Chapter

Immunological and Virological Failure among Individuals on Highly-Active Antiretroviral Therapy

Hadush Negash, Brhane Berhe and Miglas Welay

Abstract

Initiation of antiretroviral treatment decreased HIV related mortality and morbidity. Virological failure (a condition defined when the plasma viral load of HIV infected individuals greater than 1000 RNA copies/ml based on two consecutive viral load measurements with adherence support) have an increased risk of clinical progression to acquired immune deficiency syndrome (AIDS) and death. Nowadays, combination of highly active antiretroviral therapy is recommended to decrease the likelihood of drug resistance. However, there is emergence of drug resistance and treatment failure during treatment. Hence, managing and detecting antiretroviral treatment response is important to monitor the effectiveness of medication and possible drug switching for treatment regimens. Additionally, mechanisms of drug resistance and factors associated with immunological and virological treatment failure should be addressed.

Keywords: immunological response, virologic response, adverse drug reactions, HAART, drug resistance, mechanism

1. Introduction

Globally, in 2017, there were about 20.9 million HIV patients receiving highly active antiretroviral therapy (HAART) [1]. The treatment is targeted at inhibiting viral attachment and replication leading to the recovery of immune function [2, 3]. Since the introduction of HAART in 1996, there is a decline in mortality and morbidity associated with HIV [4, 5]. Due to HAART, the impact of HIV infection decreased [6] due to viral suppression, restoring and preserving immune function, improving quality of life, and reducing HIV related morbidity and mortality along the course of treatment [7–9]. There are a number of problems associated with HAART, including emergence of drug resistance, difficulties of maintaining long-term adherence, and drug-related toxicities [5] which lead to virological failure, immunological failure and clinical progression [10].

Virological failure increases the risk of clinical progression of HIV to AIDS [11]. World health organization (WHO) recommended combination therapy of HAART [12, 13]. The combination therapy improved the natural history of HIV infection from a life-ending event to a manageable chronic condition [14]. Adverse drug reactions (ADRs) associated with HAART resulted some considerable health consequences like co-morbidity with opportunistic infections [15–17].

Treatment failure to first-line regimens resulting from ADRs creates the need for very expensive and difficult-to-implement second-line regimens. Second-line HAART regimens are not easily affordable and largely donor dependent in resource-limited settings [18]. Effective viral suppression is targeted by UNAIDS to meet "90-90-90" in 90% of persons on HAART by 2020 [19]. Use of an effective and safer HAART regimen helps to promote maximal viral suppression and improved immunological and virological response [20, 21].

2. Occurrence and determinants of immunological and virological failure

2.1 Prevalence of immunological failure/immune reconstitution among HIV infected individuals on HAART

Immune reconstitution is the immunological response of immune cells (mostly CD4+ T cells) due to initiation of HAART. The response is either success or failure. Previously conducted studies reported different rates of immunological failure among HIV infected individuals (**Table 1**).

The variation among the above studies might be explained due to the differences in patient adherence, differences to define immunological failure whereby some studies defined as the reduction in number of CD4 + T cell count to baseline or below, or persistently low CD4+ T cell count (below 100 cells/μL) [31] and others defined immunological failure as reduction in number of CD4+ T cell count to baseline or below severe immune suppression (CD4+ T cell count <200 cells/μL) [24, 25, 28, 30, 32, 33]. Other studies defined immunological failure as 50% decline of CD4+ T cells from treatment peak value [28, 34] or at least 30% decline from treatment peak value [28, 35].

Moreover, the prevalence of immunological failure can be expressed with person-years among the HIV patients on treatment. As per recent studies, the rate was 2.966 [22], 2.57 [36], 8.7 [37] and 8 [38] person-years. The variation among these reports might be due to the differences in treatment adherence and the presence of opportunistic infections (status of co-morbidity). Hence, the coverage of good adherence toward the HAART was one of the determining factors for immunological success. The likelihood of having good adherence of HAART increases the treatment success rate considering the results of previous studies (**Table 2**).

Number	Prevalence of immunological failure of HAART	Reference
1.	24.7%	[22]
2.	6.5%	[23]
3.	9.8%	[24]
4.	11.5%	[25]
5.	15.1%	[26]
6.	18.4%	[27]
7.	64.4%	[28]
8.	33.5%	[29]
9.	35%	[30]

Table 1.
Occurrence of immunological failure of HIV infected individuals on HAART.

Number	Percentage of adherence from previous studies	Reference
1.	72.5%	[22]
2.	81.8%	[25]
3.	82.7%	[26]
4.	82.4%	[39]
5.	78.5%	[32]
6.	92%	[33]
7.	85.8%	[25]
8.	97.7%	[34]
9.	100%	[24]

Table 2.
Coverage of good treatment adherence of clients from different studies.

Treatment adherence differs among studies due to differences in psychosocial support of relatives or the society to strictly adhere to the treatment guidelines, stigma, and lack of commitment to take medications so that HIV patients might drop themselves from on course ART treatment, perceived feeling of unwellness from medication, and scaring of treatment side effects [31, 40, 41].

Previously, baseline CD4+ T cell counts were playing an important role for an HIV patient to initiate HAART. The median baseline CD4+ T cell counts for an HIV infected individual to start HAART is explained below (**Table 3**). However, nowadays, the target is to test and treat regardless of their CD4+ T cell counts.

2.2 Associated factors of immunological failure among HIV infected individuals on HAART

Poor adherence to HAART increased to experience failure in CD4+ T cell recovery [22, 26, 28, 33, 43]. This allows increased viral replication which in turn increases infection of new CD4+ T cells and ultimately depletion of immune cells [41]. Additionally, lower baseline CD4+ T cell count is one of the determining factors for increased immunological failure because immune recovery mostly depends on the number of baseline CD4+ T cell counts [22, 29, 38]. The timing of HAART initiation is important to optimize the CD4+ T cell immune response to medication [44].

Number	Median baseline CD4+ T cell counts	Reference
1.	196 cells/μL	[22]
2.	191 cells/μL	[24]
3.	162 cells/μL	[23]
4.	156 cell/μL	[24]
5.	152 cells/μL	[28]
6.	115 cells/μL	[32]
7.	177 cells/μL	[34]
8.	238 cell/μL	[42]

Table 3.
Median baseline CD4+ T cell counts of HIV infected individuals to initiate HAART as per previously published studies.

Number	Percentage of virological failure	Reference
1.	12.47%	[54]
2.	14.7%	[55]
3.	15%	[56]
4.	5.3%	[57]
5.	7.5%	[58]
6.	23.2%	[59]
7.	24%	[60]
8.	47%	[61]
9.	30.6%	[62]
10.	57.1%	[63]
11.	32%	[64]
12.	20.6%	[65]
13.	16.7%	[66]
14.	51.6%	[67]
15.	20.9%	[68]
16.	69.6%	[69]

Table 4.
Prevalence of virological failure of HAART among individuals infected with HIV.

These reports may highlight that patients with low CD4+ T cell count have poor long term CD4+ T cell immune response [22].

TB/HIV co-infection worsen the rate of immunological failure [22, 25, 37, 45–48]. TB infection impairs cellular immune responses through MTB-induced apoptosis of CD4+ T cells which subsequently lead to depletion of CD4+ T cells [49]. Incidence of TB during the course of HAART decreased the likelihood of treatment adherence due to its high pill burden and side-effects [50]. Although the risk of acquiring TB remains elevated, much less is known about the effect of HAART on recurrent TB [51]. All in all, recurrences of TB are lower among HIV infected individuals with higher CD4+ T cell counts [52].

2.3 Occurrence of virological failure among HIV infected individuals on HAART

Virological failure among individuals on HAART is defined as plasma viral load of the HIV infected individual is greater than 1000 RNA copies/ml based on two consecutive viral load measurements with adherence support [53]. The occurrence of virological failure of HAART among HIV infected individuals is reported below (**Table 4**).

The variation might be due to the differences in cutoff values of viral RNA copies per ml of plasma to consider virological failure [60, 63, 70], the duration of follow-up, differences of co-morbidity, variations on the treatment adherence of HAART, clinical/immunological failure [61, 71], perinatally infected [67], lower mean age [65] and shorter duration on HAART [66].

2.4 Associated factors of virological failure among HIV infected individuals on HAART

Magnitude of virological failure of HAART is not the same for all HIV infected individuals. There are factors that affect the likelihood of virological failure like

malnourishment and overweight [22, 54, 72, 73]. Abnormal body mass index (BMI) is significantly correlated with decreased CD4+ T cell counts that increases viral load by progressing into the advanced stage of the disease [74, 75].

Moreover, the occurrence of virological failure is higher among TB co-infected individuals [54, 76, 77]. Concurrent HAART and TB treatment increases the rate of virological failure due to impaired treatment adherence and pharmacokinetics drug reactions. Hence, clients on HAART with active TB should be prioritized for viral load monitoring and follow-up. Moreover, to prevent incident TB during ART INH prophylaxis is recommended. Increased viral copies compromise immunity and negatively affect treatment by contributing to the double burden side effects of TB and HIV [78].

Failure for an immune-reconstitution increases the rate of virological failure [54, 79–81]. This leads to an increase in viral replication [22]. Hence, it is a surrogate marker for virological failure. During HAART, detecting and monitoring immunological response should also be emphasized to prevent drug resistance [22, 82].

3. Immune reconstitution during chronic HAART

Despite the successful suppression of viral replication, some clients on HAART might fail to recover immune cells (immune reconstitution). It is estimated that half of HIV infected individuals on HAART might fail to reconstitute their CD4+ T cell counts to levels above 500 cells/μL. Additionally, up to 16% might fail to achieve a CD4+ T cell counts greater than 200 cells/μL, even with long term therapy of HAART [83]. There are factors determining rates of immune reconstitution including older age [84], lower baseline CD4+ T cell counts prior to HAART [85], and co-infection with hepatitis C virus (HCV) and TB [86, 87].

3.1 HAART is the most effective strategy for successful immune reconstitution

Initiation of HAART in early stages of HIV infection is associated with not detectable viral load suggesting effective inhibition of viral replication [88, 89]. During treatment initiation (during the first 4 months of HIV infection), there is lower recovery of immune cells due to a narrow restorative time. It is explained that starting HAART initiates both the rate and extent of CD4+ T cells reconstitution [90].

While treating HIV infected individuals, combining cytokine, IL-7 therapy, prevents apoptosis of T cells and is required for naive T-cell survival. This increases CD4+ T cell counts among clients on treatment [91]. The T cells remain capable of responding to antigenic stimuli and produce cytokines after polyclonal and specific antigenic stimulation. Then repopulation appears to extend cells from thymus to effector sites of the immune system [92, 93].

4. HIV drug resistance

Detecting HIV drug resistance is one of the major limiting factors in the successful treatment of HIV infection [94]. This includes genotypic and phenotypic assays. The genotypic detection is performed by matching results with lists of frequently updated HIV mutations that are known to confer drug resistance which are relatively inexpensive. However, it can only identify documented HIV mutations and may not detect new mutations that arise in a particular HIV variant. Although it is not easy to predict the actual degree of drug resistance, phenotypic testing yields

drug susceptibility of a particular HIV variant. It provides information on the sensitivity of a particular HIV variant in comparison to a control isolate with full drug sensitivity. Moreover, there is inconsistency in interpreting the detected decrease in viral drug sensitivity into actual decreases in clinical sensitivity. Hence, it needs to have large-scale clinical trials for a correlation might be made between changes in phenotypic sensitivity and actual drug resistance [95].

Investigators have assessed the effectiveness of HIV drug resistance testing in improving clinical response to pharmacotherapy, like the GART [96], the VIRADAPT [97] and the ARGENTA [98]. They reported that individuals whose drug selection was based on genotypic resistance testing had significantly lower viral loads than patients who did not receive resistance testing prior to starting therapy. This reflects reduced morbidity and mortality [97].

Several factors related to the life cycle and replication of HIV are key contributors toward the rapid and widespread emergence of resistance. Initially, the reverse transcriptase enzyme is highly prone to errors during the process of reverse transcription. Hence it makes errors in each HIV genome per round of replication process which enhances its mutation for every 2000 nucleotide bases [99]. In addition to these base substitutions, insertions can occur. The especial scenario of HIV drug resistance mechanism is also due to high rate of replication. When untreated, plasma HIV RNA levels range from 103 to 105 copies/ml or sometimes greater than 106 copies/ml in acute infection [100].

The HIV virus continues to infect new cells at a very high rate to maintain the infection to a stationary state. Additionally, increased rate of errors in the reverse transcription yields new variants with drug resistance. Some HIV variants manifest drug resistance due to intrinsic factors. Hence, antiretroviral resistance can still occur even during successful therapy of HIV infection [101].

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