Applied Sciences Research Periodicals
November 2023, Vol. 1, No. 8, pp. 33-42

Effectiveness of Combined Anti-Retroviral Therapy [cART] on Viral Load and Cd 4 Count, in Reducing Progression to AIDS, in Improving the Quality of Life of Patients of HIV/AIDS in the Context of the U.N. Sustainable Development Goals (SDGs). A 5-Year Prospective Study in Himachal Pradesh (India)

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Abstract:
Background: The increasing prevalence of the Human Immunodeficiency Virus (HIV) every forthcoming year continues to pose a serious threat to mankind. This global problem and its sequelae cause significant loss of precious lives every year despite advances in Antiretroviral (ARV) therapy. CD4 cell count is an essential component in monitoring HIV treatment outcomes but it's monitoring sometimes is unable to estimate the virological failure leading to a switch of treatment lines that leads to drug resistance and limiting of options for patients. CD4 count still is the best measurement of an HIV patient's immune and clinical status, the threat of opportunistic infections, and diagnostic decision-making, especially for patients with advanced HIV disease. Aims and Objectives: This study is an attempt to assess the effectiveness of cART on Cd 4 count and Viral load both as predictors of HIV/AIDS by monitoring the progression of the disease by determining the CD4 level and HIV RNA Viral load and reducing the progression of AIDS improving the quality of life of patients of HIV/AIDS in the context of the U.N. sustainable development goals. Material and Methods: 492 HIV patients were analyzed over five years. Models were selected, for various parameters like CD4 cell count monitoring and HIV load RNA monitoring. Effects of various covariates; gender, age, CD4 baseline count, HIV RNA baseline count, and patient's adherence to treatment were assessed for each of the fitted models. To assess the extent International or U.N. policies are being implemented concerning Viral load and CD4 testing in practice. We also draw on data from key informant interviews to contextualize the policy content and national implementation strategies, and from qualitative interviews with service providers and users to explore how tests are being conducted and interpreted in everyday clinical practice. Results: For people living with HIV/AIDS Antiretroviral therapy must be consumed throughout life to inhibit the levels of the HIV/AIDS virus as it is a chronic disabling disease and improving the quality of life depends on cART adherence and psychosocial support. Results from this analysis revealed that viral load monitoring is a better predictor of HIV/AIDS progression and deaths in HIV/AIDS patients in comparison to CD4 cell count monitoring. Conclusions: Our study concludes that both CD4 and HIV viral load should be performed on patients alternately to cover both aspects of patient management.

Keywords: Combined antiretroviral therapy (cART), CD4+ cell count, HIV RNA Viral load, Life expectancy

INTRODUCTION

This study assesses the effectiveness of cART on Cd 4 count and HIV Viral RNA load both as predictors of HIV/AIDS by monitoring the progression of the disease by determining the CD_4 level and viral RNA load before initiation of cART and viral loads after 6 months of cART initiation and difference in their levels 5 years after. When diagnosed with HIV, the patient's CD 4 count parallel viral load is done. The CD 4 count allows the attending physician to determine the state of the immune system and plan the further course of treatment. If the CD 4 count on presentation is below 200 units, the diagnosis of acquired immunodeficiency syndrome (AIDS) is done. The viral load will indicate the speeds of viral replication. Current medications used nowadays to treat HIV infection attack different phases of viral replication and hinder the process of new viruses being produced. Therefore, a fall in viral load after starting cART is an indicator that the medication is doing its job as per expectation.

The role of the CD_4 cell count to decide the treatment efficacy is changing day by day. However, CD_4 count remains the best measurement of a patient's immune and clinical status, the threat of opportunistic infections, and diagnostic decision-making, especially for patients with advanced HIV disease. For patients who are stable on ART, CD_4 cell counts are no longer needed to monitor the response to treatment where HIV viral load testing is available.

MATERIALS AND METHODS

Two milliliters of sterile blood samples were collected in a diamine tetraacetic acid vacutainer and transported to the microbiology laboratory within 1 hour. The sample was processed within one hour according to the National AIDS Control Society guidelines based on the Clinical laboratory standard institute (CLSI). CD_4 count was estimated by BD FACS machine using flow cytometry with single platform technology as the principle. The 5-year prior CD_4 counts and CD_4 counts after ART intervention of all the 492 patients were analyzed by calculating the standard error of the mean, standard deviation, and paired *t*-tests. For each visit time, blood samples were obtained for each patient's viral load determination and stored frozen until assayed. Plasma HIV RNA was measured using an HIV-1 monitor assay kit which has a lower limit of sensitivity of 50 copies/mL.

DATA ANALYSIS

In this study, the patients suffering from HIV infection were analyzed for various parameters. Out of 492 patients, there were 307 males, 169 females, and 16 children. See Figure 1 Annexure. Out of 492 patients, 390 reported a Heterosexual mode of transmission, Unknown 27. Mother to child 13, MSM 3, IDU 2. See Figure 2 in the Annexure for modes of HIV transmission. Over 5 years 26 patients died, transfer out 31, Left outs were 8, opted out 3. Out of 492 patients, 470 belonged to Himachal Pradesh while 22 were from different states working in Himachal Pradesh.

The CD 4 count was less than 150 in 157 patients, in 164 patients it was below 350, and above 350 in 171 patients. See Table 3 in Annexure. The mean CD_4 count in 492 patients before ART was 315, with a standard deviation ± 141 of the mean value. After 5 years of ART, the mean value of CD_4 count increased to 550 with ± 148 standard deviations of the mean value.

This study of 492 patients as a group after ART intervention for 5 years shows that their mean CD_4 count increased from 315 to 550, an increase of 235 a clear indication that nearly all benefited from the cART. See Table 4 in Annexure. Figure 4

The mean difference in the CD_4 count increase in patients obtained was 145 and is statistically significant ($P < 0.01$) by the paired *t*-test. The confidence limit in 95% of the patients having ART treatment for 5 years will have a mean increase of CD_4 count in between 125 and 175. See Table 5.

RESULTS

The mean difference in the CD_4 count increase in patients obtained was 145 and is statistically significant ($P < 0.01$) by the paired *t*-test. The confidence limit in 95% of the patients having ART treatment for 5 years will have a mean increase of CD_4 count in between 125 and 175.

It was observed that if we consider all patients together, it appears that the CD_4 count of the cohort has increased, but this should not be considered in totality. We separately evaluated the patients who showed a rise and fall in CD_4 count after ART to get the true picture. Patients showing a decrease in CD_4 count should be assessed for viral load and drug resistance studies. Reasons for lowering the count may be non-adherence, lack of support from families and society, social stigma, shortage, and toxicity of drugs. Viral load monitoring is a better predictor of HIV/AIDS progression compared to CD_4 cell count and viral load estimation is considered to be superior.

In our study of 492 patients baseline viral load after six months of cART was performed and the mean value in whom significant viral load above 1000 copies/ml was taken into account and others were classified into Target Not Detected (TND). 61 patients were falling in the zone of consideration above 1000 copies/ ml. They were again tested for viral load monitoring after 6 months and then the count of patients above significant viral load came down to 31. The basic viral load which was 16997 copies/ ml decreased to 11067 copies/ ml after 6 months of cART adherence. See Table 6 in Annexure. Viral load decreased by 5930 copies on average in the selected group. Therefore, we witnessed a significant decline in viral load estimation, a confirmation of the efficacy of cART in decreasing the viral load. See Figure 5 in the Annexure.

DISCUSSION

This study tries to analyze the effectiveness of Combined Anti-Retroviral Therapy on Viral load and CD 4 count, in reducing the progression of AIDS and improving the quality of life of patients with HIV/AIDS in the context of the U.N. sustainable development goals (SDGs). The CD_4 count is the best parameter for guiding general care physicians to initiate cART in the prophylaxis of HIV patients. CD_4 count can also guide general care physicians in managing late presenting patients, or patients on cART if there is suspicion of poor clinical outcome or immunological failure. In monitoring the patient's response to ART, the most reliable test continues to be viral load detection.[1] The Immune system comprises a large network of cells that work mutually in combating infections. Helper T Lymphocytes are a specific type of immune cell that expresses a molecule called Cluster Determinant 4 (CD_4). Helper T lymphocytes are generally referred to as CD_4 cells. The Human Immunodeficiency Virus (HIV) precisely targets CD_4 host cells for viral replication. As the virus replicates in the cells, it destroys its host cell and releases new progenies. Hence, as the viral load (the amount of virus present in the body) increases the host CD 4 cell count decreases. During the early stages of a person getting HIV infection, viral replication occurs at a very fast rate at the expense of CD 4 host cells. A chain of circumstances occurs, where an increase in HIV viral load occurs leading to more CD_4 cells getting infected and leading to an increase of hosts to further increase the viral load. Within the first few weeks of an HIV infection, the CD 4 count falls steeply. The significant fall in CD_4 cells is pathogenic to HIV infection.

When diagnosed with HIV, the patient's CD 4 count parallel viral load is done. The CD 4 count allows the attending physician to determine the state of the immune system and plan the further course of treatment. If the CD 4 count on presentation is below 200 units, the diagnosis of acquired immunodeficiency syndrome (AIDS) is done. The viral load will indicate the speeds of viral replication. Current medications used nowadays to treat HIV infection attack different phases of viral replication and hinder the process of new viruses being produced. Therefore, a fall in viral load after starting cART is an indicator that the medication is doing its job as per expectation.

The role of the CD4 cell count to decide the treatment efficacy is changing day by day. However, CD4 count remains the best measurement of a patient's immune and clinical status, the threat of opportunistic infections, and diagnostic decision-making, especially for patients with advanced HIV disease. For patients who are stable on ART, CD4 cell counts are no longer needed to monitor the response to treatment where HIV viral load testing is available.

Knowledge is a key factor which supports the level of adherence to ARV therapy. Human Immunodeficiency Virus (HIV) infection is a lifelong disabling chronic condition affecting the patient and their families financially and socially. Preventing the progression of the disease and its subsequent disability is a crucial factor in adherence to therapy. Early diagnosis and cART initiation impart better HIV management for the patient ultimately leading to a reduction in mortality and improvement in the quality of life.[2] In the majority of people affected the sequence of HIV infections is not clearly defined. Still, it starts from the time of acquiring of the virus till the eclipse phase through seroconversion (primary HIV infection) which is followed by a period of clinical latency due to antibody evolution. During clinical latency, there is a continuous decline of peripheral CD4 T cells, immune system amplification, and inflammation.[3,4] In HIV infection, the CD4 count decreases to differing levels as per the immune status of the patient. Current CD4 count is a good predictor of the immediate risk of acquired immunodeficiency syndrome (AIDS) or death than HIV RNA level. Antiretroviral therapy (ART) has significantly decreased the morbidity and mortality connected with HIV infection and boosted the prognosis for people living with HIV AIDS.

As per the latest guidelines cART should be started in all children, pregnant and breastfeeding women, and adolescents, adults infected with HIV, notwithstanding WHO clinical staging and CD4 cell count. The cART should be started in all children, adolescents, pregnant or breastfeeding women, adults on a priority basis with severe or advanced HIV clinical disease, and adults with a CD4 count of fewer than 300 cells/mm3 as well as children aged less than 5 years of age with WHO clinical stage 3 or 4 or CD4 count less than 700 cells/mm3. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose the treatment failure, with selective viral load testing for confirming viral failure if possible. For children above five years of age, adolescents, and adults, advanced HIV disease is defined as the presence of a CD4 cell count < 200 cells/mm3 or a WHO clinical stage 3 or 4 events. A patient is considered stable on ART based on the following criteria: on ART for at least 1 year, no current illnesses, a good understanding of lifelong adherence, and evidence of treatment success if we classify the patient as Nondetectable viral load [NTD] which means two consecutive viral load measurements below 1,000 copies/ml). Various factors influenced the adoption and implementation of WHO guidance, including historical policies on CD4 counts, governance issues, supply chain challenges, and funding mechanisms. Facility-level practices relating to the use of these tests have often diverged from International and national policies. In addition to continued support for scaling-up viral load

testing, the renewed focus should be placed on the ongoing value of CD4 testing in the era, including its important role in the assessment of disease progression and alarming the clinical management for revision of treatment if needed of cases to reduce HIV-related mortality. In 2015, the World Health Organization (WHO) recommended that patients diagnosed with HIV should be initiated on ART at any CD4 cell count (World Health Organisation, 2015), which means starting treatment on diagnosis a strategy known worldwide as the 'universal test and treat (UTT). The widespread adoption of UTT in India has been recognized as a critical step in moving towards targets to eliminate AIDS by 2030 .[5] While CD4 cell counts indicate the strength of the immune system, it does not report viral activity, which is best measured through a viral load test. However, compared with CD4 testing, viral load testing is expensive and more technically complex, reasons which were widely cited as inhibiting its wide-scale use in most South Asian countries during the first decade of ART scale-up. As evidence is upcoming on the benefits of viral load monitoring for increasing the lifespan of first-line regimens and improving patient outcomes has become established, the WHO recommended viral load (VL) monitoring as part of routine care for monitoring adherence and treatment failure among people taking ART in all settings (World Health Organization, 2017; World Health Organization, 2016). Frontline access for testing CD4 count remains critical for assessing disease progression (World Health Organization, 2017), identifying people diagnosed late with HIV (CD4 < 350 cells/μL),[6] informing differentiated care models (World Health Organization, 2017) and, more broadly, providing healthcare workers with an objective measure of a patient's health.[7] However, several factors have undermined their use including the growing availability of Viral load testing and recent guidance on its use, adoption of UTT, and a decrease in financial donor support for CD4 testing. [8] As a result, several South Asian and African countries have drastically reduced CD4 monitoring in favor of increased Viral Load testing (United States Agency International Development, 2016), and CD4 tests performed in some low- or middle-income countries are not being fully utilized to inform clinical management for revising treatment options.[9] These concerns are intensified with the suggestions that coverage of Viral Load monitoring remains less in sub-Saharan African settings [10] and even where the scale-up of Viral Load testing is under process, the test results are used sub-optimally for clinical decisions about revision.[11] Appreciating the ongoing value of conducting both Viral Load and CD4 testing, we analyzed the extent to which national policies on the use of each biological marker reflect WHO guidance and the degree to which national directives on their use are implemented at the facility level in rural India. We also tried to find out the difficulties faced in their implementation from the viewpoint of in-country stakeholders, and the experiences with the use of both tests among patients and providers. WHO recommends countries should retain their capacity to conduct CD4 testing at diagnosis and up to ART initiation, and CD4 counts remain useful in guiding the clinical management of patients failing treatment or re-engaging in care. [12] Our finding supports the recent expression of anxiety that guidelines promoting Universal tests and treatment may be misinterpreted.[13] Specifically, the importance of CD4 monitoring in identifying and treating people at risk of advanced disease has been put aside due to the attention given to increasing Viral load testing. Our study found the sub-optimal implementation of tests, such as inadequate scheduling, long turnaround times (mainly with VL), and procedures not being followed (mainly concerning CD4) compromised the utility of the markers. Challenges leading to sub-optimal implementation in these settings included a lack of facility space, a lack of refrigeration, and suboptimal laboratory capacity. Developments in the use of point-of-care testing are positive with evidence to suggest such testing is feasible, acceptable, and can increase coverage and effectively identify treatment failures for viral load testing.[14,15] Our study supports their recommendations of the need for continued efforts to train staff regularly, monitor the program, and promote demand for tests. Additionally, our study highlighted various challenges

in health workers' capacity to communicate the meaning of test results to patients and populations.One study concluded the greatest mean increase in CD_4 count of 100 cells/mL after the first year of ART. [16] Cascade Collaboration has reported the median CD_4 count increase at 6 months on ART was 119 cells/mL.[4] Other studies have opined that the negative CD_4 count slope in patients on ART was associated with virological failure. They have concluded that the CD_4 count changes correlated significantly with viral load at a group level.[17] But, this has limited utility in identifying virological failure in individual patients.[5] Some studies also reported poor CD_4 cell recovery or no increase in CD_4 count in a few patients on ART in their studies.[6]

CONCLUSIONS

Based on our study, we can conclude that CD_4 cell count to reach the risk-free zone adherence to cART therapy plays a key role and takes a longer time than for undetectable viral load because if CD_4 cell count is normal, mortality risks are reduced substantially. Significant decisions will be needed in the future regarding the use of CD_4 cell count and its use for clinical disease management. Hence, both viral RNA load monitoring and CD_4 count monitoring are essential to correlate various aspects of disease progression for improving the quality of life of patients living with HIV.

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Annexure For HIV Manuscript

Table 1: Shows the Sex Distribution

	Sex	
SNO 1	Men	307
SNO 2	Women	169
SNO.3	Children	16

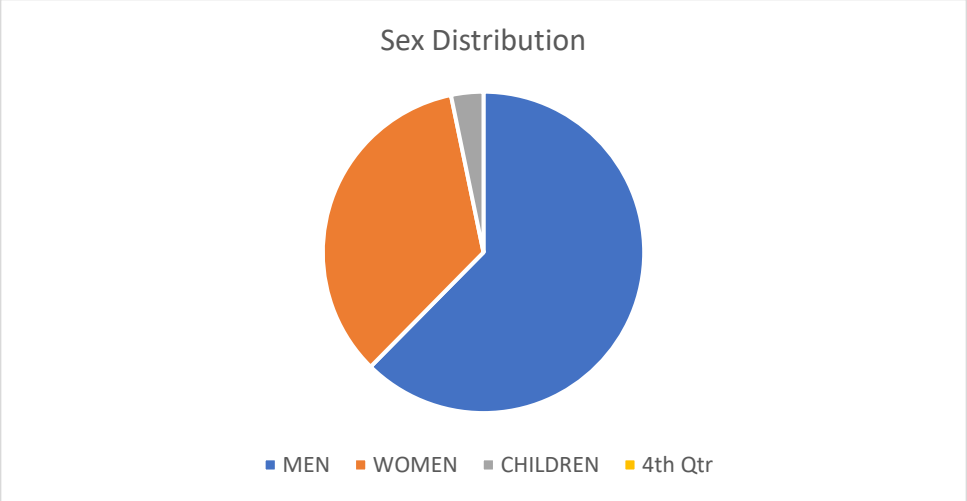

Figure 1

Table 2: Shows the Modes of Transmission

SNO	MODES OF TRANSMISSION	
1	HETEROSEXUAL	390
2	UNKNOWN	27
3	MOTHER TO CHILD	13
4	MSM	3
5	IDU	2

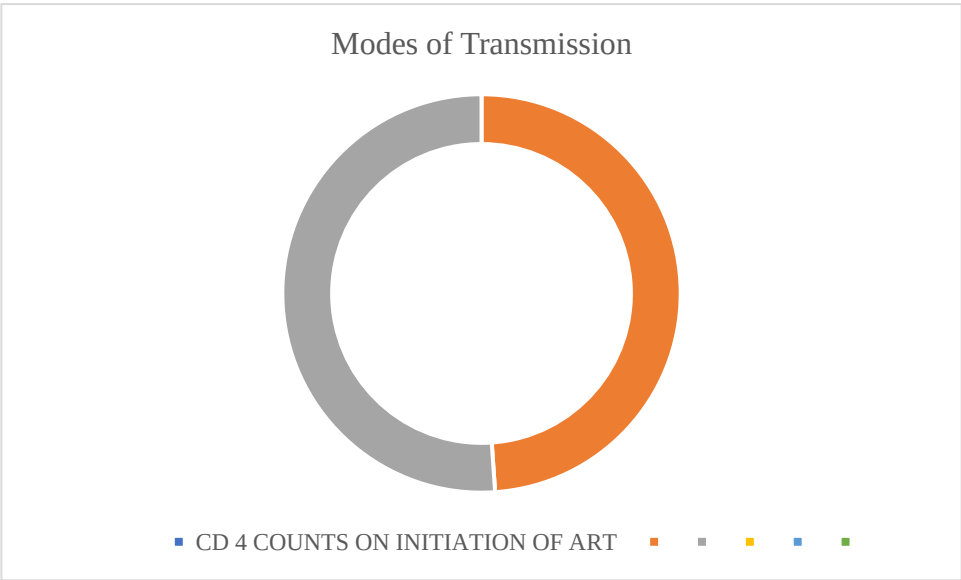

Figure 2: Shows the Modes of Transmission

Table 3: Shows Cd4 Count at Diagnosis

SNO 1	CD 4 COUNT	
1	BELOW 150	157
2	BELOW 350	164
3	ABOVE 350	171

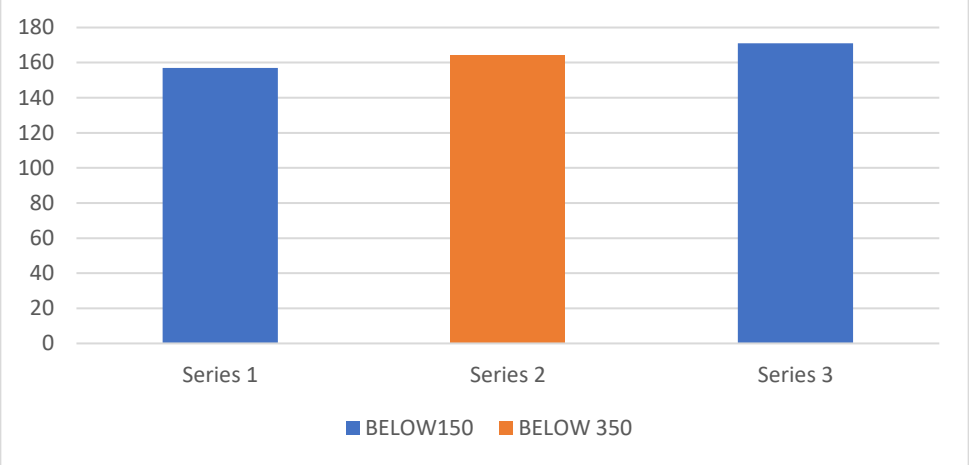

Figure 3: Shows the CD 4 Count at Diagnosis

Table 4: Shows an Increase in CD4 Count After 5 Years

SNO 1	Cd 4 Counts on The Initiation of Art	Total 492	Cd 4 Count After 5 Years of Adherence to Art	Total 424
1	Below 150	157	Below 150	77
2	Below 350	164	Below 350	199
3	Above 350	171	Above 350	148

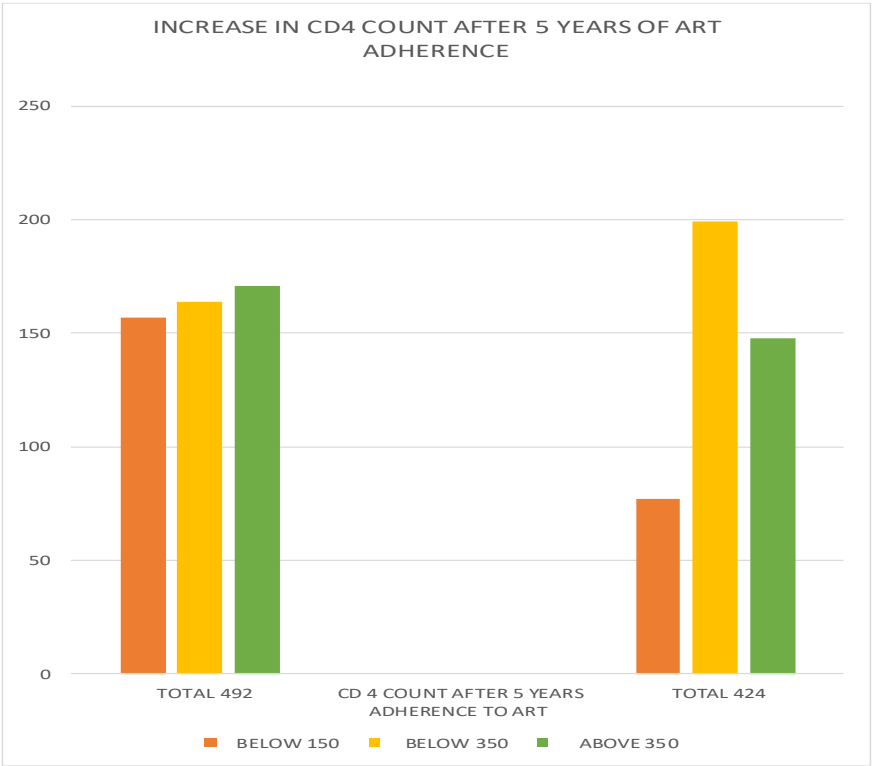

Figure 4: Shows an Increase in CD4 Count After 5 Years of Art Adherence

Table 5

CD4 Count	Baseline	After 5 years	**p-value**
BELOW 150	157	77	<0.01
BELOW 350	164	199	
ABOVE 350	171	148	

Over 5 years 26 patients died, transfer out 31, Left outs were 8, opted out 3.

Table 6: Viral Load After 6 Months Initiation of Art and 6 Months Later

	Viral Load Above 10000 Copies / ML	Viral Load Below 10000 Copies / ML(NTD)
After 6 Months of Art	431	61
After 12 Months of Art	31	461

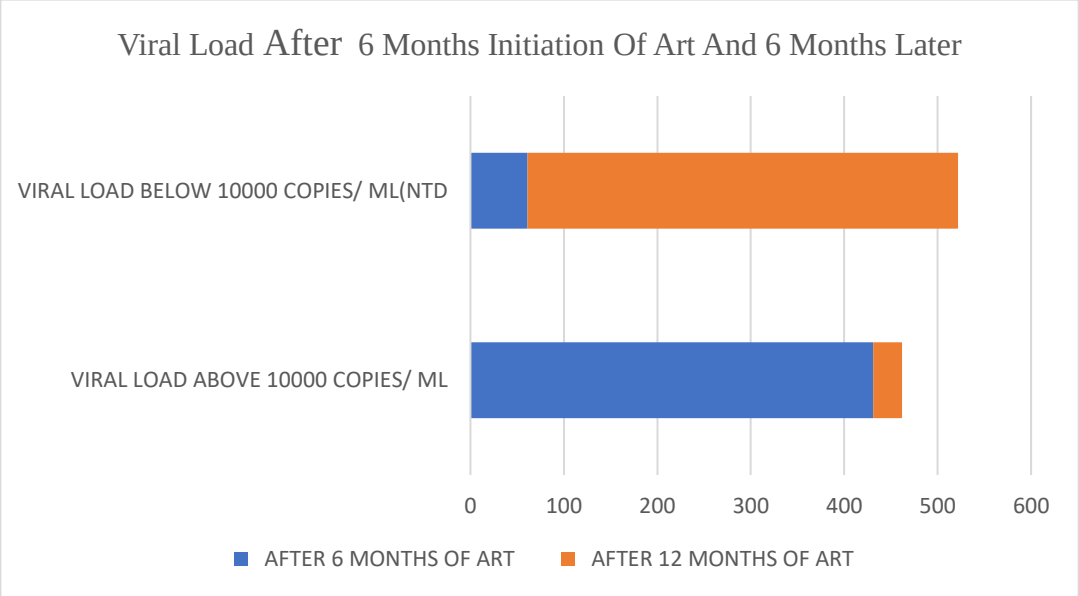

Figure 5: Viral Load After 6 Months Initiation of Art and 6 Months Later