ABSTRACT

HIV/ AIDS continue to be a major infectious problem with lots of unexpected observations. The replication of HIV takes place mainly in CD4 positive cells, particularly CD4+ T lymphocytes. The number of viruses (as measured by viral load estimations) is a major predictor of progression of the infection and CD4 count is a measure of the immune status at any point of time and reasonably predicts the risk of clinical illness. The viral load keeps on increasing, as years pass by. This usually results in a fall in CD4 count. However this relationship is occasionally modified to result in various types of discordance.

In patients started on Anti retroviral (ARV) drugs, the viral load falls and leads to rise of CD4 count. However this inverse relationship again gets modified to result in dangerously unrelated CD4 and viral load values. This might result in a deceptive evaluation of the success of ART. The discordant values may mask failure or success as well. Thus they become a major risk for the patient’s survival plans. The situations and their implications are discussed in detail.

INTRODUCTION

HIV/ AIDS remains a significant global challenge, even today, after about thirty years of its recognition by modern medical professionals. Towards the middle of 2011, it is estimated that 35 million people have developed HIV infection, 2.6 million newly infected last year and 1.8 million have died in 2010. Compared to the earlier days, when no definitive therapy was offered, situation has changed a lot, in many parts of the world. Highly Active Anti Retroviral Therapy (HAART) has made significant contribution to the lives of the PLHAs (Persons Living With HIV/AIDS). Though cure is still a dream, HAART reduces morbidity from Opportunistic infections, delays death and improves the life of PLHAs for many years even after the diagnosis of advanced HIV disease or AIDS. This also contributes to prevention. It has been calculated that the mean survival after initiation of ART is around 13 years. This is affected by many variables like the time of start of therapy, types of OIs/ malignancies, socio economic status, level of monitoring etc. As more and more people have access to ART and are started on ART early, the situation is likely to change for the better in future years.

However the picture is not all that rosy in all, because of issues like toxicities, intolerances, drug-drug interactions and failures. Many of these are definite sequences in a significant number of individuals at some stage in their survival periods. Switching over to second (or third) line drugs which could be costlier and less tolerable are common inevitable consequences. Most of these negative effects can be reduced, if not avoided with proper monitoring and follow up.

There are two main laboratory parameters that help the clinician to assess, how a person responds to therapy. The aim is to achieve a symptom free prolonged survival with good quality of life. This target is to deliver fewer drugs that are well tolerated and free of side effects and minimum drug-drug interactions. The objective is an improvement in the immune status, so that the persons can respond to treatment of treatable conditions, become symptom free and continue to be immunocompetent. The CD4 cell count indicates the immune status and the viral load the efficiency of viral replication that is more closely linked to the progression of disease. Low CD4 T-cell counts are considered to be a marker
of the progression of HIV infection and AIDS, and have been called the ‘signature’ of HIV (Balter 1997). Since HIV was first claimed to be the cause of AIDS in 1984, the CD4 cell count has been widely used to make treatment and diagnostic decisions, but the use of the CD4 cell count has been controversial, and recommendations regarding how to use them have changed many times over the years. When the CD4 cell count in someone diagnosed HIV-positive is found to be below 200, AIDS is diagnosed. This method currently accounts for over half of all AIDS diagnoses, and so is highly significant (CDC 1999). Reports show that CD4 cell counts commonly fall very low, especially if a person suffers from certain conditions. These conditions include a variety of viral illnesses, bacterial infections, parasitic infections, sepsis, septic shock, multiple organ system failure, tuberculosis, coccidioidomycosis, burns, trauma, transfusions, malnutrition, over-exercising, pregnancy, normal daily variation, psychological stress, and social isolation. In addition to low CD4 cell counts, the CD4/CD8 ratio is also considered a marker of disease progression in HIV and AIDS, and is often found to be inverted. An ‘inverted’ ratio simply means that there are less CD4 cells than CD8 cells, resulting in a ratio of less than 1.

PRIOR TO THERAPY

However not infrequently, it is seen that the fall in CD4 count that happens in the asymptomatic phase of HIV infection will not follow the typical pattern. Three types of CD 4 cell count crash are identified. These include the rapid, typical and slow patterns. In rapid decliners with CD4 cell crash, the counts fall by approximately 50 per month from a normal value of 800-1200 cells/mm³. In typical situation the fall is around 50–100 cells per year. In slow progressors (slow decliners), the counts continue at a higher level for years without significant fall. This is usually not in relation with the rise in viral load that happens over a period of time.

ON TREATMENT

Antiretroviral therapy (ART) has changed the outcome in PLWHAs. The elevation in CD4 cell count is a surrogate that is commonly used to assess response to ART. However let us remember that the antiretroviral drugs per se have no effect on the CD 4 cell. Whatever they do is to modify or inhibit various stages of viral replication. As and when the number of viruses in the body is reduced to lower levels, the depletion of CD4 cells gets arrested and this leads to rise in CD4 cell counts. This is the ideal that is expected to happen in everybody on optimum antiretroviral therapy. Thus fall in HIV viral load and rise in CD4 cell count should happen in a predictable inverse relationship.

In those individuals started on antiretroviral therapy (ART), the CD4 cell is expected to rise in about 6-8 weeks time. This is due to redistribution of the cells from tissues, regeneration of naïve T cells, or due to the reduction of immune activation mediated cell death (apoptosis) and happens in two phases. Overall, the long-term shape of CD4 cell count after HAART depends on the baseline CD4 cell count, control of viral replication overtime, the stage of the disease at baseline, duration on treatment, as well as on baseline patient factors including higher HIV RNA level, co-morbidities, presence of drug resistant viruses, sub-optimal pharmacokinetics, and potency of the ARV regimen. Thus immunologic markers have poor sensitivity (20%-33%), specificity (86%-90%), with 21% and 91% positive and negative predictive values, respectively, to identify virologic failures which could lead to continue to treat patients with failed regimen or to unnecessary switch of regimens. The criteria to define ART failures are not uniform.

According to WHO, there are three definitions: clinical failure when there is a recurrent WHO stage 4; immunologic failure when CD4 cell falls below the pre-therapy baseline, or below 50% of the on-peak value, or is persistently < 100 cells/mm³; virologic failure when plasma VL >10000 copies/ml; Virologic success when VL is < 400 or 50 copies/ml (depending on the type of the assay) after six months of treatment. According to a recent WHO guideline, which recommends VL to be done every six months, treatment failure is defined as persistent VL > 5000 copies/ml. Although not well defined, VL cut-off > 10000 copies/ml to define treatment failures is linked with subsequent decline in CD4 cell count and clinical progression. Others define immunologic failure as an increase of CD4 cells/ul < 50 at 6-12 months; < 100 at 12-24 months, or < 500 at 4-5 years irrespective of viral suppression. Virologic failure was defined as a primary failure where VL does not decrease to < 50 copies/ml on two different occasions after six months on ART; and secondary failure (viral rebound) where there is VL >50 copies/ml confirmed. It has been observed also that 75-90.7% of treatment-naïve patients reached undetectable viral load by 12 months on ART, while it was reduced to 72% after 24 months. The proportion of treatment naïve patients with viral rebound was 9.4% after one year, and 20.1-20.6% after 2 years, while it was35-7-40-1% after 2 years of pretreated patients. The risk factors for virological failure includes sex, old age, poor adherence, previous exposure to ART, lower baseline CD4 count, OIs, TB after ART, persistent lower VL, insufficient CD4 cell gain, clinical symptoms, lower weight than baseline, and emergence of drug resistant viruses.

However, in a number of subjects a discrepancy between plasma viral load and the CD4 cell recovery is observed. CD4 cell count can rise despite persistently detectable plasma viral load (virologic nonresponders), or conversely does not increase despite full plasma viral load suppression (immunologic nonresponder). Defective immune reconstitution may depend on several factors including previous therapeutic failure, duration of antiretroviral therapy, low CD4 cell count at the initiation of HAART, advanced stage of disease, low adherence.
to HAART, and previous treatment interruption. There is no definitive evidence that age, viral strain/clade, or host genetic factors play a role in these different responses to HAART. The roles of T-cell subsets, thymic function, and cytokines have been investigated. The increased T-cell activation/apoptosis has been associated with a lack of effective immunologic response. Unabated virologic replication in lymphoid tissues, despite undetectable viral plasma load, has been proposed as the underlying mechanism of cellular activation. However, this “paradoxical response” probably can be associated with other events. Insufficient CD4 cell repopulation of lymphoid tissues may be due to a thymus failure or a defect in bone marrow function. Lifelong infection, the toxic effect of antiviral drugs on T- and B-cell precursors, the stage of disease, and the low number of CD4 cells before HAART may also account for thymus exhaustion and insufficient T-cell renewal. Finally, an imbalance in the production of cytokines such as TNF, IL-2 and IL-7 may also be a crucial event for the induction of immune system failure. In patients in which CD4 cells are not increased by HAART, therapeutic strategies aimed at increasing these cells and reducing the risk of infections are needed. IL-2 and/or other cytokines may be of benefit in this setting. Some antiviral drugs may be better than others in immunologic reconstitution. Protease inhibitors may have additional, independent positive effects on the immune system. On the other hand, there may be little rationale for using immunosuppressive agents such as cyclosporine or hydroxyurea in this subgroup of immunologic nonresponder patients, as these molecules may increase T-cell decline and/or favor susceptibility to infections.

DISCORDANT/CONCORDANT IMMUNOVIROLOGICAL RESPONSES

Besides the independent immunologic and virologic failures, discordant/concordant responses are another challenge during ART. Although the frequency of discordant/concordant immunovirological responders depends on the definition (cutoff values) of immunologic and virologic responses, there are three types of immunovirological responders in clinical practices:

1. Concordant responders (VL+/CD4+) (40-60%),
2. Concordant non-responders (VL-/CD4-) (12-27.3%), and
3. Discordant responders which is sub divided as
   a. immunological non-responders (lack of CD4 cell increases despite viral suppression (VL+/CD4-), (7%-48%), and
   a. immunological responders (good CD4 cell responses in the absence of viral suppression, VL-/CD4+) (5%-18%)

RISK OF IMMUNOVIROLOGIC DISCORDANCE

Complete immunorecovery following HAART is not observed in any of the patients. Absent or modest improvements in CD4 cell counts did occur in 5–27% of the patients on HAART that achieved plasma HIV-1 RNA suppression which has clinical implications. Higher relative risk of progression to AIDS; and AIDS and non-AIDS related mortalities were reported among discordant responders as compared to those virologic and immunologic concordant responders.

Risk factors for failure or incomplete immune recovery include the degree of CD4 cell decline before and at the initiation of the treatment (the steeper the decline the steeper the rise), the rate of decline in viral-load, old age, co-infection (e.g. HCV, HIV-2, HTLV-1, HTLV-2), medications (ZDV, TDF+DDI), and persistent immune activation. However, others have reported no difference in immunological response related to baseline viral load, HIV risk factor, sex, HCV co-infection and HAART regimen. Several explanations have been given about the mechanisms by which inadequate immune CD4 cell recovery occurred in response to HAART. These included, myelosuppressive effects of ARV drugs (e.g. ZDV), thymic involution related to old age, and abnormal cell death (apoptosis) due to higher immune activation related to higher background risk of endemic infections whereas CD4 cell level which measures the strength of the immune system is the best biomarker of when to start treatment, VL test is less necessary before initiating ART as it rarely informs when to start ART.

THE RISK FACTORS FOR DISCORDANT/CONCORDANT ART RESPONSES

The mechanisms of discordant response (VL+/CD4-, VL-/CD4+) are not fully understood. Among the risk factors for VL+/CD4- were lower baseline CD4 cell count (50-100/μL), higher baseline VL (100,000 copies/ml), HAART composed of three NRTIs, the use of lamivudine (3TC)/zidovudine (ZDV), didanosine/tenofovir (DDI/TDF), poor adherence, advanced age, and being ARV naïve. The factors, which contribute VL-/CD4+ include sexual transmission of HIV, absence of clinical progression, lower baseline CD4 cell counts, higher baseline VL, low-level viral rebound during the first year after achieving undetectable VL, younger age, pretreatment and saquinavir regimen, use of 3TC/ZDV, ddI/3TC, or ddI/stavudine, ritonavir boosted protease inhibitor-(PI) based regimen, and treatment compliance). Evidences showed that the frequency and risk factors for discordant responses to HAART in developing and developed countries were comparable. However, the studies are different in terms of study design, inclusion/exclusion criteria, ethnicity, ART experience, sample size, ARV regimen, length of follow-up, and the definitions, which results in the variations of results related to the factors associated with discordant responses.
Therefore, longer follow-up studies are highly pertinent to assess the pattern as well as the long-term impact of concordant/discordant responses treatment outcomes and the risk factors associated with in the context of local settings.

IN CHILDREN

Fewer data exist regarding HIV-1 RNA levels among infected children, particularly regarding the relationship of RNA with long-term clinical outcome. Several studies of perinatally infected children have shown persistent high RNA levels (10^6 copies/mL) throughout the first 2 years of life, with only 2- to 10-fold declines from initial peak values during the first 12 months of life; these high levels may be observed despite normal CD4 lymphocyte counts and lack of symptoms. RNA levels then appear to fall slowly until 24–36 months of age, independent of antiretroviral treatment and immunologic or clinical status [10–12]. These findings may reflect the influence of an immature but developing immune system that requires several years before achieving the capacity to control viral replication to an extent similar to that observed in infected adults. In perinatally infected children, RNA levels that are extremely elevated after 1–2 months of age (approx. 300,000 copies/mL) have been associated with more rapid progression to AIDS early in life. However, because of significant overlap in RNA levels between rapid and non-rapid progressors, no single threshold level predictive of disease progression has yet been identified in children. Regardless of baseline CD4 lymphocyte percent, subjects with high baseline HIV-1 RNA levels had higher mortality than those with low HIV-1 RNA levels. Likewise, subjects with low baseline CD4 lymphocyte percent were at higher risk than those with higher CD4 lymphocyte percent, independent of baseline HIV-1 RNA level were independently predictive of mortality risk. Regardless of whether baseline HIV-1 RNA levels were above or below 100,000 copies/mL, the mortality percentage for subjects with baseline CD4 lymphocyte percent below 15% was greater than the mortality percentage among subjects with CD4 lymphocyte values above 15%. In fact, by some measures, the prognostic value of baseline CD4 lymphocyte percent was greater than the prognostic value of HIV-1 RNA levels. For example, the sensitivity, specificity, and positive predictive value of a baseline HIV-1 RNA level of 100,000 copies/mL was 67.4%, 59.9%, and 48.8%, respectively. By comparison, the sensitivity, specificity, and positive predictive value of a baseline CD4 lymphocyte percent of 15% was 48.3%, 90.1%, and 73.3%, respectively. Also, HIV-1 RNA level and CD4 lymphocyte percent variables were each statistically significant in proportional hazards models that included both markers.

The relationship between HIV-1 RNA level and CD4 lymphocyte percent, as well as their prognostic values, may be affected by the pathogenesis of HIV infection. An HIV-1 RNA measurement obtained shortly after infection (but after the initial burst of viremia) may be more predictive of disease progression than a CD4 lymphocyte measurement obtained at the same time. After a subject’s immune system has had time to be affected by the infection, however, immunologic measures are likely to become more relevant. This study group was first examined an average of almost 3.5 years after infection, and both HIV-1 RNA and CD4 lymphocyte levels were independent and complementary markers of disease stage. In many instances, a clinician may not examine a patient until several years after the initial infection. Therefore, both markers should be considered together for decision-making regarding therapy and evaluation of response to antiretroviral agents.

REFERENCES

11. Aiuti F, Mezzaroma I. Failure to reconstitute CD4 T cells de-


