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Integrated care for HIV/AIDS infected patients. The Romanian experience

Miruna-Maria APETROAEI, Marina Ionela ILIE, Andreea Letitia ARSENE

Department of General and Pharmaceutical Microbiology, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract

The human immunodeficiency virus (HIV) targets the body's immune system and, if left untreated, may result in acquired immunodeficiency syndrome. (AIDS). HIV's pathogenesis entails the gradual destruction of CD4+ T cells, which lowers the immune system and leaves the body more susceptible to co-infections and other diseases. HIV has been highlighted as a global public health concern, and since the first instances were recorded in the early 1980s, it has caused extensive morbidity and mortality. The HIV epidemic is still impacting millions of individuals throughout the entire globe, even though available antiretroviral therapy (ART) has transformed HIV infection from an almost universally fatal disease into a controllable chronic medical condition. The magnitude of the HIV epidemic varies between areas and countries. In 2021, the Joint United Nations Program on HIV/AIDS (UNAIDS) projected that 38.4 million individuals worldwide were living with HIV. The HIV integrated care approach highlights the significance of early diagnosis, care coordination, and medication adherence. This strategy incorporates a multidisciplinary team of medical specialists, including physicians, pharmacists, social workers, nurses, and mental health professionals. In addition to medication management, mental health counseling, drug addiction treatment, and peer support, HIV-integrated care includes additional therapies such as behavioral health counseling. HIV integrative care is a holistic approach to HIV infection management that addresses patients' medical, interpersonal, and emotional requirements. It has been demonstrated that this form of treatment improves health outcomes, reduces stigma, and increases community involvement in combating HIV infections.

Keywords: HIV/AIDS management, HIV/AIDS in Romania, integrated care for HIV/AIDS, HIV/AIDS burden

INTRODUCTION

According to the World Health Organization, human immunodeficiency virus (HIV) infection targets the immune system, particularly CD4 leukocytes. HIV destroys these cells, reducing the immune system's susceptibility to opportunistic infections such as tuberculosis, fungal infections, severe bacterial infections, and some malignancies. The most severe stage of HIV infection, the acquired immunodeficiency syndrome (AIDS), is characterized by the development of malignant tumors, infections, or other major long-term clinical symptoms.

In the summer of 1981, the Centers for Disease Control and Prevention in the United States reported an outbreak of Pneumocystis carinii pneumonia episodes in five homosexual men, generating the suspicion for the first time that an infectious agent was responsible for acquired immunodeficiency syndrome. In contrast, there is significant proof suggesting that HIV overcame

Corresponding author:
Marina Ionela Ilie
E-mail: marina.ilie@umfcd.ro

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the primate-human barrier much earlier, perhaps in Cameroon, West Africa [1]. In 1986, a virus with a similar morphology but a unique antigen produced AIDS in West Africa. HIV-2, an entirely novel virus, was only distantly linked to HIV-1, but it was closely connected to a simian virus that caused immunodeficiency in macaques held in captivity. Several simian immunodeficiency viruses (SIVs) were subsequently identified in over 20 monkey species in sub-Saharan Africa. Thus, for the first time, it was demonstrated that lentiviruses from several monkey species cause AIDS in humans and macaques. According to a recent investigation, SIVmac, a disease of Asian macaques, was accidentally created in US primate facilities by inoculating macaques with tissue and blood samples from naturally infected sooty mangabeys. HIV-1 and HIV-2 were both spread by means of zoonotic transmission from African monkeys [2].

Nowadays, human immunodeficiency virus isolates are categorized as HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV-1 is the primary root cause of AIDS on a global scale, whereas HIV-2 is restricted to portions of West and Central Africa. There are four subgroups of HIV-1: M (Major), O (Outlier), N (Non-M, Non-O), and P. M is the pandemic subgroup, whereas O, N, and P are less prevalent. There are several subtypes of Group M viruses, which can be found globally. They have been separated into 10 distinct subgroups, denoted by the letters A through K [3,4]. Although subtype B of HIV-1 is the most ubiquitous around the globe, it accounts for less than 12% of all infections. It is particularly prevalent in prosperous countries, Latin America, and the Caribbean. HIV-1 subtype C, on the other hand, contributes to about half (48%) of all infections globally and has the greatest incidence in southern and eastern Africa and India. It is known that the amino acid arrangement of the viral envelope glycoprotein varies by 25–35% among clades in group M and by up to 20% within a specific clade, which is a significant barrier to the creation of vaccines [5].

HIV is genetically linked to the genus Lentivirus within the Retroviridae family. Infections with lentivirus are frequently chronic, characterized by an extended duration of clinical latency, sustained replication of the virus, and impairment of the central nervous system [6]. Retrovirus genomes are comprised of two identical copies of single-stranded RNA molecules and contain the structural genes gag, pol, and env. Both the HIV-1 and HIV-2 viruses possess a genomic organization that is unique from that of other retroviruses, although they have the same fundamental structure. (i.e., the existence of the three structural genes gag, pol, and env) [7]. In addition to these three genes, the HIV-1 and HIV-2 genomes incorporate a complex mix of additional regulatory and accessory genes. Both types of viruses have the ability to produce AIDS; however, HIV-2 infection may be associated with a higher incidence of central nervous system disease. HIV-2 is less virulent and allows AIDS to develop more gradually [8].

Similarly with other retroviruses, the gag gene encodes structural proteins that make up the nucleus (p24, p7, and p6) and matrix (p17), whereas the env gene encodes viral envelope glycoproteins gp120 and gp41 that recognize cell surface receptors. The pol gene encodes the reverse transcriptase, integrase, and protease enzymes crucial to the replication of viruses. HIV particles have a 100 nm diameter and a lipoprotein-rich envelope. In viral particle membranes, the glycoprotein trimers gp120 and gp41 form glycoprotein heterodimer complexes. Because gp120 and gp41 do not bind covalently, gp120 can be eliminated spontaneously and is present in the serum and lymphatic tissue of HIV-infected individuals. The viral capsid contains two copies of the HIV RNA, as well as a nucleoprotein, reverse transcriptase, integrase, and protease [9].

TRANSMISSION ROUTES

The most prevalent modes of HIV transmission include heterosexual or homosexual sexual contact, injection of blood or blood-related products, as well as mother-to-child transmission during pregnancy, birth, or breastfeeding [10].

In addition, there is a considerable association between the use and consumption of illegal substances and the spread of the human immunodeficiency virus. As this population has a high incidence of HIV transmission and replication, drug users are recognized as a demographic category with a high risk of HIV infection. Cocaine, amphetamines, methamphetamines, heroin, and morphine are the five most widely consumed illicit drugs, and their abuse is closely linked to HIV transmission and the advancement of AIDS. In addition, a substantial number of studies have demonstrated that drugs enhance HIV replication, which leads to a rise in viral RNA concentrations, especially in the central nervous system, causing neuronal damage and cognitive impairment [11].

Further research suggested that newly infected people account for up to fifty percent of all new HIV-1

infections [12,13]. This would be associated with the elevated plasma viral load prevalent in the early stages of the illness, as well as the virus's unique characteristics [14]. Nevertheless, not all people who have been exposed to HIV become infected, and not all HIV-positive individuals develop AIDS. One in one hundred to one in one thousand heterosexual exposures result in infection [13,15], and only one-third of infants born to infected mothers are affected [14].

PATHOGENICITY OF HIV INFECTION

The arrangement of cellular proteins that the virus requires to gather in order to enter a cell dictates the tropism of HIV-1. Shortly after the discovery of HIV-1, studies confirming that CD4 is a target for the virus were published [16,17]. It wasn't until almost a decade and a half later that researchers discovered HIV-1 uses CCR5 and CXCR4 as coreceptors (chemokine receptors) [18,19]. Due to the widespread location of these receptors, there is the potential to infect not just CD4+ T cells but also antigen-presenting cells. These cells include macrophages and dendritic cells, among several others. The HIV-1 virus has adapted to the distinct biological features associated with these numerous cell types. As a result, HIV-1 may remain intact in a diversity of replication stages and tissue compartments, enabling it to thrive in the presence of highly suppressive antiretroviral regimens and host immunological responses [19].

Mucosal surfaces are a major route of entry for HIV, and once it enters the body, the virus immediately begins infecting CD4+ T leukocytes and rapidly establishing a reservoir of latently infected memory T cells [20]. Increased T cell turnover, polyclonal B cell activation, the frequency of activated phenotypic T cells (CD38+, HLA-DR+), and the generation of proinflammatory cytokines and chemokines are all hallmarks of the chronic immunological activation that follows infection of mucosal CD4+ T cells [21]. Persistent immunological activation characterized by increased T cells develops immediately upon infection of mucosal CD4+ T cells. As the immune system becomes overactive, AIDS may emerge [22].

STAGES OF INFECTION AND CLINICAL MANIFESTATIONS

The progression of HIV infection in the absence of treatment varies widely. Those with a high CD4 cell count are less likely to develop symptoms over time. Long-term asymptomatia is documented among 1%-5% of the HIV-positive population [23].

In the absence of antiretroviral therapy, the patient's clinical response to HIV involves three stages: (1) an initial acute infection; (2) a long asymptomatic phase; and (3) an ultimate growth in viremia and a concurrent reduction in the amount of healthy CD4+ T cells, throughout which AIDS develops. During the acute infection period (two to ten weeks), the number of CD4+ T cells and the amount of free virus are drastically reduced and increased, respectively. This stage of the early stages of infection is marked by acute symptoms such as fever, lymphadenopathy, pharyngitis, headache, and rash. Following this period, the number of circulating CD4+T cells recovers to "near-normal" levels, and the viral load decreases dramatically. During this latent or asymptomatic phase, HIV continues to infect new cells and reproduce, but the patient shows no outward signs of illness. Although the latent phase typically lasts 7–10 years, the disease's progression varies widely from patient to patient. This phase of asymptomatic development is followed by a precipitous decline in viral load and CD4+ T cell count. When the number of CD4+T cells in the body drops below 200 cells/mm^3 or certain opportunistic infections are present, this is considered the AIDS stage [24].

Initial HIV-1 infection is confirmed by laboratory investigations and the presence of clinical signs and symptoms, including fever, malaise, tiredness, neurological symptoms and signs, headache, myalgia, pharyngitis, diarrhea, rash, enlarged lymph nodes, meningoencephalitis, and hepatitis. In the early weeks following transmission and infection, blood tests may indicate liver failure, leukopenia, or thrombocytopenia, despite the absence of HIV-1 antibodies [25].

HIV CO-INFECTIONS

HIV/tuberculosis

According to the World Health Organization, tuberculosis (TB) is the most common cause of mortality for HIV-positive individuals. HIV weakens the immune response and reduces the body's defenses against infection, which increases the risk of TB. Patients with HIV are as much as twenty times more likely to acquire active TB than those without HIV [26]. HIV transforms TB from an infection with a slow-moving progression to one with a high fatality rate. A

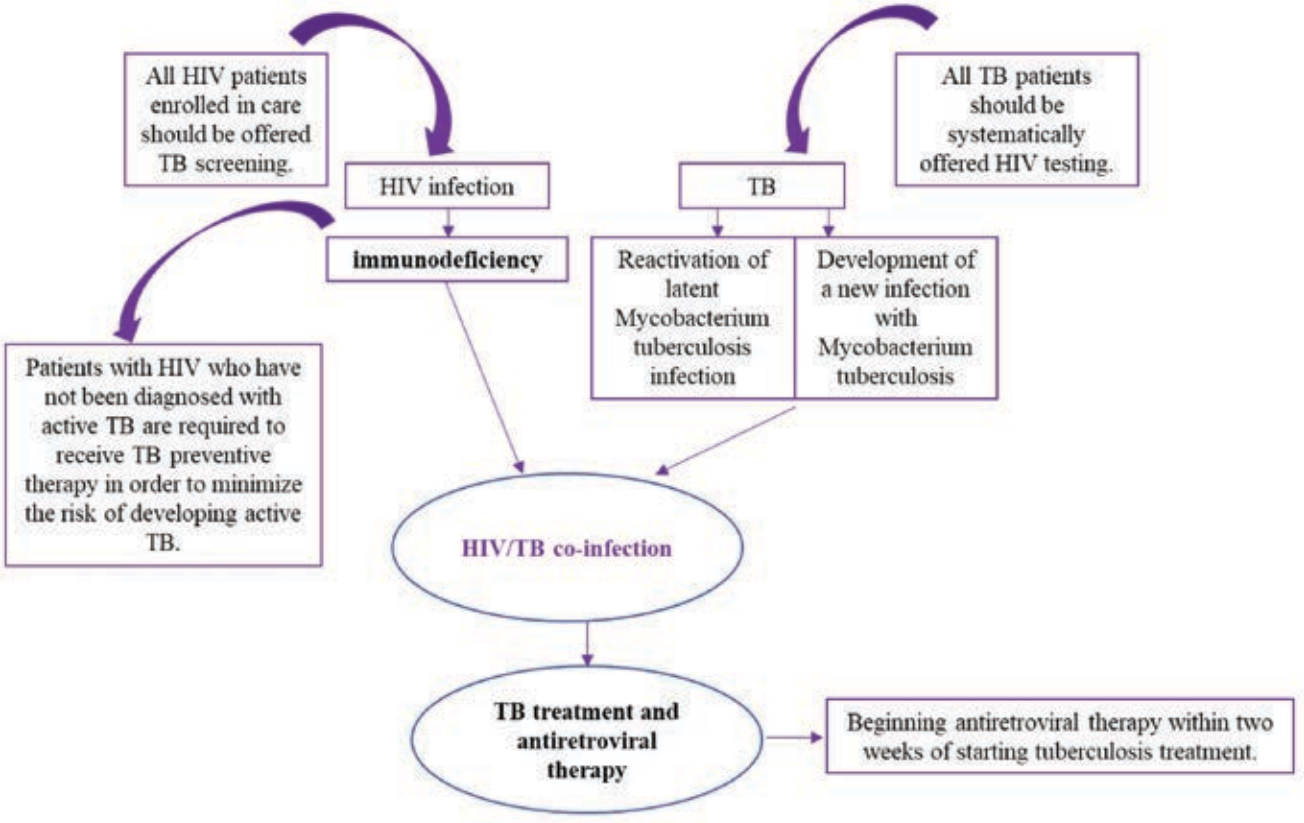

FIGURE 1. WHO recommendations for HIV/TB co-infection (Adapted from [26])

prospective multicenter cohort study has proved conclusively that the risk of TB is connected with growing immunodeficiency and that TB substantially raises the likelihood of fatality [27].

The optimum management of TB with high patient adherence and a patient-centered approach may result in effective treatment and a decrease in mortality [28]. Antiretroviral therapy has been scientifically shown to have a significant effect on the prognosis of HIV-infected patients with TB [27,29]. HIV-infected patients who suffer from TB must receive therapy for both TB and HIV concurrently. Furthermore, patients with reduced CD4 cell counts and limited access to resources continue to present challenges to medical professionals. In the first few months following ART, new episodes of opportunistic infections are possible, with TB being the most prevalent [30]. Figure 1 illustrates WHO recommendations for HIV/TB co-infection care.

Reactivation of latent *Mycobacterium tuberculosis* infection or development of a new infection are the two main causes of TB in HIV-infected patients [31]. Persistent fever, hemoptysis, a productive cough, diminished appetite, or sweating during the night are characteristic symptoms; however, these can be present together with very few other symptoms or be absent altogether [32]. The manifestations of TB depend on the level of immunodeficiency. The appearance of pulmonary TB in patients with AIDS might be abnormal and uncommon [33]. Up to 60% of HIV-infected patients with TB have extrapulmonary manifestations [34], making it one of the most common forms of TB in this patient group. In patients with low CD4 levels, extrapulmonary TB and mycobacteremia are more likely to develop [35]. Lymphadenitis, disseminated or systemic infection, and tuberculous pleuritis are common extrapulmonary manifestations of TB [34,36]. Additional non-pulmonary locations for HIV-related TB include the skin and soft tissues, pericardium, liver, spleen, kidney, digestive tract, and genitourinary system [37].

Based on the most recent research from studies involving both diseases, integrated HIV/TB therapy has been demonstrated to be practical, effective, and generate higher rates of survival in an assortment of clinical scenarios.

HIV/HBV and HIV/HCV co-infection

HIV patients who have been diagnosed as immunocompromised are more likely to contract other viruses, such as the hepatitis B virus (HBV) or the hepatitis C virus (HCV). Injecting drugs, sexual contact, and maternal-to-infant transmission are all common ways that these illnesses are transmitted through blood [38]. HIV coinfection with the hepatitis B virus and/or the hepatitis C virus is common in some populations [39,40].

Vertical transmission of HBV occurs during pregnancy, childbirth, or the first five years of life through unprotected skin-to-skin contact, blood transfusions, and traditional scarification. Most males who have had sexual relations with other men in the United States or Europe exhibit a record of having been infected with HBV before, and 5-10% have indications of chronic HBV infection. Intravenous drug users have lower HBV-HIV coinfection rates than either homosexual men or those infected through heterosexual interaction. New HBV infections, especially in younger patients, can be substantially reduced by increasing the rate of HBV immunization [41–43].

Particular risk factors for HCV transmission include direct blood-to-blood interaction and the incidence of blood-borne infection (mostly through intravenous drug abuse). HIV infection varies greatly across countries, regions, and populations. At least one in four people are infected with HCV simultaneously across Europe, Australia, and the United States; in Eastern European nations like Ukraine and Russia, that number rises to as high as seventy percent. Infants born to mothers with HCV infection had a 48 percent detection rate, and this is strongly correlated with a high viral load in the mother [44–47].

Coinfection with HIV, Hepatitis C virus, and/or Hepatitis B virus is extremely common among intravenous drug users. Hepatitis Delta Virus exhibited swift development of liver fibrosis and persistent reduction of HCV and HBV replications in treated coinfected patients. This patient group demands greater monitoring due to the potential for peaks and rebounds in undetected hepatitis B, C, and/or D viremias [48,49].

A direct cytotoxic effect on liver tissue is induced by HIV's high tropism for hepatic stellate cells and hepatocytes via chemokine (C-X-C motif) coreceptor 4 (CXCR4) and chemokine (C-X-C motif) coreceptor 5 (CCR5). Tumor necrosis factor-related apoptosis-inducing ligand expression is increased, and cellular death takes place when HIV envelope glycoprotein 120 binds to CXR4 coreceptors of liver cells [50]. Hepatocytes infected with HIV are more likely to suffer damage, especially in the presence of conditions like hepatitis B virus (HBV) and hepatitis C virus (HCV), which are linked to increased production of the apoptosis-inducing ligand tumor necrosis factor (TNF). Myofibroblastic differentiation is induced by HIV's proinflammatory cascade upon insertion into hepatocytes and hepatic stellate cells [51].

Liver failure has been identified as an important cause of morbidity and mortality in HIV-infected patients on effective antiretroviral therapy [52,53]. In addition, coinfection with viral hepatitis may add complexity to the delivery of ART by raising the potential for drug-related hepatotoxicity and influencing the choice of certain agents (e.g., those dual-active against HIV and HBV) [54]. All HIV patients should be tested for HCV and HBV infection and appropriately managed if they are found to be chronically infected, according to expert guidelines issued in the United States and Europe [52,55].

EPIDEMIOLOGY AND DEMOGRAPHICS

According to the Joint United Nations Program on HIV/AIDS (UNAIDS) [56], the yearly number of HIV infections has surged around the world over the past decade, particularly in Eastern Europe, Central Asia, the Middle East, North Africa, and South America. After a decade of decreasing, new infections of HIV are on the rise across Asia, the most densely populated area, according to UNAIDS data. Malaysia and the Philippines are among the countries experiencing an increase in epidemics, particularly among the most vulnerable communities. During 2015, HIV infections surged in 38 countries around the world. Figure 2 and Figure 3 depict the updated global HIV/AIDS situation as provided by UNAIDS.

During the period 2012–2021, a total of ten nations in the European Region (Belgium, Czechia, Estonia, France, Greece, Latvia, Poland, Romania, Slovakia, and Slovenia) regularly submitted statistics on HIV tests performed. The number of tests conducted in the aforementioned countries declined by 7% between 2019 and 2021, most likely as a consequence of reduced testing operations throughout a portion of 2020 and into 2021 as a result of the worldwide outbreak of COVID-19. Rates varied by age and gender group. Age-specific rates have

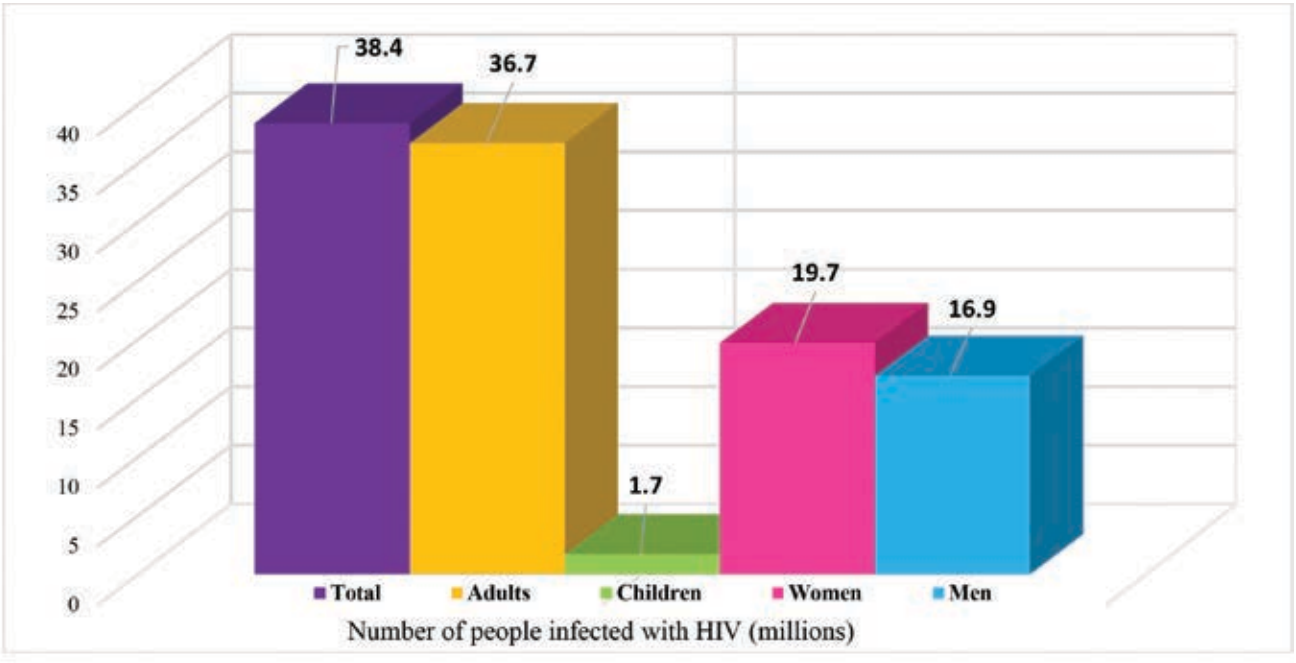

FIGURE 2. Worldwide Demographic Distribution of People Living with HIV/AIDS in 2021 (Adapted from [56])

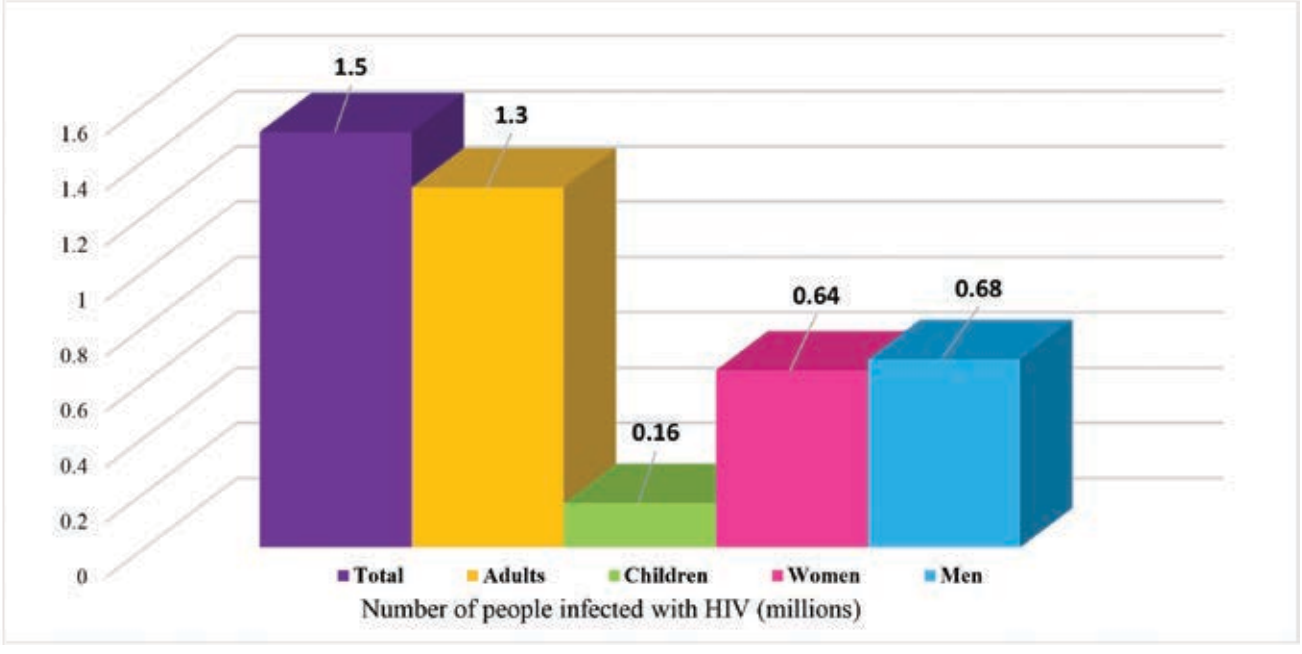

FIGURE 3. Demographic Distribution of New HIV/AIDS Cases Worldwide in 2021 (Adapted from [56])

decreased across all age groups since 2012; however, a portion of this reported drop might be due to delayed case discovery in 2020 and 2021 rather than an actual decrease [57].

In Romania, the HIV/AIDS Monitoring and Evaluation Department of the National Institute of Infectious Diseases "Prof. Dr. Matei Bals" registers HIV/AIDS cases. The graphical representation in Figure 4 depicts the HIV/AIDS situation in Romania spanning from 1985 to 2022, along with the newly reported cases in the year 2022.

Recent data indicates a rise in HIV transmission among groups that are considered vulnerable. HIV infection is prevalent among individuals who engage in the injection of illicit substances, both globally and within Romania. The demographic distribution of individuals who engage in injection drug use and have contracted HIV in the year 2022 is depicted in Figure 5.

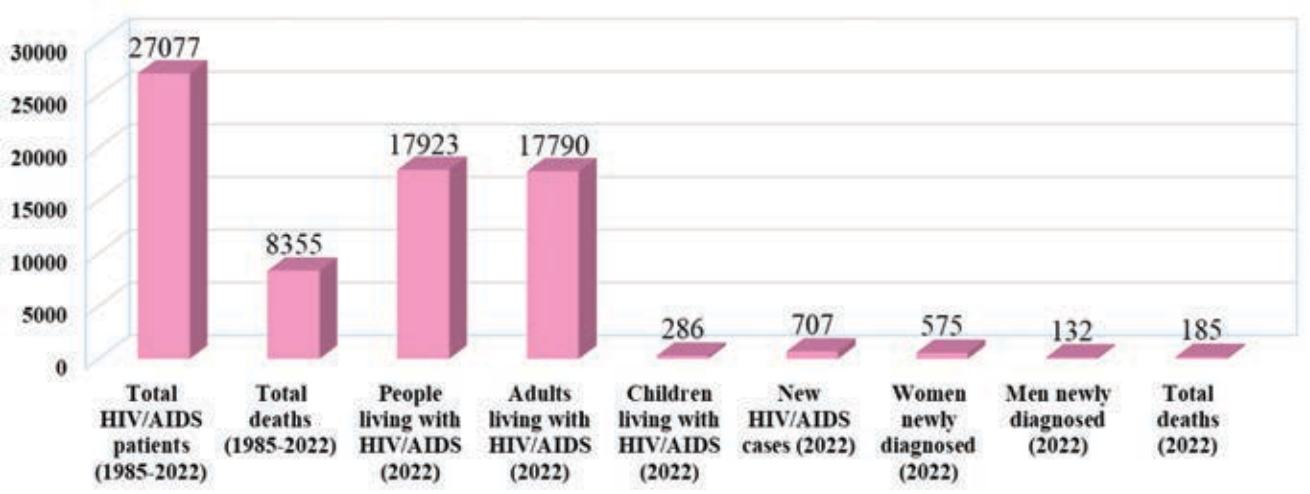

FIGURE 4. HIV/AIDS Epidemiology in Romania (Adapted from [58])

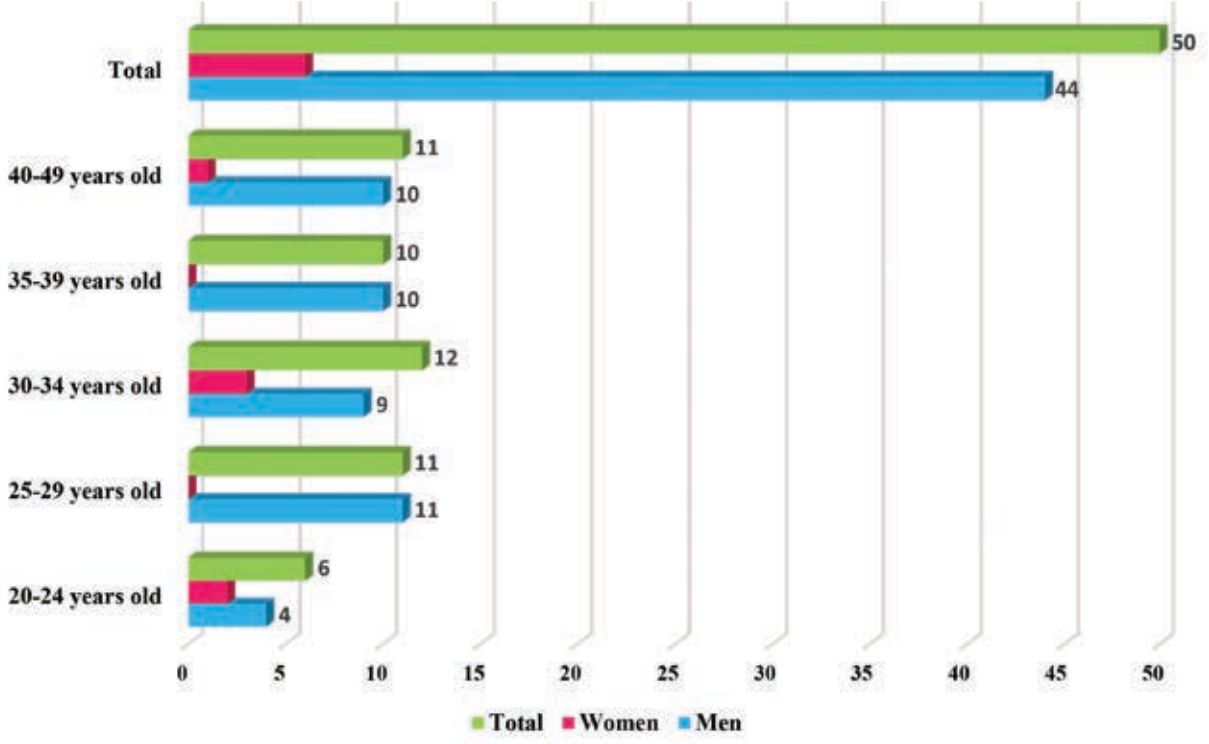

FIGURE 5. New HIV/AIDS cases (2022) with intravenous drug use transmission by age groups (Adapted from [58])

Given the fact that HIV infection targets CD4 lymphocytes and impairs the immune system, comorbidities are frequently observed in individuals who are HIV-positive. The prevalent co-infections include hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, *Mycobacterium tuberculosis* infection, and sexually transmitted diseases (STDs). The data presented in Figure 6 illustrates the proportion of individuals diagnosed with HIV/AIDS in Romania during the year 2022 who have tested positive for co-infections that are commonly associated with the disease.

INTEGRATED HIV/AIDS CARE

By combining traditional pharmacotherapy with mental health and drug dependency therapeutic interventions into a cohesive and comprehensive program, the integrative approach to HIV patients addresses the clinical difficulties associated with the multiple demands and challenges caused by HIV infection simultaneously rather than sequentially. Clinical care practitioners who have traditionally operated in silos should indeed create continuous collaborative collaborations and address

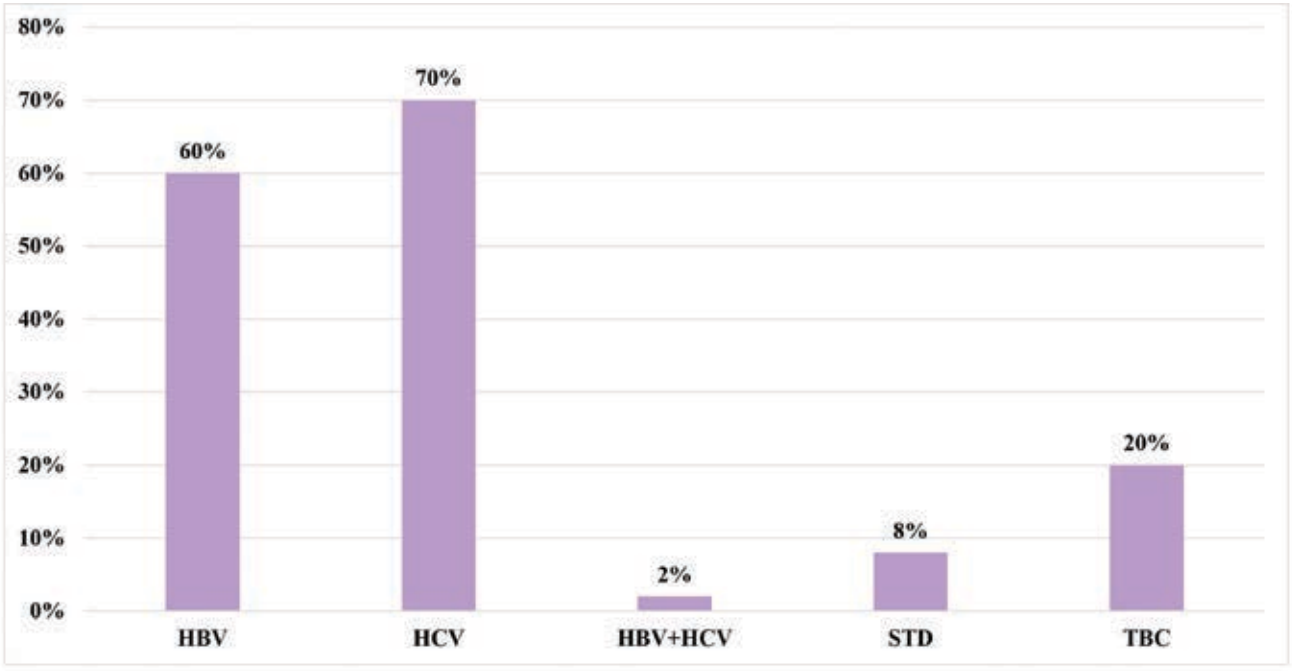

FIGURE 6. HBV, HCV, and STD in new cases of HIV/AIDS (%) with intravenous drug transmission detected in 2022 (Adapted from [58])

patients within a biopsychosocial conceptual framework to provide effective integrated HIV therapy. Proactive communication between healthcare professionals and patients, with treatments prioritized in light of individual needs.

The integrated approach to HIV/AIDS patients includes five healthcare coordination components: (1) management of cases, (2) primary HIV medical treatment, (3) behavioral therapy (mental and substance abuse screening and treatment), (4) adherence guidance (an intervention led by pharmacists), and (5) social assistance services [59].

Pharmacological therapy

Combination antiretroviral treatment (cART) has considerably decreased HIV-associated morbidity and mortality. In contrast, ART is incapable of eradicating HIV, which persists dormant in several cell types and tissues. Although this is still debatable, phylogenetic research has demonstrated that the proliferation of infected cells prior to the commencement of ART is mostly responsible for persistent viremia. With ART, drug-resistant mutations do not develop in individuals with low viral loads. Studies indicate that HIV-infected patients who have not undergone antiretroviral therapy are the starting point of drug-resistant virus [60].

In order to manage HIV infection, present antiretroviral treatment utilizes medications that target specific viral enzymes, such as nucleoside and nonnucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitor (ISTI). HIV cannot be cured, despite the fact that ART can successfully block viral replication and lower plasma viremia to undetectable levels. The virus may survive in cellular reservoirs (long-lived cells that carry replication-capable HIV), and the viral load restores shortly once antiretroviral therapy is discontinued. This is caused by HIV latency or the incorporation of a mature, replication-compatible virus (provirus) into the host genome in the absence of virus generation [61,62].

The World Health Organization recommends using an antiretroviral treatment combination, which consists of three or more drugs, to maximize the health and longevity of HIV-positive patients while decreasing the probability of further infection. Data from Western Europe and other developed countries over the past decade demonstrates that what used to be an almost universally fatal disease has developed into a controllable chronic medical condition and that currently available drugs may provide HIV-positive individuals with a life expectancy equivalent to that of uninfected individuals.

According to the guidelines published by the European AIDS Clinical Society, version 11.1, published in October 2022 [63], the pharmacological treatment of HIV-infected adult patients not previously exposed to ART is presented in Table 1.

TABLE 1. Pharmacological therapy for HIV-infected patients not previously exposed to antiretroviral therapy

Recommended regimens **2 NRTIs + INSTI**
abacavir/lamivudine + dolutegravir tenofovir alafenamide/emtricitabine/bictegravir tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/lamivudine or emtricitabine + dolutegravir tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/lamivudine or emtricitabine + raltegravir once daily or twice daily
1 NRTI + INSTI
lamivudine or emtricitabine + dolutegravir or lamivudine/dolutegravir
2 NRTIs + NNRTI
enofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/lamivudine or emtricitabine + doravirine or tenofovir disoproxil fumarate/lamivudine/doravirine
Alternative regimens **2 NRTIs + NNRTI**
tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/lamivudine or emtricitabine + efavirenz or tenofovir disoproxil fumarate/emtricitabine/efavirenz tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/lamivudine or emtricitabine + rilpivirine or tenofovir alafenamide/emtricitabine/rilpivirine or tenofovir disoproxil fumarate/emtricitabine/rilpivirine
2 NRTIs + PI/r or PI/c
tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/lamivudine or emtricitabine + darunavir/c or darunavir/r or tenofovir alafenamide/emtricitabine/darunavir/c

Legend: NRTI - nucleos(t)ide reverse transcriptase inhibitors, INSTI - integrase strand transfer inhibitor, NNRTI - non-nucleoside reverse transcriptase inhibitors, PI/c - protease inhibitor pharmacologically boosted with cobicistat, PI/r - protease inhibitors pharmacologically boosted with ritonavir.

The development of potent antiretroviral drugs, which are currently administered once daily, has changed HIV infection into a chronic illness that is clinically manageable. Presently, approximately 19 million people in the world undergo HIV treatment throughout their lives, and screening and therapy options, such as oral pre-exposure prophylaxis, might further limit HIV transmission. Nonetheless, despite these massive improvements, the prolonged decrease in plasma viral load to undetectable levels induced by combined antiretroviral therapy does not eradicate the virus, which frequently reappears very rapidly following treatment cessation. However, despite the fact that combined antiretroviral medication decreases mortality and morbidity among HIV-positive individuals over the long term, it is correlated with a significant risk of a significant number of non-AIDS events. They include cardiovascular disease, cancer, liver disease, long-term effects on the peripheral and central neurological systems, renal and metabolic dysfunction, and osteoporosis [64].

Antiretroviral drug resistance

The replication of HIV can be entirely suppressed in the majority of HIV-infected patients [65]. Inadequate adherence to prescribed medication, on the other hand, contributes to persistent HIV replication in the presence of drugs, which typically results in the selection of virus variants that confer resistance to antiretroviral therapies. The rate of resistance evolution is primarily governed by the selective advantage offered by the mutation or subsequent alterations to the virus. Modifications that impact the virus's inherent capacity to reproduce [66] and/or mutations that have only minor effects on medication susceptibility [67] develop slowly.

Rapid mutations have been demonstrated to be induced by both NNRTIs and the NRTIs, lamivudine and emtricitabine. Several NRTIs (such as tenofovir and abacavir) and some integrase strand transfer inhibitors (such as raltegravir) produce mutations more gradually than pharmacologically boosted protease inhibitors and dolutegravir (an integrase strand transfer inhibitor). Once drug resistance develops, it can be transmitted to other individuals. In countries with high incomes, the prevalence of drug resistance among transmitted variants ranges from 5% to 15% [68,69], with the United States usually having higher rates than Europe. The frequency of drug-resistant HIV transmission rose during 2004–2008 and 2009–2013, according to a meta-analysis [70].

Management of integrative therapy in a psychosocial setting

Globally, HIV infection remains a major threat to public health with a high prevalence. Increasing availability and efficacy of antiretroviral therapy has resulted in a decrease in HIV-related mortality and an improvement in life expectancy, transforming AIDS into a chronic condition requiring interconnection and maintenance of care, as well as all the resources required for maintaining the provision of care throughout the patient's lifetime [71].

These patients have both extensive health-related and psychological demands, posing a significant burden to the health system. Integrated care promises to be the

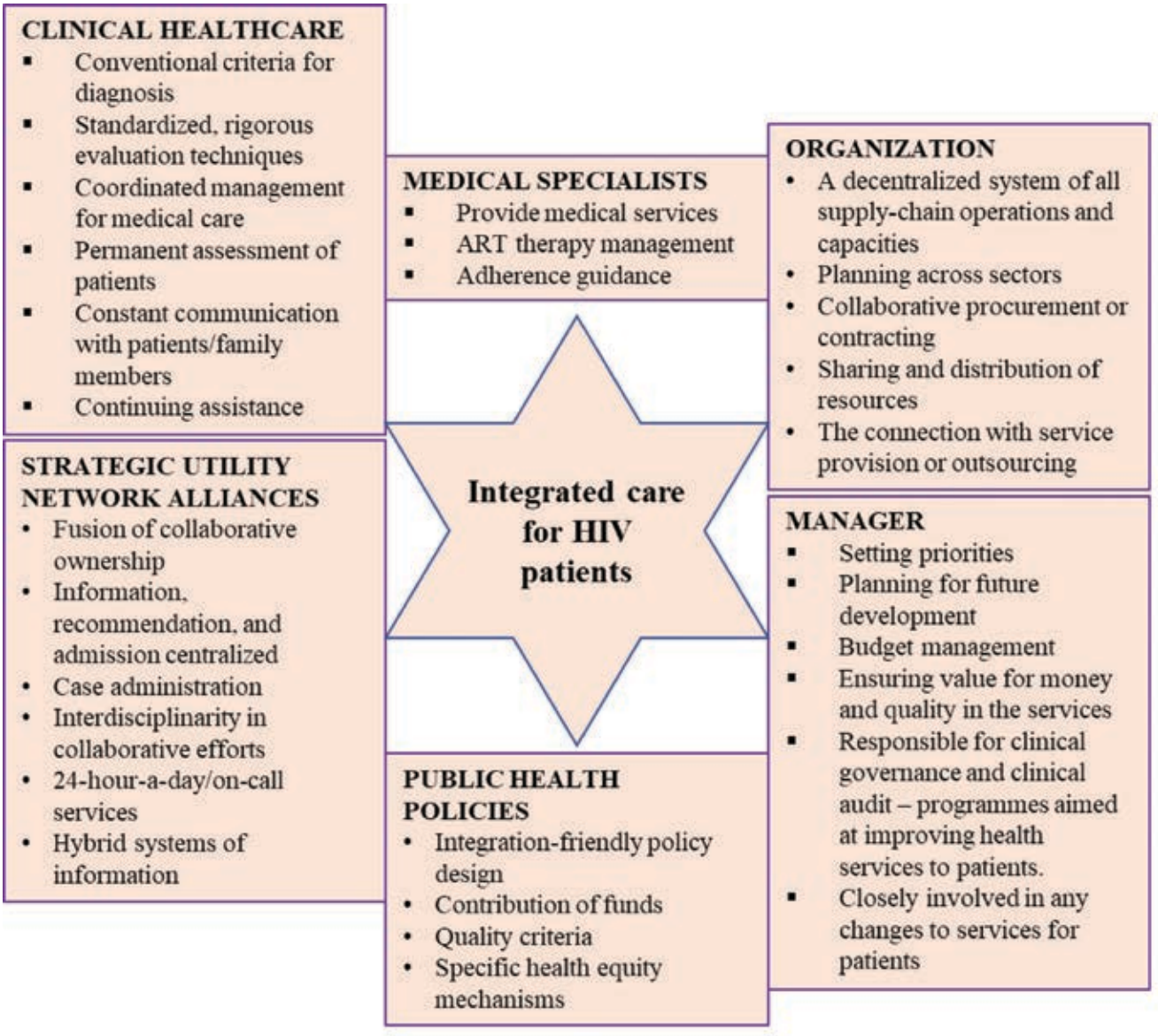

FIGURE 7. Integrated HIV care model (WHO data) (Adapted from [72])

way forward for this problem, with collaborative and coordinated efforts amongst care system components, experts, and service providers aiming at enhancing efficiency, appropriateness, and patient-centeredness. As part of the development of their condition, patients with such chronic conditions must navigate through a variety of healthcare system interfaces. The WHO advocates a multidisciplinary approach for maximizing transitions across fields for diagnosis and therapy, encompassing additional fields such as psychology, nursing, social work, and other counseling professions [72].

By standardizing integrated care procedures, both the quality of treatment and the quality of therapeutic services, as well as economic efficiency, are improved, reducing the cost of healthcare per patient.

In contrast to countries with relatively high HIV prevalence, high population density, poverty, lack of sanitary conditions, inadequate access to healthcare, or lack of access to ART, high-income countries also confront stigma and prejudice. Owing to the aggregation of difficulties, new symptoms, polypharmacy, drug side effects, and the consequent interactions, HIV/AIDS can manifest as post-traumatic stress disorder, depression, anxiety, and non-adherence. With rapid screenings, the philosophy of integrated care helps to recognize and address symptoms of mental health disorders, such as anxiety and adherence difficulties, as well as other impacts, in a timely manner [72].

Psychological and medical co-morbidities, such as depression and sleep disturbances, serve a crucial role

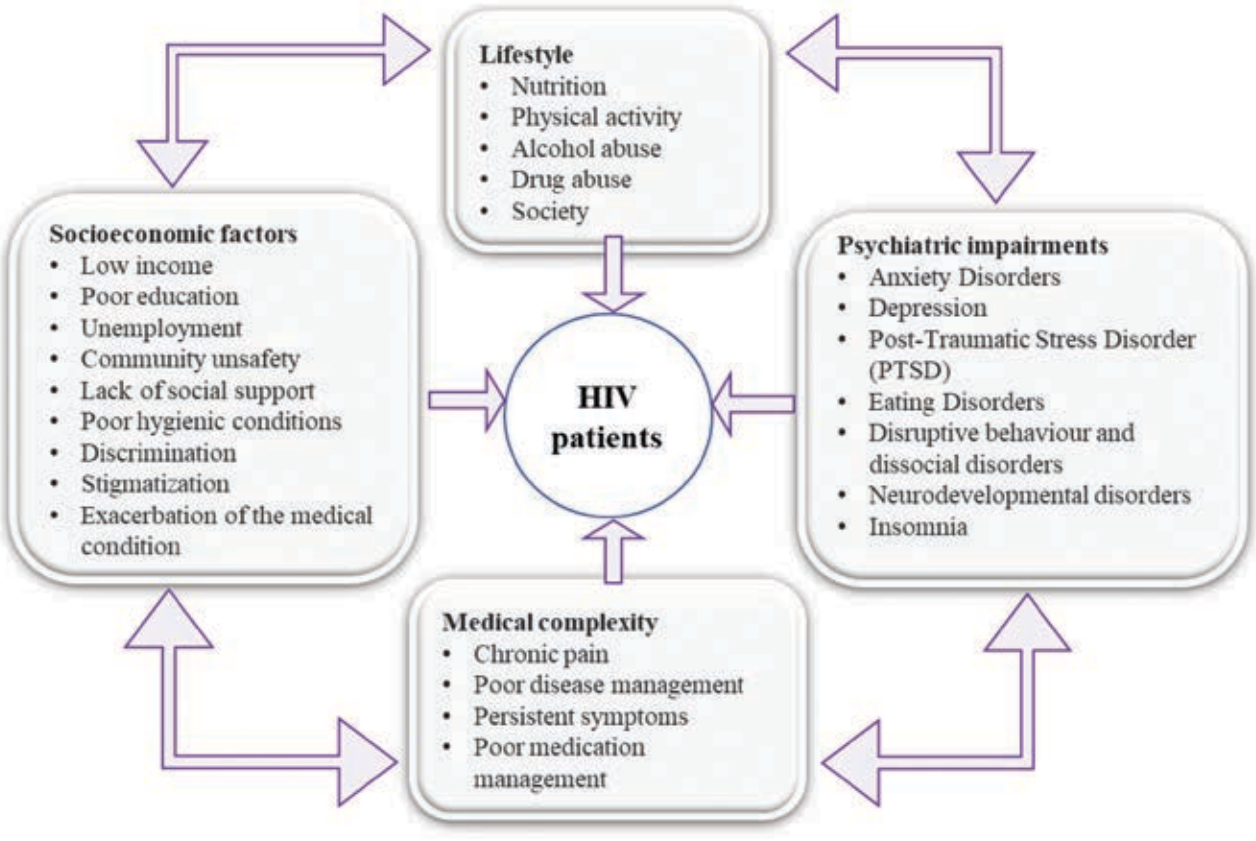

FIGURE 8. General complexity of HIV patients (Adapted from [72])

in the management of HIV/AIDS patients. These individuals suffer from depression at about double the prevalence of their HIV-negative counterparts. In addition, the majority of AIDS patients suffer from insomnia. There is a clear association between poor sleep quality and depression. Life quality has been correlated with sleep disturbances. Insomniacs, for instance, are more prone to develop daytime interference symptoms, which can have substantial consequences in numerous aspects of functionality, such as professional, social, and family life. As HIV/AIDS has evolved into a chronic illness, comorbidities that may influence the quality of life of people living with HIV/AIDS are receiving greater attention [73].

According to the World Health Organization's recommendations [74], both non-governmental organizations (NGOs) and state institutions have established support groups for AIDS patients where they are free to communicate, motivated to form interpersonal relationships, and receive psychological counseling.

Furthermore, an extensive number of seropositive individuals come from underprivileged households, have poor hygiene and low levels of education, and are addicted to alcohol, nicotine, or drugs. These conditions render patients more susceptible to potentially lethal fungal, bacterial, or viral co-infections.

The United States has incorporated the Kaiser Permanente (KP) model for chronic illnesses, which it has tailored to meet the requirements of AIDS patients, in its national public health programs. Prevention, self-management assistance, disease management, and case and care management are the pillars of the KP approach. The initial element of integrated care is HIV prevention for the entire community. "Undetectable is Untransmitable (U=U)" is the acronym for a program centered on educating people with the goal of achieving adherence. The next phase involves encouraging the establishment of self-management methods for chronic patients with stable medical conditions.

In integrated care, health professionals are constantly connected to patients. When patients achieve an elevated degree of health education, they are empowered to make independent and guided decisions regarding the use of the right service. The last stage refers to illness treatment for patients with an existing

complex disease state and a high risk of new complications with significant consequences on the patient's life [72].

HIV/AIDS IN ROMANIA

Prior to around 15 years ago, HIV infection was a taboo issue, and the fact that there were infected persons in Romania was not acknowledged. However, the situation has improved dramatically in recent years. The government has acknowledged the needs and rights of these individuals, making it simpler for them to access social assistance programs and modifying the current legal framework. Moreover, the recognition of professionally offered psychosocial services has substantially strengthened collaboration with NGOs in this sector of activity, and they have succeeded over time in making this difficult matter a concern for all [75].

Antiretroviral medication has been offered in Romania for free through the National HIV/AIDS Program since the year 2000, notwithstanding the absence of a definitive cure for HIV/AIDS. Thus, persons who test positive for HIV begin antiretroviral medication (ARV) per the advice of an infectious diseases doctor. ARV medication eliminates the effects of the HIV virus in the body, giving HIV-positive individuals the same life expectancy as other individuals [76].

Patients with HIV are included in the social assistance program. This program involves an inquiry designed to determine the patient's personal, lifestyle-related, and familial social issues and requirements. Following the social analysis and utilizing social work-specific tools and methodologies, a personalized, individualized permanence and intervention plan is developed. The ultimate objective of the intervention is to overcome challenges and crisis circumstances, as well as to sustain social and family connections, social reintegration, and psychoemotional strength. Building an effective communication and cooperation connection between the professional (social worker, psychologist) and the beneficiaries is essential to attaining the set goals. Only with their approval will services be provided, and they will be guaranteed the full confidentiality of all submitted information.

Interaction with an expert in this field has been demonstrated to provide significant benefits for the patient's disease management, both in terms of moral support and awareness of the disease's severity as well as education regarding the disease's transmission and management [75]. In Romania, HIV testing is accessible at no cost but only at a limited number of locations in each region. During testing, the patient receives extensive counseling and post-test instructions. The test result is kept confidential [77].

ERADICATING HIV/AIDS BY THE YEAR 2030

The World Health Organization's third Sustainable Development Goal (SDG-3) is to end the HIV/AIDS epidemic by 2030. (2030 Project). This objective will be met when the total number of new cases of HIV infection and "AIDS-related deaths" decreases by 90 percent between 2010 and 2030. To date, the pace of drop in AIDS-related mortality is in line with the Project 2030 aim; however, the rate of decline in new HIV infections is the reverse of the target.

Several nations have already achieved the goal of eradicating AIDS. AIDS occurrences in Australia, for instance, have decreased so drastically that the number of people diagnosed with AIDS each year is practically zero. Moreover, the number of deaths among Australians living with HIV/AIDS has decreased from its high (about 1,000 per year) in the early 1990s to less than 200 in 2018, but this figure will surely increase as the population ages. On September 4, 2018, the Australian state of Queensland announced that AIDS would no longer be a reportable condition. The government emphasized that HIV, but not AIDS, remained a threat to public health.

The drop in new HIV infections between 2010 and 2018 has been unevenly distributed around the globe. The rate was highest in sub-Saharan Africa, constant in Latin America, and rising in the Middle East, North Africa, Eastern Europe, and Central Asia. Since 2010, three countries (Cambodia, Mongolia, and Nepal) have seen a decline of at least 50 percent in new HIV infections, while 17 nations have seen a decline of up to 50 percent. On the other hand, new infections have increased in roughly fifty nations. In certain populations, such as young women in South Africa and drug injectors in Eastern Europe, there is an increasing tendency for HIV incidence, which will maintain the HIV epidemic unless adequate and targeted programs are undertaken. These areas of poor outcomes may represent a threat to the HIV epidemic as a whole. The Joint United Nations Program on HIV/AIDS (UNAIDS) identifies four

primary causes for the current trend and situation: a lack of political commitment, inadequate investment in prevention, societal obstacles to protecting the fundamental liberties of women and key populations, and an inability to methodically scale up proven programs.

All key initiatives, including vulnerability reduction, prevention and assessment of infection, linking individuals to care, and supplying antiretroviral medication, must be organized and provided continuously in order to get the 2030 Project back on track and keep it going. The success of Project 2030 is contingent on appropriate and ongoing funding to address the growing number of individuals in need of antiretroviral medication for life and enhanced combination prevention. There is reluctance to further invest in HIV/AIDS because other essential health diseases are comparatively underfunded. Other disease-specific programs (malaria, tuberculosis, and hepatitis) are likewise on the decline and confront comparable obstacles.

Accepting that HIV has little prospect of being eradicated by 2030 under the current conditions, we must consider what will occur after the 2030 Project. In general, there are four potential national, regional, and global HIV scenarios: elimination, eradication, HIV epidemic, and HIV endemic. Elimination is challenging, and eradication without elimination is unachievable by 2030. The epidemiological endpoints of elimination and eradication are separate. Elimination is the reduction of incidence and/or prevalence to zero in a specific geographic area or to an insignificant level globally. Alternatively, eradication is the lowering of incidence and/or prevalence to zero.

In the best-case scenario, in which the number of new HIV infections remains below the number of deaths among persons living with HIV, the number of people living with HIV will naturally drop. In this scenario, it will be able to halt the pandemic, and the prevalence of HIV will drop steadily over time.

Even if the 2030 Project became a reality, HIV would continue to be a pervasive health issue. Consequently, HIV/AIDS prevention and control programs cannot be terminated in the foreseeable future. Rather, this necessitates a paradigm shift from a completely top-down reaction to an integrated health systems response, offering services based on the disease load, in the direction of universal health care. This will guarantee the viability of HIV services after 2030. All of this necessitates an ongoing political commitment and greater, sustained support from national and international sources [78].

CONCLUSIONS

The successful management of comprehensive healthcare services for HIV/AIDS patients is crucial to understanding the multifaceted medical and psychological needs associated with this chronic condition. The development of antiretroviral therapy has revolutionized the management of AIDS, necessitating a holistic strategy for ensuring the needs of patients over their lifespan. The delivery of integrated care, which involves the collaborative and coordinated efforts of various healthcare system components, specialists, and service providers, presents a viable solution for tackling the intricate requirements of seropositive patients. The standardization of integrated care procedures has the potential to enhance the quality of treatment and medical services, resulting in improved efficiency, suitability, and patient-centeredness. Furthermore, it also has the potential to decrease the total healthcare expenses incurred per individual.

The effective management of HIV/AIDS patients is significantly impacted by the presence of psychological and medical co-morbidities, including sleep disturbances and depression. Timely identification and management of these coexisting conditions are imperative for enhancing the general health of people who have been diagnosed with HIV/AIDS. The efficacious execution of integrated care necessitates the active participation of interdisciplinary groups comprising healthcare practitioners, psychologists, social workers, and counselors. Integrated care demands the inclusion of support groups, psychological counseling, and education programs as crucial elements. These components facilitate the development of self-management skills among patients and empower them with the ability to make informed decisions about their therapy.

Considerable advancements have been achieved in Romania with regards to recognizing the necessities and entitlements of HIV/AIDS patients. The enhancement of antiretroviral medication availability and social assistance initiatives have facilitated the promotion of social integration, psychological resilience, and general welfare. The synergy among governmental agencies,

non-governmental organizations, and experts in the domain has been instrumental in addressing the obstacles linked to HIV/AIDS within Romania.

In conclusion, the appropriate management of individuals with HIV/AIDS via integrated care strategies is imperative in order to achieve optimal results, enhance quality of life, and alleviate the burden on healthcare systems. Sustained initiatives and financial allocations towards integrated care models, interdisciplinary cooperation, and all-encompassing support services are set to enhance the general well-being and maintain the physical condition of seropositive patients.

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