A STUDY OF ANTIRETROVIRAL THERAPY OUTCOMES IN A TERTIARY CARE CENTER IN THANJAVUR MEDICAL COLLEGE HOSPITAL, SOUTHERN INDIA

Kannan V. P[1], Babu Anand C[2], Nehru D[3]

[1]Associate Professor, Department of Medicine, Thanjavur Medical College Hospital, Thanjavur.
[2]Associate Professor, Department of Medicine, Thanjavur Medical College Hospital, Thanjavur.
[3]Professor, Department of Medicine, Thanjavur Medical College Hospital, Thanjavur.

ABSTRACT

BACKGROUND

The number of people infected with the Human Immunodeficiency Virus (HIV) worldwide was estimated to be 33.2 million at the end of 2007. The introduction of Anti-Retroviral Therapy (ART) has significantly reduced morbidity and mortality in HIV-infected patients in various developed and developing countries. However, the outcome of ART in India's National ART Programme has not been reported in detail.

The aim of the study is to-
1. Evaluate the immunological response of HIV infected adults starting Highly Active Antiretroviral Therapy (HAART).
2. Evaluate the clinical response of highly active antiretroviral therapy in HIV infected adults.
3. Assess the functional status improvement following highly active antiretroviral therapy.

MATERIALS AND METHODS

To evaluate the effectiveness of the National ART Programme at Thanjavur Medical College Hospital, we undertook a prospective observational study involving ART naive patients who were started on ART between May 2015 and October 2016. ART was offered to these patients in accordance with NACO guidelines. The regimen consisted of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor. The available drugs included efavirenz, lamivudine, nevirapine and zidovudine. The CD4+ lymphocyte (CD4) count (cells/μL) was estimated at baseline and at six months intervals during follow-up. Prophylaxis and treatment of opportunistic infections were in accordance with NACO guidelines. Anti-tuberculosis treatment was administered according to the Revised National Tuberculosis Control Programme guidelines.

RESULTS

Among 203 patients started on ART in this study, 3 died after completing 6 months of therapy and 17 died within 6 months of therapy. Out of the remaining 183 patients, 104 were males and 79 were females. The predominant route of HIV transmission is through unsafe sexual practice, which accounts for 84% of cases. Incidence of HIV is less common in literate population. Majority of patients were married in the category. Most of the patients tolerated CAT-I regimen (STV+LMV+NVP). Pulmonary TB is common in this group of patients. Improvement in the functional status was noted following ART in around 49-91% of patients. In this study, mean average CD4 count increased from baseline 141 cells/μL to 359 cells/μL after six months of initiation of ART. Immunological response seen in 64% of TB patients after ART.

CONCLUSION

1. Majority of HIV patients belonged to the economically productive age group of 20-40 years.
2. A high rate of immunological response was observed after 6 months of HAART.
3. Institution of early HAART was associated with a favourable clinical response.
4. Improvement in functional status level was observed among the HIV patients after 6 months of HAART.
5. The immunological and clinical response to HAART in HIV infected TB patients were similar to those of non-TB patients.

KEYWORDS

Outcomes of ART, HIV, HAART, Immunodeficiency.

BACKGROUND

The number of people infected with the Human Immunodeficiency Virus (HIV) worldwide was estimated to be 33.2 million at the end of 2007.[1] The introduction of Anti-Retroviral Therapy (ART) has significantly reduced morbidity and mortality in HIV-infected patients in various developed and developing countries.[2-5] However, the outcome of ART in India's National ART Programme has not been reported in detail.

In India as per the recently released report, HIV prevalence in India is estimated at 0.26% (0.22%-0.32%) in 2015. In 2015, adult HIV prevalence is estimated at 0.30% among males and at 0.22% among females. Among the states/UTs in 2015, Manipur has shown the highest estimated adult HIV prevalence of 1.15% followed by Mizoram (0.80%), Nagaland (0.78%), Andhra Pradesh and Telangana (0.66%), Karnataka (0.45%), Gujarat (0.42%) and Goa (0.40%). Besides these states, Maharashtra,

Chandigarh, Tripura and Tamil Nadu have shown estimated adult HIV prevalence greater than the national prevalence (0.26%), while Odisha, Bihar, Sikkim, Delhi, Rajasthan and West Bengal have shown an estimated adult HIV prevalence in the range of 0.21-0.25%. All other states/UTs have levels of adult HIV prevalence below 0.20%. The adult HIV prevalence at national level has continued its steady decline from an estimated peak of 0.38% in 2001-03 through 0.34% in 2007 and 0.28% in 2012 to 0.26% in 2015. Until 2004, ART was available only to a selected subset of patients through the private sector; most of the HIV-infected population was unable to afford ART. India's National ART Programme was launched on April 1, 2004, under the National AIDS Control Organisation (NACO) as an initiative of the Ministry of Health and Family Welfare of the Government of India. The programme was launched in eight institutions in six states with a high prevalence of HIV infection and in the National Capital Region of Delhi. By December 2008, 197 ART Centres were functioning in 31 states and union territories and more than 1,93,000 patients were accessing free ART through these Centres.

Settings

Thanjavur Medical College Hospital provides tertiary care to the population of 60 to 61 lakhs in and around Thanjavur, Nagapattinam, Thiruvarur, Perambalur and Pudukkottai districts. Most of its patients come from the lower socioeconomic strata. Patients with HIV infection tend to present in an advanced stages of Acquired Immunodeficiency Syndrome (AIDS) and are usually referred to the Hospital's ART Centre, which is staffed by a nodal officer, two physicians, a laboratory technician, a pharmacist, a nurse (who also acts as an AIDS educator), an ART counsellor, a data manager and a community health worker. The centre receives financial and logistic support from NACO through the Tamilnadu State AIDS Control Society.

Aims of the Study

1. To evaluate the immunological response of HIV infected adults starting Highly Active Antiretroviral Therapy (HAART).
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MATERIALS AND METHODS

To evaluate the effectiveness of the National ART Programme at the Thanjavur Medical College Hospital, we undertook a prospective observational study involving ART naive patients who were started on ART between May 2015 and October 2016. ART was offered to these patients in accordance with NACO guidelines.[6] The regimen consisted of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor. The available drugs included efavirenz, lamivudine, nevirapine and zidovudine. The medications were dispensed directly to the patients or their authorised representatives. Patients were asked to review two weeks after the start of ART and thereafter on a monthly basis. During each visit, patients were evaluated for drug toxicity, clinical improvement and opportunistic infections. Adherence was assessed during each visit by pill count and through counselling patients were motivated to adhere to therapy. Patients who failed to turn up within a week of the scheduled visit were contacted by telephone. The CD4+ lymphocyte (CD4) count (cells/μL) was estimated at baseline and at 6-month intervals during follow-up. Prophylaxis and treatment of opportunistic infections were in accordance with NACO guidelines. Anti-tuberculosis treatment was administered according to the Revised National Tuberculosis Control Programme Guidelines.[7]

Study Design- Prospective and descriptive analytical study.

Inclusion Criteria

The following criteria are used for selection of HIV infected patients-

1. Diagnosis of HIV confirmed as per WHO criteria.
2. Initiation of treatment for HIV infected patients according to WHO criteria.
3. Patients should be more than 14 years of age.

Exclusion Criteria

1. Patients less than 14 years of age.
2. The patients who have already received treatment with antiretroviral drugs outside.
3. Patients who died within 6 months after initiation of antiretroviral therapy.
4. Patients who lost follow-up after initiation of antiretroviral therapy.

Statistical Analysis- The statistical analysis for assessing the significance value of variable were done using paired samples "T" test and sign test.

Treatment Follow-up- After 6 months of initiating therapy, patient was examined in detail for change in-

1. Body weight.
2. Functional status of the patient.
3. Clinical staging as per WHO.
4. Opportunistic infections.
5. CD4 count.

6. If patient died after initiating therapy, enquiry was made into the cause of death.

RESULTS, ANALYSIS AND DISCUSSION
Age and Sex Incidence
In this study, the age of the patients varies from 20 years to 70 years. The study group comprised 104 males and 79 females (56.8% and 43.2%, respectively) Table 1. Majority of patients belonged to the most productive age group of 20-40 years (80%) Figure 1. As per the census[5,8] regarding age distribution of AIDS cases in India, majority of HIV infections (88.59%) are in the age group of 15-49 years, out of which 31.8% are in the age group of 15-29 years. The predominance of the males over the females is similar to the census statistics of AIDS cases in India.

Risk Factors for HIV Transmission
In this study, the predominant route of transmission of HIV is through unsafe sexual practice, which accounts for 84% of cases Figure 2. In census regarding route of infection in India, August 2006, the sexual transmission is responsible for 85% cases.[5,8] Since, we have not included paediatric population in this study, the vertical transmission route could not be estimated, which is the next common mode of transmission as per census.

Educational Level
In this study, majority of patients belonged to primary and secondary school level of education (77%) Table 2. The incidence is less among those with higher education (5.5%) because of their awareness of safe sexual practices using preventive methods.

Employment
In this study, employed patients (58%) have acquired the disease. No notable differences between the two groups were observed Table-3a. However, impoverished, unemployed, underemployed mobile and migrant youth are particularly vulnerable to HIV as they are less likely to have information about HIV or access to preventive measures and they may face repeated risks of HIV infection.

Marital Status
In this study, the majority of patients belonged to married category (63%). Also, the widow population contributed to 20% of cases Table 3b. In nearly, half of the affected patients, other members of their family were also affected. This gives importance of preventive measures aimed at stopping the transmission between the couples through education and adoption of safe sexual practices.

ART Regimens
The category 1 regimen accounts for 49% and category 3 accounts for 17.5%. The change in regimens CAT/5 accounts for 32%, Figure 3. This is due to the substitution of efavirenz for nevirapine in cases of intolerance to the latter or if patients are receiving rifampicin-containing anti-TB treatment. In this study, the stavudine-based ART regimen is often preferred to zidovudine-based ART while on initiation because of co-existence of anaemia in many patients making them unsuitable for zidovudine-based regimen. Regimens include CAT1-(STV+LMV+NVP), CAT2-(STV+LMV+EFV), CAT3-(ZDV+LMV+NVP), CAT4-(ZDV+LMV+EFV), CAT5-Change of regimen within above categories during treatment.

TB and HIV
In this study, pulmonary TB (15% of patients) and extrapulmonary TB (4.4% of patients) were diagnosed. They were the second most common opportunistic infection among patients next to candidiasis Table 4. These patients were initially started on ATT and ART started subsequently after 2 weeks to 2 months as soon as TB treatment is tolerated.

Assessing Functional Status Improvement to ART
The functional status of an individual is divided into three grades according to NACO, Ministry of Health and Family welfare, Government of India.
W- Able to perform usual work.
A- Able to perform activities of daily living, but not able to work.
B- Not able to perform activities of daily living.

In this study, there is an improvement in functional status level in response to ART as evidenced by an increase in patients belonging to "W" class from 49% to 91% after treatment and decrease in patients of "A" class from 50% to 8% after treatment Figure 4. This change in class is statistically significant with 'P' value <0.05. The similar observation is also seen in patients suffering from tuberculosis with HIV Table 5.

Assessment of Clinical Response to ART Based on WHO Clinical Staging
The HIV-related clinical events in adults and adolescents were classified into clinical stage 1 to 4 according to WHO, 2006, page no. 33. In this study, there is marked clinical improvement after ART. This is reflected by the following observations, Figure 5. There is an increase in clinical I stage from 2.2% to 25% and clinical II stage from 9% to 66%. The clinical II stage increase is mainly due to the patients who had improved in the clinical status from stage III to stage II. Most important observation is the decrease in stage III from 82% to 7% after treatment. All the changes are statistically significant with P value <0.05.

Opportunistic Infections
The most common opportunistic infection observed in this study are candidiasis and tuberculosis. In this study, the opportunistic infections were seen in 89 patients before treatment and reduced to 5 patients after treatment, Table 6. This is statistically significant with P value <0.05.

Assessing Clinical Response by Measuring Change in Weight after ART

In this study, the average pre-ART weight is 46 kg, which increased to 50 kg after ART. So, an average of 4 kg increase in weight is seen among the study group. On analysing statistically with paired "T" test and sign test showed a high statistical significance with P value <0.0005, Z score - 11.496, Table 7-Table 10. 13% of patients declined in weight after ART. However, majority 71% showed an increment of 0-20% after ART.

Assessing Immunological Response to ART by Measuring CD4 Count at End of 6 Months

In this study, the mean CD4 count has increased from baseline 141 cells/mcL to 359 cells/mcL after 6 months of ART, Table 11. The average increase in CD4 count was 217 cells/mcL. The statistical analysis done using paired 'T' test and sign test showed a statistical significance with P value <0.0005 and Z score-12.71, Table 12-Table 14. 2.7% of patients (5 in number) showed a decline in CD4 count after treatment. Majority of the patients (31%) showed a 0-100% increment in CD4 count. 13% of patients (24 in number) showed an increase of >500% CD4 count compared to baseline, Figure 6. Immunological failure according to WHO in this study was seen in 2.7% of patients. Study by Kilaru KR et al (2006)[9] had immunological success around 80%. 18% had increase in CD4 by more than 200 cells with a median CD4 increase of 114 cells/mcL.

Success and Failure of Treatment

Both success and failure of treatment can be evaluated using different criteria- virological, immunological and clinical. Of these, the earliest indicator is virological success or failure. On the other hand, success of treatment may be seen much earlier; many patients suffering from constitutional symptoms rapidly improve on HAART.

Immunological Treatment Failure and Success

Immunological treatment success is generally defined as an increase in the CD4 + T-cell count. Failure is usually described as the absence of an increase or as a decrease in the CD4 + T-cell count in patients receiving HAART. As with the decrease in viral load, the increase in CD4 + T-cell count also occurs in two phases. Usually, rapid increase occurs in the first three to four months, further increase is considerably less pronounced. The lower the CD4 + T-cell count at baseline, the less likely it is to normalise completely (Valdez 2002, Kauffman 2003-2005).[10,11] Virologic success is more appropriate for judging the efficacy of superior regimens. Once CD4 + T-cells have normalised and plasma viraemia remains undetectable, it is unlikely that they will reduce significantly.

Discordant Response

Failure to achieve every one of the therapeutic goals - clinical, immunological and virological is referred to as discordant response. Some patients may have virological treatment success without immunological improvement. The risk factors for a lack of immunological treatment response include age, low CD4 + T-cell counts at baseline as well as having low viral loads at the start of treatment (Florence 2003,[12] Kauffmann 2005), patients who are IV drug abusers (Dragsted 2004[13]), concomitant immuno or myelosuppressive therapies.

Gender and Immunological Response

In this study, gender does not show any difference in the outcome/immunological response. Studies by Kilaru KR et al (2006), L Fardet et al (2006)[14] also demonstrated that the age, gender risk group does not influence the treatment outcome.[15,16] However, Manfredi et al[17] showed that older age group patients have favourable immunological responses to HAART. However, their CD4 cell reconstitution is significantly slower than in younger patients despite a better virologic response.

Immunological Response in TB Patients

In this study, the immunological responses seen in TB patients with HIV (64%) were higher as that of non-TB patients (59%) receiving ART, Table 15. Vajpayee Mathu et al showed that there is no difference in treatment outcome between TB and non-TB patients. The study by Hungchienching et al (2003)[18] demonstrated similar clinical, immunological and virological responses to HAART and prognosis of HIV-1 infected TB patients who were concurrently treated with ART and HAART with those of non-TB patients. Hence, the treatments of opportunistic infections like TB may not only slow the progression of HIV disease in patients dually infected with HIV and TB, but may also be beneficial for patients facing a high risk of imminent death due to TB in developing countries like India.

Death among Patients Started on ART

Initially, 215 patients were selected for study and started on ART. In these group, 17 patients died before completion of 6 months of ART and 3 patients died after completion of 6 months of ART, Table 16.
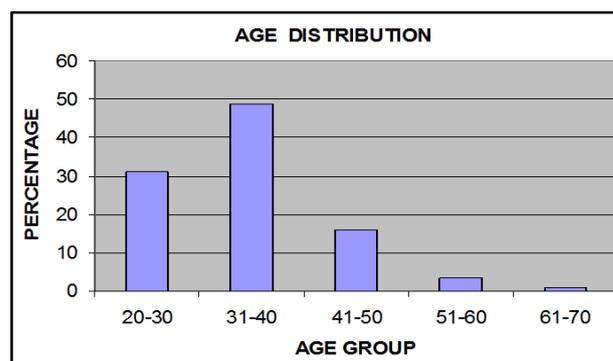

Figure 1. Age Distribution

Sex	Frequency	Percent
Male	104	56.8
Female	79	43.2
Table 1. Sex Distribution		
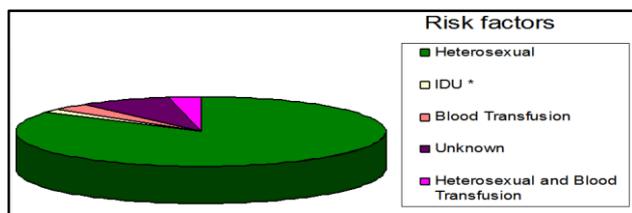
Figure 2. Risk Factors for HIV Transmission

Educational Level	Frequency	Percent
Non-literate	31	16.9
Primary school	84	45.9
Secondary school	58	31.7
College and above	10	5.5

Table 2. Literacy Level

Employed	Percent
Yes	58
No	42

Table 3a. Employment

Marital Status	Frequency	Percent
Single	22	12
Married	117	63.9
Widow	37	20.2
Separated	7	3.8

Table 3b. Marital Status
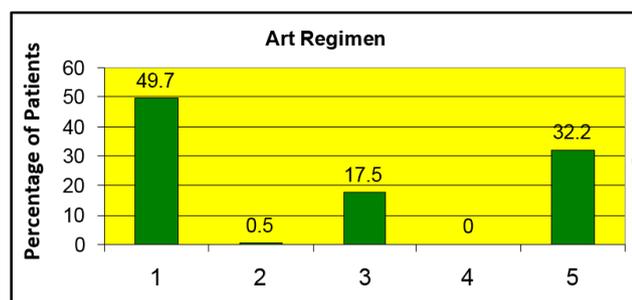
Figure 3. ART Regimen Categories

| TB	Frequency	Percent
Pulmonary	28	15.3
Extra pulmonary	8	4.4
No	147	80.3

Table 4. Incidence of Tuberculosis in HIV
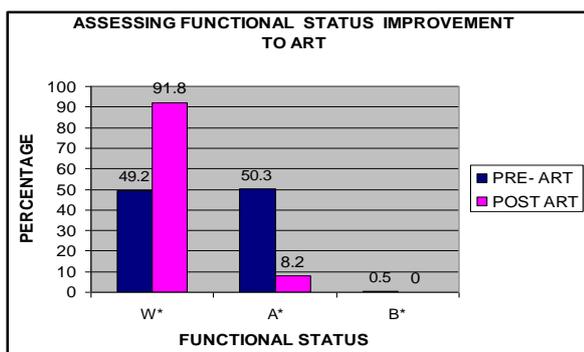
Figure 4. Assessing Functional Status Improvement after ART

Functional Status	Pre-ART (Numbers)	Post-ART (Numbers)
W	7	30
A	29	6
B	-	-

Table 5. Functional Status Observation among TB Patients with HIV
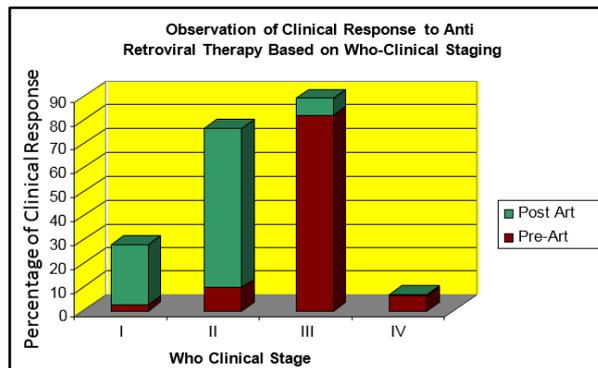
Figure 5. Observation of Clinical Response to ART Based on WHO Clinical Staging

Opportunistic Infections		
Opportunistic Infections	Before ART (Numbers)	After ART (Numbers)
Yes	89	5
No	94	178

Table 6. Opportunistic Infections

Statistically significant P value <0.05.

	Pre-ART Weight	Post-ART Weight
Mean	46 kgs	50 kgs
Median	45 kgs	50 kgs
STD deviation	7.88	8.39
STD error of mean	0.58	0.62

*Table 7. Assessing Clinical Response by Measuring Change in Weight to after ART*
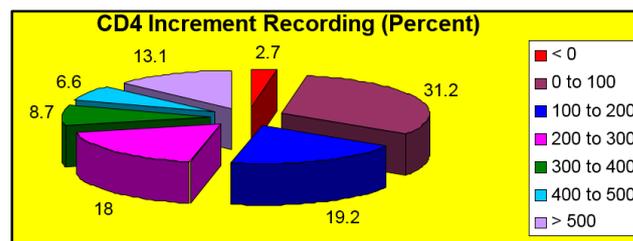
Figure 6. CD4 Increment Recording

Statistical Analysis

Pair	Paired Differences					Significance (2 Tailed) p Value
	Mean	S.D.	S.E. of Mean	99% Confidence Interval of the Difference		
				Lower	Upper	
Pre-ART Wt. - Post ART Wt.	-4.79	4.35	0.3219	-5.63	-3.95	<0.0005

Table 8. Paired Samples "T" Test

The change in weight on treatment as measured by paired sample "T" test is statistically significant with P value <0.0005 (99%, C.I.).

Sign test- The sign test determines the actual number of pairs with the negative difference, positive difference and no change (ties). The statistical significance is also calculated by "Z" score and P value.

	Frequencies	Number
Post-ART Wt. (vs.) - Pre-ART Wt.	Negative Difference (A)	9
	Positive Difference (B)	159
	Ties (C)	15
	Total	**183**

Table 9. Change in Weight Following ART

A. Post-ART Wt. <pre-ART Wt.;
B. Post ART Wt. >pre-ART Wt.;
C. Pre-ART Wt. = Post-ART Wt.

	Post-ART Wt. - Pre-ART Wt.
Z	-11.496
Asymp. Sig. (2 tailed)	<0.0005 (p value)

Table 10. Test Statistics

	Pre-ART CD4	Post-ART CD4
Mean	141	359
Median	123	356
Std. deviation	89.87	148
Std. error of mean	6.64	10.94

Table 11. Assessing Immunological Response to ART by Measuring CD4 Count

Statistical Analysis

Pair	Paired Differences					Significance (2 Tailed) P Value
	Mean	S.D.	S.E.	99% Confidence Interval of the Difference		
				Lower	upper	
Pre-ART CD4-Post ART CD4	-217	126	9.37	-242	-193	<0.0005

Table 12. Paired Samples "T" Test

The statistical analysis done by using paired sample "T" test shows the change in CD4 count to antiretroviral therapy is statistically significant with P value <0.0005 (99%, CI).

	Frequencies	No.
Post-ART CD4 – Pre-ART CD4	Negative differences (a)	5
	Positive differences (b)	178
	Ties (c)	0
	Total	**183**

Table 13. Sign Test

(a) Post-ART CD4<Pre-ART CD4; (b) Post-ART CD4>Pre-ART CD4; (c) Pre-ART CD4=Post-ART CD4.

	Post-ART CD4-Pre-ART CD4
Z	-12.71
Asymp. significance	<0.0005 (p-value)

Table 14. Test Statistics

Sign test also reveals the difference in CD4 count to be statistically significant (P value <0.0005).

	Pre-ART CD4		Post-ART CD4	
	<200	>200	<200	>200
TB patients	32 (88.9%)	4 (11.1%)	9 (25%)	27 (75%)
Non-TB patients	106 (72%)	41 (28%)	19 (13%)	128 (87%)

Table 15. Immunological Response to ART among Tuberculosis Patients

The response in TB patients receiving ART was higher (64% increase) compared to the non-TB patients (59% increase).

Death	Frequency	Percent
Yes	3	1.6
No	180	98.4

Table 16. Deaths among Patients Started on ART

Among 203 patients started on ART in this study, 3 died after completing 6 months of therapy and 17 died within 6 months of therapy.

CONCLUSION

1. Majority of HIV patients belonged to the economically productive age group of 20-40 years.
2. A high rate of immunological response was observed after 6 months of HAART.
3. Institution of early HAART was associated with a favourable clinical response.
4. Improvement in functional status level was observed among the HIV patients after six months of HAART.
5. The immunological and clinical response to HAART in HIV infected TB patients were similar to those of non-TB patients.

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