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Research Article

RESPONSE TO ANTIRETROVIRAL THERAPY (ART) IN HIV POSITIVE PATIENTS WITHOUT INITIAL OPPORTUNISTIC INFECTION

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ABSTRACT

Aim of study: To evaluate clinical and immunological response after starting antiretroviral therapy (ART) in HIV positive patients without initial active opportunistic infections and to look for unmasking type of IRIS cases.
Study design: continuous, longitudinal, prospective cohort, comparative study.
Place of study: ART centre, New Civil Hospital, Surat.
Methodology: Each patient was observed for 6 months from January 2009 to July 2010. The patients who are more than 15 year of age, ART Naïve, who were eligible according to NACO guidelines (2008)[1] to ART were included in the study. Patients who lost follow up; stopped treatment during study and who had active opportunistic infections at start of ART were excluded. Each patient is followed up for 6 month duration. Patients were regularly followed up as on given date& time, for total 5 visits. CD4 count is repeated after six months except for suspected cases of IRIS.
Results: The mean age of study population was 36.37 yrs & male to female ratio was 64:36 and 81% were married, 13% widowed, 70% were from Surat district . Mode of transmission was heterosexual in all patients. ZLN- *Zidovudine (ZDV) + lamivudine (LMV) + nevirapine (NVP)* , was started in 90 patients initially and SLN- *Stavudine(STV) + lamivudine (LMV) + nevirapine(NVP),* in 10 patients, 19 Patients out of 90 of ZLN develop anaemia during follow up (21.1%). ART therapy was effective for WHO stage I, II &III, functional status W (working) & A (ambulatory). Least effective in WHO stage IV and functional status B (bedridden). Weight gain was observed in 80.2 % of patients .Candidiasis was most common opportunistic infection observed.CD4 count increased in 94.6% of cases. Unmasking form of IRIS was observed in total 4 patients, 3 died (2 have Tuberculosis and 1 had Toxoplasmosis), and 1patient with tuberculosis survives. Mortality was 6.2% cases. Total 6 patients expired, 3 lost to follow up, 3 patients had their CD4 count decreased and 2 had no change, in rest of patients CD4 count increased. A good level of adherence was seen, only 3% cases lost to follow up.
Conclusion: Significant improvement observed which is correlating with other studies nationally and internationally.

INTRODUCTION

The first HIV positive case in India was detected from Chennai in 1986, and since then HIV infection has been reported from all over India. Initially HIV was considered death sentence but with advent of ART (antiretroviral treatment) medicines, it has become a chronic manageable disease like diabetes and hypertension. It has significantly reduced morbidity and mortality in developed and developing countries.[2,3,4,5] *Ideally ART should be given to all patients with HIV irrespective of their CD4 count and other related problems as it is an infective state, and eradication of this infection from the body should be the target. Since its burden is very high in low income countries, it would not be cost effective to treat all cases.* In

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India National AIDS Control Organisation (NACO), has launched National ART programme on 1 April 2004 as an initiative of the Ministry of Health and Family Welfare of the Government of India.

Aim of Study

1. To study demographic profile of HIV in south Gujarat.
2. To study changes in clinical stage, functional stage, weight gain and opportunistic infections after starting antiretroviral therapy.
3. To study change in CD4 count and unmasking of immune reconstitution inflammatory response syndrome (IRIS) to antiretroviral therapy.

MATERIAL AND METHODS

Study design: continuous, longitudinal, prospective cohort, comparative study.

Place and duration of study: ART centre, New Civil Hospital, Surat, for one and half year.

Inclusion criteria

1. Age more than 15 year
2. Patients who are eligible for starting ART according to NACO guidelines 2008.
3. ART Naïve Patient.
4. Patient who gave informed consent wilfully to take part in the study.

Exclusion criteria

1. Patient transferred to other centre/ lost to follow up/stopped treatment.
2. Patient not eligible for ART therapy.
3. Patient already taking ART.
4. Patients with active TB & other opportunistic infections at start of ART.

Ethical approval was taken from human research ethics committee, Govt Medical College Surat. Pre ART counselling by professional counsellor in different session was carried out before starting therapy. The regimen consisted of two nucleoside reverse transcriptase inhibitors (Lamivudine, Zidovudine or Stavudine) and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). The medications were dispensed directly to the patients or their authorized representatives. *Minimum 6 month follow up was done for every patient on given date & time at 0 day -15day-1month-3month - 6 months.* During each visit, patients were evaluated for drug toxicity, clinical improvement, weight gain and opportunistic infections .*WHO clinical staging and Functional WAB stage (W-working=able to perform usual work in or out of the house and do normal activities. A-ambulatory= able to perform activities of daily living but not able to work. B-bedridden=not able to perform activities of daily living) were compared at 6 month .CD4 count was repeated after six months except in case of suspected IRIS .* Adherence was assessed during each visit by pill count, and, through counselling, patients were motivated to adhere to therapy.

OBSERVATION AND RESULTS

A total of 100 ART naïve patients were enrolled into the study with each patient followed up for 6 months the ART centre, new civil hospital Surat.

Table-1 Gender wise distribution of patients

Gender	Male	Female
Number	64%	36%

Among 100 cases, there was male predominance with 64% of cases &female were 36%.Thus in our study male have high prevalence.

Table-2 Age wise distribution of patients

Age Group	15yrs-20 yrs	21yrs-30 yrs	31yrs-40 yrs	41yrs-50 yrs	>51yrs
Number of patients	4%	24%	49%	17%	6%

The maximum number of patients in our study is in 31-40 yrs age group (49%) followed by 21-30 age group (24%).In sexually active age group (15-49 years) 94% of patients are affected.

Table-3 District wise distribution of patients

Area	Surat	Outside Surat	Total
Number	70%	30%	100

Among 100 patients 70% were from Surat district & 30% from outside Surat from Valsad (10) ,Navsari (9) , Bharuch (4), Selvas (2), Daman(1),Viyara(1),Mahua(1),Tapi(1), Vapi(1) districts of south Gujarat.

Table-4 Marital status of patients

Marital status	Married	Unmarried	Widowed	Divorced	Total
Total	81%	5%	13%	1%	100

Maximum patients in our study are married (81%) followed by widowed (13%).

Anaemia (Hb<8gm %) at start of study was present in 10 cases (4 males and 6 females).

Females were having more anaemia at start of ART in our study; the mean Hb level in our study is 10.63mg% at start of study.

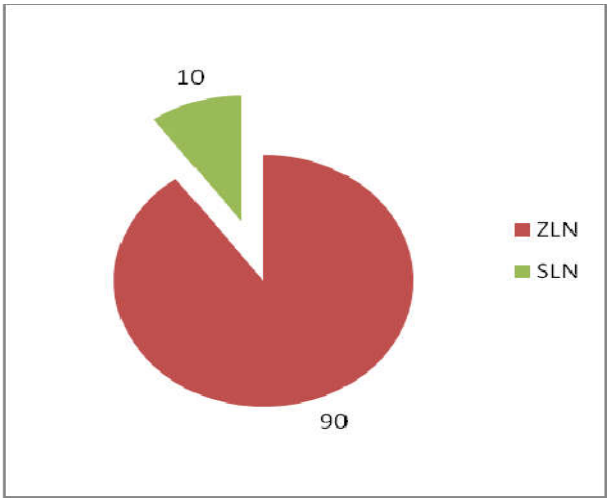

Image-1 Initial ART regimen of patients

* *ZLN*- Zidovudine(ZDV) + lamivudine (LMV) + nevirapine(NVP), *SLN*- Stavudine(STV) + lamivudine (LMV) + nevirapine(NVP)

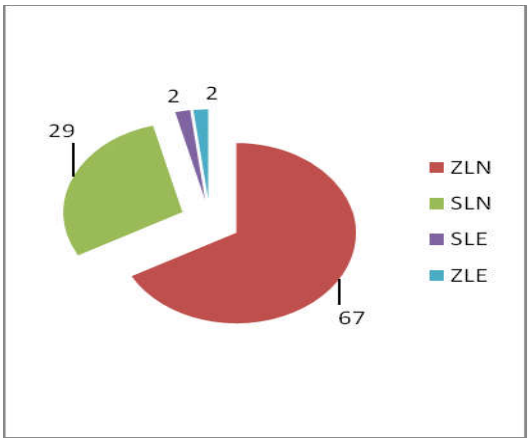

Image-2 ART regimen changed during follow up:

Out of 100 patients 10 patients were started on SLN(Stavudine, lamivudine and nevirapine) due to anaemia at baseline and 90 patients started on zidovudine based therapy , of which 19 patients developed zidovudine induced anaemia , so shifted to Stavudine based therapy. One patient developed Nevirapine induced SJS (Stevens Johnson Syndrome). *Nevirapine replaced with efavirenz in 3 patients who developed tuberculosis during the study, one patient of tuberculosis was also had anemia.*

* *ZLN*- Zidovudine(ZDV) + lamivudine (LMV) + nevirapine(NVP),
SLN- Stavudine(STV) + lamivudine (LMV) + nevirapine(NVP),
SLE- Stavudine(STV) + lamivudine (LMV) + efavirenz(EFV),
ZLE- Zidovudine(ZDV) + lamivudine (LMV) + efavirenz(EFV)

Table-5- Opportunistic infection

Opportunistic infection developed during follow up period	Number of patients
Candidiasis(C)	8
Tuberculosis(TB)	3
Diarrhoea(D)	3
Upper respiratory tract infections	2
Herpes zoster(Z)	2
Toxoplasmosis(T)	1

In our study during follow up period candidiasis was found to be the most common opportunistic infection followed by Tuberculosis & Diarrhoea.

Table-6 Comparision of WHO stage of patients at start and at 6 month

WHO stage	1	2	3	4
At start	15%	46%	28%	11%
At 6 month	68.10%	26.40%	4.40%	1.10%

In our study maximum numbers of patients were in WHO stage II at time of inclusion into the study followed by stage III, stage I & least in stage IV. After 6 months maximum patients were in WHO stage I followed by stage II &stage III, which indicates improvement in WHO stage.

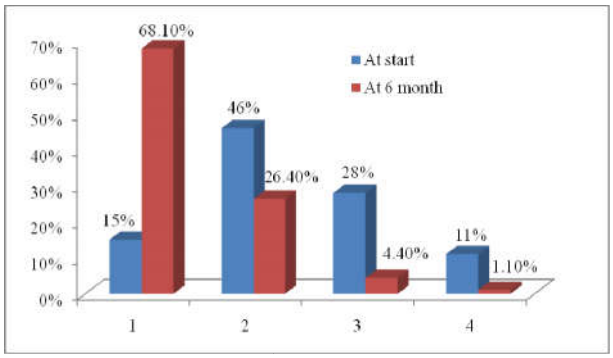

Image-3-Pictorial comparison of WHO stage of patients at start and at 6 month

Table-7 Comparision of functional (WAB) stage of patients at start and at 6 month

WAB stage	Working(W)	Ambulatory(A)	Bedridden(B)
At start	79%	17%	4%
At 6 month	96.7%	3.3%	0

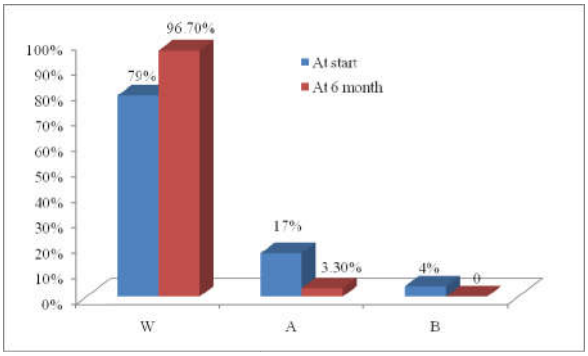

Image-4-Pictorial comparison of functional stage of patients at start and at 6 month

There was a marked improvement in functional (WAB) stage as shown in table 9. At time of enrolment into the study maximum numbers of patients were in W-working functional stage (79%) followed by A-ambulatory functional stage (17%) & least in B-bedridden functional stage (4%). After 6 months (96.7%) were in W-working functional stage followed by A-ambulatory functional stage (3.3%) indicate improvement in stage. There was no patient in B-bedridden functional stage after 6 months.

Table-8 Comparasion of weight at 0 day and 6 months

Wt gain	Total increase	No change	Decreased	Total
Total	73(80.2%)	10(11%)	8(8.8%)	91*

* 9Expired/lost to follow up

There is improvement in weight in 80.2%of patients in our study at 6 months

Table-9 Changes in CD4 count during study

CD4 % Increase	Total increase	No change	Decreased	Total
Total	86(94.6%)	2(2.2%)	3(3.3%)	91*

* Expired/lost to follow up

There is improvement in CD4 count in 94.5% of patients in our study at 6 months. At 6 months out of 91 patients 3 patients had their CD4 count decreased and 2 had no change.

Table-10 Comparision of CD4 count increase

CD4 count Increase	>50 cells/µL	<50 cells/µL	Total*
Total	72(83.7%)	14(16.3%)	86

*6 expired, 3 lost to follow up, *3 patients had their CD4 count decreased and 2 had no change.

Increase in CD4count by more than 50 found in 83.7% of patients in our study.

Table-11-IRIS cases found during study and their clinical profile

IRIS	Alive	Dead
Total(4)	1	3

Table-12WHO stage of IRIS patients

WHO stage	II and III	I	IV
Number of IRIS patients	0	1	3

Table-13 Functional stage of IRIS patients

Functional stage	Working	Ambulatory	Bedridden
Number of IRIS patients	2	1	1

Table-14 Opportunistic infections presentation of IRIS patients

Opportunistic infection	Tuberculosis	Fungal -Toxoplasmosis & Candidiasis
Number of IRIS patients	3	1

In our study Unmasking IRIS was observed in total 4 patient, 3 died within 2 months of start of ART (2 Tuberculosis, 1 Toxoplasmosis), 1 survive (Tuberculosis).All who died were in advanced WHO stage IV & vary low CD4 count at start & one who survived had WHO stage I & CD4 count high at the baseline. All the patients who died of IRIS did not show any weight gain during study in spite of improvement in CD4 count.

Table-15 Survival of patients at 6 month

Survival	Alive at 6 month	Death at 6 month
Present study(n=97*)	93.8%	6.2%

*3 lost to follow up

Mortality at 6 month in our study was 6.2% whereas 93.8% were alive at 6 month.

Table-16 Mortality and cause of death during study

Cause of death	Tuberculosis	Toxoplasmosis	Not known
Total	2	1	3

Total 6 patients expired in our study. Out of 3 patients 2 were expired due to tuberculosis & 1 due to Toxoplasmosis. They were also had IRIS & their CD4count at start of study was very low. In expired patients cause of death cannot be traced in 3 patients as most of death occurred at home & exact cause cannot be ascertained by telephone. We could not visit patient, home as home visit was not allowed by patient & their care taker because of social stigma associated with HIV. Most of patients who expired were in WHO stage IV & Functional stage B at the start of study.

DISCUSSION

Demographic profile

The male predominance noted with male 64% and females 36%, which is comparable to study conducted by *SK Sharma et al*[6], Nayak *et al*[7], NACO[8] annual report 2011-12, Ahmad *et al*[9], and Singh *et al*[10] but contradict Lowrance *et al*[11] study. Possibility of gender bias in health-seeking behaviour and ignorance of females in India may be the cause for high male predominance in various Indian studies. Worldwide, women constitute more than half of all people living with HIV/AIDS[12]. Women are at least twice more likely to acquire HIV from men during sexual intercourse than vice versa[12]. Among young people aged 15-24, the HIV prevalence rate for young women is twice that of young men. WHO has tried to overcome this bias by focusing on pregnant females in recent guidelines[13].

Majority of patients was married (81%) which is comparable to Jayarama[14] (70.3%) and Nayak *et al* (75.49%).Out of 100 patients 70% patients were from Surat district, other patients were from Navsari, Valsad ,Vapi, Bharuch, Tapi, Daman .Surat is a cosmopolitan city with large number of immigrant population as compared to other districts of south Gujarat. Living away from the family has been reported to be an independent predictor of HIV acquisition in men[15]. Surat is one of such area where migrants are in large number. Special efforts should be made by policy makers to address the question pertaining to migrants.

Mean age in our study is 36.4 years which is comparable to study by Sharma *et al* (36 years) from India & *Lowrance et al* (37 yrs) from Rwanda. The maximum number of patients in our study is in 31-40 yrs age group (49%) followed by 21-30 age group (24%).The same age group is predominant in the study by Sharma *et al* (31-40 age group=47%) & study *by Nayak et al* (31-40 age group=51.5%). These finding suggest that this age group (31-40 yrs) is most affected with HIV in India & outside India. *This age group is the main earning group and in this age most of patients migrates to factory or dense areas for earning and thus may have contacted the infection there.* And overall from 15 – 49 group of age, 94% are the affected persons in present study, which is the predominant sexually active group; these results are comparable with Nayak *et al* (90.2%) and NACO annual report 2011-12(83%).

Mode of transmission

Mode of transmission was heterosexual in all patients, which is comparable to Gupta[16] (97%) and Kothari[17], Nayak *et al* (94.12%) and Sharma *et al* (86%). IV drug abuse & homosexuality not seen in our study, this may be due to the reluctance to give true history of such practices due to social factors in India.

Opportunistic infections (OI)

Out of 100 cases, candidiasis (3.9%) is most common opportunistic infections observed followed by Tuberculosis (0.8%) & Diarrhoea (0.8%) in our study.

In the study conducted by Nayak *et al* oral candidiasis (66.7%) was the commonest opportunistic infection followed by tuberculosis (22.54%, in study by Deshpande *et al*[18], tuberculosis(62%) was most common, in study by Chakravarty

et al[19], tuberculosis(38.8%) most common followed by, candidiasis(20.3%) and diarrhoea (12.7%) was seen. Our study differ in percentage from these studies because we have excluded all the active TB and other opportunistic infections at start of study.

Regimen

Out of 100 cases ZLN- Zidovudine *(*ZDV) + Lamivudine (LMV) + Nevirapine (NVP) *regimen was started in 90% of patients of which 19 patients develop anemia so regimen was changed to SLN-* Stavudine (STV) + Lamivudine (LMV) + Nevirapine *(*NVP. *SLN was started in 10% of patients as 10 patents had anemia (6 females and 4 males) at start of study. As we had excluded all active opportunistic infections and tuberculosis at start, so efavirenz (EFV) based therapy not started at the beginning of study. Nevirapine (NVP) replaced with efavirenz (EFV) in 3 patients who developed tuberculosis during the study* Females were have more anaemia at start of ART in our study and Mean Hb level in our study is 10.63mg% which is comparable to study by Sharma *et al*. *Anaemia developed in 19 Patients out of 90 who were started on ZLN during follow up (21.11%) in the study, which is comparable to Nayak et al(30.37%), Rajesh R et al*[20] *(35.54%), and Aggarwal et al*[21] *(16.2%).one patient (1%) developed Nevirapine induced Steven Johnson Syndrome which is comparable to Nayak et al study(2.94%).*

WHO clinical stage

Initially patients with severe form of WHO Stage IV was 11% (31% in Sharma *et al* study, 17.64% in Nayak *et al*), WHO Stage III was 28% (51% in Sharma *et al*, 48.03% in Nayak *et al*,) WHO Stage II was 46% (5% in Sharma *et al*, 20.58% in Nayak *et al*), WHO Stage I was 15% (13% in Sharma *et al* and 13.72% in Nayak *et al*).

In our study 11% were in stage IV, 28% were in stage III, 46% were in stage II and rest 15%were in stage I, which were different from study done by Sharma *et al*, Nayak *et al*, because of different inclusion criteria used, we had ruled out active opportunistic infections at start, therefore patients with stage IV were less. In our study WHO stage at 6 month was consistently improved as shown in tables.

Improvement in WHO stages was as follows, stage IV (11% initial improved to 1% at 6 months), stage III (28% improved to 4% at 6 months), Stage II (46% improved to 24% at 6 months), stage I (15% improved to 62% at 6 months).

We conclude that ART is effective in all clinical stages.

Functional stage

Initially severe form of functional status Bedridden(B) was 4% 6 month it improved to 0%,initial functional stage Ambulatory(A) was 17% after 6 month it improved to 3.3%, initial functional stage working(W) was 79% after 6 month it improved to 96.7%.

In our study, most of the patients by the end of 6 months of ART therapy most patients became working and most of patients with functional status B died inspite of ART therapy. We did not find any comparative study showing functional stage outcome. Overall functional stage improved.

Weight

Weight gain was observed in 80.2% of patients which is quite comparable to study by Sharma *et al*, 61% patients with weight gain at 6 months. Average weight at start in our study was 47.37kg & at 6 months was 51.3kg. Average weight in Sharma *et al* study was 50 kg at start & 57.5 kg after 6 months. Mean weight gain in 6 months in our study is 4.8 kg which is 7.5 kg in study by Sharma *et al* at 6 months & 6.7kg at 6 months in study by Lowrance *et al* at Rwanda. These findings are quite comparable & show improvement in weight with ART.

Immunological changes

ART is effective in restoration of immunological status as there is increase in CD4 count in 94.6% of patients, which is quite comparable to study by Sharma et al in which improvement in CD4 count was seen in 96% of patients at 6 months.

Increase in CD4count by more than 50 cells/µL found in 83.7% of patients in our study which is quite comparable to study by Gautam H& Bhalla P (84.6%).

Mean CD4 count at start in our study was 174.6 cells /µL & at 6 months it was 307.93cells/µL (increase by 133 cells/µL).In study by Gautam H & Bhalla P[22] *and in study by Lowrance et al, CD4 count increase was similar. Mean CD4 count increased from 126* ±16.6 *(median 130) cells/ µL to 278* ±196.7(median 238)cells/ *µL at 3 months, in study by Lowrance et al where median CD4count increase by 98 cells/ µL at 6 months.(baseline median CD4 cells 141cels/ µL to 239 cells/ µL).*

Thus ART is effective in restoration of immune status of the patient.

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS was observed in total 4 patient, 3 died (2Tuberculosis, 1 Toxoplasmosis), 1 survive (Tuberculosis), all presented within 2 months of stating ART. All who died were in advanced WHO stage 4 & vary low CD4 count at start & one who survived had WHO stage 1 & CD4 count high(197). All the patients who died of IRIS did not show weight gain during the study. It is dysregulated immune response[23] after initiation of ART leads to immune reconstitution inflammatory syndrome (IRIS), with improvement in CD4 counts. There is paradoxical worsening of existing infection or disease process or appearance of new infection or disease process (unmasking of occult infection) soon after starting the treatment with ART. There are two common IRIS scenarios[24], Paradoxical IRIS and Unmasking IRIS. Paradoxical IRIS-worsening of symptoms of known disease during ART, Unmasking IRIS -manifestation of occult opportunistic infections during ART The frequency of IRIS has not been reported conclusively, but it may be estimated to occur in 10% – 25% of patients who receive ART. In our study, patients who died of IRIS mostly within 2 month of start of ART, due to unmasking of hidden opportunistic infections as we had already excluded patients having active opportunistic infections. Therefore incidence of death seems to be high in cases with IRIS 3 died out of 4 cases but all these are unmasking IRIS and within 2 month of start of ART, present as fulminant course, and so have more mortality, whereas in patients with paradoxical IRIS mortality is not so high as these

patients are already on treatment for the prevailing opportunistic infections. This study on unmasking IRIS needs to be done on larger number of patients. Most of studies are available on overall IRIS both paradoxical and unmasking IRIS, but this study is specially observed unmasking IRIS Type.

In study done by SK Sharma and M Soneja[25] the commonest forms of IRIS were associated with mycobacterial infections, 7.5% incidence for paradoxical TB –IRIS and 3% for ART associated TB and no patient with unmasking TB IRIS, in our study commonest form is TB-IRIS Unmasking type.

Adherence

In our study 3% patients lost to follow up which is comparable to study by *Lowrance et al, (3.4% were lost to follow up at 6 months), indicating a good level of adherence and significance of pre ART counselling and every visit re-counselling .High level of in adherence was noted >95% of patients in study by Gautam and Bhalla .Adherence level was satisfactory in our study.*

Mortality

Mortality at 6 month in our study was 6.2% comparable to study of Lowrance *et al*, 6 month mortality was 3.6%. Among 6 expired patients, 2 patients had Diarrhoea /Candidiasis along with Tuberculosis, 1 patient had toxoplasmosis, indicating severe immunodeficiency. Opportunistic infections were the major contributor of mortality in our study. In rest 3 cases cause of death could not be ascribed as they died at home and home visit was not allowed by patient & their care taker because of social stigma associated with HIV.

CONCLUSION

This study confirms that ART is effective. Most of the patients in the study showed a good clinical response to therapy, as indicated by significant weight gain and improvement WHO clinical stage, Functional WAB stage and in CD4 count. IRIS was observed in 4 cases, CD4 count increased in 94.6% cases. C*andidiasis* was most common opportunistic infections. The overall mortality rate in our study was lower than reported from other developed and developing countries .This may be because we have excluded the patients with active opportunistic infections.

Early diagnosis, antiretroviral therapy, chemo-prophylaxis, and treatment of opportunistic infections are important for the control of HIV replication, disease progression and ultimately containment of the epidemic.

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