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A Single Center Experience: Short Term CD4 Count Monitoring and Rate of Opportunistic Infections in Human Immunodeficiency Virus (HIV) Infected Patients

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Abstract **Background/Objectives:** CD4 cell count is a key measure of Human immunodeficiency virus (HIV) disease progression and for the risk of developing a life-threatening opportunistic infections (OIs). We designed this study to assess and monitor CD4 count at baseline and response to antiretroviral therapy (ART) at 6 and 12 months and to know the prevalence of OIs among all adult with HIV-infection in a tertiary care hospital in Saudi Arabia (SA). **Material/methods:** Retrospective study was conducted with a total of 61 HIV seropositive patients attended at King Abdulaziz Medical City-Riyadh from January 2005 to November 2015, data was collected and recorded form patients' charts, electronic health record system and HIV database for age, gender, nationality, CD4 count at baseline for all patients and at 6 months and 12 months for patients receiving ART and OIs. Flow cytometry was used for absolute CD4 count measurement. Identification of all causative microorganisms of OIs was performed by the standard microbiologic methods with clinical correlation. **Results:** Majority, 46/61(75.4%) of study participants were male patients. The mean age of participants was 44.39 with std of +/- 13.375 years. Mean baseline CD4 count for all study participants was 285.28 with std of +/- 306.333 cells/µL. Distribution of baseline CD4 count for all patients was, DC4 count less than 200 cells/µL were 34/61(55.7%), CD4 count from 200-500 cells/µL were 13/61(21.3%) and CD4 count more than 500 cells/µL were 14/61(23.0%). A total of 30/61 patients (49.2%) were not receiving ART and 31/61 patients (51.8%) were receiving ART. A total of 22/61 (36.1%) OIs were observed from the study participants. Commonly observed OIs were Cytomegalovirus (CMV) 14/61 (23.0%) (Positive IgG and IgM antibodies, pp65 antigen and PCR without clinical correlation), Tuberculosis 4/61(6.6%), pneumocystis pneumonia 2/61(3.3%) Toxoplasmosis 2/61(3.3%), Syphilis 2/61(3.3), varicella zoster virus (VZV) 1/61(1.6%), herpes simplex virus (HSV) 1/61 (1.6%). **Conclusions:** Half of HIV-infected patients 55.7% in this study were severely immunocompromised at the time of HIV diagnosis. Half of patients receiving ART were nonadherence to medications and 21% of patients had a poor immunologic response after one year of adherence to ART. One-third of our HIV-positive patients were infected with one or more OIs.

Keywords: *CD4 count, HIV, Opportunistic Infections, Saudi*

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1. Introduction

The most recent United Nations Programme on HIV and AIDS (UNAIDS) country progress report published in 2014 revealed that the incidence of HIV among Saudis has increased by 44% in 2013 compared to 2012 [14], however, the overall prevalence of HIV/AIDS is consistently low (< 0.2%). Since the first official case of HIV infection in SA was reported in 1984 in a blood transfusion recipient [22]. The cumulative number of all detected cases up to the end of 2013 was amounted to 20,539 cases, in 2013, 1,777 new AIDS cases were detected [23]. However, formal concerted activities related to HIV/AIDS were only launched after the inception of the National AIDS Program (NAP) as a directorate of the Public Health branch of the Ministry of Health in 1996 [15].

As known worldwide, CD4 count is a standard measure of immunodeficiency in adults infected with HIV and depletion of CD4 count is one of the hallmarks of progression of HIV infection [16]. The determination of CD4 count has become a standard measure of immunodeficiency in adults infected with HIV in resource-rich areas where the burden of the pandemic is low [16]. Observational cohort studies from Europe and North America showed that the initial response to ART treatment is strongly predictive of clinical progression [17,18]. In particular, both the HIV RNA level and the CD4 count at 6 months after treatment initiation were

independently associated with subsequent AIDS events and death either in treatment-naive or experienced Patients [17,18].

Patients who receive a late diagnosis, defined as a baseline CD4 cell count<200 cells/µl, have significantly poorer responses to ART and worse prognoses [5,6,7]. The proportion of patients who present late to diagnosis and treatment remains unacceptably high [8,9,10,11]. Although it is recommended that CD4 cell count testing should be carried out promptly after diagnosis, many patients fail to receive on-time testing [12]. After the diagnosis of HIV infection, timely CD4 cell count testing is a crucial step in determining whether the patient meets criteria for ART initiation and engaging the patient in appropriate care and treatment [16]. In the United States, an ongoing outpatient study in eight cities found that 78% of patients had a measured CD4 count within 3 months of HIV diagnosis [8] in developing countries, Studies in Thailand, Vietnam, and South Africa reported that only 34%, 49%, and 62.6% of patients, respectively, received CD4 count assessment with 6 months of HIV diagnosis [13,14,15].

Opportunistic infections (OIs) remain the single main cause of ill-health and death among HIV-infected patients [16] Research shows that about 90% of HIV-related morbidity and mortality are caused by opportunistic infections compared to 7% due to opportunistic cancers and 3% due to other causes (17). OIs such as *Pneumocystis jirovecii* pneumonia (PCP), cytomegalovirus (CMV), non-tuberculous mycobacteria (NTM), and fungal infections are frequently found in patients with AIDS [18]. The introduction of antiretroviral therapy (ART) has drastically changed the incidence of OIs in patients infected with HIV, resulting in a decline in mortality rates [19], but in the era of ART, OIs still occur and result in an increased risk of mortality among people with AIDS, the risk of OIs increases as the CD4+ count declines [20]. In a multi-centre study from France, among patients who died of AIDS events, 27% died of at least one OIs. In low and middle income countries (LMIC)there was a substantial decrease in the incidence of most OIs with ART use (from 60% to 95%), comparable to rates seen in Europe and North America, with yearly savings of at least 32 million dollars, excluding savings for pulmonary tuberculosis and toxoplasmosis which are likely considerable, according to WHO [3]. In study from SA, OIs rate in adult with HIV infection were found to be 49%, most commonly being pneumocysitis [17].

In background of very little information available with regard to HIV-1 infection and treatment outcome in Middle East countries including the Gulf Cooperation Council (GCC) states, this study was conducted to show the results of baseline CD4 count and to estimate the immunological statues of newly diagnosed HIV patients in tertiary care hospital in SA and also to know the outcome of monitoring CD4 count after 6 and 12 of ART, beside the rate of OIs.

2. Method

2.1. Ethics Statement

This study was approved by King Abdullah International Medical Research Centre at King Saud bin Abdulaziz University for Health Sciences, National Guard Health Affairs, Riyadh - SA, before starting data collection as the study does not disclose patient identity, and poses no risks to patients (Reference N. RC13/217).

2.2. Study Design and Analysis

Retrospective cohort study was conducted with a total of 61 HIV seropositive patients, all were adult with age of 19 years and older, attended at King Abdulaziz Medical City-Riyadh from January 2005 to November 2015. Data was collected and recorded form patients' charts, electronic health record system and HIV data base for age, gender, nationality,CD4 count and OIs among all participants.

CD4 count was measured at baseline for all study participants and measured after 6 a 12 months for 14 patients showed adherence to ART. Flow cytometry was used for absolute CD4 count measurement. Identification of all causative microorganisms of OIs was performed by the standard microbiologic methods. Diagnosis of mycobacteria was done using different methods, including (Culture,Zeihl-Neelsen (ZN) stain and TB PCR), Cytomegalovirus (CMV) was determined by detection of CMV IgG and IgM antibodies, CMV pp65 antigenemia and CMV RNA by PCR, broncho-alveolar lavage was tested for the presence of Pneumocystis jirovecii (PCP) by a direct antigen detection test when clinically indicated using immunofluorescence method. Toxoplasma gondii was determined by detection of IgG and IgM antibodies, Varicella Zoster (VZV) was detected by using DFA (Direct Florescent Antibody test) and viral culture, serology and PCR were used for Herpes Simplex Virus (HSV) detection. CMIA (Chemiluminescent Microparticle Immunoassay) and FTA-ABS were used for detection of Syphilis. All previous microbiology tests were done in correlation with clinical condition of patients. all obtained data was analyzed by using SPSS analytic system.

KAMC-Riyadh is a distinguished healthcare provider in Saudi Arabia as apart of National Guard Health Affair, with a capacity of more than 800 beds located in Riyadh city.

3. Results

Majority, 46/61(75.4%) of study participants were male patients. The mean age of participants was 44.39 with std of +/- 13.375 years, 57/61 (93.4%) were Saudi and 4/61(6.6 %) were non- Saudi. Mean baseline CD4 count for all study participants was 285.28 with std of +/- 306.333 cells/µL. Distribution of baseline CD4 count for all patients was, CD4 count less than 200 cells/µL was 34/61(55.7%), CD4 count from 200-500 cells/µL was 13/61(21.3%) and CD4 count more than 500 cells/µL was 14/61(23.0%) (Table 1) (Figure 1).

Gender distribution for baseline CD4 count was as, male patients with CD4 count less than 200 cells/µL was 28/61 (45.9%), CD4 count 200 to 500 cells/µL was 9/61(14.8%) and CD4 count more than 500 cells/µL was 9/61(14.8%).Baseline CD4 count for female was, CD4 count less than 200 cells/µL was 6/61 (9.8%), CD4 count 200 to 500 cells/µL was 4/61(6.6%) and CD4 count more than 500 cells/µL was 5/61(8.2%) (Table 1) (Figure 1).

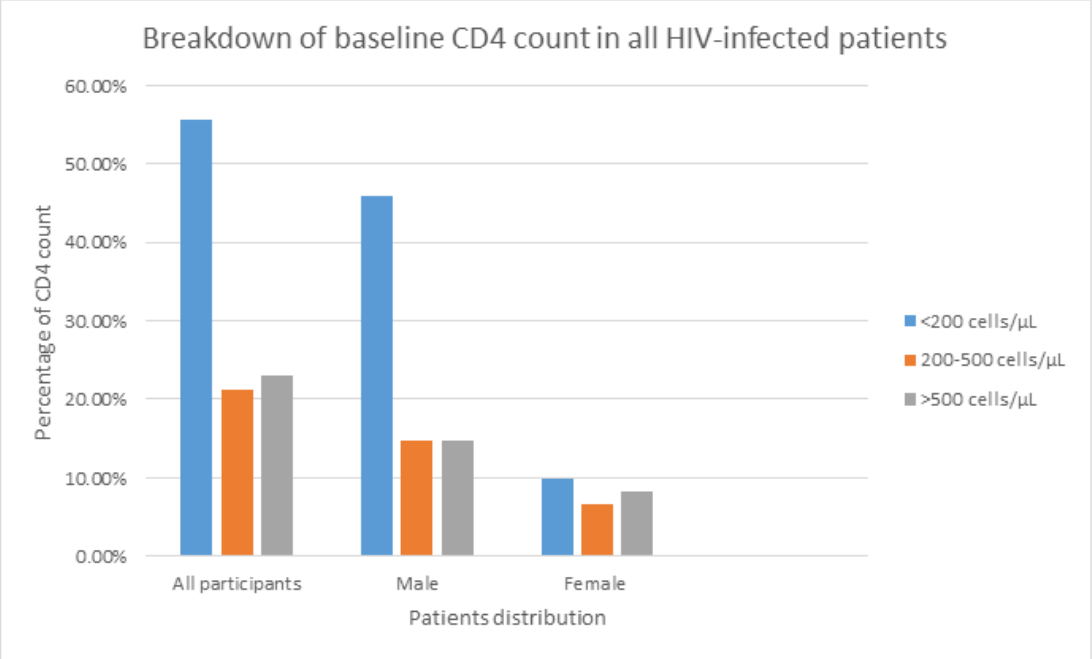

Figure 1. Baseline CD4 count distribution among all HIV infected patients and gender involvement

Table 1. General characteristics of study participations

Characters	Number/Percentage	Number/Percentage
Gender	**Male**	**Female**
Baseline CD4 count	46/61(75.4%)	15/61(24.6%)
<200 cells/µL	28/61 (45.9%)	6/61(9.8%)
200-500 cells/µL	9/61(14.8%)	4/61(6.6%)
>500 cells/Ml	9/61(14.8%)	5/61(8.2%)
Opportunistic Infections		
Positive 22/61 (36.1%)	16/22(72.7%)	6/22(27.3%)
Negative 39/61 (63.9%)	30/39(76.9%)	9/39(23.1%)
Adherence to ART	8/14(57.1%)	6/14(42.9%)

A total of 30/61 patients (49.2%) were not receiving ART and 31/61 patients (51.8%) were receiving ART. 14/31patients (45.2%) showed adherence to ART and 17/31 patients (54.8%) were nonadherence to ART. CD4 count follow-up for patients showed adherence to ART (baseline, after 6months and 12 months) was as, CD4 count less than 200 cells/µL was 7/14 (50%),4/14(28.6%) and 3/14(21.4%) respectively, DC4 count 200-350 cells/µL was 3/14(21.4%),3/14(21.4)and 2/14(14.3%) respectively, CD4 count 350-500 cells/µL was 2/14(14.3%),2/14(14.3%),and 2/14(14.3%) respectively and DC4 count more than 500 cells/µL was 2/14(14.3%),5/14(35.7%) and 7/14(50%) respectively (Figure 2).

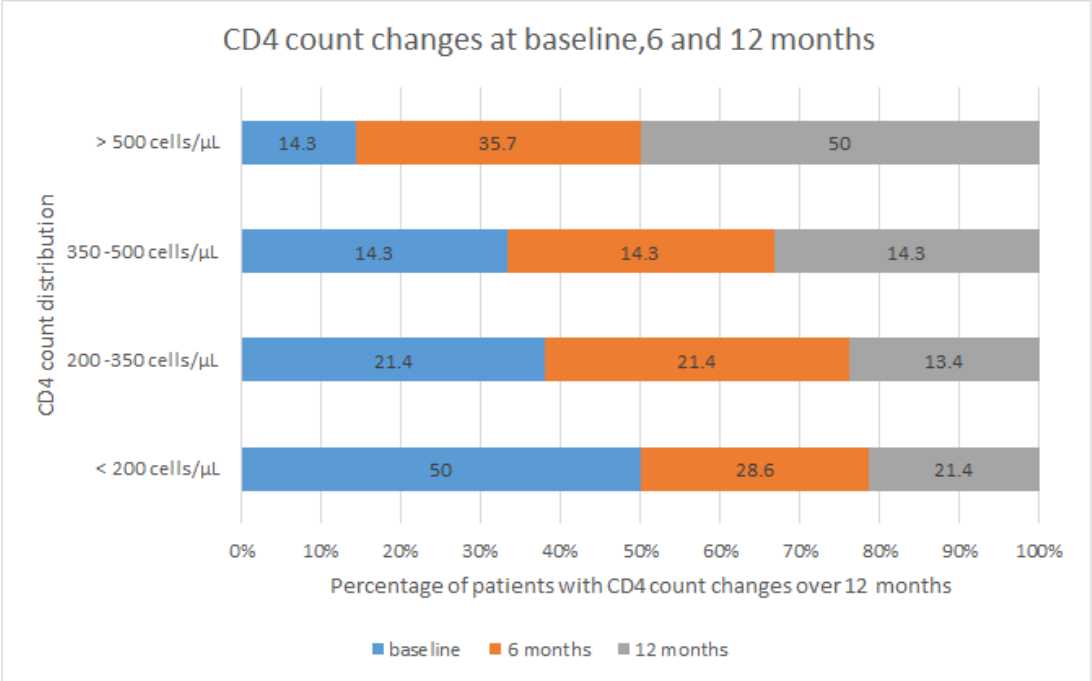

Figure 2. shows CD4 dynamics over the time period of one year for patients receiving ART

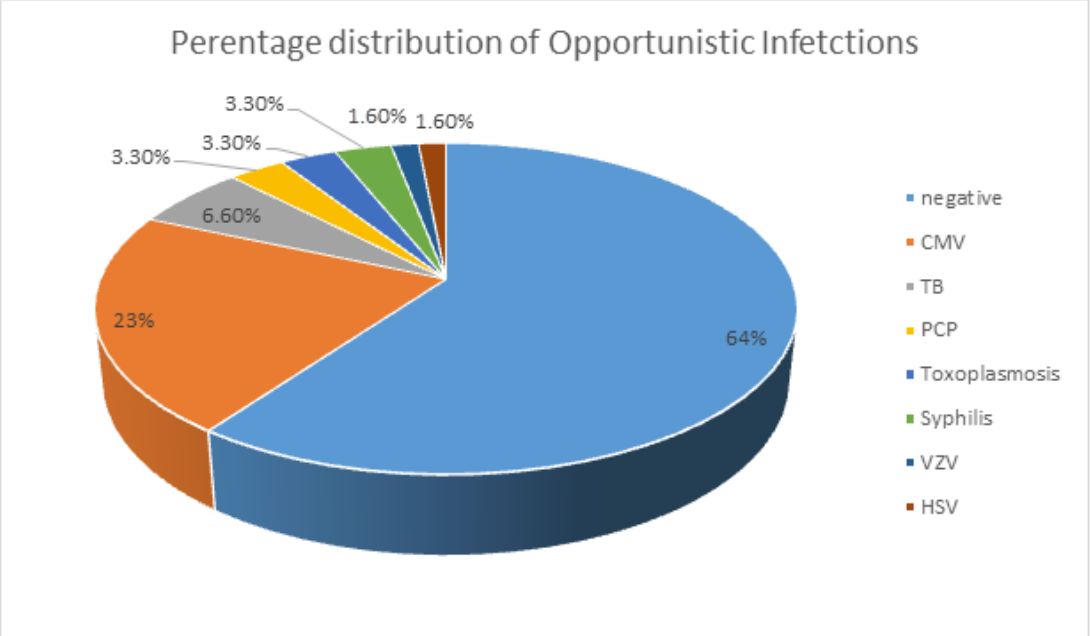

Figure 3. Distribution of Opportunistic Infections among all HIV seropositive patients

Mean baseline CD4 count for patients with adherence to ART 14/31patients (45.2%) was 242.7 cells/µL with std. 316.15221, mean CD4 count after 6 months was 378.2 cells/µL with std. 243.6864 and mean CD4 after 12 months was 427 cells/µL with std. 262.9314.Female with adherent to ART were 6/14(42.9%) and male 8/14(57.1%), mean CD4 count for female baseline, after 6 months and 12 months was 389.83, 477.5, 557.5 cells/µL with std. 420.0288, 223.3774 and 248.1481 respectively, CD4 count for male with adherence to ART baseline, after 6 months and 12 months was 132.4, 303.8 and 365 cells/µL with std. 164.7491, 244.6535 and 266.9403 respectively (Figure 4).

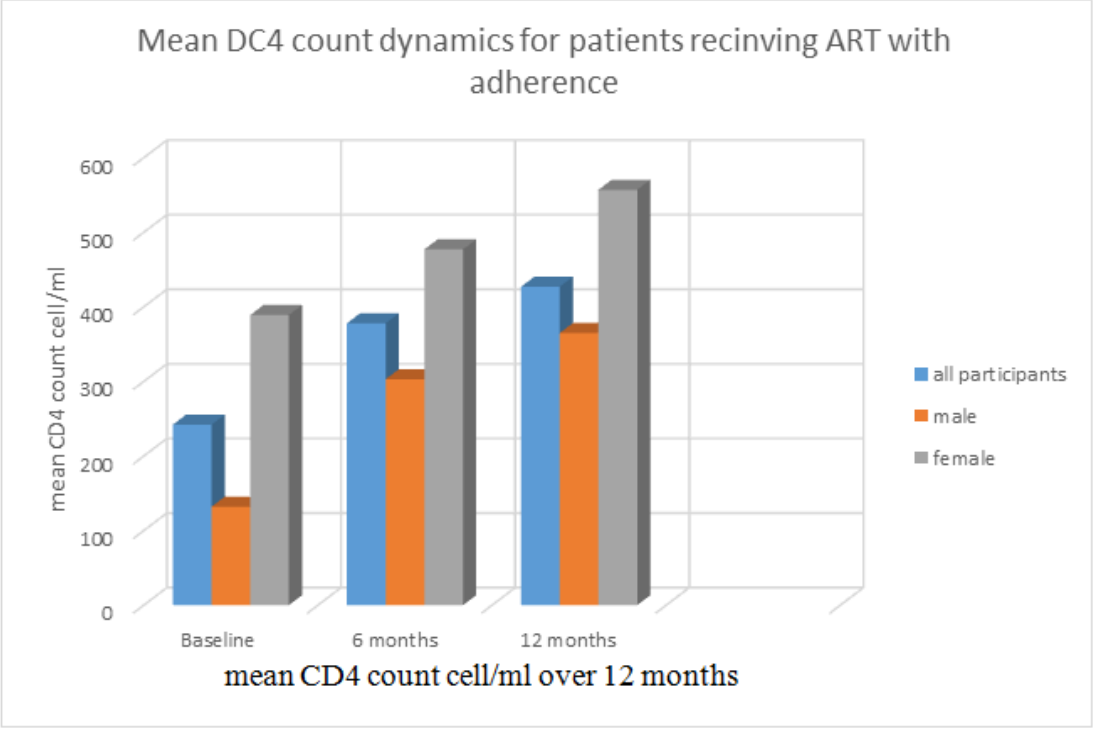

Figure 4. shows mean CD count changes over 12 months for patients with adherence to ART

A total of 22/61 (36.1%) OIs were observed from the study participants. Commonly observed OIs were Cytomegalovirus (CMV) 14/61 (23.0%) (Positive IgG and IgM antibodies, pp65 antigen and PCR without clinical correlation), Tuberculosis 4/61(6.6%)(culture showed growth of three of a typical mycobacterium (Mycobacterium avium, mycobacterium riyadhense, and mycobacterium intracellulare and one patients with mycobacterium tuberculosis), pneumocystis pneumonia 2/61(3.3%) Toxoplasmosis (Tow patients with central nervous system (CNS) toxoplasmosis) 2/61(3.3%), Syphilis 2/61(3.3), varicella zoster virus (VZV) 1/61(1.6%), herpes simplex virus (HSV) 1/61 (1.6%) (Table 1) (Figure 3).

4. Discussion

In high-income settings HIV-positive patients in regard to ART they receive individualized care. Treating clinicians use routine plasma HIV viral-load measurements and CD4 cell counts every 3–6 months to monitor the efficacy of personalized initial regimens and to trigger ART changes [4,5]. In low and middle income countries, most HIV patients receive ART through the public sector, on the basis of standardized first-line treatment regimens, with little laboratory monitoring to identify failure and trigger switches to second-line ART [4,5]. According to the 2013 World Development Report, the SA is considered a high-income country. By law, ART should be available free of charge. However, options for treating affected patients are still limited [12]. There is scarce published data on the use of ART in the SA. Presently, there are no agreed-upon national treatment guidelines; the international guidelines are presumably being used, *albeit on an ad hoc basis*. Therefore, clinical practice is likely to be diverse due to the lack of agreed-upon national or local treatment standards [12,13]. According to WHO guideline on *when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV* published in September 2015,ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence) [28].

In Our study mean baseline CD4 count for all study participants was 285 cells/μL, we found more than half of HIV infected patients 34/61(55.7%), were severely immunocompromised with low level of baseline DC4 count (less than 200 cells/μL) at the time of diagnoses with HIV, which put them at high risk of developing a life-threatening OIs and also it means likely there is a late diagnosis of disease. Mean baseline CD4 count in this study is lower in compare to local study, the mean CD4 count at the time of diagnosis was 350 cells/μL [1], in other study from SA, 977 patients living with HIV 274 (28.3%) had a baseline CD4 count of < 200 cells/μL and fifty per cent of cases had a baseline CD4 count of < 350 cells/μL [16]. Among 388,496 newly identified HIV cases, the median baseline CD4 count was 294 cells/μl and over half (N=130,442, 58.8%) were less than 350 cells/μl [6]. Of the 103 newly diagnosed adults the median CD4 cell count at the time of diagnosis was 183/μL; 52 of 103 adults (50.5%) with a newly diagnosed HIV infection had a CD4 cell count that was <200 [7]. In our patients receiving ART adherence rate was 45.2%, there is no local data from SA regarding adherence to ART in adult. Ffifty-one studies published between 1999 and 2013 worldwide reported adherence rates for 10,725 patients in 53 countries, adherence was estimated at 62% (95% CI, 57–68; I^2, 97%) overall and this varied by region as it was lowest in North America (53%) and highest in Africa and Asia (84%) [8,9,10,11], studies conducted after 2005 showed higher adherence rate (74%) than conducted pre-2005 (59%) [8].

Mean CD4 for all HIV infected patients in this study showed improvement after starting of ART (baseline, after 6 months and 12 months was 242,378 and 427 cells/μL respectively). Mean baseline DC4 count was more higher in female than male patients 389 and 132 cells/μL respectively, but immunological recovery was more better among male than female patients after one year of ART as 174.4% vs 43.2% respectively (baseline, after 6 months and after 12 months was132, 303,365 cells/μL and 389, 477, 557 cells/μL and for male and female respectively). But 3/14 (21.4%) patients failed to achieved immunological recovery despite ART for 12 months with CD4 count less than 200 cells/μL also 2/14(14.3%) patients with CD4 count 200-350 cells/μL. The relationship between male/female and HIV-1 disease progression has been investigated for decades and sex differences significantly impacts the clinical, virological and immunological responses in patients initiating ART [2]. There are remarkably discrepant results in the literature about the course of immunological, virological and clinical parameters according to sex, Some studies have found higher CD4 cell counts in women, other found higher CD4 cell counts in men, well as greater increases in CD4 cell counts following ART in women or no differences with men [24,25,26,27]. In another study by Collazos et al., HIV-1-infected women who were receiving ART had better immunological response to therapy and hence higher CD4+ T-cell counts and lower rate of clinical progression to AIDS/death compared to men [2].

In our study an overall OIs was 36.1% among participants through ten years period from January 2005 to November 2015, which is low relatively and showed some decline in the rate of in compared to other Saudi study, OIs were found in 49% of patients [1], which was the only Saudi study described OIs in HIV positive patients among a cohort of Saudi national HIV-infected patients receiving their care in SA, that till November 2014 [1] in our study the top OIs was Cytomegalovirus (CMV) (23.0%) (positive serology, pp65 antgenimia and CMV RNA PRC without clinical correlation), followed by Tuberculosis (6.6%) as the commonest OIs, in compare to Pneumocystis jirovecii pneumonia (PCP) as the most frequently diagnosed OIs (27%) followed by Candida (25%), Mycobacterium tuberculosis (MTB) and cytomegalovirus (CMV) infections was (16%) in mentioned study over 20 years period from 1989 to 2010 [1]. In recent study from Bahrein, Infection with Staphylococcus aureus was the commonest infection, present in 9.8% of total HIV-infected patients and 28.7% of members of the AIDS patient group with OIs, followed by yeast infections (9.2% and 27.2%, respectively) [21]. Mycobacterium tuberculosis was present in 3.6% of total HIV-infected patients and 10.6% of the group with OIs, while mycobacteria other than tuberculosis (MOTT) was present in 2.5% and 7.5%, respectively. PCP was observed in 5.1% and 15.1%, respectively. Herpes simplex II (HSV-II) was observed in 3% and 9%, respectively, while Cytomegalovirus antigenemia was only present in 2% and 6%, respectively [21].

This study revealed advance disease and showed critical immunocompromised state of half of newly diagnosed HIV patients in a tertiary care hospital in SA in last ten years, beside poor adherence to ART, which raised many questions regarding clinical practise, screening and care of HIV infected patients.

5. Conclusions

Half of HIV-infected patients (55.7%) in this study were severely immunocompromised with relatively

advanced disease at the time of HIV diagnosis. Half of patients receiving ART were nonadherence to medications and 21% of patients who receiving ART had a poor immunologic response after one year of adherence to therapy. One-third of our HIV-positive patients were infected with one or more OIs. Findings will encourage health care workers to improve practice of early diagnosis and treatment of HIV and OIs and possible prophylaxis and also to increase patient's awareness regarding adherence to ART in order to improve quality and expectancy of life.

Limitations of Study

This study has a limitations of small sample size and being only descriptive of an original data.

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