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REVIEW ARTICLE

Four Decades of HIV: Global Trends, Testing Assays, Treatment, and Challenges

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Abstract

More than 77 million individuals have been infected with the human immunodeficiency virus (HIV) and approximately 37.6 million people are living with HIV infection. HIV infection may increase susceptibility to cancer, cardiovascular disease, bone disease, and other co-morbid conditions. Antiretroviral (ARV) drugs are extremely potent HIV replication inhibitors. Combination ARV therapy suppresses the viral load and prolongs the lifespan of individuals who can acquire and adhere to ARV drug regimens. Indeed, viral suppression can nearly eliminate the risk of developing acquired immune deficiency syndrome (AIDS). ARV drugs reduce the risk of HIV transmission in uninfected individuals. In addition to a vital role in prevention strategies, viral transmission is still common in unprotected populations, especially in injection drug users, female sex workers, men who have sex with men (MSM), and transgender individuals. The history and timeline provide key milestones in HIV research leading to improved and advanced approaches to resolve the issue of HIV transmission. Nevertheless, it is essential to pursue breakthroughs, innovative treatments, improved prevention methods, and the development of vaccines. This article summarizes the 40-year timeline of HIV, testing assays, global burden, prevalence, treatment, and challenges related to HIV/AIDS.

Keywords: human immunodeficiency virus, AIDS, anti-retroviral therapy, nucleoside reverse transcriptase inhibitors, protease inhibitors

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INTRODUCTION

The human immunodeficiency virus (HIV) belongs to the *Lentivirus* genus within the Retroviridae family. Based on genetic attributes and differences in antigens, HIV is segregated into two types (HIV-1 and HIV-2). Epidemiologic studies have demonstrated that HIV is spread by non-human primate viruses (simian immunodeficiency virus) [1]. HIV-2 is less pathogenic compared to HIV-1 because of the lower level of viral replication. HIV-2 is prevalent in West Africa, although minor epidemics have been reported in France, Portugal, Spain, and Brazil [2]. HIV-1 is highly pathogenic compared to HIV-2, covering nearly all regions in the world. Due to the genetic resemblance, HIV-1 is classified into four vital clusters (i.e., M, N, O, and P). The apparent drift in the diversification of HIV in the past decade has influenced the proportion of circulating recombinant forms (CRFs) [3].

The first case of acquired immune deficiency syndrome (AIDS) was reported 40 years ago [4]. AIDS is a contributor to deaths in major geographic regions, including the USA, Europe, sub-Saharan Africa, Asia, and the Pacific. Approximately 77.5 million individuals

have been infected with HIV and 34.7 million individuals have died from AIDS-related diseases since the onset of the HIV epidemic in 1981. In 2022 approximately 39 million individuals were living with HIV (37.5 million adults and 1.5 million children [0-14 years old]) with a high number of infections in sub-Saharan Africa. In 2022 approximately 630,000 individuals died from AIDS globally and 29.8 million were accessing antiretroviral therapy (ART) [5]. Since the first case of HIV was reported, AIDS has created new public health challenges that need to be overcome because the people living with HIV are unaware of their serostatus.

ART is accessible for the treatment of HIV. ART is effective and essential in inhibiting or suppressing virus replication, thereby improving the immune system of individuals and reducing the probability of AIDS (the third stage of HIV) and preventing individuals from becoming infected. However, the virus can rebound within several weeks if ART treatment is stopped [6]. If untreated, HIV replication leads to CD4 + T cell loss and widespread abnormalities in the immune system. Infection with HIV also leads to morbid conditions, including bone disease, hepatic and renal disorders, and cardiovascular disease [2]. This review summarizes the historic timeline, generations of testing assays, global trends in virus prevalence, treatment options, and challenges related to HIV.

HISTORICAL OUTLINE

In 1981 AIDS was declared an epidemic due to increased homosexual (men who have sex with men) cases in New York City and California [4]. The retrovirus was isolated in 1983 from patients who were at high risk for AIDS and subsequently named HIV [7]. After HIV-1 was isolated, the cell surface molecule, CD4, was established as a major receptor for HIV [8]. Nucleotide sequencing of the virus was established in 1985 for the detection of viral load and resistance mutations in HIV-infected patients [9,10]. C-X-C chemokine receptor type 4 (CXCR4) and C-C chemokine receptor type 5 (CCR5) were identified as co-receptors for HIV in 1996 [11]. Conformational changes occurred following virus binding to chemokine receptors, which leads to the entry of X4-tropic (utilizes CXCR4) and X5-tropic HIV-1 (uses CCR5). At the same time, mutations were identified in individuals who were resistant to HIV-1 because of homozygous CCR5 deletions [12-14]. Because the disseminated virus is R5-tropic, the *CCR5Δ32* mutation prevents entry of the virus, thereby accounting for resistance to HIV infection. ARTs were developed and replication cycles were elucidated in the 1990s. Studies revealed that several host factors assist or hinder the replication cycle but are counteracted by different viral proteins involved in the replication mechanism. For example, APOBEC3G, a cytidine deaminase, inhibits HIV-1 replication but is impeded by an accessory protein, viral infectivity factor (Vif) [15]. Similarly, tripartite motif-containing 5α (TRIM5α) [16] and tetherin, also known as BST-2, is hindered and downregulated by viral protein u (Vpu) [17,18]. Deoxynucleoside triphosphate triphosphohydrolase (SAMHD1) is hindered by viral protein x (Vpx) [19]. As of January 2021, the U.S. FDA approved Cabenuva, the first injectable drug for treatment of HIV [20]. Similarly, a novel HIV vaccine candidate, HIVconsvX (a mosaic-type vaccine), is in phase I clinical trials in the UK [21]. In 2023 new CRISPR treatments were shown to prevent HIV recurrences [22] (Fig 1).

HIV TESTING

HIV testing was established nearly four decades ago, with the first antibody-detecting test becoming available in 1985. The test was designed for blood screening rather than for the specific detection of HIV. Since then HIV diagnostic testing has evolved using new algorithms for HIV diagnosis. Detecting and treating HIV early can prolong life, reduce the risk of transmission, and improve the overall quality of life. New lab diagnostic tests are readily available for the diagnosis of HIV infections, but AIDS requires a laboratory and clinical framework for detection because it is the late stage of HIV infection [23]. The subsequent use of fourth- and fifth-generation systems for HIV detection accelerates the testing process and significantly reduces the detection window (up to 2 weeks post-exposure).

First-generation assays

After the isolation of HIV in 1983, detection tests, enzyme-linked immunosorbent assay (ELISA), and chemiluminescence were established utilizing Abbot and Electronucleonics for the diagnosis of human T-lymphotropic virus type III (HTLV III) and the lymphadenopathy virus (LAV) isolate. The tests only detect IgG antibodies to HIV-1. The tests are experimentally sensitive but there is a 12-week duration post-infection for the antibody-negative window period [24]. The functional protection of the blood supply and elevated sensitivity lead to false positivity due to associated infections and unidentified conditions. Similarly, western blot analysis [25] and an HTLV III [26,27] immunofluorescence assay (IFA) are used for syphilis testing to improve specificity. Screening assays revealed that IgG antibody detection to HIV and a 6-week or prolonged window period.

Second- and third-generation assays

These assays were developed in the 1980s for better sensitivity and the screening tests involved the addition of recombinant antigens, especially P24 of HIV-1. Frequently, manufacturers attach HIV-1 group O and HIV-2 to antigen for the detection of antibodies [28]. The antibody-negative window period for second-generation decreased to 4-6 weeks post-infection. A trial was added to the algorithms because these tests detect HIV-2 antibodies in addition to HIV-1 antibodies. In the 1990s the third-generation HIV diagnosis was established by

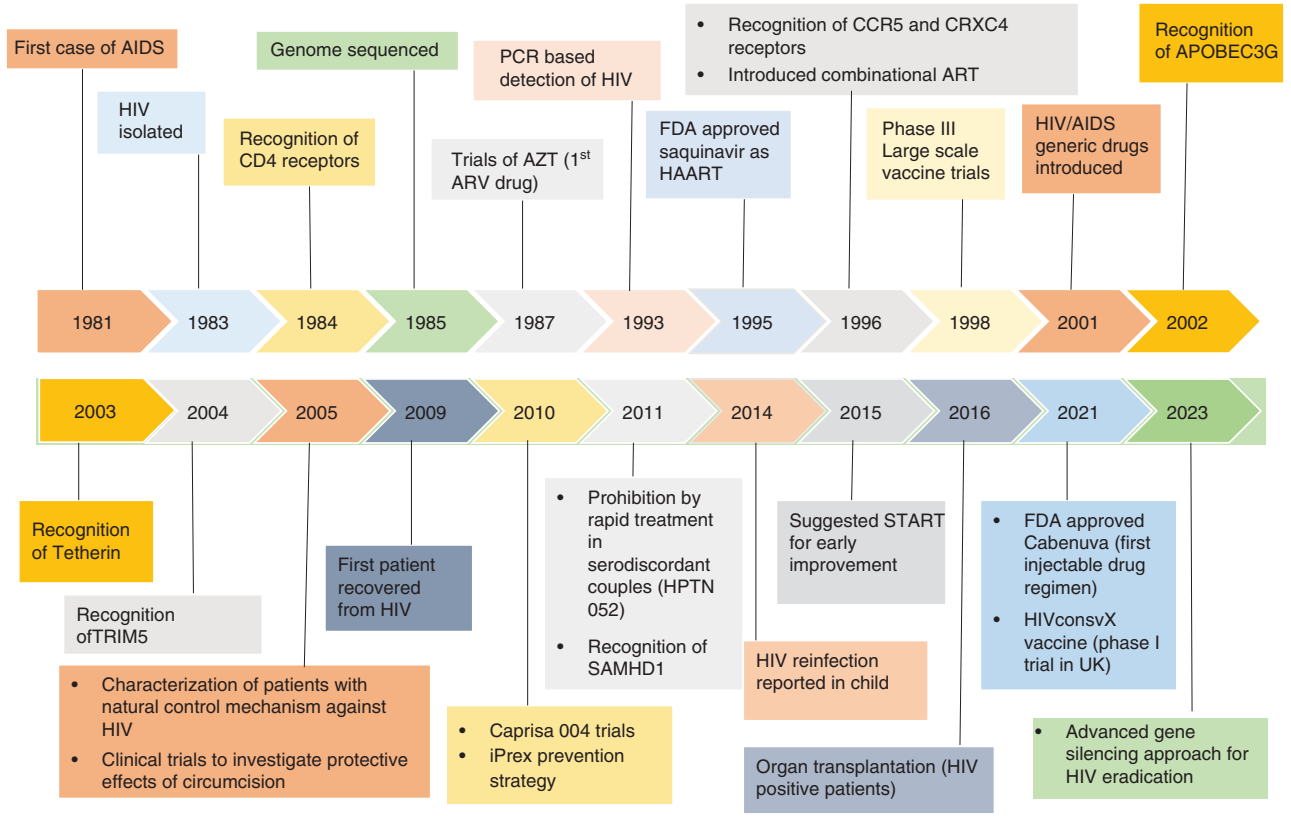

FIGURE 1 | Key milestones and major events of HIV: a 40-year glance.
AZT-azidothymidine, HAART-highly active antiretroviral therapy, CCR5-chemokine receptor 5, CXCR4- CXC-chemokine receptor 4, APOBEC3G-apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G, TRIM5α- tripartite motif-containing 5α, iPrex- initiative for pre-exposure prophylaxis, SAMHD1-SAM and HD domain-containing deoxynucleoside triphosphate triphosphohydrolase 1, START- strategic timing of antiretroviral treatment.

incorporating the detection of IgM antibodies into the assay system. Combined detection of IgG/IgM leads to a decrease in the antibody-negative window period to 3 weeks after postexposure [24]. ELISA-based detection of P24 antigen decreased the detection period to 2 weeks. The algorithms remain the same and continuous screening protocols were validated by IFA or western blot [29].

Fourth- and fifth-generation assays

New HIV assays were developed in the 1990s that combined antigens and antibodies. This combined assay system decreased the negative window to approximately 2 weeks. The test gives a positive result for both antigen and antibody, but does not determine if the positive result is due to the HIV-1 p24 antigen or HIV-1 or HIV-2 antibody. Abbot Architect was the first fourth-generation testing method to be accepted (August 2010). The study revealed that Architect has a continuous testing specificity of 99.5% and a sensitivity of up to 99.94% [30]. Similarly, the Bio-Rad GS ELISA was approved in 2011 with a specificity of 99%-100% and sensitivity up to 100% [28]. In 2012 the CDC established two new algorithms for fourth-generation testing to enhance early diagnosis and provide rapid results. However, in 2014 a single algorithm was finalized to determine whether the infected individual had antibodies to HIV-1 or HIV-2, followed by HIV-1 RNA PCR amplification. This new algorithm increased the specificity and sensitivity of antigen/antibody detection and false-positive results were reduced compared to previous testing algorithms because western blot was used in a confirmatory approach [31] (Table 1). In 2015 the first fifth-generation multiplexed assay system was introduced that enabled the detection of antibodies to HIV-1 and HIV-2 and is able to differentiate between HIV-1, HIV-2, and p24 antigens [32]. The negative window period for this multiplexed system was reduced to 2 weeks after postexposure.

CD4 and drug resistance testing assays

The CD4 count is a blood test that detects the total number of CD4 cells that persist within a sample of an infected individual's blood. The CD4 count can be used to quantify how the virus affects the immune system. The CD4 count assists in examining the consequences of extending opportunistic infections. The CD4 count also assists in affirming treatment efficacy. A viral load test evaluates the working efficacy of medications administered. The viral load examines and displays the presence of HIV in the blood. The viral load also assists in the diagnosis of AIDS. For example, HIV may lead to a low CD4 cell

TABLE 1 | Generations of HIV serologic testing in the past 40 years.

Generation	Year	Viral targets	Negative duration (weeks)	Detection (Ag/Ab)	Verification test	Specificity	Sensitivity
1st	1985	Lysate	8 to 10	IgG (HIV-1)	WB or IFA	95 to 98%	99%
2nd	1987	Recombinant & lysate	4 to 6	IgG (HIV-1 & HIV-2)	HIV-1 WB or IFA, HIV-2 ELISA & WB if HIV-1 is negative	99%	99.5%
3rd	1991	Synthetic peptides & recombinant	2 to 3	IgG & IgM (HIV-1, HIV-2 & Group O)	HIV-1 WB or IFA, HIV-2 ELISA & WB if HIV-1 is negative	99.5%	99.5%
4th	1997	Synthetic peptides & recombinant	2	IgG, IgM (HIV-1, HIV-2 & Group O) & p24 Ag of HIV-1	HIV 1 & 2 differentiation assay then PCR for HIV-1 if assay I negative	99.5%	99.8%
5th	2015	Synthetic peptides & recombinant	2	IgG, IgM (HIV-1, HIV-2 & Group O) & p24 Ag of HIV-1	Differentiation assay to HIV-1, 2 & p24 antigen	99.5%	100%

WB- Western blot, IFA- immunofluorescence assay, ELISA- enzyme-linked immunosorbent assay, Ag- antigen, Ab- antibody.

count, which indicates that the individual has AIDS. The normal range of CD4 cells in adults and adolescents is 500–1200 cells/mm^3. Detection of < 500 CD4 cells indicates the persistence of HIV in the blood. A previous study revealed that re-assessing HIV diagnosis through CD4 testing escalates the usual and frequent testing and can be essential in ART treatment. The study concluded that case surveillance of patients with a late diagnosis can progressively overestimate late persistence. Indeed, the key populace may differ. Furthermore, it was suggested that adjustments are needed for frequent and usual testers [33]. Recently, Omega Diagnostics developed a new kit (VISITECT® CD4), which detects the CD4 count to 350 cells/mm^3 [34].

A drug resistance testing assay has been used for over two decades. Genotyping and sequencing are the most frequent and adapted methods to identify and detect mutations and drug resistance in HIV patients. With advances in next-generation sequencing (NGS), HIV detection has improved. Indeed, NGS is progressively replacing standardized Sanger sequencing. A recent study concluded that sequencing provides beneficial information in cured patients based on plasma RNA who need a regimen and treatment adjustment. Care should be exercised while interpreting and decoding results. In addition, considering the overall treatment history of the patient is mandatory for appropriate decisions because sequencing methods fail to give a comprehensive and detailed view of HIV DNA documentation. Moreover, cellular HIV DNA testing studies must be required to validate drug resistance [35].

HIV TESTING STRATEGIES

There are several strategies by which HIV can be tested. These strategies include facility-based testing, community-based testing, and self-testing for the detection of HIV. Facility-based testing covers all HIV tests conducted at clinical amenities at the request of patients or facility providers who initiate patient counseling. The results of a previous study revealed that facility-based testing present yearly results in the increased adult:young ratio confirmed in the outpatient department (45% to 83%). This approach is considered to be cost-effective compared to other test types. In addition, the eligibility criteria were simpler and relaxed. The researchers concluded that facility-based HIV testing is a more cost-effective approach to the surge in the men:young ratio tested for HIV in a geographic region and reduce human reserve necessities for testing [36].

Community-based testing involves various modes, including the home, community locations, mobile units, and the workplace. This arrangement offers treatment to those who do not have access to hospital care and permits facilitators to work for individuals with HIV. A study was conducted in which a program was established in the US. The program was shown to be efficacious and cost-effective and well-accepted by the community while maintaining personal privacy [37]. Similarly, index testing is another strategy that includes tracking down sexual exposure and children of HIV patients who are admitted to the hospital and can be operated on and cared for at the community level or facility. The WHO suggests implementing community-based testing because it covers a large population and detects HIV at an early stage compared to other modes of testing [38]. In addition, community-based testing overcomes the barriers between patients and care services [39].

HIV self-testing (HST) is another approach for detecting HIV antibodies at home or in private locations. Individuals can get HST test results with accuracy within 20 min. The accessibility of HSTs may assist in increasing the recognition and realization of HIV infection for individuals who would not get an HIV test. The CDC boosts and vitalizes health centers to adopt HST as a secondary testing approach to influence individuals most affected

by HIV [40]. The OraQuick In-home HIV test was a breakthrough in HST. There are currently several types of HST kits that have been developed around the globe. The benefits of HST include elevated appropriateness and suitability by people who fear the stigma at hospitals. The HST also ensures privacy and is convenient for those who may struggle in finding time for tests. New and improved methodologies in HST have previously produced more accurate results in recent years, which have also overcome the limitations of previous test results [41,42].

HIV TESTING KITS

In addition to the availability of testing kits, approximately 30% of all individuals living with HIV are still unaware of their HIV serostatus [43]. Therefore, new diagnostic and rapid testing kits are needed for better diagnosis of HIV infections. Various testing kits have now been developed by manufacturers that utilize contrasting formats for virus detection, such as Fluorognost HIV-1 IFA, which was approved in 1992 for the detection of anti-HIV-1 antibodies. OraQuick Advance 1/2, the first HST kit approved by the U.S. FDA in 2004, detects HIV-1 and HIV-2 infections within 20 min utilizing cheek swabs [44]. OraQuick requires a lower cost for specimen collection, has a high specificity (100%), and a sensitivity up to 99.6% [45]. Similarly, new U.S. FDA-approved multiplexed nucleic acid, anti-HIV, and combination assays that detect both antigens and antibodies have also been developed, which detect HIV-1 and HIV-2 RNA (Table 2). The specificity and sensitivity of these new systems are relatively high because these assays detect the type of virus (HIV-1 or HIV-2), RNA, and antigen/antibody more efficiently.

GLOBAL TRENDS IN HIV PREVALENCE

Since the first case of HIV was reported, the global burden has increased due to HIV/AIDS epidemics in several countries and regions. Advances in ARTs decrease HIV infections in almost every geographic region, but new infections persist annually. Africa is the most dominant country and has a high number of HIV cases with a rapid increase in southern and eastern Africa.

Trends in Asia

In 1985 the first few cases of AIDS were reported in Thailand [47]. Since then, a substantial increase in HIV/AIDS began late in Asia as the epidemic of HIV spread in Pakistan, Thailand, India, Burma, and Cambodia in the late 1980s and 1990s [48–51]. Of note, epidemics have been substantially induced by sex workers and injection drug users in Asia [52,53]. The transmission chain starts from injection drug users, followed by sex workers. The following connections in the chain are the clients of sex workers in which the virus is transferred to female partners. Most infected women in Asia have been regular partners or monogamous mates of men with an increased risk of HIV [54,55]. The final link in the chain consists of children who become infected through maternal transmission.

Furthermore, it was misunderstood for many years that MSM contributes to Asian HIV epidemics [56]. In Asia, MSM plays a vital role in HIV transmission. For example, Korea reported 21% of MSM cases in the late 1990s [57]. Similarly, studies in Bangkok, Jakarta, and Phnom Penh revealed an HIV infection rate of approximately 2.5% and 22% in MSM, respectively [58,59].

By the end of 2022, Asia and the Pacific reported 6.5 million people were living with HIV infections (Fig 2), and among them there were 300,000 new infections. Teenagers and adults (15+ years old) accounted for 26% and children and adolescents (0–14 years old) for 150,000 cases with 24,000 new HIV infections [5]. In 2022 Sri Lanka was the fourth country to eliminate vertical HIV transmission, followed by Thailand, Malaysia, and the Maldives (Table 3). In 2018 ART was initiated for all pregnant women diagnosed with HIV and 97% of pregnant women diagnosed with syphilis were also receiving treatment. Mother-to-child transmission has not been reported since 2017 in Sri Lanka [60]. Similarly, in 2022 Pakistan was the third country to have an HIV prevalence of 0.1% in adults (15–49 years old; Table 3), followed by Afghanistan and Sri Lanka. As of 11 June 2019, the United Nations in Pakistan was working with the federal and provincial governments to counter the HIV outbreak and thwart a crisis. On 14 June 2019 the WHO, with support from Agha Khan University (AKU), the Field Epidemiology and Laboratory Training Program (FELTP), the United Nations Children's Fund (UNICEF), UNAIDS, DOW Medical University, and the Microbiology Society of Infectious Diseases in Pakistan, conducted epidemiologic examinations for better understanding of the source of HIV transmission and to deliver recommendations [61]. China was among the top 15 countries that encompass 75% of people living with HIV (PLHIV) and new infections. In 2015 PLHIV in China numbered 577,423. The newly diagnosed infection rate was 115,465 with a positive rate of 0.080% [62]. In 2021 there were approximately 1.053 million cases of HIV, of which AIDS-related death accounted for 351,000 in China [63]. The total percentage of heterosexual and homosexual transmission was 74.2% and 23.3%, respectively. MSM is the highest risk group for HIV infection in China [64].

Trends in Africa

Africa has an enormous number of HIV cases and AIDS-related deaths. By 2000 the geographic projection model demonstrated that AIDS was a major cause of death, accounting for 25% of all deaths [65]. According to the Joint United Nations Program on AIDS (UNAIDS), eastern and southern Africa accounted for 20.8 million HIV cases with new infections of 500,000 and 260,000 AIDS-related deaths by the end of 2022 (Fig 2). Western and central Africa accounted for 4.8 million individual HIV infections with AIDS-related deaths up to 120,000. HIV

TABLE 2 | Some of the FDA-approved detection immunoassays for HIV [46].

Antibody detection to HIV				
Product	Type	Detection method	Manufacturer	Approval year by FDA
Fluorognost HIV-1 IFA	HIV-1	IFA	Sanochemia Pharmazeutika AG Vienna, Austria US License 1631	1992
Bio-Rad Geenius HIV-1/HIV-2 Supplemental Assay	HIV	Immunochromatographic	Bio-Rad Laboratories Redmond, WA, USA US License 1109	2019
ABBOTT PRISM HIV O Plus assay	HIV-1, HIV-2	ChLIA	Abbott Laboratories Abbott Park, IL, USA US License 0043	2009
Genetic Systems HIV-2 EIA	HIV-2	EIA	Bio-Rad Laboratories Redmond, WA, USA US License 1109	1990
Multispot HIV-1/HIV-2 Rapid Test	HIV-1, HIV-2	Rapid Immunoassay	Bio-Rad Laboratories Redmond, WA, USA US License 1109	2004
Chembio DPP HIV 1/2 Assay	HIV-1, HIV-2	Rapid Immuno-chromatographic Assay	Chembio Diagnostic Systems, Inc. Medford, NY, USA	2012
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	HIV-1, HIV-2	Rapid Immunoassay	OraSure Technologie Bethehem, PA, USA	2004
Nucleic acid Assays				
Alinity m HIV-1	HIV-1	Quantitative PCR	Abbott Molecular, Inc., Des Plaines, IL, USA	2020
UltraQual HIV-1 RT-PCR Assay	HIV-1	Qualitative PCR	National Genetics Institute Los Angeles, CA, USA US License 1582	2001
APTIMA HIV-1 Quant Assay	HIV-1	TMA	Hologic Inc., San Diego, CA, USA US License 1592	2016
Abbott RealTime HIV-1	HIV-1	Quantitative PCR	ABBOTT Molecular, Inc., Des Plaines, IL, USA	2007
Amplicor HIV-1 Monitor Test	HIV-1	Quantitative PCR	Roche Molecular Systems, Inc. Pleasanton, CA, USA US License 1636	1999
Combo Assay (Ag/Ab) detection				
Elecsys HIV Duo	HIV-1, HIV-2	Immunocmemiluensence	Roche Diagnostics, Indianapolis IN, USA	2020
BioPlex 2200 HIV Ag-Ab Assay	HIV-1, HIV-2	Multiplex flow immunoassay	Bio-Rad Laboratories Redmond, WA, USA US License 16136	2015
ARCHITECT HIV Ag/Ab Combo	HIV-1, HIV-2	CMIA	Abbott Laboratories Abbott Park, IL, USA US License 0043	2010
Alere DetermineTM HIV-1/2 Ag/Ab Combo	HIV-1, HIV-2	Immunoassay	Alere Scarborough, Inc. Scarborough, ME, USA	2013
ADVIA Centaur HIV Ag/Ab Combo (CHIV) Assay	HIV-1, HIV-2	Microparticle Chemi-luminometric Immunoassay	Siemens Healthcare Diagnostics, Inc., USA	2015

IFA- immunofluorescence assay, ChLIA- chemiluminescence immunoassay, PCR- polymerase chain reaction, EIA- enzyme immunoassay, TMA- transcription-mediated amplification, CMIA- chemiluminescent microparticle immunoassay.

infections in the Middle East and North Africa accounted for 190,000 with AIDS-related deaths up to 5300 with new infections of 17,000 [5]. In 2022 all regions of Africa, including Tanzania, Zimbabwe, Kenya, and South Africa, were dominant in the HIV prevalence percentage due to an increased ratio of MSM, transgender women, people injecting drugs, and sex workers (Table 3).

In sub-Saharan Africa, one major cause for virus spread was migration from rural-to-urban areas and international travel. In addition to migration and travel, one factor in

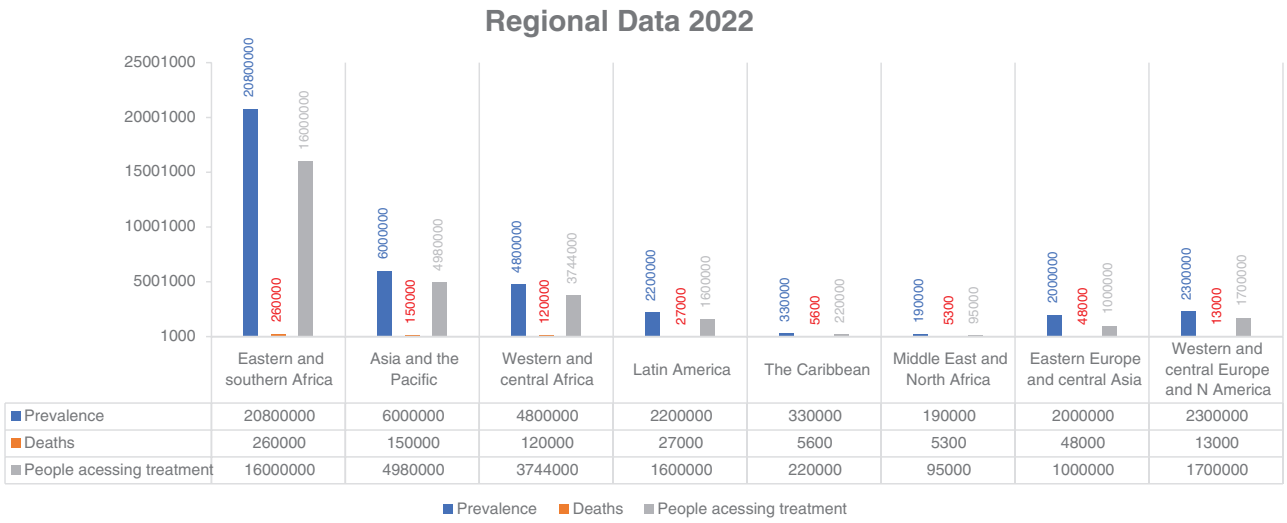

FIGURE 2 | Representation of regional data on HIV in 2022.

migration and urbanization was immeasurable communal interference [66,67]. Commercial sex was more common, prophylactic assistance was reduced or was not accessible, and sexually transmitted diseases (STDs) surged. Social destruction and cultural exchange with a rise in poverty directly influence HIV infections. These factors impact sub-Saharan Africa and escalate HIV transmission in the general population. Individuals at high risk were injection drug users, infected individual's sex partners, and blood exchange donors [68].

Trends in Europe, the US, and the Caribbean

In December 1995 the WHO reported 149,403 of 160,982 cases accounted for 92.8% of all AIDS cases in 15 European countries. Moreover, countries in the central and eastern regions, which constitutes 40% of the entire population of Europe, accounted for just 1% of all cases [69]. In December 1997, of 190,000 infections, the WHO and UNAIDS evaluated HIV/AIDS infections to have surged more than 5-fold in eastern Europe [70]. By the end of 2022, eastern Europe and Central Asian countries, including Albania, Armenia, Azerbaijan, Belarus, Bosnia, Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, the Republic of Moldova, the Russian Federation, Tajikistan, the former Yugoslav Republic of Macedonia, Turkmenistan, Ukraine, and Uzbekistan [71], reported a total of 2 million (1.8–2.1 million) HIV infections, of which the total AIDS-related deaths accounted for 48,000 (38,000–58,000) and individuals accessing ART treatment accounted for 1 million. Similarly, western and central Europe and North America reported a total of 2.3 million (1.9–2.6 million) individuals living with HIV, of which AIDS-related deaths were 13,000 (9300–17,000) and individuals acquiring ART treatment were 1.7 million (1.6–1.7 million; Fig 2) [5]. Among all European regions, Russia (the eastern region of Europe) reported a high number of new HIV cases with greater prevalence in 2017 compared to other European countries (northern, southern, and western regions of Europe; Table 3).

In 2000 Latin America and Mexico reported that 50% of AIDS cases were increased due to MSM. Similarly, in Argentina injection drug users were at increased risk of HIV infection and heterosexual transmission prevailed in the Caribbean [72]. In 2008 Latin American regions, including North America (Mexico), Andean countries (Colombia, Venezuela, Peru, Ecuador, Bolivia, and Brazil), and southern countries (Argentina, Paraguay, Chile, and Uruguay), reported HIV cases in whom MSM, female sex workers and their clients, transgender sex workers, injection drug users, and the migrant population were the major sources of AIDS. A high prevalence of HIV was observed in the age group ranging between 15 and 49 years. The male ratio was comparatively higher than the female [73]. By the end of 2022 Latin America reported 2.2 million (2–2.5 million) people living with HIV infections. AIDS-related deaths numbered 27,000 (21,000-35,000) and individuals with ART treatment numbered 1.6 million (1.4–1.6 million; Fig 2). Similarly, in the Caribbean the number of HIV cases was 330,000 (290,000–380,000) with AIDS-related deaths numbering 5600 (4100–7500), and people with ART treatment numbered 220,000 (210,000-220,000) [5].

TREATMENT

Since the onset of the HIV epidemic, critical investigations have emerged in the evolution of antiretroviral drugs. In 2016 > 40 drugs were developed that aid in controlling infection when administered in several combinations. As of 2021 the U.S. FDA approved approximately 222 antiretroviral drugs for AIDS treatment globally [74].

The mortalities and morbidities due to HIV infections have been drastically reduced with the use of

TABLE 3 | Region-wise HIV infections, mortalities, and ART treatment of infected individuals.

Regions	Countries	Individuals with HIV	HIV prevalence (%) in adults (15 to 49 years)	AIDS mortality	Individuals on ART treatment (%)	Update year
Asia	India	2.5 million	0.2	40 000	68	2022
	Pakistan	270 000	0.1	12 000	13	2022
	China	1.053 million	N/A	351 000	85	2021
	Cambodia	76 000	0.5	1100	86	2022
	Vietnam	250 000	0.3	4100	73	2022
	Thailand	560 000	1.1	11 000	81	2022
	Afghanistan	12 000	<0.1	780	9	2022
	Sri Lanka	4100	<0.1	<100	68	2022
	Indonesia	540 000	0.3	26 000	33	2022
Sub-Saharan Africa	South Africa	7.6 million	17.8	45 000	75	2022
	Niger	34 000	0.2	1100	75	2022
	Zimbabwe	1.3 million	11	20 000	94	2022
	Kenya	1.4 million	3.7	18 000	94	2022
	Tanzania	1.7 million	4.3	22 000	94	2022
	Uganda	1.4 million	5.1	17 000	84	2022
	Zambia	1.4 million	10.8	19 000	90	2022
Europe	Russia	1 million	1.2	24 000	45	2017
	Ukraine	250 000	1	5900	54	2019
	France	200 000	0.3	<1000	85	2022
	Italy	140 000	0.2	<1000	90	2022
	Ireland	7500	0.2	<100	84	2019
South America and The Caribbean	Brazil	990 000	0.6	13 000	74	2022
	Argentina	140 000	0.4	1300	68	2022
	Colombia	190 000	0.5	1500	55	2022
	Peru	110 000	0.4	<1000	82	2022
	Chile	83 000	0.6	N/A	74	2022
	Cuba	42 000	0.6	<500	67	2022
	Jamaica	30 000	1.3	1100	50	2022
	Guyana	9600	1.5	<200	67	2022
	Trinidad and Tobago	12 000	1	<500	60	2022

ART and improved immunity of infected individuals since 1996. Similarly, the lifespan of HIV-infected patients is shorter compared to uninfected individuals. In all geographic regions, including low- and high-income regions, ART has improved the life expectancy annually [75, 76]. Various antiretroviral (ARV) drugs, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transferase inhibitors (INTIs), fusion inhibitors (FIs), CXCR- 5 antagonists, and combinations of drugs for HIV, have been developed and approved by the FDA that can be utilized for the inhibition, suppression of viral load, and to hinder viral replication cycle (Table 4). In late 2022 the FDA approved a novel injectable medication (lenacapavir [Sunlenca]), a capsid inhibitor that affects and targets the shell that shields the virus, which ultimately prevents the virus from multiplying. Antibody development was a major concern to treat HIV, however, various trials of several HIV vaccine candidates and two specific trials of antibody-mediated control revealed no effectiveness in HIV acquisition. Nevertheless, four AMP (neutralizing antibody) trials affirmed that broadly neutralizing antibodies can deliver

TABLE 4 | List of FDA-approved ARV drugs [77].

Class	Year of approval
NRTIs	
Zidovudine (AZT, ZDV)	1987
Lamivudine (3TC)	1995
Abacavir (abacavir sulfate)	1997
Tenofovir disoproxil fumarate (TDF)	2001
Tenofovir alafenamide (TAF)	2015
Emtricitabine (FTC)	2003
Zalcitabine	1992
NNRTIs	
Nevirapine (NVP)	1996, 2011
Efavirenz (EFV)	1998
Etravirine (ETR)	2008
Rilpivirine (RPV)	2011
Doravirine (DOR)	2018
PIs	
Saquinavir (SQV)	1995
Ritonavir (RTV)	1996
Atazanavir (ATV)	2003
Fosamprenavir (FPV)	2003
Tipranavir (TPV)	2005
Darunavir (DRV)	2006
Fis	
Enfuvirtide (T-20)	2003
INSTIs	
Raltegravir (RAL)	2007
Dolutegravir (DTG)	2013
Cabotegravir (CAB)	2021
CCR5 Antagonist	
Maraviroc (MVC)	2007
Combination drugs	
Abacavir, lamivudine, and dolutegravir	2014
Darunavir and cobicistat (DRV/COBI)	2015
Cabotegravir and rilpivirine (CAB/RPV)	2021

effectiveness in the treatment of HIV when circulating variants are substantially responsive to bnAb neutralization. Previous studies suggested that infection was neutralized via a single VRCO1 bnAb, which confirmed that the efficacy of antibody combinations is crucial for HIV prevention. In the future, selection criteria must be prepared and developed by various research groups for effective trials [78].

Nucleoside reverse transcriptase inhibitors (NRTIs)

Nucleoside reverse transcriptase inhibitors (NRTIs) are known as the initial drugs that were developed in the 1990s. NRTIs are natural nucleosides and nucleotide analogs that bind to reverse transcriptase, thereby inhibiting viral DNA synthesis. Most of the nucleosides and nucleotides are now developed and used in combination. Classical examples of NRTIs include zidovudine (AZT), abacavir, lamivudine, stavudine, and emtricitabine. Studies have shown the potent NRTIs (delavirdine, efavirenz, and nevirapine) interact with multidrug resistance proteins (MRP-1/ABCC1, MRP-2/ABCC2, and MRP-3/ABCC3) and inhibit ABC transporters [79]. Similarly, Wang et al. conducted an experiment in which azvudine, a novel NRTI, was used alone and in combination with other drugs to examine drug resistance features against HIV-1 and HIV-2. The results revealed effective inhibition of HIV-1 with an effective concentration$_{50}$ (EC_{50} = 0.03–6.92 nM) and HIV-2 with an effective concentration$_{50}$ (EC_{50} = 0.018–0.025 nM). Furthermore, synergistic effect was shown in a human leukemia T cell line (C8166) and peripheral blood mononuclear cells when combined with six FDA-approved anti-HIV drugs [80].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) were initially developed in 1996. NNRTIs also hinder reverse transcriptase in a way that is distinct from NRTIs because intracellular metabolism is not essential for activity. NNRTIs are potent inhibitors because NNRTIs bind to a pocket near the active residue of the enzyme, leading to a conformational change in the enzyme and inhibiting reverse transcription of RNA. These drugs are safe, effective, and more potent when used in combination with other ARV drugs [2]. Treatment with etravirine, a potent NNRTI, suppresses the viral load. Approximately 60% of individuals treated with etravirine established a low viral load of 50 copies/ml in phase III trials in the 24th week [81]. Similarly, doravirine is a novel NNRTI developed by Merck & Co., Inc. in 2018 to cure HIV-1 infections. The drug had positive results in treating HIV-1 infection without any drug-resistance mutations to NNRTIs in the European Union [82].

Integrase strand transfer inhibitors (INSTIs)

Integrase strand transfer inhibitors (INSTIs) were developed in the late 2000s. These analogs interact and bind to an active residue of the integrase enzyme, leading to detachment from deoxyadenosine at the 3' end of viral DNA and subsequently blocking viral replication. INSTIs have been shown to be safe and effective in treating HIV-1 naive and infected individuals. Hare et al. reported that second-generation dolutegravir is a potent inhibitor of HIV-1 integrase (IN) variants that are resistant to first-generation INSTIs [83]. Similarly, bictegravir

(BIC [GS-9883]), a single-dose, novel, potent inhibitor of HIV-1 integrase, has ARV activity in T-cell lines and T lymphocytes with better effectiveness and less cytotoxicity [84]. BIC reveals anti-proliferative effects when administered as a combined dose with tenofovir alafenamide, darunavir, or emtricitabine, and has prolonged ARV activity against HIV-1-resistant variants [85].

Protease inhibitors (PIs)

The HIV protease enzyme is involved in the cleavage of gag and pol precursors, which leads to individual functional proteins and enzymes in the last stage of the viral life cycle when new virions mature and bud from the cell. This final stage of the viral life cycle is inhibited by protease inhibitors. PIs are effective and safe when administered in combination with other ARV drugs, especially with two nucleoside analogs. Because PIs are rapidly metabolized by the liver, these drugs are frequently administered with pharmacologic boosters (ritonavir or cobicistat) that hinder metabolic pathways [2]. Lopinavir is a PI that is co-administered with ritonavir as lopinavir; ritonavir is structurally similar. When administered as a combination, ritonavir inhibits cytochrome P450 isoenzyme 3A4, which significantly increases the drug exposure of lopinavir. Ritonavir suppresses HIV RNA for up to 2 years in ARV-naive individuals [86]. Similarly, a study showed that saquinavir (600 mg) increased the CD4 cell count in the 4th week in naive patients with HIV [87].

Entry inhibitors (EIs)

HIV-1 enters cells via the envelop glycoprotein complex (Env) by mediating attachment to target cells and membrane fusion. Env contains three gp120 subunits that mediate attachment to receptors and three gp41 subunits responsible for membrane fusion. Entry of the virus at an early stage is inhibited by fusion inhibitors. Enfuvirtide (T-20), the only approved fusion inhibitor, blocks membrane fusion by binding to gp41, leading to inhibition of post-fusion structure formation [88]. Similarly, CXCR5 antagonists are a class of entry inhibitors that are utilized mainly to inhibit HIV-1 entry into the cells. Maraviroc is a classic example of a CXCR5 antagonist that can be used as an ARV medication in combination with other ARV drugs for the treatment of naive HIV-1 individuals [89].

FUNCTIONAL CURE

Several mediations to stimulate and provoke functional cure of HIV have been revealed and explored with the goal to render the ART and drugs for a prolonged period. This can be achieved by decreasing the size of the latent reservoir (for example, provoking small molecules of dormant infected cells) by decreasing the amount of target cells, such as gene therapy. Currently, ART is very effective because ART suppresses the viral load and reduces the chances of viral replication, but the rebound occurs within several weeks of initiating ART. Therefore, gene therapy, increasing immune responsiveness, activation, the death of dormant virus is an alternative functional cure to HIV (Fig 3) [90].

Activation and death of dormant virus

One method is to bring and activate the dormant virus, which will reduce the frequency of HIV reactivation preceding immune-mediated elimination of infected cells [91]. Previous studies have shown the efficacy of single

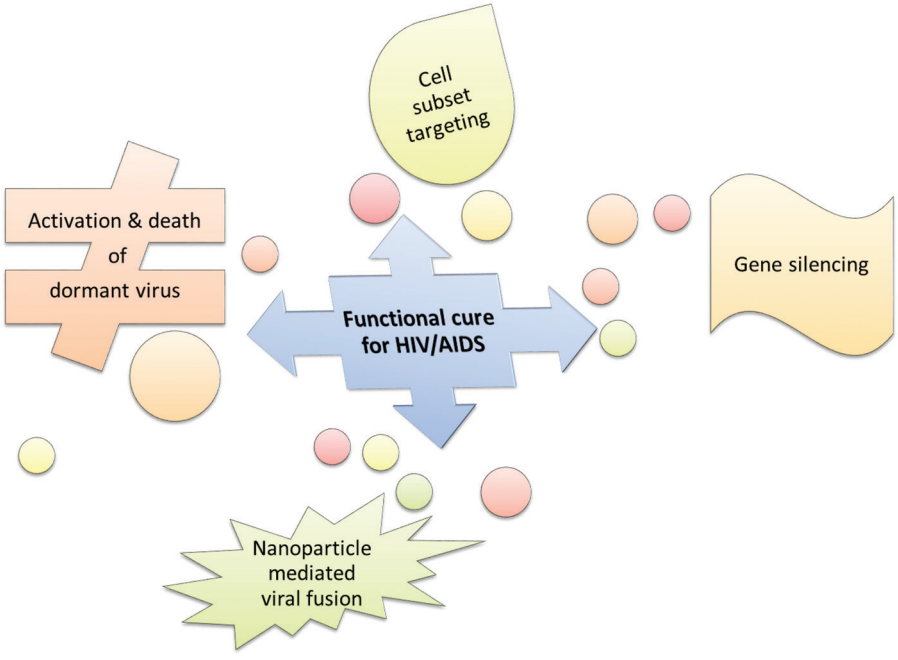

FIGURE 3 | Major functional cure approaches for HIV.

and combined approaches. Although it appears doubtful that a cure can decrease the frequency of HIV reactivation by 98%–99%, various rounds and episodes of treatment could have additional effects over time, suggesting that re-cure collectively decreases reactivation. Therefore, a cure that decreases the frequency by 45%–50% with every cure could be directed and managed twice to decrease the frequency to one-quarter of the previous amount. This type of cure would need to be given 10 times to decrease the frequency of HIV reactivation up to 1000-fold [90].

Cell subset targeting

A nominally lethal method to reservoir decline would entail specifically eradicating latently infected cells, which will preserve the integrity of the remaining cells. Nevertheless, the hushed feature of a dormant virus makes it challenging to recognize and detect these cells. Numerous studies have revealed and contrasted the points of provirus in several subsets and recognized cells that have escalated points of infection [92]. In fact, it is not the escalated point of infection in the targeted cells that is crucial, but the ratio of complete dormant virus that occurs within the subset.

Gene silencing

An essential for dormant cell recurrence is the existence of a compact genome of HIV. Immediate targeting of these genomes is a possibility to decrease the frequency of recurrences. The utilization of CRISPR-CAS-9 is a promising approach to gene targeting in which gene therapy cuts and slices the provirus, and thus removes and destroys latent HIV or suppresses HIV recurrence has been recommended previously. At present, these methods and well-studied approaches decrease the replication process by 20-fold *in vitro* and approximately 10-15-fold *in vivo* in laboratory-scale animal models [93,94]. In August 2023 the researchers developed a dual CRISPR cure to eradicate HIV DNA and control recurrences *in vitro* [22]. Present and novel perceptions and understandings of HIV biology can be effective in improving the CRISPR-CAS gene editing approaches.

Nanoparticles targeting viral fusion

Directing and affecting the replication cycle by impeding the capacity of HIV-1 to unite, fuse, or penetrate a target cell have been studied previously. Fusion inhibition escorts the inhibition of viral action and cytotoxicity. A previous study conducted by Lara et al. revealed that silver nanoparticles are antiviral agents and preventive against HIV-1 fusion to directed cells and subunits. The nanoparticles use anti-HIV action at an initial and immediate phase of viral multiplication, expected as a virucidal vehicle or as an inhibitor of entry. Silver nanoparticles muddle and fix to gp120 in a fashion that averts and blocks CD4-reliant virion compelling, fusion, and contagion, and appear as an efficient and operational virucidal vehicle against free and linked virus and subsets. In addition, silver nanoparticles prevent and stop post-entry phases of the HIV-1 cycle [95]. Similarly, another study reported that the synthesis of hydrophobic polymeric nanoparticles may decrease semen-derived enhancers of viral infection (SEVI) and fibril-initiated infection [96]. Another study revealed that coated polymeric nanoparticles mimicking and constructing CD4 + T-cells *in vitro* can also neutralize HIV infectivity by interacting with HIV-1 [97].

CHALLENGES

Various challenges, including scientific, political, cultural, ethical, drug resistance mutations to ARV drugs, vaccine development, resource-limited testing, social and behavioral, stigma and discrimination, and co-morbidities and aging, need to be overcome by adapting new prevention strategies in the future to control HIV epidemic (Fig 4). Treatment for HIV-diagnosed individuals should be inexpensive and easy to access across the globe, specifically in low-income countries where organizations lack access to kits and treatment.

ARV drug resistance

Adherence to the ARV drug regimen can fully suppress the viral load and replication of infected individuals [98]. However, incomplete attachment of the drug leads to continued HIV replication in the presence of a drug regimen, which results in mutations in the virus that confer resistance to ARV drug regimens [2]. Mutations emerge promptly for NNRTIs and NRTIs, steadily for many NRTIs and some INSTIs, and rarely for PIs and INSTIs. Drug resistance transmitted to other variants ranges from 5%–15% in high-income regions [99,100] and significantly low in middle- and low-income regions. However,

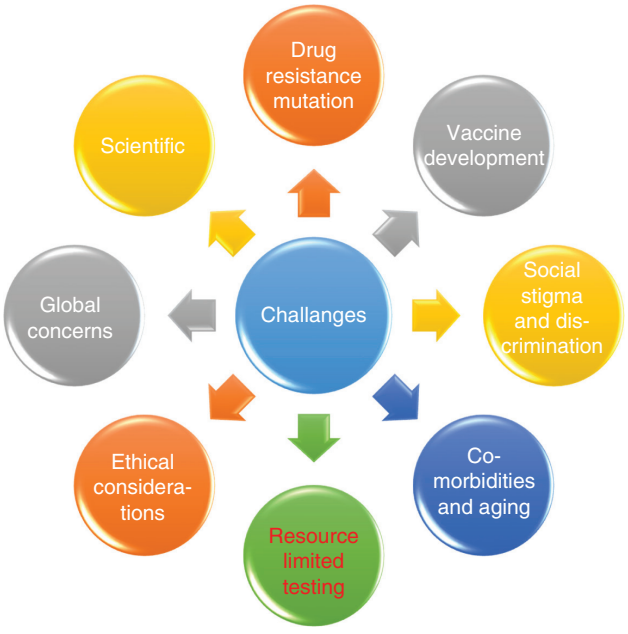

FIGURE 4 | Challenges associated with HIV manifestations.

mutations have been increased in the past few years because the application of drug regimens has increased [101].

Global concern

It is often challenging to deliver drugs on a global level, which raises logistical challenges, especially in low-income regions where the percentage of drug abusers has risen and poverty is a major concern [102]. Similarly, due to fewer resources and poverty, the female sex worker ratio is comparatively higher in low-income countries, including Kenya, Nigeria, Tanzania, Zambia, Zimbabwe, and South Africa.

Vaccine development

Several vaccine candidates have been proposed and are in clinical trials. On 5 July 2021 a novel vaccine candidate, the HIVconsvX vaccine (mosaic vaccine for the target of HIV-1 variants), was in a phase I clinical trial in the UK. However, there are numerous challenges, including a lack of the best animal model, deficit correspondence to immunity, virus target in specific immune cells, and remarkable hypervariability [103]. Similarly, there are several challenges related to neutralizing antibodies because of the hypervariability of the virus, which makes vaccine design difficult. First, the neutralizing antibody target to envelope glycoprotein (Env) on the virus surface is unstable because non-native Env on the surface of the virus influences non-neutralizing antibodies [104]. Another problem is a variable region of Env because it is immunodominant, which leads to specific neutralizing antibodies [105]. Similarly, the interaction of neutralizing antibodies is difficult because sugar molecules cover Env glycoprotein [106]. Hence, it is necessary to overcome these challenges for better candidate vaccine development.

Co-morbidities and aging

AIDS and HIV infections can be recovered with ART, but co-morbidities persist, such as tumors, renal and liver dysfunction, osteoporosis, osteopenia, cardiovascular disease, and neurocognitive disease [107,108]. Aging directly relates to co-morbidities and is a major concern because aged HIV-infected individuals with co-morbidities are thought to be susceptible to accelerated aging [109,110].

CONCLUSION

With the advances in ARV treatment, diagnostic systems, and acquired assistance drastically released and decreased the global burden of AIDS and HIV. These exceptional approaches and advances led to an increase in the life expectancy globally, especially in sub-Saharan Africa where the ratio of HIV and AIDS is comparatively higher compared to other regions of the world. With the previous burden and impact of HIV/AIDS in the past 40 years, new HIV cures and candidate vaccine development could soon lead to the goal, i.e., to end the HIV/AIDS epidemic globally and to free the next generation from HIV.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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