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Human Immunodeficiency Virus (HIV): Genomics and Proteomics Knowledge Makes Anti-Retroviral Therapy (ART) More Effective and Successful

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Abstract
Although about 35 million people worldwide are infected with HIV, yet a widely applicable and affordable cure strategy has remained elusive. However, in recent times, using tools of genomics and proteomics we have not only gained better insights of HIV pathology, host interactions both at a molecular and immunological level. These in depth studies, have suggested better drug targets, that have in turn, after extensive clinical trials tested and led to newer drugs achieving better disease management strategies. In this paper, we have described in detail the virology, natural history of HIV, HIV pathogenesis, global epidemiology some of the recent developments in identification of newer drug targets, some success stories, etc. We have also discussed their relevance to the global HIV pandemic and public health challenges in different settings.
Keywords: HIV, AIDS, Anti-Retroviral Therapy, Viral Genomics, Proteomics, Drug Classes, Vaccines

Introduction

Infection with HIV is a continuing global health concern, with ∼1.5 million AIDS-related deaths worldwide in 2013. The deployment of antiretroviral therapy (ART) using different classes of drugs have revolutionized HIV management strategies. Current combination antiretroviral therapy (c ART) reduces viremia to un- detectable levels, preventing further loss of $CD4^+$ T cells and progression to AIDS. The use of c ART allows HIV-infected individuals show greatly enhanced survival, to have near-normal life expectancy, and an improved quality of life and it is therefore hailed as a major medical success. Successful ART results in clinically undetectable levels of plasma viremia (<50 copies ml−1), allowing immune reconstitution. However, once infection is established, it cannot be cleared by current ART. Although cART is not curative, transmission can be prevented and infected individuals must remain on therapy for life to maintain their health [1].

Emergence of HIV and the AIDS Pandemic:

In 1981, the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly report first described Acquired Immunodeficiency Syndrome (AIDS) in five homosexual men diagnosed with an opportunistic infection of *Pneumocystis carinii* pneumonia in California [2]. The disease was also later identified in heterosexual individuals receiving blood products and babies born to infected mothers [3].

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In 1983, Montagnier and colleagues at the Pasteur Institute isolated an infectious agent from the lymph nodes of a patient who presented with generalized lymphadenopathy of unknown origin [4]. Electron microscopy revealed characteristic retroviral features and the group named the agent the lymphadenopathy-associated virus (LAV). Subsequent characterization revealed the virus displayed magnesium-dependent reverse transcriptase (RT) activity and was found to specifically kill CD4+ T-lymphocytes in cell culture [5]. In 1984, Gallo and coworkers at the National Institutes of Health isolated a retrovirus from a patient with AIDS, which they named human T-cell leukemia virus type III (HTLV-III) [6]. Additional studies provided the first convincing serological evidence linking exposure to HTLV-III/LAV retroviruses and immunodeficient individuals [7]. Concurrently, Levy et al. found another, comparable retrovirus from patients with AIDS as well healthy individuals from the highest risk groups which was named AIDS- associated retrovirus (ARV) [8]. The work of both Montagnier and Levy suggested that these viruses could induce both asymptomatic and symptomatic infections. A comparison of all three new retroviruses associated with AIDS in the United States, Europe, and central Africa exhibited morphologic and genetic characteristics typical of the lentivirus genus with no significant differences between them. The common name applied to all three was human immunodeficiency virus, or HIV [9,10]. In 1986, a second, immunologically distinct HIV virus was discovered in individuals residing in several west African countries such as Senegal, Ivory Coast, and Guinea-Bissau [11]. Discovery of this new virus led to the renaming of the viruses to HIV-1 and HIV-2. In comparison with HIV-1, HIV-2 has lower mortality rates, likely due to slower declines in CD4+ T-lymphocytes and much longer periods of asymptomatic infection [12].

When scientists identified HIV in 1983, they believed that HIV was a new virus, one that had just emerged from the jungles of Africa. However, using advanced statistical modeling of sequence data, the emergence of HIV-1 can be traced back to colonial west central Africa in the 1920's [13,14]. It is believed that HIV-1 started by zoonotic transmission of the chimpanzee strain of the Simian Immunodeficiency Virus (SIVCPZ) to forest hunters early in the 20th century [15]. The virus was passed, unnoticed, along the Congo River corridor for years until reaching the urban population center of Kinshasa, Zaire. Here, HIV-1 found the population density and mobility required to expand replication within the population. In fact, the oldest known infection with HIV-1 was found in samples obtained from Kinshasa in 1959 [16,17,18]. As of 2018, there were 37.9 million people in the world living with AIDS, with an average of 1.7 million new infections occurring each year. However, only 21% of those individuals had access to HIV testing, and only 62% had access to antiretroviral therapy. The majority of individuals affected by this disease are from low or middle-income countries that do not have access to proper HIV prevention and treatment. HIV testing and treatment are crucial to preventing the progression to AIDS and ending transmission of the virus. Despite these setbacks, AIDS-related deaths had decreased from 1.2 million in 2010 to 770,000 in 2018. With more efforts to increase access in resource-poor countries and investment in HIV/AIDS research by the NIH, more progress is being made towards more effective treatments and a cure [19].

HIV Classification:

HIV belongs to the genus Lentivirus, which together with genera Spumaviruses and Oncoviruses form the Retroviridae family. Other members of this family include Simian

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Immunodeficiency Virus (SIV), Feline Immunodeficiency Virus (FIV), Equine Infectious Anaemia Virus (EIAV) and the Maedi-Visna Virus (MVV). There are two types of HIV namely HIV-1 and HIV-2 (Fig.1) with similar modes of transmission, replication cycle, primary target cells (CD4+ T cells), nature of infection and origin5. HIV-2 is restricted mainly to West Africa, is less virulent compared to HIV-1, associated with limited epidemics, and is divided into 8 subtypes (A through to K); subtype C is predominant and responsible for 50% of global infections [18,19]. While, HIV-1 is more virulent, associated with the global HIV pandemic, and is divided in 4 groups: M(major), N(Nonmajor), O(Outlier) and P. There are also several circulating recombinant forms of the virus within the M group, formed in dually infected individuals [20,21].

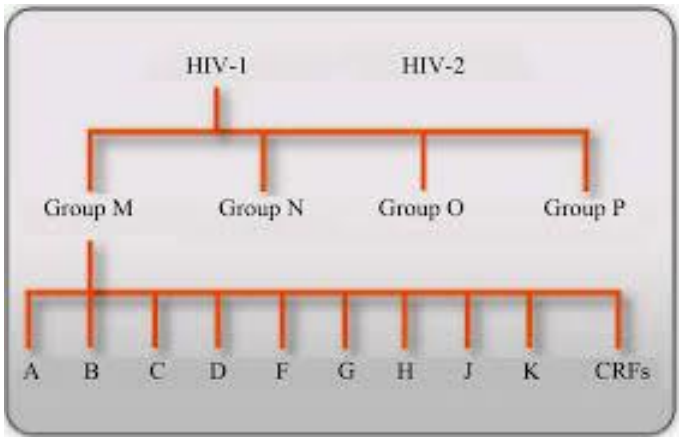

Fig 1: Based on genetic characteristics and viral antigens HIV is classified into HIV-1 and HIV-2. There are 4 major groups of HIV-1and group M is further divided into various subgroups or clades.

Transmission of HIV:

HIV is primarily transmitted through exposure to infected bodily fluids or blood via injured skin or mucosa. This can be through blood transfusions, organ transplants, sexual intercourse, breastmilk, childbirth, or contaminated needles [22]. However, since the majority of HIV cases are the result of transmission via sexual intercourse, HIV is classified as a sexually transmitted disease (STD) [22]. Additionally, pregnant women can transmit the infection to the baby during the last trimester or earlier, depending on viral titers. Although HIV could be considered a zoonotic disease in the early part of the 20th century, it is currently only transmissible between humans. HIV is not transmitted via animal vectors; it is also not spread by food or water [22].

Structure and Genome of HIV:

HIV has a particle diameter of 100nm and contains a single stranded, non-segmented, positive sense RNA. HIV belongs to the family Retroviridae and placed in the genera Lentivirus [23]. The HIV-1 genome is approximately 9-kb consisting of nine open reading frames encoding the characteristic retroviral Gag, Pro, Pol, and Env genes as well as additional small regulatory and accessory proteins. The virion is comprised of two copies of single-stranded viral RNA tightly bound by the protective nucleocapsid (NC) protein. Also attached to the viral RNA are the

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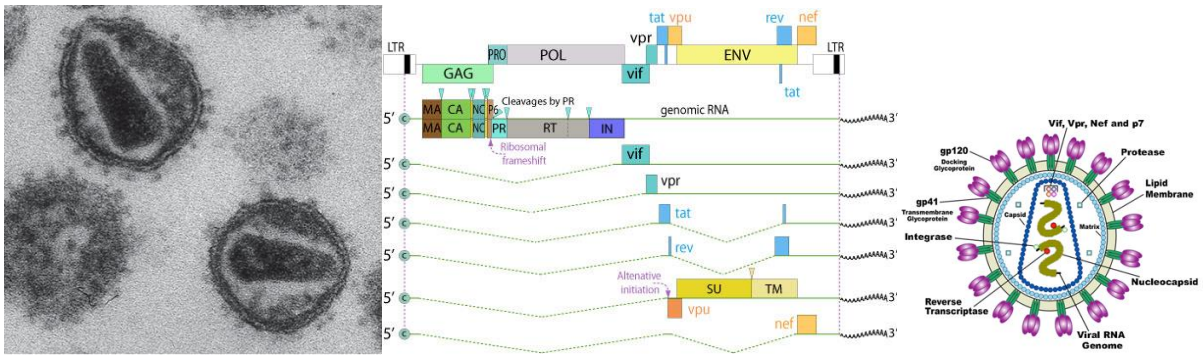
required viral enzymes Reverse Transcriptase (RT) and Integrase (IN). The viral Capsid (CA) protein forms a fullerene cone shaped core encapsulating the viral RNA complexes along with viral accessory and host derived proteins.

Surrounding the viral core in a small sub-virion space are excess CA molecules and a limited amount of host proteins followed by a thin layer of viral Matrix (MA) protein [24]. The outer envelope consists of host derived membrane with embedded viral Env glycoproteins (Env). An electron micrograph of HIV particles and a schematic of the virion structure and HIV genome can be found in Fig 2 (a, b, c).

The individual viral proteins can be broken down into four main groups: structural, enzymatic, regulatory, and accessory. The structural components of the virion are produced from the Gag and Env polyproteins. The Gag proteins CA and NC form the basic components of the viral core while MA and the Env surface (SU) and transmembrane (TM) proteins are found in the outer membrane envelope. The virion also contains essential enzymatic components produced from the Pol polyprotein. RT and IN are enzymes required for retroviral replication and not found within the host cell. The viral protease (PR) is essential for maturation of the virus by cleavage of the Gag and Pol polypeptide. Tat and Rev provide gene regulation with the host cell and are required for in-vivo replication. The accessory proteins are not necessary for in-vitro replication and can be further separated into intraparticle and intracellular components. The proteins Vif, Vpr, and Nef are found within the viral particle. Finally, Vpu assists in the assembly of the virions. A diagrammatic functional representation of the viral proteins can be found in Fig 3.



a **b** **c**

Fig 2 a. Electron Micrograph of HIV b. Organization of HIV Genome c. Structural Features of HIV Virion (Source Viral Zone – Swiss Institute for Bioinformatics)

Viral Replication:

HIV targets CD4+ T cells and gains entry by attaching to the CD4+ receptor on the surface of these cells [26]. This internalization occurs via the surface protein, gp120. This action triggers a series of conformational changes that assist in viral attachment to the host cell. The virus is then able to bind to a chemokine co-receptor, which triggers an irreversible conformational change that results in the formation of a pore by gp41. The subsequent fusion of the viral envelope to the plasma membrane releases the viral capsid into the cytoplasm of the host cell [26]. In the cytoplasm, the virus uses its reverse transcriptase to transcribe its RNA genome

into proviral DNA. Finally, the proviral DNA is transported to the nucleus and integrated into the host cell genome via an integrase., establishing latency. HIV viral reverse transcriptase has no proofreading activity, which causes additional mutations in the proviral DNA. These mutations lead to viral particles with variant genomes that are able to evade the immune system, resulting in a sustained infection [26].

HIV Illness and Symptoms:

HIV is a chronic infection that causes a depletion of CD4+ lymphocytes, which leads to a weak immune system resulting in a variety of non-specific symptoms. During the initial symptomatic phase, which lasts 2-6 weeks, infected individuals will show non- specific symptoms similar to EBV or CMV induced mononucleosis. More serious symptoms can include aseptic meningitis, meningismus, and photophobia. Individuals may also present with early symptoms including lymphadenopathy, or oral manifestations such as leukoplakia, thrush, or periodontal disease. Viral titers are highly infectious during this time. However, during the asymptomatic period, the virus enters a latent period, and the majority of patients will not show signs or symptoms until years after exposure to HIV. Even though viral titers are low during the asymptomatic period, individuals may still unknowingly spread the disease. Since there is a broad range of early signs and symptoms, physicians must be vigilant in assessing patient history and risk factors to recognize an HIV infection before it manifests into AIDS. [27].

If left untreated, HIV can cause significant CD4+ cell depletion that can lead to AIDS within 10 years from initial infection [26]. This weakened immune system leaves the body susceptible to opportunistic infections such as Pneumocystis carinii pneumonia (PCP), which is an indicating factor for AIDS. Additionally, patients can contract tuberculosis, which can be fatal in immunocompromised individuals. Neurologic effects include AIDS dementia complex, which occurs in 60% of AIDS cases. These diseases are the indirect result of an HIV infection, and many deaths occur due to the secondary opportunistic infections caused by a weakened immune system. Another sign that is indicative of AIDS is Kaposi's sarcoma, a malignant cancer that causes nodules on mucous membranes, or any organ [27].

HIV Diagnosis:

During the initial asymptomatic phase, infected individuals will not show any symptoms. Due to this reason, the early recognition of potential infections is made by assessing the patient's risk factors such as intravenous drug use, sexual contact, or exposure to blood products.

During this phase, a test for the p24 HIV core antigen can be conducted in the early stages if the assessment of risk factors forms enough evidence to suspect an infection [27]. Primary screening for HIV occurs by testing for antibodies against the virus or detecting the virus. Antibody or antigen detection by using a serological test is more commonly used because it is rapid and can be done on various bodily fluids such as plasma, blood, or saliva. However, these tests are not effective when the virus is in the latent phase because no antibodies are present. Babies born to mothers who are infected will have maternal HIV antibodies, and a test may result in a false- positive. In these situations, the viral DNA in the host's genome has to be detected using RT-PCR [25]. Current methods of HIV antibody are sensitive enough to detect the virus within 1-2 weeks of infection, which allows the individual early access to treatment and prevents further transmission of HIV [28].

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In order to determine the severity of the infection and progression towards AIDS, physicians have to determine the stage of the disease by measuring CD4+ cell count and plasma viral load using flow cytometry. Other symptoms associated with opportunistic infections are also evaluated. The time between specimen collection and laboratory assays should be minimal, so dried blood samples are used to counteract problems associated with the transportation of specimens. However, communities, where resources are limited, need more cost-effective methods for analysis such as dipstick assays, total white-counts, or CD4+ chips [25].

HIV Life Cycle & Possible Drug Targets:

Viral life cycle comprises of several steps, which can be targeted by anti-HIV-1 drugs. These steps include entry, reverse transcription, integration, transcription, assembly and budding (Figure 4).

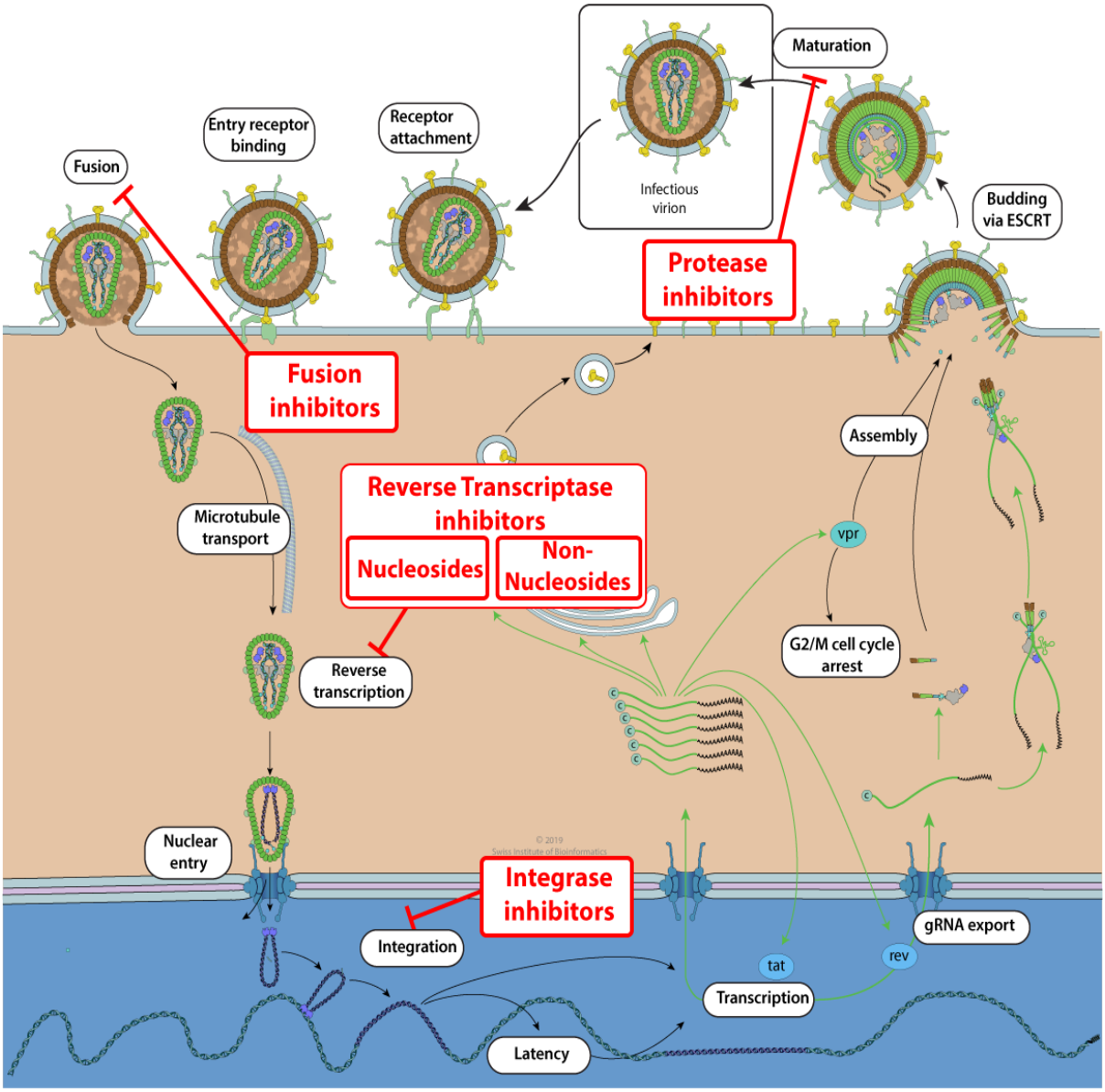

Fig 4. Different stages in the Life Cycle of HIV. Classes of Drugs that inhibit specific stage in the HIV life cycle (Source Viral Zone – Swiss Institute for Bioinformatics)

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HIV Treatment & Prevention:

The current antiviral options available for HIV-1 are diverse with over 30 drugs currently approved for treatment (www.fda.gov). The primary focus of drug development thus far has been towards viral proteins, as the risk of off target effects is reduced. Current drugs fall into one of six distinct classes: (1) nucleoside-analog reverse transcriptase inhibitors (NRTIs), (2) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (3) integrase inhibitors, (4) protease inhibitors (PIs), (5) fusion inhibitors, and (6) coreceptor antagonists (Figure 4).

The current treatments for HIV do not eradicate the virus. Instead, the treatments help prevent the progression of HIV to AIDS and HIV infection to high-risk individuals. Initially, HIV was treated with only one antiretroviral drug. As the development and discovery of HIV drugs increased to include various inhibitors of HIV essential enzymes, more drugs started to be used in combination. This combination drug therapy became known as HAART (highly active antiretroviral therapy). The main goal of this therapy is to increase the strength of the immune system by reducing viral load and increasing CD4+ T lymphocytes [28]. This treatment is effective in controlling viral multiplication and prolongs the asymptomatic stage of the infection resulting in lower risk of transmission and progression to AIDS [29]. Because HIV manifests various symptoms in different individuals, the drug combinations are modified according to the patient. Normally, HAART involves a combination of three drugs, which can include reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, chemokine receptor 5 antagonists, or integrase transfer inhibitors. Each of these drug targets viral entry, integration of viral DNA into the host's genome, or the production and assembly of the virus. HAART is recommended for all HIV patients regardless of the CD4+ lymphocyte count, and adherence to the regimen is recommended to prevent drug resistance and viral rebound [29]. Today, the term HAART is less commonly used and has largely been supplanted in the medical literature by the simplified ART (antiretroviral therapy). The change in terminology is about more than just semantics; it reflects a shift in the goals and benefits of HIV therapy and a step away from what HAART historically implied. Another advancement in therapy is the development of fixed-dose combination (FDC) drugs that can deliver complete therapy with just one pill daily. Today, there are 13 of these all-in-one drugs approved by the FDA. Single-pill formulations not only improved adherence rates but have been shown to significantly reduce the risk of severe illnesses and hospitalizations compared to multi-pill antiretroviral therapies.

HIV can be prevented by avoiding high-risk behaviors such as intravenous drug use, multiple sexual partners, and unprotected sex. For high-risk individuals, another option is pre-exposure prophylaxis (PrEP), which is used in uninfected individuals before potential exposure to HIV. This treatment prevents HIV infection by inhibiting viral replication once the virus enters the body, and it prevents HIV from establishing a permanent infection. Truvada, which is a combination of two drugs, is usually the drug of choice for PrEP [30]. When taken consistently, PrEP is an effective way to prevent new HIV infections [31]. Post-exposure prophylaxis (PEP) is used in emergencies after exposure to potentially HIV infected individuals or needles. PEP should be used within 2 to 72 hours of HIV exposure for maximum efficacy and continued for 28 days post-exposure. PrEP and PEP are useful treatments for the prevention of HIV infection when used correctly and consistently [30].

Even though some drug targets have been identified to neutralizing the HIV-1, emergence of resistance is continuing and search for new drug targets is highly demanding for elimination of the dreadful mutant HIV-1 strains contributing to drug resistance. Significant work is still conducting on viral and host specific interactions to understand the newer therapeutics at molecular level. As such HIV-1 associated Topoisomerase IIβ kinase is one of the new viral targets.

Recent studies on Topoisomerase IIβ phosphorylation has been identified in HIV-1viral progression. Subsequently a 72kDa protein which is Phosphorylating the Topoisomerase IIβ during HIV-1 replication was observed in a purified virus concentrate [32] that suggested the presence of a novel kinase. This fascinating drug target has made to explore the possibility of stymied this vital pathway in the life-cycle of HIV-1 to prevent the viral growth.

Vaccines:

Since the first appearance of AIDS in the eighties, the development of a safe and effective HIV-1 vaccine was considered to be essential to avoid further spread of the disease. However, the initial enthusiasm was quickly dampened by the finding that traditional vaccine approaches like live attenuated viruses although providing protection [33,34], are impractical due to reasonable safety concerns [35,36]. Similarly, attempts to use inactivated virus were disillusioned by the fact that they are modestly immunogenic, provide protection only against closely related viruses and inactivation procedures may represent a risk-factor or denature antigens in a way that makes them incapable to mount efficient immune responses [37,38].

Since then, further studies have been conducted on various forms of immunogens such as live or non-replicating recombinant vectors expressing HIV antigens, DNA vaccines, subunit vaccines including virus like particles, recombinant Env and gp41 proteins, epitope scaffolds, HIV synthetic peptides, artificial mosaic antigens and combinations thereof (reviewed in [39]). By inducing various degrees of immune responses and protection, several of them have proceeded to Phase I and II clinical trials and four have been tested in large cohorts of healthy volunteers [40]. With exception of the most recent RV144 trial in Thailand (16,400 participants, 31% vaccine efficiency [40]), none of the strategies have proven to be able to induce protective immunity, some even enhanced infection rates [41-44]. Historically, these vaccine approaches were designed to induce either broad neutralizing Antibodies (bnAbs)or to trigger cellular immunity to control virus replication and decelerate disease progression. As both approaches failed so far when applied alone, it is assumed that an effective vaccine will probably have to stimulate both arms of immunity. However, considering the fact that control of virus replication is unnecessary in presence of a profound bnAb response that prevents infection of any cells and HIV genome integration, triggering humoral immune responses could provide benefits compared to a T cell- based vaccine approach.

There is no effective HIV vaccine and this stems from our poor understanding of markers of convalescence which usually correlate with desirable features of a vaccine [45]. Furthermore, there is lack of suitable vaccine adjuvants and animal models that could be used in preclinical testing of candidate HIV vaccines [46]. Moreover, HIV is a “quasi-species” that is globally diverse and continuously evolves within its host and undergoes latency during the early stages of infection, which further complicates designing a vaccine that can provide global protection against HIV.

As the search continues for an HIV vaccine, it is generally accepted that an ideal HIV vaccine will have to induce robust HIV-specific CMI, with a high magnitude and avidity as such high quality responses often result in an improved control over HIV infection and delayed disease progression in humans. In addition, the vaccine will have to induce potent antibody responses which are thought to be important in preventing primary HIV infection [47]. It will be particularly important for these responses to be established at mucosal surfaces and systemically for effective prevention and control.

Conclusions

The advances made in the fields of genomics and proteomics have helped us to identify better drug targets in the HIV life cycle. Also with better tools available in drug discovery the progress in AIDS pharmaceuticals research has gathered considerable pace. It is indeed remarkable that despite the non- availability of a vaccine we now have a potential range of drugs that could improve many aspects of the traditional approach to treating HIV.It includes significant public health responses to the changing situation in which all countries now have access to some generic antiretrovirals and drug pricing will continue to drive access in all countries. It also includes some compounds that are only developed for low- and middle-income countries.

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