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HIV/AIDS: Current treatment protocols and long-term management: An updated review

Sahar Adi Albogamy
KSA, National Guard Health Affairs

Mohammed Abdullah AlZaher
KSA, National Guard Health Affairs

Hussain Mahdi Aljawad
KSA, National Guard Health Affairs

Hala Abdulaziz Alzuhair
KSA, National Guard Health Affairs

Amal Alhumidy Alenizi
KSA, National Guard Health Affairs

Abrar Fayadh Alshammari
KSA, National Guard Health Affairs

Fouad Hamed Alamri
KSA, National Guard Health Affairs

***Abstract*---Background:** Since its emergence in 1981, the human immunodeficiency virus (HIV) has led to approximately 35 million fatalities worldwide. Despite advancements in treatment, many individuals still lack access to antiretroviral therapy (ART). **Aim:** This updated review explores current treatment protocols for HIV/AIDS, highlighting the importance of early ART initiation and long-term management strategies. **Methods:** The review synthesizes recent research findings and guidelines on HIV treatment, focusing on the structural biology of HIV, infection processes, clinical manifestations, prevention methods, and long-term health consequences of ART. **Results:** With ART, individuals can achieve a life expectancy comparable to HIV-negative individuals, although disparities persist between high-income and low- and middle-income countries. Furthermore, while ART reduces AIDS-related morbidity, it does not

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Corresponding email: *akk29337@gmail.com*
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eliminate the risk of non-AIDS-related conditions such as cardiovascular diseases and neurocognitive disorders. **Conclusion:** Ongoing research is essential for optimizing ART regimens and managing long-term health issues in HIV-infected individuals. Comprehensive prevention strategies, early diagnosis, and access to ART are critical in the fight against HIV/AIDS. By addressing these aspects, healthcare systems can significantly improve health outcomes for those living with HIV.

***Keywords*---**HIV, AIDS, antiretroviral therapy, long-term management, prevention strategies, neurocognitive disorders, cardiovascular disease.

Introduction

Since its emergence in 1981, human immunodeficiency virus (HIV) has affected over 78 million individuals, leading to approximately 35 million fatalities. According to UNAIDS, in 2015 alone, nearly 36.7 million people were living with HIV, with 2.1 million new infections reported and 1.1 million deaths attributed to the virus [1]. Fortunately, significant advancements in research have led to the development of more than 40 antiretroviral drugs, which can effectively manage the infection when used in various combinations [2]. Despite the progress made in increasing access to antiretroviral therapy (ART), in 2015, 54% of HIV-positive adults, 51% of children, and 23% of pregnant women still lacked access to these essential medications [1]. Since the introduction of ART in 1996, there has been a notable enhancement in immune responses among HIV-infected individuals, leading to a significant decrease in morbidity and mortality rates. Currently, individuals infected with HIV-1 have a life expectancy that is only slightly lower than that of their HIV-negative counterparts [3][4][5]. In high-income countries, those initiating ART at ages 20 and 35 can expect to gain an additional 43.3 years and 32.2 years of life, respectively, while in low- and middle-income countries, these figures are 28.3 years and 25.6 years. Specifically, in low- and middle-income countries, women starting ART at age 20 can anticipate an additional life span of 22.9 years, whereas in high-income countries, life expectancy gains are similar for both genders. Across all income levels, life expectancy following the commencement of ART has shown consistent improvement year after year [3]. Human Immunodeficiency Virus (HIV) is a retrovirus that primarily targets the immune system, leading to acquired immunodeficiency syndrome (AIDS) if untreated. Understanding the virus's structure, infection process, symptoms, clinical presentation, and prevention methods is crucial for managing and controlling this global health issue.

Structure of HIV

HIV is composed of a lipid envelope, proteins, and genetic material. The virus's outer structure features an envelope derived from the host cell's membrane, embedded with glycoproteins, primarily gp120 and gp41. These glycoproteins are crucial for the virus's ability to infect host cells. Gp120 binds to the CD4 receptors found on the surface of T-helper cells, macrophages, and dendritic cells,

while gp41 facilitates the fusion of the viral envelope with the host cell membrane, allowing the virus to enter the host cell. Inside the viral envelope lies the viral core, containing two identical strands of RNA, the viral enzyme reverse transcriptase, integrase, and protease. The RNA serves as the virus's genetic material, and upon entering a host cell, reverse transcriptase converts this RNA into DNA, which is then integrated into the host's genome by the integrase enzyme. This integration allows HIV to replicate along with the host cell's DNA, leading to the production of new viral particles.

Infection Process

HIV infection occurs through the transmission of infected bodily fluids, including blood, semen, vaginal fluids, and breast milk. The most common routes of transmission include unprotected sexual intercourse, sharing needles or syringes among drug users, and from mother to child during childbirth or breastfeeding. Once inside the body, the virus targets CD4 T-cells, which play a vital role in coordinating the immune response. The virus hijacks these cells, using their machinery to replicate and spread throughout the body. The acute phase of HIV infection, often referred to as primary HIV infection or acute retroviral syndrome, typically occurs within two to four weeks after exposure. During this period, individuals may experience flu-like symptoms, including fever, fatigue, sore throat, swollen lymph nodes, and rash. These symptoms arise as the body begins to mount an immune response against the virus. However, many individuals may remain asymptomatic during this initial phase, making it challenging to diagnose HIV without testing.

Symptoms and Clinical Presentation

As HIV progresses, the clinical presentation may vary significantly among individuals. Following the acute phase, the virus enters a chronic phase, during which it can remain asymptomatic for several years. During this phase, the virus continues to replicate, and without treatment, the immune system gradually becomes compromised. Common symptoms during this stage may include persistent fatigue, swollen lymph nodes, recurrent fevers, and unexplained weight loss. As HIV advances towards AIDS, the individual may develop opportunistic infections and specific cancers due to the severely weakened immune system. These opportunistic infections may include pneumonia, tuberculosis, candidiasis, and various viral infections. The clinical presentation of AIDS is characterized by a CD4 T-cell count dropping below 200 cells/mm^3, coupled with the presence of opportunistic infections or certain cancers such as Kaposi's sarcoma or non-Hodgkin lymphoma. Patients with HIV/AIDS often experience a range of non-specific symptoms, including significant weight loss, chronic diarrhea, night sweats, and persistent fatigue. These symptoms reflect the body's struggle to fight off infections and maintain homeostasis in the face of a deteriorating immune system. It is essential for healthcare providers to monitor these symptoms and the overall health status of individuals living with HIV to provide timely interventions.

Prevention Methods

Preventing HIV transmission is critical to controlling the spread of the virus and reducing the incidence of new infections. Several effective prevention methods exist, including:

1. **Safe Sex Practices:** Using condoms consistently and correctly during sexual intercourse significantly reduces the risk of HIV transmission. Additionally, engaging in mutually monogamous relationships and reducing the number of sexual partners can further decrease the risk.
2. **Pre-Exposure Prophylaxis (PrEP):** PrEP involves taking antiretroviral medications by HIV-negative individuals at high risk of contracting the virus. When taken consistently, PrEP can reduce the risk of HIV infection by up to 99%.
3. **Post-Exposure Prophylaxis (PEP):** PEP is an emergency treatment initiated within 72 hours after potential exposure to HIV. It involves taking antiretroviral medications for 28 days to reduce the likelihood of infection.
4. **Needle Exchange Programs:** For individuals who inject drugs, participating in needle exchange programs can significantly reduce the risk of HIV transmission by providing access to clean syringes and promoting safe injection practices.
5. **Regular Testing and Early Diagnosis:** Routine HIV testing is vital for early detection and treatment. Individuals at higher risk should be tested regularly, as early diagnosis allows for timely initiation of antiretroviral therapy (ART), which can help manage the infection and reduce the risk of transmission to others.
6. **Education and Awareness:** Increasing awareness about HIV transmission, prevention methods, and the importance of safe practices is crucial in reducing stigma and promoting healthy behaviors in communities.
7. **Mother-to-Child Transmission Prevention:** Pregnant women living with HIV can significantly reduce the risk of transmitting the virus to their infants by taking ART during pregnancy, labor, and breastfeeding.

In conclusion, HIV remains a significant global health challenge, with a complex interplay of factors influencing its structure, transmission, and clinical manifestations. Understanding the virus's biology and implementing effective prevention strategies are critical in combating HIV infection and improving the quality of life for those affected by the virus. Through ongoing education, testing, and access to treatment, the fight against HIV/AIDS can continue to progress, ultimately leading to a reduction in new infections and improved health outcomes for individuals living with the virus.

When to Start ART

The criteria for initiating antiretroviral therapy (ART) have evolved over the first decade following the availability of these drugs. Initially, in the late 1990s, treatment was recommended for patients with a CD4 count of ≤500 cells/mm^3, despite the absence of randomized trial evidence to support this threshold. By the early 2000s, the CD4 threshold for starting treatment in asymptomatic HIV-

infected adults was lowered to <200 cells/mm³, primarily due to concerns about potential drug toxicities, particularly cardiovascular, cerebrovascular, metabolic, and renal adverse events (Fig. 1) [6]. Between 2006 and 2009, the ART initiation threshold was increased to <350 cells/mm³, and from 2009 to 2013, it was further raised to <500 cells/mm³ in three of four international guidelines (IAS, DHHS, and EACS), although the WHO guidelines did not adopt this change. By 2015, all four guidelines recommended initiating ART for all HIV-infected adults regardless of CD4 count, based on evidence from three pivotal randomized controlled trials: HPTN 052, Temprano ANRS 12136, and START [7][8][9][10]. These studies demonstrated that patients randomized to early ART experienced significantly lower overall risks of severe morbidity compared to those who deferred treatment. Additionally, early ART was associated with reduced risks of AIDS, tuberculosis, invasive bacterial infections, and Kaposi's sarcoma. The trials were conducted across diverse geographical regions and various clinical stages of HIV infection, which bolstered their collective conclusion: “HIV-infected individuals should be recommended to initiate ART regardless of CD4 count, with the objective of ART being to suppress viral replication and prevent—rather than cure—both inflammation and immune deficiency” [11].

Initiating ART early can decrease the size of the HIV reservoir [12][13], and it has demonstrated clear benefits in preventing both AIDS-related and non-AIDS-related morbidity. However, the optimal timing for starting treatment to significantly alter the establishment of the HIV reservoir remains uncertain. To clarify the impact of ART on the reservoir, Ananworanich and colleagues recently investigated immediate versus deferred ART during acute HIV infection in two cohorts in Thailand [14]. Their findings indicated that (i) the HIV DNA set-point is established early during acute HIV infection, (ii) individuals starting ART during this acute phase exhibit total HIV DNA levels in peripheral blood mononuclear cells that are 300-fold lower and integrated HIV DNA that is 100-fold lower after three years of treatment compared to ART-naïve individuals, and (iii) early combination ART (cART) offers a significant opportunity to substantially reduce the proviral HIV DNA burden. With the increase in life expectancy due to ART, the long-term effects of HIV-1 infection are under ongoing evaluation [15][16]. Several conditions typically associated with older populations, such as HIV-associated neurocognitive disorders (HAND), cardiovascular diseases (CVD), metabolic syndrome (MS), bone abnormalities, and non-HIV-associated malignancies, are now increasingly observed in relatively young HIV-infected individuals [17].

HIV-Associated Neurocognitive Disorders (HAND)

Despite the effectiveness of antiretroviral therapy (ART) leading to virological suppression, HIV-associated neurocognitive disorders (HAND) continue to represent a significant neurological complication of HIV infection [18][19]. HAND encompasses a broad spectrum of clinical severity, ranging from asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) to the most severe form, HIV-associated dementia (HAD) [20]. An analysis of cognitive diagnoses from the CHARTER (Central Nervous System [CNS] HIV Antiretroviral Therapy Effects Research) cohort reveals that there has been no change in the prevalence of cognitive impairment pre- and post-ART. Neuropsychological testing indicates that around 50% of patients demonstrate cognitive impairment in both

time periods. While the prevalence of HAD has reportedly decreased from 18% to less than 5%, the prevalence of mild symptomatic impairment has increased from 12% to 28%, and ANI has risen from 20% to 28% [21][22]. These findings indicate that while recent advances in ART have successfully reduced the incidence of HAD, other mild neurocognitive disorders such as MND and ANI are becoming more common. This increase may result from neuronal injury caused not only by the virus itself but also by chronic immune activation, inflammation, and the toxicity associated with anti-HIV medications [23][24].

Cardiovascular Diseases (CVD)

The risk of cardiovascular disease (CVD) is elevated among individuals infected with HIV compared to those who are uninfected, even after accounting for common risk factors such as hypertension, hyperlipidemia, smoking, and diabetes mellitus during the ART era. In a study utilizing data from the Veterans Aging Cohort Study (VACS) Virtual Cohort, Freiberg et al. reported that HIV infection correlates with a 50% increase in the risk of acute myocardial infarction, beyond what can be explained by recognized risk factors [25]. Furthermore, results from the SMART trial indicated that patients receiving CD4-guided intermittent treatment exhibited a 60% increased risk of CVD, associated with elevated inflammatory marker levels, thereby supporting the hypothesis that intermittent ART poses specific risks [26].

Metabolic Syndrome (MS)

As longevity increases among individuals infected with HIV, they are more likely to develop diseases akin to those observed in the general population, including obesity, type 2 diabetes mellitus (T2DM), and various cardio-metabolic disorders. Unique factors within the HIV-infected population further enhance their vulnerability to cardio-metabolic abnormalities. For instance, ART is linked to body fat redistribution and cardio-metabolic issues such as hypertension, dyslipidemia, insulin resistance, and dysglycemia [27]. Additionally, the HIV infection itself, through mechanisms of chronic inflammation and immune dysfunction, is believed to significantly contribute to dyslipidemia, atherosclerosis, and T2DM [28]. In a recent investigation, Nguyen et al. conducted a comprehensive electronic search across major databases, including Medline, CINAHL, Academic Search Premier, Africa-Wide Information, and Scopus, to evaluate the prevalence of MS and its association with HIV-specific characteristics in the global HIV-infected population [29]. They found that the prevalence of MS was significantly higher in women compared to men, among ART users versus non-ART users, and varied considerably based on participant age, duration of HIV diagnosis, severity of infection, use of non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the date of publication [29]. Routine cardio-metabolic assessments should be integrated into the comprehensive management of HIV-infected individuals. Management strategies recommended for MS in the general population are likely to provide analogous benefits for those living with HIV.

Bone Abnormalities

Bone alterations, characterized by decreased bone mineral density (BMD), osteopenia, osteoporosis, and increased fracture risk, are becoming increasingly prevalent among the HIV-infected population, particularly as these patients age [30]. Data from the Swiss HIV Cohort Study reveal multivariate hazard ratios for bone fractures occurring without adequate trauma to be 10.5 (95% CI, 3.58–30.5) for HIV-infected individuals, with ratios of 9.13 (95% CI, 4.10–20.3) for osteoporosis and 6.88 (95% CI, 3.89–12.2) for non-AIDS-defining malignancies in patients aged ≥65 years when compared to their uninfected counterparts [31].

In a comparative study assessing fracture prevalence between HIV-infected and non-HIV-infected patients, the overall fracture prevalence was significantly higher in HIV-infected individuals (2.87 per 100 persons) compared to non-HIV-infected patients (1.77 per 100 persons; $P < 0.0001$). Specifically, the fracture prevalence among males was also higher in the HIV-infected group for all types of fractures: any fracture (3.08 vs. 1.83; $P < 0.0001$), vertebral fractures (1.03 vs. 0.49; $P < 0.0001$), hip fractures (0.79 vs. 0.45; $P = 0.001$), and wrist fractures (1.46 vs. 0.99; $P = 0.001$) [32]. These findings indicate that the relative difference in fracture prevalence between HIV-infected and non-HIV-infected individuals increases with age. As the HIV-infected population continues to age, reduced BMD and heightened fracture risk are likely to become more significant concerns. Therefore, it is crucial to routinely assess bone density and implement strategies to mitigate factors contributing to increased fracture risk among HIV-infected individuals.

Non-HIV-Associated Malignancies

Malignancies are a leading cause of morbidity and mortality in individuals with HIV. The advent of ART has altered the landscape of malignancies in HIV infection, leading to a reduction in the incidence of AIDS-related malignancies, such as Kaposi's sarcoma and lymphoma, due to partial immune recovery. Conversely, there has been an increase in non-AIDS-defining malignancies, attributed to prolonged survival [33]. Recent studies indicate a heightened risk of anal cancer among HIV-infected individuals during the ART era compared to the pre-ART era [34][35]. HIV infection is recognized as a risk factor for several non-AIDS-defining malignancies, including Hodgkin's lymphoma, lung cancer, and liver cancer, even when controlling for smoking and hepatitis B and C virus status for liver cancer [36][37].

In a study conducted by Coghill et al., which analyzed cases of 14 common cancers from 1996 to 2010 across six US states using linked cancer and HIV/AIDS registries, it was found that HIV infection remained associated with elevated cancer-specific mortality for various common non-AIDS-defining cancers, including colorectal, lung, melanoma, and breast cancers, even after adjusting for cancer treatment [38]. Similarly, Zucchetto et al. reported that among 1,229 deceased individuals with AIDS in Italy, 10.3% had non-AIDS-defining cancers listed on their death certificates, with lung cancer (3.1%) and liver cancer (1.4%) being notably prevalent. This study also revealed a significant 7.3-fold (95% CI: 6.1 to 8.7) excess mortality for all non-AIDS-defining cancers combined [39]. These findings underscore the need for ongoing surveillance and management of

malignancies in the HIV-infected population, particularly as their longevity increases.

Non-AIDS-Defining Malignancies: Lung Cancer

Among non-AIDS-defining malignancies, lung cancer exhibits a notably higher incidence rate in patients with HIV, accompanied by mortality rates that surpass those of other cancers. Notably, lung cancer is the only malignancy in HIV-infected individuals not directly associated with a viral infection. The prevalence of smoking is significantly higher among HIV-infected individuals compared to the general population; however, several studies indicate that HIV infection may independently elevate the risk of lung cancer, even after accounting for cigarette smoking [40][41][42].

Research by Helleberg et al. revealed that nonsmoking HIV patients do not exhibit an increased risk of non-viral cancers when compared to nonsmoking controls [43]. This suggests that while smoking is a major risk factor, the underlying mechanisms of HIV itself may contribute to an elevated risk of lung cancer. Persistent inflammation and immune activation, commonly observed in HIV patients—even those with sustained undetectable plasma viremia—have been linked to a heightened risk of lung cancer relative to non-HIV-infected individuals [44]. Moreover, smoking may exacerbate immune activation in HIV-infected individuals, thereby increasing their risk of lung cancer [45].

Mortality rates from lung cancer are the highest among all cancer types and have been rising in Japanese men from 1993 to 2015. In 2015, lung cancer claimed the lives of 53,170 individuals (both men and women), resulting in a mortality rate of 87.2 per 100,000 Japanese persons [46]. Early detection of lung cancer through chest computed tomography (CT) is crucial, not only for the general population of smokers but also for HIV-infected individuals. Patients with both HIV and cancer face an increased likelihood of dying from their cancer compared to those without HIV. This disparity in outcomes is not solely attributable to advanced tumor stages or inadequate cancer treatment but also reflects the long-term effects of chronic HIV infection, persistent inflammation, and immune deficiency on cancer prognosis. As the incidence of co-diagnosis of HIV and cancer rises, understanding the public health implications of these outcomes will become increasingly vital.

Conclusion

HIV/AIDS continues to be a significant global health challenge despite substantial advancements in treatment protocols and long-term management strategies. The introduction and expansion of antiretroviral therapy (ART) have transformed HIV from a fatal disease into a manageable chronic condition. Initiating ART early has proven crucial for enhancing the quality of life and extending the life expectancy of HIV-infected individuals. Evidence suggests that starting ART regardless of CD4 count significantly lowers the risks of severe morbidity and mortality, thereby improving the overall health of individuals living with HIV. However, while ART effectively suppresses the viral load, it does not eliminate the long-term health complications associated with HIV infection. Studies indicate an increasing

prevalence of HIV-associated neurocognitive disorders (HAND) and cardiovascular diseases among individuals receiving ART. Factors such as chronic immune activation, inflammation, and the toxicity of certain antiretroviral medications may contribute to these conditions. As patients age, the risk of metabolic syndrome, including obesity and type 2 diabetes, also rises, emphasizing the need for comprehensive healthcare strategies that address these emerging concerns. Prevention remains a cornerstone in managing the HIV epidemic. Safe sex practices, pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), and routine testing play critical roles in reducing new infections. Furthermore, targeted interventions to prevent mother-to-child transmission are essential in ensuring healthier outcomes for newborns. In conclusion, addressing the multifaceted nature of HIV/AIDS requires an integrated approach involving early diagnosis, timely initiation of ART, and ongoing monitoring for long-term health complications. Through continuous research, enhanced treatment protocols, and effective prevention strategies, it is possible to improve health outcomes for individuals living with HIV and reduce the overall incidence of new infections globally. The fight against HIV/AIDS necessitates a collaborative effort among healthcare providers, researchers, and communities to ensure that the advancements made in treatment translate into meaningful benefits for all affected individuals.

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الملخص:

الخلفية :منذ ظهوره في عام 1981، أدى فيروس نقص المناعة البشرية (HIV) إلى حوالي 35 مليون حالة وفاة على مستوى العالم. على الرغم من التقدم في العلاج، لا يزال العديد من الأفراد يفتقرون إلى الوصول إلى العلاج المضاد للفيروسات الرجعية .(ART) **الهدف :**تستكشف هذه المراجعة المحدثة بروتوكولات العلاج الحالية لفيروس نقص المناعة البشرية/الإيدز، مع تسليط الضوء على أهمية بدء ART مبكرًا واستراتيجيات الإدارة طويلة الأمد.

الطرق :تجمع المراجعة بين نتائج الأبحاث الحديثة والإرشادات المتعلقة بعلاج فيروس نقص المناعة البشرية، مع التركيز على البيولوجيا الهيكلية للفيروس، وعمليات العدوى، والأعراض السريرية، وطرق الوقاية، والعواقب الصحية طويلة الأمد للعلاج المضاد للفيروسات الرجعية.

النتائج :من خلالART ، يمكن للأفراد تحقيق متوسط عمر متوقع يعادل الأفراد غير المصابين بفيروس نقص المناعة البشرية، على الرغم من استمرار الفجوات بين البلدان ذات الدخل المرتفع والبلدان ذات الدخل المنخفض والمتوسط. علاوة على ذلك، بينما يقلل ART من الاعتلال المرتبط بالإيدز، إلا أنه لا يلغي خطر الحالات غير المرتبطة بالإيدز مثل الأمراض القلبية الوعائية والاضطرابات العصبية المعرفية.

الخلاصة :البحث المستمر أمر أساسي لتحسين أنظمة ART وإدارة القضايا الصحية طويلة الأمد لدى الأفراد المصابين بفيروس نقص المناعة البشرية. تعتبر استراتيجيات الوقاية الشاملة، والتشخيص المبكر، والوصول إلى ART ضرورية في مكافحة فيروس نقص المناعة البشرية/الإيدز. من خلال معالجة هذه الجوانب، يمكن لأنظمة الرعاية الصحية تحسين النتائج الصحية بشكل كبير للأشخاص الذين يعيشون مع فيروس نقص المناعة البشرية.

الكلمات المفتاحية :فيروس نقص المناعة البشرية، الإيدز، العلاج المضاد للفيروسات الرجعية، الإدارة طويلة الأمد، استراتيجيات الوقاية، الاضطرابات العصبية المعرفية، الأمراض القلبية الوعائية.