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PERSPECTIVE

The Extended Impact of Human Immunodeficiency Virus/AIDS Research

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Abstract

Human immunodeficiency virus (HIV) is one of the most extensively studied viruses in history, and numerous extraordinary scientific advances, including an in-depth understanding of viral biology, pathogenesis, and life-saving antiretroviral therapies, have resulted from investments in HIV/AIDS research. While the substantial investments in HIV/AIDS research are validated solely on these advances, the collateral broader scientific progress resulting from the support of HIV/AIDS research over the past 30 years is extraordinary as well. The positive impact has ranged from innovations in basic immunology and structural biology to treatments for immune-mediated diseases and cancer and has had an enormous effect on the research and public and global health communities well beyond the field of HIV/AIDS. This article highlights a few select examples of the unanticipated and substantial positive spin-offs of HIV/AIDS research on other scientific areas.

Keywords. HIV/AIDS; collateral advantages.

The first cases of AIDS were reported in the United States 37 years ago. Since then, >77 million people have been infected worldwide, resulting in over 35 million deaths. Currently, there are 36.9 million people living with human immunodeficiency virus (HIV), 1.8 million new infections, and nearly 1 million AIDS-related deaths annually [1]. Billions of research dollars have been invested toward understanding, treating, and preventing HIV infection. The largest funder of HIV/AIDS research is the National Institutes of Health (NIH), investing nearly $69 billion in AIDS research from fiscal years 1982–2018. Despite the staggering disease burden, the scientific advances directly resulting from investments in AIDS research have been extraordinary. HIV is one of the most intensively studied viruses in history, leading to an in-depth understanding of viral biology and pathogenesis. However, the most impressive advances in HIV/AIDS research have come in the arena of antiretroviral therapy. Before the development of these life-saving drugs, AIDS was an almost universally fatal disease. Since the demonstration in 1987 that a single drug, zidovudine, better known as azidothymidine or AZT, could partially and temporarily suppress virus replication [2], the lives of people living with HIV have been transformed by the current availability of >30 antiretroviral drugs that, when administered in combinations of 3 drugs, now in a single daily pill, suppress the virus to undetectable levels. Today, if a person in their 20s is infected and given a combination of antiretroviral drugs that almost invariably will durably suppress virus to below detectable levels, they can anticipate living an additional 50 years, allowing them almost a normal life expectancy [3]. In addition, a person receiving antiretroviral therapy with an undetectable viral load will not transmit virus to their uninfected sexual partner. This strategy is referred to as "treatment as prevention" [4]. Also, administration of a single pill containing 2 antiretroviral drugs taken daily by an at-risk uninfected person decreases the chance of acquiring HIV by >95%. Finally, major strides are being made in the quest for a safe and effective HIV vaccine [5].

The enormous investment in HIV research is clearly justified and validated purely on the basis of advances specifically related to HIV/AIDS. However, the collateral advantages of this investment above and beyond HIV/AIDS have been profound, leading to insights and concrete advances in separate, diverse, and unrelated fields of biomedical research and medicine. In the current Perspective, we discuss a few select examples of the positive spin-offs of HIV/AIDS research on other scientific areas (Table 1).

Regulation of the Human Immune System

Congenital immunodeficiencies have been described as "experiments of nature," whereby a specific defect in a single component of the complex immune system sheds light on the entire system. Such is the case with AIDS, an acquired defect in the immune system whereby HIV specifically and selectively infects and destroys the $CD4^+$ subset of T lymphocytes [6]. In this respect, HIV infection functions as a natural experiment that elucidates the complexity of the human immune system. The selectivity of this defect and its resulting catastrophic effect on host defense

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Table 1. Positive Spin-offs of Human Immunodeficiency Virus/AIDS Research on Other Areas of Medicine

Regulation of the human immune system
Targeted antiviral drug development
Probing the B-cell repertoire
Structure-based vaccine design
Advances in HIV/AIDS-related technologies
Role of immune activation in disease pathogenesis
Comorbidities in HIV disease

Abbreviation: HIV, human immunodeficiency virus.

mechanisms, as manifested by the wide range of opportunistic infections and neoplasms, underscore the critical role this cell type plays in the overall regulation of the human immune system. This has provided substantial insights into the pathogenesis of an array of other diseases characterized by aberrancies of immune regulation. Additionally, the in-depth study of immune dysfunction in HIV disease has shed light on the role of the immune system in surveillance against a variety of neoplastic diseases, such as non-Hodgkin lymphoma and Kaposi sarcoma. As a result of its association with HIV/AIDS, Kaposi sarcoma was discovered to be caused by human herpesvirus 8 [7].

Targeted Antiviral Drug Development

Targeted antiviral drug development did not begin with HIV infection. However, the enormous investments in biomedical research supported by the NIH and in drug development supported by pharmaceutical companies led to highly effective antiretroviral drugs targeting the enzymes reverse transcriptase, protease, and integrase, among other vulnerable points in the HIV replication cycle, and have transformed the field of targeted drug development, bringing it to an unprecedented level of sophistication. Building on 3 decades of experience, this HIV model has been applied in the successful development of antiviral drugs for other viral diseases, including the highly effective and curative direct-acting antivirals for hepatitis C [8].

Probing the B-Cell Repertoire

The past decade has witnessed extraordinary advances in probing the human B-cell lineage resulting from the availability of highly sophisticated technologies in cellular cloning and genomic sequencing [9]. AIDS research aimed at developing broadly reactive neutralizing antibodies against HIV and an HIV vaccine that could induce broadly neutralizing antibodies has greatly advanced the field of interrogation of human B-cell lineages, leading to greater insights into the humoral response to other infectious diseases, including Ebola [10], Zika [11], and influenza [12], as well as a range of autoimmune, neoplastic, and other noncommunicable diseases [13].

Structure-Based Vaccine Design

Although a safe and effective HIV vaccine has not yet been developed, the discipline of structure-based vaccine design using protein X-ray crystallography and cryoelectron microscopy has matured greatly in the context of HIV vaccine research. The design of immunogens based on the precise conformation of epitopes in the viral envelope as they bind to neutralizing antibodies has been perfected within the arena of HIV vaccine immunogen design. This has had immediate positive spinoffs in the design of vaccines for other viruses, such as respiratory syncytial virus, in which the prefusion glycoprotein was identified as the important immunogen for a vaccine using structure-based approaches [14].

Advances in HIV/AIDS-Related Technologies

Insights into the basic immunology of HIV drove the development and optimization of several broadly applicable technologies. Using inactivated HIV as a means of altering T lymphocytes to modulate the immune response, safe lentiviral gene therapy vectors are now US Food and Drug Administration–approved to treat certain cancers (eg, acute lymphoblastic leukemia) [15]. Additionally, it was discovered early in the epidemic that HIV is associated with the loss of $CD4^+$ T lymphocytes [16]. While much of the initial research on $CD4^+$ T lymphocytes was possible due to existing flow cytometry technologies, probing the complexities of immune dysregulation in HIV infection spurred the development of multicolor cytofluorometric technologies that have proven extremely useful for studying a variety of other diseases characterized by immune dysfunction [17]. The reality of utilizing these technologies in resource-poor areas accelerated the advancement of new simplified, automated, affordable, and portable point-of-care devices with broader implications for clinical medicine [18].

Role of Immune Activation in Disease Pathogenesis

Studying the pathogenesis of HIV disease has clearly demonstrated that aberrant immune activation stimulated by virus replication is the driving force of HIV replication [19]. In essence, the somewhat paradoxical situation exists whereby the very immune activation triggered by the virus in an attempt to control virus replication creates the microenvironment where the virus efficiently replicates. Even when the virus is effectively suppressed by antiretroviral drugs, a low degree of immune activation persists [20]. In this regard, the flagrant immune activation associated with uncontrolled virus replication, as well as the subtle immune activation associated with control of virus replication, are important pathogenic triggers of the increased cardiovascular and other organ system diseases associated with HIV infection. This direct association of even subtle levels of immune activation seen in HIV infection with a variety of systemic diseases has led to considerable insight into the role of immune activation and inflammation in human disease [21]. For example, recognition of the increased incidence of heart disease in the HIV population that is associated with chronic inflammation has stimulated interdisciplinary advances in understanding and treating coronary heart disease apart from HIV infection [22].

Comorbidities in HIV Disease

Antiretroviral therapy, which has transformed HIV treatment, is shifting the incidence of certain diseases in people living with HIV. Even when well-controlled by antiretrovirals, HIV disease is associated with an increased incidence of diseases, such as cardiovascular disease, kidney and liver disease, the premature appearance of pathophysiologic processes associated with aging, and several cancers [21–24]. This is especially true for non-AIDS-defining cancers, whose incidence rates are increasing while AIDS-defining cancer rates are decreasing [24]. In lower-income countries, tuberculosis is a common coinfection with HIV, and HIV coinfection was shown to be a key risk factor for progression of latent *Mycobacterium tuberculosis* infection to active disease [25]. There are a variety of ongoing studies [21] investigating the pathogenic bases of these conditions to shed greater insight into their causes and potential interventions that might impact these diseases apart from HIV infection and immunodeficiency.

CONCLUSIONS

The collateral advantages resulting from the substantial resources devoted to HIV/AIDS research over the past 30 years are extraordinary. From innovations in basic immunology and structural biology to treatments for immune-mediated diseases and cancer, the conceptual and technological advances resulting from HIV/AIDS research have had an enormous impact on the research and public and global health communities over and above the field of HIV/AIDS. The HIV/AIDS research model has proven that cross-fertilization of ideas, innovation, and research progress can lead to unforeseen and substantial advantages for a variety of other diseases.

Notes

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