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Advanced HIV: Diagnosis, treatment, and prevention

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1. Article information

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2. Background

Individuals first diagnosed with advanced HIV have higher rates of mortality than those diagnosed at an earlier stage even after starting antiretroviral therapy (ART). Diagnosis of these individuals is hindered as many patients are asymptomatic despite being immunocompromised. Individuals with advanced HIV should have rapid ART initiation (except in those with signs and symptoms of cryptococcal meningitis), and those in whom the treatment failed should undergo switch of treatment. Key in reaching population at high risk of advanced disease includes overcoming barriers to testing and adherence and providing psychosocial care.

3. Commentary

As per World Health Organization (WHO) guidelines, advanced HIV is defined[1] as CD4 count < 200 cells/μL for adults, adolescents, and children older than 5 years with clinical stage III and stage IV, and any child younger than 5 years. Individuals with a CD4 count less than 350 cells/μL or those presenting with an AIDS-defining illness are considered to have late presentation of HIV according to European Late Presenter Consensus definition.

Advanced HIV comprises two types of patients, ART naive and ART experienced. ART-naive patients had never taken ART before and have advanced disease at the time of diagnosis. Certain risk factors including male gender, age >50 years, heterosexual, and migrant which are emphasized by various studies are not traditionally considered to be at high risk for acquiring HIV. Thus, HIV screening programs should offer counseling and testing without bias toward perceived risk. Newer emphasis is on better linkage between inpatient and outpatient care to identify HIV at earlier stages when outcomes are more favorable.

There are a high proportion of ART-experienced individuals with advanced HIV in countries that rolled out ART early. Studies conducted in South Africa, the Democratic Republic of Congo, and Kenya have shown high proportion of advanced HIV in ART-experienced patients.[2] It suggests that successful scale-up of ART initiation was not followed by sustained retention and adherence. Patients with poor adherence and receiving Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)-based ART are expected to progress to advanced disease in settings where monitoring for treatment failure is not routinely performed.

Earlier diagnosis is necessary in advanced HIV as it prevents secondary transmission as shown by PARTNER study.[3] Patients with advanced HIV have high risk of mortality in view of their poor immunological status when ART is initiated. Case finding is the first step. Many individuals are diagnosed with a concurrent symptomatic opportunistic infection on presentation, but many remain asymptomatic despite severe immunosuppression as seen in REALITY trial.[4] WHO advanced disease guidelines recommend specific interventions for certain CD4 thresholds; hence, to optimize the management of advanced HIV, the clinicians are reminded of the importance of baseline CD4 and additional screening test for screening opportunistic infections.

Tuberculosis is the leading cause of death among people living with HIV. Symptom screening remains the primary strategy for identifying patients eligible for isoniazid prophylaxis therapy; however, most patients were asymptomatic and missed by this approach. The WHO established certain diagnostic targets to screen for tuberculosis, which included sensitivity of 90%, specificity of 70%, and cost of no more than US$2. Point-of-care diagnostic modalities appropriate for people living with HIV AIDS include C-

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reactive protein, Xpert *Mycobacterium tuberculosis,* or rifampicin resistance and lateral flow urine lipoarabinomannan (LAM) test.[5] LAM test has certain advantages of rapid turnover time, ease of specimen collection especially in children, low cost, and high specificity (92–99%), making it a useful test in diagnosing tuberculosis but not excluding in patients with HIV.

Cryptococcal meningitis is another major leading cause of mortality in patients living with HIV. Screening for cryptococcal antigens is important as cryptococcal antigenemia precedes the symptoms by several weeks and delaying treatment can lead to increase in mortality. Early ART is associated with immune reconstitution syndrome (IRIS), so ascertaining of diagnosis is important to decide for initiation of ART. WHO guidelines recommend screening of cryptococcal antigens in all patients with CD4 count less than 100 cells/μl with a provisional recommendation for 200 cells/μl or less before starting ART.[1] Patients with positive cryptococcal antigens need to undergo lumbar puncture. Patients with asymptomatic cryptococcal antigenemia can be treated with fluconazole alone, but patients with cryptococcal meningitis require amphotericin-based and flucytosine-based treatments.

Other fungal infections such as *Pneumocystis jirovecii infection*, histoplasmosis, and talaromycosis lack point-of-care diagnostics.

The WHO recommends that patients with advanced HIV should be offered rapid initiation of ART except in cryptococcal meningitis. The INSPIRE[6] and REALITY[4] studies have supported the safety of integrase strands transfer inhibitors (INSTI)–based ART in advanced HIV which reduced incidence of IRIS. Dolutegravir has a high genetic barrier to resistance and superior efficacy, and it is now a first-line medication in high-resource settings and being promoted in low-income and middle-income countries as well. In 2016, Botswana became the first Sub-Saharan African nation to provide dolutegravir as a part of the national health program.

The WHO recommends cotrimoxazole prophylaxis for individuals with CD4 count <350 cells/μl, or WHO stage III or IV, prophylactic tuberculosis therapy in those without symptoms and full workup in those with symptoms, and primitive treatment with fluconazole for those who screen positive for cryptococcal antigens (and do not have symptoms of meningitis). Although azithromycin has been recommended for prophylaxis of *Mycobacterium avium* complex in high-income countries, the optimal dose, frequency duration, and exact mechanism by which drug influences mortality have not been determined.

Prevention of advanced HIV needs strategies to generate interest while removing barriers to access care to encourage individuals to seek testing at earlier asymptomatic stages of disease rather than waiting for disabling illness. Differentiated care[7] is a client-centered approach that simplifies and adapts HIV services across the cascade in ways that both serve the needs of patients living with HIV better and reduce the unnecessary burden on health system. It include community ART groups collecting medicines for groups of patients whose individual transportation cost preclude regular visit or 6 months refill instead of 3 months refill for stable patients to reduce wait time at facilities. WHO guidelines recommend community-based supports during initiation of therapy.

Implementing ART requires awareness of real-world challenges beyond just the availability of appropriate therapies. Psychosocial support and evaluation need to be carried out to understand the challenges encountered in this process.

Conflict of interest

None

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