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Immuno-Virological Responses of Adults and Adolescents on HAART: towards Ending HIV/AIDS Epidemic in Ethiopia

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Abstract

HIV is an increasing cause of morbidity and mortality globally. But with increasing access to antiretroviral therapy, the prognosis and the life expectancy of HIV infected individuals tremendously increased. But some HIV infected patients don't recover the optimum immune recovery and suppression of viral replication after receiving combination ART regimen. These immune non respondents are an increasing risk of morbidity and mortality compared to HIV infected people with adequate immune restoration following ART initiation. This review paper was summarized the immuno-virological success, failure and determinants HIV infected individuals following ART regimen in Ethiopia.

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Introduction

HIV is a major public health concern which is an increasing cause of morbidity and mortality worldwide [1]. Approximately, 38.0 million people were living with HIV by the end of 2019 [1]. Of these, 25.4 million people living with HIV were receiving antiretroviral therapy globally [1]. In 2019, the incidence and mortality of HIV infected people were 1.7 million and 690, 000 respectively. About two third (25.7 million) of all people living with HIV were found in African region which makes worsen due to inadequate diagnostic testing and life style of individuals. In Ethiopia, 718,498 people were living with HIV in 2017 [2]. Of these, 426,472 were receiving ART treatment. The annual incidence and prevalence of HIV among adults were 0.06% and 3% respectively by the end of 2018 in Ethiopia [3]. Ethiopia achieved 90% of people living with HIV were diagnosis, 91% of these were receiving ART and 73% were virally suppressed for the ambitious 90-90-90 treatment target set for 2020 for ending HIV/AIDS epidemic in Ethiopia [3,4].

With introduction of highly active antiretroviral treatment, HIV related morbidity and mortality has been declined [1]. Highly active antiretroviral treatment is targeted for suppression of HIV viral replication and allows individuals immune system recovery to fight off the infection [3-6]. Moreover, immune restoration following ART greatly declined the incidence and severity of co-infection diseases and death. Majority of HIV patient achieves suppression of viral replication and increases CD4+ T cell count after receiving combination ART regimen [5,7]. HIV patients on HAART are regularly monitored with clinical indicators, HIV viral load measuring and CD4 cell counting [8]. However, virological testing approach always challenging with interruption of supply, equipment breakage and in adequate testing coverage across the country [7,9]. This leads frequent treatment failure with an increasing risk of progression to AIDS and mortality. Approximately half of the ART treated patients may fail to reconstitute their CD4+ T cell counts to levels above 500 cells/ul [10]. Moreover, up to 16% may not achieve a CD4+ T-cell count >200 cells/Ul even in prolonged therapy. Many studies indicated that the rate of immunological failure ranges from 4.5% to 20% [11-13]. This paper was aimed to review the immunological and virological responses and determinants of HIV infected patients on highly active antiretroviral treatments.

Immunological reconstitutions

Immune restoration of CD4 cell count are the principal indicators of immune recovering after receiving HAART for a mean time [14,15]. CD4 cell count and clinical assessment remains important for identifying those at high risk of diseases progression and mortality in absence of better predictor for treatment failure [7]. Many studies demonstrated that early initiation of ART reduced the risk of progression to AIDS and increased the likelihood of immunological restoration [6,11,15]. In majority of HIV infected adults and children on HAART, the CD4 cell count increases and immune recovery starts during the first year of treatment initiation [6,16,17]. Immunological recovery is characterized by CD4 cell count >500 cells/mm3 [7]. In large retrospective study in Tigray region, the proportion of immunological recovery among those with WHO clinical stage of IV and their CD4+ T cell count <200 cells/ul at base line during treatment initiation was 28.3% [10]. In the first 6 months treatment initiation, research evidence indicated that CD4+ T lymphocyte increased and resulted adequate recovery of the immune status of individuals [13]. Optimum adherence, base line CD4 cell count and viral suppression during treatment follow up are predictors for good immunological response [6,8,18]. There are also evidences for ART initiation at younger age rapidly improves the immune restoration of individuals and may have long life expectancy [19,14,20]. Moreover, HIV patients with WHO clinical stages of I and II are more likely to increase their CD4+ T cell level at later treatment follow up [12]. The possible reason could be due to early and effective ART administration revealed less CD4+ T cell depletion, lower rate of AIDS defining events and a higher capacity for reconstitution of the immune system with reduced risk of acquiring the acute complication of immune response inflammatory syndrome (IRIS). However, immunological and clinical criteria have low sensitivity and specificity to detect treatment failure particularly at higher CD4 cell counts [7,10].

Immunological failure

Immunological failure is defined based on fall of CD4 count from base line after treatment initiation [19]. Low CD4 cell count or persistence CD4 cell count below 100 cells/mm3 is an indication of immunological failure [10,7,18]. Moreover, patients with CD4+ T cell count < 50 cells/ul, at base line or ART initiation required more time to recover compared those patients with higher baseline CD4+ T cell count [17]. Approximately only 15% to 20% of individuals who initiate ART at very low CD4 (<200 cells/mm3) counts improves immune response [12,13,21]. Likewise, approximately 20% HIV infected individuals don't restore the optimum immune recovery despite suppression of viral replication after receiving combination ART regimen [12,13] Immune non respondents are an increasing risk of

morbidity and mortality compared to HIV Infected people with adequate immune restoration following ART initiation [11, 21].

Majority of immunological treatment failure was observed in the first year of treatment initiation and follow up and then after the CD4+ T cell count becoming depleted in the further treatment follow up [11-13,18,22]. Moreover, the median time for immunological failure was 15 to 15.7 months following treatment initiation [11,14]. In one cohort study indicated that the mortality of HIV infected individuals was 9.8% within two years of treatment follow up which was greater than the mortality recorded in the deferred follow ups [11]. Another retrospective study in Dilla University hospital showed a mortality rate of 9.4% among HIV HAART attendants [20]. With this evidence, acquiring advanced diseases stages including base line CD4 cell count level (<100cells/ul) were the probable risk factors for the mortality reported [14]. Majority (67%) of the patients with WHO clinical stages of III and IV, and CD4 <50 cell/ul at base line were experienced treatment failure in the meantime despite their CD4 cell count increases following antiretroviral treatment follow up [22]. The rate of immunological failure per patient years follow up ranges from 1.85% to 2.966% in different studies [12,18]. Failure to achieve immune recovery primarily attributed to potential adherence problem, WHO clinical stage III and IV, opportunistic infection, an increasing HIV viral replication or elevated HIV RNA and non-respond to ART [9,16,23]. One study suggested that Zidovudine (AZT) based regimen is more likely prone to treatment failure compared to other combination ART regimen [11]. Furthermore, many studies demonstrated that base line CD4 cell count is the main predictor for immunological failure despite its sensitivity in detecting virological failure is low [11-13,18,22]. Sub optimum immunological monitoring and high level of immune activation following ART initiation is also increased the rate of immunological failure [13].

Incomplete Immune recovery/Immune discordant

Clinical and immunological monitoring alone is crucial for patient follow up when the CD4 cell count is below200 cells/ul. But individuals with higher CD4 cell count at base line couldn't show the immunological failure, they will keep taking the wrong or failed drug regimen, which accelerates to AIDS related morbidity and mortality [22]. Because, the sensitivity and specificity of detecting treatment failure in people who initiate ART at higher CD4 cell counts through immunological and clinical definition criteria is suboptimal [16]. Patients may experience immunological none response or failure despite HIV virological suppression which are defined as discordant respondent. Incomplete immunological recovery observed in older patients and in those who initiate ART at lower CD4 cell count. Patients with optimum immune reconstitution have comparable life expectancy to the HIV negative individuals. However, patients with immune non respondents after receiving ART are at increasing risk of AIDS related morbidity and mortality [16,24]. In contrast, one case control study in southern Ethiopia indicated that incomplete immune recovery frequently observed in the first 6 months of treatment initiation and immune restored in the next 6 to 12 months treatment follow up [11]. The base line WHO clinical stages invariably affected the immune recovery [11]. Furthermore, individuals with low base line CD4 cell count are more likely susceptible to incomplete immune recovery and opportunistic infection [12,22].

One cohort study in Gondar suggested that HIV infected patients who were asymptomatic with low level of viremia (41-1000 copies/ml), have showed an increased CD4+ T cell count in the first 6 month of treatment initiation than in the deferred treatment follow up [17]. With this findings majority of the HIV patients have showed HIV RNA suppression during their follow up [17].

Virologic Success and Determinants of Combination ART regimen

Successful control of viral replication with ART greatly improves the immune function and clinical outcomes in majority of patients [1,17]. In settings where viral load testing not accessible, the CD4 cell count and clinical monitoring were frequently used to diagnose treatment failure [7]. But WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure [7]. A viral load above 1000 copies/ml on two consecutive viral load measurements within 3 months of treatment intervals after six months of ART regimen initiation is considered as virological failure [7]. Virological monitoring is the preferred approach than the immunological and clinical monitoring for providing early and accurate indication of treatment failure for alternative drug switching and reducing drug resistance mutation for better clinical outcome [7,16]. In Ethiopia the overall national wide proportion of viral suppression was 73% in 2017 [2]. Moreover, different prospective observational studies indicated that virological success rate of HIV infected patients following HAART ranges from 73% to 87% (HIV RNA <50 copies/ml) within 24 months of median time ART initiation and follow up [2,14,17]. Unlike the virological suppression, the proportion of virological failure in different prospective

observational study ranges from 11.5% to 19% during the first 6 months of ART uptakes [14,23]. Moreover, the rate of virological failure ranges from 2% to 2.996% per patient years follow up which was reported in different studies [12,18]. The probable risk for virological failure (>1000copies/ ml) is base line CD4 cell count<200 cells/ul, advanced or WHO clinical stage III and IV, older age, suboptimal adherence of medication and drug intolerance/toxicity [12,14,23].

Conclusions

The proportion of immunological and virological failures of HIV infected individuals reported with different studies was comparable to the national findings. Ethiopia accomplished successfully earlier the first two 90-90 target set towards ending HIV/AIDS by the end of 2020. But the performance of HIV RNA suppression among HAART taking implies to put more efforts to meet the target by improving the accessibility of viral load testing for all HIV patients all over the country. CD4 cell count and clinical monitoring are the common methods used for patient management despite they have low sensitivity for diagnosis of treatment failure particularly in patients with high CD4 cell counts. This is an indication for more other immunological criteria need to be proved. Baseline CD4 cell count, potential adherence problem, WHO clinical stage III and IV, opportunistic infection and increasing HIV viral replication are the main predictors for failure to achieve immune recovery. Moreover, the possible risk factors for virological failure are base line CD4 cell count<200 cells/ul, advanced diseases stages, older age, poor adherence of medication and drug toxicity. To improve the ART drug efficacy; patients who fail to achieve viral suppression should be subjected to resistance testing for proper selection of alternative drug regimens. Large designed prospective study should be conducted to address scientifically for the possible reason of immunological and virological failure of HIV patients on highly active retroviral treatment.

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