long been selected for, while few behavioral solutions could be selected to prevent death from infectious disease in our hunter-gather past.

Our positive cultural and political response also underpinned the subsequent rapid scientific and medical progress (Fig. 46.1). The HIV epidemic has brought together an army of creative and courageous individuals driven by the needs of their time from a broad range of backgrounds. This has resulted in unprecedented collaborative gain as patient and community groups, clinicians, health care systems, public health officials, government, industry, regulators, the media, philanthropists, and many others have worked together. We have seen the same type of broad and compassionate and effective response to the recent Ebola crisis that infects monkeys and other animals in the same belt of Africa from which HIV originated. Those countries and groups that were able to respond rapidly with altruism and compassion have been rewarded with a much lower burden of disease and cost to their economies even though this was not the motivator at the time. HIV and other infectious disease have taught us time and again, "Just trust your better instincts and do the right thing without delay."

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