PREDICTORS OF GOOD OUTCOME AFTER ONE YEAR OF ANTI-RETROVIRAL THERAPY AMONG PATIENTS DIAGNOSED WITH HIV ENROLLED IN THE TREATMENT HUB OF MAKATI MEDICAL CENTER

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ABSTRACT

Setting

A surge in the incidence of HIV in the Philippines was recently observed. Makati Medical Center (MMC) was accredited in 2012 as one of the treatment hubs after the introduction anti-retroviral therapy (ARV).

Objective

Predictors good outcome were identified after a year of ARV among HIV patients enrolled at MMC Treatment Hub.

Design

This is a retrospective cohort study of 417 HIV patients treated from January 2006 to January 2014.

Results

Most patients enrolled were male (98%), single (98%), of reproductive age (91%), males having sex with males (49%) and engage in anal sex (44%). The median age at the start of treatment is 31 years old (25-35 IQR).

After a year of ARV, 92% had good outcome while 7.7% had poor outcome. Compliance and better HIV staging after a year treatment were associated with good outcome.

Conclusion

Good compliance and better HIV staging after treatment are predictors of good outcome of treatment at 1 year.

INTRODUCTION

According to World Health Organization (WHO) by the end of 2013, there are approximately 35.0 million (33.2–37.2 million) million people infected with HIV globally.[1] The prevalence of HIV and AIDS in the Philippines is still low when compared to other countries such as South Africa, Nigeria and India.[2] However, according to the Department of Health-National Epidemiology Center; the Philippines' HIV & AIDS registry for 2013 reveals an 85% increase in newly reported HIV cases, compared to the same period in 2009. For the year 2013, the highest reported new HIV Antibody seropositive individuals confirmed by STI/AIDS Cooperative Central Laboratory (SACCL) were on the months of October 2013 with 491 number cases. This was 60% higher when compared to same month from previous year (October 2012, cases of 295). Most cases were males with a median age of 27 years old and were asymptomatic. The most common mode of transmission is through sexual contact with men having sex with men (MSM).[3]

As of January 2014, there are only 5,756 out of 16,694 reported cases People Living with HIV (combined children and adults) presently on ARV.[3] Only 33.69% of the cases of HIV from 1984-2013 are receiving ARV. There are also an increasing annual number of deaths per year beginning 2011. The annual number of deaths from year 1984-2010 ranges from 2 to 26 individuals, which is lower than the annual number of deaths from year 2011-2013 (69-179 individuals).[3]

The combination therapy of ARV, which was introduced in the year 1987, has been really beneficial in reducing the morbidity and mortality.[4] However; there are only few published research papers about HIV and its treatment in the Philippines. One study showed that the risk factors to AIDS progression and mortality were higher viral load levels and lower CD4+ T cell count.[5] There are no published studies about the clinical response of Filipino patients to available ARV.

The aim of this research is to describe the typical population of HIV infected patients in Makati Medical Center Treatment Hub and to determine the predictors of good outcome for patients who have been started on ARV.

METHODS

Study Design and Participants

This study is a retrospective cohort study of confirmed HIV patients who were enrolled in MMC from 2006 to January 2014. MMC is one the approved treatment hubs by the Department of Health of the Philippines for patients with HIV. It was inaugurated in year 2012, and as of January 2014, 419 patients were enrolled and started on anti-retroviral therapy. Patients with positive HIV confirmatory test from the STD AIDS Cooperative Center Laboratory (SACCL) dated January 2006 to January 2014 were evaluated. All patients who completed at least 1 year of ARV were included in the study. Patients visiting the clinic were also asked to participate in the study provided that they agreed willingly with informed consent. However, patients who were less than 18 years of age, less than 1 year on antiretroviral therapy and lost to follow-up were excluded.

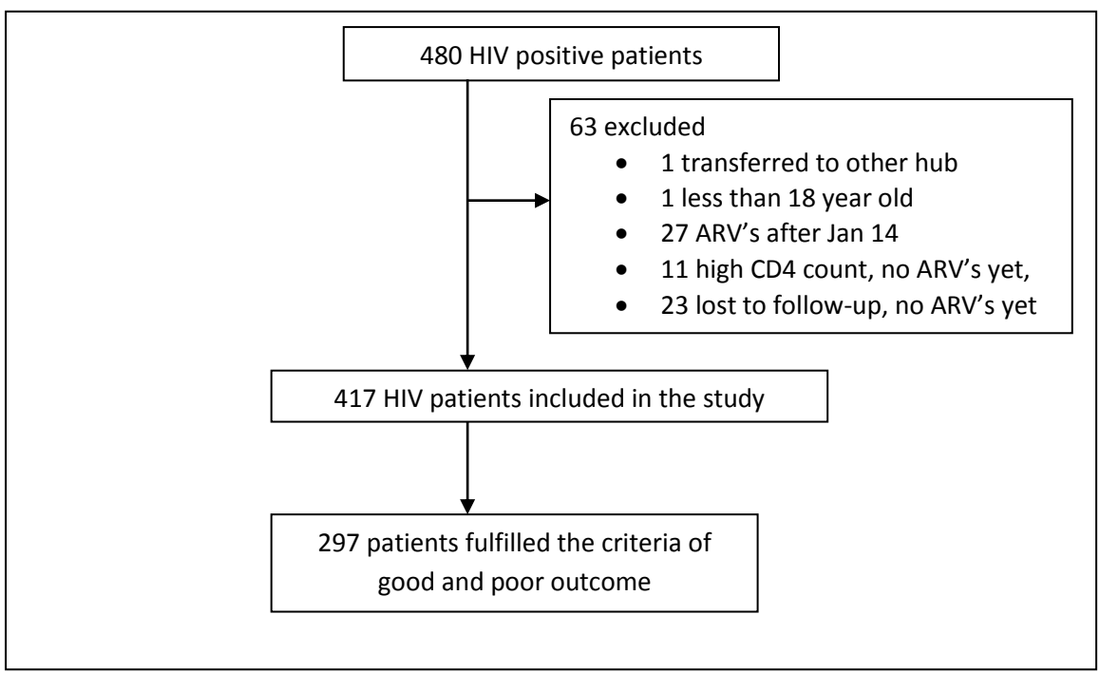


Figure 1. Study Profile

Data Collection:

Data was collected by out-patient charts review, which include the demographic profile (specifically the patient's age, gender and weight), underlying illnesses (diabetes, hypertension or previous hospitalizations), opportunistic infections, risk factors, CD4 count, viral load, antiretroviral therapy, clinical status, and baseline laboratory results (HBSAg, AntiHBS, Anti-HCV, RPR/VDRL, chest x-ray). The clinical status, weight, CD4 count and HIV viral load of patients after 6 months and after 1 year of ARV also observed. The compliance was checked by noting the pill retained every month based from the pharmacy data. Mortality rate was also calculated.

National HIV treatment guidelines released on 2009 was based on the World Health Organization recommendation for HIV infections in Adolescents and Adults 2006. Patients with HIV are started on ARV if the CD4 count is below 200 cells/mm^3, pregnant, or if there is co-infection with tuberculosis, Hepatitis B or Hepatitis C. World Health Organization released a new guideline in 2013 which advises clinicians to start ARV if CD4 count < 350 cells/mm^3. HIV viral load and CD4 monitoring is done after 6 to 12 months of treatment to determine the virologic and immunologic response. The first line of treatment is Lamivudine-Zidovudine and Nevirapine. Other ARV's that are available are Tenofovir, Efavirenz and Lopinavir/Ritonavir. Complete blood count, chest x-ray, sputum AFB, HBSAg, AntiHBS, RPR/VDRL and anti-HCV are requested to rule out OI's. Other laboratories are requested when necessary.[6]

Ethical Considerations

The protocol was reviewed and approved by MMC Institutional Review Board.

Definitions Used for Data Analysis

Staging of HIV was based on immunologic status of patients defined as follows: Stage I CD4 $\geq$ 500 cells/mm^3; Stage II CD4 350-499 cells/mm^3; Stage III CD4 200-349 cells/mm^3; and Stage IV CD4 < 200 cells/mm^3.

Drug compliance was defined as the extent to which patients take their ARV, 80-100% of the dose per month prescribed. It will be measured as average number of used pills per month for 1 year after the start of anti-retroviral therapy. Non-compliant patients were those taking less than 80% of the dose prescribed per month.

Patient has good outcome if the HIV patient was alive with resolved opportunistic infections and undetectable viral load at 6 months of treatment (viral load of < 200 copies/mL). Patient has poor outcome if HIV patient died during treatment or those patients with HIV viral load $\geq$ 200 after 6 months of treatment.

Statistical Analysis

Continuous data were expressed in median and interquartile ranges due to non-parametrical distribution. Categorical data were expressed in frequency and percentage. To compare the characteristics of patients with good outcome versus poor outcome, chi square test was used. Variables with a P value of < 0.25 in the univariate analysis were included in the multiple logistic regression model. Associations will be assessed using odds ratios (ORs) and corresponding 95% confidence intervals (CIs). To determine the predictors of good outcome, a multiple linear regression analysis was done. Any associated p-values lesser than 0.05 alpha were considered significant. IBMSPSS 21 and SAS 9.1 were utilized as statistical softwares to ensure accuracy of computation.[7]

RESULTS

A total 417 patients were diagnosed with HIV and was started on treatment from January 2006 to January 2014 (Fig 1). However, only 297 (71%) of the 417 patients had CD4 and viral load levels after 6 months from initiation of treatment. These were the patients included in the final analysis.

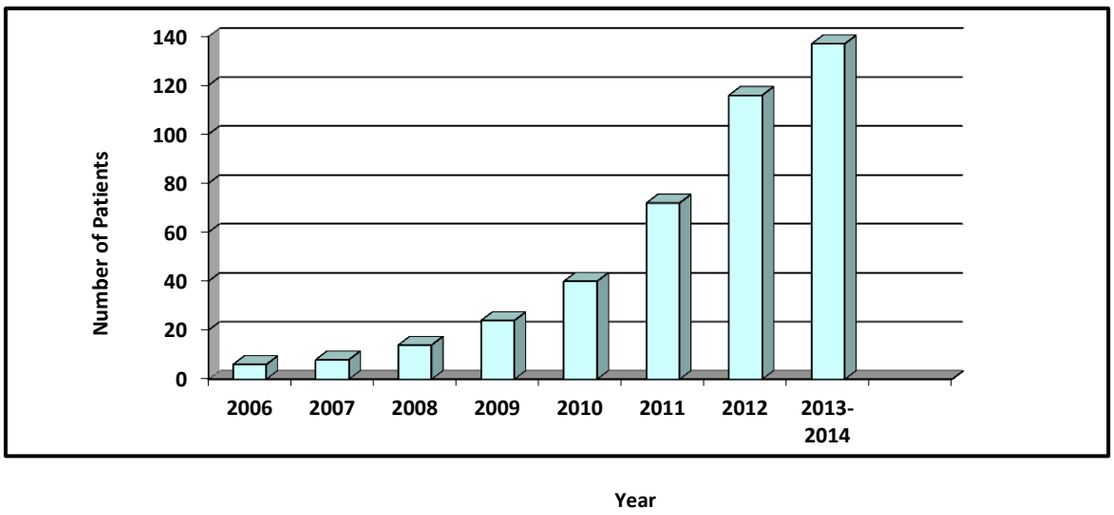


Figure 2. Number of newly diagnosed HIV patients per year at MMC Treatment Hub from January 2006 to January 2014.

Figure 2 shows the enrolment rate in MMC treatment hub from January 2006. The highest rate of enrolment was seen in the year 2013 to January 2014 (137 cases, 33%).

Most patients enrolled in MMC treatment hub were male (98%), single (98%), residing in the Greater Manila Area (88%), college graduate (57%), employed (61%) and of reproductive age (91%), Table 1. The median age of these patients at the start of treatment was 31 years old (25-35 IQR).

Most of them (98%) were circumcised with median age of 11 years old (10-13 IQR). Majority prefers to have sex with males (49%). The median number of sexual partners was 13 (10-20 IQR). Their sexual practice often involves anal sex (44% of the total population) and oral sex (47%). They can be both receptive and insertive during anal sex (26.1%). They are not usually keen on practicing safe sex with only 11% of them are using condom at all times. There was no significant difference between patients with good and poor outcome based on the socio-demographic profile.

Table 1. Socio-demographic characteristics of HIV patients enrolled at MMC Treatment Hub, January 2006-January 2014 (N=297)

Characteristics	Good Outcome n=274 n (%)	Poor Outcome n=23 n (%)	Total N=297 n (%)	p-value
Age when ARV started (years)				
18-24	30 (11)	1 (4)	31 (10)	
25-44	221 (81)	21 (91)	242 (81)	
45-64	23 (8)	1 (4)	24 (8)	
≥65	0 (0)	0 (0)	0 (0)	0.447
Male Sex	269 (98)	22 (96)	291 (98)	0.386
Single	209 (76)	17 (74)	226 (76)	0.135
Greater Manila Area	241 (88)	19 (83)	260 (88)	0.318
Education				
≤ High School	6 (2)	0 (0)	6 (2)	
College	158 (58)	12 (52)	170 (57)	
Post-Graduate	19 (7)	4 (27)	23 (8)	0.454
Employed	167 (61)	13 (57)	180 (61)	0.561
Hypertension	4 (2)	1 (4)	5 (2)	0.398
Diabetes Mellitus	0 (0)	1 (4)	1 (0)	0.088
Dyslipidemia	9 (3)	1 (4)	10 (3)	1.000
Allergies to Food	18 (7)	0 (0)	18 (6)	0.367
Allergies to Medications	29 (11)	2 (9)	31 (10)	1.000
History of Blood Transfusion	12 (4)	1 (4)	13 (4)	1.000
Smoker	52 (19)	5 (22)	57 (19)	1.000
Alcoholic drinker	74 (27)	6 (26)	80 (27)	0.793
IV drug user	8 (3)	0 (0)	8 (3)	1.000
Circumcised	267 (97)	23 (100)	290 (98)	0.372
Sexual Preference				
Male	134 (49)	11 (48)	145 (49)	
Female	9 (3)	1 (4)	10 (3)	
Both	35 (13)	3 (13)	38 (13)	0.994
Anal Sex	118 (43)	12 (52)	130 (44)	0.649
Form of Anal Sex				
Insertive	14 (5)	1 (4)	15 (5)	
Receptive	23 (8)	3 (13)	26 (9)	
Both	79 (29)	8 (35)	87 (29)	0.761
Condom				
Yes	32 (12)	1 (4)	33 (11)	
Sometimes	96 (35)	12 (52)	108 (36)	
No	29 (11)	2 (9)	31 (10)	0.372
Oral Sex	127 (46)	12 (52)	139 (47)	1.000

Table 2. Clinical status and treatment characteristics of HIV patients enrolled at MMC Treatment Hub, January 2006-January 2014 (N=297)

Characteristics	Good Outcome n=274 n (%)	Poor Outcome n=23 n (%)	Total N=297 n (%)	p-value
Previous HIV Negative Test	39 (14)	2 (9)	41 (14)	0.729
Stage before ARV				
≤ III	134 (49)	9 (39)	143 (48)	0.222
IV	135 (49)	14 (61)	149 (50)	
Stage after a year of ARV				
≤ III	227 (83)	17 (74)	244 (82)	0.124
IV	30 (11)	5 (22)	35 (12)	
Previous admission	116 (42)	14 (61)	130 (44)	0.046
Opportunistic Infections	!39 (51)	14 (61)	153 (52)	0.365
A. Pulmonary System				
Pulmonary Tuberculosis	41 (15)	4 (17)	45 (15)	0.755
PCP Pneumonia	41 (15)	4 (17)	45 (15)	0.755
Bacterial Pneumonia	5 (2)	2 (9)	7 (2)	0.037
Fungal Pneumonia	1 (0.4)	0 (0)	1 (0)	0.025
B. Gastrointestinal System				
Oral/Esophageal Candidiasis	40 (15)	6 (26)	46 (15)	0.144
Hepatitis B	24 (9)	2 (9)	26 (9)	0.992
Hepatitis C	0 (0)	0 (0)	0 (0)	1.000
C. Central Nervous System (CNS)				
CNS Tuberculosis	7 (3)	0 (0)	7 (2)	0.438
CNS Cryptococcosis	2 (1)	0 (0)	2 (1)	0.681
CNS Syphilis	2 (1)	0 (0)	2 (1)	0.681
CNS Toxoplasmosis	1 (0)	0 (0)	1 (0)	0.772
CNS-PML	0 (0)	0 (0)	0 (0)	1.000
D. Skin				
Herpes Zoster	21 (8)	3 (13)	24 (8)	0.363
Seborrheic Dermatitis	12 (4)	0 (0)	12 (4)	0.306
E. Others				
Extrapulmonary TB	24 (9)	2 (9)	26 (9)	0.992
Syphilis	11 (4)	0 (0)	11 (4)	0.327
CMV Retinitis	3 (1)	1 (4)	4 (1)	0.194
Baseline Laboratories				
RPR/VRDL (reactive)	12 (4)	0 (0)	12 (4)	0.306
Anti HbS (reactive)	81 (30)	8 (35)	89 (30)	0.600
HbS Ag (reactive)	26 (9)	2 (9)	28 (9)	0.900
Anti HCV (reactive)	0 (0)	0 (0)	0 (0)	1.000
Abnormal chest x-ray	43 (16)	5 (22)	48 (16)	0.449
Present Anti-Retroviral Therapy*				
3TC-AZT-EFV	166 (61)	14 (61)	180 (61)	0.979
3TC-TDF-EFV	72 (26)	6 (26)	78 (26)	0.984
3TC-AZT-NVP	18 (7)	0 (0)	18 (6)	0.205
3TC-ATZ-Lopinarvir/R	10 (4)	0 (0)	10 (3)	0.351
3TC-TDF-Lopinavir/R	5 (2)	1 (4)	6 (2)	0.409
3TC-TDF-NVP	1 (0)	2 (9)	3 (1)	0.000
3TC-AZT-Indinavir	1 (0)	0 (0)	1 (0)	0.772
3TC-AZT-Rilpivirine	1 (0)	0 (0)	1 (0)	0.772
Adverse Drug Reactions				
Rashes	47 (17)	4 (17)	51 (17)	0.977
Jaundice	4 (1)	0 (0)	4 (1)	0.560
Non-Compliant	13 (5)	3 (13)	16 (5)	0.090

*3TC-Lamivudine, AZT-Zidovudine, EFV-Efavirenz, TDF-Tenofovir, NVP-Nevirapine, Lopinavir/R-Lopinavir/Ritonavir
ARV-anti-retroviral therapy PML-Progressive Multifocal Leukoencephalopathy, TB-Tuberculosis, RPR-Rapid Plasma Reagin, VRDL-Venereal Disease Research Laboratory

Table 2 shows that for patients with previous negative HIV screening test results (14% of the total patients), the median duration before converting to positive is 2 years (1-3 years IQR). Majority of patients are usually at the Stage IV of the disease or labeled as Acquired Immunodeficiency Syndrome during the time of initial visit (50%). About 44% of these patients were admitted with OI. The top three most commonly identified OI's were pulmonary tuberculosis (15%), Pneumocystis jerovicii Pneumonia or PCP (15%) and oral or esophageal Candidiasis (15). The most common OI affecting the central nervous system (CNS) was tuberculosis (2%). Nine percent of the patients had hepatitis B co-infection and only 1 had hepatitis C. Most common skin infection was Herpes Zoster (8%). Other infections were extrapulmonary TB tuberculosis [9%], syphilis (late latent or secondary, 4%) and cytomegalovirus (CMV) retinitis (1%). For patients with extrapulmonary TB, the gastrointestinal system was the most commonly affected site (5%). There was a significant difference observed between patients with good and poor outcome based on previous admissions (p value < 0.046), bacterial pneumonia (p value < 0.037) and fungal pneumonia (p value < 0.025). Patients with poor outcome have significantly higher rates of previous admissions (61% vs. 42%) and bacterial pneumonia (9% vs. 2%).

Most commonly used treatment regimen in MMC treatment hub was Lamivudine-Zidovudine-Efavirenz (61%). Most of the patients were compliant with only 5% non-compliant. About 17% of the patients developed rash while 1% developed jaundice. Nevirapine (8.2%) was the most common culprit of the rash while anti-tuberculosis therapy (0.7%) was the most common cause of jaundice.

After a year of ARV, 92% of patients with HIV have good outcome while 7.7% have poor outcome. Anti-retroviral therapy has significant effect on weight, CD4 and HIV viral load of HIV patients (Figure 3). Patients were mostly showing improvement in weight and levels of CD4

after a year of ARV. Viral load levels, on the other hand, were significantly declining after a year of ARV.

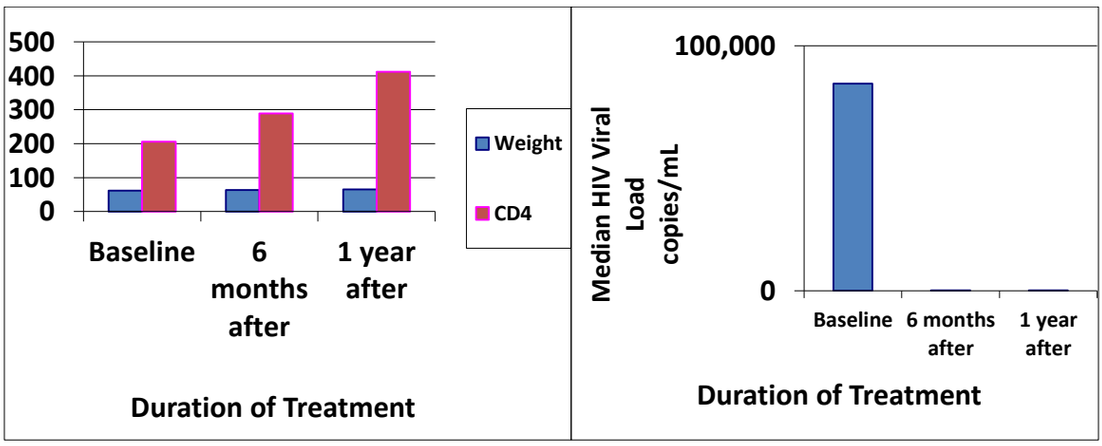


Figure 3. Effect of ARV on Weight and CD4 after a year of Treatment

In multivariate analysis adjusted for age, patients who were non-compliant (OR 7.79, 95% CI, 1.96-31.06, p value < 0.004, Table 3) and patients with CD4 count less than 200 (Stage IV) after a year of treatment (OR 3.61, 95% CI, 1.20-10.84, p value < 0.022, Table 4) were associated with increased risk of poor outcome.

Table 3. Predictors of good outcome among patients treated for HIV after a year from January 2006 to January 2014 (N=297)

Characteristics	Multivariate Analysis* OR (95% CI)	p value
Non-compliant	7.79 (1.96-31.06)	0.004
Present HIV Staging (Stage IV)	3.61 (1.20-10.84)	0.022

*Multivariate analysis adjusted to age. OR-Odds ratio, CI-confidence interval

DISCUSSIONS

Among patients who have been enrolled to ARV treatment in MMC treatment hub, we have found that a majority would have good outcome or undetectable viral load and clinical improvement (92%). High rates of good outcome would be because of low level resistance. The predictors of good outcome were found to be compliant patients (OR 7.79, 95% CI, 1.96-31.06, p value < 0.004) and patients with better HIV staging after a year of treatment (OR 3.61, 95% CI, 1.20-10.84, p value < 0.022). A study done in Melbourne, Victoria reported that hospitalization rates may be a useful marker of HIV disease in ARV treated populations and may identify groups at risk of poorer outcome and in need of intervention.[8] Moreover, in this cohort, this

was observed in the univariate analysis wherein there was a significant difference in the history of previous admissions between patients with good (42%) and poor outcome (61%), p value < 0.046. In India, HIV patients co-infected with tuberculosis were associated with poorer outcomes.[9] Co-infection with pulmonary tuberculosis was not significantly associated with poor outcome in this study (good outcome 15%, poor outcome 17%, p value < 0.755). The difference in the results might be due to the difference in the number of population, wherein 6,480 with TB-HIV co-infection were observed in the cohort study of India.[9] Even when pulmonary and extrapulmonary tuberculosis are combined in this study, the difference between good and poor outcome was still not significant (p value < 0.408). Similar study by Lapadula et al showed that higher CD4 counts before the start of ARV are associated with better prognosis.[10]

The CD4 count is the most significant laboratory indicator of immune status in HIV-infected patients. Based from clinical trials and cohort studies, CD4 count is also the strongest prognostic factor of subsequent disease progression and survival of patients with HIV.[11, 12] HIV viral load monitoring, on the other hand, is used to assess the efficacy of antiretroviral therapy.[13]

For this study, the survival rate of patients is 97%. The median CD4 increase is 206 cells/mm^3 after a year of ARV, while the HIV viral load reduction was on the undetectable levels after 6 months of ARV in a majority of cases. The patients in this cohort seem to have fared better in terms of mean increase in CD4and survival rate when compared with other cohorts. In an HIV cohort in Uganda, the survival rate was 56% after one year of treatment.[14] The median CD4 cell count increase was +55 cells/mm^3 with the median log viral load decrease of 1.4 copies/mL after a year of treatment.[15] Moreover, a cohort in India showed a mean increase of CD4 in between 104 and 174 after 6 months of ARV.[16] In Africa, 63% of people living with HIV had attain full HIV suppression after only a median of 3 years.[17]

This study was able to demonstrate improvement of patients on ARV through weight gain and increased CD4 count levels. Most of these patients were able to achieve suppression of HIV viral Load to undetectable levels after 1 year of treatment.

This study has several limitations. Being a retrospective study involving chart review, some data for the evaluated variables were missing since the out-patient charts were not standardized for research. One major limitation was that only 297 out of the 417 eligible population or only 71% of the population was evaluated in the study. The factors that lead to non-compliance to medications were not assessed.

Regardless of these limitations, this study provides a comprehensive evaluation of patient, disease and treatment for a cohort of 417 patients treated for HIV/AIDS. We were able to assess the effect of ARV on people living with HIV including the factors that would help in attaining a good outcome.

In conclusion, people living with HIV that are compliant on taking ARV and better HIV staging would probably have good outcome. The monitoring of CD4 count and HIV viral load is important in assessing the efficacy of ARV's. It is highly recommend that continuous monitoring of these patients be done and a more centralized data gathering would be implemented by the government. It is recommended that effect of treatment be evaluated by a longer duration beyond 1 year of treatment and that lost to follow-up patients be monitored.

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